Biosafety Considerations of Synthetic Biology in the International Genetically Engineered Machine (iGEM) Competition

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The International Genetically Engineered Machines (iGEM) competition is one of the largest and most visible activities in synthetic biology. iGEM serves to introduce synthetic biology to students—the pool of talent for the future of synthetic biology. Although its participants have tried to construct useful genetic devices and systems in a playful way, iGEM has also been recognized for its important role in raising students' awareness of biosafety issues. In the present study, we analyzed how the iGEM teams have quantitatively and qualitatively dealt with new safety requirements in recent years and what suggestions were made to further improve biosafety. We found an increase in the number of teams reporting safety aspects and a general improvement in the safety assessment of their projects. Although the students' safety awareness has improved, certain gaps must still be filled before iGEM can fully live up to its role as an educational competition.

Keywords: BioBricks, iGEM, safety, synthetic biology, risk

One goal of synthetic biology is to develop novel approaches to make tools that make biology easy to engineer (Gough 2007, Smolke 2009). The International Genetically Engineered Machines (iGEM) competition, which benefits from community-based efforts, is an international, interdisciplinary, undergraduate competition in which synthetic biology is used both as a scientific exercise and as an educational tool (Bikard and Képès 2008, Smolke 2009, Dress 2010).

The event, which began in 2003, has grown from 16 students in a one-month design class to three separate regional competitions, with over 1000 participants from 143 teams from 28 different countries in 2011. Because of the fast expansion of the participant field, iGEM 2011 was for the first time conducted in three different regions: (1) the Americas, (2) Asia and Australia, and (3) Europe and Africa. Sixty-six teams participated in the final competition on 5–7 November 2011 at the Massachusetts Institute of Technology, in Cambridge (see table 1).

The iGEM competition is shaped along the lines of similar engineering competitions in other fields, such as the RoboCup competition to design intelligent robots (*www.obocup.org*) and the Shell Eco-marathon to design, build, and test ultra-energy-efficient vehicles (*www.shell.com/home/content/ecomarathon*). These forms of competition build creative yet transient communities that share the same spirit, irrespective of what original technical objects the competitions are geared to produce. They are all designed to elicit enthusiasm among young scholars in science and engineering in a stimulating but stringent process and in a group of like-minded peers. This makes such competition a very successful format of education. These educational aspects are accompanied by technical developments as well, not only for fun but also for practical applications. Examples of these iGEM projects (*http://ung.igem.org/IGEM/Learn_About*) include the following: Arsenic Biodetector is a bacterial biosensor that responds to a range of arsenic concentrations and produces a change in pH calibrated in relation to arsenic concentration. The goal was to help developing countries—in particular, Bangladesh—to detect arsenic contamination in drinking water. BactoBlood was intended to develop a cost-effective red blood cell substitute by engineered *Escherichia coli* bacteria. The product should be

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Table 1. The number of participating teams and of countries represented in the International Genetically Engineered Machine (iGEM) competition.

Year	Number of teams registered	Number of teams with completed wikis	Number of countries represented
2004	5	5	1
2005	13	13	5
2006	37	37	15
2007	54	54	19
2008	84	77	21
2009	112	102	25
2010	130	116	25
2011[a]	165	143	28

Note: See *http://ung.igem.org/Main_Page* and *http://ung.igem.org/Previous_iGEM_Competitions.*
[a]In 2011, the competition was split into three regional precompetitions: (1) the Americas, (2) Europe and Africa, and (3) Asia and Australia.

able to transport oxygen in the bloodstream safely, without inducing sepsis, and should have a prolonged shelf life when it is freeze dried. The Cesium Recovery project is a bacterial system for cleaning up the radioactive contamination after a nuclear meltdown, such as the one in Fukushima, Japan. The engineered bacteria would be released into the environment (the sea) to sense and move toward cesium-137 and then accumulate it. The concentrated cesium would then be recovered in an as-yet-unspecified way, contributing to a bioremediation process.

