EUROPEAN PARLIAMENT

Making *Perfect* Life

European Governance Challenges in 21st Century Bio-engineering

Study

Science and Technology Options Assessment

STOA

The STOA project 'Making Perfect Life' was carried out by the Rathenau Instituut, The Hague (Project co-ordinator); together with the Institute of Technology Assessment (ITA), Vienna; the Fraunhofer Institute for Systems and Innovation Research (Fraunhofer ISI), Karlsruhe; and the Institute for Technology Assessment and Systems Analysis (ITAS), Karlsruhe Institute of Technology (KIT), as members of the European Technology Assessment Group (ETAG).

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Making *Perfect* Life

European Governance Challenges

in 21st Century Bio-engineering

Final Report

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Abstract

The STOA project 'Making Perfect Life' looked into four fields of 21st century bio-engineering: engineering of living artefacts, engineering of the body, engineering of the brain, and engineering of intelligent artefacts. This report describes the main results of the project.

The report shows how developments in the four fields of bio-engineering are shaped by two megatrends: "biology becoming technology" and "technology becoming biology". These developments result in a broadening of the bio-engineering debate in our society.

The report addresses the long term views that are inspiring this debate and discusses a multitude of ethical, legal and social issues that arise from bio-engineering developments in the fields described. Against this background four specific developments are studied in more detail: the rise of human genome sequencing, the market introduction of neurodevices, the capturing by information technology of the psychological and physiological states of users, and the pursuit of standardisation in synthetic biology. These developments are taken in this report as a starting point for an analysis of some of the main European governance challenges in 21st century bio-engineering.

General information

This final report *European Governance Challenges in Bio-engineering* is the result of the third phase of the STOA-project "Making Perfect Life". This phase ran from December 2010 to September 2011. A draft version of this document provided input for a workshop, which involved Members of the European Parliament (MEPs) and experts, and was held on 11 October 2011 at the European Parliament in Brussels.

This third and final phase of the project elaborated on research that was done during the first two phases, which ran from September 2009 to October 2010. This preparatory research led to an interim study (van Est et al., 2010a), which was instrumental in defining the research focus of the project and a monitoring study (van Est et al., 2010b) presenting the state of the art of four domains of bio-engineering: engineering of living artefacts, engineering of the body, engineering of the brain, and engineering of intelligent artefacts. The monitoring study also depicted the relevance of each of these four engineering fields within the European Framework Programme, and it provided an overview of the various social and ethical issues that relate to the further development of these fields. The second phase of the project was concluded with a STOA conference at the European Parliament in which the results of the monitoring study were discussed (Slagt et al., 2010).

In the final phase of the project the research focused on a number of particularly relevant developments in the four fields of bio-engineering: the rise of human whole genome sequencing, the market introduction of neurodevices, the capturing by information technology of the psychological and physiological states of users, and the pursuit of standardisation in synthetic biology. Each case study points to important regulatory challenges in the context of European policy-making. The research in this phase has been informed by expert workshops for which preliminary case study subreports have been produced (van Est and Stemerding 2011a), followed by the publication of the workshop reports (van Est and Stemerding 2011b)[1]. The present report incorporates the final results of the Making Perfect Life project (van Est and Stemerding 2011c) which have been discussed in the above mentioned STOA workshop at the European Parliament (Slagt et al. 2011).

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[1] The invited experts have been listed in a final annex to this report.

- Van Est, R.; D. Stemerding (eds.) (2011c): Making Perfect Life: Bio-engineering in the 21st Century. Final Report: European Governance Challenges in Bio-engineering. Brussels: European Parliament, STOA.
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The project *Making Perfect Life* continues our intellectual search for the social meaning of NBIC convergence, the powerful combination of nanotechnology, biotechnology, information technology, and cognitive sciences (van Est et al., 2006, 2008; Coenen et al., 2009). Many people have inspired us. In particular, this report builds both on earlier STOA projects on converging technologies (Berloznik et al., 2006) and human enhancement (Coenen et al., 2009) as well as earlier discussions with Bart Walhout, Tsjalling Swierstra and Marianne Boenink in preparing for the book *Life as a Construction Kit* (in Dutch: *Leven als bouwpakket* – Swierstra et al., 2009a, 2009b). Our project has been developed in parallel to the Danish ISSP's (Initiative for Science, Society and Policy) project on *Living technologies*, led by Mark A. Bedau and Pelle Guldborg Hansen. The results of the ISSP project (Bedau et al., 2009) as well as participating in that project have strongly stimulated our work. Finally, we would like to thank the many experts who were interviewed for our project, participated in our expert workshops, and responded in writing to our questions.

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EXECUTIVE SUMMARY

STOA project Making *Perfect* Life

The STOA project Making Perfect Life (2009 – 2011) has been inspired by the notion that scientific and technological progress in the 21st century will be strongly shaped by an increasing interaction and convergence between four key technologies: nanotechnology, biotechnology, information technology and cognitive sciences (NBIC). NBIC convergence is seen as a key factor in the development and organisation of the natural sciences, because it challenges the historical divide between the physical and the biological sciences. In the Making Perfect Life Project we have studied the growing interaction between the physical and biological sciences in terms of two bio-engineering megatrends which together constitute a new engineering approach to life: "biology is becoming technology" and "technology is becoming biology".

The "biology becoming technology" trend implies and promises new types of interventions which further enhance the manipulability of living organisms, including the human body and brain. The "technology becoming biology" trend embodies a (future) increase in bio-, cogno-, and socio-inspired lifelike artefacts, which will be applied in our bodies and brains, be intimately integrated into our social lives, or used in technical devices and manufacturing processes. These (anticipated) new types of interventions and artefacts present a new technological wave that is driven by NBIC convergence.

Given the techno-scientific dynamics in 21st century bio-engineering, European policy makers are being faced with new governance challenges. The two megatrends we have been studying in this project will slowly but surely blur familiar boundaries between science and engineering, between living and non-living, between sickness, health and enhancement, technology and nature, and between human and machine intelligence and agency. Precisely because NBIC convergence challenges basic categories that people use to understand the world and to define what is human, it is an explicitly value-loaded development and a potential cause for uneasiness within society. Accordingly, the ambitions of 21st century bio-engineering to (re)design and (re)build the living world are obviously in need of social reflection and political and public debate. The Making Perfect Life project wants to contribute to that debate by providing Members of the European Parliament (MEPs) with information about this fundamental development.

In the past decades, the development of the life sciences has already given rise in our society to a long-standing bio-engineering debate. With the growing capabilities to intervene into living organisms this bio-debate broadened from micro-organisms, plants and animals to include human beings. Today we see a further broadening of this debate to the societal aspects of info-tech interventions in the bodies and brains of animals and human beings. Moreover, in the future, this debate will more and more extend from the "biology becoming technology" trend to the "technology becoming biology" trend, in which information technology also plays a central role and which is expected to lead to various controversial issues. As developments in 21st century bio-engineering increasingly tend to blur familiar distinctions between biology and technology, new governance challenges will arise. The Making Perfect Life studies show that these developments challenge both established bioethical notions as well as established regulatory frameworks. This implies that policy makers have to move beyond bioethics to biopolitics.

Monitoring Report: Bio-engineering (in) the 21st Century

To identify the transformative ethical, social and political implications of the two megatrends, we have studied four fields of bio-engineering: engineering of living artefacts, engineering of the body, engineering of the brain, and engineering of intelligent artefacts. The results have been published in a *Monitoring Report* which has been discussed at a STOA conference in the European Parliament in November 2010 (see also chapter 2 in this Final Report).

In the Monitoring Report, we identified the "biology becoming technology" trend in synthetic biology as an emerging field which uses completely synthesized genetic material as a tool in engineering micro-organisms for the production of useful substances. Likewise, stem cells and artificially produced tissues are becoming more and more available as tools in engineering the human body. In addition to these biotech-tools, increasingly sophisticated infotech-tools are used to measure and manipulate activities in the human body and the brain. The "technology becoming biology" trend can also be identified in the field of synthetic biology with the long-term aim to build 'proto-cells' with lifelike features. A comparable future prospect is the production of artificially produced functional biological organs in the field of regenerative medicine. In the field of brain research we already find attempts to completely simulate the brain in hardware, software and wetware models. Finally, there is a great deal of effort in the field of artificial intelligence to build lifelike robots and intelligently interacting systems and environments.

Our study shows that the scientific ambition to understand the living world has become intimately connected with the engineering ambition to intervene in living organisms as well as to construct lifelike artefacts. This development implies a fundamental broadening of the bio-engineering debate in our society. In the Monitoring Report we have discussed the nature of this emerging bio-debate from three interrelated perspectives. We have described the speculative long-term visions in which life is conceived as a system that can be (re)designed and made more "perfect" (i.e. tailor-made for certain purposes) and in which the engineering of living and intelligent artefacts is seen as key in understanding complex biological and cognitive processes. We have also described how the achievement of these visions in 21st century bio-engineering will challenge fundamental concepts and dichotomies we use to make sense of our world and to make ethical judgements. And, finally, we have highlighted the great variety of ethical, legal and social issues raised by current and future developments in the four fields of bio-engineering.

Our analysis makes clear that policy makers will have to face new issues in the field of safety, privacy, bodily and mental integrity, and informed consent as a result of new types of interventions in the human body and brain. New bio-, cogno-, and socio-inspired artefacts will also raise safety, privacy and liability issues, and questions about the limits to animal experimentation and the simulation of social interactions, such as friendship or violent behaviour. Given the fact that the European Commission is strongly sponsoring research with a highly transformative potential in all four fields of bio-engineering, there is a remarkable imbalance in the way the Commission supports research on ethical, legal and social issues related to these fields. Attention to these issues mainly comes from the Directorate General for Research and Innovation with its Science and Society Programme, focusing on the societal governance of emerging technologies. Within the Directorate General for Communications Networks, Content and Technology (formerly named Directorate General for Information Society and Media), which funds most of the research in information technology and neural engineering, there is no institutionalised attention for issues of ethics and governance (apart from standard ethical review of individual projects).

General recommendation from the Monitoring Report:

The need to broaden the bio-engineering debate

Given the need to broaden the bio-engineering debate in our society in response to NBIC convergence, the European Commission should take a more prominent, integral and pro-active role in stimulating research, public awareness and debate in Europe on the ethical, legal and social aspects of bio-engineering in the 21st century.

Final Report: European Governance Challenges in Bio-engineering

Besides identifying a multitude of ethical, legal and social issues arising from various bio-engineering developments, the Monitoring report also pointed out how these issues may challenge current regulatory frameworks in society. Therefore, to face the European governance challenges in 21st century bio-engineering, reflection and debate are important but not sufficient. We also need a more profound understanding of how bio-engineering developments may challenge the ways in which issues like safety, privacy, informed consent and bodily integrity are currently regulated.

This Final Report of the Making Perfect Life project scrutinises regulatory challenges put forward by specific developments in each of the four fields of bio-engineering: the rise of human whole genome sequencing (chapter 3), the market introduction of neurodevices (chapter 4), the capturing by information technology of the psychological and physiological states of users (chapter 5), and the pursuit of standardisation in synthetic biology (chapter 6). In October 2011, these four case studies have been discussed in a STOA workshop in the European Parliament to inform and stimulate further political debate. Each case study points to important regulatory challenges in the context of European policy-making. How to protect our privacy when DNA sequencing sets no limits to the availability of genetic information? Is the European medical device regulation sufficient to secure the safety of newly developed devices that modulate brain activity? What about our mental privacy when information technology becomes a tool to monitor our state of mind? Can we make synthetic biology a building block to a sustainable future by standardising life?

This report applies a conceptual framework which highlights, on the one hand, the sociotechnical dynamics of the developments studied and, on the other hand, the extent to which these various developments challenge current forms of regulation. New bio-engineering technologies may be adopted in relatively stable sociotechnical practices, but may also lead to significant changes of established practices or to new emerging sociotechnical practices. With regard to the dynamics of these practices, current forms of regulation may be perceived as adequate, as being put under pressure, or as no longer adequate. Our four case studies indicate that the regulatory challenges raised by the bio-engineering developments are manifold, both within current regulatory frameworks and outside the confined regulated areas. These findings clarify the nature of the governance challenge that (European) policy makers have to face: how to align the dynamics of sociotechnical and regulatory practices in 21st century bio-engineering?

When taking up this challenge, policy makers have to deal with three important sources of uncertainty: uncertainty about the speed, direction and nature of (future) technological change, uncertainty about the values that are at stake in public and political debates in regard to this change, and uncertainty about the adequacy of existing frameworks to regulate this change. As a result, there are often different and conflicting understandings of the governance challenges in 21st century bio-engineering. In other words, the question of how to understand these governance challenges and their policy implications is in essence a political issue, and often also a controversial one.

We discern three options for policy makers to deal with the governance challenges arising from particular developments in bio-engineering, based on different understandings of these developments as "similar", "maybe (not) similar", and "not similar" to current sociotechnical practices and related regulatory frameworks. In the first "similar" case, it can be assumed that new bio-engineering developments can be governed on the basis of established regulatory frameworks. In that situation a wait-and-see governance approach seems to be adequate. In the second "maybe (not) similar" case, seriously addressing the question to what extent the new bio-engineering developments may challenge current regulatory systems seems to be the most appropriate strategy. Thus, a more active governance approach is needed, including research on ethical, legal and social issues and stimulating public awareness and debate. In the third "not similar" case, the societal impact of the bio-engineering development is expected to be large, and it is expected that the existing regulatory framework will have to be revised, or new forms of regulation may be needed. Such a political assessment will require a more active form of biopolitics, including steps towards revising the existing regulatory framework or developing new forms of regulation to address societal issues.

General recommendations from the Final Report:

The need for biopolitics

- Stimulating research on ethical, legal and social issues, public awareness and debate is important, but no longer sufficient when we can expect that many bio-engineering developments in the 21st century will have large societal impact and will challenge established forms of regulation. Those circumstances require policy makers to move beyond bioethics to biopolitics, that is, to take active steps towards the revision of existing forms of regulation or the development of new regulatory frameworks
- In order to increase institutional reflexivity and strengthen the preparedness of the European Parliament and other European institutions to deal with the governance challenges raised by bio-engineering in the 21st century, politicians and policymakers need to pay more close attention to the experiences of institutions which deal with regulation and its uncertainties (e.g. the EMA, EDPS, EFSA)
- To empower the current European political system to democratically guide bio-engineering in the 21st century, a dedicated and continuous effort is required to make the complex workings and failings of the relevant regulatory systems politically transparent with respect to the present and coming years

Specific recommendations related to the four bio-engineering developments

Whole genome sequencing (chapter 3)

- Existing frameworks for data-protection and informed consent in biobank research need to be revised and harmonised
- Novel forms of consent and genetic counselling need to be developed for whole genome analysis in health care, without compromising patient autonomy
- There is a need for regulatory oversight in direct-to-consumer genetic testing
- Current regulation of forensic databases is patchy and needs to be harmonised
- Public awareness of the issues and challenges raised by whole genome sequencing should be raised

Neuromodulation (chapter 4)

- From a regulatory perspective, it should be clarified (1) whether EEG-neurofeedback has to be considered a medical (therapeutic) device and (2) whether there is a need to regulate neurodevices for non-medical purposes in a similar way as neurodevices for medical use
- In the field of transcranial magnetic stimulation there is a clear tension that needs to be addressed between regulated research and unregulated (off-label) use
- Attention is needed at the European level for the lack of transparency of market approval data and a lack of harmonisation of reimbursement schemes

Biocybernetic adaptation (chapter 5)

- The current data and privacy protection framework needs to be revised given current developments in the field of IT and the developments envisioned in the context of non-professional health care and gaming
- There is a need for design strategies which embed privacy, transparency and user-control in the architecture of biocybernetic systems
- There is a need for an overseeing body to monitor developments and provide early warnings relating to societal issues and to stimulate expert and public debate about these issues

Synthetic biology (chapter 6)

- Given the high level of uncertainty about the prospect of robust and reliable engineering standards, an open, pro-active and critical approach to issues of standardisation – including technical, safety and intellectual property standards –seems to be the most appropriate governance strategy

CONTENTS

1. INTRODUCTION: BIO-ENGINEERING IN THE 21ST CENTURY

Rinie van Est & Dirk Stemerding

Summary

This chapter describes the aims and approach of the STOA project, 'Making Perfect Life: Bio-engineering (in) the 21st Century'. The main goals of the project were:

- To identify major overarching trends that are visible in the development of four fields of 21st-century bio-engineering, and the societal and political challenges related to these trends
- To discuss a number of specific developments which exemplify the major trends in the four fields of bio-engineering in more detail and highlight a range of more urgent questions for regulatory policies in these fields

The aim of the project's *Monitoring Report*, which was published in 2011, was the identification of major trends. The report described a broad range of developments in four fields of bio-engineering: the engineering of the body, the brain, intelligent artefacts (in the field of artificial intelligence) and living artefacts (in the field of synthetic biology). The present *Final Report* discusses the findings of four case studies which highlight specific developments in each of these four fields: the rise of human whole genome sequencing, the introduction of neurodevices into the market, the capturing of the psychological and physiological states of users by means of information technology, and the pursuit of standardization in synthetic biology.

The starting point of our analysis in the *Monitoring Report* was the assumption that developments in 21st-century bio-engineering are shaped by the convergence of four key technologies: nanotechnology, biotechnology, information technology and the cognitive sciences (NBIC). An important aspect of NBIC convergence is the increasing interaction between the biological and the physical sciences. The *Monitoring Report* described this growing interaction in terms of two catchphrases: 'biology becoming technology' and 'technology becoming biology'. The first phrase expresses the idea that scientists and engineers increasingly look at living organisms in mechanical terms, while the second phrase expresses the idea that engineers are increasingly introducing lifelike features such as self-assembly, cognition and learning into technology.

The 'Making Perfect Life' project adopted both catchphrases as expressions of two bio-engineering megatrends, taking a trans-technological perspective which suggests that all four fields of 21st-century bio-engineering are shaped by these two megatrends, which together constitute a new engineering approach to life. Both megatrends point to a future in which the distinction between *biology* as a science of life and *engineering* as a science of artefacts will gradually disappear. In other words, both trends evoke a future in which we engage in 'making perfect life', with 'life' conceived of as a phenomenon that can be controlled and constructed. In many respects this future is uncertain and speculative. The *Monitoring Report* showed how both megatrends can be traced in a diversity of current developments in the four fields of bio-engineering and that it is important to distinguish between technologies that already exist, technologies that are in the making, and technologies that belong to future scenarios which may currently be considered 'science fiction'.

On the basis of this comprehensive and future-oriented analysis of developments in 21st-century bio-engineering, we have identified a broad range of societal issues that need to be addressed. The growing interaction between biology and technology will increasingly challenge familiar, value-laden categories that are deeply rooted in the history of our culture, such as the distinctions between 'life' and 'matter' or 'nature' and 'machine'. The increasing manipulability of nature that the two bio-engineering trends promise, raises high hopes, but also concerns about the hubris of assuming total control. As a result, the two megatrends may become potential causes for unease and controversy within society and further fuel existing bioethical debates.

Against this background, the *Monitoring Report* discussed a variety of questions that may be raised by developments in the four fields of bio-engineering and framed these issues in terms of our trans-technological view by connecting them to the two megatrends. Again, it is important to emphasize that any such discussion must distinguish between issues that we may face today or in the near future from issues that might arise in a more distant future. As a policy option, the *Monitoring Report* emphasizes the need for the European Commission to take a more prominent, wide-ranging and proactive role in stimulating reflection on and public debate about the role of bio-engineering in the 21st century in Europe.

Based on the findings of the *Monitoring Report*, this *Final Report* focuses on those developments in the four fields of bio-engineering that are most significant to European policymaking as they may have short term implications for existing regulatory regimes in these fields. The analysis of the different cases uses a conceptual framework which highlights, on the one hand, the sociotechnical dynamics of the developments studied and, on the other, the extent to which these various developments challenge current forms of regulation.

Each case study points to important regulatory challenges in the context of European policymaking. For example, how do we protect individual privacy when DNA sequencing sets no limits to the availability of genetic information? Is the European regulation on medical devices sufficient to ensure the safety of newly developed devices that modulate brain activity? What about the privacy of our own thoughts and feelings when information technology develops tools that monitor our state of mind? Can we make synthetic biology a building block to a sustainable future by standardizing life? In terms of policy options which respond to such questions, our main conclusion is that European policymakers will have to move beyond bioethics to biopolitics, that is, take active steps towards the revision of established regulations or the development of new regulatory frameworks. Based on the findings of each case study we will further specify the steps that might be taken in this direction.

Chapter 2 of this report offers a more extensive summary of the major findings of the *Monitoring Report*, explaining the broader context and the starting point for the discussion of the case studies of more specific developments in each of the four fields of bio-engineering in Chapters 3 to 6. Chapter 7 concludes with an analysis of the findings of the case studies and addresses the question of how to cope with the whole spectrum of European governance challenges emerging from the various developments in 21st-century bio-engineering.

Scientific and technological progress in the 21st century will be strongly shaped by an increasing interaction and convergence between four key technologies: nanotechnology, biotechnology, information technology and cognitive sciences (NBIC). NBIC convergence is thought to be essential for the successful development of a broad set of new and promising bio-engineering areas such as molecular medicine, service robotics, ambient intelligence, personal genomics and synthetic biology.

This joint set of engineering fields promises a "new technology wave", which is positioned as a key factor in the development and organisation of the natural sciences, because it challenges the historical divide between the physical and biological sciences (Nordmann 2004). The science and engineering involved takes place at the interface between living and non-living material; between mind and machine; between nature and technological artefacts. Van Est et al. observe that *"NBIC convergence, as an actual and anticipated development, stimulates and substantiates both practically and ideologically the arrival of a new engineering approach to life"* (Van Est et al., 2010a: 33).

1.1. Two bio-engineering megatrends

In the 21st century we have seen the emergence of a *new engineering approach to life* which is driven by an increasing convergence of the physical and the biological sciences and can be understood in terms of two bio-engineering megatrends. The first megatrend – 'biology becoming technology' – concerns the way in which physical sciences such as nanotechnology and information technology enable progress in the life sciences. The second megatrend – 'technology becoming biology' – is driven by convergence in the opposite direction, whereby insights into biological and cognitive processes in the life sciences inspire and enable progress within the physical sciences.

Traditionally, the natural sciences have been divided into the physical sciences and the biological sciences. While the physical sciences, like chemistry and physics, were involved in studying non-living systems, the biological sciences were involved in studying living organisms. As indicated above, NBIC convergence points at the gradual dissolving of the tight borders between the physical and biological sciences. The convergence of the physical and biological sciences goes both ways, and each way represents a bio-engineering megatrend. W. Brian Arthur denotes these two megatrends with the catchphrases "biology is becoming technology" and "technology is becoming biology" (Arthur, 2009), respectively. From an engineering view on life, "biology is becoming technology" implies that we are increasingly looking at living organisms in mechanical terms. Seeing biology as a machine, however, is an old idea. *"What is new is that we now understand the working details of much of the machinery"* (Arthur, 2009: 208). The second megatrend "technology is becoming biology" implies that technologies are acquiring properties we associate with living organisms, like self-assembly, self-healing, reproduction, and cognition. "Technology is becoming biology" is about bringing elements of life-like systems into technology. Bedau et al. (2009) therefore speak about "living technology".

1.1.1. Biology is becoming technology

The first megatrend concerns the way in which the physical sciences (nanotechnology and information technology) enable progress in the life sciences, like biotechnology and cognitive sciences. This type of technological convergence has created a new set of engineering ambitions with regards to biological and cognitive processes, including human enhancement. One might say that developments in nanotechnology and information technology boast the dream that complex living systems, like genes, cells, organs, and brains, might in the future be bio-engineered in much the same way as non-living systems, like bridges and electronic circuits, are currently being engineered. In this respect, the on-going influx of the physical sciences in the biological sciences seems to go hand in hand with a growing influence of an engineering approach to life.

1.1.2. Technology is becoming biology

The second bio-engineering megatrend is driven by convergence in the opposite direction. Here the life sciences – insights in biological and cognitive processes – inspire and enable progress within the physical sciences, like material sciences and information technology. This development relies heavily on so-called biomimicry or biomimetics. The basic idea behind biomimetics is that engineers can learn a lot from nature. Engineers want to emulate nature to enhance their engineering capabilities. In this line of thinking, algae may provide a bio-solar system that is more efficient than the silicon-based solar cells our engineers have created. But although nature's achievement is impressive, engineers are convinced that there is still plenty of room for improving the engineering skills of nature. For example, algae absorb blue and red light, but not a lot of green light. Engineers would like to design more efficient bio-solar systems that can do it all. The bottom line is that our technological capability and level of understanding enables engineers to go beyond the 'simple' mimicking of nature, and make a bold step in the direction of biologically, neurologically, socially and emotionally inspired approaches towards science and engineering.

1.1.3. Four fields of bio-engineering

The aim of the STOA project Making Perfect Life is to explore these two megatrends more in detail in four different fields of bio-engineering: engineering of the body, engineering of the brain, and engineering of living and intelligent artefacts. In a foregoing Making Perfect Life Monitoring Report we have shown how both trends can be identified in the development of these four fields (Van Est et al. 2010b). From this analysis it became clear that each trend manifests itself in a specific way. The "biology becoming technology" trend implies and promises a strong increase in the types of interventions into living organisms, including the human body and brain. The "technology becoming biology" trend embodies a (future) increase in bio-, cogno-, and socio-inspired artefacts, which will be applied in our bodies and brains, and/or intimately integrated into our social lives. These (anticipated) new types of interventions and artefacts present a new technological wave that is driven by NBIC convergence.

1.2. Fundamental broadening of the bio-engineering debate

Developments in 21st-century bio-engineering are guided by imaginative and speculative long-term visions which promise the increasing constructability of nature and human life and radically broaden the existing bio-engineering debate in society. We have discussed this broadening of the bio-engineering debate from two interrelated perspectives, emphasizing the transformative social and political character of the trends, 'biology becoming technology' and 'technology becoming biology'. One perspective highlights the way in which these trends blur the boundaries between nature and technology, the living and the non-living, human and machine. The other perspective focuses more specifically on the social, legal and ethical issues raised by both trends and the need to anticipate the challenges these will create for European policymaking.

In the foregoing Monitoring Report, we not only have described both megatrends from a science dynamics point of view, but also have identified a multitude of social, legal and ethical issues raised by these trends in the four fields of bio-engineering. These issues make clear how the new technology wave, with its promise of an increasing constructability of nature and human life, is radically broadening the existing bio-engineering debate in our society.

The societal debate on genetic engineering has already broadened over the last decade from micro-organisms, plants and animals to include human beings, that is, the promises and perils of engineering the human body and mind (cf. Van Est et al. 2006 and 2008). Besides genetic interventions, the societal aspects of info-tech interventions in the bodies and brains of animals and human beings will take a centre stage position in the political and public debate.

From the "biology becoming technology" trend the debate will also more and more extend to the "technology becoming biology" trend, which is expected to lead to various controversial issues. One major topic related to "technology is becoming biology" is the fear of loss of engineering control. At the start of this century, computer scientist Bill Joy made this argument in his pamphlet *Why the future doesn't need us* (Joy, 2000). He warned that the 'living' character of gene technology, nanotechnology and robotics are "*threatening to make humans an endangered species,*" because they bring the processes of self-reproduction and evolution within the realm of human intervention. In the early stages of the debate on nanotechnology, the so-called Grey Goo scenario, in which self-replicating nano-robots destroy the world, played a role, but it was rapidly removed from the agenda because ist was seen as unrealistic.

However, current developments in the four fields of bio-engineering are breathing new life into the debate triggered by Joy. In these fields too, developments are guided by imaginative and speculative long-term visions, raising high hopes and fears. Within the "biology becoming technology" trend these visions include total engineering control over micro-organisms and human enhancement. The visions within the "technology becoming biology" trend speculate about the future possibility to build living and intelligent artefacts from scratch. These visions refer to the ultimate engineering dream of being able to construct novel forms of life, machine intelligence superior to humans, machine consciousness, and moral machines.

1.2.1. Changing fundamental categories

Starting from these long-term visions, we have discussed in the foregoing study (van Est et al. 2010b) this broadening of the bio-debate from two interrelated perspectives: Firstly, we have emphasised the transformative social and political character of the trends "biology becoming technology" and "technology becoming biology". These bio-engineering trends are slowly but surely blurring the boundaries between science and engineering, between living and non-living, between sickness, health and enhancement, technology and nature, and between human and machine intelligence and agency. As Staman points out, these trends imply a convergence that "*(should) break through the boundaries of man, nature and technological artefacts*" (Staman, 2004). Precisely because NBIC convergence challenges basic categories that people use to understand the world and to define what is human, it is an explicitly value-loaded development and a potential cause for uneasiness within society. Accordingly, the ambitions of 21st century bio-engineering to (re)design and (re)build the organic world are obviously in need of social reflection and political and public debate. The Making Perfect Life project wants to contribute to that debate by providing Members of the European Parliament (MEPs) with information about this fundamental development.

1.2.2. New regulatory challenges

A second perspective from which we have addressed the broadening of the bio-debate in the foregoing study focuses more specifically on the social, legal and ethical issues raised by developments in the four fields of bio-engineering. In all these fields we find a patchwork of regulations which cover these issues to some extent, but which are also challenged by new emerging practices in these fields. As developments in 21st century bio-engineering tend to blur familiar distinctions between biology and technology, they will also challenge established regulatory frameworks which reflect such distinctions in many ways. From a "biology becoming technology" point of view, new types of interventions in the human body and brain force policy makers to anticipate new issues in safety, privacy, bodily and mental integrity, and informed consent. From a "technology becoming biology" point of view, new bio-, cogno-, and socio-inspired artefacts also lead to new safety, privacy and liability issues, and questions regarding the limits to animal use and the simulation of friendship and violent behaviour. In a debate about the Making Perfect Life Monitoring report during a busy conference in the European Parliament in November 2010, participants indeed emphasised the need for anticipation of these challenges in European policy-making in order to safeguard human dignity in the 21st century.

1.3. Aim and content of this study

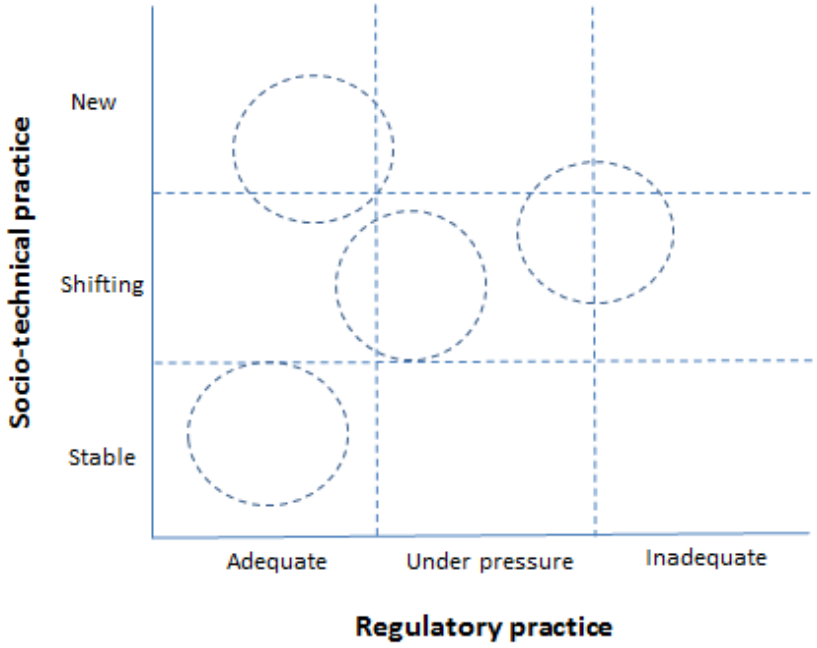
To inform and stimulate further political debate in the European Parliament, this report presents four case studies highlighting particularly pressing developments in 21st-century bio-engineering. Each case study points to important governance challenges in the context of European policymaking. Aiming to clearly identify and discuss these challenges, each case study maps (1) the ways in which established sociotechnical practices are being transformed by new bio-engineering technologies and (2) the extent to which current regulatory frameworks face challenges as a result of these transformations. The fundamental governance challenge identified and discussed in the final analysis of this report concerns *how to align the dynamics of sociotechnical and regulatory practices* in the different fields of 21st-century bio-engineering.

In this final report of the Making Perfect Life project, we have taken the analysis a step further by identifying and scrutinizing specific developments in the four fields of bio-engineering in which these European governance challenges become especially apparent. To inform and stimulate further political debate in the European Parliament, we present in this report four case studies. Each case study highlights a particularly relevant development in one of the four fields of 21st century bio-engineering: the rise of human whole genome sequencing, the market introduction of neurodevices, the capturing by information technology of the psychological and physiological states of users, and the pursuit of standardisation in synthetic biology. Each case study points to important regulatory challenges in the context of European policy-making. How to protect our privacy when DNA sequencing sets no limits to the availability of genetic information? Is the European medical device regulation sufficient to secure the safety of newly developed devices that modulate brain activity? What about our mental privacy when information technology becomes a tool to monitor our state of mind? Can we make synthetic biology a building block to a sustainable future by standardizing life?

1.3.1. Conceptual framework

For the analysis of the different cases in this study we use a conceptual framework which highlights, on the one hand, the sociotechnical dynamics of the developments studied and, on the other hand, the extent to which these various developments challenge current forms of regulation. New bio-engineering technologies may be adopted in relatively stable sociotechnical practices, but may also lead to significant changes of established practices or to new emerging sociotechnical practices. With regard to the sociotechnical dynamics of these practices, current forms of regulation may be perceived as adequate, as being put under pressure, or as no longer adequate. On the basis of this framework the sociotechnical practices described in the different case studies can be mapped along two dimensions, providing us with an overview of (1) the ways in which sociotechnical practices are (re)shaped by new bio-engineering technologies and (2) the extent to which regulatory frameworks are challenged by these practices (see figure 1).

Figure 1: Dynamics of sociotechnical and regulatory practices



In the concluding chapter of this study we will explore the governance challenges which result from this two-dimensional dynamics. Our starting point for this exploration is the assumption that the fundamental governance challenge is to get these two dynamics in tune with each other. In other words, how to align the dynamics of sociotechnical and regulatory practices in the different cases of 21th century bio-engineering that we have studied in this report?

1.3.2. Structure of the report

The four case studies are discussed in this report in the chapters 3 to 6. Each case study describes the emerging practices in the field, the main actors involved and the relevant regulatory issues, and concludes with a discussion of specific challenges for European governance. Chapter 2 presents the main findings from the foregoing Monitoring Report (van Est et al. 2010b) as a broader context and as a starting point for the discussion of the case studies. In the concluding chapter 7, we analyse the findings from the case studies in terms of our conceptual framework, focussing on the sociotechnical dynamics of the practices discussed and the extent to which these various practices challenge current regulatory frameworks. On the basis of this analysis we finally address the question of how to cope with the whole spectrum of European governance challenges emerging from these different developments in 21st century bio-engineering.

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2. TWO BIO-ENGINEERING MEGATRENDS

Rinie van Est & Dirk Stemerding

Summary

The first chapter of this report introduced a trans-technological perspective focusing on two megatrends: 'biology becoming technology' and 'technology becoming biology'. In this second chapter we will discuss in more detail how these megatrends can be identified in four fields of bio-engineering: engineering of the body, the brain, intelligent artefacts and living artefacts. The chapter further discusses the variety of ethical, legal and social issues raised by these developments and some major implications for European policymaking arising from these issues. This chapter is an adapted version of a concluding overview of the main findings of the *Monitoring Report* from 2011. It offers a wide-ranging discussion of developments in 21st-century bio-engineering, providing the context and starting point for the case studies presented in the following chapters of this *Final Report*.

The two megatrends manifest themselves in different and specific ways in the four fields of bio-engineering. Biology is becoming technology through engineering tools which allow new and more far-reaching interventions in living organisms, including the human body and the brain. Technology is becoming biology through the creation of artefacts with increasingly lifelike features, including the capacity for self-assembly, cognition and learning. This chapter shows how these intervening tools and lifelike artefacts are shaping developments in each of the four bio-engineering fields, further distinguishing between interventions and artefacts that are already available or in the making and those that are envisioned in the future.

Today, there are various biologically derived 'biotech' tools available or in development which will make possible a new range of diagnostic and therapeutic interventions and the creation of biological systems with new properties. Proteins from the human body can now be produced and engineered on the basis of genetic information and used as drugs, known as biopharmaceuticals. New advanced medical therapies are being developed in which human genes, cells and stem cells are used as therapeutic agents. The emergence of genomics is creating a huge knowledge base for a deeper understanding of health and disease on a molecular level, offering prospects of early diagnosis and prevention of disease, more targeted and individualized therapies, and the identification of new drug targets on a molecular level. Synthetic biology has emerged as a new engineering science which uses synthetically produced genetic sequences to re-engineer living cells. In the future, complete synthetic genes may be used as a tool to transform cells into biological factories or agents with a highly artificial nature, based on so-called minimal genomes as a cellular 'chassis'.

In addition to new biotech tools, 'infotech' tools which create new options for monitoring and manipulating the human brain are also becoming available. The living brain can be studied with modern neuroimaging technologies and new systems have been developed which enable interventions in the brain by connecting it to electronic devices. What used to be science fiction is now becoming scientific reality: the direct interfacing of the brain with computers. Neuromodulation and brain-computer interfaces are currently being developed which use both invasive and non-invasive tools to support, restore or augment brain or mental functions.

In most fields of bio-engineering the creation of lifelike artefacts remains a future prospect. As a long-term goal in engineering the body, we can observe a paradigm shift from restoring bodily functions to regenerative medicine – involving the (re)generation of tissues – and eventually to completely biologically derived artificial organs. In the field of synthetic biology, researchers have the long-term ambition of creating 'proto-cells' as artefacts with the properties of life, starting from non-biological molecular building blocks. An important engineering approach in brain research is attempting to mimic the brain with software in virtual representations, hardware in supercomputers and wetware in cultured neuronal networks, thus bringing the fields of IT and neuroscience together with the aim of developing a deeper understanding of the brain. The most tangible, albeit still modest, achievements in creating lifelike artefacts are found in the field of artificial intelligence, where researchers are working on the development of animalistic, humanoid and social robots with capacities to interact and to adapt and learn in response to new situations. In addition, forms of artificial intelligence with the ability to interact with users and also to intervene in their behaviour may be embedded and distributed within smart environments.

In 21st-century bio-engineering, the scientific ambition of understanding the living world has clearly become connected with the engineering ambition of *intervening in living organisms* as well as *constructing lifelike artefacts*. Given this techno-scientific dynamics, European policymakers face new governance challenges. In the past decades, developments in the life sciences have already given rise to long-standing bioethical debates. As biology and engineering become increasingly intertwined, blurring venerable boundaries between life and non-life or mind and machine, new questions and concerns will obviously be raised, fuelling further debates. While such debates are stimulated by highly speculative long-term visions of a future in which human embryos might be created from artificially derived gametes, brain activity might be externally controlled and machines might be given superhuman intelligence, our analysis in the *Monitoring Report* has also made clear that, even today, developments in the four fields of bio-engineering raise a variety of ethical, legal and social issues which may challenge current regulatory practices.

From a 'biology becoming technology' point of view, new types of interventions in living organisms, the human body and the brain should prompt policymakers to reconsider established ways of dealing with issues of safety, liability, privacy, bodily and mental integrity and informed consent. The rise of synthetic biology gives new reason for concerns about biosafety, biosecurity and intellectual property. With the rise of molecular medicine, major ethical, legal and social issues have to be addressed, concerning how increasing amounts of personal genetic and medical data are obtained and stored, what the information means and how it can be interpreted or used. Neural engineering of the brain – especially neuromodulation – is a form of behavioural engineering which is still at a very experimental stage and may result in unexpected changes in personality, which makes questions of safety, liability, bodily integrity and informed consent particularly sensitive in this area.

From a 'technology becoming biology' point of view, new kinds of biologically derived and lifelike artefacts raise questions regarding the commodification of bodily materials and the sociopsychological and legal implications of the further penetration of intelligent artefacts into everyday life. The increasing ability to use and engineer materials derived from the human body for technical and engineering purposes requires reflection and deliberation on the ethical and legal status of bodily materials considered as 'goods' and what it means in practice to use this material.

The introduction of increasingly independent robots into human environments will raise special safety and perhaps also liability issues, while privacy issues will gain new significance in relation to intelligent systems which collect and store personal data with the aim of becoming more adaptable to the preferences, needs and emotional states of individual human users.

The European Commission actively stimulates R&D projects in all four fields of bio-engineering and also supports research on ethical, legal and social issues (ELSI). However, across the different bio-engineering fields there is a clear disparity in the extent of institutionalized attention paid to the governance of ELSI. While the Directorate General for Research and Innovation has the Science in Society Programme, focusing on the societal governance of emerging technologies, there is no such programme (apart from standard ethical review of individual projects) in the Directorate General for Communications Networks, Content and Technology (formerly named Directorate General for Information Society and Media), which has a major role in supporting research on the convergence of neuroscience and information technology. Thus, the *Monitoring Report* emphasized the need for European policymakers to acknowledge that future bioethical debates will no longer be solely guided by developments in the life sciences, but will also be led by NBIC convergence of the information and cognitive sciences. In the following chapters of this *Final Report* we will address some between the major developments in the different fields of 21st-century bio-engineering which require special attention in this regard.

Policy recommendation

- Given the need to broaden the bio-engineering debate in our society in response to NBIC convergence, the European Commission should take a more prominent, integral and pro-active role in stimulating research, public awareness and debate in Europe on the ethical, legal and social aspects of bio-engineering in the 21st century.

> *"Conceptually at least, biology is becoming technology. And physically, technology is becoming biology. The two are starting to close on each other, and indeed as we move deeper into genomics and nanotechnology, more than this, they are starting to intermingle."* (W. Brian Arthur 2009: 208)

In the Making Perfect Life Monitoring Report (van Est et al. 2010b) four fields of bio-engineering have been described: engineering of living artefacts (Torgersen et al.), engineering of the body (Hüsing & Geesink), engineering of the brain (Van Keulen & Schuijff), and engineering of intelligent artefacts (Böhle et al.). To structure the description and analysis of these four fields and the societal issues they raise, we have used the trends or metaphors "biology becoming technology" and "technology becoming biology" as a conceptual lens. In this chapter we summarize the main findings of our analysis. First of all we show, in section 2.1., that these two bio-engineering megatrends present and promise on the on hand new types of interventions in living organisms, including human bodies and brains, and other hand the development of new types of bio-, cogno- and socio-inspired artefacts. In section 2.2., we argue that these envisioned new technical interventions and artefacts radically transform and broaden the existing bio-debate. To substantiate this claim we describe how bio-engineering challenges various fundamental concepts and dichotomies we use to make sense of our world and to make ethical judgements, and we reflect on the regulatory challenges arising from the various ethical, social and legal issues in the four bio-engineering fields. In section 2.3., we describe the current role of the European Commission in stimulating R&D and social reflection and debate on bio-engineering developments. We finally argue that the European Commission should take full responsibility for the anticipatory governance of future developments in the field of bio-engineering in order to safeguard human dignity in the 21st century.

2.1. A new range of interventions and artefacts

Bio-engineering in the 21st century is guided by a specific engineering concept of life which involves two types of tool-driven science. The 'biology becoming technology' trend is defined by a tool-driven engineering approach which enables a whole range of new, biotech and infotech-inspired interventions in living organisms. The 'technology becoming biology' trend is defined by a distinct type of tool-driven science, whereby engineering creates new kinds of technological entities which mimic living nature. Thus, bio-engineering in the 21st century has created the possibility of an enormous expansion of the types of interventions in living organisms and the possibility of engineering – physically or virtually – a kind of second, artificial nature as a new object of scientific study.

Both megatrends in the field of bio-engineering are driven by scientific tools and devices – like biomarkers, DNA synthesizers, functional MRI, computers – which enable the discovery of new things about life. The trend "biology becoming technology" is defined by a tool-driven approach in which engineering delivers the tools to investigate nature. "Technology becoming biology", however, is defined by a distinct type of tool-driven science. In this case, engineering provides the experimental tools, but also the object of scientific study. This engineering of new technological entities, which mimic living nature, forms a new 'bottom-up' way of doing science. This engineering approach to science is aptly summarised by Feynman's famous quote: "What I cannot create, I do not understand". In *Science*, Kevin Kelly (1998) signalled the arrival of this new way of doing science, which was not primarily about carefully setting up controlled experiments, but especially about creating insights through "*trying to create an artificial reality, an artificial life, and artificial consciousness*". Here a kind of second artificial nature – a parallel technological world, as Kelly names it – is being engineered, physically or virtually, to foster scientific understanding of the world.

In terms of these two tool-driven types of science, the trend "biology becoming technology" presents and promises a range of *new types of interventions* in living organisms, including human bodies and brains. The trend "technology becoming biology", on the other hand, presents and promises a range of *new types of artefacts*, as it aims to emulate certain lifelike features in and through technology. The following subsections give an overview of these new types of interventions and artefacts.

2.1.1. New types of interventions in living organisms

The four fields of bio-engineering show a myriad of new ambitions with regard to influencing and rebuilding organic life. Society is already accustomed to, although not always at ease with, re-making the living world with the aid of technology. In the second half of the 20th century, all kinds of bio-tech inspired and IT-inspired ways of intervening with living organisms have been put in practice. Since the 1950s, artificial pacemakers are used to regulate the beating of the heart. Since the 1970s, gene technology is employed to genetically modify E. coli bacteria in order to produce insulin to treat diabetics. The introduction of GM food on the market during the 1990s led to much debate. GM animals, like mice, rats and fish, are being used on a massive scale in laboratories all over the world. Bio-engineering in the 21st century shows the possibility of an enormous expansion of the types of interventions in living organisms. Table 1 gives the reader a quick overview.

With regards to biotechnological interventions, synthetic biology aims to bring genetic engineering to the next level through its ambition to standardise and automate the re-engineering of micro-organisms. But also in the field of engineering the human body, all kinds of new molecular (including genetic) diagnostics and therapies are promised. Think for example about the development of gene therapy or the futuristic idea of genetically enhancing sperm cells with artificial chromosomes. Other new forms of interventions in the body, like tissue engineering and stem cell therapy, use living materials often derived from the body it aims to repair.

But information technology, too, offers increasing numbers of ways of intervening in living organisms. Hybrid artefacts are created that mix cells, insects, and animal brains with semiconductors. For humans, smart pills are being developed that monitor diseases and deliver medicines within the body. Also, the brain is rapidly coming up as a new area of so-called forward engineering, based on IT-inspired interventions, including the use of electrodes put into the brain for therapeutic purposes. We are moving from the artificial pacemaker of the heart into the era of the artificial pacemaker of the brain.

Table 1: New bio- and info-tech based interventions in living organisms

Living organism	Bio-tech based interventions	Info-tech based interventions
Micro-organism	Extreme genetic engineering (synthetic biology)	Cyborg cell, cell on a chip
Insect, animal		Insect/animal brain – semiconductor hybrid
Human body	Genetic modification (gene therapy, use artificial chromosomes in gametes), stem cell therapy	Smart e-pills
Human brain	Stem cell therapy	Brain computer interfaces (BCIs), (non-) invasive neuro-modulation, persuasive technology

2.1.2. New bio-, cogno-, and socio-inspired artefacts

Traditional engineering is about building non-living artefacts, like cars and bridges, by means of non-living material. Our study shows various new engineering ambitions to build intelligent artefacts and living artefacts from components that are all non-living. We also encountered examples of so-called hybrid artefacts consisting of both non-living and living components, like animal brain – semiconductor hybrids. Table 2 presents an overview of various types of new (envisioned) artefacts.

Table 2: New types of bio-, cogno-, and socio-inspired artefacts

Source of inspiration	Bio-inspired	Cogno- and socio-inspired
Micro-organism	Proto-cell Minimal genomes	
Insect, animal	Cultured neuronal networks Hybrid artefact: animat	Animalistic robot (e.g. Paro), avatar Neurocomputer
Human	Biopharmaceuticals Engineered tissues (hybrid materials with living ingredients) Stem cells Hybrid artificial organs	Humanoid robot, avatar AI robots and softbots Social robots Ambient persuasive technology

Synthetic biology includes the aim to build a proto-cell – a living artefact – from scratch, i.e. from non-living material. Engineering a microbe with an artificial minimal genome presents a hybrid artefact, built out of living and non-living components. Other hybrid artefacts can be found based on the engineering of living material derived from insects, animals or humans. Examples are cultured neuronal networks, or animal-brain semiconductor hybrids. Bodily materials of humans are employed to engineer tissues, hybrid artificial organs and stem cells.

In particular, reverse engineering of the brain and the field of robotics are indicative of engineering ambitions to create artefacts that show intelligent behaviour. Reverse engineering of the brain aims to build supercomputers through both wetware (cultured neuronal networks) and hardware approaches (neuromorphic engineering).

As described in the Monitoring Report by Böhle et al., new robotics moves away from the rational-cognitive approach (with its computational theory of mind) towards biologically, neurologically and emotionally inspired approaches. Engineers aim to build physical robots and software "bots" or "softbots" that are capable of learning, making autonomous decisions and performing adequately in complex social environments.

2.1.3. Recognising life's special characteristics

To summarise, bio-engineering in the 21st century is guided by a specific engineering concept of life which involves two types of tool-driven science. With regard to "biology becoming technology", the role of engineering is to give science the experimental tools to reveal to mankind the secrets and laws of nature. "Technology becoming biology" is guided by an even more intricate relationship between science and engineering. Here, engineering provides the tools to build an artificial nature, which can be used as a model to study nature. The arrival of these two engineering approaches to science can partially be understood as a pragmatic way to deal with the dynamic complexities of living organisms and social processes.

But more fundamentally, it also presents recognition of the special characteristics of life itself, like its complexity, flexibility, autonomy and emerging properties. As Weber explains, *"in the age of technoscience, the dimensions of becoming, the possible and the unpredictable are of central concern and at the heart of a new techno-rationality that does not represent the living as dead material"* (Weber, 2010: 27). Life as a complex scientific object, thus, has led to an intimate relation between science and engineering. In addition, we may conclude that, in the meantime, the boundaries between experimenting and intervening with nature, and constructing living and intelligent artefacts for acquiring knowledge or for the market, are also being blurred.

2.2. Fundamental broadening of the bio-engineering debate

Both bio-engineering megatrends imply a fundamental broadening of the bio-engineering debate in our society. We have discussed the nature of this emerging bio-debate from three interrelated perspectives. We have described the speculative long-term visions in which life is conceived of as a system that can be designed or redesigned and made more perfect, and in which the engineering of living and intelligent artefacts is seen as the key to understanding complex biological and cognitive processes. We have also described how the achievement of these visions will challenge fundamental concepts and dichotomies we rely on to make sense of our world and to make ethical judgements. Finally, we have highlighted the great variety of ethical, legal and social issues raised by current and future developments in the four fields of bio-engineering, which challenge established regulatory practices related to safety, privacy, informed consent and bodily integrity.

The scientific ambition to understand the living world has become intimately connected to the engineering ambition to intervene in living organisms and our social world as well as to construct lifelike artefacts. These ambitions, if only partly fulfilled, will increase the hybridisation of the living and non-living world, through ways of intervening in human bodies by means of engineering bodily material, interventions in human brains, hybrid artefacts which consist of a mixture of non-living and living components, and artefacts that get lifelike features.

This (anticipated) broad field of bio-engineering is fundamentally broadening the bio-debate. Next to gene tech interventions, the societal aspects of info tech interventions in the bodies and brains of animals and human beings will take a centre stage position in the political and public debate. Besides "biology becoming technology", the "technology becoming biology" trend is expected to lead to debate more and more.

In the Monitoring Report we have discussed this broadening of the bio-debate from three interrelated perspectives, as explained in the following three sub-sections. First, in subsection 2.2.1. we describe long term visions on the engineering of life which form important 'spiritual' drivers of (the broadening of) the bio-debate. The next subsection focuses on the way in which new bio-engineering developments challenge some of the central concepts we use to categorise reality and make moral judgements. Finally, subsection 2.2.3. gives an overview of the ethical, legal and social issues raised by the two above mentioned megatrends. Moreover, it discusses the way in which bio-engineering may challenge current regulatory practices.

2.2.1. Long term visions

All four fields of bio-engineering share imaginative and (speculative) long term visions on engineering of life, or making perfect life. We will both look at the "biology becoming technology" trend, represented by molecular medicine, regenerative medicine, forward engineering of the brain, and "top-down" engineering of living artefacts (Table 3a), and the "technology becoming biology" trend, represented by reverse engineering of the brain, the engineering of intelligent artefacts, and the "bottom-up" engineering of living artefacts (table 3b).

Long term visions related to "biology becoming technology"

The spectacular long term view of synthetic biology and creating artificial life attracts a lot of media attention. Synthetic biology promises to radically reduce the complexity of genetic engineering by standardising the design and construction processes of micro-organisms as living machines (see Table 3a). Time will tell whether this assumption will come true or not. As Torgersen et al. argue in the Monitoring Report: *"The important factor is time: what appears science fiction today may turn out to become reality in a not too distant future, giving rise to ethical questions that are not fundamentally new but gain in salience."* However, normally it takes a considerable amount of time from the emergence of a new research field to introducing the first applications on the market. High expectations, like those raised by synthetic biologists, may thus easily turn new technology into a hype, with unrealistic plans and timescales (Mampuys and Brom, 2010).

In regenerative and molecular medicine we also find visions of futuristic applications, ranging from genetic modification of gametes or embryos through the use of artificial chromosomes to artificial meat and wombs. Such applications will be hopeful for some, but plain scary for many others. The state of the art, however, looks much more mundane and illustrates that the above futuristic visions are far away from being realised in the short or medium term.

Table 3a: Long term visions related to "biology becoming technology"

Biology becoming technology	Speculative long term perspective
"Top-down" engineering of living artefacts	Micro-organisms as standardised chemical factories Artificial animal and human chromosomes
Engineering of the body	Human enhancement (anticipate artificial chromosome) Biobanks as knowledge base for selection and enhancement Moral status of human embryos created from artificial gametes
Forward engineering of the brain	Cognitive enhancement External control of brain activity

In 2005, Lord Winston, the president of the British Association for the Advancement of Science, admitted that the potential benefits of embryonic stem cell research have probably been oversold to the public (Amos 2005). He argues that some of the huge uncertainties in developing cures for degenerative disorders need to be emphasised in the debate.

Currently, gene therapy and cell therapy are slowly moving closer to clinical applications. However, safety issues have to be thoroughly addressed. In particular with respect to gene therapy, the fact that several patients died because they developed severe immune reactions, has slowed down progress seriously and has dampened expectations in this field. One of the recurrent themes is that research leads to new insights, but at the same time and maybe even at greater speed, new complexities are unravelled. Science is confronted with a complexity paradox. For example, the Human Genome Project elucidated all kind of puzzles – only 23,500 genes, 'junk' DNA – that showed that life is not a straightforward computing machine, as many promoters of the digital control paradigm of life might have expected.

From a public perspective, forward engineering of the brain may be one of the most sensitive research areas, since it concerns influencing people's personhood. Future visions include cognitive enhancement, but also outside manipulation of the brain by others. Although little is known about how particular neuro-modulation techniques work, the field of forward engineering the brain already presents a huge emerging global market. This has led to a discussion in the United States and Europe on whether the regulatory framework on medical devices, for introducing neuro-stimulators on the market, still suffices.

Long term visions related to "technology becoming biology"

In contrast to forward engineering of the brain, reverse engineering of the brain and social reflection on it are currently in their infancy. The long term vision that accompanies this novel field is engineering a conscious machine (see Table 3b). Since the brain is one of the most complex systems known to mankind, the attempts to reverse engineer the brain has met with a lot of scepticism form other scientists. Like with synthetci biology, only the future can tell whether it is is possible to re-engineer the brain.

Table 3b: Long term visions related to "technology becoming biology"

Technology becoming biology	Speculative long term perspective
Reverse engineering of the brain	Machine consciousness / computational singularity
Engineering of intelligent artefacts	Need for or fear of ethical robots / moral machines Machine intelligence superior to humans
"Bottom-up" engineering of living artefacts	Artificially created novel forms of life

Currently the field of engineering intelligent artefacts is experiencing a new revival through the inspiration of new heuristic paradigms, such as situated AI and affective computing (so-called social AI). Throughout history, 'strong' AI has always competed with 'weak' AI for media attention and funding. Today's version of strong (classical) AI is represented amongst others by Ray Kurzweil, who predicts the arrival of machines with superhuman intelligence – so-called technological singularity – is near. With strong (nouveau) AI, future expectations refer to machines that feel emotions, instead of machines that act 'as if' they have emotions, and moral machines that can make ethical decisions. However, the reality of AI is far more mundane. Thus, in the Monitoring Report, Böhle et al.warn that "policy makers should be aware of the risk of overhyping the field in question, and should not lose sight of what is the real core of the R&D activities." According to the authors, the real R&D core is guided by 'weak' AI and not the spectacular future visions that are predicted by strong AI.

2.2.2. Gradually changing fundamental categories

The way we view the world and make moral decisions is mediated through culturally defined concepts and classification schemes. These schemes jointly make up what the well-known anthropologist Mary Douglas (1966) named our 'symbolic order'. This symbolic order literally orders or structures our way of living, thinking and judging by drawing boundaries, and making fundamental distinctions for instance between life and death, natural and artificial. According to Swierstra et al. (2009: 214) *"Technological innovation is an important cause of change and as such of 'symbolic confusion'."* This section describes how the trend "biology becoming technology" and "technology becoming biology" challenge some of the fundamental categories and dichotomies we nowadays use to understand ourselves and the world we live in, and make ethical judgements (see Tables 4a and 4b).

"Biology becoming technology" challenging fundamental categories

Synthetic biology considers and reduces life to an information-processing system. In this way, life, at least on the level of microbes, is seen as a construction kit. Moreover, the aim is to create easy translations between the virtual world in which the life process is modelled and the material world of living organisms. This blurs the basic distinction between biology and technology, the material world and information. The standardisation and automatisation of the genetic engineering of micro-organisms also raise the question of whether genetic engineering will always stay an activity only mastered by highly educated scientists and engineers or whether genetic engineering will be democratised and turn into a do-it-yourself type of synthetic biology.

Molecular medicine changes the meaning of health and illness. Sickness is no longer solely connected to visible and for the patient noticeable symptoms, but it becomes a phenomenon at the molecular level. This offers the possibility of diagnosing disease before the symptoms of disease have revealed themselves to the 'non-sick' patient. But even more, molecular medicine can reveal predictive information on individual health risks. Certain diseases then change from something that happens (fate) to people actively having to prevent it from taking place. Health becomes a personal responsibility, and a product of self-managing a healthy lifestyle. Finally, molecular medicine provides information that may be used to select people, during life, but also from the first beginning of life. This would have an influence on our attitude towards the start of life – e.g. do we accept it as a gift, or do we want to specify the genetic features of newborn children – but also on the way we judge people. Do we want to be judged based on our genetic make-up?

Table 4a: "Biology becoming technology" challenging fundamental categories

Biology becoming technology	Challenging fundamental categories
"Top-down" engineering of living artefacts	Relationship between biology and technology, material and information Reductionism: life as an information-processing system, life as a construction kit Democratisation of genetic engineering (do-it-yourself synthetic biology)
Engineering of the body: molecular medicine	Blurring borders health and illness Self-management of health Genetic reductionism (life as an information-processing system) Attitude towards start of life
Engineering of the body: regenerative medicine	Body as a resource of tradable material Body as a construction kit Attitude towards end of life
Forward engineering of the brain	Technology as integral part of the body Person extends beyond the body (remote control) Transparent brain

Regenerative medicine challenges the way we look at our own body and at other humans. This scientific approach views the body as consisting of parts that can be replaced and repaired. The body, in that sense, becomes a kind of technological artefact; the body as a construction kit. Looking at the body as a repairable machine will also change our views on the finiteness of our lives. Our bodies not only present a construction kit, but also the resources or building blocks for repairing or reconstructing the body. Such awareness may change our views on our bodies and other human beings.

Do we want to be looked at in terms of a commodity? This is aptly expressed by Scheper-Hughes in *The Last Commodity*, which deals with the (illegal) organ trade: *"The ethical slippery slope occurs the first time one ailing human looks at another living human and realizes that inside that other body is something capable of prolonging or enhancing his or her life"* (Scheper-Hughes 2008: 40-41).

Forward engineering of the brain introduces technology into the brain, which challenges the distinction between mind and matter; nature and technology. Should we consider the electrode that stimulates the brain of a Parkinson patient as an integral part of his body or even his mind? All kinds of techniques to image and influence brain functions challenge the idea of the brain as a wholly isolated and impenetrable black box. Do we want our brains and thoughts to be transparent for other people? Engineering of the brain also extends the brain beyond the body and opens up the possibility of remotely controlling it.

"Technology becoming biology" challenging fundamental categories

Also the trend "technology becoming biology" challenges various fundamental concepts and dichotomies we use to categorise reality (Table 4b). In the Monitoring Report, Böhle et al. argue that the engineering of intelligent artefacts gradually erodes fundamental categories of the lifeworld ("Lebenswelt"). The vision of conscious machines, which is included in the Neuro-IT roadmap, assumes that there will be machines with real autonomy and adaptability and a genuine capacity to cooperate with human beings, and that such machines need consciousness. Reverse engineering of the brain might be a way to develop a machine with some sort of consciousness. New artefacts, such as brain-semiconductor hybrids that can control a flight simulator, raise new questions with regard to our relation to animals and machines.

Besides, new artificial environments challenge traditional boundaries between nature and culture and may alter our sense of responsibility for the world we live in. Most of the experts interviewed for our study also expect a further symbiosis between human lives and technology; between our bodies and technology; between the virtual and physical world; between human and machine intelligence. Reverse engineering of the brain and "bottom-up" synthetic biology exemplify these tendencies. The former aims at building a brain. Here the brain is regarded as a conscious machine, which can be built. With its attempt to create artificial life, "bottom-up" synthetic biology treats life as a construction kit, and blurs the boundaries between the natural and the artificial, and between living and non-living material.

Table 4b: "Technology becoming biology" challenging fundamental categories

Technology becoming biology	Challenging fundamental categories
Reverse engineering of the brain	Brain as a construction kit Wet computers
Engineering of intelligent artefacts	Hybridisation of real and virtual life Symbiosis between humans and technology Arrival of a second nature Views on corporeality of animals and humans 'Raising' machines to become responsible 'autonomous' actors
"Bottom-up" engineering of living artefacts	Blurring of natural and artificial, non-living and living New forms of life Life as a construction kit

2.2.3. Regulatory challenges

The four fields described in the Monitoring Report provide an impressive list of ethical, legal and social aspects related to 21st century bio-engineering. This section describes how the trends "biology becoming technology" and "technology becoming biology" challenge the way we currently regulate issues like safety, privacy, informed consent and bodily integrity (See Tables 5a and 5b).

"Biology becoming technology" challenging regulatory practices

"Top-down" synthetic biology

"Top-down" synthetic biology brings up various societal issues: safety, security, intellectual property and governance. The debate on synthetic biology follows in the footsteps of the discussion on GM micro-organisms. In contrast to the GM food and GM animals debate, the debate on GM micro-organisms has never really raised much public controversy. Van den Belt (2009) expects that as long as synthetic biology only deals with microbial life, this scenario will not change. Still, genetically modified micro-organisms have raised complex regulatory issues, like safety, security and intellectual property rights (IPR). Current bio-safety regulations assume that engineering starts with a parent organism. "Top-down" synthetic biology does not challenge that idea in a fundamental way ("bottom-up" synthetic biology does, see below). The fact that synthetic biology presents a form of 'digital biology' does challenge the way bio-security and IPR are regulated nowadays. With respect to IPR, a basic question is whether this should be guided by the culture of the pharmaceutical industry (heavy patenting, which sometimes reaches the limits of practicality) or by the culture of the software industry (with open and shared forms of access). Bio-security is about how to control the proliferation of dangerous micro-organisms and knowledge and skills. The extra risks that stem from DNA synthesis challenge the current regulatory practice.

Molecular medicine

Research in molecular medicine depends on the existence of well-functioning and well-regulated biobanks, which collect bodily material and health related information. The regulation of biobanks should strike a proper balance between the need for medical research and the donor's right for self-determination. This implies that the gathering of bodily substances and personal medical data must be subject to the donor's informed consent. Molecular medicine is inherently reductionistic, because it sees disease primarily as a molecular event, steered by genetic factors. To counterbalance and complement this myopic view on disease, R&D into environmental and lifestyle factors is needed.

Over the past two decades, the cost of the testing of genetic traits has decreased exponentially. It is expected that this trend will lead to the sequencing of an entire human genome in one day at costs between 1000 and 100 dollars (Singer, 2008). High-throughput genomic techniques make it urgent to re-examine established ethical and legal concepts (privacy, confidentiality and informed consent) that guide the current research and genetic testing practice. At the moment, genetic testing is mainly confined to analysing a few genes, mostly related to rare monogenic hereditary diseases, and guided by medical staff specialised in genetics. Some principles that guide genetic testing today are: right of self-determination and the idea of genetic exceptionalism (including the principle of informed consent and the right not to know one's genetic status, and genetic counselling before and after testing). Cheap techniques to test genetic traits will severely challenge this practice and the ethical and legal principles that guide it. In the Monitoring Report, Hüsing and Geesink make policy makers alert about a near term avalanche of new biomarkers that need to be sufficiently validated before being brought to the market. The authors also note that the availability of information about genetic factors that contribute to cognitive traits, psychological behaviour and sexual orientation, may be used for selection; before birth (pre-implantation diagnostics, or prenatal screening) but also during our lifetime (e.g. higher education, sports career).

Regenerative medicine

The use of bodily material for medical research and applications has proved to be an ethically and politically very sensitive topic. Human dignity prevents human bodily material to be used in a pure instrumental way, as things or artefacts. Bodily material, ranging from brain-dead bodies to leftover embryos in fertility clinics, has an explicit moral and politically negotiated legal status. In general, the policy challenge is to prevent the exploitation of people as sources of cells, tissues or organs. Guiding principles are informed consent and transparency. The FP7 Framework also does not give research funding for the creation of embryos for research or stem cell procurement and human productive cloning. The moral status of human embryos created from artificial gametes may be one of the most sensitive topics for debate in the future. For now, the collection, engineering and trading in bodily material has already become a substantial market. An important question that policy makers need to address is to what extent bodily material can be treated as goods. A complex set of issues play a role here: intellectual property rights and the moral issue of whether we should allow the "patenting of life", to what extent should we allow competition between public and private organisations, shift from an altruistic donor system towards a commercial system based on donor compensation, the (cross-border) trade of bodily materials, and the danger of exploiting desperate poor people.

Forward engineering of the brain

In the Monitoring Report, Van Keulen and Schuijff explain that the ethical, legal and social issues related to the forward engineering of the brain result from the following characteristics. First of all, neural engineering may lead to personality changes, and thus may imply behavioural engineering. Second, this type of engineering is based on the convergence of neurology and IT. These two aspects combined with the experimental nature of forward engineering leads to a list of traditional bioethical issues: safety, informed consent, mental and bodily integrity, remote control issues, liability and privacy.

Neural engineering of the brain is a drastic medical treatment because it may change the behaviour of the patient. Both in the EU and US there is a debate on whether the regulation of (invasive) neuro-stimulators as medical devices is stringent enough. There is a complaint from patient groups that the current regulation neglects the protection of patients. Along this line of reasoning, the European Group on Ethics (2005) argued that implantable devices for medical purposes should be regulated in the same way as drugs when the medical goal is the same. The notion that non-invasive devices might still be mentally invasive raises the question whether non-invasive medical devices indeed lead to lower risks, as current regulations suggest. Another safety concern relates to the use of neuro-stimulation for the purpose of enhancement.

Table 5a: Regulatory issues related to "biology becoming technology"

Biology becoming technology	Regulatory issues
Engineering of living artefacts: "Top-down" synthetic biology	Safety Security Intellectual property (digital biology) Patenting versus open or shared access Governance ELSA research integrated within EU Framework New engineering Public awareness is low
Engineering of the body: Molecular medicine	Collection and use of genetic information (anticipate whole genome sequencing) Safety and efficacy of treatments Informed consent: open-consent approach genetic counselling Privacy: confidentiality of medical information Biobanks
Engineering of the body: Regenerative medicine	To prevent exploitation of people as sources of cells, tissues and organs Safety and efficacy of treatments Informed consent: obligatory or presumed Bodily integrity: moral and legal status of bodily material Bodily material as goods Intellectual property rights ("patenting life") Commercialisation, donor trade
Engineering of the brain: Forward engineering	Concerning treating brain diseases and preventing misuse Safety and efficacy of (non-) invasive neuro-modulation (for enhancement) Informed consent Mental and bodily integrity Remote control Mental privacy Neuroimaging data giving clues about cognitive state Privacy impact of brain implants Brain Databases Liability issues Increase laboratory animals

Self-evidently, neural engineering needs the informed consent of the patient. In some cases, like severe depression or a locked-in state, it can be questioned whether patients are physically or mentally reasonably capable of giving informed consent beforehand. In the case of the engineering of the brain, informed consent is guided by the principles of bodily integrity and mental integrity. Based on these principles, the European Group on Ethics (2005) argued that ICT devices should not be used to change mental functions or personality traits. The fact that the settings of some implantable devices, like deep brain stimulation, can be remotely controlled, raises an important question with respect to mental integrity: who is in control? Van Keulen and Schuijff recommend the development of a benchmarking system to help doctors decide in what situations it is possible and desirable to give patients control over their own brain settings. Another issue related to bodily integrity is the question whether neural implants should be legally considered as part of the body.

The experimental stage of neural engineering leads to many unintended side-effects, like psychosocial problems, which may change the life of the patient. This makes the issue of mental integrity even more problematic. Nevertheless, for many patients the benefits seem to outweigh the risks. The experimental nature of neural engineering, however, causes doctors who give the treatment to worry about liability issues. Such liability questions need further research and legal consideration.

Van Keulen and Schuijff believe that, in the long term, the issue of mental privacy might become just as important as genetic privacy. The underlying assumption is that, as the technology evolves through time, measuring brain activity will come closer to measuring one's cognitive state or even thoughts. In that case, all kinds of neural applications that collect neuro-imaging data might endanger the mental privacy of patients. The European Group on Ethics (2005), therefore, pleads for a privacy impact evaluation of ICT implants. Analogue to biobanks, also the privacy of patient's brain data stored in large brain-databases should be safeguarded. One important question is whether the current EU directive on personal data protection suffices to deal with these upcoming privacy issues.

"Technology becoming biology" challenging regulatory practices

"Bottom-up" synthetic biology and reverse engineering of the brain

The debate and ethical reflection on "bottom-up" synthetic biology and reverse engineering of the brain mirror the state of the art of the science, which still is in a very early stage. One of the issues concerns the safety of artificial life and its risk assessment. In the case of genetically modified organisms, safety regulations are guided by long term experience with the behaviour of parent organisms. In the case of artificial life, there is no longer a parent organism to compare with. The question then becomes how the risk assessment should be set up. Reverse engineering projects rely on the use of non-human primates. In contrast to the use of non-human primates for medical research on neuro-degenerative diseases, societal support for their use for future IT applications seems very questionable.

Engineering of intelligent artefacts

The development of intelligent artefacts has a much longer history, and so has the debate. To increase the applicability and acceptability of intelligent artefacts in various social contexts, like the home, hospital, or battle field, engineers aim to build artefacts that can learn on the spot, look like humans and/or animals, and show social and emotional behaviour. In order to incorporate lifelike features into artefacts, like robots, these social practices have increasingly become a target for engineering. This engineering tendency to blend our social life with technology raises new challenges with regards to familiar issues, like privacy, informed consent and liability. And it also brings up relatively new issues, like how to deal with the increasing intimate relationship between artefacts and people. In the remainder of this subsection we will focus on the societal issues related to learning robots and anthropomorphic robots.

According to Sharkey and Sharkey (2010), the embodiment of robots and their lifelike appearance is unique to robots, and this is in need of closer scrutiny because of its social consequences. First, these features may enable these artefacts to get "closer" to human beings in all sorts of ways. Privacy is a well-known IT related issue. Affective computing techniques, like facial coding and posture reading systems, however, pose new types of privacy issues. Who may use these techniques, in what kind of situations, and should people be informed about it (informed consent)? In addition, robots and softbots with a lifelike appearance may be able to persuade people to hand over sensitive private information. Finally, these types of intelligent artefacts often depend on the personal knowledge of various users. How do we prevent such information from being stolen (identity theft)?

Table 5b: Regulatory issues related to "technology becoming biology"

Technology becoming biology	Regulatory issues
Engineering of living artefacts: "Bottom-up" synthetic biology	Safety 'Unfamiliarity' with existing organisms Governance Need to start debate
Engineering of the brain: Reverse engineering	New types of animal use Increase in laboratory animals Animal brains as controlling devices Governance EU (DG Information Society and Media) is not funding ELSA projects on neurosciences or neural engineering
Engineering of intelligent artefacts	Related to (semi-)autonomous robots and software agents Safety Liability: uncertainty about sources of agency Related to anthropomorphic/social robots Privacy and informed consent Simulation of friendship: emotional bonding Simulation of violent behaviour (rape, torture, murder, child sexual abuse) Governance At EU level ELSA are not dealt with in an encompassing way Gap between techno-scientific developments and public dialogue

The existence of anthropomorphic and zoomorphic robots also raises questions on whether we will accept their owners to use them for the simulation of abject violent behaviour, such as rape, torture or sexual child abuse. Whitby (2008) pleads for a public discussion right now. He would like to see a list of activities of which their development is unacceptable, a list which may influence professional codes of conduct or laws regulating the use of anthropomorphic and zoomorphic robots. Such lifelike robots with affectivequalities also raise new ethical issues with regard to emotional bonding and the automatisation of some basic duties, like taking care of children or elderly people. A first question is to what extent we will employ robots to take over such basic duties. A follow-up question is whether we allow the use of 'companion' robots in case of people who may not fully understand their mechanical and instrumental character, like children or people with dementia. The principle of informed consent plays a role here.

In the Monitoring Report, Böhle et al. notice that the development of physical and virtual robots makes it increasingly hard to distinguish between human and machine agencies. This raises liability questions. The use of situated AI for enabling robots to learn requires a new perspective on liability issues, because a robot's ability to learn entails that the manufacturer cannot longer predict the robot's actions. Matthias (2004) talks about a "responsibility gap" with respect to damages caused by learning robots. This leads to a discussion among experts whether current ethical and legal frameworks are able to deal with such a new situation. While some experts think current frameworks are sufficient, others argue for a new concept of liability, similar to the ones we have for our children or pets. They propose a mix of safe engineering, shared responsibilities and social awareness.

2.3. The European Commission's governance challenge

The European Commission actively supports many R&D projects in all four fields of bio-engineering. Given this role, there is a remarkable imbalance in the way the Commission supports research on ethical, legal and social issues related to these fields. Therefore, the *Monitoring Report* argued that the Commission should take a more prominent, comprehensive and proactive role in stimulating reflection and public debate about current developments in bio-engineering and its future prospects in Europe in the 21st century. The broad challenge of safeguarding human dignity, should prompt the European Commission to assume full responsibility for the anticipatory governance of this new wave of technology in a way that truly reflects its transformative character.

In the Monitoring Report we tried to come to grips with the new technology wave that is expected from NBIC convergence. For this purpose we studied four bio-engineering fields: engineering of living artefacts, the body, the brain, and intelligent artefacts. To describe these engineering terrains and reflect on their societal meaning we used the metaphors "biology becoming technology" and "technology becoming biology" as conceptual lenses.

We showed that the trends "biology becoming technology" and "technology becoming biology" present and promise both new types of interventions in living organisms, including human bodies and brains, as well as the development of new types of bio-, cogno- and socio-inspired artefacts. We further argued that these envisioned new technical interventions and artefacts may radically transform and broaden the bio-debate.

Finally, we also discussed in the Monitoring Report the ways in which the European Commission is currently involved in stimulating R&D in bio-engineering and to what extent it stimulates social reflection and debate on these developments.

2.3.1. The European Commission's current role

The European Commission actively stimulates many R&D projects that fit within both megatrends. While the "biology becoming technology" trend is often accompanied by research on ethical, legal and social issue, the "technology becoming technology" trend is to a large extent still lacking support for such critical social reflection and debate.

"Biology becoming technology": Funding and stimulating reflection

With respect to "biology becoming technology," the European Commission, mainly within the thematic area "Health", strongly sponsors the development of molecular and regenerative medicine. The involvement of industrial partners in all related projects suggests that research is oriented towards future commercial applications. The European Commission, however, is not funding many forward engineering activities that focus on the development of neuro-modulation technologies. For the European Commission, the importance of synthetic biology has been comparatively high over the last years. Research focuses on strengthening metabolic engineering ("top-down" synthetic biology).

The Human Genome project was the first large scale R&D project that was accompanied by research on the ethical, legal and social aspects of genomics. At the beginning of this century and partly in reaction to past problems with agricultural biotechnology, so-called ELSA research became mainstream in Europe with the arrival of nanotechnology. In the Monitoring Report, Torgersen et al. argue that scientists in the field of synthetic biology seem to be particularly sensitive to the social implications of their work. This is reflected in the research programs of the European Science Foundation and the European Commission. In both cases, various research activities that deal with philosophical and ethical implications, safety and security, governance and regulation, and so on, are being funded.

EU funded research projects in the field of molecular and regenerative medicine are not accompanied by ELSA research. However, applicants must address potential ethical issues related to the used methodology and possible applications in their proposals. It is not always clear, however, what the impact of this requirement is. Besides, the FP7 ethical framework excludes three areas of research from funding because of its highly sensitive nature: human reproductive cloning, intentional germ line modification (unless related to gonad cancer) and the creation of human embryos for research or stem cell procurement.

"Technology becoming biology": Funding, but lack of support for reflection and debate

Since the beginning of this century, the European Commission, in particular the Directorate General for Communications Networks, Content and Technology (formerly named Directorate General for Information Society and Media), is very actively stimulating the convergence of neuroscience and information technology. Most cutting edge projects centre on developing intelligent artefacts, reverse engineering the brain, and developing brain-computer interfaces (BCIs). "Bottom-up" synthetic biology, like proto-cell research and chemical synthetic biology, gets only limited attention.

In the Monitoring Report, Böhle et al. argue that important ELSA aspects of research related to the development of intelligent artefacts are already widely studied under such labels as robot ethics and information ethics. However, despite the fact that the field of neuro-ethics is quickly developing, Van Keulen and Schuijff note that there are no large EU funded ELSA research projects surrounding neuroscience or neural engineering. The authors explain that DG Communications Networks, Content and Technology, which funds most of the neural engineering projects, has little institutionalised attention for the governance and ethics of information technology (apart from standard ethical review of individual projects).

Whereas the Directorate General for Research and Innovation has the Science in Society Programme which focuses on the societal governance of emerging technologies, there is no such programme in DG Communications Networks, Content and Technology. In contrast to the life sciences, the benefits to society of intelligent artefacts seem to be taken for granted. As a result, critical review is regarded unnecessary.

According to Rosenberg (2008: 369), "*this viewpoint must be challenged*". Van Keulen, Schuijff and Böhle et al. agree on this matter, especially because information technologies are converging with the life sciences. These authors are concerned about the current "gap" between developments in the field of intelligent artefacts and the public dialogue about it, and advise the European Commission to deal with the ethical, legal and social issues of information technologies in a more comprehensive fashion.

2.3.2. Safeguarding human dignity in the 21st century

> "*Progress in science will bring confusion and misery to humankind unless accompanied by progress in ethics.*" (Haldane, 1923)

The transformative character of NBIC convergence, therefore, induces the European Commission to take a more prominent, integral and pro-active role with regards to stimulating reflection and public debate concerning the role of bio-engineering in Europe in the 21st century. Speculative long term visions, shifting fundamental concepts and social and ethical issues that challenge current regulatory all may cause uneasiness within society and may lead to political conflict.

Policymakers should be aware of the risk of being spoon-fed by these spectacular future visions and overhyping the field in question. But they also need to acknowledge that these speculative visions already have a real impact on the way we steer science and technology and discuss and regulate its societal meaning. On the one hand, the dreams of engineers provide hope for a better future. On the other hand, bio-engineering in the 21st century induces the fear that human dignity is under pressure in various ways. In order to safeguard human dignity, policy makers are confronted with a whole range of ethical, legal and social challenges (often driven by gradually shifting fundamental concepts, like man, machine, living and non-living). The broad challenge of safeguarding human dignity, prompts the European Commission to assume full responsibility for the anticipatory governance of this new technology wave in a way that truly reflects its transformative character.

A crucial first step is to acknowledge that the bio-engineering debate in our society is no longer solely guided by the life sciences, but by NBIC convergence. Our study shows that the attention for ethical, legal and social issues differs across the different bio-engineering fields. The fact that science and society issues are treated differently for different fields seems to relate to the fact that the research in these fields is commissioned by different DGs. DG Communications Networks, Content and Technology, which very actively stimulates the convergence of neuroscience and information technology, needs to pay more attention to the ethical, legal, and social aspects of information technology. For this, it is crucial to acknowledge that the benefits to society of information technology can not automatically be taken for granted. Such awareness is already growing within the IT industry. For example, Harper et al. argue that "*the bottom line is that computer technologies are not neutral – they are laden with human, cultural and social values. We need to define a new agenda for human-computer interaction in the 21st century - one that anticipates and shapes the impact of technology rather than simply reacts to it*" (Harper et al., 2008: 57). It is important that the European Commission takes advantage of this trend and further stimulates it.

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3. PRIVACY, DATA PROTECTION AND POLICY IMPLICATIONS IN WHOLE GENOME SEQUENCING

Piret Kukk and Bärbel Hüsing

Summary

The megatrends 'biology becoming technology' and 'technology becoming biology' are manifest in 21st-century biomedicine. Firstly, the human body has become a source of biomaterials which serve as the basis for regenerative engineering of the body. Secondly, the human body has become a source of information which enables the knowledge-based development of new forms of intervention, with the aim being to prevent and cure disease. In this chapter, we focus on important issues raised by this latter development, which is especially representative of the 'biology becoming technology' trend.

Over the last two decades, the analysis of the hereditary blueprint of human bodies, which is encoded in the human genome (made up of DNA), has become a very important conceptual approach and a research priority. The analytical technique for deciphering this genetic information is called DNA sequencing. Due to tremendous technological advances, the analysis of the whole genome of an individual can soon be done within days and for as little as several hundred euros, considerably expanding the frequency, purposes and contexts in which genome analyses might take place in the near future. As genetic information is highly sensitive personal information, ethical issues and privacy concerns have already arisen and been extensively discussed in the context of genetic testing (i.e., the analysis of only one or a small number of genes within a genome). This is now regulated by supranational conventions, national regulations and sector- or profession-specific guidelines and codes of conduct. It is the aim of this chapter to analyse to what extent these existing governance principles will be suitable for whole genome sequencing.

Starting with an overview of the current state of DNA sequencing technologies and expected future developments, the chapter will then outline the present and future applications of whole genome sequencing. Following this, the impact of the advances in sequencing technology and the challenges this will pose to established governance models for genetic testing will also be discussed, with special reference to potential privacy infringements. Finally, we will offer recommendations concerning how to address the governance challenges arising from whole genome sequencing in a European policy context.

Recent developments in DNA sequencing technology have significantly improved its speed and reduced its cost as such that devices are now commercially available which allow genomic analyses to be carried out within days, and at a cost of under a thousand euros. Consequently, DNA sequencing can be done much more frequently and extensively, as well as on a more routine basis, and its application range is broadening considerably. DNA sequencing techniques are already firmly established in fundamental and leading-edge biomedical research, and in around ten years will be used as a routine general purpose diagnostic tool in health care. Furthermore, new applications will also emerge, for example, genome analyses, which at present are offered to individuals by private companies on a direct-to-consumer basis. In forensic analyses (providing evidence in criminal investigations and assisting in identifying victims of crime or disasters), DNA sequencing will complement established DNA profiling methods.

These developments will transform existing sociotechnical practices of genetic testing in research and have an impact on patients, consumers, parents, participants in epidemiological or clinical research and on the population in general. There are several reasons for this. Firstly, the amount and comprehensiveness of the information made available by whole genome sequencing goes far beyond the amount of information that can be gleaned from established genetic testing – comprehensive information about potential medical conditions, non-medical traits and ancestry may be revealed. Secondly, the interpretation of whole genome analyses is highly dependent on current knowledge about the relationship of a DNA sequence to a corresponding trait, and it is highly likely that a subsequent re-analysis of the DNA sequence will reveal additional information not foreseeable at the time of the original DNA sequencing, making the results highly provisional. This also renders established procedures for obtaining informed consent obsolete in certain cases and raises new ethical issues (e.g., dealing with unanticipated findings, benefit-sharing with trial participants and patients who provide their genome information for research), requiring ethical deliberation. Thirdly, it will become more difficult to apply established safeguards concerning privacy as the anonymization of whole genome data is impossible, with confidentiality not necessarily guaranteed in contexts outside health care. In addition, due to internationalization in research and forensics, an increasing amount of DNA and data exchange across borders is occurring, but there are different levels of national safeguards and regulations in place, as well as a lack of harmonization of these regulations. Therefore, the foreseeable developments in DNA sequencing and its application significantly increase the possibility and likelihood of the unintended use or misuse of sensitive, personal genetic data, and could lead to discrimination, stigmatization and privacy infringements.

This chapter details how the established governance models are or will be challenged by the adoption of whole genome sequencing in the fields of fundamental and leading-edge biomedical research, especially in the context of biobanks, in direct-to-consumer genetic profiling and in forensics, and suggests options for their amendment and modernization. Generally speaking, the existing governance models developed for genetic testing were not designed to deal with the challenges posed by whole genome sequencing and therefore need to be adapted. If the benefits of the huge investment in genome research are to be realized, the legal, ethical and social framework will also have to evolve accordingly.

Policy recommendations

- Firstly, the findings suggest a need for even more stringent safeguards for data protection and confidentiality to combat the unauthorized use of data. Therefore, specific national regulations governing whole genome sequencing and databasing in the context of research, biobanks, health care and criminal investigations should be implemented. Moreover, high-quality standards and a stricter monitoring of whole genome sequencing and databasing practices in research, health care and forensics should be implemented.
- Secondly, given the international networks in which the development of whole genome sequencing takes place and the patchy nature of existing national regulations, the EU should take an active role in striving for the international harmonization of national regulations, and in harmonizing enforcement levels with respect to the relevant regulations in European member states.

- However, legislative action should also be accompanied by broader ethical deliberation on the issues at stake. Therefore, it is recommended that a broad debate about whole genome sequencing be actively initiated and supported. This debate must not remain confined to professionals or experts, but should also seek to engage the general public. The debate should aim for ethical deliberation, it should attempt to strike a fair balance between the public interest in knowledge generation on the one hand, and individual civil rights and liberties on the other, and also focus on determining the cornerstones of the relevant regulations, codes of conduct and sociotechnical practices, thus enhancing public trust in research as well as medical and forensic practices. A first step might be to raise awareness of the issues and challenges posed by whole genome sequencing for various purposes.

3.1 Introduction

This section briefly explains why whole genome sequencing is an important enabling technology, exploiting the human body as a source of information about how it is built and functions. This knowledge is crucial for a better understanding of health and disease and for the development of new treatments. An overview of the trends in whole genome sequencing which lead to the expectation that existing regulations governing genetic testing will not be sufficient to deal with the challenges posed will also be given. In addition, this section provides an overview of the issues that will be analysed and discussed in this chapter.

This paper is part of the three-stage project "Making Perfect Life" which explores two bio-engineering megatrends of technology convergence, denoted with the catchphrases "biology is becoming technology" and "technology is becoming biology" (Arthur 2011; van Est et al. 2009).

With respect to engineering of the human body (van Est et al. 2010), these catchphrases describe novel ways of intervening into the human body, in the sense that the human body, or parts of it, or bodily functions, become increasingly mouldable, can increasingly be controlled, designed, built and exploited. An example for this is tissue engineering, which aims at engineering human tissue in a way that a regeneration of diseased tissue or even the growing of entire organs or bioartificial organs may become possible. However, a prerequisite for rational engineering of bodily functions is a detailed understanding of how the body functions in health and disease, and this understanding must be informed by an inventory of the functional parts, their blueprints and their coordinated interaction. Therefore, research in the past decades has aimed at substantially enlarging our knowledge of how biological systems are built and work by using the human body in the first place as a source of information. It is expected that this information could successfully be used as an essential research and design resource for the development of new or improved interventions into the human body, such as new diagnostics, new drugs or biomedical devices, and novel advanced therapies such as gene therapy or tissue engineered products.

One of the most prominent endeavours in elucidating information underlying the "blueprint of life" was the "Human Genome Project". It provided the complete sequence of a human reference genome (The Celera Genomics Sequencing Team 2001; The International Human Genome Sequencing Consortium 2001; The International Human Genome Sequencing Consortium 2004). In recent years, we have seen a very dynamic development of technologies for DNA sequencing, improving speed and throughput by several orders of magnitude while at the same time decreasing costs considerably. Experts are of opinion that it will be possible within the coming five years to sequence the genome of an individual for approximately 1,000 US$ per genome in a few days to hours.

In this section, we focus on these new technological developments in human genome analysis, namely next and third generation DNA sequencing technologies, because they bear the potential to challenge existing regulations and ethical principles regarding data protection and the handling of genetic

information: with the new, highly time- and resource-efficient technologies for DNA sequencing that are being developed, it is highly likely that DNA sequencing will in future

- yield much more information, as not only selected genes, but whole individual genomes will be sequenced
- be performed much more frequently than today and on a routine basis
- will have new applications in basic and biomedical research
- will be applied routinely in health care
- will be applied in many more areas outside basic research and biomedical research, by different players and for different purposes, compared to today

However, genetic information is sensitive personal information that does not only give information about the person from whom the DNA was taken, but also about the person's relatives. Regulations and ethical principles presently govern DNA sequencing and DNA analysis based on the assumption that it is mainly confined to research and human genetics in health care. They aim at safeguarding autonomy and the right not to know, as well as privacy and data protection. However, these regulations might no longer be fully appropriate if the upcoming quantitative and qualitative changes in genome analysis come into reality in the coming years, or will have to be adapted to new contexts in which DNA sequence analysis is being performed.

Against this background, this sub-report aims at identifying the societal, political and regulatory challenges that arise from next and third generation DNA sequencing technologies, in a European political context. It is intended to inform stakeholders and EU policy makers about this technology-driven development, its possible impacts and relevant issues to be addressed in a timely manner in EU policy making. It differs from the other sub-reports within the Making Perfect Life project phase 3 in that it focuses on specific types of information derived from the human body. Thus, it is neither an intervention nor an artefact, but an essential prerequisite for enabling such interventions and artefacts.

In this sub-report the following issues will be discussed and analysed:

- Status quo of human DNA sequencing and the expected progress in the midterm
- The set of academic, industrial and clinical actors that are driving the development, and their intentions
- Possible users or beneficiaries of DNA sequencing
- Possibilities for privacy-infringing uses and practices
- Applicability and validity of existing ethical principles for DNA analyses and genetic testing (e.g. the right not to know, informed consent and so on) and of legal regulations for privacy and data protection to next and 3rd generation DNA sequencing technologies
- Key challenges and recommendations with regard to policy and regulatory approaches at the R&D and application phases of new DNA sequencing technologies, to ensure the right to privacy

3.2 A short introduction to DNA sequence analysis and genetic and genomic information

This section provides a short introduction to the technical terms that will be used throughout the chapter, explaining what 'sequencing' means and pointing out that sequencing alone is of little use unless knowledge into the relationship between a DNA sequence and a biological function can be used in the interpretation of the raw sequence data. The features that make genetic information highly sensitive personal information will also be presented, along with the specific safeguards in terms of privacy and data protection that are required.

Genetic material contains the hereditary information on how a living organism is being built and how it functions. It is contained in every cell of a living organism in the form of a macromolecule, the deoxyribonucleic acid (DNA). This macromolecule is made up of four different building blocks: nucleotides (often compared to letters; termed A, C, T and G after the chemical name of the nucleobase within the nucleotide). The genetic information is laid down in the exact sequence of these four building blocks in the DNA macromolecule. Several wet chemistry methods have been developed to determine the sequence of the four building blocks along the DNA strand; these are DNA sequencing methods. Such a sequencing exercise results in a series of nucleotide names (e.g. AATTCGATGGGA...) which can be stored in digital form and be analysed further in silico.

A DNA sequence as such is of little value unless the "meaning" or function that is encoded in this DNA sequence is known. Therefore, a major challenge in molecular genetics is the elucidation of the functions which are being coded by the respective DNA sequences (functional genomics). For any applications of whole genome sequencing, the sequencing exercise must be followed by an analysis of these raw data. This is done by applying software which integrates the latest scientific knowledge of the relationship between DNA sequence and biological function (e.g. health, disease and non-medical traits) (Health Council of the Netherlands 2010, p. 7).

In terms of privacy and data protection, genetic information is personal, sensitive information that is characterised by the unique combination of the following aspects:

- Identifying. Each individual has a unique genomic sequence. Therefore, the whole genome sequence could act like a unique bar code to identify individuals. Because persons inherit half their DNA from their mother and half from their father, DNA sequence information can also be used to identify their relatives. Close relatives have a DNA sequence that is more alike than distant relatives or than someone who is unrelated (GeneWatch UK 2011). If the full genomic sequence is known, it is impossible to de-identify or anonymise the DNA sample or the DNA sequence.
- Diagnosis of genetic diseases. Approximately 3,000 diseases are known to be caused by mutations in a single gene or a small number of genes (although the causative genes may still be unknown). DNA sequencing can show whether the gene is mutated or not. DNA sequencing can therefore be used for diagnosis when clinical symptoms are evident, but also before symptoms occur (predictive). Moreover, heterozygous carriers of this mutation, who will not become ill themselves but may transfer the mutation to their offspring, can be identified.
- Prediction of predispositions. Many multifactorial diseases and complex non-health related traits, such as behaviour, cognition and personality, have a genetic component, but other factors also contribute. DNA sequencing can be used to identify and characterise the genetic portion of the trait. If the genetic component can be determined, a certain predisposition can be stated, but it is a question of probabilities rather than certainties whether the trait or disease will develop in the "predicted" way in the individual.

- Individual and familial nature of genetic information, shared information. Due to the hereditary nature of genetic information, most genetic information flows between generations. Therefore, the abovementioned implications do not only apply to the individual from whom the DNA was taken and analysed, but it may extend to the family and beyond to larger groups of people linked by common ancestry. In a clinical setting, genetic information may reveal that individuals as well as family members may be affected by a disease or predisposition to a disease, challenging individual autonomy and consent as well as the duty to warn and the right not to know. If a particular genetic condition is prevalent in a specific subpopulation, harm may arise for those who are part of this population.
- Risk of discrimination and stigmatisation. Genetic information may put individuals, families and communities at risk of discrimination and stigmatisation due to their genetic condition, especially if they are not (and may never become) ill, but are still predisposed to disease or asymptomatic heterozygous carriers.
- Availability. DNA is contained in every human cell. Certain types of DNA analysis can be done from picogram amounts of human DNA which is available from a few dozens of human cells, which can be taken from, for example, blood, hair roots, oral mucosa cells in saliva, or skin. Therefore, it is possible to take and analyse a person's DNA without his knowledge or consent, simply by collecting cells that are both unintentionally and unavoidably left behind.
- Long-term availability. If stored properly, DNA-containing biological samples and isolated DNA are available for long, indeterminate periods of time. Techniques are available to amplify the DNA. Samples taken once can therefore be amplified and re-analysed repeatedly, e.g. as technology and scientific understanding develops.
- Availability before birth and after death. Most of the genetic information of a person remains constant over lifetime. It can be analysed whenever DNA-containing biological material from this person can be made available. Therefore, genetic information can already be obtained before birth (e.g. during prenatal genetic testing; preimplantation screening) or after death (even decades to centuries after death, depending on the preservation of the biological material).
- Symbolic meaning. Genetic information is socially often perceived as a blueprint representing the essence of human life and as such has a symbolic quality.

3.3. Overview of DNA sequencing technologies

This section provides an overview of DNA sequencing technologies. Starting with the first techniques developed in the late 1970s, it outlines the present state of the art in DNA sequencing and commercially available devices before presenting an overview of likely technological developments in the coming decade. The discussion reveals that major breakthroughs have been achieved, resulting in a high grade of automation and high throughput, unprecedented speed and significant cost reductions for DNA sequencing. However, further improvements, especially with respect to sensitivity and accuracy, as well as reducing the need for computation, are still necessary. These issues are being addressed in current R&D activities.

3.3.1. The first attempts on DNA sequencing and the Sanger technology

In the late 1970s, several groups described methods to chemically determine the base sequence of DNA by utilising either chemical cleavage of DNA (Maxam, Gilbert 1977) or incorporating dideoxynucleotides during DNA synthesis, thus terminating the reaction of further DNA strand elongation (Sanger et al. 1977). In both cases, the radio-labelled products of the reaction were separated by size by electrophoresis followed by visual inspection of the banding pattern of the DNA sequence. The method of choice became the chain-termination method, the so-called Sanger technology, named after its inventor, Frederick Sanger. It is rapid, robust, has >99.9 per cent raw base accuracy (the frequency in which the method correctly identifies a nucleotide from a known template sequence), and can typically read DNA molecules with a lengths of up to 1,000 to 1,200 base pairs.

In the following years, the method was developed further by replacing the radio-labelled dideoxynucleotides by fluorescently labelled dideoxynucleotides (Smith et al. 1986) and by substituting gel electrophoretic separation of the labelled DNA fragments by automate capillary electrophoresis (Gocayne et al. 1987). By further automation and miniaturisation and by introduction of shotgun sequencing, the basic Sanger technology was also used in the Human Genome Project for the sequencing of the entire human reference genome of 3 billion base pairs. It remains the gold standard and mainstay of DNA sequence analysis for most laboratories, and it is adequate for the majority of clinical applications involving the analysis of single genes with limited polymorphism (Anderson, Schrijver 2010).

The drawbacks of the Sanger technology and its improvements over the years are the need for sequencing primers, the restriction to read lengths under 2 kilo base pairs, the relatively high cost and restricted throughput, as well as a level of sensitivity for the detection mutations at 10-20 per cent, which may be insufficient for the detection of clinically relevant low-level mutations (Zhang et al. 2011; Anderson, Schrijver 2010).

Sequence production, not sequence analysis, is the rate limiting factor in traditional Sanger sequencing (Mardis 2008).

3.3.2. Next generation sequencing technologies

In order to overcome the drawbacks of the Sanger technology, innovative approaches for DNA sequencing are being developed. The ideal DNA sequencing platform would combine the advantages of high-throughput, rapid sequence analysis with the capability to sequence long stretches of DNA. Long-read lengths would significantly decrease the computational power required to perform genome assembly and allow the detection of genomic copy number variations.

The innovative approaches were initially triggered by the US National Institutes of Health (NIH) through the 'Technology development for the $1,000 genome' programme1 that promised funding support and a 10 million US$ award to develop rapid and accurate genomic sequencing technology (Mardis 2008).

There are several technologies available for new generation high-throughput DNA sequencing that outperform the older Sanger-sequencing technologies by a factor of 100-1000 in daily throughput, which has increased from 1 GB to over 100 GB per run (figure 1), making it possible to sequence entire human genomes in a matter of weeks and at the same time reduce the cost of sequencing one million nucleotides to 4-0.1 per cent of that associated with Sanger sequencing (Kircher, Kelso 2010; Koboldt et al. 2010). If one compares this development in sequencing technology with computer hardware development, in the last years DNA sequencing has developed faster than Moore's Law, which describes the performance improvement in computer hardware.

[1]http://www.genome.gov/ 11008124#al-4

Currently, there are five next-generation sequencing platforms commercially available:

- Roche/454 FLX
- Illumina/Solexa Genome Analyzer IIx and HiSeq 2000
- Applied Biosystems (ABI) SOLiD Analyzer
- Helicos HeliScope
- Polonator G.007

While the first three platforms currently dominate the market, the latter two have only recently been introduced and are not yet widely used (Zhang et al. 2011; table 1). Each of the commercially available high-throughput sequencing platforms utilises a slightly different method, generates different base read lengths, different error rates, and different error profiles compared to Sanger sequencing data and to each other (Zhang et al. 2011; Mardis 2011; table 2).

Figure 1: Changes in instrument capacity over the past decade and timing of the major sequencing projects. Source: Mardis 2011.

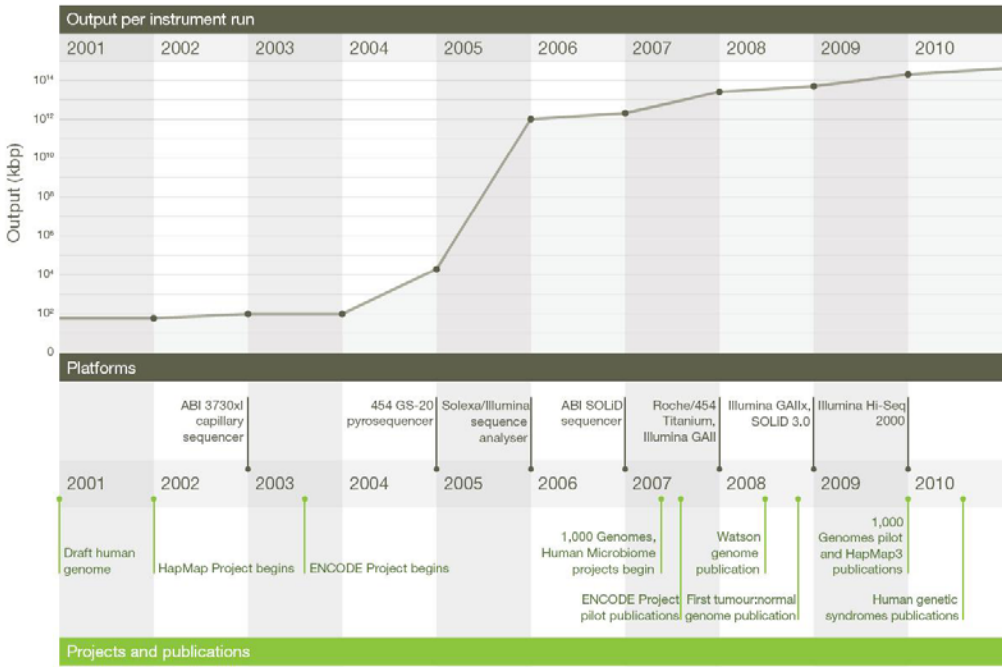


Table 1: Installed next generation sequencing machines worldwide, by platform

Sequencing platform	Number of installed instruments
Illumina Genome Analyzer 2X	611
Illumina HiSeq 2000	387
ABI SOLiD	308
ROCHE 454	272
Ion Torrent	32
Pacific Biosciences	15

Source: http://pathogenomics.bham.ac.uk/hts/stats. Please note that this is not official information. The presented data are based on information taken from the website http://pathogenomics.bham.ac.uk/hts/stats, which does not provide information on how the data was gathered or when it was last updated. Even if not correct in detail, the table gives an impression of the already wide distribution of high throughput sequencing machines.

Table 2: Comparison of different next generation DNA sequencing platforms

	Roche/454 Life Sciences	Applied Biosystems/ SOLiD	Illumina	Pacific Biosciences
Amplification method	Emulsion PCR	Emulsion PCR	Enzymatic bridge amplification	Not applicable
Sequencing method	Polymerase mediated	Ligation based	Polymerase mediated	Polymerase mediated
Time/run	7 h	5 days	4 days	
Detection method	Light emission	Fluorescent emission	Fluorescent emission	Fluorescent emission
Error model	Insertion/ deletion errors	End of read sub-stitution errors	End of read sub-stitution errors	Insertion/ deletion errors
Read length	400 b	75 bp	150 bp	>1000 bp
Cost per MB	80 USD	6 USD	6 USD	
Strengths	Long read, short run time	Software open source, cheaper		
Weakness	Low throughput, highest cost per base		Low quality on longer runs	15 % error rate (single reads)

Source: Mardis 2011. For the latest information, see: http://knowledgebank.blueseq.com/sequencing-platforms/comparison-of-sequencing-technologies/

Next generation sequencing platforms are being implemented all over the world, now. Table 3 gives an overview of the current distribution of main sequencing facilities and machines worldwide. They do not only make DNA sequencing faster and more affordable, but also allow new research approaches and applications (section 3.4.). All in all, a human genome in the resolution of 100 GB can currently be sequenced for 45,000 US$ (including reagent, equipment and labour) with these next generation sequencing platforms, with the potential to drive costs further down to 1,000 to 5,000 US$ (Babiel 2011). In addition, the next generation DNA sequencing instruments are so powerful that no longer sequence production, but sequence analysis has become the bottleneck.

Table 3: Overview of the regional distribution of next generation sequencing facilities and machines

Region	Number of sequencing centres/facilities	Number of next generation sequencing machines
USA	211	721
EU 27	195	383
UK	41	119
Germany	32	83
France	23	25
Spain	18	42
Australia	22	50
Canada	15	84
Brazil	14	15
China	10	199
By continent		
North America		811
Europe		416
Asia		338
Australia		51
South America		16
Africa		2

Source: http://pathogenomics.bham.ac.uk/hts/stats. Please note that this is not official information. The presented data are based on information taken from the website http://pathogenomics.bham.ac.uk/hts/stats, which does not provide information on how the data was gathered or when it was last updated. Even if not correct in detail, the table gives an impression of the already wide distribution of high throughput sequencing machines.

3.3.3. Technologies in the pipeline – 3rd generation sequencing

On the way to an ideal DNA sequencing platform, single molecule DNA sequencing technologies bear large potentials. As such, advanced single DNA molecule sequencing technology has been defined as "3rd generation DNA sequencing technology". It has the potential to deliver whole human genome sequencing at less than 1,000 US$ per genome (Babiel 2011).

The Helicos HeliScope platform is the first single molecular sequencing technology commercially available (table 1). In addition, several different single-molecule DNA sequencing technologies are currently under development; however, little information has been made publically available. These instruments are expected to become commercially available from 2015 onwards (Babiel 2011).

In order to achieve significant advances, the adoption of new technologies is required, e.g. nanotechnologies, electron microscopy, or semiconductor technologies. One of the emerging DNA sequencing technologies makes use of scalable, low-cost semiconductor manufacturing techniques, which are used to make an integrated circuit capable to directly perform the non-optical DNA sequencing of various genomes. Sequence data are obtained by directly sensing the ions produced by template-directed DNA polymerase synthesis, using all-natural nucleotides on this massively parallel semiconductor-sensing device or ion chip. Use of the most widely used technology for constructing integrated circuits, the complementary metal-oxide semiconductor (CMOS) process, enables for low-cost, large-scale production and scaling of the device to higher densities, and larger array sizes (Rothberg et al. 2011; Zakaib 2011) than the other current technologies described above.

Although the current capacities of real-time sequencers would not permit whole human genome sequencing in a single run, the near-term application of these instruments could be on focused evaluation of specific human genes or on the genomes of pathogens for diagnosis, prognosis or therapeutic prescription (Mardis 2011).

3.4. DNA sequencing applications

This section discusses the most important fields of application for DNA sequencing methods now and in the future, namely research, health care and forensics. In research, DNA sequencing provides valuable insight into the human genome's structure, function and regulation and aims to elucidate how health and disease result from an interplay between genetic factors and environmental influences. In health care, DNA sequencing is currently primarily confined to the testing for rare medical conditions, but will most likely be established as a routine general purpose diagnostic tool in the coming decade. It will contribute significantly to realizing the concept of personalized medicine, which also comprises genome-wide diagnostic testing and genome-wide screening. In forensics, it is unlikely that whole genome sequencing will replace the well-established method of DNA profiling that is currently widely used in criminal investigations and for the identification of individuals. It is more likely that whole genome sequencing will have some role in solving specific problems in forensic genetics.

3.4.1. In research

Presently, the most important and diverse applications of genome sequencing and next generation sequencing technologies have been in research.

A landmark was the completion of the Human Genome Project. It has provided the international research community with (Lander 2011):

- A significant expansion of the number of species for which entire reference genomes have been sequenced. In 2000, genomes of just 42 species had been completely sequenced, but these were only species with relatively small and simple genomes. By 2011, the number of species for which full genome sequences are available has risen to 4,250, with the plan to increase this number to 10,000 for vertebrate species (corresponding to approximately one full genome sequence per genus). These genome sequences will be a rich resource for comparative research approaches, applying sequence comparisons across species.
- Insight into human genome structure, function and regulation. The human genome contains astonishingly few protein-coding genes: only approximately 21,000 (1.5 per cent of the genome). However, also non-protein-coding sequences are functional. They make up for more than 6 per cent of the human genome. Many of them have important regulatory roles in early development, but the majority of the functions still remain to be discovered. Moreover, the importance of non-protein coding RNAs has now been recognised, yielding an important regulatory mechanism that had been overlooked until recently. The goal of ongoing and future research is to understand all the functional elements encoded in the human genome, i.e. all protein-coding and non-protein coding genes and transcripts, all epigenetic modifications and all interactions between proteins, RNA, and DNA.
- The novel approach of investigating biological phenomena in a hypothesis-free manner.
- A framework or comprehensive scaffold for assembling often fragmentary information into landscapes of biological structure and function. As it remains difficult to assemble complete genome sequences de novo from sequencing experiments, most sequencing applications place the resulting short DNA reads onto the scaffold of an existing genome sequence to count their density or look for differences from the reference sequence. Due to the construction of specific "signatures" or "tags" for genes, proteins, cells, physiological states and so on, it has become possible to re-identify them based on such signatures or tags. Moreover, accurate inference of gene structures, polymorphisms and mutations across the genome has become possible.

Next and third generation sequencing will play a crucial role in realising the research agendas for the coming decade. This will be outlined in the following paragraphs:

- Understanding of all functional elements encoded in the human genome. The goal is to characterise complete genomes, transcriptomes and epigenomes for research purposes. This can only be done by massively parallel, low-cost DNA sequencing of all protein-coding and non-protein coding genes and transcripts and all epigenomic modifications and by assay miniaturisation for molecular interactions.
- Creation of a catalogue of all genetic variants in the genomes of humans. While the vast majority of variants with frequencies > 5 per cent in human genomes have been discovered, and 95 per cent of heterozygous SNPs in an individual are represented in current databases, less frequent variants have so far escaped detection with conventional approaches and technologies. Therefore, next and third generation re-sequencing of human genomes from different ethnicities will be key to setting up a catalogue of genetic variants with a frequency of > 1 per cent across the genome and > 0.1 per cent in protein-coding regions. Projects such as the 1000 Genomes Project (www.1000genomes.org) contribute to this goal.

- Identification of disease genes for (rare) Mendelian diseases. There are approximately 3,000 inherited disorders caused by defects in single – yet still unknown – genes. In addition to the analysis of families in which the respective diseases are prevalent, systematic next generation genome (exome) sequencing of parents and offspring offers an additional approach for identifying these genes. In 2010, an International Rare Disease Research Consortium (IRDiRC) was agreed upon by the European Commission and the US National Institutes of Health to deliver 200 new diagnostic tests and therapies for rare diseases by 2020. Moreover, it is expected that multifactorial common diseases can also be addressed by this strategy. On the one hand, many rare Mendelian diseases hide among complex diseases due to the similar symptoms; on the other hand, causative or mechanistic insight gained from rare diseases may also guide future research into multifactorial diseases (Check Hayden 2009).
- Identification of disease genes and pathways of common, multifactorial diseases. The strategy is to combine large genome-wide association studies with whole genome sequencing, also informed by results from studying rare inherited disorders.
- Identification of all genes that are significant targets of somatic alterations in all human cancer types. Large-scale international projects (e.g. Cancer Atlas and the International Cancer Genome Project) have been set up to detect somatic mutations in cancers by sequencing the entire tumour DNA. This information is expected to lead to new and additional diagnostic methods and to inspire the development of new small molecule cancer drugs specifically targeting the mutated cancer cell functions. It will hopefully lead to improved cancer therapies. In the medium to long term, it will be necessary not only to study genomic variants of tumour DNA, but also variants in the patient's (host's) genome in order to achieve personalised cancer therapies.

All in all, research that aims at elucidating the complex relationship between genetic variation, environmental factors and health, and the ability to cheaply and quickly sequence complete genomes for individuals is an important tool in this endeavour.

All over the world, many projects – often the cooperation between large international consortia – have been set up, which aim at collecting the relevant biological samples and health information, gather the relevant data and analyse them according to the research priorities listed above. Major data gathering projects are, for example, The 1000 Genomes Project (www.1000genomes.org), the Personal Genome Project (www.personalgenomes.org), the Cancer Genome Atlas, the Protein Atlas and MRM Atlas, Eurexpress, the Novartis expression database, ENCODE, the NIH Epigenetics Consortium, TREAT1000 (www.treat1000.org), OncoTrack and many more. In Europe, large projects have been set up which provide the infrastructure for this type of large-scale research, e.g. the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI, www.bbmri.eu), EATRIS (European Advanced Translational Research Infrastructure in Medicine), ECRIN (European Clinical Infrastructure Network) and so on.

Whole genome sequencing of individuals will explicitly be performed in the "1000 Genomes Project", as well as in the "Personal Genome Project":

- 1000 Genomes Project. The 1000 Genomes Project is the first project to sequence the genomes of a large number of people in order to provide a comprehensive resource of genetic variations in humans. The project is designed in a way that most genetic variants that have frequencies of at least 1 per cent in the populations studied will be discovered.

- Personal Genome Project (PGP). The Personal Genome Project goes beyond the 1000 genomes project. It is planned to not only sequence the whole genomes of a large number of healthy individuals, but to additionally collect the most extensive information technically available about their phenotype: medical records, various biochemical measurements, MRI images, tissue samples, stem cell lines and so on. Such integrated biospecimen and data collections are important drivers of progress in functional genomics, enable systems biology based insights into the mechanisms of human health and disease, and allow researchers to test various hypotheses about the relationships between genotype, environment and phenotype (Drmanac et al. 2010). All this data will be made freely available over the internet, with minimal or no access restrictions, in order to enable data sharing by default, so that data are transferable outside the original research study or individual. Not only researchers, but also the participants have full access to all data. An important part of the project is also the analysis of ethical, legal and social issues and challenges, associated with large-scale whole genome sequencing, especially in the areas of privacy, informed consent and data accessibility (Lunshof et al. 2010). In October 2008, the first whole genomes sequences of ten participants were published.

3.4.2. In health care

Extensive use of advanced genome sequencing technologies in research also paves the way to establishing DNA sequencing as a routine general purpose tool in biomedical health care, provided that genome sequencing can be done simply and routinely, and costs are only a few hundred euro per genome.

Among others, the development is inspired by the vision of "personalised medicine" (Hood, Friend 2011). This vision comprises of health risk assessment being carried out for everyone, especially for healthy people. This assessment will be informed by an analysis of the whole genome sequence of the individual, complemented by family health history, individual health records, individual exposure to environmental factors, lifestyle, imaging and molecular data of various biomarkers. It should make possible:

- the identification of (still) healthy persons with elevated risk for a certain disease with the aim of providing lifestyle advice and other prevention measures,
- the detection of disease in a very early, perhaps presymptomatic stage, where cure or a positive course of the disease can be achieved with early intervention,
- a more accurate diagnosis of disease subtypes which require different treatments,
- targeted drug therapies or adapted drug doses, based on molecular characteristics of the disease subtype and the individual patient,
- improved monitoring of disease and therapy.

This vision of personalised medicine also implies that a 'proactive' approach to health care is being taken, where one does not wait for people to exhibit disease symptoms, but health risks are mapped out while the people are still healthy (Health Council of the Netherlands 2010, p. 17). This also implies that disease is no longer seen as "fate" that calls for solidarity of the healthy with the sick, but that health is a condition that can and must be actively strived for, putting much more responsibility on the individual for one's own health than today (ABFTA 2009).

The following major future applications can be distinguished (Health Council of the Netherlands 2010):

- Genetic diagnostic testing of a limited number of genes. This is the established clinical application of genetic testing for which guidance and regulatory and ethical frameworks have been developed. Informed by family medical history or symptoms, specific mutations are tested that are the known cause of the genetic diseases to be diagnosed. Costs may be several thousand euro per analysis although this may become cheaper with more efficient sequencing technology. In addition to diagnosing Mendelian diseases, molecular diagnostics and in the future also DNA sequencing are routinely applied in targeted (personalised) drug therapies for AIDS and in cancers, and they are recommended by professional clinical guidelines or even required by drug approval. Molecular testing or sequencing of a limited set of genes will remain the desired diagnostic format in the next 5-10 years (Babiel 2011).
- Genome-wide diagnostic testing. Genome-wide diagnostic testing, in contrast to genetic diagnostic testing, does not look for specific mutations in confined parts of the genome in a targeted fashion, but searches the entire genome for variations that may be the possible cause of a disease. This approach is currently chosen in cases of diseases with unexplained causes, e.g. unexplained mental retardation in children. Today, DNA microarrays are being applied in order to detect clinically significant chromosomal imbalances, advancing the diagnostic evaluation of children with idiopathic developmental delay, major intellectual disability, autism and birth defects (Lander 2011). They are likely to be replaced by whole genome (exome) sequencing in the coming years. However, no clear borderline can be drawn between genome-wide diagnostic testing and screening.
- Genome-wide screening. Genome-wide screening, in contrast to genome-wide diagnostic testing, is performed without a concrete medical indication or purpose. It would be a part or even a prerequisite of the vision of personalised medicine, as outlined above. Benefits for the individual could be lifestyle advice, early detection of diseases, detection of carrier status, and input into reproductive decisions. Genome-wide screenings are already offered by more than 30 private companies worldwide for several thousand euro. Many of these companies operate on a direct-to-consumer (DTC) basis, i.e. without the involvement of a health care provider (Hennen et al. 2008; Javitt 2010). The number of people using genetic profiling services and whether this is currently leading to any actual harm is not known (Nuffield Council on Bioethics 2010). However, there is consensus in the scientific community that the utility of such genetic profiling services for the customer presently is very low to non-existing and "not worth the money".

In principle, genome-wide screenings can be performed on any human genomic DNA, i.e. not only on genomic DNA from adults, but also from children, newborns, unborn foetuses during pregnancy (prenatal screening) and in the context of in vitro fertilisation on genomic DNA from in vitro embryos before implantation into the uterus (genome-wide pre-implantation screening). Screening of newborns would be motivated by the assumption that analysing personal genomes would at best be done as early as possible in life, and the established neonatal heel prick screening could be used to obtain samples for whole genome sequencing of neonates. In the context of prenatal screening, established invasive prenatal diagnostic genetic testing procedures could be expanded to whole genome approaches by testing for more conditions than indicated. However, research is well underway to extract foetal DNA from maternal blood, so that the risky, invasive procedure of aspiring foetal cells will no longer be required (Go et al. 2011). Thus, technically the threshold to perform whole genome prenatal screening on a routine basis will be lowered (Greely 2011). Preimplantation genetic screening of in vitro embryos is done in order to select embryos for transfer that promise the highest probability of implanting in the uterus, thus improving the success rates for in vitro fertilisation, and in order to reject embryos that show developmental or genetic abnormalities. However, there is no evidence of a beneficial effect of PGS as currently applied on the live birth rate after IVF (Mastenbroek et al. 2011).

3.4.3. In forensics

Developed in 1985, the method of forensic DNA profiling (Jeffreys et al. 1985) is widely used for forensic purposes. It differs significantly from the quality of information from whole genome sequencing, as will be outlined below. However, it is not unlikely that forensic DNA profiling in forensic applications will be complemented by whole genome sequencing in the midterm.

Forensic DNA profiling is based on the finding that human DNA contains certain regions in which repetitive stretches of short base sequences (so called short tandem repeats, STR) can be found. The number of repetitions in these regions varies from individual to individual. If the number of repetitions is determined at 8-13 loci, distributed over the entire genome, a DNA profile will result which is specific for this individual. The chance that any randomly chosen person in the population at large would have the same profile is one in one billion. If a DNA profile of unknown identity or origin is compared to other DNA profiles of known identity, with statistical support, a profile match provides strong evidence for individual identification (except for monozygotic twins), whereas a mismatch does not. Highly similar profiles may indicate the involvement of closely related individuals and this familial searching warrants a more complex statistical interpretation (Kayser, de Knijff 2011).

Because DNA is shared with relatives, a person's DNA profile can be used to identify their parents or children and even more distant relatives with certain probabilities; it is therefore also applied in paternity testing. The main uses of forensic DNA profiles are:

- to identify potential criminals whose DNA may match evidence left at crime scenes;
- to exonerate persons wrongly accused of crimes;
- to identify crime and disaster victims where matching profiles between human remains and ante mortem samples belonging to the victim, or profile similarities with genotyped relatives, provide identification evidence;
- to establish paternity and other family relationships (Jobling, Gill 2004; Kayser, de Knijff 2011).

The DNA profile is not based on the whole sequence of a genome (which would currently be still too expensive in every day practice). DNA profiles only allow the analysis whether DNA from a given person is identical (or related) to another DNA sample (e.g. of known origin or identity). However, DNA profiles do not allow us to infer personal characteristics of a person, or only to a limited extent: biogeographic ancestry may be deduced because profiles are much more common in certain populations and an exception in others. When applying additional methods of forensic DNA phenotyping, targeted at the (non-coding) DNA regions of the Y chromosome and mitochondrial DNA, they may provide information about sex and statistical interpretations about phenotypic traits (Kayser, de Knijff 2011).

DNA profiles are usually stored in forensic databases as a digital number code: the string of numbers is based on the number of repeats at each of the tested DNA loci. Forensic databases usually contain DNA profiles from two different sources: crime scene DNA samples and individuals' DNA samples. The most usual means of use of these national DNA databases is through the matching of crime scene samples to profiles in the database. It also allows "speculative searching", yielding new suspects for the crime for further criminal investigation (GeneWatch UK 2011).

Worldwide, at least 120 countries use DNA profiling in criminal investigations; 54 countries have established forensic national DNA databases with at least 16 million DNA profiles, and additionally 26 countries plan the setting up of new DNA databases (Interpol DNA Unit 2009). The largest DNA database worldwide is in England and Wales, the UK Police National DNA Database, with over 5 million DNA profiles.2 In the United States, the CODIS network of several smaller databases in total contains over 7.8 million offender DNA profiles and over 300,000 forensic profiles. As of January 2009, DNA databases throughout Europe contained over 6.8 million offender profiles, over 750,000 crime scene profiles and database searches have yielded over 1.2 million matches (crime scene to crime scene and crime scene to suspect). Over 4 million of the offenders included were from the United Kingdom, as were over 900,000 of the matches.

Data-sharing, involving the transfer of information across international borders, is also on the increase (Prainsack, Hindmarsh 2010). In 2005, Belgium, Germany, Spain, France, Luxembourg, the Netherlands and Austria signed the Prüm Treaty. It – among others – allows direct access by the law enforcement agencies in the participating states to the forensic databases of the other states for searches. These arrangements were, in principle, extended to all EU member states in 2007, when the Council agreed to integrate the main provisions of the Prüm Treaty into the EU legal framework (Council of the European Union 2008a; Council of the European Union 2008b), to enable wider exchanges of biometric data between all EU Member States in the fight against terrorism, illegal migration and cross-border crime (Stajano et al. 2008). Until 2010, the EU Member States were required to amend domestic laws in order to comply with the EU regulation. Several member states had difficulties in meeting the mid-2011 deadline for the implementation of the provisions on automated data exchange (Council of the European Union 2010).

As outlined above, DNA profiles used by the police are not based on the whole sequence of someone's DNA, but only on parts of it. This means that the information contained in them is more limited than that contained in a person's whole genetic makeup (GeneWatch UK 2011). However, there are several trends and drivers that make it likely that whole genome sequencing may also be used for certain forensic purposes in the midterm:

- Research is underway to use genomic biomarkers, so called single nucleotide polymorphisms (SNPs), instead of or in addition to STRs for forensic purposes. SNPs were – technically speaking – research tools in genomic research that were (and are) widely used before whole genome sequencing became affordable. They are usually tested with DNA arrays, a technology that is also being challenged by next and third generation DNA sequencing. Provided that more research is still carried out, the use of SNPs could allow the inference of genetically determined appearance traits from DNA, such as body height and stature, eye, skin and hair colour, skin pigmentation such as freckles, hair morphology (e.g. woolly hair or male baldness) or cleft lip. Of special interest, but still largely unexplored, are genetic factors that determine facial morphology (Kayser, de Knijff 2011). Experts are of opinion that SNP testing will most likely be adopted first in forensics in the identification of disaster victims and in kinship testing once commercial kits become available for these purposes, due to some scientific-technical advantages of SNP testing over STR-based identification in these applications (Kayser, de Knijff 2011). However, the incompatibility of SNP testing with existing STR-based testing in terms of stored DNA profiles is a significant hurdle to changing practice in criminal investigations, because it would mean that existing forensic databases would have to be built again from scratch.

[2]http://www.dnaforensics.com/

On the other hand, in countries that have not yet established a forensic database, the use of SNP-based identification could be taken into consideration (Kayser, de Knijff 2011), thus establishing the basis for deducing phenotypic appearance solely from DNA in criminal investigations. All these traits of interest in criminal investigations could also – or perhaps even better – be analysed with the help of DNA sequencing.

- A remaining challenge in forensics is the analysis of mixed DNA samples, especially if the different persons whose DNA are mixed in the sample are of the same sex. Experts are of opinion that third generation sequencing of single molecules, without the need for PCR amplification, will help solve this problem. Moreover, single molecule sequencing may be very useful, if small amounts of degraded DNA have to be analysed. Therefore, there is a specific technical need to establish third generation sequencing technologies in forensic labs which would also technically allow whole genome sequencing of other samples than the challenging mixed DNA samples.
- There are policy initiatives, e.g. in the UK, the Netherlands and several US federal states (Colorado, Florida) to increasingly use familial searches in DNA databases, because they may open up new investigative leads. Although these policies are disputed due to unresolved privacy concerns, lack of scientific data and a weak legal framework (Gershaw et al. 2011), they point out the demand for additional technologies and approaches in criminal investigations. Whole genome sequencing promises to offer a wealth of such novel approaches, and might therefore also be taken into consideration by policy.

3.5. Actors involved in DNA sequencing technologies

This section provides an overview of the actors who are driving developments in whole genome sequencing and the beneficiaries of these technologies. These actors include technology providers, users of basic biomedical and pharmaceutical research, and users in health care. In addition, the police and the state also use sequencing technologies in forensics.

3.5.1. Technology providers

The main drivers behind the development of new DNA sequencing technologies are academics and the companies that have developed the commercially available sequencing platforms, such as Roche/454 FLX, the Illumina/Solexa Genome Analyzer and the Applied Biosystems (ABI) SOLiD Analyzer, that are currently dominating the market. There are also two newcomers, Polonator G.007 and Helicos HeliScope, that have entered the market, but they are not that widely used (table 1). Companies that develop third generation DNA sequencing technologies that have not yet reached market maturity, are Pacific BioSciences, Visigen Biotechnologies, U.S. Genomics, Genovoxx, Oxford Nanopore Technologies, NABsys, Electronic BioSciences, BioNanomatrix, GE Global Research, IBM, LingVitae, Complete Genomics, base4innovation, CrackerBio, Reveo, Intelligent BioSystems, LightSpeed Genomics, Halcyon Molecular, ZS Genetics, Ion Torrent/PostLight and Genizon BioSciences (Zhang et al. 2011).

Another important group of companies are providers of kits and consumables for new generation sequencing technologies. Among them are Ambion, Life Technologies, NuGen, Qiagen, Invitrogen, Promega and Sigma Aldrich. IT companies are also entering the market, for example, IBM announced a collaboration project with Roche to develop a nanopore-based DNA sequencing technology. Focused on advancing IBM's recently published "DNA Transistor" technology, the collaboration will take advantage of IBM's leadership in microelectronics, information technology and computational biology, and Roche's expertise in medical diagnostics and genome sequencing (IBM 2010).

Especially the huge amounts of data that have to be processed and stored in whole genome sequencing require a sophisticated IT infrastructure as well as advanced software to analyse the data. Therefore, this field is of interest to both IT hardware and software providers.

3.5.2. Basic research

In basic research, the main funding has come from public sector sources that provide the infrastructure, IT, maintenance costs of biobanks and other basic research costs. Over the last decade, there have been a number a international scale research projects related to DNA sequencing that all started off after the completion of the Human Genome Project in 2001 (Lander 2011). Major data producing projects for different purposes and research questions are, e.g. The 1000 Genomes Project, the Personal Genome Project, the Protein Atlas and MRM Atlas, Eurexpress, the Novartis expression database, ENCODE, the NIH Epigenetics Consortium, TREAT1000 (www.treat1000.org) and OncoTrack. Cooperation with private sector companies is part of these academia-led projects. For example, in 2008, Google announced that they were going to invest in the "Personal Genome Project" (see also section 3.4.1.). Cooperations are established both with companies that are providers of the technology, as well as with companies that apply the technologies and findings, e.g. pharmaceutical companies.

3.5.3. Medical and pharmaceutical research and health care

Research in view of realising the vision of personalised medicine is already being undertaken within the 7th EU research framework programme, but it is expected to become a priority of EU funded research from 2014 onwards[3].

In medical research, the second generation DNA sequencing technologies have also enabled researchers in academic research laboratories and clinical laboratories, as well as medical doctors in university hospitals, to investigate disease mechanisms in translational and clinical research (Anderson, Schrijver 2010).

Pharmaceutical and diagnostic companies are actively developing drug-diagnostic combinations within the concept of personalised medicine. They apply next generation sequencing in these efforts and they also make use of the research findings coming from genome sequencing projects.

Within health care, next generation sequencing is currently being applied in sequencing a limited number of genes, e.g. in the context of diagnosing hereditary diseases, or in whole exome sequencing in the case of diseases with unexplained causes, e.g. unexplained mental retardation. Sequencing of tumour DNA in cancer patients is an upcoming health care application. Relevant actors are human geneticists and oncologists, as well as clinical laboratory services and pathologists.

In addition to classical medical and health care players, a new business sector has developed in recent years, which offers direct-to-consumer genetic profiling and whole genome screening to the general public. There are more than 30 companies on the market, mostly SMEs in the USA and Europe. Services are offered mainly over the internet, making them readily available to consumers worldwide. Consumers are interested in these services for a variety of reasons, ranging from pure curiosity to the exploration of disease predispositions (Javitt 2010; Hogarth et al. 2008; Hennen et al. 2008).

However, the number of people actually using genetic profiling services is not known (Nuffield Council on Bioethics 2010). Software companies such as Microsoft and Google significantly invest in and cooperate with DTC genetic profiling companies, such as 23andMe and Navigenics, located in the USA.

[3]See e.g. http://ec.europa.eu/research/health/policy-issues-personalised-medicine_en.html

3.5.4. Forensics

Since the mid-1990s, most EU Member States have established a national forensic DNA database. These mass repositories of DNA profiles enable the police and immigration officers to identify DNA stains that are found, for example, at crime scenes, or needed for the migration controlling issues (Van Camp, Dierickx 2008).

As an international police organisation, INTERPOL advocates the international comparison of DNA profiles in accordance with international standards, to combat cross-border crime and criminals (Interpol DNA Unit 2009).

3.6. Privacy infringements and ethical issues

This section outlines the issues and concerns that may arise and the unintended impact of using whole genome sequencing in research, health care and forensics. Although many of these issues have already been extensively debated in the context of genetic testing, there are several features which specifically distinguish whole genome sequencing from genetic testing. These are the overwhelming amount and comprehensiveness of genetic information that can be obtained by whole genome sequencing, the difficulty of effectively applying established levels of data protection and privacy (e.g., anonymization of data), the provisional nature of the interpretation of whole genome sequence data, which is strongly dependent on current knowledge and thus may change over time, the diffusion of genome sequencing to new contexts (e.g., direct-to-consumer genetic services), and the increasing internationalization, rendering national regulations and safeguards in part obsolete.

Due to the specific features of genetic information, as outlined in section 3.2., whole genome sequencing and analysis will yield a wealth of personal data which do not only relate to the donor of the genomic DNA, but also to his relatives. Although the social, ethical and legal issues related to genetic testing have extensively been explored in the last decades and they, in principle, also apply to whole genome analysis and therefore are not new, the scale and the context are – in part – new and specific to whole genome analysis and therefore require a closer look (Health Council of the Netherlands 2010; Curren et al. 2010; Heeney et al. 2011; Taylor 2008; Stajano et al. 2008).

In the following paragraphs, we will first give an overview of the possible privacy infringements and concerns associated with whole genome sequencing and analysis (section 3.6.1.). We will then outline, in more detail, issues which arise in research, health care and forensics.

3.6.1. Overview

The following possible privacy infringements and concerns associated with whole genome analysis have been voiced (Stajano et al. 2008; Lunshof et al. 2010); they may apply to the donor of the genomic DNA as well as to his relatives (e.g. ancestors and offspring):

- The disclosure of genomic information to the public or to third parties, with the risk of unintended and harmful use of this information,
- Use of genomic data to identify the DNA donor in other confidential settings (e.g. research studies, health care, criminal investigations).
- Use of disclosed genomic information without knowledge or consent by the donor to infer paternity or other features of the donor's genealogy;
    - reveal the possibility of a disease or unknown propensity for a disease or carrier status for a genetic disease, thus also influencing reproductive choices;
    - reveal non-medical traits with a genetic basis, such as aberrant behaviour, sexual orientation, intelligence and so on;

- use genetic information to infer phenotypic traits, e.g. facial morphology, skin, eye and hair colour, stature and so on, thus identifying the DNA donor or a relative, e.g. in a confidential setting or for biosurveillance purposes;
- claim statistical evidence that could affect employment, insurance or ability to obtain financial services;
- claim a relation to criminals, criminal suspects or involvement in crimes;
- make synthetic DNA and use it for identity theft, to falsely identify the DNA donor or, to put the synthetic DNA at a crime scene;

- Attempted or actual stigmatisation, discrimination and other forms of negative treatment due to disclosure of personal genomic information or its interpretation, in the context of education, employment, insurance, health care services, financial services, social contacts, criminal investigations and so on.

The related privacy concerns and ethical issues of whole genome analysis show a broad overlap with well-known and elaborated privacy concerns and ethical issues concerning genetic testing for research and medical purposes, genetic profiling for forensic purposes, and privacy issues of medical information. However, the following combination of features is new and specific for whole genome sequencing:

- The sheer amount and comprehensiveness of information made accessible by whole genome sequencing and analysis. It goes far beyond single gene information or simple identification (as through DNA profiles). Information about medical conditions, non-medical traits and ancestry may be retrieved. It significantly increases the possibilities and likelihood of unintended use or misuse of the data with respect to discrimination, stigmatisation and privacy infringements. It implies an urgent need for (even more) stringent safeguards for data protection and confidentiality and against unauthorised use of data. It also impacts established procedures for obtaining informed consent and raises ethical issues.

- The difficulty or even impossibility to apply established safeguards for privacy, such as confidentiality or anonymisation of whole genome data.

- The tentativeness of the results of whole genome analysis, due to incomplete knowledge at the time of consent or analysis, and the highly possible option that future re-analyses of the sequence data will reveal additional information not foreseeable at the time of DNA sequencing. This opens up new possibilities of unintended or abusive analysis of personal genome data, and it also impacts established procedures for obtaining informed consent and requires ethical deliberations.

- The change of contexts (players, codes of conduct) in which whole genome sequencing and whole genome analysis is being performed, as compared to genetic testing, genetic research and health care. This relates mainly to the need to amend and adapt established governance models such as codes of conduct or sector-specific regulations to the new requirements.

- An increasing internationalisation and DNA and data exchange across borders, but with different levels of national safeguards and regulations in place, and a lack of harmonisation of these regulations. This increases the possibility of unintended uses and privacy infringements when personal genome data or genomic DNA cross borders.

3.6.2. Issues in research and biobanks

As outlined in section 3.4.1., an increasing number of research projects are carried out, and research biobanks are set up in which comprehensive datasets of whole genome sequences, together with extensive phenotypic information (based on comprehensive environmental and trait data), are collected and stored. As these projects require significant resources which can hardly be made available by a single player, they are preferably carried out in cooperative settings, be it in international cooperation or cooperation between partners from academia, private not-for-profit organisations or for-profit companies with a commercial focus. Moreover, the benefits of these resource-intensive endeavours can only be adequately harnessed if the information is widely shared with and distributed to all cooperation partners, or if access is even made possible for all interested parties. As a consequence, data sharing is an essential part of the research process (Lunshof et al. 2008).

The key challenge is to use all the possibilities that these kinds of projects and biobanks offer for research, and to have the public trust and their support by participating in research by donating samples to biobanks and providing personal data (e.g. medical and lifestyle). Some studies suggest that attitudes in the general population vary greatly across Europe (Gaskell et al. 2011; Gaskell, Gottweis 2011). Privacy issues and uses of data (for knowledge generation, commercial purposes or individual benefit) play an important role in shaping the attitudes. It would, however, be detrimental to research if there were a profound loss of public trust with a declining willingness to take part in future research.

The Personal Genome Project is a very illustrative example for this type of research project and it will therefore be described here in more detail: It aims at collecting the most comprehensive collection of molecular information (e.g. whole genome sequence, transcriptome, proteome and metabolome data), as well as whole body imaging and most comprehensive health and lifestyle information from healthy volunteers, and uses the data for elucidating the relationship between genetic condition, environmental influences and health.

Traditionally, legal frameworks have sought to balance the privacy of data subjects with the benefits of research by relying heavily on informed consent and anonymisation (Lunshof et al. 2008), meaning that the protection of identity of participants in research projects is guaranteed. This is achieved by the maintenance of the confidentiality of personal information through mechanisms such as data only being released in an aggregated form or after identifying variables have been removed (Heeney et al. 2011). To a certain extent, these mechanisms can still be applied to whole genome sequencing and analysis: e.g. it is technically possible to make accessible only a part of the raw sequence data (e.g. specific genes) which are of interest for a specified research question, or to allow the analysis of the whole genome sequence only for a specific purpose (e.g. a specific medical condition, but no non-medical traits). However, a comprehensive anonymisation is impossible for the raw sequence data, as they are a unique identifier for the individual. Moreover, together with the multitude of other personal data in the dataset, a re-identification of a specific participant may be possible also with incomplete genomic data. That a re-identification is possible, in principle, has already been demonstrated (Curren et al. 2010). As a consequence, with whole genome sequencing and analysis a certain level of data protection and confidentiality can be implemented, but it is unrealistic to promise absolute data protection to participants in genomics research.

Against this background, a key feature of the Personal Genome Project is that is does not guarantee anonymity, privacy and confidentiality for the participants. Rather, volunteers are urged to seriously consider the scenario where all of their data and identity would be accessible by a large number of people. As a consequence and novelty in research ethics, the concept of "open consent" was developed (Lunshof et al. 2008). It is put into practice by comprehensive information for the volunteers, an entrance exam to test their knowledge and understanding of what their consent really means, and an eligibility screening. For these purposes, a number of project specific tools and resources have been developed (Lunshof et al. 2010).

Another critical question concerns the reporting of research results back to the participants. There is a traditional viewpoint that research subjects should not receive identifiable research data. However, as is shown in consumer genetic profiling, is the population has a certain interest in getting to know their own genome sequence, and there are no good reasons to withhold this information from the donor once it has been obtained with his consent in a research context. Moreover, obtaining this information may be a significant incentive for participation in this research and a "fair trade" for the concessions that research subjects have to make with respect to privacy and confidentiality.

However, as will be outlined in section 3.6.3. in more detail, the traditional informed consent procedure, as implemented for genetic testing of defined genes or for specific diseases, is not applicable here, due to the multitude of medical conditions that may, eventually in the future, be analysed with the possible clinical ramifications not fully known or not even envisioned. Therefore, there is uncertainty about the regulations governing the return of genomic research results directly the participants, although there will be a need to distinguish between findings with proven clinical relevancy, and findings in which disease association is less robust. Moreover, the possible impact of false-positive or negative results has to be taken into consideration (Lunshof et al. 2010). In the Personal Genome Project, open research is advocated as one possible solution. Open research implies veracity on the part of the researchers, active and interactive modes of participation, and openness from both researchers and participants (Lunshof et al. 2008).

All in all, this shows that existing informed-consent models for whole genome sequencing and analyses need to be modernised (Lunshof et al. 2008), as compared to established informed-consent models for (mono)genetic research, especially with respect to

- the level of confidentiality and data protection that can realistically be promised to the participants,
- the type of information that has to be given during the process of obtaining informed consent, taking into account the uncertainty, especially of future research uses and analysis of personal data, type of players gaining future access to the data, and type of conditions that may be revealed to the participant,
- new ways of benefit sharing between research and participant, e.g. by novel ways of participant involvement in research, such as reporting research findings back to participants.

3.6.3. Issues in health care and direct-to-consumer (DTC) genetic profiling

Of specific concern of whole genome sequencing and whole genome analysis is that all genetic information available based on the current state of knowledge, health related and not, will be obtained. This may be information considered useful by the patient, it may be information causing harm to the patient or his family if revealed to him, and it may be information with changing relevance over the patient's lifetime (e.g. for reproductive decisions, late-onset diseases, or end-of-life decisions); but a large portion of the information may also have unknown significance and as yet not be fully understood.

Irrespective of whether whole genome sequencing will be performed in the context of genome-wide diagnostic testing or genome-wide screening, the majority of findings will be unsought for findings. Although unsought for findings are common with certain medical practices (e.g. medical imaging), genome-wide analyses significantly increase the probability of such findings (Health Council of the Netherlands 2010).

Based on the both the right to know and the right not to know, the established ethical framework for such diagnostic and screening purposes means that people should be given the opportunity to make such choices in advance in a fully informed way. Against this background, guidelines and quality standards have been implemented concerning how genetic counselling should be performed for diagnostic genetic testing, in order to obtain valid, informed consent. It comprises a detailed discussion of all possible findings with respect to nature, severity and treatability. However, it will be impossible to apply this standard in whole genome sequencing and analysis because of the amount and variety of the information, as well as the fact a great deal remains unclear or uncertain (Health Council of the Netherlands 2010). As a possible solution, a "generic consent" model has been proposed. In this model, a selection of typical examples of diseases and possible results are explained to the patient or participant, and consent is sought on the basis of these exemplary explanations.

Moreover, it requires consideration that whole genome analysis will yield mainly information for which the clinical significance is as yet unclear, but might be elaborated in the future, because this impacts early decisions during the informed consent procedure; for example, to which extent raw sequencing data should be stored, under which conditions the raw data should be accessed and analysed again, and to which extent unclear or health information from analysis should be disclosed to the patient (Health Council of the Netherlands 2010). This applies to:

- Storage of data. A differentiation must be made between the raw data, which is the product of sequencing, and the outcomes of the sequencing analysis. Only if raw sequencing data are stored, can they be used for future analysis. The generation of the raw data by sequencing does not need to be repeated, and progress in knowledge about relationships between DNA sequence and health could be applied. Provisions have to be made on how to deal with the information. This must already be clarified during the consent procedure in order to respect the patient's autonomy.
- Aftercare and reassessment of raw data. In an ongoing doctor-patient relationship there is a clear framework within which the doctor may be expected to inform the patient about new, relevant insights. It is open to discussion, however, to what extent recontacting after the termination of the treatment relationship should be a standard of aftercare, and whether this only encompasses the original request to seek medical advice, or whether it also extends to other health-related conditions. Especially in the context of genome-wide screening, it is foreseeable that a shift in the GP's or doctor's task conception is likely to occur: he or she will shift from being solely a complaint-oriented care provider to a 'health monitor' who also advises patients on all possible aspects of health, on his or her own initiative. As a consequence, the scope of responsibility and role of practitioners and specialists in the doctor-patient relationship will have to be clarified in terms of how to organise the cooperation and how to share the responsibilities between GPs and specialists.

The question of how to deal with unsought-for findings and findings of unclear clinical relevance becomes even more critical if whole genome analysis is carried out on newborns, children or even prenatally, because the most affected persons in these cases are unable to consent.

In addition to genome-wide diagnostic testing and genome-wide screening being performed in the health care sector within the classical doctor-patient relationship, these services are also provided on a direct-to-consumer basis without the involvement of a health care provider and on a private contractual, commercial basis. So the classical concept of confidentiality, as firmly established in the doctor-patientrelationship, no longer applies in the case of DTC genetic profiling companies (Hogarth et al. 2008). Of concern are the following possible downsides of DTC genome-wide screening (Nuffield Council on Bioethics 2010):

- The test results can be unreliable and difficult to interpret.
- 'Good' results may lead to complacency in lifestyle.
- Learning about risk of disease could be upsetting, particularly if no treatments are available.

- People may seek unnecessary further tests or advice from their doctor.
- There is a potential for misuse of personal genetic information, because there is no overview or control over how the complete and detailed data sets are stored electronically, which presents a threat to privacy of the individuals, whose data is used in DTC testing (Javitt 2010).

However, it is not known how many people actually use genetic profiling services and whether this currently leads to any actual harm (Nuffield Council on Bioethics 2010). Therefore, there is an ongoing debate whether and how the new situation should be dealt with, as the existing regulatory regimes of confidentiality in the doctor-patient relationship are no longer tenable with the DTC testing companies as new actors (Hogarth et al. 2008). On the one hand, there are voices which advocate a strict regulation of these companies, similar to the regulations established for medical professions. On the other hand, others call for new governing models, not just an extension of existing regulations (Prainsack et al. 2008).

3.6.4. Issues in forensics

Ethical, legal and practical questions arise from the use of DNA profiles for forensic purposes and from the establishment of forensic DNA profile databases. They are

- the coverage of forensic DNA databases, i.e. from whom and under which preconditions samples should be taken and DNA profiles should be stored. Individual human rights are at stake, not only due to the widening of the group of individuals (not crime scene samples) from whom DNA can be taken and then retained (GeneWatch UK 2011), but also bodily integrity and privacy as well as more general legal principles, such as the presumption of innocence, proportionality of measures, the right not to know and the burden of proof.
- the duration of sample storage and data storage in forensic DNA databases.
- the question for which purposes and under which preconditions forensic DNA databases may be accessed and searches may be run. In this context, the function creep is most relevant (Prainsack, Hindmarsh 2010).

In general, these questions are often governed by national regulation specific for the national databases. However, out of the 54 countries worldwide with a national DNA database, only 28 countries have implemented database-specific DNA database legislation (Interpol DNA Unit 2009). Moreover, in international comparison, there is a very wide range of ways in which these questions are solved on a national basis, so the rules on what data can be collected and stored and how data can be used differ significantly between different countries (GeneWatch UK 2011).

For example, with respect to the coverage of forensic DNA databases, the scope ranges from databases in which only DNA profiles of convicted criminals who have committed a severe crime (e. g. murder or rape) are being stored, to countries that plan to set up comprehensive population databases (e.g. plans in the Arab Emirates, Uzbekistan, Bermuda and Pakistan). In countries where DNA profiling is being restricted to severe crimes, the definition of what is being considered "a severe crime" has often been changed to less severe crimes, often triggered by individual cases (Kayser, de Knijff 2011). A significant percentage of data stored in forensic databases does not comply with the national regulations: e.g. regulation often stipulates that DNA profiles of suspects or from mass screenings in a certain investigation must be deleted from the data bases once the investigation has been closed and a suspect been convicted; this in order to prevent exonerated, innocent suspects from being kept in the database. However, surveys by data protection officers show that there are deficits in everyday practice to comply with these regulations (Der Landesbeauftragte für den Datenschutz in Baden-Württemberg 2008).

For example, an investigation of 493 samples in the forensic DNA database of the German state Baden-Württemberg showed that 208 data sets (42 per cent) did not comply with the regulations. Moreover, certain social groups are overrepresented in these data bases, pointing to a discriminatory imbalance in the practice of collecting DNA profiles from suspects.

To sum up, ethical, legal and practical questions associated with the use of DNA profiles for forensic purposes and from the establishment of forensic DNA profile databases are not yet sufficiently dealt with in the following respects:

- The level of awareness and reflection of these issues differs strongly between states;
- Many countries lack specific regulations governing these issues: in international comparison, the regulatory landscape is not only patchy, but also diverse and non-harmonised;
- In countries where specific regulations exist, there may be difficulties and shortcomings in implementing these regulations; cases of non-compliance with existing regulations have been reported.
- High quality standards need to be implemented to prevent any miscarriages of justice due to errors in DNA profiling. This becomes even more pressing by international linking of forensic databases, since the probability of errors to occur is raised with the number of profiles and comparisons.

As a consequence, there is a need to improve the current situation with DNA profiling.

Presently, sequencing of whole individual genomes is not yet done for forensic purposes. However, several drivers have been identified which let us assume that forensics will acquire the technologies and methodologies that are required to carry out such analyses, and that there is a demand for inferring more information from crime scene or suspects' relatives DNA samples (e.g. phenotypic trait information) that may be helpful in criminal investigations. The sunk investment in existing forensic databases, based on DNA profiles, is a significant hurdle to switching to whole genome sequencing in the foreseeable future. Therefore, whole genome sequencing will most likely remain restricted to relatively rare, specific criminal investigations. Nevertheless, it is to be feared that the existing problems with DNA profiles will become even more relevant in the midterm should whole genome sequencing and whole genome analyses be introduced into forensics.

3.7. Regulatory and policy aspects regarding privacy impacts

This section provides an overview of the relevant regulations designed to ensure data protection, safeguard genetic information and prevent its misuse, as well as avoid privacy infringements and discrimination. With respect to the time horizon of development and its possible impact, the section concludes that whole genome sequencing is most relevant to research and biobanking as well as in health care and personalized medicine. Whole genome sequencing is already established in these fields, or will be in the coming decade, placing existing governance frameworks increasingly under pressure. The section then discusses how the gaps identified in these application areas might be filled, presenting options for amendments to the regulations or new governance models. The section closes with recommendations as to how the governance challenges identified might be addressed in a European policy context.

3.7.1. Relevant regulations

It is an ongoing debate whether genetic information, due to the unique combination of the features outlined in section 3.2., is exceptional, and therefore requires a special regulatory framework to prevent threats to privacy and misuse, or, whether despite its sensitive nature, genetic information can be adequately protected under regimes that currently regulate personal data or other medical and health information. However, the assumption of an exceptional character of genetic information is an integral principle underlying major regulations; e.g. the Council of Europe's European Convention on Bio-medicine, Article 11, EU's Charter of Fundamental Rights, Article 21 and UNESCO's "Universal Declaration on Human Genome and Human Rights", Article 6, all prohibit any discrimination based on genetic data. The Convention on Human Rights and Biomedicine (the Oviedo Convention) furthermore allows predictive genetic testing for medical purposes only.

In the USA, an act that specifically addresses genetic information has been in force since 2008; The Genetic Information Non-Discrimination Act (GINA) provides protection from discrimination based on presymptomatic genetic information in health insurance and in the workplace, and creates a national uniform standard regarding data protection of genetic information.

In the European Union, the Article 29 Data Protection Working Party is an independent European advisory body on data protection and privacy. It has – among others – the task to provide expert opinion from member state level to the Commission on questions of data protection. The Working Party emphasises in its Working Document on Genetic Data that data protection law in Europe also requires strong protection of genetic data (Article 29 Data Protection Working Party 2004). However, as some authors point out, in many respects the Art. 29 Data Protection Working Party only identifies issues and questions, without providing conclusive answers (Stajano et al. 2008). The examples include: the question of whether a person may be forced to disclose his or her genetic data to blood relatives, where such data are relevant in view of safeguarding their health; the exercise of the right, inside a group, not to know one's genetic data, and with respect to biobanks, "the issue of prescribing practices applying anonymisation [that] could be a possibility to address issues from the data protection perspective" (Article 29 Data Protection Working Party 2004). However, it then also noted that "there has been evidence that stored DNA is capable of being linked to a particular person – provided certain additional knowledge is available, even though it may not be stored in a directly person-specific way" (Article 29 Data Protection Working Party 2004).

Moreover, the EU's data protection directive (Directive 95/46/EC 1995), that is based on the 1980 OECD "Recommendations of the Council Concerning Guidelines Governing the Protection of Privacy and Trans-Border Flows of Personal Data", also covers privacy of genetic data (Stajano et al. 2008; for information on its enforcement in EU member states, see[4].

Regulations in forensics

In 2005, Belgium, Germany, Spain, France, Luxembourg, the Netherlands and Austria signed the Prüm Treaty. It – among other things – allows direct access by the law enforcement agencies in the participating states to the forensic databases of the other states for searches DNA profiles, fingerprint data and vehicle data. These arrangements were, in principle, extended to all EU member states in 2007, when the Council agreed to integrate the main provisions of the Prüm Treaty into the EU's legal framework (Council of the European Union 2008a; Council of the European Union 2008b) to enable wider exchanges of biometric data between all EU Member States in the fight against terrorism, illegal migration and cross-border crime (Stajano et al. 2008).

[4] http://ec.europa.eu/justice/policies/privacy/law/implementation_en.htm

Until 2010, the EU Member States were required to amend domestic laws in order to comply with the EU regulation. However, some member states had difficulties to meet the mid-2011 deadline for the implementation of the provisions on automated data exchange. The problems identified include IT and financial problems, logistic, legal and political decision making problems, as well as shortage in personnel (Council of the European Union 2010).

Out of the 54 countries worldwide with a national DNA database, 28 countries have implemented database-specific DNA database legislation (Interpol DNA Unit 2009). However, rules on what data can be collected and stored and how it can be used differ greatly between different countries (GeneWatch UK 2011). It can therefore be concluded that many countries lack specific regulations for forensic uses of DNA profiles. In international comparison, the regulatory landscape is not only patchy, but also diverse and non-harmonised.

3.7.2. Reflections on current developments in the field of whole genome sequencing

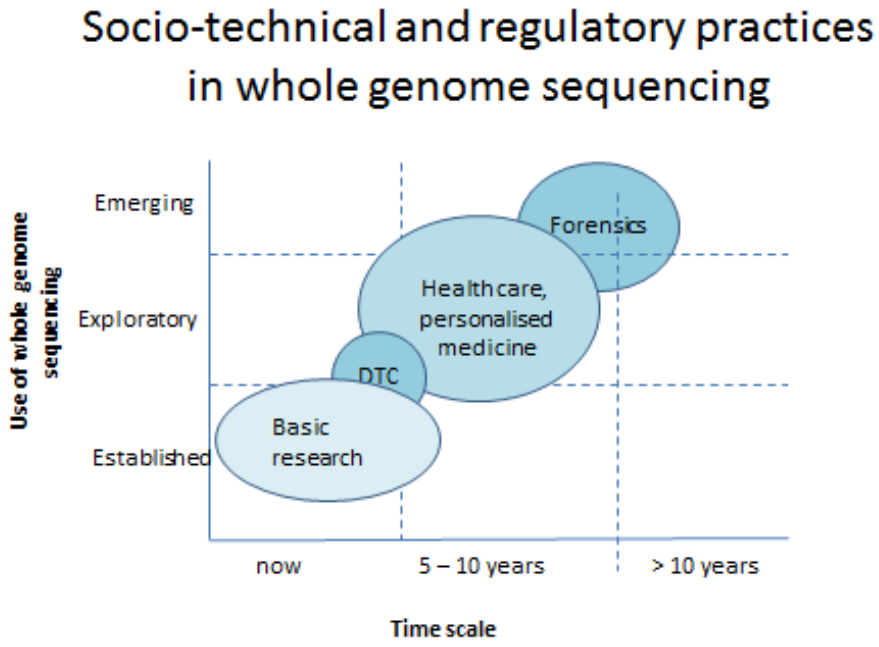
Time horizon of developments

With second generation DNA sequencing techniques on the market, whole genome sequencing costs and time requirements have plummeted dramatically, making it possible to sequence whole human genomes in the resolution of 100 GB in a matter of days for 45,000 US$. Significant further advances are expected from third generation sequencing technologies, which will reach market maturity within the coming decade, bringing the sequencing costs further down to 5,000 and then to 1,000 dollars. As a consequence, the scope of applications for whole genome sequencing will broaden considerably within the coming decade.

In the previous sections, the state of the art and likely future development was analysed of whole genome sequencing in basic and biomedical research, in health care provision as well as in forensics. It can be concluded that whole genome sequencing is now firmly established in leading edge basic and biomedical research projects worldwide and in the EU. It is only applied in relatively rare cases in health care provision for diagnosing specific syndromes with an unknown, but suspected genetic cause. In the coming five years, the preferred format for DNA sequencing in health care will remain the sequencing of a small number of defined genes. However, within the coming decade, the possibility of genome-wide diagnostics, genome-wide screenings and the expansion of genome-wide approaches also to prenatal diagnosis, newborn screening and reproductive medicine is likely to materialise. Certain forms of genome-wide screenings for "fun", for probing ancestry and with the intention to obtain more information about one's health condition, are already offered by private companies directly to healthy consumers.

These services are mainly offered over the internet, are therefore not confined within national borders, and operate – despite the often medical character – outside the traditional health care sector. In forensics, whole genome sequencing will most likely play no role within the coming decade. However, in the future it could become an important additional tool for specific tasks within criminal investigations. An overview of the timescale of these applications of whole genome sequencing is given in figure 2.

Figure 2: Time scale of use of whole genome sequencing in different application areas



Shifts in sociotechnical practices and implications for the current regulatory scheme

Basic research and biobanks

The increasing use of whole genome sequencing together with the linking of whole genome data with most comprehensive health and lifestyle data in biobanks, combined with more extensive data-sharing across borders and in public-private cooperations, leads to a significant shift in sociotechnical practices in basic and biomedical research. The traditional governance mechanisms, such as confinement to academic research without commercial interests and research that is only on anonymised data and samples – thus guaranteeing data protection and privacy – can no longer be applied in an unaltered form. It is, for example, unrealistic to promise absolute data protection to participants in whole genome sequencing research.

All in all, this shows that existing governance of biobanks and informed consent models in research need to be modernised (Lunshof et al. 2008) for whole genome sequencing and analyses, especially with respect to

- the level of confidentiality and data protection that can realistically be promised to the participants,
- the type of information that has to be given within the process of obtaining informed consent, taking into account the uncertainty, especially of future research uses and analysis of personal data, type of players that gain future access to the data, and type of conditions that may be revealed to the participant,
- new ways of benefit sharing between research and participant, e.g. by novel ways of participant involvement in research, such as reporting research findings back to participants.

Currently, we witness a controversial debate on how this modernisation could be shaped. The main controversy relates to the question to which extent the up to now predominant libertarian values should still apply. This liberal position ranks the freedom of the individual as very high and assigns a high priority to safeguarding privacy and autonomy of the individual. As a consequence, informed consent and a high level of data protection and confidentiality form core elements. On the other hand, communitarian positions have gained influence in recent years. They stress the (moral) obligation of the individual to contribute to collective interests (e.g. by taking part in biomedical research, even if no benefit for the individual or even harm for the individual can be expected) and give high priority to values such as solidarity, reciprocity and citizenship. The models of open consent and open research, as implemented e.g. in the Personal Genome Project, are examples of how these communitarian positions could be put into practice. However, governance schemes which mediate between these positions have also been proposed, e.g. by the German Ethics Council. They propose a five-column-concept. It comprises of (Deutscher Ethikrat 2010)

- a biobank secret guaranteed by law (i.e., data and samples in research biobanks are not accessible to, e.g. police, insurance companies and so on),
- the stipulation of the possible uses of samples and data and an informed consent; however, this consent can be broad or open, but it must always offer a choice for the research participant and maintains his right to revoke the consent at any time,
- the mandatory consultation of ethics committees,
- appropriate mechanisms of quality insurance and data protection, as well as
- transparency.

It can be concluded that the current frameworks governing research are being put under pressure both with regard to the level of confidentially and that data protection that can be promised to participants, and with regard to the process of obtaining informed consent. However, the regulatory landscape is diverse, patchy and not internationally harmonised. Therefore, it would be desirable to continue the ongoing expert debate about these issues, to come to an appropriate balance of libertarian and communitarian positions, and in the medium term to put up regulation in the EU which sets certain standards, e.g. with respect to biobanking and research on humans.

Health care and direct-to-consumer (DTC) genetic profiling

Health care practices may undergo a major shift in sociotechnical practices as a result of whole genome sequencing and its related vision of personalised medicine.

Issues that can no longer be dealt with in the traditional way are the practice of genetic counselling for genetic testing: it is traditionally based on a narrow form of informed consent for a specific disease, and this will no longer apply with genome-wide diagnosis or genome-wide screening. Other forms, such as broad or generic consent, will have to be used. Moreover, the following options must also become an integral part of the consent process: to what extent should raw sequencing data be stored, under what conditions should the raw data be accessed and analysed again, and to what extent should unclear or health information from analysis be disclosed to the patient?

Expert discourses as well as public consultations will have to be initiated in the midterm in order to assess risks and possible benefits from genome-wide screenings, especially if neonates or children should be screened. In this context. the issue of unsought-for findings which will be produced at unprecedented scale by whole genome sequencing must also be addressed in an interdisciplinary manner.

Should whole genome sequencing be used to realise the vision of personalised medicine – in the sense of predictive health information being obtained as an integral part of a proactive approach to health care – the balance of autonomy versus solidarity or libertarian versus communitarian positions is at stake. If communitarian positions become more important than today, disease would no longer be seen as a "fate" that calls for solidarity between the healthy and the sick; rather, health is a condition that can and must be actively strived for, putting much more responsibility on the individual for one's own health than today and bearing the danger of establishing sanctions against unhealthy lifestyles (ABFTA 2009).

Moreover, the scope of responsibility and the role of practitioners and specialists in the doctor-patient relationship may shift from being a "complaint-oriented care provider" to a "health monitor" who also advises patients on all possible aspects of health on his own initiative. This raises new questions about the future care relationship between doctor and patient.

Against this background, private companies' offer of genome-wide genetic profiling and whole genome sequencing can be seen as an even more radical new sociotechnical practice, because it is emerging outside the current health system, involving individual health consumers outside existing regulatory regimes of confidentially in the doctor-patient relationship. There is an ongoing debate whether and how the new situation should be dealt with, especially as the number of persons using these services are not known, as is the fact whether any harm has been done. Policy options how to deal with the situation have been outlined in a recent report commissioned by STOA (Hennen et al. 2008): On the one hand, there are voices that advocate a ban of direct-to-consumer medical tests, thus leaving the analysis of clinical diagnostics to specialists (Beaudet 2010). On the other hand, others call for new governing models, not just an extension of existing regulations (Prainsack et al. 2008). Therefore, the regulatory challenge and at the same time the guiding principle for any intervention by policy makers is "to create standards that adequately protect consumers from harms associated with unsafe tests, while ensuring access to tests that are analytically and clinically valid in a manner that provides appropriate context and counselling. Regulatory requirements must be proportionate to the risks posed by the tests, and must recognize that some tests carry greater risks than others" (Hennen et al. 2008, p. 55)". Building on this guiding principle, the UK Nuffield Council on Bioethics takes a liberal position with respect to DTC genetic profiling, by concluding and recommending the following:

- Regulators should request evidence for any claims being made by companies about the clinical value of their tests.
- Government websites should provide information about the risks and benefits of personal genetic profiling, including the relevance for insurance.
- Companies should not knowingly analyse the DNA of children unless certain criteria are met.
- Doctors should receive training on giving advice to patients about commercial genetic profiling services.
- Companies should voluntarily provide clear information on the limitations of genetic profiling and what will happen to people's data (Nuffield Council on Bioethics 2010).

Given the fact that it is not known how many people actually use genetic profiling services and whether this is currently leading to any actual harm, the governance challenges seem less pressing and urgent than those in research and health care.

Forensics

DNA profiles have been used for forensic purposes for several decades. They are an established part of police work in at least 120 countries worldwide and 54 countries have set up forensic databases. However, there is a large variety of ways in which forensic databases are set up, run and monitored, and the regulatory frameworks governing these issues are not only equally diverse, but also patchy and non-harmonised. Currently, there is a tendency in many countries to expand DNA databases for police and forensic uses. This tendency is referred to as "function creep", i.e. the widening of the scope of purposes for which DNA profiling and databasing are used. This function creep comprises the inclusion of DNA profiles from a wider range of persons; the increasing cross-border use of other national databases for searches, as stipulated in the Prüm Treaty and the EU regulation (Council of the European Union 2008a; Council of the European Union 2008b), as well as the broadening of kinds of information that can legally be obtained from the analysis of DNA samples (e.g. familial searching, Prainsack, Hindmarsh 2010). Whole genome sequencing is not yet being considered within this function creep, but it could especially contribute to the latter.

There are presently no indications that "dark scenarios" will materialise, e.g. that governments will use forensic DNA profiling and databasing (or even whole genome sequencing) to establish DNA registries of all citizens. This is – next to civil rights considerations – also due to the fact that the existing DNA profile databases would no longer be compatible with whole genome databases, the latter therefore being a system that would have to be established from scratch.

Presently, sequencing of whole individual genomes is not yet done for forensic purposes, and it will most likely be applied, as sequencing technology improves further, for relatively rare, specific tasks within criminal investigations. The sunk investment in existing forensic databases, based on DNA profiles, is a significant hurdle to switch to whole genome sequencing in the foreseeable future. Therefore, whole genome sequencing will most likely remain restricted to relatively rare, specific criminal investigations. Nevertheless, it is to be feared that the existing problems with DNA profiles will become even more relevant in the midterm, should whole genome sequencing and whole genome analyses be introduced into forensics.

As a consequence, whole genome sequencing in the near term does not yet change sociotechnical and regulatory practices in forensics, per se. However, there are several weaknesses in the existing regulatory practices and in their enforcement in practice with DNA profiling that should be addressed by policy and stakeholders. Therefore, it is recommended to address the following issues in the coming years:

- The implementation of specific national regulations governing forensic DNA profiling and databasing for forensic purposes, and striving for an international harmonisation and implementation of international standards, especially as cross-border searches of national databases are increased.
- The implementation of high quality standards and stricter monitoring of DNA profiling and databasing practices, in order to reduce breaches of privacy regulations and to prevent miscarriages of justice due to errors in DNA profiling.
- To actively initiate and support an increase in transparency and a broad debate about DNA profiling, databasing and whole genome sequencing for forensic purposes. These debates should address scientific soundness, governance and oversight and must not stay confined to professional experts; they should also seek civic engagement. Such broader discussions will also contribute to enhancing public trust in forensic practices, if a (national) consensus can be achieved on how a fair balance can be struck between the public interest in efficient criminal investigation on the one hand, and individual civil rights and liberties on the other hand (Prainsack, Hindmarsh 2010).

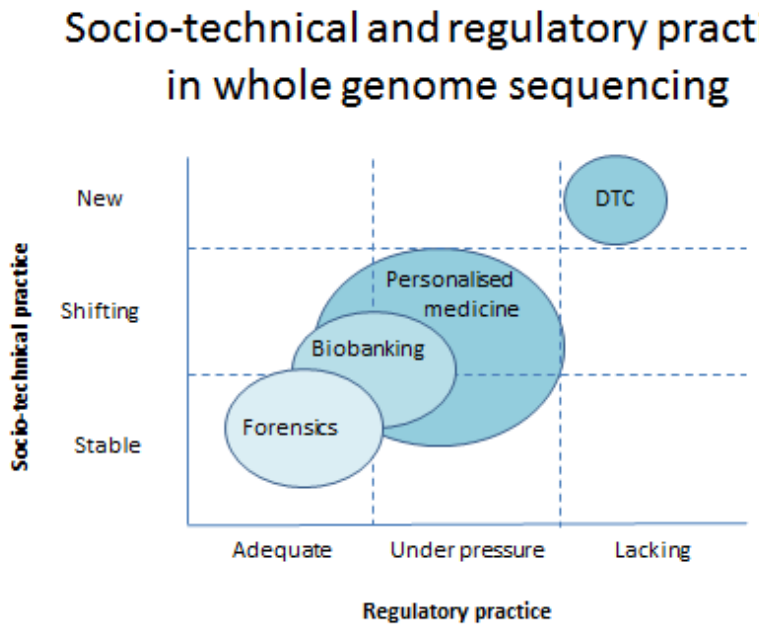
Summary of European governance challenges in whole genome sequencing

Figure 3 summarises the reflections on shifts in sociotechnical practices and implications for the current regulatory scheme. Most relevant is the impact of whole genome sequencing in research and biobanking as well as in health care and personalised medicine: in these fields, whole genome sequencing is already established, or it will do so in the coming decade, and existing governance frameworks are increasingly put under pressure. The need to modernise existing governance models comes on top of the prevalent situation that the regulatory landscape and the existing governance practices are diverse, patchy and internationally not harmonised. The current variety in regulatory approaches, public debate and philosophical positions pertaining to genome-wide sequencing results from different operational and political traditions. That is, there are different established practices and understandings of "how things are done", and differences in the general concepts and values of the social order (Prainsack, Hindmarsh 2010), e. g. the balance of libertarian and communitarian values and norms.

In order to address these governance challenges, the following is recommended:

- To raise the awareness of the relevant issues and challenges of whole genome sequencing.
- To actively initiate and support a broad debate about whole genome sequencing for different purposes, which must not stay confined to professional experts, but should also seek civic engagement. Such broader discussions will also contribute to enhancing public trust in research, medical and forensic practices, if a (national) consensus can be achieved on how a fair balance can be struck between the public interest in knowledge generation through research, high quality health care and efficient criminal investigation on the one hand, and individual civil rights and liberties on the other hand (Prainsack, Hindmarsh 2010).
- To implement high quality standards and stricter monitoring of genome-wide approaches and databasing practices in research, health care and forensics.
- To implement specific national regulations (also) governing whole genome sequencing and databasing in the context of research, biobanks, health care and criminal investigations. These national regulations should take the nationally established practices and understandings of "how things are done" into account and be based on the general concepts and values of the social order in the respective country. In addition, an international harmonisation and implementation of international regulations at the EU level should be strived for.

Figure 3: Shifts in sociotechnical practices and implications for the current regulatory scheme



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4. ENGINEERING OF THE BRAIN: NEUROMODULATION AND REGULATION

Ira van Keulen & Mirjam Schuijff[1]

Summary

We may distinguish between reverse and forward engineering of the brain. While reverse engineering of the brain is illustrative of the bio-engineering megatrend of 'technology becoming biology' in its aim to mimic the brain in computer hardware, software and wetware, forward engineering of the brain is an example of 'biology becoming technology' because its aim is to develop tools to support, manipulate or enhance the working of the human brain, such that it is increasingly connected to electronic or other devices.

In this chapter we focus on neuromodulation as a specific form of forward neural engineering. Neuromodulation involves altering neural activity in order to change an individual's behaviour or cognition for medical or non-medical reasons, such as the enhancement of cognitive performance. With respect to regulatory and governance issues relating to the field of neural engineering, we believe that neuromodulation devices present many more current and pressing issues than reverse engineering practices, since most of the latter research is still confined to the laboratory. The market for neuromodulating devices is still in its infancy but has grown steadily over recent years. Further growth is predicted, especially since the medical device market is more accessible than the market for psychopharmaceuticals (as there are less stringent regulations), particularly for small companies. Additionally, disappointing research results in relation to new psychopharmaceuticals have also led large pharmaceutical corporations to broaden their activities to include neurodevices.

This chapter explores whether and how this growing market for neuromodulating devices, in particular EEG neurofeedback, transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS), poses new regulatory and governance challenges to the European Union. Specifically, we focus on the question of whether the European regulation framework (the Medical Devices Directive (MDD) and the Active Implantable Medical Devices Directive (AIMDD) and other governance frameworks adequately address:

- The safety of the users. In this regard, we look into issues of intended use as described by the manufacturer, non-medical use, the standardization of treatment protocols, and the training and certification of professional users
- The harmonization of requirements related to bringing neurodevices to the market with respect to promoting innovation and trade in this sector. Here we address in particular the harmonization of reimbursement policies.

EEG neurofeedback uses EEG equipment to give patients insight into their actual, real time brain activity, which is usually measured by three electrodes attached to the skull. The aim is to train patients to self-regulate their abnormal brain-wave patterns and thus their behaviour.

[1] Based on desk research and interviews done in 2011 in collaboration with Thomas van Zoest and Ellen Moors of the Utrecht University.

While its efficacy – except in the case of ADHD – is still disputed, EEG neurofeedback is also used as a treatment for other conditions, such as epilepsy, autism and learning disabilities. The risks, side effects and adverse events associated with EEG neurofeedback treatment range from mild (anxiety, insomnia) to severe (inducing epileptic seizures).

Transcranial magnetic stimulation (TMS) is a non-invasive technology which alters brain activity near the skull by inducing an electrical field in the brain. This electrical field, in turn, is generated by a large coil generating a magnetic field. TMS is used for research, diagnostic and treatment purposes. TMS therapy for depression has been the most widely studied, and has been shown to be effective in the treatment of severe depression that is resistant to other forms of therapy. The side effects and adverse events associated with its use are relatively rare, but include seizures and psychiatric complications such as hypomania, as well as headaches and hearing loss. TMS is also being explored for the purpose of cognitive enhancement.

Deep brain stimulation (DBS) is an invasive neuromodulation technology, in which electrodes are implanted deep in the brain. These are connected by leads to a pulse generator placed in the chest or abdomen. DBS alters brain activity and is most commonly used to treat the tremor symptoms of Parkinson's disease. The use of DBS to treat psychiatric conditions such as severe depression or obsessive compulsive disorder is also being investigated. DBS could be used for enhancement purposes, although it is not used for this purpose at present. The implantation of the DBS system requires surgery, and it can have severe side effects or lead to adverse events such as bleeding, infection or changes in perception or mood.

The regulatory issues mostly concern the non-invasive neurodevices. With respect to EEG neurofeedback systems, there are three issues: 1) a lack of clarity on the status of these systems (are they a *medical* device or not?), 2) a broad description of the intended use by manufacturers (questioning whether the performance of these systems is actually assessed for all possible medical uses), and 3) the use of these systems for non-medical purposes, such as gaming or enhancing artistic, sporting and cognitive performance (creating opportunities to bypass the MDD regulation). The regulatory issues associated with TMS primarily concern off-label use. The intended purpose of TMS devices, as described by manufacturers, allows for diagnostic or research use, but in some clinics in Europe it is being used therapeutically despite its efficacy and efficiency not yet being proven (except in the case of severe depression). The use of TMS in private clinics therefore might divert patients from currently more established therapies such as cognitive or pharmaceutical therapy.

Governance issues concern aspects which are not regulated by the EU directives but are governed by the market itself or through other institutional arrangements. Take, for example, reimbursement. In most European countries therapies based on EEG neurofeedback and TMS are not reimbursed, and while DBS is reimbursed for Parkinson's, the situation for other conditions varies between countries. European harmonization of national reimbursement policies is required to assist the growth of the market. Namely, at present it is difficult for new companies or devices to enter the market, since its potential size is unknown and the development of new medical devices and neurodevices in particular is a costly process.

Another issue is certified training. Professional associations offer training in the use of EEG neurofeedback but this is not mandatory, and there is no standard training in the use of TMS for clinicians. This situation is undesirable, as unskilled use can result in seizures or other unwanted side effects.

The final governance issue concerns protocols. There are some standard therapy protocols available for EEG neurofeedback, but not for all conditions. TMS has more standard protocols, but they are not enforced in clinical practice in the way they are in research practice, which requires the approval of a medical ethical committee. Thus, patients must choose their practitioner with great care.

Finally, our study shows it is difficult for social researchers to collect data on the exact intended use of the neurodevice or the different regulatory routes that manufacturers of neuromodulation technologies have taken in order to get a CE marking for their medical devices. The database Eudamed which contains this information only facilitates the exchange of information between the manufacturers, the Competent Authorities and the European Commission. Social scientists, journalists, patient organisations or individual citizens have no access to Eudamed. More transparency might encourage public debate – when needed – on the (questionable) entrance of a particular medical device on the European market at an early stage.

Policy recommendations

- Clarification about whether EEG neurofeedback should be seen and regulated as a non-medical device or as a medical therapeutic device
- Specification of the intended use of non-invasive neuromodulation devices as described by manufacturers to avoid off-label use and stimulate better assessment of the devices for different conditions
- Consideration of whether neurodevices used for non-medical purposes (i.e., for improving performance and gaming) should meet the same, stricter requirements as those set for their medical use
- Consideration of the lack of harmonization of national reimbursement policies in Europe, making it an even riskier endeavour for companies to develop new neurodevices, since this involves huge R&D costs with the returns highly uncertain
- More public transparency about the way in which the medical use of neuromodulating devices is regulated by making the Eudamed database publicly accessible

4.1. Introduction

Technology can be used to electronically stimulate or assist the brain and mental functioning. This is called neuromodulation. This chapter is about medical devices used in neuromodulation, in particular EEG neurofeedback, transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS), all of which are available on the European market. In fact, there is a growing market for neuromodulation devices. This chapter explores whether and how this growing market poses new regulatory and governance challenges to the European Union. Specifically, we focus on the question of whether the European Medical Devices Directives provide adequate regulation with respect to the following issues: the intended purpose of the device as described by the manufacturer, their non-medical use, reimbursement, standardization of treatment protocols, and the training and certification of professional users.

In this chapter we will focus on forward engineering of the brain and in particular on neuromodulation (and *not* on brain-computer interfaces which is a form of forward neural engineering as well). Neuromodulation refers to altering neural activity in order to change someone's behaviour or cognition for medical or other reasons such as enhancement of cognitive performance. When it comes to regulatory and governance issues, we think that in the field of neural engineering, neuromodulation devices are related to much more current and pressing issues than reverse engineering practices since most of that work is still taking place in the labs or – when it comes to brain computer interfaces – the market is still rather small. The market of neuromodulating devices is still in its infancy as well but growing much faster. It's therefore relevant to take a good look at how these new (medical) products enter the European market and what regulatory and governance issues can be identified.

In this chapter we will both address invasive (i.e. implantable) and non-invasive neuromodulation techniques. There are different kinds of neuromodulation devices which are used for different purposes. Most likely, there are still many applications to be discovered and developed. The global as well as European market for neuromodulation devices has experienced a lot of growth over the last decade, and is expected to continue to grow (Kalorama, 2011; Onopchenko, 2011; INS, 2011). That makes it worthwhile to take a closer look at the emerging market for neurodevices in the European Union. How are these devices used in clinical and research practices? Is the regulatory framework that is currently in place in Europe equipped to deal with these new technologies that can have long-lasting effects on the brain? Is the safety of patients and other consumers sufficiently guaranteed? Are there any other governance issues at stake?

There has already been – and still is – some academic and public debate about whether the regulation on neuromodulating devices such as neurodevices is stringent enough. In 2005, the European Group on Ethics (EGE) published its opinion on *Ethical Aspects of ICT Implants in the Human Body*. They had studied electrical implants in the human body and also looked at a neuromodulating device, i.e. deep brain stimulation. The EGE argued that "implantable devices for medical purposes should be regulated in the same way as drugs when the medical goal is the same. […] The EGE recommends that the European Commission should launch legislative initiatives in these areas of ICT implant applications" (EGE, 2005, p.35). Also, in the United States there has been some debate initiated by the non-governmental organisation Public Citizen. They have been criticising the process by which the US Food and Drug Administration (FDA) approves medical devices, especially neurostimulation devices (Hines *et al.*, 2010). The consumer group charges that the FDA allows lower approval standards for devices than for drugs. The lead author of the report, John Hines, states in an interview that "we don't see a justifiable reason for that distinction. Many of these devices are being used to treat disease, so it is hard to fathom why one wouldn't require the same level of rigor in approving them as is required for drugs." On the other hand, the majority of the 200 respondents of a public consultation round (with industry, regulatory bodies and so on) done by the European Commission on new medical device regulation, rejects this. They argue that adoption of a pharmaceutical-like regulation for medical devices would lead to delay and higher costs for placing new devices on the market, and would have an adverse effect on the small and medium-size enterprises which make up around 80% of the market. The business model of the medical device (including neuromodulation) market is quite different from the pharmaceutical market. Small start-ups cannot afford large, randomised, controlled trials like large pharmaceutical companies can. Patients in need of – many times a last resort – treatment by neuromodulation devices might consequently be the victim of stricter regulation. The debate about adapting the existing regulatory framework for neuromodulation and implantable devices is not settled yet. This chapter does not aim to give any definite answers to the above questions.

4.1.1 Research and structure of this chapter

The central question of this chapter is to assess devices for neuromodulation and the Medical Devices Directices to see if any regulatory and governance issues arise or the devices are adequately regulated. This chapter is based on desk research, a workshop with five experts and personal interviews with twenty experts (see 4.9 for names of the quoted experts). We include three specific kinds of neuromodulating devices: EEG neurofeedback, transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS). The research has indicated issues concerning the intended purpose of the devices, other uses than medical uses, certification of the users, standardisation of therapy protocols, reimbursement, and transparency of data on regulatory procedures and outcomes.[1]

We will continue this chapter by addressing the concept of neuromodulation (4.2). Then we look into the three devices for neuromodulation in more depth: EEG neurofeedback (4.3), transcranial magnetic stimulation (4.4) and deep brain stimulation (4.5). In section 4.6, we explore the market for neurodevices in Europe and for the three selected technologies in particular. Section 4.7 discusses the regulatory framework of devices for neuromodulation. In section 4.8, we will compare the regulatory and governance issues concerning these three devices focussing on reimbursement and training and certification. We draw up some final conclusions on possible regulatory wastelands in section 4.9.

4.2. Neuromodulation

Devices for neuromodulation (or neurodevices) can be either invasive (e.g., electrodes inside the brain) or non-invasive (e.g., magnetic stimulation of the brain from outside the skull). Some devices directly alter brain activity (e.g., the activity of a large group of neurons is suppressed or stimulated), others work indirectly (e.g., the patient has to learn to change their own brain activity based on visualizations of it). Neurodevices can be used as therapy, but also for diagnostic, research or leisure purposes. There are already many neurodevices on the market, which has grown steadily over recent years. Further growth is predicted, especially since the medical device market is more accessible than the market for psychopharmaceuticals (due to less stringent regulations), particularly for small companies. Additionally, disappointing research results in relation to new psychopharmaceuticals have also led large pharmaceutical corporations to broaden their activities to include neurodevices.

4.2.1 Introduction: Devices for neuromodulation

The term *neuromodulation* originally refers to the release of neurotransmitters that stimulate groups of neurons. Traditionally, these neurotransmitters have been stimulated or inhibited by pharmaceutical therapy in order to assist the brain to function normally again or even to augment the brain. Nowadays, neuromodulation mostly refers to therapy with *devices* that, instead of chemically, electronically stimulate or assist to stimulate the brain and mental functioning. The effects of these neuromodulating devices can be the same or even better than those of psychopharmaceuticals.

The use of neurodevices is growing, but by no means common practice yet. Most of the neuromodulating devices currently in clinical use are usually deployed as a last resort therapy, for example, for drug resistant patients. This is the case with deep brain stimulation (DBS) for Parkinson's patients as well as with transcranial magnetic stimulation (TMS) for severe depression.

[1] It is not within the scope of this study to evaluate the different regulatory routes that the three different types of neurodevices have completed in order to be able to carry a CE mark for medical devices.

Types of neuromodulation

While the term neuromodulation is relatively new, research on and practices in electronically influencing the functioning of the brain and the mind have been around for a long time. Since the 1870s, scientists have been trying to change the functioning of the brain with electrical modulation (Schwalb & Hamani, 2008). Nowadays, neuromodulation of the brain can both be pursued non-invasively and invasively. In non-invasive neuromodulation, the functioning of the brain is altered using a device that is outside of the head. In invasive neuromodulation, a device is implanted underneath the skull, in (or on) the brain. Another distinction which can be made is that some neuromodulating devices directly stimulate the brain, for example by electrical stimulation in DBS. Neuromodulation can also work indirectly, like with EEG neurofeedback by training the subject to produce a desired pattern of brain activity by presenting real time his or her brain activity. There are many different devices for neuromodulation, which can be used for different reasons: diagnostics, research, therapy or leisure purposes.

4.2.2. Neuromodulation and neurodevices: Growing market

As said, neuromodulation has been around for a while; for example, EEG neurofeedback can be traced back to the 1960s, TMS to 1985 and DBS to 1997 when it was first approved for treatment of essential tremor. But new devices and applications enter the market regularly.

Neuromodulation is part of the bigger market for neurodevices. The current market for neurodevices includes many different devices (Neurotech Industry Organisation, 2010), such as neuroprosthetics used to substitute a part of the body like cochlear or retinal implants, neuromodulation devices, neurosurgical equipment and neurosoftware such as the software for neurofeedback systems. Most devices available on the market aim to treat patients who suffer from disabling neurological conditions (Infinity Research, 2010). Examples of very successful neurodevices are cochlear implants for deaf people, neurostimulating devices for pain treatment and neurovascular interventions to prevent stroke (TWA, 2011).

The neurodevice market is a small part of the entire medical device market. There are different estimates on the worth of the entire neurodevice market (MDDI 2006). In 2006, the global market for (medical) neurodevices was estimated in various reports to be worth around $2.3 billion, $3.4 billion and $3.07 (MDDI, 2006). The market has grown steadily over the last years, and is expected to continue to grow. The International Neuromodulation Society states that the global neuromodulating market has been expected to grow to USD 4.5 billion in 2010 (INS, 2011).

There are several reasons given for the expected growth of the neurodevice market. The first is that psychopharmaceuticals are not very successful when it comes to treatment of strokes, treatment-resistant patients with (neuropathic) pain, and epilepsy (NIO, 2010). New molecular knowledge of the brain has so far not resulted in new, effective psychiatric drugs. In fact, major pharmaceutical companies are no longer investing in drugs for the central nervous system (Miller, 2010) and some are investing their funds in neuromodulation companies such as the recent investment of Pfizer in Neuronetics, an American manufacturer of TMS machines.[2] Another reason is the continued growth and diagnosis of neurological and psychiatric disorders and conditions, amongst others because of demographic shifts in the aging of the population. This means that the consuming market for neurodevices and thus the profits are expected to continue to grow. A third reason is that the regulatory regime for placing medical devices on the European market is different from pharmaceuticals.

[2] http://www.onset.com/2011/05/16/neuronetics-inc-raises-30-million-in-series-e-financing

As mentioned before, new pharmaceuticals go through more rigorous testing to obtain market authorisation, whereas the process for conformity assessment with the CE (*Conformité Européene*) mark is seen as less time consuming and less costly. One of our interviewed experts (AP from Medtronic) estimates that up to two to four years can pass before a new drug is allowed to be sold in Europe, while three to four months are necessary to introduce a medical device to the European market.

4.2.3 Focus on three types of neuromodulation

As said, in this chapter we will discuss three ways of neuromodulation in more detail. These are EEG neurofeedback, transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS). In EEG neurofeedback, someone's brain activity is recorded using EEG technology. The brain activity is displayed in real-time and used to train someone to influence her or his activity up to a desired level. In TMS, a coil, which is held above someone's head, induces a magnetic field which passes through the skull and changes the electrical activity in the brain. DBS entails the implantation of electrodes that stimulate the brain and the battery that supplies power for the stimulation. All are used to treat diseases, although EEG technology itself and TMS can also be used as diagnostic devices and EEG neurofeedback is also offered for non-medical reasons.

We choose these three different technologies in order to explore differences in neuromodulation technologies and practices. They differ in their invasiveness and involve different manufacturing, research and clinical practices. There are big and small manufacturers, patients who seek treatment and consumers who seek entertainment, neurosurgeons or psychologists offering treatment, and so on. For example, EEG neurofeedback, which is a form of indirect neuromodulation, can be used for both diagnostic treatment and non-medical purposes such as enhancement or gaming. Transcranial magnetic stimulation is a form of direct, non-invasive neuromodulation. It can be used for research, diagnostics and therapy. Deep brain stimulation is an invasive method of neuromodulation which is used as a last resort treatment for patients with Parkinson's and other diseases. As a consequence of these differences, the three devices are classified differently according to the Medical Device Directives.

4.3. EEG neurofeedback

EEG neurofeedback uses EEG equipment to give patients insight into their actual, real-time brain activity, which is usually measured by three electrodes attached to the skull. The aim is to train patients to self-regulate their abnormal brain-wave patterns and thus their behaviour. While its efficacy – except in the case of ADHD – is still disputed, EEG neurofeedback is also used as a treatment for other conditions, such as epilepsy, autism and learning disabilities. The risks and adverse events associated with EEG neurofeedback treatment range from mild (anxiety, insomnia) to severe (induced epileptic seizures). The latter rarely occurs if the device is used by trained personnel. EEG neurofeedback is also offered for non-medical purposes, including gaming and improving athletic abilities. It is not expected that the technology used in EEG neurofeedback will change significantly, with the possible exception of the development of a new type of recording electrode, the so-called 'dry electrode', which is more user-friendly.

In this section, we focus on EEG neurofeedback, which can be loosely explained as a mental training or operant conditioning based on neuro-imaging technology.

4.3.1 Introduction

Electroencephalography (EEG) was developed by Hans Berger in the early 1930s, although he already published the principle of measuring the electrical activity of the brain in 1929. He also described certain frequencies of brain waves that characterise certain modes of awareness (Van As *et al.*, 2010). With EEG, it is possible to record the different brain waves that someone has in different parts of his or her brain. By putting the EEG electrodes on the head, only the brain activity near the scalp is recorded. EEG recordings are used for clinical (e.g. testing for epilepsy) as well as research purposes.

The recordings of the different brain waves also play a role in EEG neurofeedback, which was developed in the 1960s (Van As *et al.*, 2010, p.42). It is not exactly known how EEG neurofeedback works (Van As *et al.*, 2010, p.45). EEG neurofeedback uses EEG recording to train patients to (self-)adjust abnormal patterns of brain waves claimed to be characteristic of certain diseases and conditions. The term 'neurofeedback' in EEG neurofeedback refers to the real-time auditory or visual feedback of the brain waves.

In EEG neurofeedback, first a *quantative* EEG (or qEEG) is made using approximately twenty electrodes. This results in a map of the activity of the different brain waves in each area of the brain. The qEEG is compared with standard or normal distributions of brain activity across the brain to find the locations with abnormal brain waves. In EEG neurofeedback, people are often treated on the basis of their qEEG and not on the basis of a diagnosed condition or symptoms (Van As *et al.*, 2010, p.44). For example, some studies have shown that forms of ADHD are characterised by an abundance of slow brainwaves and a diminished quantity of fast wave activity (Butnik, 2005). By doing a qEEG, the sites and brain waves that need to be trained during the sessions are identified. Treatment is dependent on the patient's qEEG and is therefore patient specific.

In a typical EEG neurofeedback session, a patient is trained to adjust his or her abnormal brain wave patterns. It is a therapy which requires active participation of the patient who has to self-regulate relaxation and his or her brain activity. The brain wave patterns are recorded using (mostly three) electrodes and is presented in real-time to the patient. For example, if the brain activity is too high, then a bar might be shown on a computer screen that is bigger than the bar displaying optimal brain activity. If the activity reduces, the bar representing the patient's brain activity will become smaller. A clinician might give the patient (cognitive) exercises, coach him or give additional feedback to help the patient (Hammond, 2006, p.28).

4.3.2 Technology used in EEG neurofeedback

EEG neurofeedback is based on EEG technology and an interface that presents the recorded brain activity to the patient in an intuitive way (instead of the recordings themselves), for example by way of a crackling fire or a moving airplane. The EEG technology consists of a machine that records the different brain signals and the electrodes placed on the scalp. The electrodes can be connected to the device by cables or they can be wireless. The electrodes are usually so-called wet electrodes, which means that a gel has to be used when they are placed on the scalp to promote conduction. There are efforts to develop reliable dry electrodes[3], which will not require the gel, but in most cases wet electrodes are still used. For the auditory or visual feedback representing the brain waves, special software is used that transforms the recorded brain signals into feedback for the patient. If the patient's brain waves match the desired level, the software might, for example, play a favourite song or video undistorted, while it plays distorted when the activity is not matching the optimal level.

[3] At the moment dry electrodes are only able to reliably measure alpha waves.

However, one of our interviewees believes that the feedback should be presented in a straightforward manner, using videos or music only from time to time as a secondary reward. Presenting the feedback in a straightforward manner stimulates the learning process of the patient. Presenting music or even video games might be entertaining, but it does not stimulate the learning process (Sherlin *et al.*, in press).

In the future, EEG neurofeedback might use dry electrodes more often, if they are able to reliably measure other brain waves than alpha waves as well. When it comes to the basics of the EEG technology, no fundamental changes are expected or wished for. The interviewed experts expect little progress in the EEG machinery itself. It was said that manufacturers focus their R&D on improving the quality of the recorded brain activity, the ease with which the system can be used, and the interfaces for the patient and clinician.

Other forms of neurofeedback are being developed as well, like neurofeedback by use of another brain imaging technology such as functional magnetic resonance imaging (fMRI). fMRI is already used in studies on neurofeedback (Johnston *et al.*, 2010), although the costs of fMRI equipment might prevent it from becoming widely offered in clinical practice. So far it has been mostly used for research purposes, to study which brain areas can be activated under what circumstances (interview JB). Advantages of fMRI neurofeedback in comparison to EEG neurofeedback are: A better spatial resolution of the imaging technique which allows feedback on and training of highly specific cognitive and emotional functions (like pain and anxiety) involving specific and deeper lying brain areas (Goebel, 2011). fMRI neurofeedback will not be discussed here further, as it is outside the scope of this study.

4.3.3 Applications, efficacy and risks

A lot of research is still being done on the efficacy of EEG neurofeedback for various diseases and conditions. Examples are ADHD/ADD (Arns *et al.*, 2009), epilepsy, autism, learning disabilities and insomnia (Hammond, 2006), but also anxiety and addiction (Angelakis *et al.*, 2007). To treat patients, more than one session is required. Treatment of anxiety might take as little as fifteen sessions, while the treatment of ADHD or learning disabilities might need forty to fifty sessions (Hammond, 2006, 480; Arns *et al.*, 2009).

Efficacy

So far, for most indications, there is no sound body of scientific literature describing studies that prove efficacy or efficiency of the therapy (Van As *et al.*, 2010; Angelakis *et al.*, 2007; Hammond, 2007). The treatment of ADHD by EEG neurofeedback is the one indication for which the empirical evidence is closest to scientifically robust (Sherlin *et al.*, 2010; Arns *et al.*, 2009; Gevensleben *et al.*, 2009). The efficacy of the technology of the EEG neurofeedback system itself (i.e. performance) to measure brain activity and offer feedback in some form to the patient or consumer should be assessed as an essential requirement of the CE marking process.

For ADHD, the evidence for the applications of neurofeedback is often critiqued for methodological reasons (no control group, not enough participants, and so on) and have not always been replicated (interview JB). There has been some randomised clinical trials recently. In a study by Lansbergen *et al.* (2011), both the treatment group and the control group in a randomised controlled trial of EEG neurofeedback treatment for ADHD improved (although the treatment group improved a bit more and the results lasted longer).[4]

[4] This study has been critiqued for using unconventional neurofeedback protocols and a small sample size making generalizations of the results problematic (interview MA).

And in a study by Gevensleben *et al.* (2009) 50% of the children with ADHD were responders with on average 25% improvement on behavioural rating scales. In this study the improvements in the neurofeedback group were superior to those in the control group. Despite the lack of scientifically robust evidence of efficacy, except for ADHD, there are clinics offering EEG neurofeedback as a treatment for the abovementioned diseases or conditions.

Side effects and adverse events

There are side-effects and adverse events possible during the treatment with EEG neurofeedback. Most side-effects mentioned in the academic literature are mild (interview JB). Patients can feel tired, have a headache or feel anxious during or after the session. Also, difficulty falling asleep afterwards has been reported. If patients report the side-effects to the clinician, often the sessions can be altered a bit to make the side-effects decrease or disappear (Hammond, 2006, p.32). A possible adverse effect is that EEG neurofeedback can have no effect at all on the symptoms or even increase them (Hammond, 2006, p.32). This can happen if the brain activity is accidentally trained wrongly. Furthermore, if neurofeedback is administered wrongly or by an untrained professional, epileptic seizures might be induced (Stockdale & Hoffmann, 2001; interview MA). However, there are no scientifically robust data on the occurrence of seizures; literature on it is based on anecdotal evidence only. There has recently been one case reported on impaired memory and disorientation with a patient who was treated with neurofeedback (Todder *et al.*, 2010). In general, it is better to have a qEEG made before and after treatment, to ensure not only that adverse reactions are detected, but also that the appropriate treatment protocol is selected (Striefel, 2002; Hammond, 2001, Stockdale & Hoffman, 2001).

Non-medical use

However, EEG neurofeedback is not only offered as a treatment for medical conditions; it is also offered for non-medical purposes, such as "the improvement of mental functioning and the awareness of brain states"[5]. Neurofeedback is also claimed to enhance athletic performance (specifically in golf and swimming), as well as to be effective for artistic gifts, and emotional and life problems[6]. Not much scientifically robust research has been done on the effects of EEG neurofeedback for enhancing artistic, sports or cognitive performance of 'healthy' people. A clear association with EEG neurofeedback and enhanced performance has yet to be established (Vernon, 2005). Yet, it is offered for these and other reasons.

Beside the use of EEG neurofeedback in clinics as a treatment for medical diseases and conditions and for spiritual or enhancement purposes, there is one more type of application. Similar – but usually simpler – EEG technology is used in games as a brain machine interface. The American company Neurosky is an important manufacturer of these systems which they sell – amongst others – to gaming companies. For example, the MindFlex game uses a head set that is claimed to measure whether you focus. The recorded concentration is essential for the game as it turns on a fan, which blows a ball in the air that you have to manoeuvre around. Supposedly, if your ball floats, you are concentrating well enough. If it does not, you have to try harder. However, with these EEG neurofeedback systems – many times with dry electrodes – it is claimed by some researchers that instead of brain activity, muscle contraction in the forehead is measured. However, in the future, brain machine interfaces based on EEG neurofeedback for gaming or other entertainment purposes might well develop into reliable systems.

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[5] According to Brainmaster, http://www/brainmaster.com# accessed on 070811.

[6] According to NeuroCare clinic, http://www.neurocare.nl/nl/node/43 accessed on 080811. English: http://www.neurocare.nl/en/node71

4.4. Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a non-invasive technology which alters brain activity near the skull by inducing an electrical field in the brain. This electrical field, in turn, is generated by a large coil generating a magnetic field. TMS is used for research, diagnostic and treatment purposes. TMS therapy for depression has been the most widely studied and shown to be effective in the treatment of severe depression that is resistant to other forms of therapy. Side effects and adverse events are relatively rare, but include seizures and psychiatric complications such as hypomania, as well as headaches and hearing loss. TMS is also being explored for the purpose of cognitive enhancement. The main challenges relating to TMS do not lie in the further development of the equipment but in the different therapeutic applications and their protocols.

This section focuses on a specific non-invasive neuromodulation device: transcranial magnetic stimulation (TMS). TMS is used for different purposes: research (e.g. producing virtual lesions allowing to temporarily inactivate a brain area in order to check the behavioural consequences), diagnostics (e.g. testing nerve conduction and velocity as part of the diagnosis of neurodegenerative diseases) and therapy (e.g. for depression treatment of patients who do not benefit from antidepressants).

4.4.1 Introduction

Transcranial magnetic stimulation appeared in the 1980s (cf. Lipton and Pearlman, 2010; The Health Council in the Netherlands (HCN) (Gezondheidsraad), 2008; Wassermann 1998). For many years, TMS had an experimental status and developed slowly in specialised laboratories, because more knowledge on clinical neurophysiology was required. Like with many other neuromodulating technologies such as deep brain stimulation, and even though TMS technology has been in use since the 1980s, the exact mechanism is still unknown (HCN, 2008; Helmich *et al.* 2004). Researcher AS agrees that it is still not known what TMS does chemically or metabolically on the neural level.

4.4.2 Technology used in transcranial magnetic stimulation

TMS is a non-invasive stimulation technique that uses a small coil of wire through which a powerful and rapidly changing current passes. This coil generates an electromagnetic field. When the coil is held close to the head, the magnetic field is able to reach the brain through the skull and induces an electrical field in the exterior areas of the brain, for the electromagnetic field penetrates only one to three centimetres in the skull. This means that current TMS technology is able to stimulate the human cortex, spinal roots and peripheral nerves but not the deep brain regions which are usually more interesting for clinical applications (interview AS). Its direct effects are thus limited to superficial brain areas.

It is known that the electrical field can decrease or increase the excitement of neurons in the brain, depending on the parameters of the coil (Lipton and Pearlman, 2010; Rossi *et al.* 2009; HCN, 2008; Helmich et al. 2004; Wassermann, 1998). Because the field is not electrical, pain receptors are not triggered and patients do not feel the stimulus. However, the patient may feel muscle contractions on the head (Helmich *et al.*, 2004; Wassermann, 1998). The coils generally have an "8" shape; the magnetic field is generated where the circles meet.

New developments in the technology of TMS appear to focus on the coils (Rossi *et al.* 2009). Most people in the field of TMS hope for coils that are more focal[7], stronger and able to reach deeper brain areas. On experiments with larger coils, these generate stronger electromagnetic fields and are able to penetrate deeper into the brain. Due to their size, these coils are less focal. In order to avoid the overheating of coils, water, oil and air cooling is implemented by several manufacturers. Newer theoretical varieties of the coils are 'H' coils and circular crown coils. Coils intended to stimulate deeper regions of the brain are larger than the current coils, have a lower decay of the stimulus and are less focussed. Some of the "H" shaped coils have a higher intensity and frequency than regular coils, and some of these coils are already on the European market (Rossi *et al.* 2009). Expert MA en AS indicate that these 'H' coils are not revolutionary and have generated only temporarily the attention of the field. The Californian company Neostim is developing multi-coil devices to reach and modulate deeper brain regions, i.e. up to six centimetres below the surface instead of the 3.5 centimetres regular coils can reach.[8] The downside of this is that everything in between the deeper-lying region and the coil is stimulated as well (interview AS).

Most of the experts interviewed for this case-study, however, expect more developments in different therapeutic applications of TMS and their accompanying protocols than in the TMS technology itself. We will get back to this in the next section.

4.4.3 Applications, efficacy and risks

There are different ways to determine where to stimulate exactly with TMS. One common method is the motor threshold. The coil is used to stimulate a specific area of the motor cortex that induces movements in the fingers. When the individual finger area of the subject is determined then the clinician or researcher tries and estimates the presence of other areas from there.[9] This is not a very accurate way of determining where to stimulate. Nowadays, the golden standard according to researcher AS is to employ TMS neuronavigation, which uses, for example, an MRI scan of the individual and infrared cameras to help to track the motion of the head and the TMS coil in real-time. That way, the coil can be positioned exactly in the millimetre range of the area you want to excite or inhibit. Other standards are less precise; the question then pops up whether the most optimal point for the best therapeutic results is stimulated. However, the devices and software needed for TMS neuronavigation can be quite expensive for commercial clinics; that's why TMS neuronavigation is mostly used in academic or clinical research.

Also, the intensity needed for optimal stimulation is different per person. Stimulation protocols often use percentages of the stimulation needed to excite the earlier mentioned motor threshold (Rossi *et al.*, 2009). The protocols presented in Rossi et al. are, also according to some of the interviewed experts, more or less 'standard protocols', because they are the result of a consensus conference among a very large group of scientists in the field of TMS.

TMS is applied in pulses. If TMS pulses are repeated, they can decrease or increase cortical excitability which can either last shorter or longer afterwards ('off-line effect'). The decrease or increase and its off-line prolongation depend on the parameters of stimulation, for example: variations in frequency, intensity, train duration and inter-train interval times (Lipton and Pearlman, 2010; Rossi *et al.*, 2009).

[7] The most focal coils today stimulate in the vicinity of centimetres, stimulating hundreds of thousands of neurons at the same time.

[8] www.neostim.com/neostim-innovation.html

[9] For example, from this spot it is supposed to be five or six centimetres to the dorsolateral prefrontal cortex that is stimulated if TMS is used for the treatment of depression.

TMS Therapy

There are different types of TMS therapy. The names depend on the pulses that are applied. There is single-pulse TMS (sTMS), applying one stimulus at a time. Another type of TMS refers to pulses in trains, called repetitive TMS (rTMS). The most used protocols of this rTMS type are the Theta Burst Protocols (TBS) developed in 2005. Interviewee AS indicates that new rTMS protocols like the TBS create a much stronger and long-lasting inhibition effect. Ideally, the protocol has to be personalised because of inter-individual differences. Some patients react differently than others and show different patterns. The results of the magnetic stimulation of the brain with TMS are temporary. Multiple sessions of about twenty minutes are needed to create a longer lasting, although not permanent, effect. Maintenance sessions may prolong the effect.

The amount of (clinical) studies on rTMS has increased steadily the last few years. Single pulse TMS has been studied as a treatment for medical indications which do not encompass gross changes in brain structure, for example tinnitus and migraine. Repetitive TMS has been studied for a broader range of indications, such as neurologic and psychiatric disorders. Lipton and Pearlman summarise the indications for which sTMS and rTMS have been studied: "Psychiatric disorders: depression, acute mania, bipolar disease, panic disorder, schizophrenia, post-traumatic stress disorder, and substance abuse. Neurologic disorders: Parkinson's disease, dystonia, tinnitus, epilepsy, stroke, as well as a variety of pain syndromes including neuropathic pain and migraine" (Lipton and Pearlman, 2010, p. 205). Although all these indications have been studied, so far, robust scientific evidence is lacking for most of these indications. Only for severe or treatment-resistant depression the efficacy of rTMS is more or less proven (Slotema *et al.,* 2010; Schutter, 2010; Schutter, 2009; Lam *et al.*, 2008). TMS for Parkinson's disease and epilepsy has been object of study for a longer period of time. TMS seems to be promising for these medical indications but there is still no academic consensus on the robustness of the scientific evidence for most of these indications (cf. Lipton and Pearlman, 2010; Rossi *et al.* 2009; HCN, 2008). Another promising use of TMS might be stroke rehabilitation: promising because stroke is a not a complex psychiatric or neurological disorder of which we still not understand the underlying neurobiological mechanisms, but rather a 'simple' injury (with considerable effects on the patient of course). Stroke is a brain suffering from a lesion where neurons have died, resulting in a 'black hole'. Many patients recover spontaneously from a stroke because the plasticity of the brain is so large that other brain areas can take over functions. TMS can support this recovery process by suppressing parts of the healthy brain which stand in the way of full and fast recovery (interview AS[10]).

Per possible indication, it is important to study the intensity and frequency of the stimulation. Also, finding the optimal spot for the best therapeutic results of TMS for a particular patient is important. That's why scientific findings about the mechanisms of the (individual) brain will definitely favourably influence the research on clinical TMS applications (AS). It is important that a clinician knows the exact position and can reliably stimulate that spot in the successive therapy sessions (MvB).

The main advantages of rTMS are that it is a relatively easy to employ, non-invasive, painless and relatively safe technology. In comparison to electroconvulsive therapy (ECT) for depression, rTMS is more comfortable: patients do not need to be given a general anaesthetic and do not experience memory disturbances. However, whether rTMS is as effective as ECT still has to be proven.

[10] In 2010, the expert received a starting grand from the European Research Council for his research on TMS and strokes.

The biggest expectations of rTMS are in the realm of new medical indications. Or as interviewee DA states: "It is not in changing the technology, it's in learning how to apply it. Figuring out which protocols to use in which situation and what their actual physiological effects are, can be one major step forward. The holy grail would be to develop protocols to help people for instance to regain brain function after stroke or to help them with anxiety disorders."

Side effects and adverse events

The Health Council in the Netherlands conducted a meta-analysis of TMS applications in 2008 and concluded that if one uses TMS for the current indications and according to the current protocols, the technology can be considered as a safe technology (HCN, 2008). Still, single pulse TMS, paired pulse TMS and repetitive TMS can have several adverse effects. Loo (*et al.*, 2008) elaborates on several safety issues (induced currents in electrical circuits, histotoxicity[11], electromagnetic field exposure, and safety in pregnancy), adverse effects (headache, effects on hearing, pain, and psychiatric complications), accidental seizures and induced hypomania. They state that it is possible to screen patients in order to reduce the prevalence of the more serious adverse events and conclude that rTMS is a safe technology, when applied within the recommended guidelines. Lipton and Pearlman (2010, p. 210) also conclude that "TMS has a long track record of safety in a broad range of applications, both diagnostic and therapeutic. Years of research, investigational applications, and clinical use has provided extensive patient exposure demonstrating high levels of both safety and tolerability. These studies show that rTMS and sTMS administration are safe for the treatment of a variety of neurological and psychiatric disorders." The interviewed experts underline the conclusions of their colleagues. For example, DA concludes: "The incidence of side-effects happening with TMS is very, very low. We are talking tenths of a per cent." And when it comes to seizures, the most serious possible side effect of TMS, AS mentions that since 1985 only about seventeen cases are reported where people had a seizure due to TMS.

However, there still appears to be some doubt about the therapeutic use of TMS for specific groups of patients. D'Agati (*et al.* 2010) investigated rTMS for depression in adolescents. He recommends further research on the efficacy and safety of rTMS in this specific group of patients. The patients responded well, but there were not enough data to draw firm conclusions about the benefit of TMS therapy for this specific group.

Non-medical use

Next to therapeutic applications, there is a new line of research with TMS which is becoming very popular. It aims to enhance different brain and cognitive functions in healthy persons. In 2010, the TMS summer school in London was dedicated to "brain stimulation to enhance sensory, motor and cognitive functions". Interviewee AS mentions the research of Gregor Thut in Glasgow in this respect. Thut is using a certain frequency to entrain an oscillation pattern (i.e. rhythmic or repetitive neural activity) in the brain. If you decode the natural oscillation pattern of a certain area responsible for having visual detection or any other cognitive function, then you can externally use TMS to bring the brain in that same rhythm, thus having beneficial effects for enhancing visual of cognitive functions in healthy subjects (Thut et al., 2011).

[11] Histotoxicity means TMS can be poisonous to tissue.

4.5. Deep brain stimulation

Deep brain stimulation (DBS) is an invasive neuromodulation technology in which electrodes are implanted deep in the brain. These are connected by leads to a pulse generator placed in the chest or abdomen. DBS alters brain activity and is most commonly used to treat the tremor symptoms of Parkinson's disease. The use of DBS to treat psychiatric conditions such as severe depression or obsessive compulsive disorder is also being investigated. DBS could be used for enhancement purposes, although it is not used for this purpose at present. The implantation of the DBS system requires surgery, and it can have severe side effects or lead to adverse events such as bleeding, infection or changes in perception or mood. Technological improvements – for example, thinner leads, more durable batteries, a closed-loop system to adjust the stimulation in real-time – are expected in the future, as well as new therapeutic applications.

In this section, deep brain stimulation (DBS) will be discussed. DBS has sometimes colloquially been described as a pacemaker for the brain and it is most commonly used to treat the symptoms of Parkinson's disease and other neurological diseases with tremor like symptoms like dystonia.

4.5.1 Introduction

DBS treats symptoms and does not cure diseases.[12] How DBS – or any of the other techniques that stimulate the brain electrically – works or why it can be beneficial for neurological disorders is not yet known. It is thought that it controls the release of neurotransmitters (Albert *et al.*, 2009, p.1044). However, DBS could also work by inducing "reversible lesions" by the electrical field (Appleby *et al.*, 2007, p.1722). Although there are many hypotheses about the exact effect of the stimulation on the release of neurotransmitters, it is not exactly known yet.

The electrical stimulation of DBS works on the targeted brain area. However, since the brain is vastly interconnected, the stimulation can also have effects in other parts of the brain. The electrical stimulation itself does not directly affect other parts of the body. Drugs used to treat psychiatric or neurological diseases are primarily ingested and, in order to bridge the blood-brain barrier often in rather high doses, reach not only the parts of the brain they are supposed to work, but also other parts of the brain and the body (interview WE). This widespread circulation of medication through the body can be a reason to favour DBS over medication.

4.5.2 Technology used in deep brain stimulation

Deep brain stimulation is a technology for invasive neuromodulation. It stimulates the targeted nerve cells electrically. It consists of three parts: one or two leads (the electrodes that stimulate the brain), a battery or pulse generator that generates the pulses for the stimulation and extension(s) that connect the lead(s) to the battery (Albert *et al.*, 2009, 1048; Denys, 2009; NINDS). The entire device is implanted. The electrodes are implanted in the brain; the battery is either placed under the clavicle or in the abdomen, and the connecting leads are implanted.

[12] It has been shown that even after seven years of treatment with DBS, depression will come back as you switch off the stimulator (personal communication Thomas Schaepfer).

Once the DBS system is implanted, the system has to be programmed to find the correct stimulation settings. For this, clinicians use programmers to control the DBS system. These can read and change the settings of the implanted device using telemetry. Often, several sessions are needed to find the optimal stimulation settings (Schwalb & Hamani, 2008, p.9). Patients receive a patient controller, which allows them to switch the neurostimulator off or on and sometimes even change the settings (Schwalb & Hamani, 2008, p.9; Medtronic, 2010a[13], p.26). This can be useful, for example when the DBS system accidentally switches off because of electromagnetic interference (Medtronic, 2010a).

There is a lot of technological progress made and expected in the field of DBS. There are various types of improvement of the current technology possible. For instance, having a DBS system requires many follow-up visits to the doctor to find and maintain proper settings of the technology and doses of additional medication. The frequency of these visits might be reduced if the procedures for adjusting and programming the stimulation settings are made easier, comparable to other neurostimulators, like spinal cord stimulators (Schwalb & Hanami, 2008, p.9). A better understanding of what the most responsive symptoms or patients for DBS treatment are, as well as the corresponding area to be targeted in the brain, might also help in reducing the time needed to find the optimal settings after the surgery (Schwalb & Hamani, 2008, p.9). The development of more durable leads can be an improvement for the patients' daily lives (Bronstein *et al.*, 2006), as patients now are warned to avoid activities that "may put undue stress on the implanted components of your DBS System. Activities that include sudden, excessive, or repetitive bending can cause component fracture or dislodgement" (Medtronic, 2010a, p.49). Some interviewed experts also think that future leads might be thinner as well as more durable, or have a different design that allows for different stimulation (VV, WE).

Technical improvements are foreseen in the life-expectancy of the batteries and in rechargeable batteries. Currently, both Medtronic and St. Jude Medical – the two companies that already have DBS systems on the European market – offer rechargeable as well as non-rechargeable systems. There are conditions that require high stimulation settings, like the treatment of obsessive compulsive disorder, which means that the battery will be empty quite fast. An empty battery has to be replaced in a surgical procedure, as batteries are implanted. Rechargeable batteries, which last much longer before they wear out and need replacement, might seem like a good solution. Recharging the battery needs to de done a couple of times a week, and can take up to four hours (Medtronic, 2010a, p.60). Unlike non-rechargeable batteries, this requires consistent compliance from the patient. Recharging the battery is by some patients seen as a constant reminder of their condition, which can be negatively experienced (interview VV). Rechargeable batteries that need less frequent recharging or greatly reduced recharging time will be avenues for further exploration.

Another future development might be that DBS technology will be combined with medication, resulting in some sort of drug delivery system. The system will measure when and how much of the drug need to be released. The drug will be released at the targeted site instead of being ingested orally. Currently, almost all patients have a combination of DBS and drug therapy to be maximally effective in treating the condition of the patient. A combination of DBS with a drug delivery system could be used for the treatment of Parkinson's disease, for example.

[13] Your Medtronic Deep Brain Stimulation Therapy. Patient Therapy Guide

Another important research area is closed-loop DBS therapy. In a closed-loop system, feedback from the stimulation site would be processed by the system in order to tailor the stimulation in real-time, either increasing or decreasing it. This could be used for conditions that are episodic and therefore do not require continuous stimulation, such as epilepsy. Both depending on a closed-loop system and a combined stimulation and drug delivery system might shift the risk of failure towards the technology (for instance by delivering wrong or suboptimal stimulation because of a mistaken software decision) according to interviewee WE. This, of course, raises the question of liability when such highly complex, autonomous medical systems come onto the market. This could be an obstacle for realising such DBS systems.

4.5.3 Applications and risks

By 2010, over 75,000 people worldwide had received a DBS system (Shah *et al.*, 2010). In Europe, DBS is currently mainly used for the treatment of the symptoms of Parkinson's disease, dystonia and essential tremor. Yet, Medtronic – the largest manufacturer of DBS technology – also has a CE marked system for the treatment of refractory epilepsy[14] and for obsessive compulsive disorder[15] (see table 4 in 4.7). DBS has also been used for the treatment of treatment resistant depression and Tourette's syndrome in Europe. These and other neurological and psychiatric indications are still considered to be experimental.

Regarding the treatment of Parkinson's disease, one interviewee, VV, sees a trend of implanting the DBS system earlier, although it remains a last resort treatment. According to VV, this has the benefit that the patient's physical condition improves much earlier in the disease, which might mean that they can continue to work. This is important for the quality of life for the patient. She emphasises that DBS should always remain a last resort treatment. Interviewee MD thinks that implantation as-early-as-possible is an important direction in the research on and treatment of Parkinson's disease. According to him, there is an economic incentive to use DBS earlier in the disease and for more patients: patients' symptoms are relieved and fewer drugs are needed – which could mean that they can work longer or live longer, more fulfilling lives.

In the future, DBS might also be used for hypertension, chronic pain, obesity and eating disorders such as anorexia nervosa (Schwalb & Hamani, 2008) or Huntington's (interview VV). One of our interviewees, MD, thinks that for future psychiatric indications "the sky is the limit. People are looking into anorexia nervosa, obesity, schizophrenia, gambling addictions, you name it". He even thinks DBS will prove useful for more conditions than currently expected. However, he also says that if a drug or gene therapy will be developed that can actually cure Parkinson's or depression – instead of providing relief of the symptoms – this will be chosen over DBS. In that sense, DBS can be seen as more of a transitional technology.

[14] Medtronic, News Release 'Medtronic Receives European CE Mark Approval for Deep Brain Stimulation Therapy for Refractory Epilepsy', 16 September 2010.

[15] Medtronic, News Release 'World's First Deep Brain Stimulation Device Approved For Treatment of Psychiatric Condition in Europe', 14 July 2009.

Side effects and adverse events

A DBS system is implanted during a surgical procedure, which includes implanting the lead(s) in a carefully selected brain area via a route through the brain tissue that has been planned using brain imaging. Like any surgery, there are risks to implanting a DBS system. These include infection, seizures and bleeding, and can be serious or even lethal (Synofzik & Schlaepfer, 2011; Medtronic[16]). Once implanted, a patient can experience short-term side-effects such as effects on his or her mood, like elevation or sadness. Long-term side effects include depression and suicidality[17], cognitive impairments (for example trouble with speaking), maladjustment after successful treatment or severe disappointment in case of unsuccessful (last resort) treatment. Some of the side-effects might be reduced by different settings of the device, but others can be a (permanent) consequence of the electrical stimulation. Marital problems, arising from the sudden change in the health of the chronically ill partner, are also not uncommon. Long-term stimulation might change neural networks in the brain. This means that DBS therapy might not be as reversible as it is considered to be. In any case, the procedure is psychologically irreversible – the disappointment of the failure of what is often a last resort treatment or conflicts with a partner will not go away once the stimulation has been switched off (Synofzik & Schlaepfer, 2011). The formation of scar tissue in the brain over time can also be a result of the procedure when the lead is not entirely 'fixed' in the brain but can move around a little bit. This can result in brain lesions (interview WE). Furthermore, there is a possibility of electromagnetic interference from other devices, so patients have to be careful around certain types of equipment (e.g. security gates in airports or theft detectors in stores) in their daily lives.[18] According to interviewees VV, up to 30 per cent to 40 per cent of all Parkinson's patients who have received a DBS device (in the subthalamus, a specific brain area) experience some level of side-effects. Other interviewees are more positive and state that 20 per cent to 30 per cent (MD) or even lower 10 per cent (AP) experience side-effects. But then again, psychopharmaca can also have significant side effects; according to interviewee VV, DBS has been disproportionally criticised on its adverse events.

[16] See for example: http://professional.medtronic.com/products/activa-pc-deep-brain-neurostimulator/indications-safety-and-warnings/index.htm or http://professional.medtronic.com/wcm/groups/mdtcom_sg/@mdt/@neuro/documents/documents/dbs-mv-ifp-add.pdf page 8

[17] Patients who are treated for OCD or depression might not become depressed as a result of unsuccessful treatment (they already could have been or were), but they can become suicidal. However, both depression and suicidal tendencies are not limited to the treatment of psychiatric conditions.

[18] http://professional.medtronic.com/wcm/groups/mdtcom_sg/@mdt/@neuro/documents/documents/dbs-ifp.pdf

TABLE 1: Adverse events in case of movement disorders according to Medtronic[19]:

- Allergic or immune system response to the implanted materials
- Infection
- Lead, extension, or neurostimulator erosion through the skin or migration
- Persistent pain at the neurostimulator site
- Seroma or hematoma at the neurostimulator site
- Intracranial haemorrhage, immediate or delayed, which could result in temporary or permanent muscle weakness, paralysis, aphasia, or death.
- Lead and extension fracture
- Loss of therapeutic effect
- Mental impairment such as attention or cognitive deficits, memory disturbances, confusion, or psychiatric disturbances
- Motor problems such as paresis, weakness, incoordination, muscle spasms, gait disorders, tremor, dystonia, or chorea
- Seizures
- Sensory changes
- Speech problems such as dysphasia or dysarthria
- Undesirable sensations such as paresthesia that could be either temporary or
- Permanent visual disturbances, such as diplopia, oculomotor difficulties or other visual field effects

Non-medical use

Deep brain stimulation is not used for other purposes than medical ones, since the technology is invasive, expensive and can have quite some side-effects. However, there is clinical evidence that it can also have enhancing effects. For example, there has been a case of a patient with Obsessive Compulsive Disorder (OCD) who received a DBS implant and after the operation instead of being relieved of her symptoms – washing her hands more than hundred times a day – a permanent, happy feeling came over her. Her psychiatrist, however, decided to replace to electrodes in order to treat her OCD symptoms.[20] Maybe in the future, when the technology has developed further (less invasive for example), it might become possible that DBS is used for enhancing cognitive performance or moods (interview VV). Dutch psychiatrist Damiaan Denys speculates that in potential DBS can be used "to activate the aggression centres of soldiers, inhibit their moral reasoning or decorum, activate the pleasure centres of prostitutes, strengthen the diligence and dedication of a cleaning woman, inhibit the religious belief of fundamentalists or incite it with non-believers, make traffic controllers or pilots more stress immune, police and security services more cautious or reckless" (Denys, 2011, p. 50).

[19] http://professional.medtronic.com/wcm/groups/mdtcom_sg/@mdt/@neuro/documents/documents/dbs-mv-ifp-add.pdf

[20] Personal communication with psychiatrist Damiaan Denys.

4.6 European market for neuromodulation devices

The market for neuromodulation is part of the market for neurodevices, which is in turn a small subset of the market for medical devices; nevertheless, estimates of its total worth range from USD 2.3 to USD 3.07 billion (in 2006) and USD 3.05 billion (in 2011). The market for neuromodulation has grown over the years and many predict further growth. The reasons for this growth include disappointing R&D results in neuropharmacology and that less time and money are required for the market admission of neurodevices compared to new pharmaceuticals. Both manufacturers and retailers of EEG neurofeedback, TMS and DBS are active on the European market. It is not known how much the European market for neuromodulation or for these specific technologies is worth annually.

In this section, we first look at the market for neuromodulation devices. We estimates its annual worth and growth. Also, we give several reasons for the growth of this market. We also take more in-depth looks into the European markets for the three selected technologies, EEG neurofeedback, transcranial magnetic stimulation and deep brain stimulation. In these sections, we look at manufacturers and resellers as well as clinics and hospitals using the technologies to estimate the size of the market.

4.6.1 Neuromodulation and neurodevices: A growing market

As said, neuromodulation has been around for a while; for example, EEG neurofeedback can be traced back to the 1960s, TMS to 1985 and DBS to 1997 when it was first approved for treatment of essential tremor. But new devices and applications enter the market regularly. Neuromodulation is part of the bigger market for neurodevices. The current market for neurodevices includes many different devices (Neurotech Industry Organisation, 2010), such as neuroprosthetics used to substitute a part of the body like cochlear or retinal implants, neuromodulation devices, neurosurgical equipment and neurosoftware such as the software for neurofeedback systems. Most devices available on the market aim to treat patients who suffer from disabling neurological conditions (Infinity Research, 2010). Examples of very successful neurodevices are cochlear implants for deaf people, neurostimulating devices for pain treatment and neurovascular interventions to prevent stroke (TWA, 2011).

The neurodevice market is a small part of the entire medical device market. There are different estimates on the worth of the entire neurodevice market (MDDI 2006). In 2006, the global market for (medical) neurodevices was estimated in various reports to be worth around $2.3 billion, $3.4 billion, and $3.07 (MDDI, 2006). The market has grown steadily over the last years, and is expected to continue to grow. The International Neuromodulation Society states that the global neuromodulating market has been expected to grow to USD 4.5 billion in 2010 (INS, 2011). The American business information provider VisionGain is more modest and estimates the global value of the neuromodulation devices market in 2011 to be worth $3.05 billion.[21]

There are several reasons given for the expected growth of the neurodevice market. The first is that psychopharmaceuticals are not very successful when it comes to treatment of strokes, treatment-resistant patients with (neuropathic) pain, and epilepsy (NIO, 2010). New molecular knowledge of the brain has so far not resulted in new, effective psychiatric drugs. In fact, major pharmaceutical companies are no longer investing in drugs for the central nervous system (Miller, 2010) and some are investing their funds in neuromodulation companies such as the recent investment of Pfizer in Neuronetics, an American manufacturer of TMS machines.[22]

[21] www.visiongain.com/Report/693/Neuromodulation-Devices-World-Market-Prospects-2011-2021

[22] http://www.onset.com/2011/05/16/neuronetics-inc-raises-30-million-in-series-e-financing

Another reason is the continued growth and diagnosis of neurological and psychiatric disorders and conditions, amongst others because of demographic shifts in the aging of the population. This means that the consuming market for neurodevices and thus the profits are expected to continue to grow. A third reason is that the regulatory regime for placing medical devices on the European market is different from pharmaceuticals. As mentioned before, new pharmaceuticals go through more rigorous testing to obtain market authorisation, whereas the process for conformity assessment with the CE (*Conformité Européenne*) mark is seen as less time consuming and less costly. One of our interviewed expert from Medtronic (AP) estimates that up to two to four years can pass before a new drug is allowed to be sold in Europe, while three to four months are necessary to introduce a medical device to the European market.

4.6.2 European EEG neurofeedback market

There are different EEG neurofeedback systems available on the European market. Some products are manufactured in the European Union, others use European distributors. Companies with EEG neurofeedback technology on the European market include MindMedia, Neuroconn and Brainmaster Technologies. In 2011, there were at least eight companies active on this market.

The market for EEG neurofeedback technology in Europe is rather small, with the Netherlands and Switzerland as the two largest markets – followed by Germany and the UK – since EEG neurofeedback is clinically more accepted these countries (interview EH, MA). The lack of robust clinical evidence for its efficacy could be the reason why this still is a small market. Another reason is that there have been some "bad quality" EEG neurofeedback systems on the European market, which, according to manufacturer EH, have "spoiled" the market to some extent.

How many clinics offer EEG neurofeedback in Europe as a treatment is unknown, since there is no mandatory registration for medical or psychological clinics offering it. Furthermore, there are also people offering – in the words of interviewee MA – "spiritual neurofeedback". These are people who claim to be able to readjust someone's energy balance. According to interviewee MA, these people often have no proper education or training that allows them to treat people or use EEG neurofeedback technology. However, this is still being practiced, since the technology is becoming easier to use.

4.6.3 TMS Market

According to our interviewee MvB, distributor in the Netherlands of MagStim machines, the European market for TMS for diagnostics is saturated – no innovation is taking place anymore – but the market for selling TMS for research and therapy is still growing. "When it comes to TMS for therapeutic purposes we foresee a clear growth, because there is absolutely more interest in TMS therapy for depression." Some of the credit of this upsurge of interest – also in Europe – can be attributed to the American company Neuronetics who in 2008 got FDA approval for their TMS system for severe depression. Other companies manufacturing or reselling TMS equipment in Europe include Magstim and Mag & More as well as three others.

Market reports like Neurotech Reports foresee a growing market for TMS as well. Next to the growing clinical research on TMS, another important reason these reports give is: TMS is an non-invasive treatment and does not require surgical implantation, and thus suffers less from regulatory impediments to rapid commercial growth. To get FDA approval or a CE marking for more invasive forms of neuromodulation continues to be difficult, is the prediction. The downside is that in comparison to pharmaceuticals such as antidepressants, the upfront costs of neuromodulating devices such as a TMS system are considerably greater.

It is hard to find data that is publicly accessible on how many machines there are at clinics and universities in Europe.[23]

4.6.4 DBS Market

In Europe, two firms offer deep brain stimulation devices, Medtronic and St. Jude Medical. Both offer more than one system. Medtronic was the first to develop the technology in 1997 for treatment of essential tremor and St. Jude Medical entered the European market in 2009. Today, Medtronic is still the European (and worldwide) market leader in the field of deep brain stimulation devices. Philips spin-off company Sapiens is developing a deep brain stimulation device for Parkinson's, according to MD, one of the founders of the company. Another Belgium company is 3Win who are developing a DBS system for Parkinson's disease.[24] Boston Scientific has been mentioned a couple of times in different interviews as a firm planning on entering the European DBS market, but so far it has no CE marked DBS system available. Innovation in DBS systems is supposed to take up speed now that more companies are entering the market and Medtronic is not the only manufacturer on the market (interview VV).

The global annual DBS device sales are currently worth about USD 200 to 300 million. The distribution of market shares has been quite stable: the US had 85 per cent of the market and Europe 15 per cent (interview MD). Worldwide DBS device sales were expected to increase from USD 44.1 million in 2000 to USD 818.1 million in 2010 (Eberle, 2009). Although the predictions have not been realised, new players on the market, Sapiens and 3Win, still expect enough profit to invest in developing and marketing new DBS systems.

4.7. Regulatory challenges of neuromodulation devices

In Europe, neurodevices are regulated pre- and post-market by the Medical Devices Directive (MDD, 93/42/EC) and the Active Implantable Medical Devices Directive (AIMDD, 90/385/EC). The MDD and AIMDD are concerned with protecting the safety of users (both doctors and patients) on the one hand, and harmonizing the requirements for bringing medical devices onto the market, thereby promoting trade, on the other. In this section we explore possible regulatory issues concerning the three technologies described in this chapter: EEG neurofeedback, transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS). With respect to EEG neurofeedback systems, there are three regulatory issues: a lack of clarity on the status of these systems (are they a *medical* device or not?), a broad description of the intended use by the manufacturers (questioning whether the performance of these systems is actually assessed for all possible medical uses) and the use of these systems for non-medical purposes (creating opportunities to bypass the MDD regulation). The regulatory issues associated with TMS primarily concern off-label use. The intended purpose of TMS devices allows for diagnostic or research use, but some clinics in Europe are currently also using them for therapeutic purposes, despite their efficacy and efficiency not yet being proven (except in the case of severe depression). In this study we have found no specific regulatory issues related to DBS.

[23] TMS manufacturers are private companies and thus do not publish annual reports and the commercial market reports that do claim to have data on the TMS market are too expensive. Based on our interviews with three interviewees MA, RW and MvB, we can only give an estimation of the amount of TMS machines in the Netherlands: at least thirty machines and probably more. Every academic hospital (8) has one or more machines, some regional hospitals also have a TMS machine and every university (14) also has at least one. In addition, there are four Dutch private clinics who offer TMS treatment.

[24] www.3win.be/news/2011-06-01,%20Start-Up.pdf

In this section, we present the general structure of the regulatory framework applying to neuromodulation in Europe. Devices for neuromodulation are medical devices if they are intended for diagnostic or therapeutic purposes. In Europe, there are three Directives regarding medical devices: In vitro diagnostic medical devices Directive (98/79/EC), the active implantable medical devices Directive (AIMDD, 90/385/EC), and the medical devices Directive (MDD, 93/42/EC). The devices for neuromodulation in this case study fall under the last two Directives, so we will only discuss these here.

4.7.1 European Medical Devices Directives

The MDD defines medical devices as "any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

and with does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means" (MDD, Article 1.2(a))[25].

An active implantable device is defined as "any active medical device which is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain there after the procedure" (AIMDD, Article 1.2(c)). A medical device is said to be *active* if it requires electrical energy to perform its function.[26]

There are four classes of medical devices specified in the MDD (class I, IIa, IIb and III, MDD Annex IX). Following the definitions of medical device and active implantable medical device, we can conclude that TMS is an active medical device and that DBS is an active implantable medical device. There is some discussion on whether EEG neurofeedback is an active medical device or not. We will get back to that in section 4.7.2.

The MDD and AIMDD are concerned with protecting the safety of the users (doctors and patients) on the one hand, and harmonising the requirements for bringing medical devices on the market to promote trade on the other hand (Faulkner, 2009, 36).

[25] The definition of medical device in the AIMDD is almost the same: "any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, *together with any accessoires*, including the software…" The rest is the same. (AIMDD, Article 1.2(a))

[26] Active medical device is defined as "any medical device relying for its functioning on a source of electrical energy or any source of power other than that directly generated by the human body or gravity" (AIMDD, Article 1.2(b)).

Medical devices should not pose any risk of compromising the condition of the patient, or be dangerous in other ways to those in contact with the device (patient or medical staff). The side-effects of a medical device have to be acceptable and be outweighed by the benefits of using the device.[27]

Both the MDD and AIMDD specify essential requirements that medical devices have to meet (Annex I). First and foremost, there are general requirements which deal with protecting the health and safety of those who use the devices under normal conditions. More specific requirements concern design and construction, which deal amongst other things with sterilisation of the devices and the information that the manufacturer must supply on the label and in the instructions for use. The manufacturer must demonstrate compliance with the essential requirements by clinical evaluation according to both the MDD and the AIMDD. A clinical evaluation does not always have to be in the form of a clinical trial: "Either a critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose of the device, where:

- There is demonstration of equivalence of the device to the device to which the data relates, and
- The data adequately demonstrate compliance with the relevant essential requirements" (MDD, Annex X, Article 1.1.1; AIMDD, Annex 7, Article 1.1.1).

For class III devices of the MDD and active implantable devices, clinical evaluations are mandatory, unless "it is duly justified to rely on existing clinical data" (MDD, Annex X, Article 1.1a; AIMDD, Annex 7, Article 1.2). It is not specified how "duly justified" should be interpreted. Most likely, this is decided on a case by case basis by a Notified Body asked to assess whether a medical device complies to one of the Directives.

A key term in the MDD and AIMDD is *intended purpose(s)*: "'[I]ntended purpose' means the use for which the device is intended according to the data supplied by the manufacturer on the labelling, in the instructions and/or in the promotional materials" (MDD, Article 1.2(g); AIMDD, Article 1.2(f)). Each device must have a specified purpose, which must be formulated by the manufacturer. Safety and performance of the device (meaning: does the device do what it is supposed to do) are evaluated against this intended purpose. Manufacturers are free to formulate the intended purpose of their devices in a specific sense or more broadly.

In order to affix the *Conformité Européenne* (CE) mark, which means that the manufacturer declares compliance with all legal requirements of the European Union, a manufacturer has to follow designated procedures to verify that the quality system, design of the product and the surveillance procedure complies with the MDD or AIMDD. For the neuromodulation devices described in this chapter, this means that the devices must be examined by a Notified Body, which is an independent organisation. If all is adequate, the manufacturer can declare to be in accordance to the directives and affix the CE mark to his medical device. There are different procedures to be (minimally) followed for the different classes of medical devices and active implantable medical devices (although manufacturers can always opt for the strictest procedure, the EC Declaration of Conformity – full quality assurance (MDD, Annex II) for class I, IIa or IIB devices). How elaborate the quality system, examination of the design and the surveillance procedure is, depends on the class of the device. We will not present all routes and procedures here, but will address the procedures where needed in the sections on the three technologies.

[27] Where medical devices also fall under other Directives, these apply as well. For example, DBS uses telemetry, which means that the radio and telecommunications terminal equipment (R&TTE, 1999/5/EC) also applies.

Once medical devices are on the European market, incidents and adverse events have to be reported to Competent Authorities. Manufacturers also have to have a quality system, which has to fulfil European requirements. A part of this quality system is the post-marketing surveillance system, which includes procedures to notify the Competent Authorities of all deterioration of the characteristics or performance of the medical device, as well as mistakes in the instruction leaflet or labelling that have caused the deterioration of a patient's condition or even a fatality. The post-marketing surveillance quality system must also specify a procedure for notifying the Competent Authorities of "any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer" (MDD, Article 10.1(a) as well as Annex 2, Article 3.1; AIMDD, Article 8.1(a) and Annex 2, Article 3.1). Notified Bodies carry out periodic inspections that can be unannounced, to ensure that the quality system is applied by the manufacturer (MDD, Annex II, Article 5.3 and 5.4; AIMDD, Annex 2, Article 5.3 and 5.4). If there are serious incidents, a Member State may take temporary actions while further research is being done.

To facilitate the exchange of information between the Competent Authorities and to the European Commission, a database is currently being developed. This database is called Eudamed, and its use has been mandatory since May 2011. It contains information on manufacturers, devices and clinical evaluations. The aim of central registration of this information is "to strengthen market surveillance and *transparency in the field of medical devices* by proving Member States competent authorities with fast access to information on manufacturers and authorised representatives, on devices and certificates and on vigilance and clinical investigation data, as well as to contribute to a uniform application of the Directives, in particular in relation to registration requirements" (emphasis added)[28]. This transparency is limited to the Competent Authorities and the European Commission as Eudamed is not publically accessible. We will get back to this in the conclusions.

The MDD and AIMDD both deal with medical devices. Devices that use similar or even the same technology but not for diagnostic or therapeutic purposes are, by definition, *not* medical devices. They are not regulated via the MDD or the AIMDD. There are two ways devices or similar technology can be used for non-medical purposes. In the first case, a device might be intended to be used for diagnostic or therapeutic purposes by the manufacturer, but in practice it is used for other purposes (i.e., off-label use). For example, this could hypothetically happen if DBS technology is not used to treat depression, but to make a mentally healthy person feel happy. In the second case, a device that is similar to a EEG neurofeedback system is being sold for the purpose of enhancing a healthy person's concentration; this seems to be an existing practice (see section 4.7.4). So here a medical device is used for non-medical purposes. In this case, it might be possible that a device does not need compliance to the MDD (or AIMDD).[29]

In the coming three sections, we will elaborate on the different regulatory issues specific of the three technologies which are the focus of this report. Unfortunately, we are not able to specify the different regulatory routes that the manufacturers of the three neurodevices have taken to get a CE mark for their device. It is very difficult to retrieve this since there is no public database – like the FDA has in the US – on the regulatory pathway the manufacturers choose to follow while introducing their device on the European market. This information is only available through the manufacturer itself and it is not mandatory for them to give this information. The information is also saved in the European database Eudamed which is only accessible the Competent Authorities and the European Commission.

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[28] http://ec.europa.eu/consumers/sectors/medical-devices/market-surveillance-vigilance/eudamed/ accessed on 310811.

[29] There are also EEG neurofeedback devices being manufactured as medical devices, which are in practice also used to improve concentration. Note that this is an illustration of the *first* case.

4.7.2 EEG neurofeedback & the regulatory framework

Following the definition of a medical device in the Medical Devices Directive (MDD, 93/42/EEC), EEG neurofeedback is a medical device, if it is a machine (including the software) that is "[…] intended by the manufacturer to be used for human beings for the purpose of: diagnosis, prevention, monitoring, treatment or alleviation of disease; diagnosis, monitoring, treatment of or compensation for an injury or handicap; investigation, replacement or modification of the anatomy or of a physiological process" (MDD, Article 1.2(a)).

The interviewees did not agree with whether EEG neurofeedback is a medical device or not. On the one hand, one could postulate that EEG neurofeedback systems *only* monitor brain activity but they are not a therapy in itself (like TMS or DBS); based on the feedback of the brain activity, the subject still has to learn to modulate their own brain activity by relaxation or activation. Unlike with psychopharmaceuticals or other neuromodulation devices, the device itself is *not* the therapy. On the other hand, most of the systems are sold with the purpose of "treatment or alleviation of different diseases" or clinical indications (see Table 2). So medical claims are being made by the manufacturer which would automatically classify the systems as medical devices. As a result of this lack of clarity on the classification of EEG neurofeedback, some manufacturers are selling EEG neurofeedback systems without the CE mark for medical devices and some do (see Table 2).

One of our interviewees – the CEO of EEG neurofeedback systems manufacturer MindMedia – stated that he want to have a CE mark for medical devices anyhow because it shows potential customers that his systems have been tested for safety (interview EH). Because of the lack of an official technical description of neurofeedback technology in Europe – in contrast to the US where the FDA did so in 1998 (product code: HCC) – anything can be sold as a neurofeedback device.[30] EH decided he wanted to discern his systems by carrying a medical device CE mark.

But the same technology can also *not* be a medical device if it is manufactured with the intention to be used for the purpose of enhancement of sports, artistic, or cognitive performance or entertainment (for example gaming). This is an important difference, since the requirements for affixing the CE mark to general products are different and much less stringent than those of medical devices. This could mean that devices, very much alike or even similar to the medical devices EEG neurofeedback, could be sold and bought on the European market without having been assessed for safety and performance in the way MDD requires for class IIa devices. In Table 2 it shows that the companies without CE marking 93/42 Medical Device Directive are also the companies who both mention non-medical use of their EEG neurofeedback systems next to medical indications.

Of three companies that sell EEG neurofeedback technology – market leaders Thought Technology[31], MindMedia[32] and the Russian company Mitsar[33] – we know that they have classified their devices as class IIa. This is probably because EEG neurofeedback is not invasive, it is active (it is a battery powered device) and it could be seen as a device for diagnostics that is "intended to allow direct diagnosis or *monitoring of vital physiological processes*" (MDD 93/42/EEC, annex IX, 3.1, rule 10; italics added).

[30] In the new approach directive – which is being developed at the moment – European technical standards for different devices will be given more importance within the essential requirements (interview RG).

[31] Personal communication with interviewee EH.

[32] http://www.mindmedia.nl/english/products.php accessed on 080811.

[33] http://www.mitsar-medical.com/page1.php?id=quality accessed on 080811.

TABLE 2: Manufacturers of EEG neurofeedback systems on the European market

Company	CE mark 93/42 MDD	(Medical) indications according to website[34]
Thought Technology (Canada)	Yes (classification IIa)	Neurological self-regulation (not specified) and Neuroracer (game)
Mindmedia (the Netherlands)	Yes (classification IIa)	Attention disorders and learning disabilities, epilepsy and seizure disorders[35]
Mitsar (Russia)	Yes (classification IIa)	Clinical application (not specified)
Neuroconn (Germany)	Yes (classification not known)	ADD/ADHD, epilepsy, tinnitus[36], migraine and other disorders
Brainmaster Technologies (US)	No (CE mark for products not being medical devices)	Clinical and personal neurofeedback, peak-performance, self-improvement, education, self-exploration and brain-controlled systems, in addition to games, art, sports, recreation, brain calisthenics, mental conditioning and improvement
Deymed Diagnostic (Czech Republic	Yes (classification not known)	Neurotherapy (not specified)
Brainclinics (The Netherlands)	No	Golf performance enhancement, epilepsy, experimental purposes and brain-computer interfacing
Schufried (Austria)	Yes (classification not known)	ADS/ADHS therapy

[34] Exclusive of diagnostics. All retrieved 4 Sep 2011.

[35] Mindmedia is careful in describing possible applications. They add to the already mentioned indications in the table: "There are indications that Neurofeedback (NFB) may also be useful for treatment of anxiety, stress, depression, drug abuse and sleep disorders, but we believe these areas require more research before anything more definitive can be said." (retrieved 4 Sep 2011)

[36] Hearing noise or a beep-tone.

Next to the discussion on whether EEG neurofeedback systems are medical devices or not, there is also the issue of the intended purpose of use – an essential requirement to get a CE marking for medical devices – that the manufacturers have assigned to their products. The exact description of the intended purpose is not always easy to retrieve; it has to be mentioned in the manuals accompanying the devices, but these manuals are usually not publicly available (on the manufacturer's website for example). However, one of our interviewees, EH, CEO of MindMedia, has sent us the manual for their NeXus-10 system which states the intended use: "The NeXus-10 is a battery powered biofeedback device, intended to monitor and feedback physiological parameters on the human body for relaxation training, muscle re-education and prescription use." In fact, this is the same intended use as described in the product classification of biofeedback systems[37] by the FDA.[38]

Relaxation training can be interpreted quite broadly. As interviewee EH describes it, it means to train oneself through real-time feedback to self-regulate *relaxation* (and activation) patterns of brain activity. The idea behind neurofeedback – as described in section 4.2 – is that patients or clients with different disorders or complaints can benefit from this. Thus, the NeXus-10 system can be used for quite different purposes as there is not one specific (medical) indication mentioned. The question is now whether the performance of the device is assessed for all the possible medical purposes or just for the monitoring and feeding back of physiological parameters in general.[39] Most probably it is the latter, since – as said – there has been little scientifically robust evidence of the clinical efficacy (and efficiency for that matter) of EEG except for the treatment of ADHD.

Manufacturers who do not consider their EEG neurofeedback systems to be medical and thus do not follow the requirements in the MDD, do *not* have to give a description of the intended purpose of their systems. This is probably why exactly these companies – BrainMaster Technologies and Brainquiry – are mentioning non-medical purposes as well (see table 2). Although these devices do have to adhere to European requirements for electronic devices, the question is whether it is desirable to have EEG neurofeedback systems on the market without a CE marking for medical devices; even though the technology has proven to be relatively safe, *if* used by a skilled professional.

Another issue with the regulation of EEG neurofeedback technology has already been referred to: the use of EEG neurofeedback systems – whether or not in a technically simplified version – for enhancement or entertainment purposes. These systems do not require adherence to the MDD, yet very little is known about their mechanism of action. The similarity to EEG neurofeedback as a medical device, however, raises the question whether these technologies should be treated with more caution and perhaps be regulated under a similar or the same regime as the medical EEG neurofeedback devices.

[37] Neurofeedback is one type of biofeedback focused on imaging brain activity and training of it.

[38] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm?ID=3259

[39] There has been an ongoing discussion on the interpretation of performance: is it only the technical performance or also the medical benefit enclosed in the concept of performance which should be assessed? (interview RG).

4.7.3 TMS & the regulatory framework

TMS machines are class IIa devices, according to the CE marking of the TMS machines of different manufacturers such as Magstim and Magventure. TMS can be considered an active therapeutic device intended to administer or exchange energy without being potentially hazardous (MDD 93/42/EEC, annex IX, 3.1, rule 9). In this section we want to discuss the intended purpose of TMS as assigned by TMS manufacturers. See Table 3 for an overview of the indications of TMS which are mentioned on the websites of (upcoming) TMS manufacturers on the European market.

The intended purpose of a medical device is not always easy to retrieve. The largest TMS manufacturer in Europe, MagStim, is the only company that has put the manuals of their different TMS machines on their website. Manuals of medical devices should describe the intended purpose of the device. In case of the three MagStim standard TMS devices, the following purposes are described:

- MagStim200: "stimulation of neuromuscular tissue";
- MagStim BiStim2: "stimulation of peripheral nerves for diagnostic purposes";
- MagStim Rapid (for rTMS): "stimulation of peripheral nerves and the human cortex for diagnostic and research purposes".

Especially the MagStim Rapid is interesting to take a look at, since this machine is used for rTMS which can in principle be used for clinical therapeutical purposes. The other two machines are suitable for clinical diagnostic purposes. (All three machines are used in research, but such use does not require a CE mark for medical devices, just a label 'for research use only'.) In fact, the MagStim Rapid is used for treatment of depression in private clinics (for example in one Dutch clinic), and on the website of MagStim depression is also mentioned as a possible application of their TMS technology: "The Magstim stimulators are used in diagnosing and assessing a variety of nervous disorders, in monitoring the spinal cord during surgery, for therapy in muscular injury and for the treatment of depression." At the same time in the manual, the intended purpose of the MagStim Rapid describes only diagnostic and research purposes. The information from the manual is therefore contradictory to day-to-day practice and to the information on their website.

To what extent is that problematic? The efficacy of rTMS for severe or treatment resistant depression is supported by different meta-analyses. Still, it seems that in Europe – based on an internet search – there are not that many clinics offering TMS therapy for depression or other indications. This probably has to do with the fact that rTMS therapy is often not reimbursed by (national health) insurances. Also, the technology is relatively safe to use. On the negative side, the efficiency of rTMS therapy in comparison with other therapies has not been proven yet. And if rTMS is offered in clinics as a therapy for other indications than severe depression, it might divert patients from therapies which that have a more established history of effectiveness, like certain drug therapies. Further research should point out whether the intended use as described by the other TMS manufacturers on the European market also deviates from clinical practice in Europe. This is especially important since distributors and market reports predict that rTMS technology for clinical applications is on the rise.

Another interesting point that can be made on the intended purpose of the MagStim Rapid – and the other devices as well – is that the purpose is quite broadly described, especially in comparison with the FDA approval of rTMS (only for the treatment of drug resistant depression). "Stimulation of peripheral nerves and the human cortex" or "stimulating neuromuscular tissue" is a lot broader, also in comparison with the descriptions of the intended purposes of deep brain stimulators or even EEG neurofeedback.

This might be based on the fact that TMS can be used for many different purposes: research, diagnostics and therapy. If TMS manufacturers in Europe would be compelled to describe the intended purpose in a stricter way, there might be less room for different manufacturers of TMS technology on the European market in the future. In the US for example, there is only one company, NeoStim, who has FDA approval to sell TMS devices for treatment of depression. Interviewee MA states that: "In America rTMS is linked with a specific medical indication and that blocks the market. While in Europe it is more up to the professional group how and when to use the technology."

TABLE 3: (Upcoming) manufacturers of TMS devices on the European market

Company	CE mark 93/42 MDD classification IIa	Medical indications according to website[40]
Magstim (UK)	Yes	Muscular injury, depression
Magventure (Danmark)	Yes	Research in therapies within rehabilitation and psychiatry
Nexstim (Finland)	Yes	Research into brain therapy[41]
Mag & More (Germany)	Yes	Depression, tinnitus, stroke
Deymed Diagnostic (Czech Republic)	No	"DuoMag XT rTMS stimulator available soon"

4.7.4 DBS & the regulatory framework

Deep brain stimulation is not regulated in Europe under the Medical Device Directive (MDD, 93/42/EEC), but under the Active Implantable Medical Devices Directive (AIMDD, 90/385/EEC). DBS technology does not only have to meet the requirements of the AIMDD, but also the requirements of the Directive on Radio and Telecommunications Terminal Equipment (R&TTE, 1999/5/EC), as both the physician's programmer and the patient's controller use electromagnetism to communicate with and change the settings of the DBS system, and the system can be influenced by electromagnetic interference.

The term 'intended purpose' is important in the AIMDD. The active implantable medical devices must have a purpose specified by the manufacturer (see Table 4) and the device must achieve this purpose in a safe way for the users. Medtronic has specified the indications for its DBS systems in a very precise manner in comparison to the indications in the manuals of EEG neurofeedback and rTMS devices.

[40] Exclusive of diagnostics.

[41] Next to "Clinical diagnostic applications include neurosurgery (cortical mapping) and stroke (testing for motor tract integrity)."

For example, in the manuals for their Activa Therapy devices and on their indications sheet it says: "Medtronic Activa Therapy is indicated for patients with disabling tremor or symptoms of Parkinson's disease. Recent studies have shown that deep brain stimulation with Activa System components is effective in controlling essential tremor and symptoms of Parkinson's disease that are not adequately controlled with medications. Additionally, deep brain stimulation is effective in controlling dyskinesias and fluctuations associated with medical therapy for Parkinson's disease. Medtronic Activa Therapy is also indicated as an aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and segmental dystonia, hemidystonia, and cervical dystonia (torticollis) for individuals 7 years of age and older."[42] The described intended purpose of DBS devices do not seem to be problematic in any way, as was the case with TMS and EEG neurofeedback.

TABLE 4: (Upcoming) manufacturers of DBS systems on the European market

Company	CE mark	Clinical trials
Medtronic	For Parkinson's, essential tremor, dystonia, obsessive compulsive disorder (OCD) and epilepsy	Medtronic is currently doing mostly post-market studies to study efficacy and risks of DBS for essential tremor, OCD and epilepsy in the longer term (AP)
St. Jude Medical	For Parkinson's	Depression
Boston Scientific	No	Parkinson's
Sapiens	No	Parkinson's
3Win	No	Parkinson's[43]

The AIMDD requires a clinical evaluation of the device (Annex 1, Article 5a) to prove safety and performance, unless "it is duly justified to rely on existing clinical data" (Annex 7, Article 1.2). It is unknown whether, and if so how often and on what grounds, this clause is used for DBS systems, since information about the Declaration of Conformity procedures for medical devices is not publicly accessible in Europe like in the US, as mentioned before in the introduction of this section.

[42] http://test.stimulus-dbs.org/DBS3/img/ActivaPrescribingInfo.pdf

[43] According to website www.3win.be.

If it did happen with DBS systems that clinical data is used from another DBS system from another manufacturer with the same clinical indication or from another DBS system with a different clinical indication – which actually happened in the US with Medtronic's DBS system for Obsessive Compulsive Disorder (OCD)[44] – then this raises the question whether it would be preferable to have a clinical evaluation for each and every single active implantable DBS device, even though technically similar devices have been used for the same or a different intended purpose. The risks associated with devices like DBS systems, ranging from unwanted side-effects of the stimulation to depression (sometimes including suicidal feelings) to fatal bleedings, are, after all, quite serious.

4.8. Governance challenges of neuromodulation devices

The Medical Devices Directive (MDD, 93/42/EC) and the Active Implantable Medical Devices Directive (AIMDD, 90/385/EC) do not regulate all aspects of the design and use of medical devices and neurodevices. Some aspects such as technical standardization, reimbursement, therapy protocols, training and certification are governed by the market itself or through other institutional arrangements. In this section we identify these governance challenges in relation to the three technologies described in this chapter: EEG neurofeedback, transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS). In most European countries, therapies based on EEG neurofeedback and TMS are not reimbursed, and while DBS is reimbursed for Parkinson's, the situation for other conditions varies between countries. The European harmonization of national reimbursement policies is required to assist the markets, as currently it is difficult for new companies or devices to enter the market, since its potential size is unknown and developing new neurodevices is a costly process.

Certified training is offered for EEG neurofeedback by professional organizations, but is not mandatory for users, and there is no standard training for clinicians in the use of TMS. This situation is undesirable, as unskilled use can result in seizures or other unwanted side effects. While there are some standard therapy protocols for EEG neurofeedback, they do not cover all conditions. TMS has more standard protocols, but they are not enforced in clinical practice in the same way as in research practice. This means patients must choose their practitioner with great care.

The database Eudamed contains information about the exact intended use of the neurodevice or the different regulatory routes that manufacturers of neuromodulation technologies have taken in order to get a CE marking for their medical devices. However, Eudamed only facilitates the exchange of information between the manufacturers, the Competent Authorities and the European Commission. Social scientists, journalists, patient organisations or individual citizens have no access to Eudamed. More transparency might encourage public debate – when needed – on the (questionable) entrance of a particular medical device on the European market at an early stage.

[44] Medtronic's DBS device for OCD has been approved by the FDA via a humanitarian exemption (HDE). Because of this, Medtronic did not have to do clinical trials since the FDA ruled that the system was substantially equivalent to other uses, already approved, for this device.

The MDD and the AIMDD do not regulate all aspects of the design and use of medical (neuro)devices. Some aspects like technical standardization, reimbursement, therapy protocols, training and certification are governed within the market itself or through other institutional arrangements. For example, standards or norms for various categories of devices are established by CEN, ISO and national normalisation institutes like the Dutch NEN. As an example, there is a norm on safety requirements for EEG equipment (NEN-EN-IEC 60601-2-26:2003).[45] Another example is reimbursement which is in fact not harmonized in Europe. In all Member States, there are different ways of determining whether or not devices will be reimbursed. Usually, there is a body who determines whether clinical efficiency of the device is demonstrated (i.e. delivers the device a more effective treatment than other devices, procedures or drugs) and reimbursement is in place or not. Having a CE mark is no guarantee that the device is reimbursed. It is not sure that a CE marked device will be reimbursed and thus be used. Developing new medical (neuro)devices can be a costly process, and not knowing whether it will be reimbursed and thus not knowing the size of the potential market means that it is difficult for new companies or new devices to enter onto the market (interviews MD, AP).

Besides European directives and standards and member state regulation, there are often also voluntary, self-regulating policies from professional organisations or industry in place. These deal, for instance, with therapy protocols and certification of users. Where they are relevant for the three technologies, we will discuss the different governance issues in the following sections.

4.8.1 EEG neurofeedback and governance issues

Reimbursement

Reimbursement for EEG neurofeedback sessions varies across European countries and insurance providers, but seems in most cases not to be reimbursed. It might be that psychologists code neurofeedback services as psychotherapy to increase the likelihood of reimbursement (interview EH). In the Netherlands, neurofeedback therapy used to be reimbursed, but this changed when the College van Zorgverzekeraars (CvZ) – the governmental organisation for implementation and advice on reimbursement of medical procedures – has published a negative advice on neurofeedback therapy for different indications: ADHD, autism, anxiety disorders, tinnitus, psychological or physical disorders.[46] The reason they give is that neurofeedback "does not meet the criteria of evidence based science and practice." The neurofeedback community of practitioners in the Netherlands argues that neurofeedback should not be compared with a psychopharmaceutical intervention – as the CvZ did – and deplores the decision (interview MA). It does happen in the Netherlands that therapists who use EEG neurofeedback in their 'alternative' practices does get their therapy reimbursed (interview MA). In both Germany and the UK, websites or the organisations like the Dutch CvZ do not mention anything on neurofeedback therapy.

[45] ISO norms are worldwide norms, NEN-EN are European norms.

[46] http://cvz.nl/binaries/live/cvzinternet/hst_content/nl/documenten/standpunten/2009/sp0911+neurofeedback+kinderen+met+adhd.pdf

Training and certification

The side-effects of neurofeedback therapy are relatively mild, but as mentioned before, unskilled use can increase existing symptoms and could prompt a seizure. Also, the technology is sometimes complex to use and the data obtained is complex to understand which requires considerable skill (Striefel, 2002). However, there is no mandatory training or educational requirements for the users. The field of neurofeedback therapists does try to regulate the use themselves by offering certificates and courses. For example, courses are offered by the Biofeedback Certification International Alliance (BCIA), but certification is not mandatory for operating the equipment. On the website of the BCIA, a patient or client can retrieve who is a certified user according to the BCIA. It differs per country whether professional organisations for psychologists or clinical neurophysiologists offer training.

In the Netherlands, the Dutch Association for Psychologists (NIP) has a separate chapter for psychologists who work with or are interested in neurofeedback.[47] The manufacturers sometimes offer trainings themselves or refer on their websites for workshops, online courses accredited by the BCIA and organised locally in different European countries (and the US).

Therapy protocols

Based on a qEEG and the comparison with a database with 'normal' EEGs, a practitioner diagnoses neurological and epileptiform abnormalities and decides on the treatment protocol. Sometimes EEG abnormalities are quite evident, but many times the abnormalities are not so easy to detect. As a consequence, the protocols can vary widely. Then again, this can also happen with pharmaceutical or cognitive therapy (interview JB). There are some standard protocols for specific medical indications, like Lubar's protocol for treatment of ADHD, but not for all indications. Therefore, researchers often caution that it is extremely important to choose one's practitioner with care. Hammond (2007) describes the EEG neurofeedback market as a 'buyer beware market'.

4.8.2 TMS and governance issues

Reimbursement

When it comes to the market for TMS therapy, there is of course the question of reimbursement. One session costs about 35 euro (exclusive of the psychotherapy session which is usually reimbursed for a certain amount of sessions). The extent to which TMS is reimbursed differs very much per European country. In the Netherlands for example, rTMS therapy for severe depression or any other indication is not reimbursed. In Belgium it is still unclear whether patients can get reimbursement for TMS sessions (interview MvB). In Germany[48] and the UK[49], rTMS is also not covered by public health insurance.

The willingness of insurers to reimburse cost of TMS therapy is an uncertainty at the moment. TMS therapy in comparison to other therapies might be cost-effective in the long run, but it still has a high initial cost. Moreover, there is still discussion (and research going on) on the effectiveness of rTMS therapy for different indications, even depression.

[47] http://www.psynip.nl/website/sectoren-en-secties/intersector/neurofeedback/neurofeedback (retrieved 5 Sept 2011).

[48] http://rtms-therapie.de/kosten_rtms.html

[49] http://www.nice.org.uk/usingguidance/donotdorecommendations/detail.jsp?action=details&dndid=414

Protocols

In order to avoid adverse effects of TMS as much as possible, there are standard guidelines that can be followed by researchers and clinicians. TMS experts present at the earlier mentioned 2008 international workshop on TMS, reached an agreement about the stimulation parameters that are considered safe, parameters that are considered unsafe, general safety guidelines, ethical considerations (also for clinical studies), the kinds of people that should apply TMS, training for TMS, contra-indications and precautions before TMS can be applied, and a standard screening questionnaire for rTMS candidates (see Rossi et al., 2009). The workshop was supported by the International Federation of Clinical Neurophysiology (IFCN) and its European Chapter, the National Institute of Neurological Disorders. Furthermore, there are some medical guideline clearing houses that have issued treatment protocols of TMS. For example, NICE in the UK has issued an Interventional Procedure Guideline for TMS for severe depression (IPG242). These standard guidelines are not mandatory or enforced by any local, national or European authority. This is different for *research* on therapeutic applications of TMS done at universities or academic hospitals. Here researchers have to deal and comply with the pronouncement on the design of their study by the medical ethical committee.

These differences in safety monitoring between research and (commercial) clinical practice is viewed as a "surprisingly big gap" by three of the interviewed experts. MM states: "Research conducted in commercial clinics does not always pass medical ethical committees for approval. In the commercial clinics multiple sessions of rTMS in Parkinson's and depression are applied which is not allowed here [at the university] without the approval of a committee. And not all the protocols they use in those commercial clinics, although "sold" as treatment, are always evidence based."

Training and certification

Besides the standard guidelines compiled by the professional group of TMS users on *how* and *when* to use TMS devices, there is also the question of *who* is permitted to use TMS technology. All of the interviewed experts agreed that training is absolutely necessary to operate TMS devices. AS illustrates this by saying: "There are many rules and safety guidelines on what you should and should not use in terms of intensity and frequency combinations to avoid risk of a seizure. You should also be trained to be able to see the beginning of such side effects early enough in order to stop the stimulation. And one should know how to measure the individual excitability level. All these things require certain expertise and theoretical knowledge." The interviewees also mentioned that it is difficult to misuse the technology itself, since nowadays there are many security measures – like shielded coils with temperature sensors – built in the technology. In the manuals of the TMS systems of MagStim – Europe biggest manufacturer of TMS technology – it is stated that their systems are "for use by and or under supervision of a medical practitioner only" (see the manuals available via www.magstim.com[50]). This reservation is made in case of clinical situations, when the TMS device is used for research purposes this reservation is not applicable (interview MvB).

The manufacturer or the distributor of the technology can, in principle, sell the technology to everyone (MvB, distributor of MagStim technology in the Netherlands). It is not compulsory to ask for certain certificates to determine whether the buyer has had training or is familiar with using the machine. Distributors usually do give instructions on how the machine technically works, but they also inform their buyers on the medical applications of the TMS machine.

[50] For example: http://manuals.magstim.com/en/2002.pdf.

Manufacturer MagStim, however, is organising annual TMS summer schools with the University College of London (UCL), but mostly on recent research in the area with less focus on training. They also organise TMS training with other institutions, for example Duke University in North Carolina or with the University of Southampton (especially for physiotherapists on "facilitating motor relearning with brain stimulation techniques"[51]). Another well-known TMS training course is organised two or three times a year at Harvard Medical School. People who attend these courses organised at or with universities usually get a certificate when the course is finished.

In summary, there is no standard TMS training available, not by manufacturers, distributors or universities, nor by professional groups such as the International Federation of Clinical Neurophysiologists (IFCN). In contrast with EEG neurofeedback, there is also no worldwide professional organisation endorsing certificates. Still, there seem to be opportunities to get acquainted with TMS technology and it's standard protocols through different trainings offered worldwide; however, most of these trainings are focused on using TMS for research purposes.

4.8.3 DBS and governance issues

Reimbursement

Whether DBS therapy is reimbursed is decided on Member State level, and does vary between the different Member States. In Belgium, for example, all patients eligible for DBS must be presented by their surgeon to a hospital committee that decides whether they can have the DBS system (interview VV). In the Netherlands, DBS for Parkinson's disease is reimbursed, but DBS for treatment resistant depression, OCD and Tourette's syndrome is not.[52] In the UK and Germany, whether DBS is reimbursed or not is decided locally and sometimes even per patient (interview AP and VV). In both countries, it is possible that DBS is reimbursed when a physician can demonstrate that a patient has no other alternatives. In other Member States, different decisions are made. This leads, however, to the situation that a CE marked treatment, commercially available in the whole European Union, is not equally accessible for all European citizens. This is especially problematic since DBS is a very expensive therapy – the device costs around EUR 10,000 to EUR 15,000 and the procedure and follow-up visits approximately the same – and thus not something most patients will be able to pay for themselves. Also, it is difficult for clinicians to explain to patients, especially in border regions, that they cannot have an available, last resort treatment (interview VV). Finally, lack of harmonisation of reimbursement means that it is far from clear for manufacturers how big their market really is once they have developed a CE marked device. Manufacturers can estimate how big the potential market is from data on the incidence of indications the DBS system is being developed for, but they cannot know in advance how much of that market can be realised if this is dependent on the decision of individual insurance companies or national reimbursement authorities. This makes developing innovative, novel devices a risky endeavour for companies as it involves huge costs when the payoff is highly unsure and potential manufacturers might be discouraged.

[51] www.magstim.com/support/15945.html

[52] College voor zorgverzekeringen, http://www.cvz.nl/binaries/live/cvzinternet/hst_content/nl/documenten/standpunten/2010/sp1012-deep-brain-stimulation.pdf

Training, certification and protocols

In contrast with EEG neurofeedback and TMS, DBS therapy requires a large multidisciplinary team of doctors to implant and program the DBS. There is no specific educational training for surgeons; most of them are trained on the job by a more experienced colleague (interview VV). It differs per European country how it is decided who is permitted to give DBS therapy. In the Netherlands, a patient is compelled to go to a certain hospital that is permitted to do the operation for a DBS implantation. In Belgium, a patient can go to every hospital as long as a peer review committee has evaluated whether the DBS treatment is fit for the patient. According to interviewee VV, the Dutch procedure is preferable since fewer hospitals are doing more operations and are therefore more experienced.

Protocols for DBS treatment are usually developed within professional working groups, for example on functional stereotactics for movement disorders, who discuss the incidence of complications, the latest research results and try to develop treatment protocols (interview VV). National clearing houses for medical guidelines have also issued guidelines on DBS treatment. For example, NICE in the UK publishes interventional procedure guidelines for different medical indications for DBS.[53]

4.9. Conclusions

The sociotechnical practices associated with the three neurodevices studied here are relatively stable and even becoming more established. For EEG neurofeedback, transcranial magnetic stimulation (TMS), and deep brain stimulation (DBS) an increase in clinical application is foreseen. A widening of clinical applications for DBS is occurring and research on the use of all three types of devices for other medical conditions is being carried out. However, the only really new practice is the use of EEG neurofeedback for gaming purposes. In this section we conclude with an outline of the most important regulatory and governance issues – especially with respect to non-invasive neurodevices – that must be addressed by EU policymakers.

In this case study we have studied if and how the growing market of neuromodulating devices poses new regulatory and governance challenges for the European Union with a focus on:

- three different neuromodulation technologies: EEG neurofeedback, transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS);
- the intended purpose of the device as described by the manufacturer, non-medical use, reimbursement, standardisation of treatment protocols, and the training and certification of users.

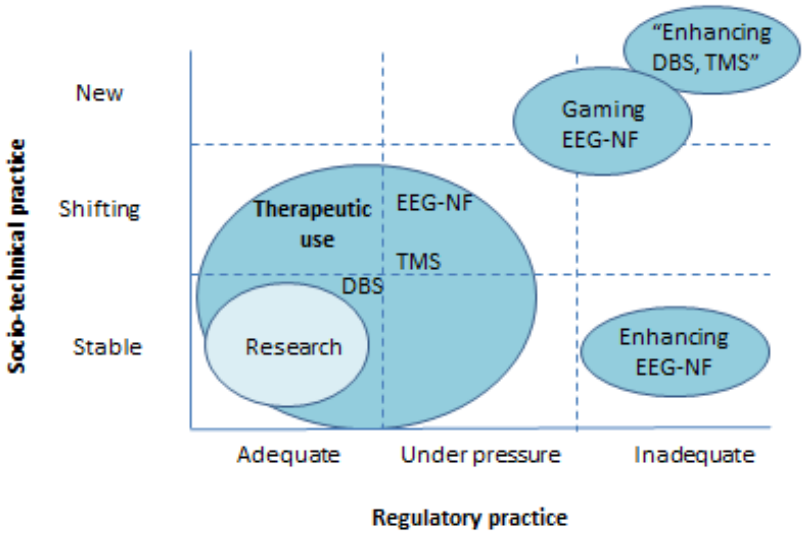
It is not within the scope of this case study to evaluate the different regulatory routes manufacturers of the above mentioned neuromodulation technologies have taken in order to get a CE marking for their medical devices. More research should be done on this – for example on the question to what extent manufacturers can rely on existing clinical data or not – although as mentioned before it is very difficult for a public (research) organisation to collect these data. We will get back to this at the end of this section.

[53] These are the IPG019 (Parkinson's disease), IPG188 (tremor and dystonia), and quite recently IPG381 (intractable trigeminal autonomic cephalalgias[53]) and IPG383 (refractory chronic pain syndromes).

In the introduction we have briefly described the relatively modest but ongoing debate on the regulation of neuromodulation devices on the European market. For example, the European Group on Ethics (EGE) advocate that *implantable* devices – such as deep brain stimulation – for medical purposes should be regulated in the same way as drugs when the medical goal is the same (EGE, 2005). However, contrary to the opinion of the EGE, based on our study of the manufacturing and clinical practices of the three neuromodulation devices, we have identified regulatory issues mostly in the domain of the *non-invasive* neurodevices, which we will summarise here. The table below gives an overview of where and for what the different neuromodulations are offered.

In this conclusion we will analyse the findings of the three sections on EEG neurofeedback, TMS and DBS in terms of changing sociotechnical practices in research and clinical use of these emerging neuromodulation technologies, and consequently a possible need for the adaptation of existing regulation and governance or new forms of regulation. Let's start with the question to what extent we can identify shifts in the neuromodulation practices we have studied.

Figure 1: Social-technical and regulatory practices in research and therapeutic practices of EEG neurofeedback, transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS)



4.9.1 Sociotechnical practices

When we look at EEG neurofeedback – an imaging technology assisted mental training – there is an existing practice of clinical use since the 1960s, when it became known as an 'alternative' therapy. Lately clinical use gains popularity in at least some European countries like the Netherlands, Switzerland, Germany, and the UK where, nowadays, it is to some extent perceived as a more accepted medical treatment. This might be a consequence of the fact that neurofeedback is gaining more attention from mainstream researchers studying the efficacy and efficiency of EEG neurofeedback for different medical indications. At universities there is also an emerging interest in studying other imaging technologies like fMRI for purposes of neurofeedback.

Manufacturers of EEG neurofeedback devices also seem to be eager to upgrade the market by getting their devices CE marked as a medical device. However, in most if not all cases, the therapy, which is usually not reimbursed, is offered in private psychological practices and not in hospitals.

A well-known indication neurofeedback is offered for is attention deficit hyperactivity disorder (ADHD), but it is also offered for other indications like epilepsy, tinnitus, migraine, autism, anxiety, addiction and also learning disabilities. EEG neurofeedback technology has therefore followed an unusual pathway, not from lab to clinic but from clinic to lab. Most importantly, EEG neurofeedback has not always only been offered for medical purposes but also and still is offered for non-medical purposes such as the enhancement of cognitive, sports or artistic performance. A rather novel non-medical use of EEG neurofeedback technology is in the gaming industry, where the technology is offered as a replacement of the console; the user is able to play the game by learning to control certain brain activity patterns.

Transcranial magnetic stimulation (TMS) has been an established technology like EEG neurofeedback but mostly for diagnostic purposes (i.e. testing nerve conduction and velocity as part of the diagnosis of neurodegenerative diseases). Nowadays, TMS is on the rise, especially in neurocognitive research, to create virtual lesions that allow a temporary inactivation of a brain area in order to check the behavioural consequences. But also the therapeutic application of TMS is gaining popularity. The most common indication is therapy resistant depression where rTMS (repetitive TMS) is used as a last resort treatment. Like EEG neurofeedback, in most European countries rTMS is not reimbursed as a treatment. It is usually not offered in hospitals but it is offered in private clinics, also for other indications of which the efficacy is usually not proven yet. Here, too, mainstream research is getting more and more interested in studying other possible indications that rTMS can be a treatment for, from psychiatric disorders to neurological ones such as stroke. Non-medical use of TMS is not offered in clinics as far as we know, but research on TMS for enhancing cognitive performance is an important new research area.

Deep brain stimulation (DBS) is a relatively new neuromodulation technology and it has been used in clinical practice since 1997. DBS is only offered in certain hospitals since it requires a highly specialised and multidisciplinary team of doctors to implant and program the device. It is well-known as a treatment for Parkinson's disease and other movement disorders like dystonia and essential tremor. However, there is a shift going on in the indications for DBS treatment, from neurological to psychiatric disorders like obsessive compulsive disorder (OCD), anorexia nervosa and obesity. These indications are mostly still under study and are not always reimbursed. As far as we know, DBS is not offered commercially at this moment, probably because the treatment is too expensive. Non-medical use has not been studied, but DBS has been known to have mood enhancing effects based on clinical experience with DBS patients for Parkinson's and OCD.

In summary, it can be stated that the three practices are relatively stable and even getting more established. At the same time, in all three cases an increase in clinical application is foreseen, and a widening of clinical application (for DBS) and research on new medical indications (for all three) is happening. The only real new sociotechnical practice is the use of EEG neurofeedback for gaming purposes.

4.9.2 Regulatory and governance issues

As far as the scope of this study goes, no new forms of regulation are needed, except maybe for the non-medical use of neuromodulation devices, especially EEG neurofeedback. If a manufacturer is bringing his technology onto the market for entertainment or enhancement purposes alone, a CE marking for medical devices is not mandatory (only the 'regular' CE procedure, which is much less stringent[54]).

[54] Manufacturers have to carry out a conformity assessment, set up a technical file and sign an EC declaration of conformity and then they can affix the CE mark themselves on the product.

TABLE 5: Overview regulatory and governance frameworks for EEG neurofeedback, Transcranial Magnetic Stimulation and Deep Brain Stimulation

Technology	EEG neuro-feedback	TMS	DBS
Practice			
Research	Regulated through medical ethical commissions and the declaration of Helsinki	Regulated through medical ethical commissions and the declaration of Helsinki	Regulated through medical ethical commissions and the declaration of Helsinki
Medical use	MDD: Medical Devices Directive. Focused on safety and (technical) performance to protect patients and enable the market. Not focused on effectiveness.	MDD: Medical Devices Directive. CE marking is focused on safety and (technical) performance to protect patients and enable the market. Not focused on effectiveness.	AIMDD: Active Implantable Medical Devices Directive. Same principles as MDD.
Hospital	This treatment is often not paid for by health insurance	This treatment is often not paid for by health insurance	This treatment is mostly reimbursed for Parkinson's Disease but for other indications reimbursement varies per country
Commercial clinics	Is offered for treatment of attention disorders, epilepsy, tinnitus, migraine, etc. There is yet no scientifically robust proof that it works.	Is offered for treatment severe depression, tinnitus and stroke. There is only scientifically robust proof for treatment of drug resistant depression.	-- Demands too much technical expertise
Non-medical use	Offered.	Not offered. Research on enhancement of cognitive performance is being done.	Not offered. Clinical experience that it can have mood enhancing effects.

Safety and performance is consequently not tested (although manufacturers are liable). However, in some cases the technology is the same as the neurofeedback devices which are now on the market for medical use. From consumer safety perspective, this might be an undesirable situation. More research on the risks of EEG neurofeedback for enhancement and gaming is needed, and it should be considered whether these devices should meet the same essential requirements as medical neurodevices. In the future, the same question might apply for TMS and DBS if offered for non-medical purposes.

Although – as we said – the existing practices are quite stable, in some cases the existing regulatory and governance framework seems to be under pressure because of regulatory uncertainty (i.e. lack of clarity on how to apply regulations), or because of a regulatory or governance vacuum (i.e. tension between the regulatory or governance framework and practice).

4.9.3 Regulatory uncertainty

The classification of the three neuromodulation devices according to the Medical Device Directives is problematic only in the case of EEG neurofeedback. There is a lack of clarity on whether EEG neurofeedback is, in fact, a medical device. Some EEG neurofeedback devices on the European market do not carry a CE marking for being a medical device.

The discussion is about whether EEG neurofeedback systems are only monitoring devices and are not a therapy in itself as is the case with TMS and DBS. Patients themselves have to learn – based on the feedback they get – to modulate their own brain activity patterns. On the other hand, most of the systems are sold with the purpose of treating different diseases (except when sold for enhancement or gaming purposes).

4.9.4 Regulatory vacuum

In some cases the intention behind the regulatory framework does not match the existing practice. For example, this is true in the case of off-label use, where the intended purpose as described in the manuals of the devices does not correspond with the purposes for which it is offered in clinical practice. In the case of TMS, one of our findings was that although the manual of the rTMS MagStim device said it could only be used for diagnostic and research purposes, at the same time the same devices are offered in private clinics for clinical purposes such as treatment of depression.

Also, the intended purpose of EEG neurofeedback ("to monitor and feedback physiological parameters on the human body for relaxation training") – as far as our research goes – is described in a very broad sense, particular in comparison to the intended purpose ascribed to DBS devices. Relaxation can be broadly interpreted in terms of the self-regulation of relaxation patterns of brain activity which is supposed to be beneficial for patients and clients with different disorders and complaints. Such a broad description stimulates the (clinical) use of the device for different indications, while the efficacy (and efficiency) of EEG neurofeedback therapy is often minimally or not proven. At the same time, the performance of the device has to be proven in order to get a CE mark as a medical device, but this is usually assessed in a more medical-technical way; it is assessed whether the device is indeed able to monitor and feedback physiological parameters on the human body.

The question is whether both cases of a regulatory vacuum are problematic, for example because the safety of the patient or client is at issue. Both technologies are relatively safe when used by a skilled practitioner, but since these technologies are usually offered in private clinics, supervision on skilled use is less guaranteed than when it would be offered in more regulated environments like hospitals.

Figure 1 gives an overview of the regulatory issues we identified within the scope of this case-study. Enhancement practices of DBS and TMS have quotation marks since these practices are still non-existent but we still think it is advisable to think about future regulatory challenges in these application fields.

4.9.5 Governance vacuum

Next to the regulatory EU framework, other aspects of the European market for medical neurodevices are taken care of in (national) regulatory or governance frameworks. For example, the essential requirements as formulated in the Medical Device Directive and Active Implantable MDD are concerned with the safety of users (practitioners and patients) and the performance of the device. The health care authorities in the different European countries call for requirements on the medical efficacy and efficiency of the devices in order for decisions to be made on whether the devices and treatments get reimbursed or not. Also, the certification of users and therapy protocols are the responsibility of the professional group themselves (professional ethics). Based on our case study we have identified some vacuums in these governance frameworks.

For example, TMS and EEG neurofeedback therapy are generally not reimbursed in European countries, since the extent to which their efficacy and efficiency is scientifically robustly proven is under discussion. Still, these therapies are offered in private clinics. This might divert patients from currently more established therapies like cognitive or pharmaceutical therapy.

Another vacuum is the certification of end-users. Those able to use the devices for clinical purposes are usually regulated by the professional group themselves. In the case of DBS treatment, the surgeons are usually trained on the job by a more experienced colleague. Since the treatment is offered in an (academic) hospital environment, there is usually no cause for concern here. When it comes to EEG neurofeedback, which is mostly offered in private clinics, there is the possibility of registration with the international Biofeedback Certification International Alliance (BCIA), but registration is not mandatory for operating the equipment. In some countries, like the Netherlands, professional organisations for psychologists offer trainings. Manufacturers of EEG neurofeedback devices also offer trainings locally. With TMS, there is no official certification organisation like the BCIA.

However, different trainings are offered by either manufacturers, universities or manufacturers and universities in cooperation with each other. Again, these trainings are not mandatory, although unskilled use can very occasionally result in adverse events like seizures.

The standardisation of treatment protocols is also based on self-regulation within the professional group. In case of research, the medical ethical committees evaluate the proposed protocols. With TMS, the professional group has developed standard guidelines through an international consensus conference on TMS. Also national medical guidelines clearing houses such as NICE in the UK have developed an Inventional Procedures Guidance for TMS (IPG 242). The same goes for DBS. Professional working groups within hospitals develop treatment protocols but here, too, NICE has issued Inventional Procedures Guidance for different medical indications of DBS. In case of EEG neurofeedback, there are some standard protocols, like the Lubar's protocol for treatment of ADHD, but not for other indications. We have not found any medical guidelines issued by national health authorities for EEG neurofeedback. For patients it is therefore important to choose their practitioners with care.

Another well-known vacuum in the governance framework of medical devices and other medical treatments, for that matter, is the lack of harmonisation of reimbursement in Europe; this varies per country. In the case of DBS, this leads to the situation that a CE marked treatment (for certain medical indications), available in the whole European Union, is not equally accessible for all European citizens. This happens more often of course, but it is especially problematic since DBS is a last resort treatment and a very expensive therapy, thus not something most patients will be able to pay for themselves.

The lack of harmonisation of reimbursement means also that it is far from clear to manufacturers how big their market really is once they have developed a CE marked device. This makes developing innovative, novel devices such as DBS a risky endeavour for companies, as it involves huge costs yet the payoff is highly unsure and might even discourage potential manufacturers.

4.9.6 Transparency

We would like to end this conclusion of our case study with a recommendation. Recently in Europe, the database Eudamed has been set up with the aim "to strengthen market surveillance and transparency in the field of medical devices by providing Member State competent authorities with fast access to information on manufacturers and authorised representatives, on devices and certificates and on vigilance and clinical investigation data, as well as to contribute to a uniform application of the Directives, in particular in relation to registration requirements."[55] Its use has been mandatory since May 2011. This is, of course, a very commendable development. However, Eudamed is not accessible for (social or journalistic) research purposes or public organisations like patient organisations or individual citizens. This makes it difficult, for example, in our case study, to study the exact intended use of the medical device or the different regulatory routes that manufacturers of neuromodulation technologies have taken in order to get a CE marking for their medical devices (e.g. did they rely on existing clinical data or not?). These have to be retrieved by approaching the individual manufacturers, although they are not compelled to hand over this information to anyone but health care authorities like the competent authorities or Notified Bodies.

Creating more transparency surrounding, for example, the intended purpose for which conformity to the European requirements is declared makes it harder for medicasters to claim the safety of their products or services for purposes they were never intended for. At the same time, it can contribute to keeping patients and their organisations informed and making it easier for them to choose safe and evaluated applications of devices. Also, (social or journalistic) research on the implementation of the MD directive for any medical device can provide interesting information on certain regulatory or governance issues.

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[55] http://ec.europa.eu/health/medical-devices/market-surveillance-vigilance/eudamed/index_en.htm

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5. BIOCYBERNETIC ADAPTATION AND HUMAN COMPUTER INTERFACES: APPLICATIONS AND CONCERNS

Knud Böhle, Christopher Coenen, Michael Decker and Michael Rader

Summary

The case study on biocybernetic adaptation and human-computer interfaces is an example of the megatrend of 'technology becoming biology', involving what are known as 'intelligent artefacts'. In this field, we can observe a move towards 'situated artificial intelligences', which is the incorporation of aspects of intelligence related to having a body and emotions, as well as living and acting in complex social environments. In this context, the approach of biocybernetic adaptation deserves particular attention because it is expected to become the single most widespread research topic in artificial intelligence (AI).

Biocybernetic adaptation is a new approach aiming to optimize human-computer interfaces. On the one hand, this has the aim of freeing the user from the effort needed to operate technology. On the other hand, it can also be seen as an attempt to deliberately make a computer appear as an interactive partner, able to 'understand' or 'anticipate' user needs. The chapter starts with a review of the state of the art of the technology, identifies the main actors involved in the development and application of technologies incorporating biocybernetically adaptive components and concludes by addressing the principal concerns and regulatory challenges in this area.

A major vision of contemporary AI is to create artefacts with characteristics beyond those linked with 'cold' rationality – artefacts that are capable of displaying emotions and appearing as a genuine partner to human beings. The computer's responses will appear sympathetic or display signs of emotions. In the following, we focus on the implications of such technology for the human side of the human-computer relationship.

Recent developments in the technology of human-computer interfaces include sensors of various types able to register visual and vocal cues of human emotion or to pick up chemical, electrical, mechanical, thermal and magnetic signals emitted by the human body as it changes its state. Sensors are employed in approaches such as affective computing or physiological computing, which incorporate knowledge about the user in order to personalize the computer's behaviour.

Neurophysiological computing goes beyond outward evidence of emotion and attempts to identify concealed emotions through the visualization of patterns of brain activity which have been experimentally matched with emotions. Practical uses currently include the control of machines by handicapped persons, but this technology has also captured the imagination of the producers and users of computer games, which are of increasing economic importance and an important leisure-time occupation. While there are many potential fields of application, three general types of systems are particularly worth distinguishing:

- The computer as a *sensitive interaction partner*, designed to take the place of human communication partners such as parents, teachers, nurses, doctors, friends and so on. Typical applications are in health care, the treatment of patients with neurological disorders, gaming, the control of systems and e-learning. Such systems already exist, although their practical use is mostly at the clinical testing stage.

- Computer systems to *monitor and measure human states* such as performance, attention, fatigue and boredom, in order to intervene when the state becomes undesirable. Here, we will see applications in driving, aviation and other forms of travel. Applications in surveillance are also conceivable. There are already systems in place to monitor car drivers on the basis of bodily signals, with the reaction on the part of the system triggered by the crossing of a fixed threshold.
- *Ambient intelligence* or *ubiquitous computing* is an important application area for biocybernetic approaches. In these cases, the user-interface practically disappears and becomes virtually imperceptible. Pioneering applications include ambient assisted living intended to provide greater independence for the elderly and infirm. If such pioneering applications are successful, ambient intelligence will spread to other areas, including 'intelligent' homes, health care and support for the disabled, as well as industry and business. To date, complete systems are not in practical use, but it seems likely that individual components will be adopted as they achieve maturity, so that systems will be built up gradually.

Most of the applications foreseen are still at the prototype stage with practical experience largely coming from laboratory tests and experiments. The novel features of biocybernetically adaptive systems can be summarized in four interconnected points, which also suggest problems potentially connected with their use: 1) They collect huge amounts of data on people, and various players have a strong desire to access this for their own purposes, such as marketing and the development and distribution of technology. 2) They interpret this data and draw conclusions about human users, which might be right but also wrong. 3) They make decisions based on this data, which might also be right or wrong. 4) The decision results in an action, which, when right, as it should be in the majority of cases, benefits the user, but if wrong, can potentially cause harm to the user.

The long-term vision in this area of 'technology becoming biology' includes autonomous robots and eventually even artificial intelligence equal or superior to that of humans. Once such a vision is realized, human and other forms of natural life will no longer be unique. While we are currently far from realizing this vision, technology able to monitor and interpret human emotions is on the brink of widespread application. This does not mean that technology can actually understand human emotions or is capable of developing its own emotions. However, such technology might display signs of emotion according to a plan determined by human programmers. In this case, the 'technology becoming biology' metaphor should not be taken too literally, as it might create unnecessary hype.

Of greater importance is that biocybernetically adaptive systems are also able to make decisions based on the complex processing of various types of information. While these decisions are based on computer programmes, they cannot be predicted or readily validated by the programmers. This raises various issues, for example: To what extent do the programmes make their own decisions? Who is responsible for the decisions?

Policy recommendations

- The current paradigm of data protection is no longer suitable and will be increasingly challenged by developments in the field of IT, particularly because these developments are increasingly pervasively distributed and of a connected nature. There is a need to develop a 'fair information framework' for networks. This appears to be especially urgent in the application fields of assisted living, ambient intelligence (in practices of care) and even brain-computer interfaces for gaming.

- There is a need for design strategies which embed privacy, transparency and user-control into the architecture of systems. Thus, policy should seek to stimulate research supporting the strategy of 'privacy, transparency and control enhancing technologies'.
- There is a need for an overseeing body to monitor developments and provide early warnings relating to ethical, legal and social issues and to stimulate expert and public debate about these issues (also to anticipate challenges which may only become relevant in the longer term).

5.1. What is the Issue?[1]

Biocybernetic adaptation and human-computer interfaces exemplify the trend towards 'technology becoming biology', involving 'intelligent artefacts'. Biocybernetic adaptation is a new approach aiming to optimize human-computer interfaces. On the one hand, it has the aim of freeing the user from the effort needed to operate technology. On the other hand, it is also be grasped as an attempt to make a computer appear as an interaction partner, able to 'understand' or 'anticipate' user needs.

The 'intelligent artefacts' we are concerned with may not be immediately visible to their user, except possibly in the shape of new input devices measuring signals coming from the human body, or they may be parts of more visible intelligent artefacts such as robots or 'intelligent environments'. One example is a sensor for the measurement of blood pressure to detect stress.

The analysis in the chapter is restricted to adaptive systems incorporating a feedback loop which use the changing mental or physical state of the user as a signal to change their own functionality and appearance.

"Making life more perfect" is the ultimate goal of technology development in general and of the developers of intelligent artefacts in particular. They wish to make the user feel more comfortable using the system and this is realised by user-friendly interfaces. Biocybernetic adaptation is a new approach to optimise Human-Computer Interfaces. By biocybernetic adaptation we mean applications in which vital data of a person in a given situation are collected by a computer-based system and interpreted by the system in order to trigger its own adaptive processes to then instantaneously change its functionality or appearance, such as the software interface. The field of biocybernetic adaptation is of growing importance. Pantic et al. (2008) claim that it is "likely to become the single most widespread research topic of AI", if not of computing as a whole (p.184).

Generally speaking, the aim of endeavours in this field is to make the use of technology simpler for the average user. This can mean that the user is freed from the effort needed to operate technology (the disappearing computer: Streitz et al. 2007, Gates 2003, EU "Disappearing Computer" Initiative[2]). This idea is implicit in visions of "invisible computing" (Norman 1998) which comes with "ambient intelligence", "ubiquitous computing" and "pervasive computing". "Biocybernetic adaptation" can also be employed to deliberately make a computer appear as an interaction partner able to "understand" or even "anticipate" user needs. The overall requirement in technical terms – for both visions – is to increase the autonomy and adaptive capability of computer-based systems, making them "smarter".

[1]From a methodological point of view, this paper is based on a review of literature by the Institute of Technology Assessment and Systems Analysis (ITAS) of Karlsruhe Institute of Technology (KIT), an expert workshop held in Karlsruhe on 14 July 2011, and a questionnaire survey among experts following the workshop. Reports of the expert workshop and the survey data are available on the following page: http://www.itas.fzk.de/deu/projekt/2009/deck0956.htm

[2]http://www.disappearing-computer.net/

The "intelligent artefacts" we are concerned with here are not immediately visible to their user, except possibly in the shape of novel input devices measuring signals coming from the human body. They can also be part of more visible intelligent artefacts like robots or "intelligent environments".

There is little doubt among experts that the major goals of biocybernetic adaptation will be achieved and that a two-way exchange of information between the user and the system will take place. Computers will no longer respond in a deterministic and totally predictable fashion as they become sensitive to the context of the user. "Hype" is an ever-present problem, i.e. it is making greater claims for the technology than it can hold or reading more into applications than they actually accomplish. One of the engineers responding to a project questionnaire thus outlined the challenge facing developers: "We need to be realistic and to manage the public's expectations. There are lessons we can learn from what happened to AI when the public's expectations for that technology ran way ahead. The basics of detecting and rudimentarily classifying physiological states are achievable in the short term and this alone opens up a lot of possibilities".

In this report we will not be addressing all types of "biocybernetic adaptation" but will focus on those adaptive technical artefacts incorporating a *"biocybernetic feedback loop"*. Such biocybernetically adaptive systems use the changing psycho-physiological state of the user in order to change their own functionality and appearance. For instance, teaching systems can adapt to the perceived ability of the learner to take things in by changing the teaching style, e.g. by repeating information more often. Sometimes such systems incorporate avatars, which change their physical appearance in response to the user's mental state. *Biocybernetically adaptive systems* in this sense are coupled with *biocybernetically adaptive user interfaces*. Systems with this adaptation property can be distinguished from systems which simply collect vital data without direct and instantaneous feedback to the user.[3]

We start with a review of the state of the art of the technology, attempt to identify the main actors involved in the development and application of technologies incorporating biocybernetically adaptive components, and conclude by addresssing the principal concerns and regulatory challenges in this area.

5.2. State of the Art of Technology

Recent developments in the technology of human-computer interfaces include sensors of various types able to register visual and vocal cues of human emotion or to interpret changes of a chemical, electrical, mechanical, thermal or magnetic nature occurring in an individual. Such sensors are employed in applications which incorporate knowledge about the user and adapt the computer's behaviour. Three types of system are particularly prominent: the computer as a *sensitive interaction partner, computer systems to monitor and measure human states*, and '*ambient intelligence*' or '*ubiquitous computing*'. One example is neurophysiological computing, which goes beyond the outward evidence of emotion and attempts to identify concealed emotions. Health care and care of the elderly and infirm seem likely to be the first realms in which biocybernetically adaptive systems will find use. Gaming is also likely to be a field where the technology will find early adoption. Most of the applications foreseen for the technology are still at the prototype stage, with practical experience largely coming from laboratory tests and experiments.

[3]Of course there are many applications where vital data are collected for the use of third parties, e.g. in medicine, brain research, marketing, surveillance technologies.

5.2.1. Basic Concepts

We introduced biocybernetic adaptation as systems that use the changing psycho-physiological state of the user in order to change their own functionality and appearance. When describing the basic concepts of biocybernetic adaptation, it makes sense to distinguish data expressing emotions or psychological states (e.g. voice or facial expression) from vital physiological data and neuro-physiological data. "Adaptive computing" can be identified as a basic concept referring to psychological states by using acoustic and visual signals (expressing emotions and those psychological states). Physiological and neuro-physiological computing can add to this. We briefly explain the three concepts in the following.

Affective computing was defined by MIT's Rosalind Picard (1995, p.1) as computing that relates to, arises from, or influences emotions. Affective computing goes beyond physiology by analysing vocal and visual cues such as facial expression, gesture and posture. Furthermore, conversational knowledge and knowledge about social rules and habits (politeness and so on) are taken into account (cf. Malatesta et al. 2009). To incorporate knowledge about a user – in general unnoticed – into a computing system is one of the basic ideas of affective computing.

Physiological computing (including neuro-physiological computing) started in the 1990s and exploits the fact that the human body is chemical, electrical, mechanical, thermal and magnetic in nature. In the case of *physiological computing*, a person's physiological state is sensed and measured in order to improve the adaptation capabilities of computing systems. The more or less unconscious processes of the human body which produce vital data were usually measured and revealed in medical settings only (an inflicted patient and a trustworthy physician). Now they are used to increase the adaptability of computing (Allanson & Fairclough 2004 p. 858 ff.).

To give some examples:

- Temperature measured by infrared cameras.
- Electroencephalograms (EEG) can be used e.g. to monitor the state of alertness. This technology is also being used to transmit silent commands to machines (Porbadnigk et al. 2009).
- Electromyograms (EMG) can be used to inform about the activity of a muscle; e.g. the activity of the muscle of the eyebrow corresponds to pleasant and unpleasant stimuli. EMGs are also used to measure the activity of facial muscles in interpreting so-called "silent speech" (Jou et al. 2005).
- Electrooculograms and pupillometry provide information about visual attention.
- Blood pressure may indicate a state of challenge or stress.
- Electrodermal activities react to audio and visual stimuli (music, violent pictures, erotic stimuli).

Neuro-physiological computing goes beyond outward evidence of emotion and attempts to identify concealed emotions through the visualisation of patterns of brain activity which have been experimentally matched with emotions. Practical uses currently include the control of machines by handicapped persons, and this is a technology currently being adapted for control in computer games.

5.2.2. Application Fields

The survey among experts for the "Making Perfect Life" project came to the conclusion that health care and care of the elderly and the infirm will be the first areas where biocybernetically adaptive systems will find use. As is frequent in the case for novel developments in computing, gaming is considered to be a field where the technology will find early adoption. Opinions on military applications were divided: on the one hand, it was seen as likely that military applications would be of major importance to the technology; on the other hand there was scepticism due to possible side effects and security aspects. Education, safety critical systems and assistance systems were also more controversial with respect to their importance as early application areas for biocybernetically adaptive systems.

So what is the current state of development regarding such systems? We can identify many potential fields of application, but there are three broader areas particularly worth distinguishing, since there already are pioneering applications or these will be realised in the foreseeable future.

First, we can identify a broad array of applications where the computer is becoming a *sensitive interaction partner*, often taking the place of human communication partners such as parents, teachers, nurses, doctors, friends and so on. A second broad application field can be found where systems *monitor and measure human states* such as performance, attention, fatigue, boredom and so on, in order to intervene when the state becomes undesirable: think of assistance systems in all kinds of vehicles and systems in the context of large and complex technical safety-critical fields. Thirdly *"ambient intelligence"* or *"ubiquitous computing"* is an important application area for biocybernetic approaches. In these cases, the user-interface practically disappears and becomes virtually imperceptible.

Computers as sensitive interaction partners

Health care is a major application field targeted specifically by developers. At MIT, researchers are working on an "Interactive Social-Emotional Toolkit" (iSET) designed to help children with disorders linked to sensory processing, such as autism, understand emotions in other people (cf. Khandaker 2009, Sharry et al. 2003, Hudlicka et al. 2008).

In this field, applications have been developed as biofeedback games to treat children with the Attention Deficit and Hyperactivity Disorder (ADHD). Playing the game motivates such children to produce a desirable pattern of brain activity, i.e. by attempting to produce "positive" patterns instead of "negative" patterns associated with the disorder.

Brain-Computer Interfaces were originally developed at MIT for use by persons with disabilities and are being modified for healthy users "in order to enhance productivity or to deliver new forms of gaming experience".[1] The previously mentioned experiments with computer input via EEG also fall into this category: the person concentrates on a word or phrase which is identified by the system and can be used as a command for the system.

Games and interactive media are another important application field: A FAQ on physiological computing[2] describes the Wii and Kinect gaming consoles as in a way being examples of physiological computing in that they monitor overt and observable behaviour. However, they do not tap a data source directly. Instead, the consoles provide the possibility to infer covert psychological states from movement, i.e. the way in which people move in front of these consoles can be used to draw conclusions on their mental state (cf. Choi 2010).

[1] cf. http://www.physiologicalcomputing.net/wordpress/?page id=227

[2] www.physiologicalcomputing.net/

Brain-computer interfaces are currently being developed for gaming (Plass-Oude Bos et al. 2010 a & b) and helmets with small numbers of electrodes as sensors are already being sold commercially. The challenge here is to adapt interfaces developed for impaired users in a way that is attractive for healthy users. Research is also being conducted on the development of emotionally adaptive games, e.g. to avoid boredom and frustration by increasing or lowering challenge levels according to the current state of the gamer (Tijs et al. 2009).

In *e-learning*, affective computing can be used to adapt the presentation of a teacher avatar when the student is frustrated, pleased or bored. In gaming applications it is already possible to scan the expression of the face of the gamer and transport the same expression real-time onto the face of his or her avatar. An interesting example stemming from game development is Project Natal, where a human being in front of a screen makes gestures and movements to which a computer-generated anthropomorphic character responds with gestures and facial expressions.

Assistance systems, systems for safety-critical applications

Daimler is equipping cars with "Attention Assist", a drowsiness-detection system to warn drivers from falling momentarily asleep. The system produces an individual driver profile at the beginning of every journey. This is continuously compared with incoming sensor data measuring steering wheel movements and steering speed. If the system detects typical indicators of drowsiness, it emits an audible signal and a display advises the driver to take a break.[3] It does not actually modify the interface to the driver, so it is not a genuine biocybernetically adaptive system. While the description does not mention recording, it would easily be possible to create a permanent record of an individual driver's behaviour. In some cases, the application functions as an "intelligent mirror", which allows the user to learn about him- or herself and to adjust performance according to requirements. There is obviously great potential for military applications in this area, e.g. to warn when a warrior's attention is waning.

An important motive for the development of direct brain-machine interfaces is the reduction of reaction times in critical applications. An early example is piloting of military aircraft (Asher 2002), which was part of a DARPA program on brain-machine interface. Among the other application fields that could potentially benefit from this research, Asher (2002, p. 357) mentions "learning and training, automobile control, air traffic control, decision-making, remote sensing of stress, and entertainment". In connection with air traffic controllers, there is the suggestion that an "alertness signal" could be used to "wake him up" when his attention drifts "beyond acceptable limits" (ibid.). Similarly, systems incorporating input on the (psycho)physiological states of drivers could be used to reduce car-to-car spacing on otherwise congested highways.

Military and security-related applications include systems that recognise emotion. Bullington (2005) quotes a solicitation from DARPA for such a system to be applied in the "discrete observation of potential enemy threats" (p.96). This has to be understood as a special case of a more general surveillance issue: recognition of emotions as a new strand of surveillance technologies.

Ambient intelligence

Typical application areas include "intelligent" homes, healthcare and support for the disabled, industry and business.[4] Among the new products and services enabled by an intelligent environment of this nature are home networking, health management, interpersonal communication and personalised information services.

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[3]http://www.daimler.com/dccom/0-5-1210218-1-1210332-1-0-0-1210228-0-0-8-7165-0-0-0-0-0-0-0.html

[4]cf. http://moriarty.tech.dmu.ac.uk:8080/index.jsp?page=681764

Much research effort is being devoted at EU level to the concept of "ambient assisted living" for the infirm and elderly which basically consists of prototype applications of the ambient intelligence vision. It is characterised as follows: "the ambient intelligence environment must be unobtrusive (i.e. many distributed devices are embedded in the environment, and do not intrude into our consciousness unless we need them), personalized (i.e. it can recognize the user, and its behaviour can be tailored to the user's needs), adaptive (i.e. its behaviour can change in response to a person's actions and environment), and anticipatory (i.e. it anticipates a person's desires and environment as much as possible without the need for mediation). Therefore, the emphasis is put on greater user-friendliness, more efficient support of services, user-empowerment, and support for human interaction" (Gill 2008, p. 5).

Much of the discussion on ambient intelligence systems has focussed on independent living for the elderly and disabled as well as health monitoring (cf. Gill 2008, Schuurman et al. 2009, Bechtold & Sotoudeh 2008). Most AmI scenarios predict a sunny view of the technological future, while the EU project SWAMI (Safeguards in a World of Ambient Intelligence) also constructed so-called "dark scenarios" to show where things could go wrong and where safeguards are needed (Friedewald et al. 2006).

5.2.3. State of Research and Development of Technology

According to experts that participated in the workshop and the questionnaire survey, most of the applications foreseen for the technology are still at the prototypical stage with practical experience largely coming from laboratory tests and experiments. Scientists involved in research and development would probably not regard existing applications using such things as data helmets for gaming, various forms of physiological input for gaming or driver assistance systems as true embodiments of biocybernetically adaptive computing.

One researcher active in the field identified a strong need for less invasive, more reliable and robust hardware devices and artefacts. The greatest need for the realisation of visions in this area is for more natural, less obtrusive sensing devices which are also better able to separate noise from signal. The public as users and observers of these developments might, on the other hand, be impressed and read more into the technology than is actually justified by technology itself.

The areas considered by experts as most likely to witness *early applications* of biocybernetically adaptive systems are healthcare and gaming. There is less consensus on the viability of such systems for applications in education and learning, or applications in safety critical and assistance systems. However, expert assessments depend on the perceived nature of adaptability: one expert at the workshop doubted that there was much use in a system that adapted to the current mood of a pilot.

In general, there is still much research to be done if visions with respect to affective computing, physiological computing or ambient intelligence are to be realised.[5] Allanson and Fairclough (2004, 870) state "(a) reliable and usable system should aim to maximise the sensitivity, diagnosticity and reliability of candidate measures whilst keeping the intrusiveness to a minimum". Pantic et al. (2008) note that "most present approaches to machine analysis of human behaviour are neither multimodal, nor context-sensitive, nor suitable for handling longer time scales" (p.183).

[5]In the specific case of ambient intelligence, the time horizon set for diffusion in the well-known paper for ISTAG (Ducatel et al. 2001), namely 2010, has long since passed. It seems likely that first applications will be realised for health care or ambient assisted living for the elderly, but that these will only gradually be realised with a linking of components ("islands of ambient intelligence") largely already in existence. Over all, it is felt that the vision of universally applicable ambient intelligence is still some 10 to 15 years at least from realisation.

Despite the huge amount of research still needed to achieve the visions existing on biocybernetic computing, the first applications using information extracted on the user have achieved sufficient maturity for routine use. This demonstrates the viability of the concept and encourages further research for practical applications.

However, Park (2009) points out the limitations to the method of psychophysiology and to the danger of misinterpretation linked with it. The products of research that have reached or are close to reaching practical applications are mainly in areas that are regarded as acceptable by society, such as the treatment of patients with disorders, teaching and learning, ambient intelligence, and safety and security. Systems displaying true emotions or equivalent to human intelligence in other respects still do not exist, and opinion is strongly divided on whether it is fruitful or desirable to pursue research in this direction.

Not all applications require levels of emotional intelligence and responsiveness approaching those of humans. Requirements in this respect depend on the context and the target user group, the tasks the system is to perform and the emotional needs of the user in the context of the application.

Allanson & Fairclough (2004), Pantic et al. (2007, 2008) and Gunes, Piccardi & Pantic (2008) propose agendas for future research work in the field specifically targeting current shortcomings.

- The success of biocybernetic adaptation depends on the identification of appropriate variables to evoke desirable and undesirable psychological states, and this requires basic research into the psycho-physiology of cognitive-energetically variables, such as workload, lapses alertness, anxiety, boredom and so on. For gaming this applies to such concepts as "threat" and "challenge".
- A fundamental challenge for research is that one physiological variable may stand in relation to several psychological elements, or several physiological elements may be associated with an array of psychological elements, especially awareness and attention. In the case of single indicators for several psychological elements in particular, there is the problem whether the indicator is always evidence for the presence of all psychological elements or there is a need to decide which psychological factors are actually involved in the specific case. The more complicated the relationship between physiology and psychology is, the greater the uncertainty and the greater the need for research on the relationship.
- There is a need to clarify how psycho-physiology can be used to represent affective dimensions. The degree of granularity depends on applications: a simple dichotomy can be sufficient for yes or no decisions, but other applications may require measurement on a scale.
- An important aspect in making things work “in the wild” is the integration of knowledge from research on such fields as hardware, software, cognitive sciences and human-computer interfaces.

As a matter of principle, Pantic et al. propose treating the problem as a single complex problem rather than decomposing it into detached problems in human sensing, context sensing and human behaviour understanding (ibid.).

Some of the more specific research problems are:

- There is a lack of consensus on whether information communicated by behavioural systems relates to emotions, social motives, behavioural intentions or all three.
- There is controversy on whether affective states are a separate type of message communicated by behavioural signals or whether behavioural signals are simply illustrators or regulators aimed at controlling the trajectory of a given social interaction.
- There are problems regarding the precision of operationalisation of variables to prevent ambiguity. False diagnoses can lead to inappropriate or unintended responses by the system.

- There is a lack of a comprehensive study on the topic of minimal modal requirements for robust and accurate human behaviour analysis. In cases where several modes are used to collect data, there is the problem of the optimisation of the fusion of data.
- Robust real-time systems must be capable of handling noise and distractions from the environment. The system should be able to detect meaningful changes in received data, which has consequences for the sample rate.
- There could be a need for systems to (re)learn for new users and contexts.

5.3. Main Actors Involved in or Affected by Biocybernetically Adaptive Systems

A useful distinction in relation to sophisticated computer applications is that between organizations and individuals, which reflects the asymmetric power relationship between these two types of parties with respect to organized data processing and communication. In this regard, it is particularly relevant to the issue of data protection. Examples of such pairs include public administration and citizens, private enterprise and customers, health care providers and patients or their family, gamers and game producers, internet users and service providers, and research organizations and potential users. While the relationship between patients and health-care professionals is currently fairly well regulated, there are many open questions in important areas such as e-learning, surveillance or gaming. This issue is examined in relation to systems designed to monitor, assist and, if necessary, to replace the human user in critical situations.

5.3.1. Approach: Power Relationships between Organisations and Individuals

A useful distinction employed by data protection authorities, such as the Independent Data Protection Centre in the German state of Schleswig-Holstein, is that between organisations and individuals. This distinction is made due to the realisation that there is an asymmetric power relationship between these two parties in organised data processing and communication. Examples of the dichotomy are:

- Public administration versus citizens;
- Private enterprise versus customers;
- Practices, institutes and communities versus their patients and clients;
- Scientific organisations versus their objects of research, such as individuals, subjects or people;
- The IT infrastructure providers versus their users;
- Institutions versus their personnel and members.

Each relationship can already be subject to regulation by contracts or laws which require examination if biocybernetically adaptive systems change the power relationship in any way. In the following, we apply this approach to the three broad areas identified earlier.

5.3.2.Computers as sensitive interaction partners

Health care: Here, we are usually dealing with patients and inmates of institutions, such as hospitals or homes for the elderly. Major changes due to biocybernetically adaptive systems can be anticipated in situations where the state of a patient or client is monitored so that part of his or her treatment or environment can be adapted to this state. Prime examples are applications in health care or in ambient assisted living for the elderly and infirm. This could be in hospitals or homes or in the individual's home. Organisations in this relationship are usually represented by professionals, such as physicians or administrators. There is probably a need to log measurements by the biocybernetically adaptive system in order to ascertain why the system behaved as it did, especially if something goes wrong. There might also be a need for measurements over a time period in order to establish "normal" patterns and changes to these patterns. In cases where measurements are available to doctors and other medical personnel, the situation is probably covered by existing legislation and regulations effective in health care, such as the EU Data Protection Directive (95/46/EC), the Directive on Privacy and Electronic Communications (2002/58/EC), the Directive on Protection in the Telecommunication Sector (97/66/EC) as well as the European Convention for The Protection of Human Rights and the EU Charter of Fundamental Rights.

Brain-Computer Interfaces: Again, we are initially dealing with patients, either receiving treatments or controlling devices designed to make their lives more comfortable. The relationships existing in this area should again be covered by the previously mentioned directives. Since this is an area with much research, scientific organisations are important actors.

Games and interactive media: As indicated previously, there is great interest in enhancing gaming experience which would be possible with data helmets as brain-computer interfaces. Again, data over longer periods of time might be stored to tailor the game to the personality of the gamer. While this could be done automatically without intervention from the game developer, a gaming platform or a service provider, games are frequently integrated in networks. The developer has an interest in evaluating experiences with the game in order to develop the same game further or to create new games; gaming platforms have an interest in keeping the games attractive, and this could mean the adoption of measures to prevent cheating.

Games are increasingly no longer played in isolation on a personal computer or games console, but in networks. Since enjoyment can be spoiled by cheating, gaming platforms are adopting measures to prevent cheating. A system called PunkBuster monitors gamer behaviour by inspecting the displayed screen, processes and files associated with each computer system on which a game is running. While PunkBuster claims they do not transmit private data, it does transmit screen shots of gameplay, which are *not considered as private data* by PunkBuster. Similarly, the gaming platform "Steam" claims to own user-generated information, such as chat, forum posts, screen names, game selections, player performances, usage data, suggestions about products or service and error notifications. This information can be used by Steam without further notice or compensation (information provided by Michael Sträubig at the project workshop).

One expert in the questionnaire survey who has a special interest in developing technologies with built-in privacy protection asserted that biocybernetic adaptation already exists and is widely deployed in internet advertising: the information we receive "is determined based on individual characteristics, and it is adaptive (heuristic) as more information is obtained". In this case we are dealing mainly with relationships between enterprises and their customers.

As it is, users might not always be aware that information on them is being collected for marketing purposes or recommendation systems, and there might be need to investigate whether such data collection requires regulation. Since concern about privacy is traditionally a barrier to participation in e-commerce, there is also debate on how to design such systems for maximum user acceptance (cf. Teltzrow & Kobsa 2004).

E-learning: At present, e-learning usually involves a human supervisor (teacher) who monitors the progress that the pupil is making with the adaptive teaching system. Similar to the situation with computer games, program developers have an interest in access to data for the further development of software, i.e. to make it more attractive and to develop new programs.

While existing data protection regulations govern the use of patient data in healthcare applications, the main actors in regulation beside the patient are healthcare professionals. There are, however, other actors with strong interests in access to the huge amounts of personal data collected in the process.

- Is access and use of this data sufficiently regulated to protect against its misuse by unauthorised parties?
- Should teachers or supervisors of e-learning systems have access to data on emotional and physical states of pupils? Is there any need for such access?
- In what form should user data be made accessible to developers wishing to develop systems further or to develop new applications?
- There is also the issue of "emotional attachment" to systems superficially displaying emotions. Attachment to systems could substitute attachment to humans, either because human emotion is substituted in care applications (for financial reasons or because there are no family members nearby) or because it is more difficult for some people to form attachments to other humans (e.g. addicted gamers).

5.3.3. Assistance systems, systems for safety-critical applications, surveillance

Surveillance of public spaces to ensure greater public safety is an area being discussed in connection with practically all technologies with potential in this respect. In the questionnaire distributed to a number of experts following the project workshop, the project team asked the question whether surveillance "is a likely, suitable and desirable application field for physiological and affective computing". One expert, who is actually active in the field of developing such systems, regarded such applications as undesirable because the monitoring of physiology which would be essential for technology of this kind should only be performed with the consent of the individual. Furthermore, this expert insisted that such technology could only function with the necessary precision if links between physiological activity and psychological concepts were fully validated in the field as well as in the laboratory.

Public reaction to developments in this direction can be gauged from an attempt at a field trial of a system attempting to visually identify potential hooligans in a crowd attending a football match. A trial in Karlsruhe was abandoned due to the public outcry which caused club leadership to deny any knowledge that such a trial was planned.[1] In other cases, public resistance was apparently not sufficient to prevent such trials. Waugh (2011) reports: "Cops were able to identify football hooligan ringleaders in crowds at West Ham games with the help of…software".

There is much demand for greater public security and experts claim that acceptance is increasing (Waugh, 2010), so that promising technologies would likely find a market. However, the validation problem looms large, since this would require the collection of data from subjects with genuine criminal intent, and not simply simulating such intent, as was pointed out at the project workshop.

[1]http://www.ftd.de/wissen/leben/:gescheiterte-feldforschung-karlsruher-institut-stoppt-projekt-zur-gesichtserkennung/60084936.html

Tests of biometric face recognition technology in the US at the beginning of the new century failed (Feder 2004), but Osama Bin Laden was identified by means of face recognition after he had been shot (Waugh 2011). Such successful applications are used by its proponents to underline the maturity of the technology. Waugh (2011) also claims that "[g]overnment officials believe that the September 11 attacks could have been prevented, if biometric face detection system were used in airports".

The actors in this field are the public at large (citizens) and public authorities, such as police services and other security services. In some cases, security services are offered by private enterprises and in such cases, the treatment of personal information is particularly sensitive.

In the case of assistance systems, the main actors are the "agent", such as a driver, pilot, operator and so on, his employer (if any – such systems might be used by drivers for private trips), supervisory authorities and insurance companies. Such applications raise important questions, such as:

- Are users obliged to use the system at all times, and what happens if they do not?
- What happens if the user disagrees with the system?
- Is the user entitled or even obliged to override the system if he or she has the feeling that the system is drawing the wrong conclusion?

5.3.4. Ambient intelligence

The most likely applications of ambient intelligence are "ambient assisted living" for the elderly and disabled. As one expert pointed out, this area has received much public funding and support due to urgency as a result of demographic trends in many industrialised countries. The main actors in this application are the patient or elderly person, care givers and medical personnel, authorities, and family members. Most of these actors are present in medical applications previously discussed.

- A major question in the use of such issue systems is the amount of assistance the systems should provide. Should this be adaptive according to the user, or should the same amount of assistance be provided to each user?
- Who decides on the level of assistance: the user, the user's family, or a specialist? How can the level of assistance be reduced if a patient's or elderly citizen's condition improves?
- In the case of ambient intelligence systems for "normal" citizens, much the same questions arise, but there is also the question as to what extent the system confines the user. If it responds to known profiles, wishes and preferences, how can it enable the user to explore new things or question his or her own preferences?

5.4. Principal Concerns and Possible Needs for Regulation

The most obvious and important social, legal and ethical issues in this kind of application are privacy and data protection. Another major issue is the autonomy of the user; that is, the user may have the feeling that he or she is being manipulated by the technology. Extremely sensitive data on human users is already being collected, such as data related to the user's health or emotional state in medical applications. This can be extended to healthy users, ostensibly for the purpose of making computer applications more user-friendly. The collection of data is a necessary condition for enabling full adaptation by the system. It is obvious that such data can easily be misused or used for purposes other than those for which it was originally collected. Transparency in relation to data collection, processing and use is thus an important requirement. In addition, systems that can intervene may erode skills and reduce user competence. Another concern is the ability of systems to 'read minds'; however, this is not currently on the horizon.

5.4.1 Main Concerns

The most obvious and important social, legal and ethical complex in this kind of application is privacy and data protection. A second major issue is the autonomy of the user, i.e. the user may have the feeling that he or she is being manipulated by the technology.

In all of these applications, extremely sensitive data on human users is collected, such as data related to the user's health or emotional state. This is ostensibly for the purpose of making the application more user-friendly. Therefore the collection of data is a necessary condition for enabling full adaptation by the system. It is obvious that such data can easily be misused or used for other purposes than those for which it was originally collected.

With respect to autonomy, one of the experts attending the workshop pointed out that this includes a number of distinct aspects:

- The right to voluntary dependency
- The right to be independent
- The right to choose or change the situational context of dependencies
- The right to deliberately ignore even against one's own rational interests
- The right to deliberately "not know", even if this is counter to the notion of rational choice

The discussion of impact on autonomy is thus not as simple as it might appear at first glance, i.e. is the user's autonomy reduced or not?

5.4.2. "Mind Reading" and Persuasive Computing

In connection with brain scans, the issue is already being discussed under the heading of "brain privacy" or "mental privacy" (e.g. Farah 2005, Thompson 2008, Highfield 2008).

Brain scanning (or "brainotyping", Farah 2005, p. 35) has similarities with brain-computer interfaces monitoring emotional states and the data gained for this purpose could be used to predict mental health vulnerabilities. It has also been shown, for instance, that unconscious racial attitudes are manifest in brain activities (ibid).

Much the same problems arise in connection with measurements of data on body functions or on gestures, facial expressions when these are related to the mental or physical state of users, and so on. Farah points out that the public tends to view brain scans as more accurate and objective than in fact they are (ibid.). There is a widespread belief that "the brain does not lie", which manifests itself in popular writing on such issues as brain-scan based lie detection, and by analogy it would also apply to body measurements, the meaning of facial expressions and gestures, and so on. In the case of affective computing, system capabilities have sometimes been described as bordering on "mind reading" (Bullington 2005, p.98).

The use of EEG to enable silent speech by asking a person to concentrate his or her mind on a word which is then recognised with the help of a sensor helmet is currently not completely accurate and requires the person to concentrate strongly on the word in question. Improved sensor techniques and better noise filtering might ultimately enable something bordering on mind-reading in future.

Affective computing could be applied in systems deliberately trying to influence peoples' attitudes or behaviour. This is discussed in connection with use of such systems by political regimes, but it is also at the root of "neural marketing". Lay persons in an ETICA[2]project focus group were, indeed, concerned that computers would be able to "read their minds", and this question is central to the ethical question of a "right to mental privacy".

However, one of the engineers pointed out, "human brains can't yet understand human brains", so we are nowhere near being able to create artificial brains that can read human minds. She put especial emphasis on communication from science to the public about the vast limitations that research was facing. Her colleague explained this in detail: "People need to understand that measuring psycho-physiological data will deliver a quantitative characterisation of a psychological state or experience. It is true to say that the technology will 'read minds' but only with respect to a crude, impoverished representation of the mind. Nevertheless, the capability of technology to represent the mind of the user, even in this crude form, is likely to be a cause for concern - particularly if these data are shared with others or represented at the interface in a public space. 'Mind reading' is not in reach."

One direction of affective computing has been termed *persuasive computing* (Fogg 1998). Persuasion can be understood as the attempt to shape, reinforce or change behaviours, feelings or thoughts about an issue, object or action. In many cases, persuasion will require motivation. Persuasion requires intentionality and as computers do not have intentions of their own, a computer qualifies as a persuasive technology only if those who create, distribute, or adopt the technology do so with the intent of affecting human behaviour. Considering brain-computer-interfaces, the meaning of persuasive computing may become extended to actions like reading or manipulating the mind.[3]

5.4.3. "Body Reading" and Intimate Computing

Biocybernetic technology is designed to "tap private psycho-physiological events" (Fairclough 2008, p.9) for use in dynamic human-computer interfaces. Rogers (2009, p. 1) actually states that "even the human body (is) now being experimented with as (a) potential place (...) to embed computational devices, even to the extent of invading previously private and taboo aspects of our lives". Ostensibly, this is to the user's advantage, although previous sections have described ways in which the data can be abused.

Physiological computing is closely linked to *intimate computing*, where intimate knowledge about a person is made available to a computer, which is able to process it and to react on this input. The w*earable computer* is an interesting case of intimate computing; examples are watches with ambient temperature sensors, heart straps for joggers, pedometers for dieters and so on. The news is that these artefacts are becoming wireless and applied outside a clinical setting providing direct feedback to the wearer without intermediation by professionals (Teller 2004, S. 917ff.). Again, the presupposition here is the same: computers should "have knowledge" about the user in order to interact more appropriately with human beings.

[2] The EU 7th Framework Project ETICA (Identifying Ethical Issues of Emerging Information and Communication Technologies). Homepage: http://moriarty.tech.dmu.ac.uk:8080/

[3]In popular culture, the film Inception (2010), directed by Christopher Nolan, plays with the idea of planting an idea within a person's subconscious mind by manipulating dreams.

Questioned in the expert survey about risks and threats, one expert expects new methods of surveillance. Intracorporal surveillance in medicine may be an important starting point. Others argue that there is nothing new under the sun, because computers are essentially vulnerable and open to surveillance. Manipulation by computing systems is seen as a real danger. And these threats are indeed imminent since we cannot think that only 'good guys' will make good use of such devices. A broad international academic and societal discourse is necessary and this should also consider cultural differences in attitudes to such things as privacy and enhancement.

5.4.4. Data Misuse

One of the data protection experts drew attention to the fact that projects such as Facebook, Ambient Assisted Living and Smart Grids were simply ignoring existing regulations on privacy and data protection. The market and the rule of law were no longer effective in rectifying this situation. Thanks to biocybernetically adaptive systems, organisations would have access to improved databases while the consequences for the subjects of this data were not clear.

In this connection, there is the question of how much privacy is really left due to the existence of social networks and of surveillance technology in public places, which are both important trends in changing societies.

In some cases, the user is not informed about the data and its interpretation and use to adjust the machine; in fact, unobtrusiveness of the interface is regarded as a desirable property. This is, for instance, the case in ambient intelligence and ambient assisted living. On the other hand, there are also cases in which mechanisms are deliberately transparent as part of a learning process.

Depending on the amount of data collected and the conclusions that are drawn from the data on the individual, it is possible to develop detailed personal profiles of various natures:

- Typical reactions in various classes of situations (e.g. stress or loss of control);
- Behaviour patterns (e.g. typically low performance at certain times in a week, following late nights and so on.), which can be used to discipline users;
- Assumptions about stress tolerance, ability to work under pressure and so on;
- Assumptions about personal strengths, weaknesses and anomalies.

This is particularly the case in assistance systems and safety critical applications, but data which could be used for similar purposes can also be collected in applications of e-learning or gaming. Data can be used to draw assumptions that might not be known by their subject and these assumptions could be used to make decisions on personnel: hiring and firing, promotion and so on.

A problematic aspect of use of personal data lacking transparency is its interpretation, which is frequently automatic and mostly not subject to consent by the user. Another critical aspect is the tension between the collection of very large amounts of data to enable very specific adjustments by the system, and the restriction to few indicators thought to be most relevant in the context of any application, which might be misused to draw very rough and general distinctions. It may be assumed that there are also personal and cultural factors to be considered in such applications, for instance, the meaning of facial expressions can vary widely.

One of the philosophers completing the questionnaire asserted that privacy and computers do not go together well at all. “Privacy = control over my personal data. Computers = loss of control over all sorts of data. Privacy ≠ Computers”.

Another expert pointed out that an emphatic understanding of privacy equates it with total self-determination, without any influence by heteronomous powers. All other concepts of privacy are based on this idea. "Forget privacy" means "Forget autonomy". Physiological Computing applications should not be allowed if they constrain autonomy. Technology can be justified if it gives new possibilities for action and if it takes the load off humans.

One of the developers commented that notions of privacy were changing over time: "[…] my understanding is that what concerns my generation in terms of privacy does not concern the following generation to the same extent. My nieces and nephews - all teens - do not think about data protection and privacy. This kind of paranoia about who will steal my data and how it will be used against me is learned behaviour. I read 1984 as a school text and Huxley paranoia about state control seemed prescient. But the world we've actually created is very different from his dystopian vision. We used to be able to pass our belief systems - good and bad - onto our children. But we're not their only source of information any longer. Their shared online culture, though not without its issues, is much more open, creative and collaborative. So in summary I don't believe there are any urgent concerns to be discussed and solved today."

A more pragmatic view acknowledging privacy concerns was expressed by the other developer: "my feeling is that users will desire clear information about privacy and data protection that places them in full control before they will be willing to use these systems."

The visions for ambient intelligence currently in existence imply that ultimately all members of society will use biocybernetic systems and thus be affected by them. However, pioneering applications are intended for use by the handicapped and infirm or elderly persons and by specialists in safety-critical situations. A very obvious critical issue in this connection is that of privacy. It is sometimes argued that it could be impossible to design, for instance, ambient intelligence systems in a way that completely prevents unauthorised access to personal information (cf. Heersmink et al. 2010, 33).

Brey (2005, 99) summarises privacy issues in relation to Ambient Intelligence: "The privacy risks of AmI are so great because of the often highly sensitive types of personal information that are recorded and encoded, the scale on which this information is recorded, and the ease with which it could potentially be disseminated and made available to other parties."

Fairclough (2008, p.9) mentions another threat to privacy through the way in which explicit feedback from the system is communicated to the user, namely whether it can also be perceived by colleagues or other persons in the same space as the computer. This applies especially to auditory feedback.

5.4.5. The Vision of Symmetry in Human-Computer Interfaces

Developments resulting from the opportunity to track the state and needs of human users are sometimes described as progress towards *symmetry in human-computer communication*:in the past, the user had much information about the technology he or she was using, but the technology had virtually no information about the users and had to "treat" each user in the same way (Kelly 2006). While several participants at the project workshop regarded this as a non-issue, the expert survey showed that it is a genuinely controversial issue.

A system that is designed to achieve greater symmetry in the communication between the user and the system has, in fact, potential to create asymmetry with respect to data protection (Fairclough 2008, p.9). According to current data protection regimes, the user retains formal and legal ownership of psycho-physiological data (Hancock, Szalma 2003 in Fairclough op. cit.). Certain data can also give evidence for the existence of medical conditions of which the individual might be unaware, potentially providing means for covert health monitoring.

In this connection, Kelly (2006) has proposed four criteria for information exchange between systems and their users:

- I know what information is being collected, where and why, and by whom.
- I assent to it either implicitly or explicitly, and I am aware of it.
- I have access to correct it, and can use the data myself.
- I get some benefit for doing so (recommendations, collaborative filtering, or economic payment).

As stated above, the idea of greater symmetry between humans and machines is rather controversial. While engineers interpret symmetry as the adaptation capacity of computers to user needs, philosophers object: "A better vision would be to clearly develop an asymmetrical vision where humans and machines have own identities".

Another philosopher states that there are more urgent ways to improve the user friendliness of computing systems: "[…] user friendliness, in particular GUIs, still has a lot of open questions. Why not solve these first?" The most radical statement starts that today "the system knows more about the user than the user about the system". The same expert denies the viability of the vision of adaptation to an individual: "A system always supports the user as a stereotype". The main problem he encounters is "the disappearance of the system as a means". In other words, to him it does not appear to be desirable for machines to appear as partners, team players or in other social roles.

5.4.6. Manipulation

Even in cases with good intentions, such as making systems easier to use and more "user-friendly", the user is, in a sense, being "manipulated" by technology. An important issue in this context is who retains control over the process of manipulation. Picard and Klein (2002) argue that affective computing systems should support self-management of data rather than treating the user as a passive recipient.

To the extent that computer interfaces become unobtrusive and seamlessly blend with their environments, data collection is not consciously experienced although users might well feel uneasy in the knowledge that they are constantly being monitored and profiled.

Data gathered by systems on health-relevant behaviour could be employed to influence the future behaviour of individuals, e.g. by offering a lower insurance premium if the individual adopts a healthier lifestyle.

A view expressed in the expert survey was that "people will likely reject anything seen as someone else's view of "good for them" or anything conceived as a mechanism of behaviour modification or control." This aspect is also present in the view of philosophers, who are particularly concerned about long-term effects: The impact on human self-perception is a long term-effect that is not restricted to these devices but concerns the digital field as a whole or the impact of digitisation on our perception of reality. We need a deeper philosophical understanding of such changes that concern our relation to the world and to ourselves, and not 'just' the impact of digital devices on a human subject that would (and should) remain apparently unchanged. Another voice regards the loss of autonomy of man and the impact on self-perception as major problems. Attitudes of planning one's own life and the belief in engineering will increase; the dependency on complex and intelligent systems will increase too. A critical reflection of technology claims (Geltungsreflexion) is required.

5.4.7. Influence of Systems on Decisions and Skills

Current systems suffer from measurement and interpretation errors, and errors in the context of Ambient Intelligence could well cause harm to users, e.g. by falsely identifying persons as a threat to security in surveillance systems.

One danger of systems appearing as intelligent to their users is that too much will be read into superficial behaviour, i.e. that users might feel that the system understands them, or that, on the other hand, it could desensitise them to genuine emotional behaviour. Self-definition of humans could well change in a world inhabited by apparently intelligent and emotional computers.

In the case of assistance systems designed to step in in cases where a human is perceived to be performing sub-optimally, there is the danger of erosion of skills, since the user relies on the system taking over when he is tired, makes mistakes and so on. An important issue here is that of personal working styles and the thresholds for intervention of the system: if the expert has an idiosyncratic, but nonetheless effective working style, the system could intervene too early. This in turn could influence the expert's future behaviour so that he or she adapts to what is expected by the system. This could, in turn, affect the expert's effectiveness.

5.4.8. Social Impacts

According to results of two focus groups organised by the European Commission's ETICA project, citizens are most worried about the potential loss of human contact and emotion, as well as loneliness, which could be caused by "emotional" computers replacing human contacts.

Michelfelder argues that pervasive computing, which builds largely on psycho-physiological computing, compromises existential autonomy: "the right to decide for ourselves at least some of the existential conditions under which we form and develop our ways of life, including our relations to information technology" (2010, p. 61).

Feelings of being disenfranchised by technology are frequently mentioned in connection with systems for ambient assisted living, even though there is a statutory requirement that patients must give informed consent to medical treatment (Schuurman et al. 2009, p. 133). There is tension between having one's actions supervised and living autonomously (Bechtold et al. 2008, p. 18).

5.5. Research on Biocybernetic Adaptation

With respect to biocybernetically adaptive systems, we are dealing with a technology that is still at a very early stage of development. Recommendations can thus first be made with regard to the research required for the further development and implementation of these systems. Three kinds of research can be distinguished in this context: (1) privacy, transparency and control-enhancing research, (2) basic research on concepts, and (3) research on the philosophical, ethical, technical and societal dimensions as well as cultural differences within Europe and between Europe and other regions of the world.

The first type of research is especially urgent with regard to systems and applications which are already in development. Technology can only be successful if it is sufficiently transparent to the user and if it is considered to be beneficial during the interaction. At the general level, a machine should be designed to require the permission or control of its user concerning the degree of assistance it automatically provides.

There is also still much need for research on the relationship between physiological measurements and observations and psychological and emotional states. Basic research is needed on sensor technology, algorithms and software development.

5.5.1. Opening Remark

The options for decision-makers in relation to biocybernetic adaptation include support or, in extreme cases that are not yet apparent, prohibition of research in the area and measures concerning the existing regulatory framework. With biocybernetically adaptive systems, we are dealing with a technology that is still at a very early stage of development, so that its final state is difficult to recognise. Hence it is not possible to confidently provide recommendations. Furthermore, we are dealing with an enabling technology similar to existing interfaces, which thus has to be viewed in specific contexts.

In general, the novel features of biocybernetically adaptive systems can be summarised in 4 points which also point towards problems potentially connected with their use:

- They collect huge amounts of data on humans which other actors strongly desire to access for their own purposes, such as marketing, development and distribution of technology and so on.
- They interpret this data and draw conclusions about human users, which can be right or wrong.
- They make decisions based on this data, which can also be right or wrong.
- The decisions result in actions, which when right, as they should be in the majority of cases, benefit the user, but if wrong, can potentially cause harm to the user.

In this coming section we will address options related to research and the design of technology, and in the subsequent, final section, we will address the regulatory framework governing the development of biocybernetically adaptive systems.

5.5.2. Design and Characteristics of the Technology

Technology experts, such as those who responded to the questionnaire, recognise that technology can only be successful if it is sufficiently transparent for the user in its interactions and if it is assessed by its benefits during this interaction.

The expert on privacy technology described the lack of transparency as the most urgent concern related to biocybernetically adaptive systems: "We know far less than we should about how these techniques are deployed, what their purpose is, how their effects are measured, who profits from their use, and who is responsible for their actions.

While the notion that the user should have full control over the technology sounds sensible, it is regarded by some as unrealistic: computers do not have such control potential for users, even experts. Explicit control would probably be contra-productive in contexts where the computer is supposed to "disappear" to enable particular experience and interactions. However, the expert on privacy technology felt that technology that collects and interprets a person's vital data without the person being aware of the fact is "poorly designed technology".

One of the data protection experts described "control by the user" as the central paradigm of modern proactive, technically oriented data protection. This implied that the machine should perform in a foreseeable manner within the boundaries of the system, even if it could theoretically perform "intelligently" and "autonomously" in a manner not predictable by the user or most other parties.

At the general level, no machine should provide assistance without the permission or control of its user. This applies particularly to assistance systems, but also to ambient intelligence systems, including those for ambient assisted living. This is an important required condition to attribute responsibility and liability. As noted previously, an autonomous user might voluntarily choose to be dependent on a care giver or an intelligent system which responds to his needs and his physical and psychological states.

Ambient assisted living is most probably the entry point for biocybernetically adaptive systems into society. The need for careful design will probably make such systems expensive, which raises the issue of justice: should health care systems be obliged to provide ambient assisted living to every patient who needs it?

Theoretically, it should be possible to design a machine that is technically and organisationally subordinate to the user.

One of the experts had been a driving force behind the concept of privacy enhancing technologies, which he described as "techniques that minimise or eliminate the collection of personally identifiable information".

In all biologically adaptive systems, there is the question of who is in control of the on and off switch and who decides whether the system should be switched on or off. Another issue is whether the user has the power to delete data or conclusions that the system has drawn on the basis of such data.

A question resulting from decisions on these matters is whether the user needs to justify why he or she switched off the system, e.g. resulting in the interruption of a time series of measurements for scientific purposes. Can an insurance premium be increased due to greater risk if the system is switched off? This question is of particular importance in connection with assistance systems or ambient intelligence, especially AAL.

Users would most likely be required not to work against the machine. This is due to economic concerns, which put issues of responsibility and liability in the foreground. It would then not be possible to deliberately ignore safety measures that worked against "intelligent assistants". In cases of conflict, the user would have to prove that he or she acted in a system-conforming manner. But precisely this rule-setting from outside undermines the user's right to informational self-determination.

The potential for the use of new technologies for monitoring and surveillance exists, as does the risk of personal data falling into the wrong hands, but developers in particular would solve any problems through tradeoffs between surrendering personal data in return for benefits, such as more personalised services.

5.5.3. Basic Research on Concepts

There is still much need for research on the relationship between physiological measurements and observations and psychological and emotional states. Basic research is needed on sensor technology, algorithms and software development. There is a need to determine the benefits and disadvantages of holistic and piecemeal approaches respectively, and to examine how interdisciplinary cooperation can best be encouraged.

5.5.4 Policy Options

Are *"privacy enhancing technologies"* a means for protecting citizens' interests? Is the EU pursuing this line of technological development in its research and development funding?

The EU could support *research on the relationship between physiological measurements and observations and psychological and emotional states*, basic research on sensor technology, algorithms and software development.

There is a need to determine the benefits and disadvantages of *holistic and piecemeal* approaches to biocybernetically adaptive systems respectively and to examine how interdisciplinary cooperation can best be encouraged.

Research could be done on the *specific data protection aspects* of technologies logging, storing and accessing affective and physiological data.

At the more basic level, there might be a need for an *in-depth contextual analysis* of biocybernetically adaptive technologies, considering their philosophical, ethical, technical and societal dimensions and cultural differences within Europe and between Europe and other regions of the world.

For emerging technologies, a monitoring process might be set up to provide early warning of *ethical, legal and social* issues. An *overseeing body* (observatory) for this purpose is a major recommendation of the ETICA project.

Once systems for ambient assisted living are fully developed and available on the market, should health insurance institutions be *obliged to provide* such systems to anyone who needs them?

5.6. The Regulatory Framework

The current paradigm of data protection is no longer suitable and will be increasingly challenged by developments in the field of information technology, particularly because these developments are increasingly pervasive and of a connected nature. There is a need to develop a 'fair information framework' for networks. This appears to be especially urgent in the application fields of assisted living, ambient intelligence (in practices of care) and even brain-computer interfaces for gaming.

There is a need for an overseeing body to monitor developments and provide early warnings related to ethical, legal and social issues and to stimulate expert and public debate about these issues (also to anticipate challenges which may only become relevant in the longer term).

5.6.1. Approach

In this final section, we will address the need for new regulation due to the novel aspects of biocybernetically adaptive technology. As explained in the introduction of this report (section 1.3.1.), we employ the dimensions "sociotechnical practice" and "regulatory framework".

In the dimension of sociotechnical practice, we distinguish by the degree of novelty of the practice:

- is it a stable, already existing practice
- does it constitute a shift or advance in existing practice, or
- is it completely new?

Examples of new sociotechnical practices include ambient assisted living and "mind reading"; shifting practices include new gaming experience through new types of interface and new challenges due to biocybernetic adaptation and covert health monitoring, while stable practices relate to many applications in health care.

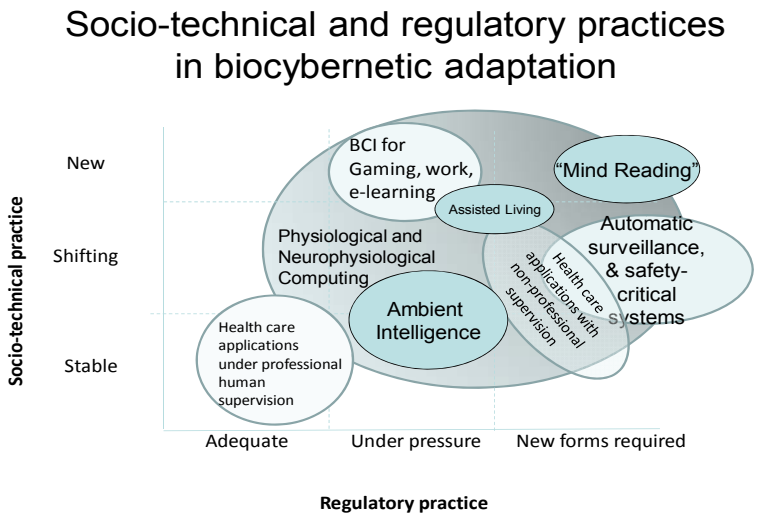
In the regulatory dimension, we distinguish according to whether

- the existing regulatory framework is sufficient and requires no change,
- the existing regulatory framework requires adjustment, i.e. it is developed in the right general direction but does not sufficiently cover certain novel aspects of emerging sociotechnical practices,
- the existing regulatory framework is insufficient and requires redesign or completely new forms of regulation to adequately address biocybernetically adaptive technologies.

In figure 1 we have mapped the technology and its various application fields according to these two dimensions. The new technology itself is perhaps best termed *"physiological and neurophysiological computing"* (represented in the diagram as the large oval). The systems incorporating this kind of computing are *biocybernetically adaptive systems*. These are applied in various contexts which are governed by regulatory practices. Whether such practices are adequate, under pressure or inadequate and needing new forms of regulation depends on specific sociotechnical practices.

These have been examined for the examples used throughout the text, which are by no means exhaustive. The diagram shown above is not able to grasp the dynamics and interdependencies of technologies, application areas and regulatory schemes, but it may serve to guide the debate about regulatory efforts needed.

Figure 1:



5.6.2. General Issues

The data protection aspect is present in all of the application areas discussed in connection with biocybernetically adaptive artefacts. The most relevant regulations in Europe are the EU Data Protection Directive (95/46/EC), the Directive on Privacy and Electronic Communications (2002/58/EC), the Directive on Protection in the Telecommunication Sector (97/66/EC) as well as the European Convention for The Protection of Human Rights and the EU Charter of Fundamental Rights.

According to existing data protection regimes, monitoring must be for a specific purpose, be "fair and lawful" and not involve the retention of more data than is appropriate. Data may not be retained for a period in excess of what is necessary to serve the purpose, and measures must be taken to ensure that the data is accurate. This sets requirements for the interpretation of data, i.e. how to ensure that the interpretation is accurate, which might create problems for biocybernetically adaptive technology creating semi-permanent profiles based on disputable interpretation of measurements.

A problem related to many kinds of new information and communication technologies was particularly highlighted by one of the data protection experts:

- There is a need for the reform of existing regulations to cope with a *multitude of components and their operators* and the development of a *"fair information framework"*. In the longer term, data protection regulation might seek to be *proactive*.
- Similarly, there is a need to address *issues of data sharing* and the *rights of the individual* with respect to data from his or her own body data network. Encryption and anonymity are partial solutions. There might be a need for model contracts between users and service providers. A possible option is to require the *solution of privacy and security issues* before technologies are launched into applications by the introduction of licensing processes.

- Regulations could ensure that machines *perform predictably*, within the confines of a defined system. They could also require the user to *grant permission* for the machine or system to provide assistance or determine who, in each situation, has the *right to switch the machine or system off*.

5.6.3. Issues Related to Health Care

Relationships between patients and health care professionals are adequately regulated and the new technology should do little to change the general situation. This applies particularly to applications in cure and therapy (left hand side of bottom third of the diagram). However, applications in care, including ambient assisted living, increasingly involve actors who are not health care professionals, such as care-givers, family members and the patients themselves. The roles of these actors are currently not sufficiently regulated, e.g. who is entitled access to what data, how this data should be handled, and so on.

5.6.4. Ambient Intelligence

Actors here include the owners of private spaces equipped with ambient intelligence, their occupants (partly the same), visitors and actors involved in the running and maintenance of the spaces. While the aim of ambient intelligence is to make life more comfortable for people inhabiting spaces equipped with the technology, there is the problem that huge amounts of data can be accumulated by outsiders and it is not clear what use can be made of the data, e.g. use of profiles of individual users or spaces for advertising, health monitoring etc. There is also the question whether visitors entering or approaching spaces equipped with ambient intelligence should be made aware of the presence of the technology.

5.6.5. Automatic surveillance and safety-critical systems

Can biocybernetically adaptive systems be used for monitoring and surveillance? How reliable are current technologies for the purpose, and do the benefits outweigh possible impacts on privacy and personal freedom?

It is sometimes asserted that privacy regulation focuses strongly on Western attitudes. Since the development, production and application of technology is globalised, insistence on Western values might, in the long run, isolate Western industrialised countries. Here, the question is whether there will be separate developments according to existing values, or whether there will be pressure to surrender values to global competitiveness.

A broad international academic and societal discourse is necessary, and this should also consider cultural differences in attitudes to privacy and enhancement.

In automatic systems, there is a need to regulate to what extent the systems should be allowed to follow their diagnosis and adaptation with actions, e.g. to isolate or disarm individuals identified as potentially dangerous. Current systems still have a "human in the loop", but automatic systems would normally function without human supervision.

Should users have the *right to ignore assistance systems* where these exist, and are there situations where the use of such assistance systems, when they exist, should be *compulsory*? In what situations is the user entitled to ignore their advice? Who bears the consequences in cases of conflict regarding the outcome of use or non-use of assistance systems?

Does the requirement not to work against the system undermine a *user's right to informational self-determination*? If so, how can dilemmas between this right and the need for safety be resolved?

5.6.6. The use of Brain-Computer Interfaces for Gaming, Work or Learning

Brain-computer interfaces are being developed mainly for use in health care applications, where their use is regulated through the health care professional-patient relationship. As is almost always the case, new kinds of human-computer interfaces attract the attention of computer games developers and gamers, seeking to provide new types of gaming experiences. New kinds of data could be produced by games incorporating biocybernetic adaptation. The handling of this data definitely puts pressure on existing regulatory practice, e.g. regarding the uses of data accumulated during gaming, which is of great interest to games developers and other actors.

Brain-computer interfaces are also of great interest in working-life applications where humans are controlling tools or devices and unable to use other kinds of input, because their hands and feet are needed for other functions and the environment is dangerous or noisy. Since the system might collect more data than is essential for its functioning, regulation needs to be examined with respect to any need for revision.

E-Learning, another conceivable field of application for novel interfaces, is frequently supervised by qualified teachers, but it can also be used without supervision or as freely available software. How will the use of data be regulated in such contexts?

5.6.7. "Mind Reading"

Although true mind reading is not within reach, the capability of technology to represent the mind of the user, even in a crude form, is likely to be a cause of concern for citizens. One the one hand, this means that researchers will have to be very clear and transparent about the goals of research in this area, but on the other hand, there will be a need to investigate requirements for regulatory practices to frame applications.

5.6.8. Attitudes and Values

Finally, it may be observed that privacy concerns vary according to culture and generation: privacy concerns might well disappear due to changes in society as a whole. The opinion that there is already not much privacy left due to trends such as social networks and a demand for greater security in public spaces has already been mentioned. A survey could be conducted to establish whether this is the case, and if so, seek to identify trends and reasons and investigate the need for changes to existing regulations.

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6. STANDARDISING SYNTHETIC BIOLOGY: CONTRIBUTING TO THE BIOECONOMY?

Markus Schmidt and Helge Torgersen

Summary

The megatrend of 'biology becoming technology' implies that scientists and engineers increasingly look at living organisms in mechanical terms. Synthetic biology is a good example of this trend as it aims to construct living organisms for useful purposes. To do so, it applies engineering principles in a much more fundamental way than traditional biotechnology. One of its aims is to turn existing micro- and other organisms into fully predictable 'living machines' through standardized interventions. Although not living up to all the optimistic predictions, stunning results have already been achieved.

In addition, the reciprocal trend of 'technology becoming biology' is manifest in the even more ambitious aim of producing 'artificial life' from scratch, using non-living matter and endowing it with all the necessary features. Some progress has been made in building whole bacterial genomes from chemical substances, but thus far the essential information has not yet been 'devised from scratch', nor has the complicated molecular apparatus of a cell been fully reconstructed. Therefore, claims of having 'created life' are, at best, exaggerated.

Being conceptualized as an engineering field, synthetic biology has the capacity to bridge the gap between basic or applied research and technological development. Even at present, in the early stage of synthetic biology, practical applications are central, serving highly economically relevant purposes, such as fighting malaria or producing energy sustainably. Thus, synthetic biology promises to substantially contribute to a future bioeconomy.

The engineering principles applied follow those governing fields such as electronics or mechanics. One of the most important is standardization, which makes it possible, for example, to use ready-made parts and combine them at will. Methods from molecular biology and information from genomics serve to construct standardized genetic building blocks with known functions, designed to be universally applicable (at least in micro-organisms), substantially increasing the freedom of combination and the variety of ends pursued.

However, all this is based on the reductionist premises that genetic parts can be designed to a sufficient level of standardization, performance and reproducibility, and that organisms are clearly defined by their genome sequence. A substantial section of the synthetic biology community believes this is the case; however, thus far only a few standardized elements have been constructed and been proved to function as intended.

The deliberate engineering approach in synthetic biology invites analogies. In the popular media, standardized genetic elements are often compared to Lego bricks, as both can be freely combined and used in a wide variety of similar tasks. More serious analogies are derived from information technology (IT), especially with respect to standardized building blocks – genetic elements are compared to electronic parts which are assembled into circuits. Taking this comparison further, IT practices, such as separating design, construction and assembly, are also important in synthetic biology. Analogies even pertain to the future technical importance of the field and anticipated benefits. Like IT, some consider that synthetic biology will develop quickly and become immensely powerful and economically important. Whether this will occur is unclear because many obstacles still have to be overcome. Some experts even say that for fundamental reasons this will never occur.

The main question is how to appraise the importance of synthetic biology in relation to other fields of biotechnology. Across Europe, political reactions have been non-uniform and until recently funding has been patchy in many places. To cope with the existing US dominance, European involvement might entail not only massive funding but also promoting the establishment of technical standards.

A by-product of the anticipation, realistic or not, that synthetic biology will be hugely important is a controversy over how to handle emerging intellectual property. As in IT, open source or open access approaches stand opposed to a process of extensive protection of intellectual property through patents. Although a mixed practice seems to be emerging, accepted standards are also required here. Another effect of the anticipated technical power of synthetic biology is the fear of potential misuse and accidents, entailing the demand for new safety standards. Although existing standards appear to be sufficient at the moment, this could change. Synthetic biology itself might contribute to the development of new safety and security methods but only if there are adequate incentives at hand.

Finally, synthetic biology has frequently been attributed with the potential power to blur the boundaries between life and inanimate matter. High-level expert reports have repeatedly addressed concerns, primarily with respect to 'creating life'. This may not only lead to ethical problems but also to public unease, with some fearing that synthetic biologywill be rejected by certain sections of the general public in the same way as plant biotechnology. They therefore advocate outreach activities and a public discourse early on to bring potential concerns to the fore. Ultimately, limits to certain applications could be discerned according to societal standards developed in a public debate.

The policy challenges posed by synthetic biology can be condensed into **options for standard-setting activities** in four areas:

Technical engineering standards would be something relatively new to biology as they are largely absent today. Options include:

- Wait and see: watch the development without extensive influence
- Foot in the door: contribute moderately to the establishment of standards
- Massive support: invest heavily and set standards to catch up with the US

Safety standards should set clear rules to ensure technological development while preventing dangerous or unwanted effects. Options include:

- Business as usual: rely on the traditional biotechnology regulation
- Monitoring: continuously assess whether existing regulation is adequate
- Precautionary action: adopt new approaches in which synthetic biology offers to ensure safety/security

Intellectual property management is a key factor in technology implementation. Today, open source and open access stands opposed to comprehensive patenting. Options include:

- Business as usual: leave it to the synthetic biology experts, they will determine what to do
- A helping hand: promote research and institutions to facilitate open approaches
- Active openness: enforce a legal basis in areas such as open access

Societal standards should develop out of the public debate, but such a debate may imply the risk of negative public opinion. Options include:

- Business as usual: leave the fate of synthetic biology to supply and demand
- Anticipating concerns: stimulate public debate to reveal concerns and devise measures
- Mandatory assessment: actively prevent societal misuse by monitoring each project

6.1. Definition of the term and role of standards

Synthetic biology is understood as the design and construction of new biological parts, devices and systems, and the redesign of existing, natural biological systems for useful purposes. As in all engineering fields, comprehensive technical standards would streamline use and thus contribute to the bioeconomy. Professional and safety standards would facilitate its embedding in society. The blueprint for standardization could come from information technology (IT). Since standards not only enhance performance but also give a competitive advantage to those who set them, efforts in standardization could pay off. However, whether it will be possible to standardize living objects in the manner of electronic circuits remains to be seen.

6.1.1. Synthetic biology and the bioeconomy

The concept of a knowledge-based bioeconomy emphasises economic opportunities for high-tech interventions into living organisms in order to establish an efficient and environmentally beneficial industrial biotechnology (European Commission 2004). The original focus of the concept was on plant biotechnology, but other areas have come into focus as well. Among the aims are: the replacement or supplementation of chemical activities, the enhancement of sustainable energy production, the abatement of environmental degradation and the effective generation of knowledge-based products, such as novel drugs (European Commission 2005). More recently, Synthetic Biology with its aim at making biology a true technology promises to fit in nicely, as its engineering-inspired approach offers new ways to reach the above goals (Henkel and Maurer 2007). The idea of creating living artefacts has been hailed as a technical revolution, evoking ideas of total engineering, ultimate precision and applicability of biological objects. The question is whether this approach will fulfil the expectations.

Previous efforts using more conventional or, as some consider them, 'artisan' forms of biotechnology were often hampered by problems from the seemingly arbitrary behaviour of the components of complex living systems, giving rise to some unpredictability in the outcome, and a lack of full comparability and interchangeability of experimental setups. Engineering, in contrast, aims at standardising parts and systems to the extent that it becomes irrelevant who uses them in which setting – essentially, they should function according to their definition, provided all parameters have been set correctly, almost irrespective of contingencies (Ellis et al. 2011). Thus, standards are at the very heart of the approach.

Although the term 'Synthetic Biology' (here abbreviated as SB) was already used 100 years ago (Leduc 1910, Leduc 1912), the contemporary version is a relatively young field at the intersection of biology, engineering, chemistry and information technology (Campos 2009). Typical for an emerging technoscience, a variety of definitions are circulating, and there is no single definition that would receive total support by all researchers involved in SB activities. The probably least contested definition can be found on the SB community webpage:[1]

Synthetic Biology is: A) the design and construction of new biological parts, devices, and systems, and; B) the re-design of existing, natural biological systems for useful purposes.

Thus, SB aims to 'make biology easier to engineer' in two respects. Firstly, it aims at a profound reconstruction of living organisms for useful purposes, at 'living machines', in ways not found in nature. Reconstruction is to be considered in a top-down way, with biology becoming technology. Secondly, SB aims at constructing organisms from non-living matter, which constitutes a bottom-up approach of turning technology into biology, resulting in artificial life.

[1]http://syntheticbiology.org/

Frequent analogies to other engineering fields illustrated these ideas. Especially during the early days of contemporary SB, they were taken almost literally, rendering somewhat exaggerated comparisons with mechanical and electronic engineering. For example, during an early international conference in 2006 (SB 2.0), frequent analogies were made to the industrial revolution[2], and it was claimed that SB would trigger a similar epic change. Another example is the ubiquitous 'electronic and software speak' to describe biological systems: the cell and its subsystems are being compared to computer and software and the concept of a biological part is explained in analogy to an electronic part.

However, this aim and related metaphors used by individuals who heavily promote standardisation in SB have also raised criticism from and doubt within other scientists. In contrast to the rather optimistic point of view of engineers who push forward the 'real' engineering of biology, many biologists are much more cautious and doubt that biology can be engineered in such a way. Some theoreticians have pointed out that they see SB as yet another attempt at applying an extremely reductionist and positivistic perspective to the science of biology (O'Malley et al. 2008). The main counterargument is that biology is too complex to be fully understood, standardised or engineered at will. So the question is: can engineering approaches tame the complexity of living systems?

Indeed, even supporters agree that there are many challenges looming on the way from biology as a science towards biology as a technology. In a feature for the journal *Nature* (Kwok 2010), the author quotes a Harvard graduate student saying that "[t]here's a lot of biology that gets in the way of the engineering." Concretely, major obstacles are identified in five fields, namely in the definition of parts, in the predictability of circuits, in mastering systems' complexity, in the mutual compatibility of the parts used and in the variability of systems. In other words, biological engineering relying on properly functioning, compatible and predictable standardised parts and systems is but a dream at present.

However, this is not a general argument against the feasibility of definitions and standardisation in synthetic biology. From previous examples of technology development and implementation (from the 19th century's nuts and bolts to the 20th century's computer systems; for a history of standardisation attempts see Wenzelhuemer 2010) we know that it always took some time to arrive at mutually accepted standardised formal languages, parts, procedures and measurements. Despite the incredibly complex tasks of the engineering successfully achieved today, there is still a long way to go to master the unprecedented amount of complexity in biological objects.

Against this background it becomes clear why standardisation has become a crucial issue in synthetic biology, although not to the same degree for all involved. Regarding the role of standards, two schools of thought can be discerned:

Not the least as a precondition to making biology easy to engineer, a well-understood and highly structured science of 'cell-omics' is being developed, where standards are important tools. If, however, the full standardisation of parts would turn out to be impossible, SB would be able to live on.

In contrast, enthusiasts for a 'real' engineering approach consider standardised parts and procedures available to engineers for construction purposes as essential, so they link the success of this endeavour to the future of SB as a whole.

Whether the ambition of the engineering approach in SB will succeed – as important actors are convinced – or is doomed to fail – as sceptics believe – is crucially dependent on the question of standardisation. Since many promises regarding contributions to practical applications come from protagonists of standardisation, this is a key issue for SB's future role in a knowledge-based bioeconomy.

[2]made possible by a new technique that used coal/coke instead of wood as fuel to produce iron in furnaces.

6.1.2. Standards and some of their functions

Standardisation in some form is ubiquitous in almost all fields of science and technology. Essentially, a standard determines the principles of design, production and performance of a product or process.[3] It may serve several purposes:

- Standardisation within a scientific context involves the development of a common language and common tools, which make the life of researchers easier because they can name and measure the world in ways that create mutual understanding. Standards are thus means to make sense of scientific findings within a field and thus to better understand nature.
- Standardisation within the engineering context is primarily an act of facilitating the application and streamlining the use of technologies to practical ends. Engineers may rely on the properties of a standardised object – without bothering with its internal structure – in order to fit it into their designed system as a functional element.

These forms of standards pertain to scientific objects as well as to research and development methods. They are usually developed bottom-up, i.e. they are set by scientists and engineers in their own interest to facilitate their work. Thus, bottom-up standards tend to be more easily accepted; they can be adapted to technical progress, and compliance is high in most cases.

Apart from standards pertaining to objects and scientific methods, there are also standardised forms of behaviour or of dealing with the contingencies of scientific and engineering work:

- Professional standards such as codes of conduct for those involved in science and technology are essential to 'running the business'. For example, it is through peer review that a scientific community defines what is to be accepted as a relevant research result and may therefore enter the corpus of knowledge. Thus, standards of practice to substantiate a claim are safeguarded while being recurrently modified according to the latest state of technology.
- Related to this, standards on how to deal with intellectual property develop out of a need to determine ways to commercially exploit scientific insights and engineering achievements, and reflect the tradition in a field.
- Safety standards are set up to prevent harm, foremost for those who work with the pertaining object or method, so scientists and engineers develop such standards first and foremost for their own well-being. When it comes to security questions, i.e. the prevention of intended harm, professional standards also become relevant as a form of self-defence.

However, the moment other members of society are affected, more general considerations come into the picture and some see a need for regulation beyond voluntary agreements such as codes of conduct.

- For many technologies, compulsory standards are considered necessary to prevent harm to human health and the environment, i.e. to ensure safety and security.
- Standardisation within a regulatory context may also be seen as more encompassing, namely by involving forms of governance that aim at a socially and economically robust development of the technology. Not only should it satisfy safety or security demands, it should also serve to pursue broader aims such as sustainability and wellbeing.

[3]Sometimes the term 'standard' is also applied to a product itself in the sense of a 'prototype' that serves as a benchmark for other similar products. Although economically important, we do not refer to this understanding in the following.

In contrast to technical and professional standards as well as safety standards regarding the hazards that lab workers are exposed to, such standard-setting usually evokes more criticism among scientists and engineers as it may entail an additional burden on their work rather than facilitate it. Nevertheless, successful and trustworthy standardisation, in a societal sense, is crucial, because it is a precondition for a new field to fulfil the economic and societal expectations it raises.

It has to be kept in mind, though, that standard-setting is not a purely technical endeavour even when it comes to *bona fide* technical standards. There is always social interaction in the development of standards, be it in the form of a dominance of some actors over others or by way of an agreement upon a common understanding (Mai 2011, Stemerding and Hilgartner 1998). Standards may heavily influence the way a field develops and privilege some actors while discriminating against others. History shows that in the beginning of a field's development, a lack of or multiple standards may impede collaboration and integration. Later in the development, suboptimal standards haphazardly developed from practice may result in a path dependency that is difficult to overcome (David 1985). In addition, those who could impose their standards on others had an advantage in technology development and subsequently, trade and revenue generation, rendering standardisation an eminent technical, economic and political issue (Hesser 2006). Thus, standard-setting might also be seen as a sensitive act of governance requiring a clear regulatory framework.

6.1.3. Standards in biology

With biological organisms, attempts at standardisation are not new. From taxonomy to agriculture to modern biotechnology there are standards galore – although not always indicated as such. Biotechnology heavily builds on defined strains of micro-organisms or enzymes. Cell culture lines to be selected and retrieved from institutional collections are standardised to perform to certain parameters.

Historically within the life sciences, standardisation has been closely linked to language and terminology to denote, describe and analyse living objects. From Linnaeus' 18th century attempt to categorise the overall *imperium naturae* by means of a binary nomenclature, up to the genomic description of biological species and the digital ontologies and annotation standards used in systems biology, biological terminology has been the subject of standardisation. Standardisation in the context of basic research is as much a technical necessity as it relates to an ontological proposition about the (living) world.

Now, the introduction of an engineering, i.e. synthetic perspective into biology brings an entirely new challenge. Although there are many different schools and subfields in SB, one of the most prominent ones highlights standardisation as the most important aim to make biology easier to engineer. Thereby, it introduces a new way of structuring the world according to the traditions of (a) computer-based design and testing, (b) abstraction hierarchies, and (c) decoupling of design, construction and assembly.

Objects of synthetic biology, accordingly, are assembled ideally from basic building blocks into functioning systems (Ellis et al. 2011). Vice versa, elements of biology are being treated as if they were mechanical or electronic artefacts. Both ways blur the border between biology and technology much more so than traditional approaches of biotechnology. Objects of SB therefore fall between the categories of living organisms and non-living artefacts; of material objects and pieces of information. Processes can accordingly be considered interventions into both living and non-living systems, as manipulations of matter and as modifying information content.

Not only epistemic and ontological aspects are affected; rather, the new perspective entails big changes in many practical aspects such as particular ways of dealing with intellectual property related to traditions in computer science. To make biology easier to engineer, proponents of this form of SB adapt biology to a new culture rooted in an engineering tradition, in particular from computer engineering. This involves a new understanding of the role of technical standards; or rather, the meaning of the term 'standard' transgresses the understanding as applied in conventional biotechnology.

In the following, we will concentrate on this approach within SB, namely the intended production of standardised biological parts and their assembly into systems, because it is most prominent in the discussion of potential applications that may contribute to a knowledge-based bioeconomy. We will describe, in a first part, the landscape of main actors promoting this approach. We will then investigate some aspects relating to, and preconditions necessary for, technical standardisation in more detail. In a separate section, we will deal with the question of where SB stands in the innovation path, what might be hope and what could be hype. The next section is dedicated to socially relevant implications such as the impact on safety standards, intellectual property rights and other socially relevant issues. After a short overview over ELSI activities and SB funding in Europe, the final section is dedicated to governance options that derive from these insights.

Conclusion: Synthetic biology (SB) promises to contribute to a knowledge-based bioeconomy in many ways, as it includes many research areas. A prominent aspect is the standardisation of parts and procedures. In biology, various standards have long been applied, but the engineering perspective of SB results in a new understanding of technical standards, with potentially broad implications. However, it is not yet clear whether engineering standardisation can be emulated with biological objects in the same way as with traditional technical objects.

6.2. Major approaches, communities of researchers and the public image

Synthetic biology is a multifaceted field: activities differ with respect to the object (chemical molecules, simple or complex organisms), the aim (synthesis of genes, whole genomes or life forms) and the time horizon (carried out today, rendering first experimental results or pertaining to distant future projects). Today, the 'BioBrick' approach is most prominent, producing standardized genetic building blocks (often compared to Lego bricks) to be put together and mounted into simple organisms to perform useful tasks. Here, standardization is as paramount as nuts and bolts are in mechanics. A whole community has been established around this approach, with US scientists, many originating from IT, dominating and shaping the image of synthetic biology in the public arena. Other groups are gaining ground, some Europeans among them.

6.2.1. A dominant voice in a chequered field

Activities falling under SB are currently performed in several diverse fields (Bedau and Panke, 2009; Benner and Sismour, 2005; Deplazes, 2009; Luisi, 2007; O'Malley et al., 2008; Schmidt et al., 2009; Schmidt and Pei 2011):

1. DNA synthesis (or synthetic genomics)
2. Engineering DNA-based biological circuits (based on genetic engineering but using real engineering principles)
3. Defining the minimal genome (or minimal cell)
4. Building protocells (or synthetic cells)
5. Xenobiology (or chemical SB)

These activities differ not the least in the amount of complexity and 'unfamiliarity', a measure of 'artificialness' as compared to standard biotechnological approaches, so far. Table 1 gives an overview of different activities and the associated complexity and unfamiliarity.

The area of metabolic engineering might constitute a separate column; however, if it largely follows established practices of genetic engineering (though more ambitious) it would clearly have to be considered 'familiar'; more advanced forms would perhaps fall under column B (genetic circuits).

The list is far from exhaustive – for example, with regard to complexity, in the more distant future one could also think of engineered tissues and organs, of altered multi-cellular and higher organisms, or even of entirely synthetic ecosystems composed of fully synthetic organisms.

For a number of reasons (e.g. different school of thoughts), scientists do not always refer to these diverse activities when talking about SB. For the time being, fields number 1 and 2 are most prominently covered in the popular media when they report on synthetic biology, not the least due to individual scientists from these fields who are particularly active in communication. It appears sometimes as if SB is mainly about synthesising genomes and engineering DNA circuits.

For the issue of standardisation, however, these fields are the most important. The reason is that main actors and driving forces behind standardisation in synthetic biology are working in these fields. Most of them are located in the US, where a particular group of scientists has emerged that in their aims transgresses the boundaries of a purely scientific community; rather, one may speak of a 'movement' promoting a particular form of SB. In the following, we concentrate on describing their ideas and visions, because when it comes to standardisation, this movement is of eminent importance, as standardisation is at its heart.

Table 1: Complexity levels (1-4) and 'unfamiliarity' levels (A-E) in SB (Schmidt and Pei 2011)

	A: DNA synthesis	B: Genetic circuits	C: Minimal genomes	D: Protocells	E: Xenobiology
1:Biochemistry	-	-	-	Standard or alternative biochemistry	Alternative biochemistry, xeno nucleic acids (XNA), unnatural bases and amino acids
2: Genes/parts	Synthetic genes	Genes and bioparts, bioparts	-	Engineered phospholipids	Changing the codon assignment of genes
3: Biological systems	Artificial chromo-somes synthetic viruses	Enhanced metabolic engineering * bioparts and devices	-	Cellular vesicles lacking key features of life	Development of novel polymerase and ribosomes
4: Organelles, single-cell organisms	Whole genome synthesis	-	Top-down SB reducing existing organisms' genomes	Real synthetic cells, bottom-up SB, manufacturing whole cells	Xeno-organisms, chemically modified organisms

*** Such as the synthetic artemisinin project**

The beginning of the movement can be pinpointed to the year 2003, when Tom Knight and Drew Endy attempted to 'apply engineering principles to biology'.[4] Knight and Endy, both with an engineering background, became interested in biotechnology and were apparently disappointed by the lack of design and engineering principles in the field of genetic engineering when compared to other fields like electronics, mechanics or automotives. Coming as an outsider to the field of biotechnology, Tom Knight, a senior research scientist at MIT Computer Science and Artificial Intelligence Laboratory CSAIL, developed the so-called 'Assembly standard 10' in 2003 (see below), that laid the foundation for the Registry of Standard Biological Parts[5] and the 'Biobricks' Foundation.

The Registry of Standard Biological Parts, founded in 2003 at the MIT, is a collection of genetic parts (i.e. DNA sequences) that are used in the assembly of systems and devices in synthetic biology. 'Biobrick(s)' is a trademark describing a particular type (or brand) of standard biological parts[6,] and the foundation's aim is to promote this particular approach. Drew Endy, a junior fellow and then assistant professor at the Department of Biological Engineering at MIT, teamed up with Tom Knight to further develop and promote Biobricks.[7] The following quotes by some of the 'founding fathers' explain the impetus of this form of SB:

> *'…the standardization of pitch diameter and form of screw threads (provided) the infrastructure which allowed the industrial revolution to take off.'* Tom Knight, 2003 [8]
>
> *'Much of the power of these assembly techniques arise from consistent, widely available set of components.'* Tom Knight 2002[9]
>
> *'tremendous costs accrue owing to the lack of standards in biological engineering.'* Drew Endy, 2005

6.2.2. Building a community

During MIT's Independent Activity Period (IAP) in January 2003, student teams designed biological oscillators that were coupled to fluorescent reporters. These biological constructs were intended to improve on the so-called Elowitz's Repressilator, a device that is widely acknowledged as one of the first successful synthetic biological circuits (Ellowitz and Leibler 2000).[10] During MIT's IAP in January 2004, student teams from five US universities[11] designed genetic systems to create patterns from cell aggregations (e.g. 'bull's eyes' and 'polka dots', dynamic designs where bacterial cells were genetically instructed to swim together). From these designs, standard biological parts (i.e. DNA sequences) were designed and synthesised. Based on the experience of these two IAPs, the summer of 2004 saw the first official International Genetically Engineered Machine competition (iGEM), although the five participating teams all came from the US. However, over the coming years, more and more teams from all around the world started to participate in the following annual iGEM competitions (see table 1). In retrospect, iGEM's function of community building has been deemed immensely important.

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[4] although a few articles were published before (Arkin and Endy 1999).

[5]http://partsregistry.org/Main_Page

[6]http://BioBricks.org/faq/

[7] Currently the BioBricks Foundation board of directors consist of Drew Endy, Tom Knight, David Singh Grewal, Richard A. Johnson, Jack D. Newman, Randy Rettberg, Pamela Silver and Mark A. Fischer.

[8]http://web.mit.edu/synbio/release/docs/BioBricks.pdf

[9]http://openwetware.org/images/e/e9/BBFRFC7.pdf

[10]http://parts.mit.edu/wiki/index.php/Iap_2003

[11]Boston University, CalTech, MIT, Princton Universtiy, University Texas Austin

What is the iGem Competition?

The International Genetically Engineered Machine competition (iGEM) is the premiere undergraduate Synthetic Biology competition. Student teams are given a kit of biological parts at the beginning of the summer from the Registry of Standard Biological Parts. Working at their own schools over the summer, they use these parts and new parts of their own design to build biological systems and operate them in living cells. This project design and competition format is an exceptionally motivating and effective teaching method.

Table 2: iGEM competition chronology: the number of participating teams and countries represented[1].

year	teams	countries
2004	5	**1**
2005	13	**5**
2006	32	**15**
2007	54	**19**
2008	84	**21**
2009	112	**25**
2010	130	**25**
2011	165*	**24**

*** In 2011, the competition was split into three regional pre-competitions: The Americas, Europe-Africa, Asia-Australia**

The iGEM competition is shaped along the lines of similar engineering jamborees in other fields such as the Robocup competition[2], Shell's ECO-marathon[3], and so on. They are all designed to elicit enthusiasm among young scholars in engineering and to trigger these scholars' self-commitment for a limited and stimulating but hard time in a group of like-minded peers. They compete against other similar groups for the sake of joy and honour only; any financial interest is secondary to the issue of winning the contest. This form of building a strong yet transient community gives a very similar picture irrespective of the technical objects the competition is about. Thus, it is a very successful and eye-catching format of education rather than a research endeavour and it provides opportunities also to outsiders. Nevertheless, there have been significant technical developments as well, with an eye not only for just having fun, but also for practical applications, as is shown below.

[1]http://ung.igem.org/Main_Page and http://ung.igem.org/Previous_iGEM_Competitions

[2]www.robocup.org

[3] http://www.shell.com/home/content/ecomarathon/

Examples of iGEM team projects

Arsenic Biodetector: The aim was to develop a bacterial biosensor that responds to a range of arsenic concentrations and produces a change in pH that can be calibrated in relation to arsenic concentration. The team's goal was to help many under-developed countries, in particular Bangladesh, to detect arsenic contamination in well water.

BactoBlood: The UC Berkeley team worked to develop a cost-effective red blood cell substitute constructed from engineered E.coli bacteria. The system is designed to safely transport oxygen in the bloodstream without inducing sepsis and to be stored for prolonged periods in a freeze-dried state.

E. Chromi: The Cambridge team project strived to facilitate biosensor design and construction. They designed and characterised two types of parts – Sensitivity Tuners and Colour Generators – in E. coli engineered to produce different pigments in response to different concentrations of an inducer. The availability of these parts revolutionised the path of future biosensor design.

Heidelberg: In addition to their wetlab project, the Heidelberg team dedicated themselves to the ethics aspect of their project. Their aim was to inform the public, prevent fear and provide to the public the knowledge necessary to form an opinion on the upcoming field of synthetic biology. Source: iGEM 2011[4]

An important insight into the background of the iGEM competition can be derived from the list of sponsors over the years, especially regarding the increase and decrease, respectively, of different groups of actors. It turns out that the interest of the industry has so far been moderate; in contrast, the interest of the US defence community is ongoing or increasing[5].

6.2.3. Standardisation beyond BioBricks

The group of scientists that initiated and stand behind the iGEM competition, in particular Drew Endy, also promote the development of standards as the following quotes illustrate:

> '*Standards are also needed to support a vibrant, constructive and responsible community of biological engineers.*' Drew Endy, 2005
>
> '*If synthetic biologists continue crafting tools that simplify genetic engineering, it will become much easier for anyone, regardless of training, to construct novel biological systems.*' Billings and Endy, 2008[6]

After Endy moved from MIT to Stanford University, he co-founded a new movement for the standardisation of biological parts, the so-called 'biofab'. The biofab is presented as the BioBricks Foundation's Research and Development service.

[4]http://ung.igem.org/IGEM/Learn_About

[5] For example, the US Defense Threat Reduction Agency was the main sponsor of the SB 5.0 conference in 2011 http://www.dtra.mil/Home.aspx. Also, the FBI has conducted several synbio workshops, see e.g. http://virtualbiosecuritycenter.org/event/fbi-synthetic-biology-iii-workshop.

[6]http://openwetware.org/images/7/73/16cribsheet.pdf

About the biofab

The International Open Facility Advancing Biotechnology (biofab) was founded in December 2009 as the world's first facility for biological design. This professionally staffed public-benefit endeavour was initiated by a grant from the National Science Foundation (NSF) and is led by bioengineers from UC Berkeley and Stanford University. The biofab is operated in partnership with the Lawrence Berkeley National Laboratory (LBNL), the BioBricks Foundation (BBF), and the Synthetic Biology Engineering Research Center (SynBERC).

Biofab projects will be designed to produce broadly useful collections of standard biological parts that can be made freely available to both academic and commercial users, while also enabling the rapid design and prototyping of genetic constructs needed to support specific needs of partner efforts such as the SynBERC Testbeds. The biofab will thus also represent the first significant focused investment in the development of open technology platforms underlying and supporting the next generation of biotechnology. Once fully operational, the biofab facility will be capable of producing tens of thousands of professionally engineered, high-quality standard biological parts each year. Source: Biofab 2011[1]

Although members of biofab and BioBricks are most prominent with regard to standardisation, there are also a number of other institutions, organisations, networks, and so on, dedicated to setting and developing standards in SB.

Synthetic Biology Open Language (SBOL) Group: A group of (mainly US) scientists trying to develop a formal language for synthetic biology (see table 3 for more information)[2]

Gingko Bioworks: A SME based in Boston and co-founded by Tom Knight that uses a combination of reusable standard biological parts and synthetic meta-genomics approaches to design multi-gene pathways with the help of CAD tools.[3]

Table 3: Synthetic Biology Open Language (SBOL) Meetings

Considerable efforts have been made in the US to arrive at a commonly accepted standardised Open Language

Date	Topic
April, 2008	Standards and Specifications in Synthetic Biology Workshop Seattle, WA 2008
July, 2009	Synthetic Biology Data Exchange Working Group Meeting Stanford, CA 2009
June, 2010	SynBioDEX Group Meeting Anaheim, CA 2010
January, 2011	SBOL Workshop Blacksburg, VA 2011
June, 2011	SBOL Workshop San Diego, CA 2011

[1]http://www.biofab.org/about and http://newscenter.berkeley.edu/2010/01/20/biofab_synthetic_biology/

[2]http://www.sbolstandard.org/

[3]http://ginkgobioworks.com/

Synbiostandards: A BBSRC funded British network of scientists aiming to create a space for sharing ideas and developing a common language and set of tools for SB research. [4]

Centre for Synthetic Biology and Innovation (CSynBI): Based at the Imperial College London, the centre aims to establish a robust engineering framework for the design and optimisation of new SB parts, devices and systems and to integrate this research with emerging ethical legal and societal issues.[5]

EC-US Task Force on Biotechnology Research held a workshop on Standards in Synthetic Biology in June, 2010, in Segovia, Spain, where US and European scientists discussed technical issues.[6]

EC FP7 funded project on SB standards: A 4 year project currently under negotiation will probably start autumn, 2011, involving several key scientists and industry groups throughout Europe (see Annex A for the call text).

DARPA Living Foundries Program: A new funding scheme from DARPA provides $30 mio for creating technological advances and innovations to push the boundaries of biological design towards the ultimate vision of point-of-use, on-demand, mass-customisation biological manufacturing.[7]

DNA Synthesis Companies: Several DNA synthesis companies support standardisation efforts via a cheap supply of custom-made DNA and biological software service. The market for on-demand DNA is expected to grow significantly over the coming years, and successful engineering and thus a scale-up of biology might give the field an additional boost.

***Conclusion**: The 'BioBrick' and 'biofab' approach is the most important school of thought in SB that emphasises standardisation of parts and circuits. It is dominated by some US engineers and scientists, although Europeans (mainly from the UK) contribute, too. More recently, a number of new groups and institutions have enriched the standardisation debate. Drawing from traditions mainly in computer sciences, there is a strong emphasis on community building. Through the annual student competition iGEM, promoters managed to create a thriving and growing international SB community promoting efforts in standardisation.*

6.3. The link to information technology: analogies and technical standards

Some scientists consider living organisms to be information-processing machines and model synthetic biology on principles applied in information technology (IT). For example, 'abstraction hierarchies' have been introduced in which levels of biological organization in organisms are compared to levels in computer organization. Standardization applies when assembling genetic parts into circuits, which requires universal plug-ins. This would allow a division of labour, separating design, construction and assembly. Communication may use special 'design languages' similar to those used in electronics. Thus, IT and biology are deeply entangled in synthetic biology.

[4]http://www.synbiostandards.co.uk

[5] http://www3.imperial.ac.uk/syntheticbiology

[6]http://ec.europa.eu/research/biotechnology/ec-us/workshop-on-standards-in-synthetic-biology-2009_en.cfm

[7] see: Pennisi E. 2011 DARPA Offers $30 Million to Jump-Start Cellular Factories. Science. Vol. 333: 147, and https://www.fbo.gov/index?s=opportunity&mode=form&id=77b10102cba5c98c6be6b5c3d7a11387&tab=core&_cview=0

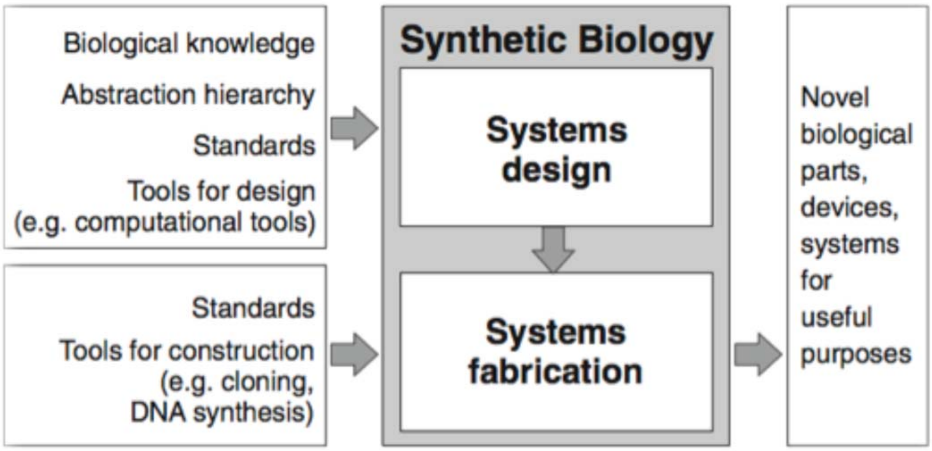
6.3.1. Making biology an engineering discipline

A Scientist discovers that which exists. An Engineer creates that which never was.

Theodore von Karman

Today, the ability to engineer biology in a rational manner is still limited. As a consequence, the complexity of things that bioengineers can make is rather low. SB, with its engineering vision, aims to overcome the existing fundamental inabilities in systems design and systems fabrication by developing foundational principles and technologies that ultimately enable the successful engineering of biological systems for improved and novel applications (Figure 1). According to the supporters of the BioBrick school in SB, there are several engineering principles that need to be implemented in biology in order to make it a real engineering discipline with societal and economic impact (Endy 2005, Heinemann and Panke 2006). Accordingly, standards are a keystone.

Figure 1: Standards as a keystone for SB. Encompassing systems design and fabrication, each part has its specific prerequisites and inputs. (Heinemann and Panke 2006)



6.3.2. Computer-based design and testing

In areas not related to biology, engineers can usually draw upon a sound knowledge base. In-depth understanding facilitates the computer-based design of new systems by going through iterations between computer models and simulations. This allows an extensive *in silico* testing of new design variants (Heinemann and Panke 2006, see figure 2 and table

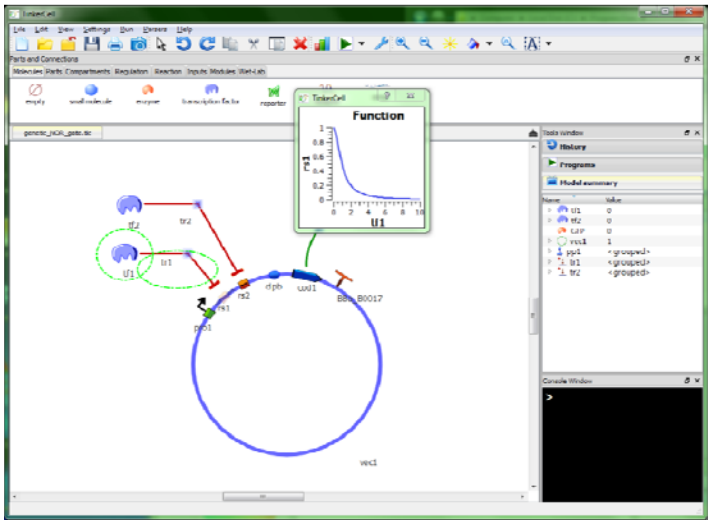


Figure 2: A number of computer aided design software tools have been written for SB, albeit with limited success so far. This is a screenshot from the Tinkercell software (http://www.tinkercell.com).

4). Although a proliferation of new computational methods and software tools for SB design has emerged in recent years, SB has not yet reached the stage where the design and construction of novel systems has become routine. To a large degree this is due to the inherent complexity of biological systems.

A key concept in engineering is the ability to assemble simpler standardised modules into systems of increasing complexity. It has yet to be adequately addressed how this approach can be applied to biological systems. In particular, the use of computer-aided design tools common in other engineering disciplines may become central to SB only if the stochasticity and complexity of biological systems will be adequately dealt with (MacDonald et al., 2011).

Table 4: List of software for synthetic biology design (source: MacDonald et al., 2011).

Type of software	Software name	Website
Automated circuit design	Genetdes	http://soft.synth-bio.org/genetdes.html
	RoVerGeNe	http://iasi.bu.edu/Bbatt/rovergene/rovergene.htm
	OptCircuit	http://maranas.che.psu.edu/
	GEC	http://research.microsoft.com/en-us/projects/gec/
GUI circuit design	BioJade	http://web.mit.edu/jagoler/www/biojade/
	GenoCAD	http://www.genocad.org/
	SynBioSS	http://www.synbioss.org/
	ClothoCAD	http://www.clothocad.org/
	TinkerCell	http://www.tinkercell.com/
	CellDesigner	http://www.celldesigner.org/
Biomolecular design	Rosetta	http://www.rosettacommons.org/
	ORBIT	http://www.mayo.caltech.edu/index.html
	RBS Calculator	http://voigtlab.ucsf.edu/software/
	caDNAno	http://cadnano.org/
DNA assembly	GeneDesigner	https://www.dna20.com/genedesigner2/
	GeneDesign	http://baderlab.bme.jhu.edu/gd/

6.3.3. Abstraction hierarchies

The application of abstraction hierarchies is a common characteristic in almost every engineering endeavour and results in several practical advantages. First, the introduction of system boundaries hides certain information and it is thus a way to manage complexity. In other words, abstraction is useful as it allows individuals to work independently at each level of the hierarchy. It is an organisational prerequisite for combining parts into complex systems (see figures 3 and 4, Heinemann and Panke, 2006).

The BioBricks Foundation conceptualises abstraction hierarchies as follows: at the lowest hierarchical level are base-pair sequences from standard biological parts that can be put together to form so-called devices. These devices again can be assembled to higher order systems. In contrast to how genetic engineering is done today, this approach allows the specialisation of different engineering tasks at different levels of the hierarchy.

Consequently, engineers may specialise in different tasks as well. A parts engineer, for example, would not have to know anything about base pairs or devices. This can be compared to an electronic engineer who designs electronic circuits on silicon chips. He or she does not need to know anything about quantum physics or software engineering (Endy, 2005). The division of labour thus adds to the efficiency of the engineering approach.

Figure 3: Comparison of abstraction hierarchies in computers and how they could be conceptualised in cells (Source: Andrianantoandro et al., 2006).

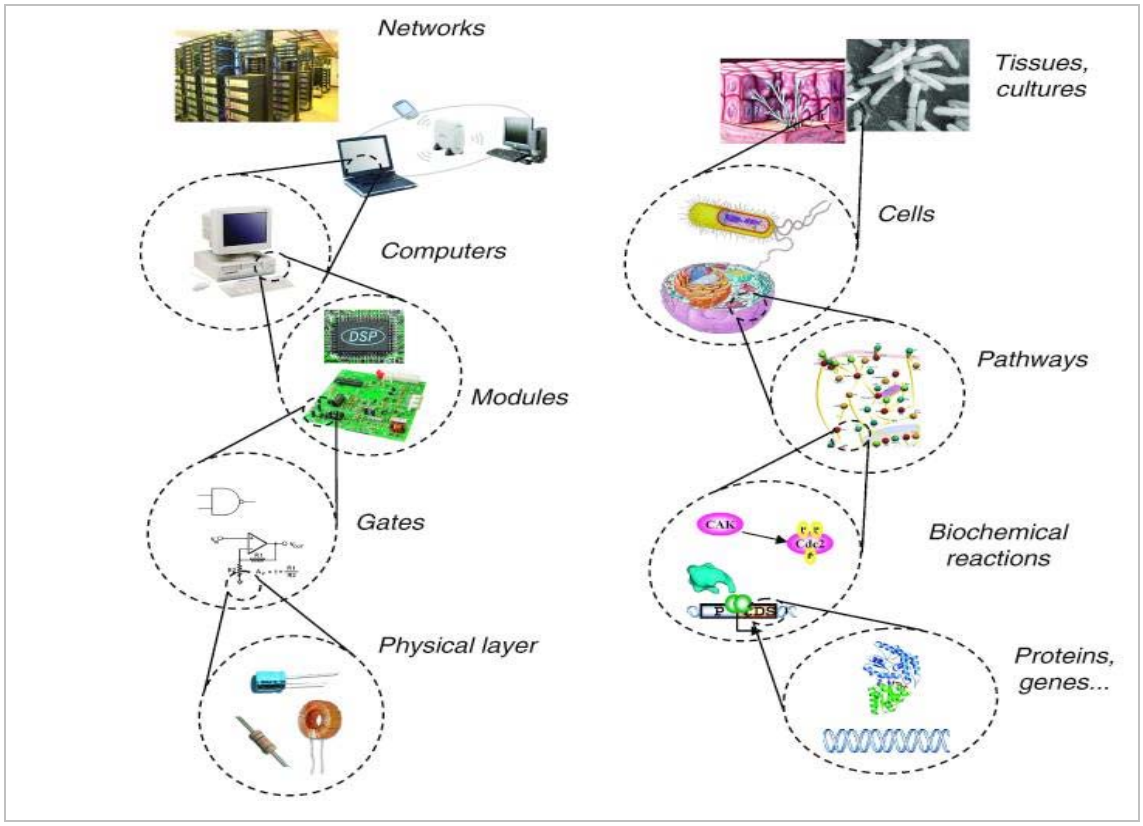
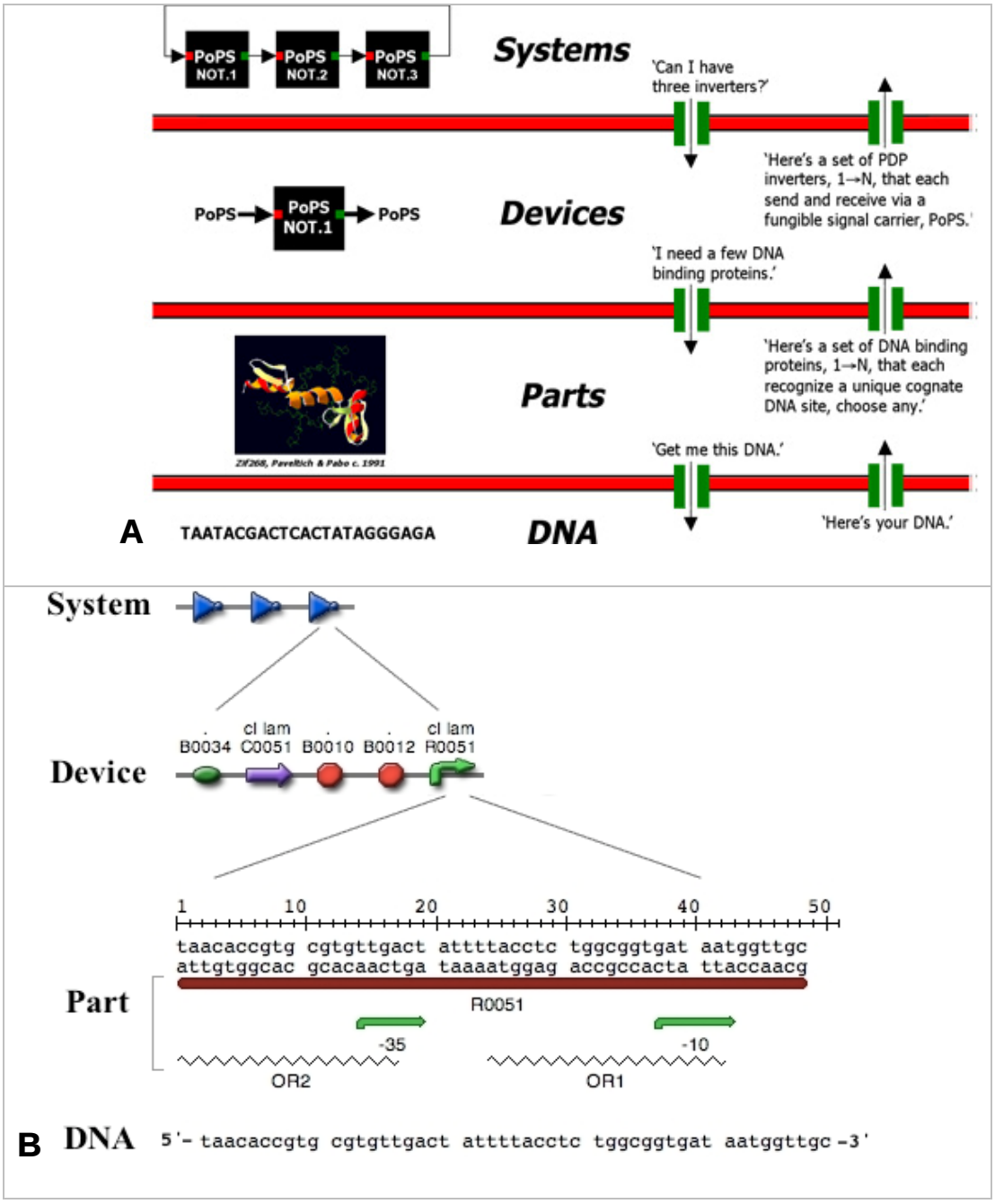


Figure 4: Different illustrations of abstraction hierarchies. (A) and (B) show how the BioBricks foundation foresees the separation of different levels of the hierarchy in bio-engineering (Source: Endy, 2005).



6.3.4. Standardisation approaches

The idea that standardisation is incredibly important to engineering proved to be invaluable in the field of mechanics and later also proved to be essential to electronics. No wonder therefore, that the initial argumentation in favour of standardisation in SB made reference to historical examples of engineering successes through standardisation in other technologies (Knight 2005). The main fields from which comparisons were drawn are:

- **Mechanics:** e.g. nuts, bolts and screws [1]
- **Automotive:** e.g. the term chassis is frequently used in SB
- **Electronics:** resistors, capacitors and TTL registries as models for the registry of standard parts
- **Software:** through use of computer-aided design
- **Internet:** standards and so-called Request For Comments (RFC) as created and published by the Internet Engineering Task Force[2]
- **Biotechnology**: to a lesser extent, references are made to other life science fields, such as stem cells (Baker, 2011b) or systems biology

Similarly in SB, in order to guarantee 'plug-and-play' compatibility of different components in an abstraction hierarchy, the connections between the different parts need to be defined, i.e. standardisation is required. Only broadly implemented standards for the components themselves and their in- and output criteria would ensure that interfaces between components fit, even when they are designed and fabricated by different laboratories or companies. (Heinemann and Panke 2006)

The BioBrick approach foresees the application of assembly standards such as the Assembly standard 10, which has proven to be a suitable underpinning for the idea of freely combining different elements originating from various laboratories.

Example of a technical standard in SB: Assembly standard 10

Assembly standard 10, also known as the original BioBrick assembly standard, is the standard underpinning most of the parts in the Registry of Standard of Biological Parts. The key innovation of the BioBrick assembly standard is that a biological engineer can assemble any two BioBrick parts, and the resulting composite object is itself a BioBrick part that can be combined with any other BioBrick parts. The physical composition standard underlying BioBrick parts has two fundamental advantages. First, the BioBrick assembly standard enables the distributed production of a collection of compatible biological parts. Two engineers in different parts of the world who have never interacted can each design a part that conforms to the BioBrick assembly standard, and those two parts will be physically composable via the standard. Second, since engineers carry out the exact same operation every time that they want to combine two BioBrick parts, the assembly process is amenable to optimisation and automation, in contrast to more traditional *ad hoc* molecular cloning approaches. (source: [3])

While standardisation in SB may be consistently argued, it remains unclear on which level standards should be introduced. In principle, technical standards can be set on different levels and may pertain to different artefacts, methods and tools such as:

[1] see e.g. ASME 2005. The United States Standard Screw Threads
http://anniversary.asme.org/2005landmarks3.shtml

[2] see: http://www.ietf.org/

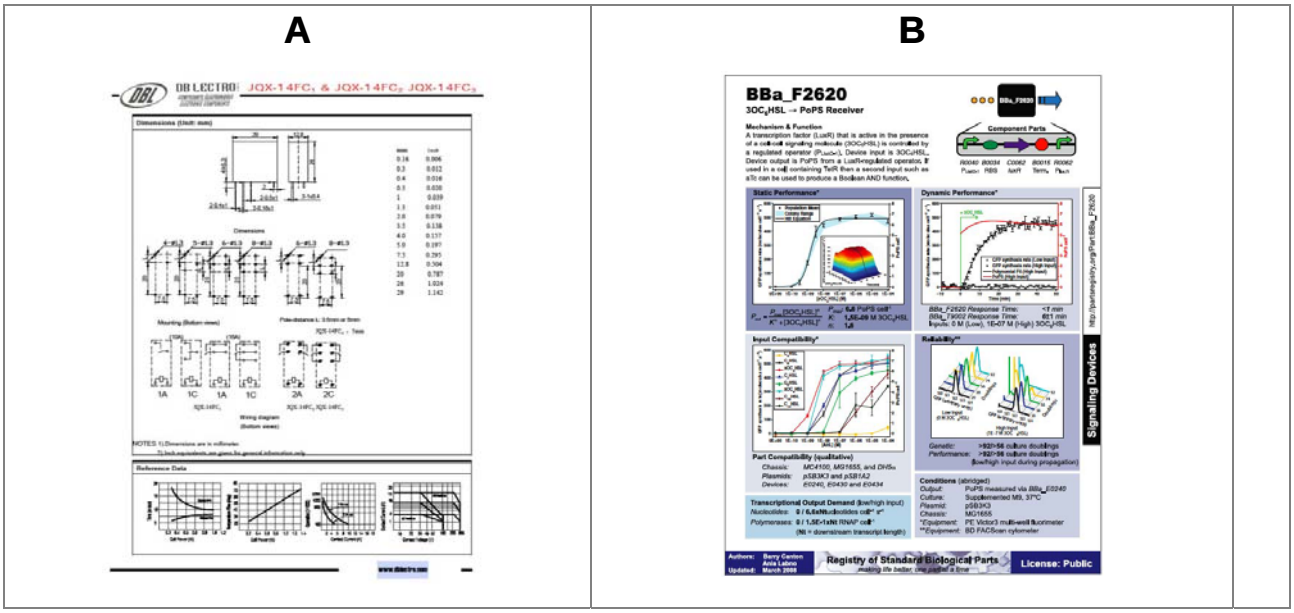
[3] see: http://partsregistry.org/Assembly_standard_10

- **Molecules:** using different chemicals to sustain living processes, e.g. alternative bases pairs to enlarge the genetic alphabet, different chemical backbones for the DNA, or non-canonical amino-acids (Schmidt, 2010).
- **Assembly methods:** see text box below for an example.
- **Processes:** e.g. quantitative measurement and the categorisation of key biological functions such as promotor strength (Kell, 2009).
- **Codes:** the genetic code explains how codon triplets are translated into amino acids and represents a natural biological standard; other man-made genetic codes would represent different standards (Budisa, 2005).
- **Measurements:** quantifying biological processes is a major problem for any attempt to convert biology into an engineering discipline. Ideally, similar units like those used in electronics such as voltage and current could be invented or found in biology. Examples for would-be units are 'Polymerases Per Second' (PoPS) or 'Ribosomes Per Second' (RiPS)[4]. PoPS represents the rate at which the RNA polymerase complex moves past a given position in the DNA. In some sense, it can be thought of as analogous to a current flowing through a particular point in a wire.
- **Computer tools:** Not only technical parts-design tasks can be standardised, but also computer tools to generate models of biological parts and devices *in silico*. An example is the Systems Biology Markup Language (SBML) derived from the related but distinct field of systems biology.

6.3.5. Decoupling design, construction and assembly

Finally, another characteristic feature of 'true' engineering is the decoupling of the design process from the actual fabrication of components or systems. Both tasks require a distinct set of skills and expertise, which is typically not provided by the same individuals. Decoupling would thus lead to higher efficiencies and scale-ups (Heinemann and Panke, 2006).

Figure 5: Use of datasheets in electronics (A) and SB (B).

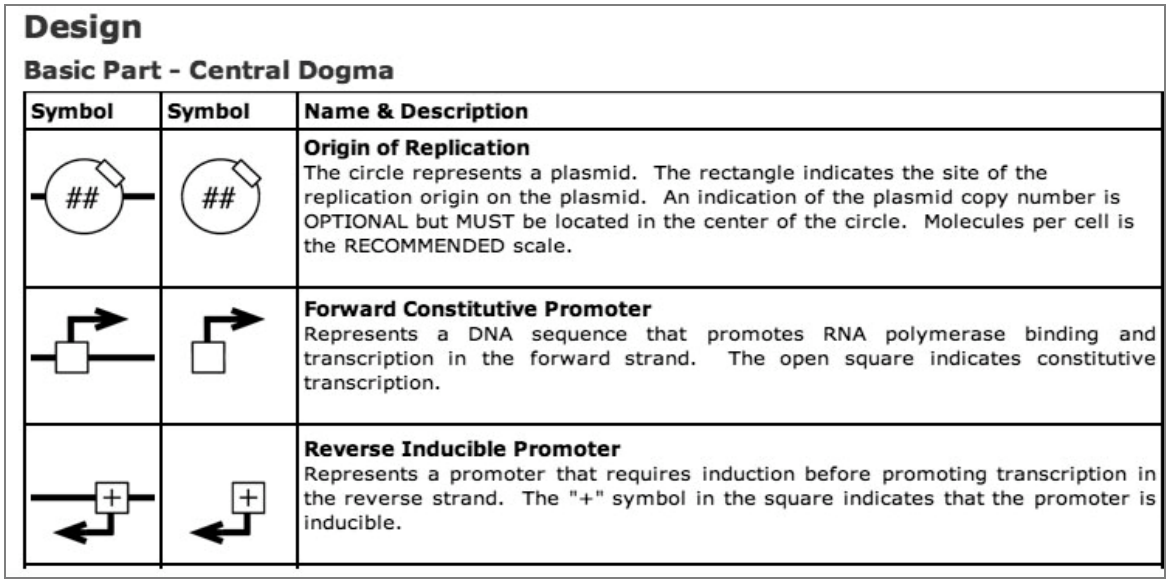


[4]http://partsregistry.org/Part_Types:Measurement_Systems and http://parts.mit.edu/wiki/index.php/Abstraction_hierarchy_and_PoPS and http://openwetware.org/wiki/PoPS

Decoupling shows itself e.g. through the use of datasheets that describe elementary parts (figure 5). Datasheets allow engineers to select and use parts without having to know how these parts were manufactured. Originally, they describe standardised components in electronics (A). Similarly, in SB, datasheets are also used to describe the technical characteristics of standard biological parts (B).

Another feature of decoupling is the use of abstract signs that stand for more complex parts or devices (see figure 6). In an ideal world, the designer is not required to understand much about the physical characteristics of these parts or devices, and still will be able to compose useful circuits. For example, in the Synthetic Biology Open Language, such symbols are connected to form more complex biological circuits in analogy to electronic circuits.

Figure 6: Example of the abstract symbols used by the Synthetic Biology Open Language (source: [5]).



***Conclusion**: According to the BioBrick community, four major engineering concepts related to standardisation have to be applied to biology to make it a real engineering* discipline: computer-based design and testing, abstraction hierarchies, standardisation of *parts and circuits and decoupling of design, and construction and assembly. Before this approach can reap benefits, many technical problems must be solved.*

6.4. Analogies beyond technical aspects and their limits

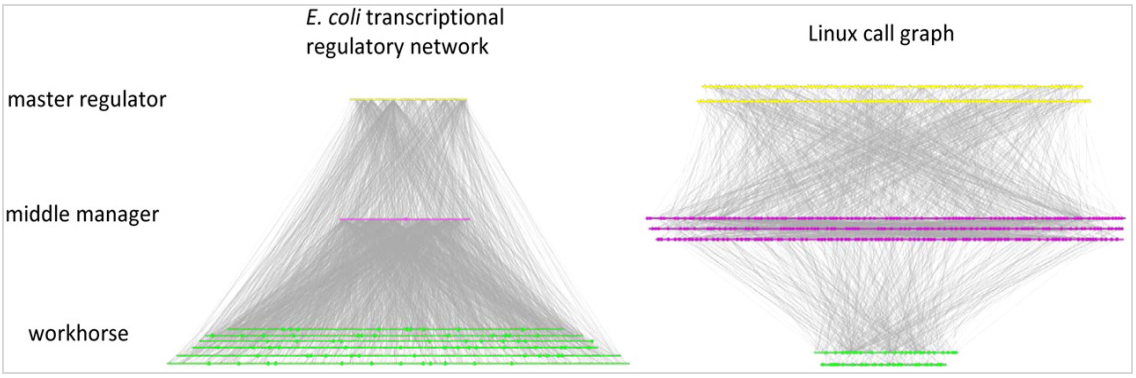
Similarities between IT and synthetic biology beyond the purely technical have also been emphasized. For example, the increasing speed of gene deciphering has been compared to the gain in computer memory ('Moore's law'). Such analogies invite speculation that synthetic biology will become a very important field. Early results, such as Craig Venter's synthesis of a bacterial genome, seem to prove these expectations right. However, other researchers believe that these expectations are exaggerated, and claim that biological objects are too complex to be standardized. They argue that many genetic parts do not behave as they are expected to, some are even incompatible, and variability in the system makes them unpredictable. Nevertheless, the field is very attractive to students, who continue to join the BioBrick community through the worldwide iGEM competition.

[5]see: http://www.sbolstandard.org/initiatives/sbol-visual

6.4.1. Analogies and metaphors

As already mentioned, analogies to other engineering fields play a major role in promoting SB. Comparisons of cells and their subsystems to computers and software (Figure 7) are frequent, and biological parts are often put in analogy to electronic parts. This often entails taking over practices from the field of IT: the 'Request for Comments' (RFC) system used to develop new internet standards by the Internet Engineering Task Force was taken up by the BioBricks foundation.[6] Another allusion to the electronics and software world is visible in names. For example, the name 'biofab', International Open Facility Advancing Biotechnology', refers to the use of recursive acronyms for software operating systems, where the acronym is also one of the primary words in the definition (e.g. GNU stands for 'GNU's Not Unix', LINUX for 'LINUX is not Unix').[7] The idea of electronic datasheets taken up in SB, too, further illustrates this practice.

Figure 7: Comparison of the architecture of genomes and computer operating systems (source: Yan et al. 2010)



The exuberant use of analogies and metaphors, however, has its limits. As deLorenzo (2011) noted, *'…analogies and meta-languages are most useful in a first instance to map unknown territories, open new fields and inspire action, but at some point they need to evolve into specific methodologies (not just analogies).'* According to critics within the SB community, stretching the analogies to computer engineering too far might obscure the peculiarities associated with the dealing with biological material. Therefore, it might falsely suggest progress that has not yet materialised.

6.4.2. DNA synthesis: considerable acceleration

Nevertheless, there are fields where progress has been breathtaking. The most obvious area is DNA chemistry, in sequencing (reading) and synthesis (writing). SB, and especially the bio-circuit branch, is fuelled by the expectations that follow the increase in the technological capacity in these fields. The cost for sequencing and synthesis has fallen at an exponential rate for about two decades now. This leads some observers (e.g. Rob Carlson) to compare these curves to Moore's law in electronics; see figure 8.

The cost of DNA sequencing and synthesis decreased to over 1 million base pairs sequencing for 1 US$, and 2-10 synthesised base pairs for the same amount (A). This caused the feasibility of producing even longer pieces of synthetic DNA, culminating with the 1 million base pair genome by the Venter institute, May 2010. There are reasonable arguments as to why this curve will start growing once it reaches the 1-10 billion base pair range: the order of magnitude of eukaryotic species (B). However, as mentioned before, the sheer capability to synthesise DNA does not mean that scientists can actually design useful genomes.

[6] see: RFC Process at http://BioBricks.org/programs/technical-standards-framework/

[7] see: http://en.wikipedia.org/wiki/Recursive_acronym

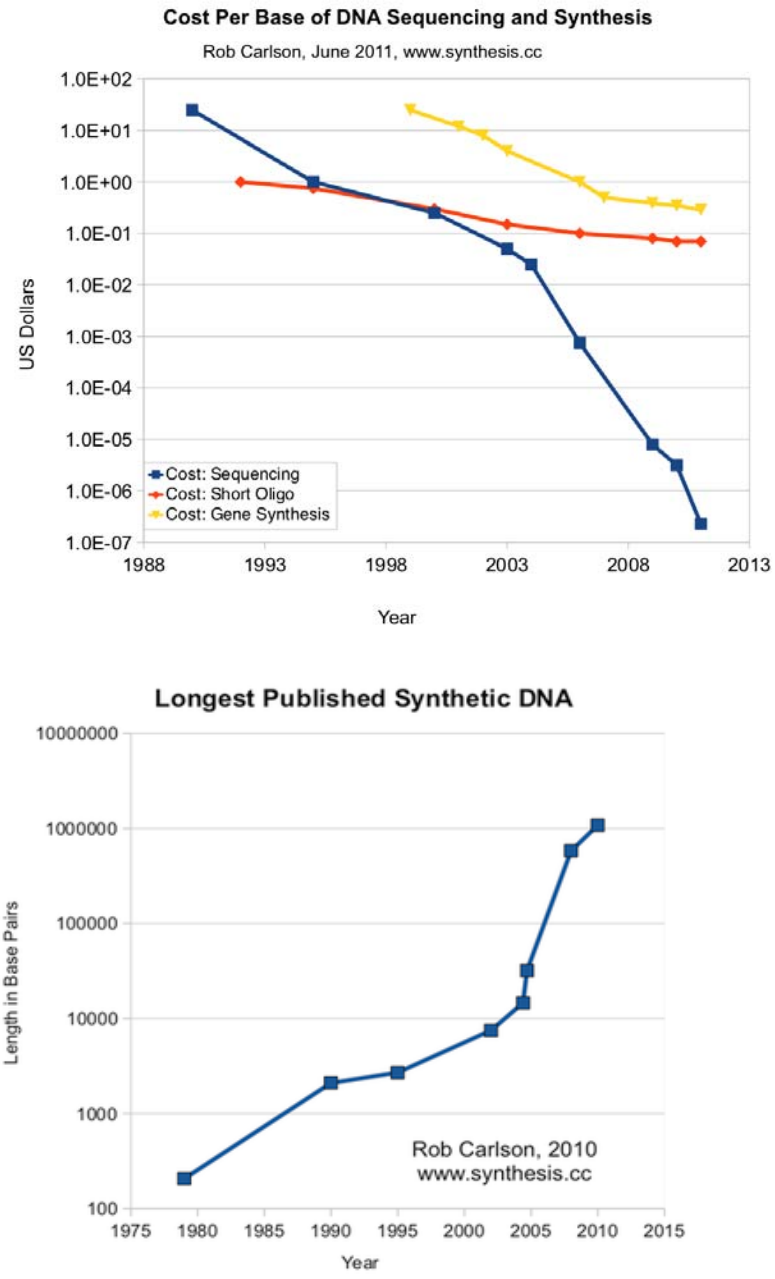


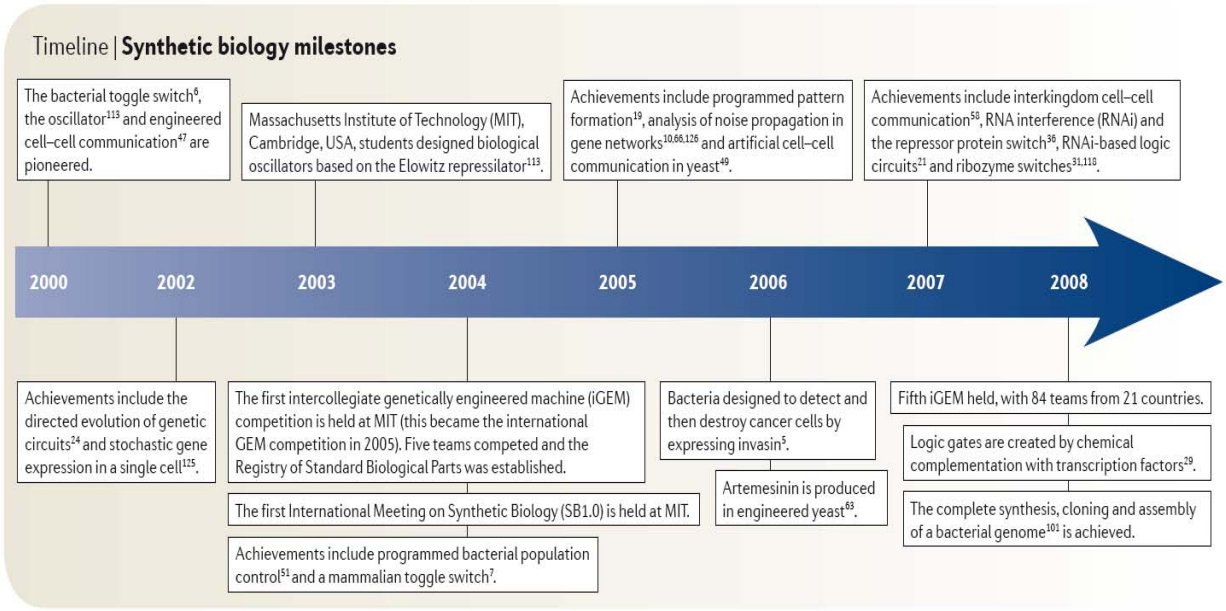
Figure 8: Cost of DNA sequencing and synthesis (Source: Rob Carlson[8])

The following diagram (Figure 9) shows some of the achievements in SB since 2000. At first sight, they are really substantial (for source and references, see Purnick and Weiss, 2009). The pace has accelerated ever since; a major public event after 2008, for example, was a publication by the Craig Venter Institute on the first artificial bacterial genome that could be 'rebooted', i.e. that was functional (Gibson et al., 2010).

However, this event showed some of the problems associated with publicising scientific breakthroughs in SB. While some scientists involved made reference to the popular phrase of 'creating life', many of their colleagues denied that this was the case, as the sequence of 'Synthia' (as the seemingly novel organism was dubbed in the press) was more or less identical to the original template. Significant progress in genome synthesis notwithstanding, the PR strategy to popularise the event seemed to have backfired in part.

8 see: www.synthesis.cc

Figure 9: Synthetic biology achievements since 2000 (Source: Purnick and Weiss, 2009).



6.4.3. Future challenges

Not only on the occasion of the Venter announcement, many biologists proved to be cautious in their belief that biology can be engineered like computers or electronic circuits. Especially the lack of tangible applications, so far, gave rise to critical comments that SB 'needs to deliver'. A recent article in the MIT technology review (Bourzac 2011) criticises that

'While the creation of the synthetic cell, at the J. Craig Venter Institute, hints at a future in which synthetic biologists can redesign living cells to perform whatever tasks they dream up, that goal is still distant. Most research has focused on coaxing microbes to perform tasks that are similar to what they already do, such as transforming sugar into fuels using processes and materials that resemble the ones they use in nature.'

The *Nature* news feature in 2010 by Roberta Kwok explored the challenges for the field and how they might be resolved (or not). On p. 288, she showed two famous cartoons comparing DNA to Lego bricks that had appeared in the magazines *The New Yorker* and *Wired*. The capture said that

'[t]he 'parts' work like Lego. Images such as these […] portray synthetic biology as simple design and construction. The truth is that many of the parts are not well characterised, or work unpredictably in different configurations and conditions.'

Accordingly, some (very optimistic) synthetic biologists say that in the future, when designing new forms of life, only our own imagination will be the limit. Researchers might soon program cells to produce biofuels or pharmaceuticals from renewable sources, carry out bioremediation activities or even work as living computers. *'Such analogies don't take into account the daunting knowledge gap when it comes to how life works, however.'* The gap gets particularly prominent when comparing the abilities to synthesise DNA (good, and becoming better) and designing genetic circuits (mediocre at best, no major improvement foreseeable).

A 2009 review by Purnick and Weiss concluded that

'Over the past few years, however, activity in the field has intensified, as reflected by an increased number of published experimental circuits. Surprisingly, the actual complexity of synthetic biological circuitry over this time period, as measured by the number of regulatory regions, has only increased slightly; it is possible that existing engineering design principles are too simplistic to efficiently create complex biological systems and have so far limited our ability to exploit the full potential of this field.'

Also Peter Carr and George Church (2009) stated:

'DNA synthesis dwarfs current capacity for functional design and debugging. If the scale of available synthesis can be considered the size of the canvas on which we may paint, the available choices of brushes and colors are still rather modest.'

Even Drew Endy conceded that '*we can compile megabases of DNA, but no one is designing beyond the kilobase scale*', concluding that '*can write DNA, nothing to say*' (Baker 2011). Kwok (2010) identified several main reasons for this stagnation that she boiled down to the so-called 'five hard truths for synthetic biology':

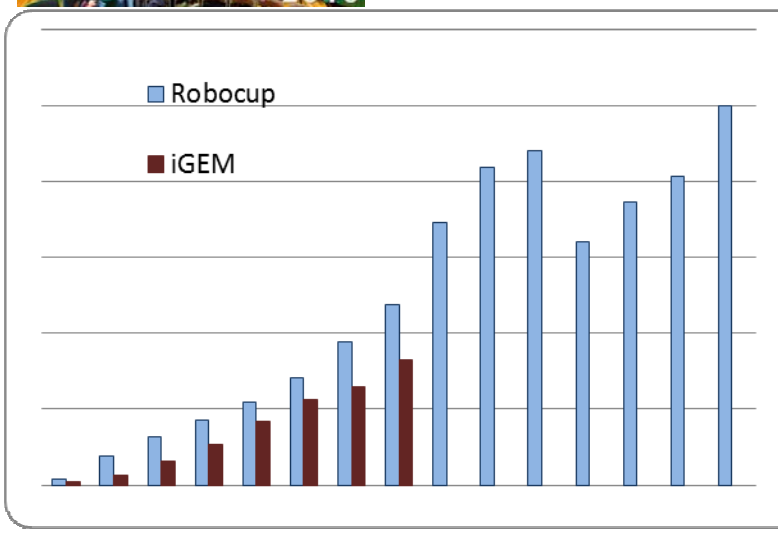
- Many of the parts are undefined
- The circuitry is unpredictable
- The complexity is unwieldy
- Many parts are incompatible
- Variability crashes the system

In a somewhat similar endeavour, though in a more positive light, in a recent commentary a group of seven influential European SB scientists identified the 'ten grand challenges' most relevant for synthetic life (Porcar et al. 2011). Surprisingly, standardisation was not among the ten challenges, and it does not seem to be high on the agenda of many European SB scientists. It may also reflect the attitude of major European research funding agencies (see chapter 5.4.2).

6.4.4. (Not so) novel community building

The approach at building an engineering community might not be so new, either. As already mentioned, iGEM is shaped along the lines of other successful student engineering competitions. Several others enjoyed a similar or even higher appraisal by high tech-students such as the Shell Eco-marathon (fuel-efficient cars) or the Robocup competition (robots that play football). Taking the older Robocup event as a guideline for the younger iGEM, one can see a similar increase in international participation during the early years, leaving room for speculations that iGEM may still grow for at least 5 more years up to approximately 300 to 400 teams and then level off (see figure 10 for details).

Figure 10: Number of international teams (y-axis) over time (x-axis, year by year), participating at the student competition Robocup (light blue, since 1996) and iGEM (dark red, since 2004).



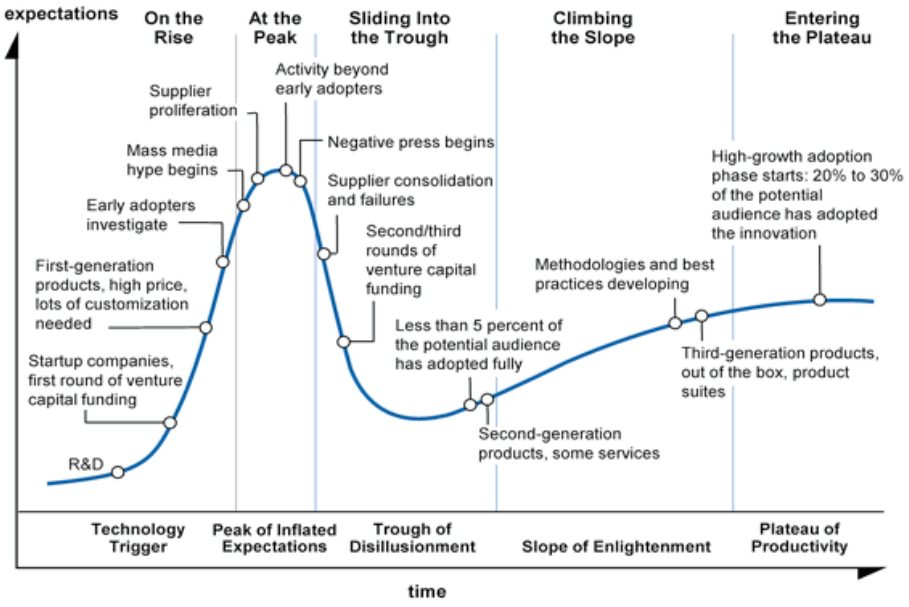
6.4.5. The hype cycle

However, identifying exactly where SB stands today, and where it could stand in 5 or 10 years, is no easy task. Scientists are ambiguous about their appraisal and criticism of SB, and their statements can be plotted on a polar distribution. The one pole contains scientists mostly from traditional biological (and thus rather analytical) disciplines, who argue that life is too complex and will never become a true engineering discipline. The other pole, consisting mainly of (bio)engineers, does see a chance of making biology easier to engineer.

Those who are (cautiously) optimistic about the future of SB have been observed to pursue an ambivalent strategy to describe its potential. When it comes to 'selling' SB to funding agencies and investors, SB tends to be depicted as 'a revolutionary approach' that will bring a whole lot of new applications and techniques, and it is very different from existing genetic engineering. When it comes to (potentially negative) public perceptions and the question of regulation, it appears as if, all a sudden, SB is 'practically the same as genetic engineering, only a gradual change from genetic engineering' and 'perhaps quantitatively different, but nothing qualitatively new' (Ganguli-Mitra et al., 2009). Thus, relying on stakeholders' assessments is prone to error if the context is not taken into account.

Another way of trying to assess the phase of development in which SB might be situated is Gartner's Hype Cycle. This hypothetical curve characterises the typical progression of an emerging technology from over-enthusiasm through a period of disillusionment to an eventual understanding of the technology's relevance and role in a market or domain. Each phase is characterised by distinct indicators of market, investment and adoption activities (see Figure 11).

Figure 11: Gartner's Hype Cycle (Source: [9])



It is certainly difficult to clearly assign SB to a specific spot on this curve; however, there are indications that SB might be placed in the vicinity of the 'peak of inflated expectations' region, as some disillusionment can be noted (Mampuys and Brom, 2010). SB is no longer considered to be confined to a small early adopter group, in other words, the 'technology trigger' region of the hype cycle; it has arrived in the mainstream of science and engineering. The mass media hype went up in 2009 and especially in 2010 after the announcement of the 'synthetic cell' by the Venter Institute. Supplier proliferation could be seen especially with respect to DNA synthesis companies. Although not outright negative, critical press reports emerged beginning in 2010.

Wrapping up, the *Nature* feature (Kwok 2010) cited several scientists who conceded progress but warned against exaggerated hopes:

'Despite the challenges, synthetic biologists have made progress. […] some systems have advanced from bacteria to more complex cells. The field is also gaining legitimacy, […..but t]he time has come for synthetic biologists to develop more real-world applications, says Fussenegger. "The field has had its hype phase," he says. "Now it needs to deliver"'

'[...] several companies are pursuing biofuel production via engineered microbes. But most applications will take time. As the cost of DNA synthesis continues to drop and more people begin to tinker with biological parts, the field could progress faster, says Carlson. "It's a question of whether the complexity of biology yields to that kind of an effort."'

***Conclusion**: Currently, progress is rapid. A main driver is the speed increase and cost decline in DNA sequencing and synthesis. The pace of the emergence of bioparts has accelerated; however, the complexity of engineered biocircuits stagnates. Even voices from within the SB community start to doubt the promises made. According to Gartner's hype cycle, SB's possible current phase may be near, or even past, the 'peak of inflated expectations'.*

[9]http://www.gartner.com/DisplayDocument?id=1758314&ref='g_fromdoc

6.5. Adequate safety standards, IPR rules and societal goals

It is unclear whether existing biotechnology safety standards are sufficient with respect to constructing entirely new organisms. To date, new rules have not been found necessary, but since security issues are anticipated, monitoring is an option. New safety regimes oriented to the 'unnaturalness' of a new organism have been proposed, and synthetic biology itself might offer novel safety regimes. Standards also play a role in intellectual property management. Strong patenting regimes (in biotechnology) stand opposed to notions of open source and access (in areas of IT). A mix of both could combine the advantages but may produce ambiguity. Synthetic biology is also said to promote societal goals such as sustainability. Although it remains to be seen whether technical standardization will go ahead, its impact is imminent, since those who come first may reap the economic benefits.

Standardisation is usually considered part of how to technically deal with an upcoming technology. In other words, standards mostly pertain to artefacts and methods that serve to construct something novel from elements of the new technology.

However, there are other aspects, too, that can be subject to standardisation. Safety standards can be set with regard to, e.g. occupational or workers' safety or to public and environmental safety. Many safety standards are enforced by law, i.e. they have a strong regulatory component.

Another aspect is intellectual property rights (IPR), which either applies to or explicitly does not apply to (some or all) products of the technology. IPR standards define the accessibility of processes or products and provide important terms of reference for the distribution of the benefits they bring about.

Finally, societal standards are intended to promote social aims. While standards for safety and IPR are usually considered necessary to be explicitly defined, there are different opinions on whether or not societal aims should be incorporated into standards for a particular technology. In the following, predominantly the aspects of standardisation regarding IP and safety will be considered.

6.5.1. New objects under established safety standards?

SB raises a number of safety and security issues. Security (the prevention of intended harm, e.g. from terrorism) is the most important topic regarding societal implications of SB among US scientists and regulators. Biosafety (the prevention of unintended harm, e.g. from accidents) is also an issue in the European discussion (Ganguli-Mitra et al., 2009). Both areas of concern have in common that SB might entail unwanted effects due to new technical capabilities that escape current oversight. For example, presently, the possibility to construct whole, or parts of, pathogen genomes in vitro is on the agenda, and elicits activities among commercial companies synthesising pieces of DNA to prevent this from happening. Voluntary standards are being adopted not in the least to prevent regulation.

Whether or not unwanted effects are intended, however, is less of a question than the assessment whether or not they are really imminent. Therefore, the subjects of biosecurity and biosafety are not explicitly distinguished in the following. Safety standards would have to be applicable in both fields.

6.5.2. Regulatory aspects

SB develops in the context of existing biosafety rules, regulations and laws mainly put into place to deal with genetic engineering. According to the European Group on Ethics, most current activities in SB and its foreseen fields of application are already regulated at the EU level (EGE 2009). The main argument supporting this opinion is a difficulty to distinguish early stages of SB from enhanced stages of genetic engineering. As a consequence, the regulatory context for genetic engineering also applies to the initial (current) developments of SB, as already stated. So first SB products will have to comply with the existing regulations that include:

European regulations

- **risk assessment and risk management:**
  Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms,
  Regulation (EC) 1946/2003 on trans-boundary movements of genetically modified organisms,
  Council Directive 98/81/EC amending Directive 90/219/EEC on the contained use of genetically modified micro-organisms.
- **new medicinal products:**
  Regulation (EC) No 726/2004,
  Directive 2001/83/EC,
  Directive 2003/94/EC,
  Directive 2003/63/EC);
- **medical devices:**
  Directive 93/42/EEC,
  Directive 90/385/EEC;
- **gene therapy, cell therapy and tissue engineering:**
  Regulation (EC) No 1394/2007 amending Directive 2001/83/EC,
  Regulation (EC) No 726/2004,
  Directive 2001/83/EC,
  Directive 2004/23/EC,
  Directive 2002/98/EC;
- **clinical trials:**
  Regulation (EC) 2001/20 amended in 2003 and 2005;
- **cosmetic products:**
  Directive 1976/768/EC;
- **data protection:**
  Directive on the processing of personal data and the protection of privacy in the electronic communications sector;
- **chemicals:**
  the entire REACH rules;
- **biological risks:**
  Council Directive 82/894/EEC,
  Council Directive 2000/29/EC of 8 May 2000;
- **occupational health:**
  Directive 2000/54/EC onsafety and health for workers exposed to biological agents at work;
- **patents:**
  Directive 98/44/EC.

Global provisions

- **WHO biosafety standards**
- **The Cartagena Protocol**
- **World Trade Organisation (WTO) agreements**
- **Trade-Related Aspects of Intellectual Property Rights (TRIPS)** on the limits of safety regulation measures
- **Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction**
- **UN Security Council Resolution 1540**

Hence, the full arsenal of current biotechnology regulations applies to SB activities and products as well. Allegations that SB is not regulated (ETC 2007), therefore, are not taking into account the vast array of biotechnology regulations in place already. Departing from this regulatory context, however, experts pointed out the need to adapt safety rules to upcoming developments in SB (Schmidt and Pei 2011, Schmidt 2010, Ganguli-Mitra et al., 2009).

6.5.3. Are current standards sufficient?

The issue of safety standards also raised the interest of the European Group on Ethics in Science and New Technologies (EGE 2009). In their recommendations, which transgressed classical issues of bioethics by far, the Commission members emphasised *'[…] that EU Biosafety standards for Synthetic Biology products […] are adopted […]'.*

The underlying reason for the concern is that with health and occupational safety standards, problems with anticipating risk from SB might arise. Established risk mitigation measures are built upon classifications of naturally occurring organisms. Since products of synthetic biology are intended to be entirely novel, it may become questionable whether these classification schemes fully apply. Therefore, the question arises whether and how fundamentally novel objects derived from SB can be assessed applying the traditional approaches of comparing unknown living organisms with known ones (Schmidt 2009). Risk assessment might have to change because

'…. safety risks for genetically modified organisms might not be best judged from the behaviour of the parent organism, once modification is pursued at the 'deep' systemic level that synthetic biology should enable.' (IRGC 2010, p.5)

Hence, the question is whether it is adequate to rely on current assessment as well as on standardisation practices from biotechnology, or whether strategies of standardisation from other areas of engineering would be more appropriate (Henkel and Maurer, 2009). It may also be that the process of standardisation has to be completely rethought for this field. In their 'priority paper', Ganguli-Mitra et al. (2009) summarised possible future demands with respect to safety standards, in particular new (standardised) methods in risk assessment to decide whether a new synthetic biology technique or application is safe enough. They identified the following areas:

- DNA-based biocircuits consisting of a larger number of DNA 'parts',
- the survivability and evolvability of novel minimal organisms used as platform or chassis biocircuits, and
- 'exotic' biological systems based on an alternative biochemical structure.

In addition, synthetic biology itself may contribute to overcoming biosafety problems by facilitating the design of safer biosystems, for example by

- designing less competitive organisms by changing metabolic pathways;
- introducing metabolic pathways with a dependency on external biochemicals;
- designing evolutionary robust biological circuits;
- using alternative biological systems to avoid e.g. gene flow to and from wild species;
- designing proto-cells that lack key features of living entities.

A third aspect addressed was skill diffusion (e.g. through do-it-yourself SB to amateurs or biohackers). Accordingly, everyone using the resources of SB should have awareness of and training in relevant biosafety techniques. In addition, appropriate mechanisms (laws, codes of conduct, voluntary measures, access restrictions to key materials, institutional embedding, and mandatory reporting to Institutional Biosafety Committees) should be in place to avoid unintentional harm.

Awareness about SB related safety issues is also promoted through the iGEM competition. For a team to win the gold medal, and thus qualify to become the overall winner, the teams have to answer a set of safety related questions.

Safety at iGEM

iGEM teams are asked to detail how they approached any issues of biological safety associated with their projects. Specifically, teams should consider the following questions:

- Would any of your project ideas raise safety issues in terms of:
  - researcher safety,
  - public safety, or
  - environmental safety?
- Do any of the new BioBrick parts (or devices) that you made this year raise any safety issues? I yes,
  - did you document these issues in the Registry?
  - how did you manage to handle the safety issue?
  - How could other teams learn from your experience?
- Is there a local biosafety group, committee, or review board at your institution?
  - If yes, what does your local biosafety group think about your project?
  - If no, which specific biosafety rules or guidelines do you have to consider in your country?
- Do you have any other ideas how to deal with safety issues that could be useful for future iGEM competitions? How could parts, devices and systems be made even safer through biosafety engineering?

Source: http://2011.igem.org/Safety

Sooner or later, therefore, the current set of regulations and provisions could turn out to be insufficient to fully deal with more advanced forms of SB (see figures 12 and 13, de Lorenzo, 2011). Since there is no defined threshold between genetic engineering and synthetic biology, but rather a gradual increase in 'artificialness', any boundary would have to be deliberately set. Hence, defining SB and subjecting the so defined field to regulatory conditions different from biotechnology at large would demand a bold political decision. However, since technical progress might be considerable regarding some aspects, regulators may need to be alert to upcoming challenges.

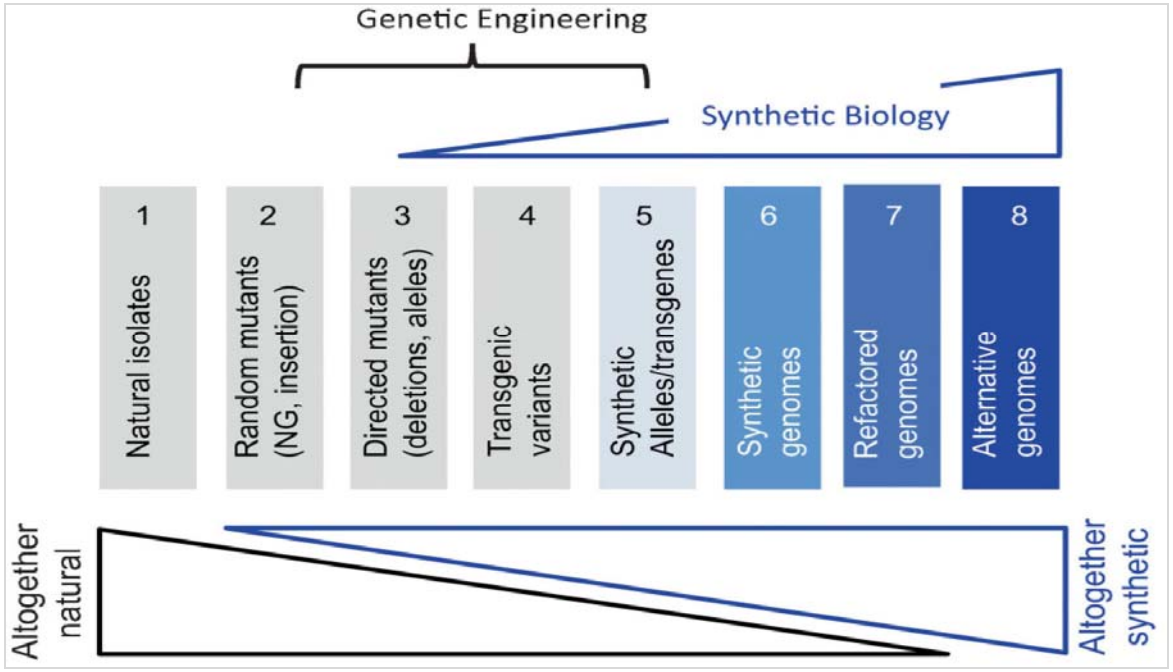
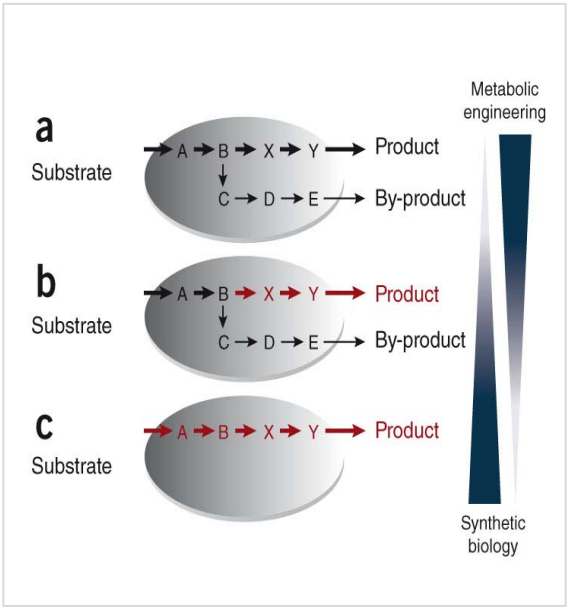


Figure 12. Stages of transition between naturally-occurring organisms and wholly synthetic microbes. There is a considerable overlap between genetic engineering and SB. (Source: deLorenzo, 2010)

Figure 13: Illustration of the overlap between metabolic engineering (a) and synthetic biology (c) by the use of three different approaches to produce a desirable product. Right now, science has only reached stage (b) (Source: Nielsen and Keasling 2011).



Two major long-term challenges for policy makers and regulators might entail:

- At a certain but yet unknown point in the not-so-distant future, the current set of regulatory and governance options might turn out to be insufficient, in part, to cover all SB techniques and possible fields of applications.
- When this situation takes place, the regulatory system could either be fine-tuned and tinkered with to include the latest developments, or undergo a major revision to take into account the dynamic and rapidly changing technological capabilities.

6.5.4. Intellectual Property Rights – open source or patenting?

A particular important aspect is the link between standards, the determination of a particular technological path and the way intellectual property rights are handled. Each path derives from a certain tradition, and these traditions quite substantially influence the ways in which intellectual property is looked upon and dealt with. In the context of standardisation, to ensure that biological parts are complementary, therefore, the issue of how IPR is protected gets all the more important.

The main reason is that standardisation usually entails a lock-in, which has rather different implications depending on the form of IPR attached to the particular technological path (Rai and Boyle 2007). In their 2010 report on SB, the US Presidential Commission for the Study of Bioethical Issues thus recommended an

'effort to determine whether current research licensing and sharing practices are sufficient to ensure that basic research results involving synthetic biology are available to promote innovation, and, if not, whether additional policies or best practices are needed.' (PCSBI 2010, p. 7)

The European Group on Ethics in Science and New Technologies emphasised that *'… debates should include also what can be object of patent and what should be available through open access'* (EGE 2009).

There are historical examples (e.g. from information technology or biotechnology) of a lock-in due to particular forms of IPR protection (Hope 2008). Such examples can be used to derive insights into potentially upcoming problems, in other words, to learn from past experiences. Here it is important to trace the particular (though often implicit) traditions in the field or discipline that is considered to be the benchmark. The question is which technology traditions influence the standardisation process in SB (those from the pharmaceutical industry, from IT, from technical engineering or from other fields)?

Since there are multiple ways of protecting intellectual property (or denying protection, respectively), it is also important to look at the self-assigned 'mother discipline' of particular stakeholders that are influential in designing an IPR regime. In SB there is a particular situation (though not unique among techno-sciences) where several disciplines merge and provide their respective traditions and practices. Often, these practices are difficult to reconcile, and this opens up entirely new forms of dealing with IPR.

In SB, there is an obvious tension between the strong open source movement among certain stakeholders and the preoccupations of other practitioners who prefer classical patenting. Between these poles, we can see new forms of protection emerging such as various forms of copyright or utility models, which open up possibilities for arriving at a socially fruitful handling of intellectual property. However, it is unclear which of the proponents' different views regarding the most appropriate forms of standards will have the potential to develop into a realistic and widely accepted practice. The question is which IP regimes will prevail – patents, copyright, open source or open access?

In a proactive move, the BioBricks Foundation, together with eminent lawyers from the Boston area, have developed a legal model to facilitate sharing of bioparts. The BioBrick Public Agreement (BPA) is a free-to-use legal tool that allows individuals, companies and institutions to make their standardised biological part free for others to use. The BPA was developed for sharing the uses of standardised genetically encoded functions (e.g. BioBricks). Here is an excerpt from the BPA that altogether contains 10 paragraphs.[10]

[10] see: http://BioBricks.org/bpa/users/agreement/

*§ 1 **Authority**. By clicking "Agree" User agrees to the terms of this User Agreement and shall therefore have the right to use the Materials insofar as the Materials are within the public domain or the Contributors have promised not to assert any of the Contributors' proprietary rights against User by way of the applicable Contributor Agreements.*

*§ 2 **Use of the Materials.** User acknowledges that the Contributor is asked to represent and warrant if, to the best of the Contributor's knowledge: there are any issued patents or pending patent applications, copyrights, or data rights owned by the Contributor that protect any portion of the Materials […]. any composition containing the Materials, or their use including but not limited to a nucleic acid sequence within the Materials, any compositions containing the Materials, and/or any use of the Materials, and that the Contributor, in connection with the Materials, will not assert or threaten to assert such patent; will not initiate International Trade Commission proceedings; will not threaten assertion of any rights that may be granted through issuance of a patent application; will not invite license rights to the Materials; and will not enforce any such intellectual property rights in the Materials in any manner against either the Foundation or Users[…]*

*§ 3 **Identification and Attribution.** As to attributing Contributors: If Contributor has requested attribution under the Contributor Agreement, User will make reasonable efforts to recognize the Contributor as specified in Paragraph 5 of the Contributor Agreement when User makes available, commercializes, or otherwise distributes the Materials, including any descriptions of the Materials in packaging, product inserts, websites, publications, or other public displays.*

*§ 4 **Applicable Laws.** User is obliged to comply with laws and regulations applicable to the Materials, including laws and regulations governing export control and safety. User will also respect the valid property rights of others in the Materials. Because laws and regulations vary around the world and change frequently, the Foundation cannot advise User concerning compliance with any applicable laws or regulations, nor can the Foundation make any determination regarding intellectual property rights. The existence of this User Agreement does not indicate that the contribution, distribution, or use of the Materials is permitted by applicable law.*

*§ 6 **Fees and Other Undertakings.** User understands that no fees will be charged for providing access to or use of the Materials. […] nothing in this User Agreement shall preclude User and any Contributors from voluntarily entering into a separate agreement with User or another party regarding the Materials that may vary from or supersede the terms of this User Agreement or the Contributor Agreement. Any such separate agreement, however, shall not diminish or derogate from the rights of the User in the Materials as provided under this User Agreement.*

*§ 9 **Interpretation of this User Agreement.** This User Agreement shall be interpreted under the laws of the Commonwealth of Massachusetts and the United States of America.*

The BPA seems to have been inspired by the digital world, in particular by the creative commons licence, that aims to develop, support and steward the legal and technical infrastructure that maximises digital creativity, sharing and innovation.[11] Notable differences are the explicit mentioning of safety risks and export controls that honour the difference between pure information-based rights and those attached to the physical world. Another interesting difference is the geographic denomination, since it is stated that laws of Massachusetts and the USA apply, whereas any such notions are missing in the creative commons.

The open access and open source approach by the BioBricks foundation, however, is not shared by all stakeholders. Biotechnology cooperations and many collaborators in science remain sceptical about giving away all IPR for free. In their overview over IPR and SB, Oye and Wellhausen (2009) summarised different views from different advocates (Table 5).

[11]see:http: //creativecommons.org/aboutand
http://en.wikipedia.org/wiki/Wikipedia:Text_of_Creative_Commons_Attribution-ShareAlike_3.0_Unported_License

Table 5: Perspectives on commons and property in the SB community (Oye and Wellhausen 2009)

Type		BioBricks Foundation commons	SynBIO firms property advocates	Summary of US law
Infrastructure	Registry of parts	Public research and education exemption	Varies across registries and purposes	US no research exemption, exemptions vary international
Standards	Interoperability	Public domain	Public domain	Ownable
	Performance	Public domain	Public domain	Ownable
Methods	Design tools	Public domain	Public domain	Ownable
	Testing methods	Public domain	Public domain	Ownable
Biological parts	Fragment of DNA	Public domain	Public domain	Not ownable
	With useful function	Public domain	Private property	International variation
	Performance data	Public domain	Conditional	Ownable
	Redesigned chassis	Public domain	Public domain	Ownable

Another example is biofab, the open technology platform framed in view of the proposition that basic biological parts should be non-proprietary, accessible and freely available for use and reuse in an ongoing fashion. There are a number of reasons for this framing, but most pronounced is the proposition that synthetic biology will not maximally contribute to health, wealth and security unless such openness becomes a characteristic of biotechnology (see below). Biofab has declared its intention to place all of its work in the public domain. Putting this intention into practice, however, has proven difficult (biofab, 2010).

A principal difficulty concerns the fact that biofab is located in mixed inventor organisations, i.e. UC Berkeley, Lawrence Berkeley National Labs and Stanford University. Such organisations take as a core assumption that inventions developed by one researcher or team of researchers within that organisation are likely to have proprietary connections to inventions (past and future) made by others in that same organisation. As such, it is not clear how or whether to facilitate the declared intentions of a single researcher or research team to give work away. This organisational difficulty consists of one part habit, one part disposition, and one part process.

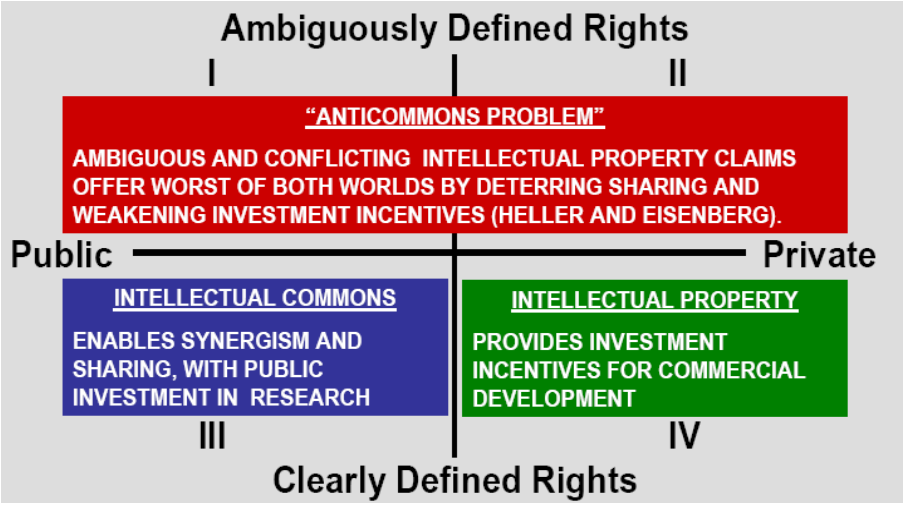
- With regard to habits, technology transfer officers are accustomed to making one of two primary decisions in relation to ownership of inventions not subject to copyright protection: whether to patent that work or not. Placing work in the public domain is simply not customary (Torrance, 2010; Rai and Boyle, 2007).

- With regard to dispositions, the decision not to patent is not the same as declaring an object to be in the public domain. The latter means foregoing proprietary benefits connected to that work, derivative works or other inventions closely connected to it (Hope, 2008; Kelty, 2009). In the case of the institutions housing biofab, there is not yet sufficient interest in risking either the loss of such proprietary gains in the face of the yet-to-be-proven benefits of open biotechnology or assuming possible liabilities associated with infringing on other patents.
- With regard to process, the problem is straightforward: even where the institution is willing to place work in the public domain, it is not clear how this should be conducted. As discussed in the report, placing an object in the public domain neither assures that it will stay there nor that accessibility will result in facilitation. That is to say, just because an object is declared free-to-use does not mean worthwhile uses will come of it.

6.5.5. Ambiguously defined IPR

A major problem that registries such as the one on standardised parts based at MIT face is the conundrum of ambiguity. Ambiguous protections of biological intellectual property may be caused by technical complexity, a lack of familiarity with emerging biotechnologies, ethical and moral issues, and international divergence of IP rights. Oye and Wellhausen (2009) provided a framework for analysis for such a case (Figure 14).

Figure 14: A framework for analysis of intellectual commons and property (source: Oye and Wellhausen 2009)



The effect of ambiguity is as much of a problem as the so-called patent thicket, where a company (or researchers) need to clear hundreds of patent titles before they can proceed. The ambiguous protection of IPR causes a situation where a researcher or company does not even know whether or not there are patents behind the technology or methodology they would like to use. This is especially a problem when venues such as the registry of standardised parts claim to contain 'open source and open access' parts, where in fact this is not the case. A biotechnology examiner at the European Patent Office once mentioned that many of the parts contained in the registry were probably already patented and thus would cause problems should anybody try to use them for research (where there is no research exemption) or for business.[1] The BioBrick Public Agreement (BPA, see above) caters for this case in point 2:

[1] Personal communication Dr. Berthold Rutz 2009

'User acknowledges that the Contributor is asked to represent and warrant if, to the best of the Contributor's knowledge: there are any issued patents or pending patent applications, copyrights, or data rights owned by the Contributor that protect any portion of the Materials'.

However, the term 'best of knowledge' will most probably not keep patent sharks at bay in the case that a patented part is unwillingly 'donated' to the public realm. As the ambiguity of rights increases, a 'submarine' patent owner may make a claim and incur costly litigation.

'Such patent owners, or 'patent trolls,' may purposely or inadvertently wait to reveal and enforce claims until follow-on innovators have made lucrative discoveries. Though large firms can perhaps afford the ex post facto risk of payouts to litigants, smaller innovators in emerging fields like synthetic biology may be deterred by the expected costs that litigation imposes on successful downstream research' (Oye and Wellhausen 2009).

To solve this problem, the authors demand an 'anti-IPR-ambiguity task force' that should check each and every donated part against patent databases, ensuring that the parts in the registry are really free to use without risking eventual legal battles[2]. Right now, neither the BioBricks Foundation nor any other group has come forward to provide the financial and expert support to carry out such a highly needed IP cleaning mechanism.

6.5.6. Other societal goals

The question whether societal goals such as sustainability should be cast into standards for new technologies has been controversially discussed for a long time. So far, explicit socioeconomic standards have rarely made it into modern biotechnology regulation. The only exception is the Norwegian law on GMOs (sustainability clause) and a section in the Austrian law on the 'social sustainability' of GMOs, which, so far, has not been activated.

However, when it comes to the promotion of biotechnologies, researchers and industry often refer to broader societal values, including the common good and sustainability. This is also the case with proponents of SB when they sketch out a future where SB will deliver applications with a huge benefit, such as new drugs, means to protect the environment, benign energy generation methods, and so on. First, widely popularised applications of SB have also been linked to common good aspects. An example is the development of an efficient production pathway in micro-organisms for Artemisinin as a Malaria drug.[3]

It was, however, a case of metabolic engineering without BioBricks or the likes, and thus more akin to advanced genetic engineering. Nevertheless, such argumentation may indicate an inherent awareness within the SB community for sustainability issues. So far, this has not translated into initiatives to arrive at standards.

In a similar way regarding IPR, the quest for open access often goes along with a reference to broader societal values. For example, biofab (see above) was designed to deliver non-proprietary, accessible and freely available parts with the explicit proposition that SB should contribute to health, wealth and security, through openness (biofab 2010). However, this again refers more to attitudes and customs, i.e. the 'culture' and desires of the community, than to formal standards.

The difficulties in determining sustainability are not surprising in the light of the status of SB. For the time being, most efforts go into making the technology work rather than developing practical applications. However, since sustainability is a property that can only rarely be assigned to a technology as such without a view to its applications and their context, it takes no wonder that determining sustainability in the case of SB appears at least premature.

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[2] Personal communication Prof. Kenneth Oye (MIT), 2007

[3] http://www.rollbackmalaria.org/artemisininenterprise/index.html

Regarding their socioeconomic impact in general, it has already been emphasised that not only technical specifications but also political choices influence technology standards. This is particularly salient regarding risk assessment and mitigation, as well as IPR. However, standardising building blocks also confers a more subtle form of power. Those who can impose their (technical) regime on others have an advantage not the least in economic terms; they are the 'early birds' and first movers able to harvest strategic network effects, even more so if particular forms of IPRs are attached to standards.

It is therefore important who sets the standards. In the case of SB, so far mostly scientists and engineers (as innovators and stakeholders) have determined the rules. This is a long established practice in engineering. However, the tradition of stakeholder involvement differs from one technological area to the other. As SB involves several scientific disciplines and engineering fields, the question is which tradition should be guiding, or whether there should be an entirely new approach. So far, information technology seems to have taken the lead.

This tradition also emulates with the so-called do-it-yourself community said to rapidly increase. This informal group of (mostly lay) people want to do synthetic biology in their home facilities, not unlike the garage shops in the early ages of the personal computer fabrication. Whether or not this is a realistic aim is questionable, though, as working on the genetics of micro-organisms usually demands more laboratory infrastructure than writing software. On the one hand, standardisation would surely increase the broad availability of functioning parts and devices and thus contribute to democratising biotechnology; on the other hand, it might pose restrictions on the use of certain parts due to safety concerns.

Conclusion: Ethical, legal and safety (ELS) issues discussed most prominently are safety and security standards and intellectual property rights. Most scientists see no need to tighten existing regulatory safety and security regimes. In the future however, adaptations to technical progress might be necessary, but it is unclear when and what might be changed. Regarding IPR, a strong open source movement embodied in the BioBricks community faces challenges from patenting practices in biotechnology. Other societal goals such as sustainability are only rhetorically relevant. However, socioeconomic implications of setting technical standards should be kept in mind.

6.6. Coping with societal challenges and funding demands

Numerous studies have investigated potential ethical, social and legal issues (ELSI) concern synthetic biology. Apart from safety/security and intellectual property questions, ethical concerns (for example, about 'creating life') have been identified and a potentially negative public perception confronts the scientific and economic promises. As across Europe, there is no common appraisal of the importance of synthetic biology, countries have allocated public funding to different degrees for synthetic biology research as well as for ELSI studies.

6.6.1. ELSI activities

Following early scientific and engineering activities in SB, from 2004 on social scientists on both sides of the Atlantic started to work on the societal aspects of SB (Figure 15). Most of these projects dealt with typical ELSI topics with a link to questions of standardisation, such as safety, security and intellectual property rights. In addition, also ethics, science communication, public perception and governance were prominently dealt with. These activities resulted in a comparatively high number of articles and book chapters[4]. Bioethics committees have identified SB as an interesting study object[5] i.a. in

[4]For example, in 2009: August: EMBO Reports: Science and Society; October: Systems and Synthetic Biology: Societal Aspects of Synthetic Biology, and Synthetic Biology: the technoscience and its societal consequences, Springer; December: Nature Biotechnology: Focus on Synthetic Biology

- **The Netherlands:** Commission on Genetic Modification (COGEM) (2007-2009)
- **European Commission**: European Group on Ethics in Science and New Technologies (EGE) (2008/09)
- **Germany:** Ethics Council to the German Parliament (in 2009), German Ethics Council (Deutscher Ethikrat) (2009/10), DFG-Acatech-Leopoldina (2009)
- **Switzerland**: Federal Ethics Committee on Non-Human Biotechnology (2009/10)
- **United States:** Presidential Commission for the Study of Bioethical Issues (2010)
- **Europe:** European Academies' Scientific Advisory Council (2010)
- **Denmark:** Danish Council of Ethics and Danish Board of Technology (2011)

[5]In the United Kingdom, the Nuffield Council of Bioethics took up the issue three times (in 2006, 2007 and 2008) and each time decided not to put it on the agenda.

Figure 15: US and European research activities focusing on different societal implications of SB (source: Schmidt, 2010)

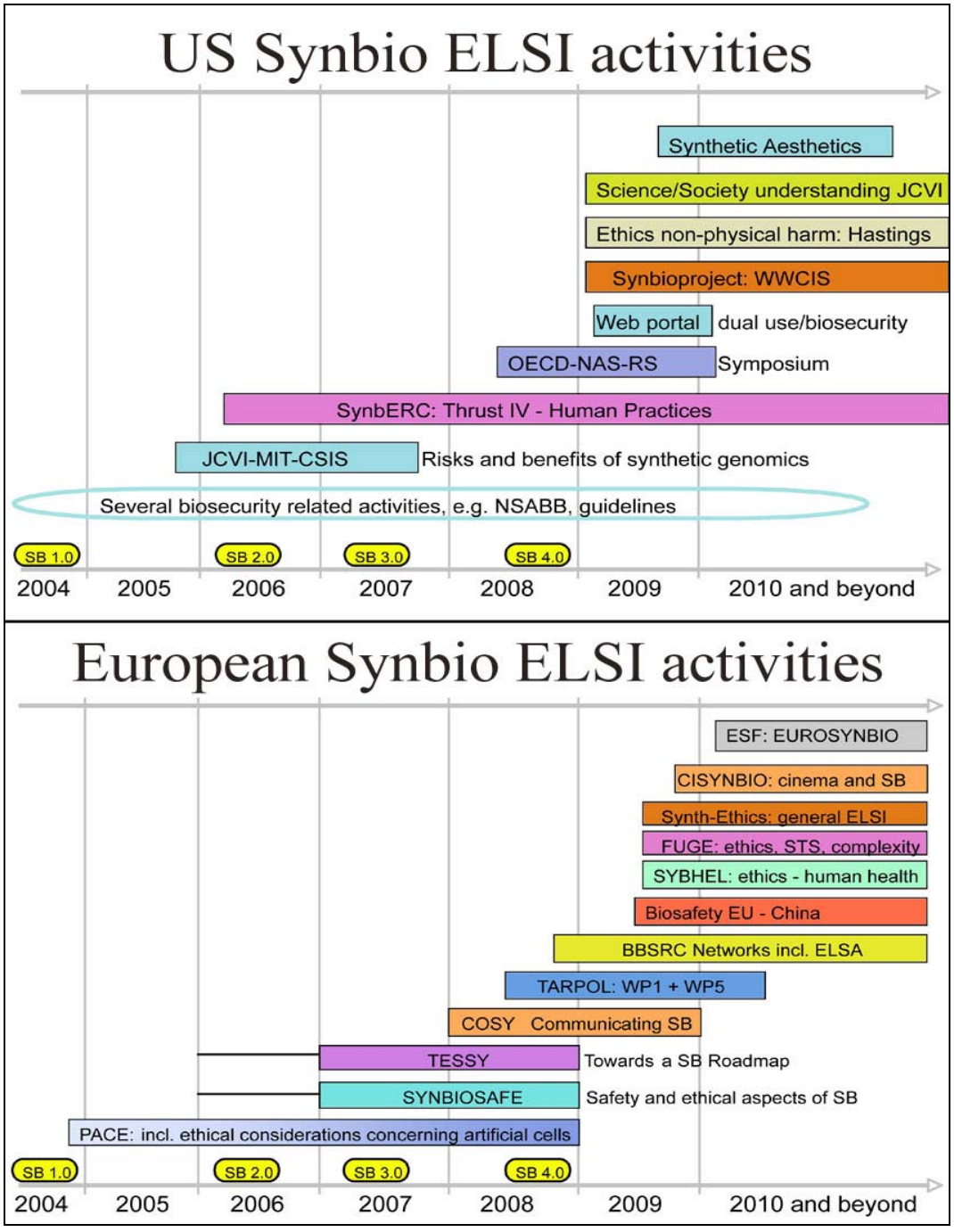


Table 6 and 7 summarise and compare the respective recommendations given by the US and the EC bioethics commissions. Although they seem to be largely complementary, a major difference can be noted regarding the reaction towards uncertainty. While the Europeans tend to refer to the *precautionary principle*, the US commission explicitly refuses to take that approach; instead they use the term *prudent vigilance*[6].

[6] What this exactly means remains unclear. The US bioethics think tank 'The Hastings Centre' is currently looking into the meaning of this new term.

Table 6: Overview of the recommendations given by the US Presidential Commission on Bioethical Questions, called New Directions: The Ethics of Synthetic Biology and Emerging Technologies

US recommendations (U1-18)			
category	**No.**	**content**	**Reference to Europe**
	U1	Public funding review and disclosure	E24, E25
	U2	Support for promising research (DOE, NIH, and fed agencies)	E5p, E8, E24
	U3	Innovation through sharing (NIH, DOE, NASA, PTO, industry. academic, and NGO)	E11p, E14, E16
Responsible stewardship	U4	Coordinated approach to SB (no additional body)	E2p, E13p
	U5	Risk assessment review and field release analysis. (SB as L probability - H impact)	E1
	U6	Monitoring, containment and control (built-in containment)	E6p
	U7	Risk assess. prior to field releasing (EPA)	E4p
	U8	Intl. coordination and dialogue (safety & sec) DS, HHS and DHS to WHO, Intl. Bioeth Org	E15p, E18p
	U9	Ethics education (outside medical setting)	E21p, E25p
	U10	Ongoing evaluation of objections (implication of SB on human, other species, nature and env.)	E26p
Intellectual freedom & responsibility	U11	Fostering responsibility and accountability (evaluated and re-env. HIHG re DNA research)	E2p, E3p, E14
	U12	Periodic ass. of sec. and safety risks (both institutional and non institutional setting)	E1p
	U13	Oversight control (make compliance with certain oversight or reporting measures mandatory for all researchers)	E11p
Democratic deliberation	U14	Scientific, religious and civic engagement	E21, E26
	U15	Info accuracy (employ clear and accurate language)	E22p, E23p
	U16	Public education (expand to diverse non research populations via various sources)	E21
Justice & fairness	U17	Risks in research should not be unfairly or unnecessarily borne by certain individuals, subgroups or populations.	No ref
	U18	Risk and benefit in commercial production and distribution	E7p

Table 7: Overview of the recommendations given by the European Group on Ethics in Science and New Technologies on SB (EGE, 2009).

EGE recommendations (E1-26)			
Category	**No.**	**content**	**Reference to the US**
Safety	E1	Use of SB should be conditional on specific safety issues especially regarding risk assessment procedures	U5, U11p, U12p
	E2	EC start an international debate with relevant counterparts to facilitate a **standardised approach** to biosafety of SB	U4p, U6p, U11p
	E3	Code of Conduct for research on synthetic microorganisms should be prepared by the Commission	U11p, U13p
Environmental application	E4	Ecological long term impact assessment studies carried out before an SB organism is released into the environment.	U7p
Energy and sustainable chemical industry	E5	Use of synthetic biology for alternative energy supply	U2p
	E6	Competent authorities monitor the authorisation procedures for the production of SB- derived chemicals and materials	U6p
	E7	Protect consumer right, labelling should be explored	U18p
Biomedicine and - pharmaceuticals	E8	Specific ethics considerations have to be addressed by the competent authorities	U2
Security, prevention of bioterrorism and dual use	E9	Convention on Biological and Toxicological Weapons (BTWC) should incorporate provisions on the limitation or prohibition of research in SB	No ref
	E10	Define comprehensive security and ethics framework for SB	No ref
	E11	Make open database, legal system for company to report suspicious sequences	U3p, U13p
Governance	E13	Propose a robust governance framework for SB and put it in place in the EU	U4p
	E14	Relevant science communities should be encouraged to establish ethical, preferably global, guidelines	U11
	E15	EU takes up the question of governance of SB in relevant global forums	U8p

EGE recommendations (E1-26)			
Category	**No.**	**content**	**Reference to the US**
Patents & heritage	E16	Debate on public access to results of SB	U3
	E17	EGE to assess ethics implications related to patents	No ref
Trade & global justice	E18	Ethical issues of SB should be address internationally (e.g. WTO, Doha)	U8p
	E19	EU Biosafety **standards** for SB products are adopted as minimal standards for EU import-export of SB products	U18p
	E20	Avoid new gaps between EU and developing and emerging countries, or within EU Member States	No ref
Science & society dialogue	E21	Promote debates and engagement among stakeholders to define main societal concerns	U9p, U14, U16
	E22	Promote responsible reporting on SB by the media	U15p
	E23	Stimulate actions to address implications of SB in the media	U15p
Research	E24	Support (FP budget) basic research	U1, U2
	E25	Properly finance (FP budget) interdisciplinary research: risk assessment and safety; security; ELSI; governance; SiS	U1, U9p
	E26	initiate an open, intercultural forum on concepts of life, including philosophical and religious input	U10p, U14

6.6.2. Public funding

A good indicator of the pace of society's reaction is the degree to which public funding agencies have adopted special programmes for SB and its ELSI aspects, and whether or not social scientists have taken the opportunity to study SB.

In a recently published paper by Pei et al (2011), funding agencies in six European countries were interviewed to analyse their reaction to the dawn of a new techno-science. The study shows that the funding situation for SB varies considerably among European countries. Some countries have – in proportion to the population – a sizable R&D community in SB; in others, the R&D community seems rather fragmented and less established.

The situation for ELSI research communities is different. Groups working on SB are scattered over Europe; Germany is the only country where, in particular, security issues for DNA synthesis are pursued by the private sector. The UK is the only country with an established funding scheme for both R&D and ELSI. See Table 8 for details.

Table 8: Funding landscape for SB and its ELSI research in six European countries (Pei et al., 2011)

Country	Synthetic Biology (SB)		ELSI of SB		Link between funding and community
	Community	Funding	Community	Funding	
Austria	not existing	potentially available	existing	available	no Austrian SB community despite available funding, ELSI funded
France	existing	hardly available	emerging	not available	general lack of funding
Germany	emerging	potentially available	existing	available	community and funding hardly synchronised, more money available than spent
Netherlands	emerging	available	emerging	hardly available	SB: good, ELSI: funding difficulties
Switzerland	existing	available	emerging	not available	SB: good, ELSI: funding difficulties
UK	existing	available	existing	available	overall good situation, community and funding available & synchronised

Public sources provide most of the funding for SB in Europe. The increasing commercial prospects of SB might attract additional public funding to foster a technology-driven economy as well as funding from the private sector, which is still not the case in Europe. Apparently, US scientists more easily manage to move their research nearer to commercialisation. In view of company representatives, US research in SB seems to be more application driven than European research.[7]

Pei et al. (2011) also found that in order for the funding agencies to accept a proposal as fitting to SB, reference to standardisation was not relevant. Even in the sub-field of bio-circuits, SB was equally accepted with or without the use of standard biological parts. So at least for funding agencies today, the future of SB does not seem to be jeopardised if standardisation approaches should turn out to fail (see Table 9).

[7] This was at least the argument for BP to invest €333 million ($500 million) in the Energy Bioscience Institute at UC Berkeley. According to a statement from BP, in the context of a European forum on synthetic biology organised by the European Commission in March 2010, they could not find an appropriate partner for their activities in Europe (Pei et al. 2011).

Table 9: Definitions of synthetic biology by funding agency representatives interviewed. Several subfields of synthetic biology were presented to interviewees: '+' means that it was accepted as part of synthetic biology, '-' means that it was not, '?' means we don't know. AT-1 and AT-2: interviewees Austria, CH: Switzerland, F: France; NL: Netherlands; UK, United Kingdom; DE: Germany.

	AT-1	AT-2	CH-1	DE-1	DE-1	FR-1	FR-2	NL-2	NL-2	UK-1	UK- 2
biocircuits using standard biological parts	+	+	+	+	+	+	+	+	?	+	+
biocircuits *without* standard biological parts	+	+	+	+	+	+	+	+	?	+	+
engineering cells to produce fine chemicals	+	-	+	+	+	+	+	+	+	+	+
creating artificial life	-	+	+	-	-	+	+	-	?	+	+
computer software for biocircuit design	-	+	+	+	+	+	+	+	-	+	-
artificial ecosystems	-	-	+	?	?	+	+	-	-	+	-
enlarged genetic alphabet	+	+	+	+	+	+	+	+	+	+	+
DNA with chemically different backbone	+	+	+	+	+	+	+	+	+	+	+
minimal genome	-	-	+	+	+	+	+	+	?	+	+
understanding the origin of life	+	-	-	+	+	+	+	-	+	+	+

***Conclusion**: The reaction from politics and funding agencies varies across Europe. Some countries swiftly decided to support SB while others are more relaxed. Standardisation does not seem to play a big role in funding technical research. A major political reaction was funding ELSI activities and assigning major bioethics committees to screen SB for upcoming challenges, notably the European Group on Ethics and the US Presidential Commission for Bioethical Questions.*

6.7. Policy options

Policy options may be grouped into business as usual approaches, leaving development more or less to its own; moderate governance approaches, steering development without taking too many risks; and active governing approaches, implementing a clear political will. The areas of action that have been identified are technical standard-setting, safety standards, intellectual property management and societal standards emerging from public debates.

6.7.1. Sociotechnical and regulatory practices

SB aims at introducing engineering principles into biology. This means, either, to render it possible to (re)construct living organisms or their parts to gain insights into their functioning (according to the motto of 'I only understand what I can construct'); alternatively, it means to render biology a real engineering discipline similar to computer, automotive, chemical or any other engineering field. Among the proponents of the latter are prominent members of the BioBrick and biofab community, who have succeeded to publicly render their agenda almost congruent to the agenda of SB in general.

Regarding technical standards, there is a clear effort among this community to establish a standardised set of parts, 'circuits', tools and measuring devices that would determine the future path of the field. Likewise, they intend to make this body of building blocks freely available – on the condition that future developments would be incorporated under the same premises. How intellectual property will be dealt with in the future, however, is not fully clear.

They not only introduced engineering principles into biology, but also (computer) engineering mindsets and practices. This includes vivid student competitions in building new devices, the promotion of 'open source' rather than heavy patenting as the preferred way of managing intellectual property, and the establishment of a 'do-it-yourself' community aiming at doing SB in their home garages. It might also result in a certain reluctance to acknowledge new and potentially stifling safety and security measures that are necessary to protect an emerging field from potential, maybe tiny risks. Finally, this understanding heavily builds on enthusiasm for technology not only among professionals but also among young people and, eventually, the public at large. The biggest risk, accordingly, would be that the public's enthusiasm might wane as it happened with agricultural biotechnology or, before, with nuclear power.

However, there are voices that call for caution. Firstly, it is not clear whether engineering principles common in many traditional fields can be emulated into biology. The slowdown in the complexity of new biocircuits may be an indication that after all, it will not be so easy to persuade living systems to behave equally predictably as electronic circuits. This raises the question whether standardisation of parts and circuits as promoted today will really entail the hoped-for gains in efficiency and reproducibility. Prominent scientists warn against over-hyping SB as a panacea for new applications at a point in time when there are very few of them available. Since the field is in its beginnings only, supporting exaggerated expectations may turn into disappointment if results fall short in fulfilling them soon.

Secondly, current safety and security standards seem to be reasonably sufficient for the time being. The often prominently discussed question whether SB is something entirely new, or whether it is a mere extension of traditional biotechnology, seems to be of secondary importance, as long as safety standards are apparently sufficient. However, it is foreseeable that technical developments could challenge established practices and thus demand that standards get adapted irrespective of the epistemic status of SB.

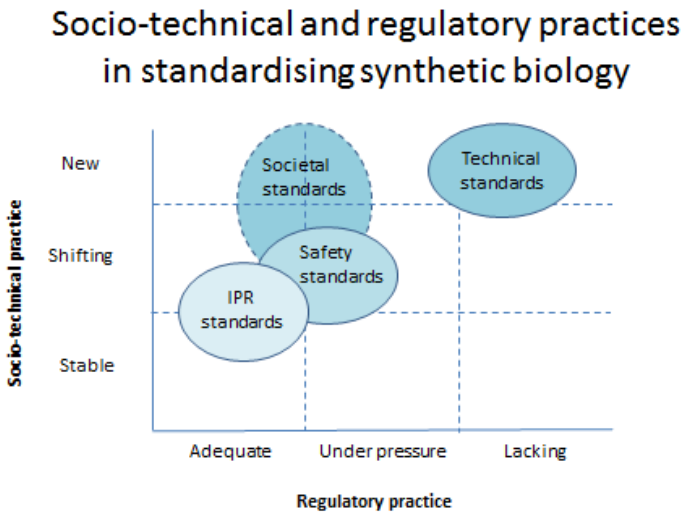
Thirdly, since SB is an interdisciplinary endeavour, different practices from fields such as molecular biology and computer sciences may turn out to be irreconcilable. This is most noticeable today when it comes to different rationales regarding IP management. Although there are established forms of IPR, coming to terms with contradictory demands regarding protection of individual rights and the general accessibility of knowledge is a challenging task.

Finally, whether SB will turn out to be a real game changer and thus a major factor determining future competitiveness cannot be established yet. Major political and financial engagement, therefore, has to take into account uncertainty. Moreover, whether the public will appreciate SB as they like computers, or whether they will extend the dislike of (green) biotechnology to SB, is more or less unpredictable. In other words, in addition to safety and security standards, there may also be broader, societal standards that SB has to address in order to be accepted as a responsible and legitimate endeavour. These standards may be explicit or implicit, based on previous experiences with new technology, with regulatory performance and other factors – or just on traditions of various kinds. They may refer to various categories such as democracy, equity, sustainability or particular morals; hence, they are difficult to define. Assessing such societal standards therefore exceeds the remit of this project.

In addition, differences in political, funding and discourse cultures are substantial among countries, and the subject might raise entirely new aspects that will have to be addressed. This challenge goes somewhat unnoticed still, as the salience of SB in public debate is currently low. However, there is a possibility that salience will grow along with applications becoming available and interest among the public getting more substantial.

If we try to analyse these ambiguities, two dimensions emerge: on the one hand, there are (potential) changes in sociotechnical practices through SB that, on the other, challenge regulatory practices. Both are related to the question of keeping, changing or developing standards. Sociotechnical practices may be stable; they may undergo change or entirely new ones may emerge. Regulatory practices may be considered adequate (at least for the time being); some others may get under pressure from new developments, while in some areas, they are entirely lacking. If we try to assign a place for the identified domains where standards play an important role (technical, safety, IPR and societal) along these axes, we arrive at Figure 16.

Figure 16



Regarding *sociotechnical practice*, the question is to what extent SB will turn out to be a real game changer:

- SB may be considered as a stable practice as long as it is seen as an advanced form of traditional genetic and metabolic engineering (SB = biotech).
- If SB is seen as moving towards a new approach to engineering life, it can be defined as a shifting practice (SB = biotech?).
- If SB is defined as the making of a new engineering discipline, it will be considered as a new and promising emerging practice (SB ≠ biotech).

Regarding *regulatory practice*, the question is to what extent standards may be considered adequate or not:

- Technical standards for construction are lacking, but they are perceived as the principal constituent elements of a postulated radically new practice of bio-engineering. While aiming at engineering practices, such technical standardisation also impinges on ethically relevant categories of life and non-life.

- Dealing with safety (and security) clearly has undergone changes over recent years, Safety standards seem adequate still but might get under pressure as SB may develop into a more far-reaching practice of bio-engineering.
- IPR standards (e.g. patenting and open source) can be considered established. However, as practice shifts from traditional genetic engineering to 'real' bio-engineering (in the sense of technically standardised SB), some actors strongly prefer 'open source' over established standards of patenting in biotechnology.
- If SB (in contributing to a bio-economy) should move further towards (re)engineering life, including plants and animals, it might raise more substantial concerns about societal standards of sustainability as well as public sentiments about the dangers of 'meddling' with life.

In general, as issues are moving from the bottom left to the top right in our diagram, governance challenges might increase. However, for any particular issue, this is clearly also a matter for critical debate (and controversy). For example, even though issues of technical standardisation appear at the top right in our diagram, this is not to say that these issues raise governance challenges that are really pressing and immediate. Irrespective of (different levels of) challenges for governance, there are several options that may be at disposition. In general, options can be sorted into three general categories according to the level of action involved:

- The first option is to carefully await further developments while sticking to business as usual, as much as possible.
- The second option entails cautious action, for example official bodies giving actors a helping hand to facilitate a politically desired development.
- The third option is to actively engage in measures bringing about a politically aimed result – even against potential resistance.

In the following we will address the four areas identified and (non-comprehensively, of course) flag out some options that European policy-makers might wish to consider.

6.7.2. Options regarding technical standards

First of all, technical standards will be developed from initiatives in the scientific community in response to the need to create mutual understanding and to facilitate an exchange of knowledge, models and materials. Most of the leading initiatives in synthetic biology are taking place in the US, with European scientists contributing to, but so far not spearheading, approaches and methods of standardisation in SB.

Some European scientists have suggested starting a European version or 'brand' of standards in biology, going beyond the concepts and ideas of the BioBricks foundation and other US initiatives. They tried to outline different concepts such as the standardisation of processes or functions. So far, these calls have not received much support.

There is also a political dimension here, because standards may create advantages in an economic sense. This raises the question whether there is a need for European policy initiatives to support efforts in technical standardisation with a view on facilitating and promoting the work of European scientists, engineers and, ultimately, companies. The explicit political aim to establish a knowledge-based bioeconomy in the EU might suggest such a conclusion. However, since SB is a global scientific endeavour, it remains doubtful whether a separate European initiative would render the hoped-for success in terms of competitiveness. The disparate policy across EU member countries with respect to setting up special funding programmes for SB seems to reflect this ambivalent assessment.

Any policy effort with respect to SB might meet an additional problem. SB is a rather varied field, and what seems to make up its heart, according to the vociferous and mostly US-based BioBrick community, is standardisation. This is in contrast to what many European scientists conceive to be the essence of SB. For them, standardisation would be nice to have but is not the ultimate challenge. Whether the particular approach at standardising biological parts and circuits as promoted by the BioBrick community will turn out to be successful is not sure. The policy of European funding agencies so far seems to support this interpretation.

Are Europeans about to 'miss the train' again as with other cutting-edge technologies before, such as various information technologies or genetic engineering? Would it be necessary to massively invest in the development of, say, a European brand of BioBricks to catch up with the NSF and DARPA programs and to establish a knowledge-based bioeconomy? Or should Europeans be careful not to indulge into a hype-driven development – a bubble that will burst sooner or later? Could it turn out to be a bottomless pit like the case of nuclear fusion power, where, due to principal difficulties, pouring in money will nevertheless not render returns in a foreseeable future?

There is no doubt that standardisation is an issue that needs to be taken into account. The European Commission has reacted to the challenge and funded a research project exploring standardisation in SB (see Annex A); further activities might depend on the outcome of this endeavour.

In general, there are several possible ways at reacting to the development of an increasing community promoting standardised parts and circuits:

Wait and see

An option could be to carefully watch the development without taking too much effort to influence it. On the one hand, this would save resources and, on the other hand, provide the opportunity to participate in the exploitation of parts and circuits as soon as they are available, and even more importantly, when they eventually turn out to be reliable. The downside to such a strategy would be that European actors would forego the opportunity to actively influence the path of development. However, there is an argument that technical progress has already been so quick that a path dependency has established; in other words, there is little that could be influenced in a fundamental way anymore. As the 'early birds' already have caught the worm, latecomers will have to do with what is left. This might cause quite substantial opportunity costs from chances foregone.

Keep a foot in the door

Since SB in general, and standardisation approaches in particular, are in their infancy, the above lean-back stance may be premature. Hence, efforts could be spent to at least keep a foot in the door by actively contributing to the technical development in the field. Countries such as the UK or Switzerland seem to follow such a strategy. However, on a European scale there are only little efforts at active contribution. The first step in this direction is the EU funded project on standardisation, and similar endeavours could be supported in a more coordinated way among member countries and on a broader scale. Since standardisation is a potentially powerful tool, an option would be to reflect on an appropriate time schedule and fruitful strategies for the process of standard-setting. Likewise, different ways to ensure the implementation and appropriate adoption among stakeholders could be considered.[8]

[8] An interesting proposal was made during the workshop, namely to learn from similar standardisation approaches in other fields such as systems biology. Here, comparatively little money spent on co-ordination efforts such as organising meetings and providing infrastructure could buy substantial benefits in terms of progress towards developing a common understanding and language.

Massive efforts

SB in its guise as an engineering field built around defined and standardised building blocks may turn out to be the basis for a new industrial revolution. Such a possibility cannot be excluded, and any consideration regarding future European competitiveness in general, and a knowledge-based bioeconomy in particular, must take it into account. This line of thought immediately leads to the conclusion that in the long run, the most expensive thing to do is to leave the field to others. Therefore, a heavy investment might be spent on catching up with, and probably passing by, the developments in the US.[9] Funds would have to be diverted from other fields, though, so resistance among the scientific communities in various disciplines would have to be anticipated. In addition, should the standardised building block approach in SB turn out to fail, the backlash not only in SB but also in other fields that are stripped from resources would have to be dealt with. Thus, opportunity costs would be high as well.

6.7.3. Options regarding safety standards

Standards relating to safety, security, IPR and – perhaps – sustainability are a different matter, because scientists and engineers will often perceive them as an additional hurdle rather than help. This also implies a different role for policy-making. Here, regulators are not perceived as supporters but as intruders that jeopardise the otherwise sufficient self-regulation that the scientific community might prefer.

However, with biotechnology as well as nanotechnology, the industry had repeatedly emphasised the need to introduce a clear regulatory safety framework to ensure the technology's unhampered development. With other issues, especially touching moral problems, ethical committees were commissioned to provide guidance. With SB, science and industry rarely called into question the existing regulatory safety framework. Rather, prominent ethics committees played a leading role also with regard to determining whether contemporary safety standards would suffice. The US Presidential Commission and the European Group on Ethics, for example, made proposals for how to set up the minimal necessary environment for the safe development of the novel technology. Apart from ethical considerations, their recommendations centred on the task of ensuring safety and security.

SB, as a form of biotechnology, is subject to the entire existing biotechnology regulation. While most experts consider this to be sufficient and also various ethics committees have come to the same conclusion, the main question is whether this can be sustained in the future. After all, technical progress is envisaged to be tremendous, so new aspects inevitably will have to be taken into account. However, it is unclear which safety or security aspects would pertain to developments that are only vaguely predictable at present. Both the EGE conclusions and the US Presidential Commission report therefore contain an element of precaution (or 'vigilance') intended to raise awareness to as yet unknown developments. However, it is not clear if, how and when potential hazards will be emerging and which concrete measures will eventually have to be taken to prevent or mitigate them.

In many discussions, the problem was framed as deciding whether or not, and in what respect, SB is different from biotechnology, what this difference might consist of and when the difference is substantial enough to expect safety or security problems. Ensuing questions are:

[9] An option could be to set up a European institution dedicated to not only developing standards but indulging into designing and testing the equivalent of BioBricks and biocircuits competing with the US products and maybe even outcompeting them.

- When will the first regulatory gaps appear? Since there is no objective method to determine the 'difference' to biotechnology, nor the pace of development, this moment remains obscure. Again, it is not only a technical question, but also a political decision that might be influenced by non-technical parameters, such as public perceptions of contingencies like accidents or problems with other fields of technology spilling over.[10]
- In which areas will the regulatory obsolescence occur? This is also subject to speculation; however, there are a number of areas where demand for action might ensue. Among them are novel molecules (e.g. XNA, i.e. nucleic acids chemically different from DNA), assembly methods and processes, different genetic codes, measurements, algorithms and software.
- How could policy makers react to these challenges? They could rely on expert advice or call upon lay participation, take into account a wider variety of stakeholders or decide politically. Measures could entail new or amended regulation, special codes of conduct or other means of governance.

Irrespective of whether SB is considered different from biotechnology or essentially the same, particular developments may present new challenges to safety and security. To address them, a variety of options can be imagined:

Business as usual

Departing from the view that SB is a form of biotechnology that is substantially equivalent, safety and security problems in SB can be considered essentially the same as in biotechnology at large. Hence, regulations for biotechnology do not have to be amended to cater for SB. This position could be upheld as long as no clear indication for a scientifically measurable additional risk from SB emerges. If such a case should occur, reactions would remain as low-key as possible in order not to impede technology implementation and progress.

Assess whether SB raises new questions

Since it is foreseeable that, at some point, additional problems from SB approaches could occur, an option would be to monitor and repeatedly assess, in a stepwise procedure and on the basis of scientific expertise, whether the current body of standards and regulations still is sufficient. Such an assessment might then lead to a partial amendment of the pertaining rules even before concrete risks ensue, in accordance with the scientific community's advice. In particular, if production is intended to be scaled up, the safety and risk assessment would also have to be appropriately scaled up or otherwise adapted. Such a procedure would probably be in accordance with both a precautionary approach and with the call for vigilance.

Radically new approaches

Since SB provides a toolbox of entirely novel safety measures, this potential could be tapped. Hence, SB could be subjected to a range of novel measures that are specifically designed to address potential risks ensuing from specific processes and products unique to SB. Thus, a range of new safety standards could be developed and implemented, making use of approaches such as chemical orthogonality, novel genetic codes, and so on. These standards would have to be made mandatory, after having been exhaustively tested, for any new approach within SB.

[10] Remember the coincidence in the late nineties of the BSE crisis: the non-commissioned import of GM soy and the advent of Dolly the sheep.

6.7.4. Options regarding intellectual property rights

The aim of any approach regarding IP is to provide an equitable and just protection of intellectual property that fosters technical progress, broad access to the technology and adequate returns to the inventers. The problem as to which avenue to follow – basically, patenting or open source – is mostly up to the scientific and engineering communities themselves and their preferences. At first glance, state regulators seem to have only limited possibilities to influence the way intellectual property is dealt with in SB. In addition, there is a strong interdependency to patent legislation in other countries, so any particular rules regarding SB would have to take into account the international situation.

Nevertheless, there are many ways intellectual property can be dealt with. Apart from patenting and open source, approaches such as open access, (compulsory) licences, utility patents, copyrights, trademarks, creative commons and so forth, may be considered. The traditional way of patenting as is customary in biotechnology is not the only possibility to make available new technology while protecting the rights of the originator. Especially the analogy to software and other products of computer engineering have enhanced the choice of different forms of IP protection. Analogies, however, have their limits. For example, a personal computer as the essential tool to produce new software is within the reach of a private person even when this person is not particularly rich. A professionally equipped laboratory is not.[1]

For the time being, it is not yet clear what intellectual property management in SB will look like. This opens up a range of possible options.

Business as usual

The first option would be to apply all IP rules to SB as with any other field of biotechnology, irrespective whether SB is involved or not. This would entail, probably, a continuation of the practice to patent any result from research that appears patentable. Similar to publications, patents would serve to measure the success of research and development projects also in SB. Exploitation could be facilitated by the expectation of revenues. The downsides are the same as with biotechnology in general: i.a. there is a danger of a patent thicket that must be cleared even before a research project can be started, and some results might never be exploited due to excessive patent protection.

A helping hand

In the case open source approaches are favourably perceived, politics could facilitate a more open approach, if so desired, by way of initiating research. Since there is a lot of ambiguity for the time being, projects could, for example, investigate under which conditions which form of intellectual property management would render the best results. Thus, the conditions for those in need of choosing an adequate form of IP management could benefit from more openness and clarity.[2]

[1] Although the do-it-yourself movement within the SB community aims at exactly this: a garage factory within the reach of the average citizen.

[2] More concretely, there is a demand for methods to check whether elements of SB in an openly accessible registry (such as BioBricks) really belong to the public domain.

Active promoting openness

A strong community demands making SB building blocks freely available by default. Measures could be devised to ensure that this becomes possible; in particular, experiences from open access publication and so on, could be used. For example, funding agencies could demand, or at least accept, creative commons rather than patents as the result of research projects.[3] In addition, the EU could consider ensuring a European legal basis for open access – while creative commons are internationally acknowledged, this might not be the case for biological circuits for example.[4]

6.7.5. Options regarding (other) societal standards

SB has elicited a lot of attention among social scientists, ethicists and interested stakeholders with respect to its societal ramifications. This has, however, not resulted in a clear concept of how to deal with this new form of biology becoming technology. While some stakeholders fear negative public sentiments, others have repeatedly demanded to pro-actively stimulate public debate in order not to experience 'the same thing happening as with GM crops'. Sometimes this preventive attitude seems to be the main reason why dealing with societal implications is considered necessary altogether.

Regulatory action, however, does not appear to be the measure of choice to guide a fruitful societal dialogue over SB. Nevertheless, politics have to take into account that, apart from safety, security and intellectual property, there is an increasing number of questions arising from SB activities that society at large might be interested in. After all, one of the 'ten grand challenges' to artificial life recently identified (Porcar et al. 2011) refers to 'coupling scientific development and public opinion information'.

Opinions are split on how to best deal with societal aspects of SB, including sustainability considerations. Some think that technology, if only left alone, might convince people of the great benefits to expect. Others are wary of criticism from within society. Finally, some think that SB, due to its very nature rendering life amenable to technological manipulation, should be carefully watched beforehand. In this ambiguous situation, there are several options for political action.

Business as usual

As in other fields, an option would be to adopt a wait-and-see attitude. This would entail support for the scientific and technological development, without making any difference to other technologies. Such a strategy would leave the fate of SB to the properties of its products to elicit demand and its ability to supply what has been demanded. Societal acceptability, then, would be a phenomenon of the public sphere that does not warrant political intervention. If public sentiments should turn out to be detrimental for the development of SB, then this may be bad luck, but nothing to cater for.

Anticipate societal concerns

Politics could choose to foresee public concerns about synthetic biology and cater to them by engaging in efforts at anticipatory governance. This could be achieved by stimulating societal debate, for example through funding projects aiming at public understanding, or by organising participatory events, science fairs and so on, in the framework of a knowledge-based bioeconomy. It could even exceed such efforts by allowing for more substantial deliberation.

[3] To be stipulated in the pertaining consortial agreements.

[4] This could be accomplished by a publicly accessible registry for products and elements of SB similar to that in the US.

For example, in suitable events a picture of desired or undesired futures could be drawn, where standardisation in SB could contribute to – or jeopardise – a socially sustainable, economically viable and scientifically fruitful development, and appropriate measures could be designed to arrive at a more desirable future. Such endeavours and events might turn out to be futile, however, if developments run much faster than any societal debate is able to follow them.

Mandatory assessments

Given that SB is a most powerful technology (if promises turn out to become true, at least), it might not only elicit unfounded anxieties among the public; rather, it might give rise to real misuse and extremely dystopian futures. Institutions or expert committees could be set up with a view to check future projects or applications of SB for their social and environmental sustainability. Apart from questions of feasibility, however, this would probably meet resistance from the side of scientists, engineers and the business sector, among others, as it could slow down the development of the new technology and prevent beneficial applications from being implemented.

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ANNEX

A Call for a EU funded project on standardisation in SB

KBBE.2011.3.6-03: Towards standardisation in Synthetic Biology

Call: FP7-KBBE-2011-5

Description: Some of the most relevant challenges that Synthetic Biology is facing are the definition, understanding and eventual cataloguing of biological parts. The issue at stake is to bring natural existing biological modules to the point of context-independence, which will be needed for serious engineering. This includes also the pursuit of a consensus language for describing biological functions in a quantitative format, as well as a good understanding of whether existing biological systems can be re-factored to be orthogonal. Only sufficient compliance with these standards will ensure that a designed element of the system has a high chance of re-utilisation. A successful project must take into consideration, besides the scientific/technical issues, training, ethics and safety.

Funding scheme: Collaborative Project (large-scale integrating project).

Additional eligibility criteria: The requested European Union contribution shall not exceed € 6 000 000.

Additional information: Interdisciplinary training is particularly important in synthetic biology because students not only require a detailed knowledge of their primary discipline and how it pertains to the field, but also a thorough grounding in the other scientific disciplines involved. In addition, they need to be fully conversant with the ethical, societal and economic issues, which are germane to synthetic biology. Applicants should adhere to the Opinion No 25 of the European Group on Ethics in Science and New Technologies to the European Commission 'Ethics of Synthetic Biology'.

Expected impact: A European project will create the appropriate platform for an international dialogue on standards, use and applications in Synthetic Biology. Participation of industrial partners, in particular SMEs, should contribute to achieving the expected impact.

7. EUROPEAN GOVERNANCE CHALLENGES IN 21ST CENTURY BIO-ENGINEERING

Rinie van Est & Dirk Stemerding

Summary

This *Final Report* discussed four case studies (whole genome sequencing, neuromodulation, biocybernetic adaptation and standardization in synthetic biology) focusing on particular developments in the four fields of 21st-century bio-engineering that were explored more extensively in the earlier *Monitoring Report* (respectively, the engineering of the body, the brain, intelligent artefacts and living artefacts). The aim of the case studies was to inform and stimulate political debate in the European Parliament by highlighting the bio-engineering developments in each field that have more immediate implications for European policymaking.

To make the governance challenges that are posed by these developments more transparent for policymakers, this report introduced a conceptual framework which uses two dimensions in the description of the cases. One dimension refers to the variety of *sociotechnical practices* in which new bio-engineering developments are taking shape, while the other refers to the patchwork of *regulatory practices* that may be affected by these developments.

The four case studies show that new bio-engineering technologies are being developed and adopted in a wide variety of sociotechnical practices, involving different applications and actors. New bio-engineering technologies may be adopted in relatively stable sociotechnical practices, but may also lead to significant changes to established practices or to newly emerging practices. The case studies further explored how this dynamics affects current regimes of regulation relevant to the different sociotechnical practices in which new bio-engineering technologies are taking shape. With regard to this regulatory dimension, three situations can be distinguished. Current regimes of regulation may be perceived as adequate, as being put under pressure, or as no longer adequate (or lacking).

On the basis of this conceptual framework we can map the bio-engineering developments described in the different case studies along two dimensions, providing us with an overview of (1) the ways in which sociotechnical practices are being shaped and/or reshaped by new bio-engineering technologies and (2) the extent to which established regulatory regimes are being challenged by these changing practices. In reference to these two dimensions and the dynamics between them, this chapter discusses the nature of the governance challenge that European policymakers face. The fundamental governance challenge, as we will argue, is to attune these two dimensions. In other words, how can we *align* the dynamics of sociotechnical and regulatory practices with respect to the four cases of 21st-century bio-engineering studied in this report?

We have identified twenty different sociotechnical practices that are being shaped and/or reshaped by or are emerging from the bio-engineering technologies presented in the four case studies. An important question for policymakers raised by this sociotechnical dynamics is to what extent current regulatory practices are able to adequately respond to the short-term and long-term implications of the bio-engineering technologies studied here. As the case studies have made clear, there is already a patchwork of regulatory practices in place in the different fields of bio-engineering. Thus, the precise question is: To what extent can current regimes of regulation be perceived as adequate or in need of change?

The findings from the four case studies strongly indicate that bio-engineering in the 21st century will pose a clear regulatory challenge to European politics and policymakers, especially with regard to issues of safety, privacy, bodily and mental integrity, informed consent, transparency and harmonization. The simultaneous impact of bio-engineering technologies on a diversity of existing or emerging sociotechnical practices reveals that the regulatory challenge will often be multifaceted. Existing regulatory frameworks can thus be seen as partly adequate, partly under pressure and partly inadequate, depending on the sociotechnical practice under consideration.

This chapter distinguishes two different situations in which potential tensions and misalignments between sociotechnical and regulatory practices may occur: the *regulatory zone* and the *regulatory wasteland*. In the regulatory *zone*, sociotechnical practices are guided by established regulations that may be considered robust enough to deal with changing or newly emerging practices. In other words, the regulations in place can be considered future-proof in their potential to be adapted to or realigned with changing or new sociotechnical practices. In the regulatory *wasteland*, regulations are lacking or may be seen as inadequate to guide existing, changing or newly emerging sociotechnical practices. In this situation, there will be a genuine need for changes in existing regulations or for the development of new forms of regulation.

As we point out in this chapter, the need for the alignment of sociotechnical and regulatory practices poses a governance challenge which is both fundamental and difficult because it relates to future developments which may have a great impact but which are also uncertain in several respects. When dealing with this governance challenge, above all policymakers face technoscientific uncertainty, that is, uncertainty about the speed, direction and nature of technological change in 21st-century bio-engineering. Technoscientific developments may also change the social and political values that inform the societal and political debate concerning notions such as autonomy or privacy for example, and thus may create uncertainties about the values that should underpin regulatory initiatives. Finally, policymakers face uncertainty about the adequateness of existing regulatory frameworks, that is, about the alignment or misalignment of sociotechnical and regulatory practices in the near or more distant future.

These various uncertainties lead to different and sometimes conflicting opinions about the potential impact of bio-engineering developments and the regulatory challenges that may arise from them. Therefore, in our view, political debate is required to determine the nature and urgency of the governance challenges in 21st-century bio-engineering and the ways to deal with these challenges. Accordingly, our analysis distinguishes three different *options for governance* which correspond to different interpretations of the bio-engineering developments discussed in the four case studies. The recurrent political question is whether future sociotechnical practices enabled by new bio-engineering developments can be considered substantially equivalent to sociotechnical practices with which we are already familiar:

- If this is the case, it can be safely assumed that established regulations for these practices will also apply to the new bio-engineering developments and a wait-and-see strategy would be an appropriate option for governance
- If there are reasons for doubt about the equivalence of new sociotechnical practices to already existing forms, the monitoring and assessment of these developments would be an appropriate governance option to determine whether current regulations are adequate
- If new bio-engineering developments lead to sociotechnical practices that are evidently different from present practices, existing regulatory frameworks may have to be revised (within the regulatory zone) or new forms of regulation may have to be developed (within the regulatory wasteland)

Our concluding reflections on the findings of the different case studies indicate which policy options are most appropriate according to the assessment presented in each case, which is based on consultation with various experts. In the case of whole genome sequencing and biocybernetic adaptation, it was argued that future changes in sociotechnical practices will urge policymakers to start revising and harmonizing existing regulatory frameworks. In addition, new sociotechnical practices are emerging which might require new forms of regulation in the near future. In the case of neuromodulation, it was found that, in general, current regulations are adequate, but need more clarification, transparency and monitoring on various specific points. In the case of synthetic biology, no particular governance options were recommended, on the grounds that the future of this field is too uncertain to promote a particular strategy. We simply do not know whether synthetic biology will become a real game changer.

In the *Monitoring Report* we argued for a broadening of activities in the field of bioethics because in the 21st century the bio-engineering debate no longer solely concerns the life sciences, but also NBIC convergence. From our analysis in the *Final Report* it becomes clear that we should not only broaden the field of bioethics, but also move beyond bioethics to *biopolitics*. The report namely reveals that bio-engineering in the 21st century poses a major challenge to European politics and policymakers. This implies that the governance of bio-engineering in the 21st century not only concerns stimulating scientific reflection and public debate on technological change and its societal implications, but also the *political regulation* of shifting and newly emerging sociotechnical practices in society. Politicizing bio-engineering developments thus requires more attention to regulatory uncertainties raised by bio-engineering developments.

Policy recommendations

- In order to increase institutional reflexivity and strengthen the preparedness of the European Parliament and other European institutions to deal with the governance challenges raised by bio-engineering in the 21st century, politicians and policymakers need to pay more close attention to the experiences of institutions which deal with regulation and its uncertainties
- To empower the current European political system to democratically guide bio-engineering in the 21st century, a dedicated and continuous effort is required to make the complex workings and failings of the relevant regulatory systems politically transparent with respect to the present and coming years

The Monitoring Report studied four fields of bio-engineering: engineering the body, the brain, living artefacts and intelligent artefacts (Van Est et al., 2011). It was concluded that the developments in these four bio-engineering areas go hand in hand with a multitude of ethical, legal and social aspects. Moreover, it was argued that the two bio-engineering megatrends, "biology becoming technology" and "technology becoming biology", challenge the way we currently regulate issues like safety, privacy, informed consent and bodily integrity (See Chapter 2). This third and final phase of the Making Perfect Life project aims to provide members of the European Parliament a more profound understanding of the governance challenges put forward by these two bio-engineering megatrends.

In this phase, therefore, our research focused on the social and ethical issues,as well as the regulatory challenges that are associated with specific technological developments within each one of the abovementioned bio-engineering fields. With regard to engineering of the body, Kukk and Hüsing (Chapter 3) studied the rapidly developing field of whole genome sequencing. In the domain of engineering the brain, Van Keulen and Schuijff (Chapter 4) scrutinised three neuromodulation techniques.

With respect to the R&D effort to develop intelligent artefacts, Böhle, Coenen, Decker and Rader (Chapter 5) studied biocybernetic adaptation as a means to improve the interface between humans and computers. In the field of engineering of living artefacts, Schmidt and Torgersen (Chapter 6) focused on standardisation issues in the field of synthetic biology.

This chapter aims to draw some conclusions with regard to the European governance challenges that bio-engineering in the 21st century poses to the European Union and its member states. Section 7.1 reflects on the sociotechnical dynamics of the various social practices that were identified in the four case studies. Besides, it explores to what extent these various sociotechnical practices challenge current models and rules of regulation. What do these four specific developments teach us about governance challenges put forward by bio-engineering in the 21st century? Section 7.2 briefly points at the fact that over the last decade awareness has grown that different types of policy problems and distinct dynamics of sociotechnical practices require different governance strategies. Section 7.3 explores the relationship between the dynamics of sociotechnical and regulatory practices that were described in the four case studies. Our point of departure is that the basic governance challenge is to align these two dynamics. In section 7.4 we finally discuss the available options for European policy-making with regard to this governance challenge in the four cases.

7.1. Changing sociotechnical practices and regulatory challenges

To make the regulatory challenges that arise from developments in 21st-century bio-engineering transparent, this chapter used a conceptual framework which allows us to map these developments according to two dimensions: (1) ways in which new bio-engineering technologies are changing existing sociotechnical practices, and (2) the degree to which these changing practices challenge established regulatory practices. Each of the four case studies (whole genome sequencing, neuromodulation, biocybernetic adaptation and standardization in synthetic biology) illustrated that new bio-engineering technologies can have a simultaneous impact on various sociotechnical practices. In total, twenty sociotechnical practices were identified across the four studies, which further showed that the majority of these sociotechnical practices put established regulatory regimes under pressure or reveal them to be inadequate. These findings strongly suggest that bio-engineering in the 21st century will pose a clear challenge to European politics and policymakers.

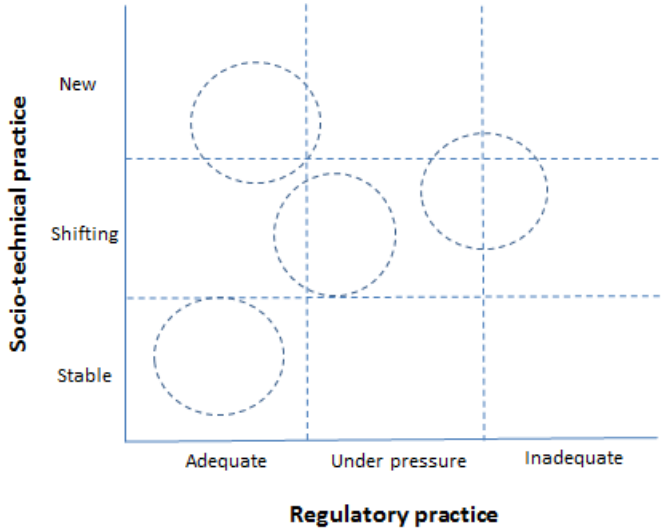
7.1.1. Conceptual framework

In this part of the Making Perfect Life project, we studied four specific technological developments. In the introductory chapter of this report (section 1.3.1.) we introduced a conceptual framework to make the regulatory challenges that are posed by these developments more transparent for policy makers. One dimension of this scheme refers to changes in *sociotechnical practices*, the other to the degree in which these sociotechnical practices challenge current *regulatory practices* (figure 1).

The practices in which technologies are developed and adopted for particular purposes, like diagnosis or therapy in medicine, we call sociotechnical practices. We distinguish between sociotechnical practices on the basis of their novelty. A sociotechnical practice might be an existing practice that is stable or experiencing a shift. Besides, new sociotechnical practices may be emerging. With regard to the regulatory dimension, we also distinguish between three categories: current regulation is either regarded as adequate, as getting under pressure, or as inadequate. If the existing regulatory framework is regarded as adequate, clearly there is no need for change. Current regulation is getting under pressure when there is large uncertainty about the question whether or not the current framework will be able to deal with new sociotechnical developments in an appropriate manner.

At the same time, it is assumed that adjusting the current regulatory framework to the new circumstances will be possible and sufficient. Finally, the current regulatory system is seen as inadequate when it is either expected that the current system is in need of far-reaching redesign, or when new forms of regulation are required.

Figure 1: Dynamics of sociotechnical and regulatory practices



In conclusion, using our conceptual framework will provide an overview of the ways in which new technologies are changing existing sociotechnical practices and enabling the emergence of new practices. Second, it clarifies to policy makers to what extent these stable, shifting and newly emerging sociotechnical practices challenge current regulatory frameworks and concepts. It makes transparent to what extent the existing regulatory frameworks are considered to be adequate and future-proof.

7.1.2. Shifting sociotechnical practices and new emerging ones

Each of the four cases illustrate that new technical developments can simultaneously impact various sociotechnical practices. For example, neuromodulation techniques can be applied for therapeutic uses, but also for gaming purposes, and further into the future, maybe also for human enhancement.

The impact of these new bio-engineering technologies on sociotechnical practices is diverse. The technology might leave the existing sociotechnical practice untouched or even strengthen the current practice. But technology might also cause a practice to gradually change. Moreover, technology might stimulate new practices to emerge.

Table 1 provides an overview of the findings from the four case studies, and shows that the whole spectrum – ranging from stable, to shifting, to new practices – can be found. The categorisation of sociotechnical practices as stable, shifting or new is based on an assessment made by the various authors, informed by the literature and expert opinions (from workshops that have been held). In several cases, practices have been put by authors in two categories at the same time. As a result, in fact, five (partially overlapping) categories can be distinguished: stable, stable & shifting, shifting, shifting & new, and new.

Table 1: Overview of (stable and shifting) existing sociotechnical practices and new emerging ones in bio-engineering.

Case study	Sociotechnical practice		
	Stable	***Shifting***	***New***
Whole genome sequencing	Forensics		
	Bio-banking		
	Personalised medicine		Direct-to-consumer genetic testing
Neuromodulation	Research		Gaming EEG-Neurofeedback
	Therapeutic use		
	Enhancing via EEG Neurofeedback		"Enhancing via DBS, TMS"
Biocybernetic adaptation	Health care under professional human supervision		
	Health care applications with non-professional supervision		Brain-computer interfaces for gaming, work and learning
	Ambient Intelligence		
		Assisted living	
		Automatic surveillance and safety-critical systems	"Mind reading"
Standardising synthetic biology	Safety standards		Technical standards
		IPR standards	
	Societal standards		

In total, twenty sociotechnical practices have been distinguished in the four cases studies. Four of those practices were found to be stable. Six new sociotechnical practices were identified. Some of these new practices are already emerging; for example, direct-to-consumers genetic testing or brain-computer interfaces (BCI) for gaming. Others represent practices that might emerge in a more distant future (well beyond ten years), like mind reading and the use of Deep Brain Stimulation (DBS) and Transcranial Magnetic Stimulation (TMS) for enhancing the brain. In table 1, the speculative nature of these potential future practices is indicated by using quotation marks. Ten social practices were thought to be gradually changing (of which 6 stable & shifting; 2 shifting; 2 shifting & new).

It can be concluded that the bio-engineering technologies studied are expected to leave certain practices more or less untouched, to lead to shifts in other existing sociotechnical practices and, in the near or more distant future, to create new sociotechnical practices. In this last category we also find some bio-engineering technologies that still have a highly speculative nature. An important question for policy makers is to what extent current regulatory practices are able to adequately respond to those short-term and long-term sociotechnical changes.

7.1.3. Sociotechnical practices challenging regulatory practices

To begin with: the four specific bio-engineering developments studied are by no means regulation poor areas. To illustrate this, in their chapter on whole genome sequencing, Kukk and Hüsing sum up the following (incomplete!) list of international instruments that prohibit discrimination based on genetic data: Council of Europe's European Convention on Bio-medicine, Article 11; EU's Charter of Fundamental Rights, Article 21; UNESCO's Universal Declaration on Human Genome and Human Rights, Article 6; The Convention on Human Rights and Biomedicine (the Oviedo Convention); The US Genetic Information Non-Discrimination Act (GINA); the Working Document on Genetic Data of the EU's Article 29 Working Party, and EU's Data Protection Directive (Directive 95/46/EC). Indeed, as we see in all four cases, new developments and applications in bio-engineering are confronted with an extensive and complex patchwork of established regulatory principles and frames.

The question our study addresses is to what extent shifting and new emerging sociotechnical practices challenge these existing frameworks. Table 2 presents an overview of the twenty sociotechnical practices that were described and analysed in the four case studies and the extent to which these practices challenge current regulatory regimes. Are the current regulatory practices perceived as being adequate or under pressure, or are they thought to be inadequate to deal with various sociotechnical developments or practices?

Five of the sociotechnical practices studied the concurrent regulatory practices were thought to be adequate. Research on neuromodulation techniques and the regulated use of biocybernetic adaptation technology in health care provide two examples. Genetic forensics is also seen as a practice for which an adequate regulatory framework does exist, at least in the near to medium term in which whole genome sequencing will most likely not play a role in forensics.

For another six sociotechnical practices, current regulatory practices were found to be under pressure. Biobanks, personalised medicine, the therapeutic use of particular neuromodulation techniques, and the safety of synthetic biology were seen as sociotechnical practices that were currently regulated in an adequate manner. In the(near) future, however, bio-engineering developments were expected to put the current regulatory system under pressure. For the use of brain-machine interaction (BMI) for gaming, work and e-learning this was already perceived to be the case. With regard to ambient intelligence, for example, the use of biocybernetic adaptation in the field of ambient assisted living, the regulatory framework was also believed to be under pressure, but in this case it might even become inadequate in the near future.

Table 2: Overview of the extent to which sociotechnical practices challenge current regulatory practices.

Case study	Regulatory practice		
	Adequate	***Under pressure***	***Inadequate***
Whole genome sequencing	Forensics		
	Bio-banks		
	Personalised medicine		Direct to consumer genetic testing
Neuromodulation	Research		Gaming EEG-NF
	Therapeutic use		Enhancing EEG-NF "Enhancing DBS, TMS"
Biocybernetic adaptation	Health care under professional human supervision		Health care applications with non-professional supervision
		Assisted living	
		Ambient Intelligence	Automatic surveillance and critical safety systems
		BCI for gaming, work and learning	"Mind reading"
Standardising synthetic biology	Safety standards		Technical standards
	IPR standards		
	Societal standards		

Finally, with respect to nine sociotechnical practices, the current regulatory patchwork is regarded as inadequate. For example, direct-to-consumer testing (DTC) was distinguished as a new sociotechnical practice which has emerged outside the current health system. DTC involves individual health consumers in completely new ways where it concerns practices of DNA screening and research. As a result, the framework that regulates the traditional health care system is not applicable in this new commercial DTC practice. Other examples of such newly emerging sociotechnical practices that develop outside the scope of existing regulatory frameworks are the use of EEG-Neurofeedback (EEG-NF) for gaming or enhancement purposes, and the use of biocybernetic adaptation techniques to automate surveillance or critical safety systems.

7.1.4. Conclusions

Although there is no lack of regulation, the bio-engineering technologies studied bring along a different set of regulatory challenges. Our findings that these technologies have a simultaneous impact on a diversity of (existing and new) sociotechnical practices remind us that the regulatory challenge is often multi-faceted. This leads to the paradoxical situation in which existing regulatory frameworks can be seen as both adequate, under pressure and inadequate, depending on the social practice one looks at. Our study shows that the regulatory challenges raised by the twenty identified sociotechnical practices are manifold. Moreover, outside the confined regulated areas, various unregulated sociotechnical practices – so-called regulatory wastelands – exist. These findings from the four case studies strongly indicate that bio-engineering in the 21st century will pose a clear challenge to (European) politics and policy makers. The following section reflects on ways of understanding and dealing with that governance challenge.

7.2. Governance of problems and practices

In this chapter, the notion of 'governance' includes both traditional and new instruments of policymaking, indicating that the government and the state not only depend on hierarchical forms of coordination but increasingly on other forms of social coordination. The notion of governance has been applied to issues of risk, emphasizing that different types of risk require different strategies for risk governance. This insight into the relationship between different types of problems and different types of governance is the starting point for our discussion of the governance challenges arising from 21st-century bio-engineering. By including the social and institutional context from which problems arise in our discussion, we bring into focus the relationship between the dynamics of sociotechnical practices on the one hand and emerging problems of regulation on the other.

Over the last years, the insight has grown that various types of policy problems require different types of responses from the government and other social actors (Renn, 2005; Hoppe, 2010). This insight also informs our own approach. For a discussion of the types of policy problems that governments are facing, we also need to have a good idea of the sociotechnical practices involved, and to see whether these practices comply or are at odds with current models of regulation. This section explores the relevance of this perspective in order to understand the governance challenges related to bio-engineering in the 21st century, and to find options for dealing with these challenges.

7.2.1. Governance: acknowledging society

Over the last two decades, governance has become a fashionable term. Governance refers to new (participatory) instruments to involve a variety of societal actors in policy-making, like covenants, public-private partnerships, interactive policy making, and public consultations, as opposed to traditional instruments of government, like regulation, economic incentives (e.g. R&D tax incentives), and public information campaigns (Bemelmans-Videc et al., 2003). As one of the main protagonists of the 'hollowing out of the state' has observed, "the traditional instruments of government co-mingle, compete and conflict with the new instruments of governance to variable effect" (Rhodes, 2007, quoted in Lyall et al., 2009, 263). Here, we use the term governance to include both 'traditional' and 'new' instruments of policy making, indicating that the government and the state not only depend on hierarchical forms of coordination, but increasingly also on other forms of social coordination, like the market system and social networks (Hoppe, 2010).

7.2.2. IRGC risk governance framework

The International Risk Governance Council (IRGC), and in particular its *White Paper on Risk Governance* (Renn, 2005), has been very influential in applying the concept of governance to issues of risk relating to science, technology and innovation. Risks in this context are broadly conceived, not only including issues of harm and safety, but also issues of social change resulting from scientific and technological innovation. Based on the different states of knowledge about various (types of) risks, the IRGC risk governance framework distinguishes between 'simple', 'complex', 'uncertain' and 'ambiguous' risk problems (see table 3).

The classical risk approach only suffices for 'simple' risk problems. The other three types of risk problems require other policy decision-making processes and types of organisation. Resolving 'complex' risk issues requires discussion among experts. Klinke and Renn (2002) plea for an "epistemic discourse" within which experts will argue over the factual assessment and the best estimation for characterising the risks under consideration. The management of risks characterised by a high level of 'uncertainty' should be guided by a "reflective discourse", which should include policy makers, stakeholder groups and scientists. Besides dealing with the clarification of knowledge, reflective discourse is about finding a balance between over- and under-protection.

Table 3: Risk characteristics and their implications for risk management (Source: Renn, 2005: 16)

Knowledge characterisation	Risk management strategy	Stakeholder participation
'Simple' risk problem	Routine-based	Instrumental discourse
'Complexity-induced risk problems	Risk-informed & Robustness-focused	Epistemological discourse
Uncertainty-induced risk problems	Precaution-based & Resilience-focused	Reflective discourse
Ambiguity-induced risk problems	Discourse-based	Participative discourse

Finally, 'ambiguous' risk problems point to a situation in which risk information is not only interpreted differently by various stakeholders in society, but also involves intense conflict over values and priorities of what should be protected. According to the IRGC, this type of risk problem, which is characterised by interpretative and normative ambiguity, demands a participative discourse. Participative discourses are meant to search for solutions that are compatible with the interests and values of the people affected and to resolve conflicts among them.

7.2.3. Mind the sociotechnical dynamics

The IRGC risk governance framework thus distinguishes between four types of problem situations and related risk management strategies. The conceptual clarity of the framework can help policy makers in getting an overview of the diverse set of governance challenges put forward by certain technological developments. As such, the framework has really stimulated the debate on risk governance, also implying that policy makers should involve a wider set of societal actors for dealing with types of risk problems that are characterised by uncertainty and ambiguity. We will, therefore, take this framework as a proper starting point for our discussion on governance challenges arising from 21st century bio-engineering.

However, we would also like to bring the discussion one step further. Besides taking the type of problem situation as a point of departure for thinking about risk governance, we should include into our considerations the social and institutional context from which these problems arise. In this way, we bring into focus the relation between the dynamics of sociotechnical practices on the one hand, and emerging challenges in the field of regulation on the other. In a recently published discussion of 'guidelines for the appropriate risk governance of synthetic biology', the IRGC has also pointed to the intricate and complex relationship between the dynamics of innovation and policies of regulation (IRGC, 2010). In this context, the IRGC introduces *appropriate risk governance* as a concept that seeks to balance the aims and needs of both innovation and regulation. In the following we are seeking a similar approach and want to explore its value for coming to grips with the European governance challenges in 21st century bio-engineering.

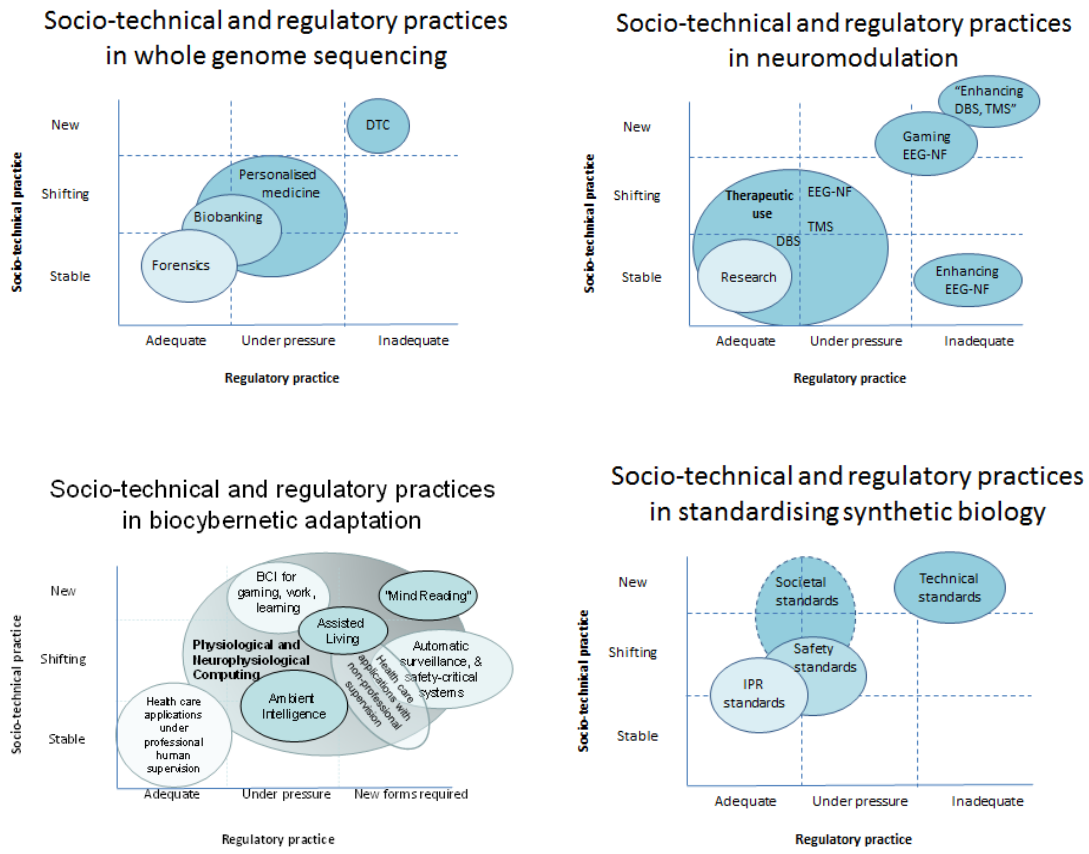
7.3. Governance challenges

Our analysis translates into a fundamental governance question: How can we align the dynamics of sociotechnical and regulatory practices in 21st-century bio-engineering? We have used our two-dimensional conceptual framework to map the alignments and misalignments between sociotechnical and regulatory practices in the four cases studied. In a detailed analysis of the findings from the case studies we distinguish between developments in the *regulatory zone*, where a regulatory framework is in place, from developments in the *regulatory wasteland*, where regulation is lacking or inadequate. We further distinguish between three different options for governance in response to the uncertainties that policymakers will face when dealing with future bio-engineering developments.

In section 7.1 we presented an overview of existing (stable and shifting) sociotechnical practices and new emerging ones in bio-engineering. Moreover, we illustrated the extent to which these sociotechnical practices challenge current regulatory practices (see table 2). In this section we want to explore the relationship between the dynamics of sociotechnical and regulatory practices in order to gain more insight into the governance challenges arising from these bio-engineering developments. Our point of departure is the notion that the basic governance challenge is to get these two dynamics in tune with each other. To put it stronger, within our technological culture, "the essence of democracy is found in the interaction between political and techno-economic practices and ideas" (Van Est, 1999: 283). In the context of our analysis, this basic assumption translates into the central governance question: how to align the dynamics of sociotechnical and regulatory practices in 21th century bio-engineering?

The alignment or misalignment between the sociotechnical and regulatory practices has been mapped in the four case studies by using the conceptual scheme that was described at the beginning of section 7.1. We summarised the findings from the case studies in the tables 1 and 2 above. In figure 1 below, these findings are combined in four diagrams from the case study chapters, representing the two-dimensional – sociotechnical and regulatory – dynamics in the fields of whole genome sequencing, neuromodulation, biocybernetic adaptation and synthetic biology standards. Here we want to reflect on the meaning of these four analytic diagrams.

Figure 1: Sociotechnical and regulatory practices in four fields of 21st century bio-engineering



In general, as one moves from the bottom left to the top right of the diagrams, the governance challenge increases. In this respect, we can distinguish between two situations: *regulatory zone* versus *regulatory wasteland*. In the *regulatory zone* a regulatory framework exists. Moreover, it is expected that the existing regulatory framework is robust enough to deal with changes in or new emerging sociotechnical practices. In other words, it is expected that the regulatory practice is future-proof, either without changes (i.e. adequate regulatory practice) or with some adaptations (i.e. regulatory practice under pressure). The fact that a regulatory framework is in place does not, of course, automatically mean that it is efficient and effective. Still, in the regulatory zone, sociotechnical practices are guided by existing regulatory models, rules and values.

In contrast, in the *regulatory wasteland* the guidance from such existing regulatory models, rules and values is no longer self-evident. Here, regulations are simply lacking or current regulations are seen as inadequate to politically guide existing, shifting or newly emerging sociotechnical practices. The governance challenge is to develop new ways of dealing with this mismatch between the dynamics of sociotechnical and regulatory practices. Various policy options are at hand.

One might take a laissez-faire approach or, on the contrary, forbid a certain sociotechnical practice. Another policy option might be to broaden an already existing regulatory framework – i.e. widening the regulatory zone – so that it comes to include the current regulatory wasteland. Finally, one might opt for developing whole new forms of regulation.

We would like to note that for any particular combination of sociotechnical and regulatory practice, it is a matter of societal and political debate to assess what the governance challenge is. As the case studies show, in such debates, various stakeholders – scientists, industry, regulatory bodies, patient groups and so on– may have different views on the governance challenges that may arise from particular bio-engineering developments. In other words, how to align the dynamics of sociotechnical and regulatory practices will always be a contested question. It is, in essence, a political task to decide what the regulatory challenge related to a certain sociotechnical practice is thought or expected to be, and how to deal with it (by regulation or by other means). We will keep this in mind when reflecting on the four case studies. For each case, we will first characterise the dynamics of the sociotechnical practices and the uncertainties involved in assessing this. Secondly, we will describe the regulatory challenges put forward by the sociotechnical dynamics. Finally, we will set forth some options for governance to align the sociotechnical and regulatory practice. First of all we will focus on synthetic biology, because the authors of this case study have structured their considerations about options for governance in a way that is also useful in our discussion of the other three cases.

7.3.1. Governance challenges in synthetic biology

Schmidt and Torgersen (Chapter 6) hold that it is currently impossible to judge what the future of synthetic biology will look like. Synthetic biology aims at introducing engineering principles and (computer) engineering mindsets and practices into biology. Central to this effort to radically innovate the practice of bio-engineering is the need to develop technical standards. However, Schmidt and Torgersen argue that, since many scientific and normative uncertainties are in play, it cannot be established yet whether synthetic biology will really turn out to be a game changer. On the technical side it is not clear whether engineering principles can be fully emulated into biology.

Since the future of synthetic biology is so unpredictable, Schmidt and Torgersen discuss for any issue of standardisation three different options for policy, which may be seen as different scenarios (see table 4). The basic uncertain factor is whether synthetic biology will be able to turn biology into a real engineering discipline or not. Three scenarios are distinguished: 1. Synthetic biology will not really radicalise biotechnology (SB = biotechnology); 2. Synthetic biology might possibly revolutionise biotechnology (SB = biotechnology?) or, 3. Synthetic biology will be a real game changer (SB ≠ biotechnology). The authors do not have any preference for one of these scenarios which, as they have shown, represent diverse and conflicting visions of actors in the field. Indeed, as we have argued in section 7.3 above, such an assessment is basically a political decision. And the political choice that is made will, of course, be partially instrumental in shaping the future. Schmidt and Torgersen clarify the policy issues and options that correspond to the above three 'political' perspectives on the future of synthetic biology.

As becomes clear from these different scenarios, the governance challenge goes hand in hand with the agenda for stimulating synthetic biology. If synthetic biology is seen as substantially equal to the current practice of bio-engineering (scenario 1), no real extra public effort will be put into stimulating synthetic biology. Correspondingly, it is expected that the current regulatory framework is appropriate and there is little need to put extra regulatory effort into dealing with issues of standardisation.

Table 4: Central political questions to be answered for characterising the governance challenges in synthetic biology and related policy options.

Governance challenges in synthetic biology (SB)	Regulatory zone		Regulatory wasteland
	Low	Moderate	High
Political assessment	SB = biotechnology	SB = biotechnology?	SB ≠ biotechnology
	SB is substantially equivalent to the current practice of bio-engineering	SB might radically transform the current practice of bio-engineering	SB will radically transform the current practice of bio-engineering
Technical standards	**Wait and see**	**Keep a foot in the door**	**Massive public efforts**
	Carefully watch developments	Actively contribute to innovation	Large investments to catch up with US
Safety and security	**Business as usual**	**Assess whether SB raises new questions**	**Radically new approaches**
	Regulations do not have to be amended	Monitor and assess whether current regulations suffice	Use potential of SB to develop novel safety measures
Intellectual property rights (IPR)	**Business as usual**	**A helping hand**	**Actively promoting openness**
	Continue current patent practice	Investigate which form of IP management would render best results	Develop methods to ensure that SB building blocks are freely available by default
Societal standards	**Business as usual**	**Anticipate societal concerns**	**Mandatory assessments**
	No political intervention in public sphere	Stimulate public debate by various means: research, public understanding and participation	Set up institutions or expert committees to assess social and ecological issues of future SB applications

Scenario 3 suggests a totally different story about the governance challenge. Here, high expectations of synthetic biology's potential to radically change the practice of bio-engineering – even seeing synthetic biology as the basis of a new industrial revolution – leads to massive public efforts to stimulate this field. Stimulating this particular scenario implies that, at the same time, policy makers anticipate that the current stable regulatory regime may come under more severe pressure. This means that policy makers have to anticipate the possibility that in the (near) future, gaps with regard to regulating safety and security may appear, IPR management may change and societal standards for synthetic biology may become subject of more heated public debate.

Basically, the judgement that synthetic biology will not (at least in the near future) change the practice of bio-engineering leads to a wait-and-see strategy. Taking seriously the possibility that synthetic biology might greatly challenge the sociotechnical and regulatory practice of biotechnology will lead to a different type of political strategy, which the authors compare with the European precaution-based approach or the American strategy of prudent vigilance. This strategy is characterised by an open, proactive and critical attitude: developments in synthetic biology are actively being monitored, possible scenarios, issues and policy options are actively being studied, and political and public debate is stimulated. Politically characterising synthetic biology as a real game-changer even suggests a more active involvement: a concerted effort to stimulate as well as regulate the anticipated development of synthetic biology becomes a major governance challenge. That is, the governance challenge is not only about managing risks, but also about managing promising opportunities. If indeed governments would choose for large-scale investments in synthetic biology, based on high expectations of the revolutionary character of this new emerging science, it might also become necessary to seriously invest in institutionalised forms of assessing and debating its ethical, legal and social aspects.

7.3.2. Governance challenges in neuromodulation

It is expected that the number of clinical applications for EEG neurofeedback, Deep Brain Stimulation (DBS) and Transcranial Magnetic Stimulation (TMS) will increase. Research on the use of these three neuromodulation techniques for new medical indications is flourishing. In addition, a widening of clinical applications is already happening for DBS. At the same time, EEG neurofeedback is being applied in private clinics for enhancing purposes. In the future, DBS and TMS might also be used to enhance the brain and consequently behaviour. Such a future is conceivable, since clinical experience has shown that DBS can have mood-enhancing effects, and TMS is an important new research field for enhancing cognitive performance. At this moment, a new sociotechnical practice is also on the rise: the use of EEG neurofeedback for gaming purposes.

Challenges within the regulatory zone

The medical use of neuromodulation techniques are regulated by the Medical Device Directive (MDD, 93/42/EC) and the Active Implantable Medical Devices Directive (AIMDD, 90/385/EC). These regulations are aimed at taking care of the safety and (medical-technical) performance of medical devices to protect patients and enable market development. Although Van Keulen and Schuijff (Chapter 4) have found several regulatory issues that require the attention of EU policy makers, they conclude that there is no need for new rules to regulate the medical use of neuromodulation devices.

Since DBS is an implantable brain device, its medical use is regulated by the AIMDD. In 2005, the European Group on Ethics (EGE, 2005) advised the European Commission to launch legislative initiatives with respect to implantable devices for medical purposes, like DBS. The ECE (2005, 35) argued that "implantable devices for medical purposes should be regulated in the same way as drugs when the medical goal is the same". Based on their research – focused only on the intended purpose stated by the manufacturers –

Van Keulen and Schuijff argue that in the case of the medical use of DBS, the AIMDD remains an adequate regulatory framework. At the same time, they urge that more research is needed on the exact regulatory routes DBS devices have taken before they enter the European market. These data are currently difficult to retrieve since the available database – Eudamed – is not publicly accessible.

More challenging regulatory issues are raised, according to the authors, by developments in the domain of non-invasive neurodevices. They find that with regard to EEG neurofeedback, it is not clear how the current regulatory scheme is to be applied. They advise policy makers to clarify whether EEG neurofeedback should be seen (and thus regulated) as a non-medical (monitoring) device, or as a medical (therapeutic) device. Moreover, sometimes a tension exists between the regulatory practice and the way non-invasive neuromodulation techniques are applied in practice. The authors give the example of an rTMS device of which the intended purpose refers to diagnostic and research purpose, but it is also used off-label in private clinics for treating depression. This tension between the regulatory framework and the actual use in practice undermines the original policy aims of the existing framework. Van Keulen en Schuijff plea for more public transparency about the way in which the medical use of neuromodulation devices is regulated. Therefore, they recommend that the European database Eudamed, which is mandatory since May 2011 and includes data on devices and certificates, registration requirements, vigilance and clinical investigations, will be made publicly accessible for patient organisations, researchers, journalists and individual citizens.

Challenges within the regulatory wasteland

EEG neurofeedback is also used for non-medical applications: for example, for gaming and enhancement purposes. As indicated above, in the future, TMS and DBS might also be used for non-medical purposes. If a manufacturer is bringing this technology on the market for entertainment or enhancement purposes alone, a CE marking for medical devices is not mandatory. Since the devices used for non-medical purposes are, in most cases, similar to the ones used for medical purposes, Van Keulen and Schuijff doubt whether, from a consumer safety perspective, this is a desirable situation. The authors argue that the basic political question that needs to be addressed is whether devices used for non-medical purposes should meet the same requirements as neurodevices for medical use.

In this case, the regulatory challenge refers to a conceivable, but also speculative and uncertain future. Accordingly, we might distinguish, analogous to the synthetic biology case, between three scenarios. In the first scenario (neurodevices for non-medical use = neurodevices for medical use), it is decided that from a consumer safety perspective, neurodevices for non-medical and medical use should meet the same requirements. This would imply that the existing framework for regulating the medical use of neurodevices would be broadened to include their non-medical use. In this way, the current lack of regulation is dealt with. In the second scenario (neurodevices for non-medical use = neurodevices for medical use?), the question is raised whether non-medical use of neurodevices should be dealt with in a similar way as the medical use. In this case, more research on the safety risks of non-medical use is needed.

In the third scenario (neurodevices for non-medical use ≠ neurodevices for medical use), the emerging sociotechnical practice of non-medical use of neurodevices is not seen as a relevant development yet. Carefully watching the developments would then be the proper policy strategy to follow. Van Keulen and Schuijff advise policy makers and politicians to take scenario 2 seriously, and they plea for more research on the risks of EEG neurofeedback for enhancement and gaming.

7.3.3. Governance challenges in whole genome sequencing

Today, whole genome sequencing is increasingly used in leading edge medical research, leading to significant changes in biomedical research practices. Currently, extensive data-sharing takes place across borders and in public-private co-operations. Moreover, (whole) genome data will increasingly be linked with comprehensive health and lifestyle information in biobanks, thus enabling the collection, analysis and sharing of an unprecedented amount of highly personal information in research settings. Whole genome sequencing still plays a minor role in health care, mainly creating new possibilities for searching for new mutations in a clinical genetics setting. In the coming decade, however, technologies are likely to be marketed that will be able to sequence a whole human genome for several thousand or several hundred euro, and thus they will come at the price of established advanced medical diagnostic procedures. This will considerably broaden the scope of applications for whole genome sequencing inside and outside the health care sector. Kukk and Hüsing (Chapter 3) foresee the possibility of genome-wide diagnosis and screening of both newborns and prenatally, and an increasing use of predictive, yet probabilistic, genetic risk information in general health care (personalised medicine). This may change the relationship between doctors and patients from being oriented towards "complaints" to being focused on "monitoring health", implying a proactive approach towards health and sickness and also an increasing individual responsibility for health. Outside the medical sector, genome wide screenings for curiosity, probing ancestry and obtaining health information are already offered direct-to-consumers (DTC) by private companies over the internet. In forensics, whole genome sequencing is expected to play a role only in the long term (> 10 years) in a small range of selected applications.

Challenges within the regulatory zone

The significant shift that is taking place in basic and biomedical research undermines the traditional mechanisms that guarantee data protection and privacy, like confinement to academic research without commercial interests, and research only on anonymised data and samples. Kukk and Hüsing conclude that the traditional governance approach needs to be adjusted both in regard to the level of confidentially and data protection that can be promised to participants, and the process of obtaining informed consent. The political statement they make is: whole genome sequencing ≠ traditional DNA research. The governance challenge then becomes how to revise the current regulatory practice.

An expert debate about this question already exists, which Kukk and Hüsing see as an important condition and incentive for future policy-making. They observe that the current regulatory system is primarily based on liberal values, putting the privacy and autonomy of the individual first. However, communitarian values, which emphasise the interests of the community rather than personal autonomy and focus on solidarity, reciprocity, and citizenship, are increasingly advocated with the purpose of amending regulatory practice.

These values are being referred to in order to justify the introduction of new regulatory models, like open consent and open research, as already implemented in the Personal Genome Project. Open research implies veracity on the part of the researchers, and also (inter)active modes of participation and openness from both researchers and participants. The current regulatory landscape in Europe with respect to biobanking and research on humans is, as Kukk and Hüsing point out, diverse, patchy and internationally not well harmonised. As a result, expert discussions have already been initiated which may lead to EU regulation aiming at uniform standards in the EU. The authors would like to see that the specific challenge of using whole genome data is adequately and explicitly addressed in this context.

In the medium term, health care practices may undergo a major shift as a result of whole genome sequencing and its related vision of personalised medicine. In particular, the established practice of genetic counselling with its current form of narrow informed consent no longer suffices and is likely to become outdated. The challenge is to define a broader or even generic form of consent, which nevertheless will protect the patient's autonomy in a sufficient manner. Whole genome sequencing will also significantly raise the likelihood of unsought-for findings. Therefore, the issue of how to deal with these findings is an urgent one. Provisions are required for the conditions for the storage of and access to data, as well as conditions for the analysis and disclosure of its results to patients. To prepare for this anticipated shift, the authors plea for setting up expert discourses and public consultations about the risks and benefits of genome-wide screening. Special attention should be given to the issue of screening neonates and children.

Although whole genome sequencing in principle bears the potential to radically alter DNA forensics in the long term, Kukk and Hüsing conclude that the current practice is unlikely to undergo major shifts in the (near) future, because of sunk investments in established working methods and databases. However, the regulatory landscape governing forensic DNA profiling and databasing is also "patchy, diverse and non-harmonised" and requires improvements with respect to harmonisation, standardisation and quality assurance, even if whole genome sequencing does not play a role in the medium to long term.

Challenges within the regulatory wasteland

The offer of private companies to perform DTC genome-wide genetic profiling and whole genome sequencing presents a new sociotechnical practice, as it has emerged outside the regulated health system. In this new situation, the existing regulatory regimes of confidentially in the doctor-patient relationship no longer uphold. The existing regulatory framework, therefore, does not apply to this new commercial practice, which bypasses the institutionalised and established healthcare system. As such, DTC genetic profiling represents a regulatory wasteland.

Kukk and Hüsing sketch various options to deal with this new sociotechnical practice. Some call for a complete ban of this commercial practice, thus restricting genetic testing to professional practice within the regulated health system. This option would dissolve the regulatory wasteland. Another option would be to extend the current regulatory system to include the commercial practice of DTC genetic profiling. However, in their discussion, Kukk and Hüsing also refer to a recently published report of the Nuffield Council on Bioethics, arguing that at this moment it is not sufficiently known how many people actually use genetic profiling services and whether this is leading to any harm. This seems to suggest that the governance challenges in DTC genetic profiling may be less pressing and urgent than those in research and health care. This suggests that, analogous to scenario 2 in our discussion of synthetic biology, the current situation asks for monitoring this new practice and assessing the risks involved.

7.3.4. Governance challenges in biocybernetic adaptation

Biocybernetically adaptive systems depend on physiological and (neuro)physiological computing. Originally, these technologies have been primarily used in research and in medical health care, and cure settings under professional supervision. Nowadays the number of potential applications outside the medical domain is growing. To indicate the field's increasing importance, Böhle, Coenen, Dekker and Rader (Chapter 5) refer to the claim of Pantic et al. that (neuro)physiological computing is "likely to become the single most widespread research topic of artificial intelligence (AI)" (Pantic et al., 2008, 184). (Neuro)physiological computing has become central to achieving the new ambient intelligence (AmI) vision, including the concept of "ambient assisted living" for the elderly and disabled. However, much research is still needed to realise such an AmI vision.

An application that is already more relevant today is the use of brain-machine interaction (BCI) in gaming, work and for learning. (Neuro)physiological computing may also be used in automatic surveillance and safety-critical systems. Experts expect that early applications of (neuro)physiological computing will first appear in health care and gaming. They disagree about whether biocybernetic adaptation in education and safety-critical systems will be feasible and reliable enough. Finally, "mind reading" is not in reach, and it may never be. Still, the possibility of very crudely representing the minds of people already presents a cause for concern.

Challenges within the regulatory zone

Important principles underlying the EU Data Protection Directive (95/46/EC) are: collection limitation, data quality, purpose specification, use limitation, security safeguards, and the accountability principle. The authors indicate that this paradigm no longer matches the current situation in the field of IT. The Directive was designed when data protection was restricted to personal data and when few identified processors and data controllers had taken measures against unauthorised access. Nowadays, vast amounts of data are generated and stored in computer systems, which are often operated by many parties from different countries. This makes it harder and harder to comply with the above list of fair information principles. To illustrate this point, Böhle et al. refer to statements of some experts who believe that "Projects like Facebook, Ambient Assisted Living and Smart Grids simply ignore existing regulations on privacy and data protection". The authors argue that a widespread introduction of (neuro)physiological computing applications would seriously worsen the already problematic nature of the current regulatory system.

From a political perspective, the basic question is whether the privacy issues related to current (e.g. social media) and near-term IT developments (e.g. (neuro)physiological computing applications, like ambient assisted living and BCI for gaming) can be seen as similar to the privacy issues raised by the IT applications from the 1990s, which the EU Data Protection Directive from 1995 was intended to regulate. Again, we can distinguish three answers to this question, implying three different scenarios in terms of political strategies. The assessment that "IT now & near-term = traditional IT" suggests a wait-and-see strategy. Assuming that privacy is still being viewed as an important political and public value, the second scenario "IT now & near-term = traditional IT?" would require active research and debate in order to assess whether the current regulatory system is still functioning. Under the same condition, the third scenario "IT now & near-term ≠ traditional IT" would legitimate dedicated steps towards developing a new regulatory framework. However, if the political assessment would be that privacy is indeed to be seen as an issue of the past, then the wait-and-see strategy would be a most probable scenario.

Böhle et al. hold the view that privacy remains to be an important value and they believe that the current privacy protection framework is already clearly under pressure, whereby applications of (neuro)physiological computing will increase this pressure. They think it is wise to start working towards a fair information framework, which will guarantee baseline protection to ensure fair treatment (scenario 2). Privacy by design would be an important aspect of the new regulatory approach. The authors think a broad international expert and public debate is necessary to reach that aim. Since, from a political perspective, public attitudes are crucial in thinking about the governance challenge in the field of biocybernetic adaptation, cultural differences in attitudes towards privacy should be also more widely discussed. As an input for such debates, a survey might be conducted to study whether and to what extent privacy concerns are growing or disappearing. In line with the results of the ETICA project, the authors propose to set up an overseeing body (an observatory) to monitor developments and provide early warning for ethical, legal and social issues. The authors also plea for user empowerment by stimulating public awareness and education, which should enable users to exercise their right to self-determination. In the case of vulnerable groups, like elderly patients, support by 'delegates', e.g. their children, should be made possible.

Challenges within the regulatory wasteland

The use of automatic monitoring and surveillance systems and safety-critical systems not only present a governance challenge with regard to privacy. The discussion is also about safety (how reliable these new systems are) and about personal autonomy. Böhle et al. argue that there is a need to regulate to what extent such systems should be allowed to function automatically, without human supervision, and to what extent users should be able to overrule the system. As a first step towards regulation, the authors plea for an international academic and societal discourse on these matters.

7.4. Conclusions

In our conclusion we discuss the assessments made by the case studies concerning the major governance challenges that arise from 21st-century bio-engineering and the options for governance in relation to these challenges. We identified three types of uncertainties which result in different and sometimes conflicting visions of the future developments in bio-engineering and which make political judgement of these developments a fundamental challenge. In the *Monitoring Report* we argued that a broadening of activities in the field of bioethics is required to face this challenge. Our analysis in this report makes clear that this European governance challenge also implies the need to move beyond *bioethics* (stimulating scientific reflection and public debate on technological change and its societal implications) to *biopolitics*, a continuous political effort to align sociotechnical and regulatory practices in 21st-century bio-engineering.

This study shows that bio-engineering in the 21st century will influence society in many ways. It will strengthen established sociotechnical practices, gradually or radically shift them, and enable the emergence of new sociotechnical practices. Accordingly, this will challenge current regulatory rules and models in diverse ways. To adapt to the changing sociotechnical practices, regulatory frameworks will need to be revised. Moreover, in order to regulate new, unregulated sociotechnical practices, existing regulatory frameworks need to be extended or new forms of regulation need to be developed.

In the earlier published Monitoring Report, of which the major findings were summarised in Chapter 2, we have described the scale and broadness of the challenge. In this final report of the Making Perfect Life project, we have focused on four case studies in order to give an in-depth picture of selected aspects of the overall challenge. As became clear from the case studies, among actors in the field we found different and sometimes conflicting understandings of the governance challenges that are arising from 21st century bio-engineering. These alternative understandings also involve different views with regard to both the possibility, and desirability of particular bio-engineering developments and futures envisioned in the field. In this sense, as we already emphasised in section 7.3., the question of how to understand these governance challenges and their policy implications is in essence a political issue, and clearly also a controversial one. We may distinguish three types of uncertainties that make such a political judgement difficult and often controversial: techno-scientific uncertainty, uncertainty about social and political values (cf. Grin et al., 1997; Renn, 2005), and regulatory uncertainty (Hood et al., 2001).

Political judgements are made under *uncertainty about the technological dynamics*, i.e. the speed of technological development, its direction, and its nature. It is important to estimate in which ways science and technology will impact the dynamics of sociotechnical practices. This, of course, also depends on the amount of political support given to the related technological development and the way it is guided. Technology can both have a stabilising and transformative effect. For example, in the case of synthetic biology, Schmidt and Torgersen argue that the future of this field and the way it will transform biotechnology cannot be foreseen at this moment. With respect to direct to consumer(DTC) genetic profiling, Kukk and Hüsing note that it is not sufficiently known how many people actually use genetic profiling services.

Technological developments enable existing sociotechnical practices to change or new ones to arise, and these sociotechnical dynamics also influence, as the cases illustrate, the *landscape of social and political values* that play a role in public and political debate. Developments in the field of whole genome sequencing lead to debate in which the liberal values underlying the current regulatory framework are questioned, raising the political question whether communitarian values shouldn't play a bigger role in the future. New technological developments in the field of human-computer interaction may entail shifts in public and political understanding of the values of privacy and autonomy. The (software) engineering spirit that drives the emergence of synthetic biology puts into question the value of patenting as a form of intellectual property, whereby communities dedicated to this new science promote an open source approach.

Finally, sociotechnical dynamics also leads to uncertainty about the question whether existing *regulatory frameworks* are still adequate, whether they need to be extended to new practices, or whether new sociotechnical practices should be met by new regulatory rules and models. As we have indicated above, in this context the challenge that policy-makers have to face boils down to three political options, based on different understandings of the bioengineering developments discussed in the four case studies. Tables 5 and 6 provide an overview of the central political questions and options that these different understandings imply for policy making, in and outside the regulatory zone, respectively.

As we have argued in section 7.3, the fundamental governance challenge is to align the dynamics of sociotechnical and regulatory practices. Consequently, the recurrent political question is whether the sociotechnical practice enabled by new bio-engineering developments can be considered as substantially equivalent to the sociotechnical practices, which the existing regulatory system intends to regulate. If this is the case, it can be assumed that bio-engineering developments can be regulated by the existing regulatory framework. If this is obviously not the case, and the societal impact of the bio-engineering development is large, the existing regulatory framework has to be revised (within the regulatory zone) or new forms of regulation have to be developed

Table 5: Central political questions to be answered for characterizing the governance challenges in four bio-engineering developments *within the regulatory zone*. The position of the authors of the case studies is put in **bold.**

Bio-engineering development	Political options		
	=	=?	≠
	Similar	*Maybe (not) similar*	*Not similar*
Whole genome sequencing (WGS)	WGS in health care = classical genetic research & testing	WGS in health care = classical genetic research & testing?	**WGS in health care ≠ classical genetic research & testing**
Neuromodulation (NM)	EEG neurofeedback = therapeutic device	**EEG neurofeedback = therapeutic device?**	EEG neurofeedback ≠ therapeutic device
Biocybernetic adaptation (BA)	IT now & near term = traditional IT	**IT now & near term = traditional IT?**	**IT now & near term ≠ traditional IT**
Standardising synthetic biology (SB)	Synthetic biology = biotechnology	Synthetic biology = biotechnology?	Synthetic biology ≠ biotechnology
Appropriate governance strategy	• Wait-and-see	• Monitor sociotechnical developments • Assess whether current regulations suffice • Create awareness via expert and public debate	• Map ethical, legal, social issues • Map and debate underlying ethical and social values • If societal impact is expected to be large on short to mid-term *start revision of the existing regulatory framework*

(within the regulatory wasteland). If there are good reasons to suspect that the shifting or new sociotechnical practices cannot be considered similar to established practices, an appropriate governance strategy would be to monitor these developments, assess whether current regulations are still adequate, and create awareness via expert and public debate.

Table 6: Central political questions to be answered for characterizing the governance challenges in four bio-engineering developments *within the regulatory wasteland*. The position of the authors of the case studies is put in **bold.**

Bio-engineering development	Political options		
	=	=?	≠
	Similar	*Maybe (not) similar*	*Not similar*
Whole genome sequencing (WGS)	DTC genetic testing = genetic testing in professional health care settings	DTC genetic testing = genetic testing in professional health care settings?	**DTC genetic testing ≠ genetic testing in professional health care settings**
Neuromodulation (NM)	Neuro-devices for non-medical use = neuro-device for medical use	**Neuro-devices for non-medical use = neuro-device for medical use?**	Neuro-devices for non-medical use ≠ neuro-device for medical use
Biocybernetic adaptation (BA)	Automatic surveillance systems = traditional IT	**Automatic surveillance systems = traditional IT?**	Automatic surveillance systems ≠ traditional IT
Standardising synthetic biology (SB)	Synthetic biology = biotechnology	Synthetic biology = biotechnology?	Synthetic biology ≠ biotechnology
Appropriate governance strategy	• Extend current regulatory framework	• Monitor sociotechnical developments • Assess whether current regulations suffice • Create awareness via expert and public debate	• Map ethical, legal, social issues • Map and debate underlying ethical and social values • If societal impact is expected to be large on short to mid-term *start developing new regulatory forms*

7.4.1. Policy advice on appropriate governance strategies

The author's assessment of the governance challenge put forward by the four specific bio-engineering developments and the corresponding *appropriate governance strategy* is put in bold in tables 5 and 6. According to Kukk and Hüsing, developments in the field of whole genome sequencing force policy makers to start revising the existing regulatory framework for biomedical research and diagnostic testing and screening within health care settings. In a similar way, Böhle, Coenen, Decker and Rader believe that current and near-term (like (neuro)physiological computing) IT developments ask for a revision of the current data protection frameworks. In those two areas, the demands resulting from the principles that the current regulatory frameworks are built upon can no longer be fulfilled in practice. With regard to the governance challenge put forward by neuromodulation, Van Keulen and Schuijff stress the need to start a process that clarifies, from a regulatory perspective, whether EEG neurofeedback should be regarded as a therapeutic device and whether neurodevices for non-medical purposes should be regulated in a similar way as neurodevices for medical use. As indicated above, such a

process includes monitoring sociotechnical developments and creating awareness via expert and public debate. Kukk and Hüsing plea for a similar governance strategy with respect to DTC genome-wide profiling. Finally, Schmidt and Torgersen do not put forward a preferred governance strategy with regards to synthetic biology. Their argument is that the future of synthetic biology is just too uncertain to promote a particular strategy. We would argue, however, as authors of this conclusion, that the governance strategy already taken by the European Commission is in line with the assessment that synthetic biology might possibly change the field of biotechnology in a radical way. We would like to advise the European Commission to affirm and explicate that stance and act accordingly.

7.4.2. Closing remarks

We started our discussion in chapter 2 with the Making Perfect Life Monitoring Report, which concluded that the broad challenge of safeguarding human dignity prompts the European Commission to assume full responsibility for the *anticipatory governance* of the new wave of bio-engineering developments, in a way that truly reflects its transformative character (section 2.3.). The aim of our current report is to provide members of the European Parliament with a more profound understanding of the governance challenges put forward by bio-engineering in the 21st century. Such a deeper insight is needed to start a political debate about how anticipatory governance of the new technology wave actually should look like.

It has become widely acknowledged that separating the promotion of technology from the regulation of technology, which is the core of the 'modernist' practice of managing technology, is not sufficient in dealing with the governance challenges raised by science and technology (cf. Schot 2003). In his book *Risk Society*, Beck maintains that such a modernist regulatory practice is disempowering the political system, because "the political institutions become the administrators of a development they neither have planned for nor are able to structure, but nevertheless somehow justify" (Beck, 1992: 187). His analysis of science and technology as a major source of risk in modern societies implies that there is a more firm role to play for politics and democracy in shaping innovation.

Despite all the critique, the modernist practice of managing technology is still dominant. In the life sciences we have seen, over the last decade, the emergence of *bioethics* as a field which deals with the ethical, legal and social implications of research and technological development. As a result, the modernist practice was complemented by activities in ethical commissions and ELSI-research programs. In the Monitoring Report we have argued for a broadening of activities in the field of bioethics because in the 21st century the biodebate no longer needs not engage itself solely with the life sciences, but with NBIC convergence.

In this context, we also pointed out that the attention of the European Commission for ethical, legal and social issues differs across the different bio-engineering fields. The Commission pays due attention to ELSI-research in biotechnology and nanotechnology, but relatively little institutionalised attention is paid to ELSI-research in the field of information technologies and their convergence with cognitive sciences.

However, we should not just broaden the field of bioethics, we also need to move beyond bioethics to *biopolitics*. Our study shows that the governance of bio-engineering in the 21st century is not only a matter of reflecting on scientific developments and its societal implications. It is also about regulating (gradually and/or rapidly) shifting and newly emerging sociotechnical practices in society. We found that current bio-engineering developments are creating many tensions between sociotechnical and regulatory practices. Thus, we have emphasised in this conclusion as a basic governance – and political – question: how to align the dynamics of sociotechnical and regulatory practices in 21th century bio-engineering?

The modernist practice of managing technology, complemented with bioethics, is not sufficient to deal with that political question. In order to safeguard human dignity in 21st century bio-engineering we need more engaging and democratic forms of biopolitics. Of the three types of uncertainties we have distinguished in the foregoing (section 7.4), bioethics mainly deals with techno-scientific uncertainties and uncertainties relating to values. Far less attention is given to regulatory uncertainties and to the question of how policy makers and politicians should deal with them. Accordingly, bioethics fails to provide policy makers and politicians with the proper information to address the above basic governance question.

Our study shows that politicising bio-engineering developments requires more attention for regulatory uncertainties raised by bio-engineering developments. However, this also implies that we need to give more close attention to the experiences of institutions which deal with regulation and its uncertainties (e.g. the EMA, EDPS, EFSA). That is, we need to make politically transparent the complex workings and failings of relevant regulatory systems, for now and the coming years. Such an effort could increase institutional reflexivity and strengthen the preparedness of (European) institutions to deal with the governance challenges in bio-engineering in the 21st century.

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ANNEX

Invited experts for the case study workshops

Privacy, Data Protection and Policy Implications in Whole Genome Sequencing		
1.	Reiner Babiel	Roche
2.	Tomasz Dylag	European Commission
3.	Ingrid Geesink	Rathenau Instituut
4.	Jane Kaye	University of Oxford
5.	Jeantine E. Lunshof	Maastricht University
6.	Emilio Mordini	Centre for Science, Society and Citizenship (CSSC)
7.	Hans-Hilger Ropers	Max Planck Institute for Molecular Genetics
8.	Michael Friedewald	Fraunhofer ISI

Engineering of the Brain: Neuromodulation and Regulation (for experts who have been interviewed see annex chapter 4)		
1.	Douglas Robinson	Qnode
2.	Auke Poutsma	Medtronic
3.	Dennis Schutter	Utrecht University
4.	Robert Geertsma	RIVM
5.	Nicole Denjoy	COCIR
6.	Ellen Moors	Utrecht University
7.	Thomas van Zoest	Utrecht University

Biocybernetic Adaptation and HCI: Applications and Concerns		
1.	Dr. Michael Friedewald	Fraunhofer-Institut für System- und Innovationsforschung (ISI)
2.	Martin Rost	Unabhängiges Landeszentrum für Datenschutz, Schleswig-Holstein, ULD
3.	Philip Schütz	Fraunhofer-Institut für System- und Innovationsforschung (ISI)
4.	Prof. Dr.-Ing. Tanja Schultz	Cognitive Systems Lab, Institut für Anthropomatik, KIT
5.	Michael Straeubig	freiberuflicher Spielekonzeptentwickler
6.	Prof. Dr. Klaus Wiegerling	TU Kaiserslautern, Fachgebiet Philosophie
Standardising Synthetic Biology: Contributing to the Bioeconomy?		
1.	Christina Naneva	European Commission, DG Research and Innovation Unit
2.	Ioannis Economidis	Former official at the European Commission, DG Research and Innovation
3.	Victor deLorenzo	Professor and senior scientist at the Spanish National Center of Biotechnology.
4.	Michele Garfinkel	Manager of the Science Policy Programme at the European Molecular Biology Organization.
5.	Emma Frow	Genomics network forum in Edingburgh
6.	Dirk Stemerding	Rathenau Instituut project officer

This document is the final report of the STOA study: 'Making Perfect Life (in) the 21st Century. European Governance Challenges in Bio-engineering'.

A summary of the study is also available.

The STOA studies can be found at:

http://www.europarl.europa.eu/stoa/cms/studies

or requested from the STOA Secretariat: STOA@ep.europa.eu

In addition a short Options Brief is also accessible through the STOA studies website, or via this QR code:

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