Like synthetic biology itself, iGEM grew out of the interdisciplinary cooperation of engineering science, chemistry, computer science, and life science. For many of the students, iGEM is their first experience in working with microorganisms and genetic engineering techniques, and it is the first time they have had to deal with biosafety precautions.

Just as most other fields are, synthetic biology is subject to specific regulations to ensure that research is done in a responsible and safe manner (Check 2005). The iGEM competition is an important showcase event for synthetic biology, for both the professional and amateur contenders. It therefore raises the inevitable key questions: How can it benefit our society? What are the challenges? Is it safe? Are there risks?

Biosafety and ethics are very important issues, especially for those technologies that can potentially make the leap from the research ideas to commercial products. It therefore comes as no surprise that the iGEM event has also brought up new challenges regarding ethical, social, and legal issues (Goodman 2008). Any new kind of technology may present a risk to the environment or to public health.

In the early years of the iGEM competition (before 2007), the organizers focused mainly on attracting more teams to the event and on improving logistics. Considering the potential biosafety risks of constructing novel genetic devices and systems, the iGEM organizers decided in 2008 to make safety issues (i.e., answering certain biosafety questions) a mandatory requirement. Since then, no iGEM team was eligible to win any medal or grand prize if they did not address biosafety questions properly.

Our study was designed to determine how many teams have addressed biosafety issues in their iGEM project and whether any trend can be observed. We reviewed all the iGEM projects between 2008 and 2011, with a particular focus on their biosafety responses. We describe here the evolution of safety requirements and reporting in iGEM and determine the differences between years. We then analyze how teams responded to the safety questions quantitatively and qualitatively. We conclude by proposing further ideas to make iGEM an even better and more safety-aware platform for the next generation of synthetic biologists.

Analyzing biosafety at iGEM

We took several approaches in our analysis of biosafety at iGEM. They are outlined below.

Data sources. We reviewed all the iGEM projects from the wiki pages of all the teams from 2003 to 2011. All data on the content of and safety issues associated with the project available on the teams' Web pages were collected. Between 2008 and 2011, the iGEM teams were required to answer a set of mandatory biosafety questions. We conducted an analysis of all the safety reports. The collected data were used to quantitatively and qualitatively analyze the different responses to safety issues. The relevant study was conducted using the online iGEM wiki archive (*http://igem.org/Team_List?year=2008*, *http://igem.org/Team_List?year=2009*, *http://igem.org/Team_List?year=2010*, *http://igem.org/Team_List?year=2011*).

Qualitative analysis. Because of certain changes in the mandatory safety questions in the iGEM competition between 2008 and 2011 (see supplemental table S1, available online at *http://dx.doi.org/10.1525/bio.2013.63.1.7*), we analyzed the characteristics of these changes—for example, how to deal with potential risk of BioBricks parts, devices and systems; the role of institutional biosafety committees; and ideas to improve future iGEM competitions.

The aim of the data collection process was to integrate all the registered records of every team into a report on how biosafety has been tackled in iGEM competition. We analyzed the data from all the wikis that concerned the presence or absence of the safety section as such, the responses of every team to the mandatory questions, the self-appraisal of the biosafety risk in the project, and the suggestions on how to improve biosafety for future iGEM competitions. In the first step of the analysis, the relevant text passages were simplified and assigned individual codes. Then, we sorted the codes into tentative categories. The categories were cross-checked to ensure that they reflected the original text passages correctly. In the last step, we combined the information on the types of responses to the questions and analyzed the change of every type of response over time and rated the strength of the matter of each category. We paid particular attention to detailed safety answers, appropriate risk identification, a reasonable solution for concrete safety issues, acknowledgement of well-established safety institutions and rules, fresh ideas to improve iGEM, and projects that were specifically focused on the theme of safety.

Quantitative analysis. Our analysis included projects on a wide range of research topics with differing quality levels, and we weighed them accordingly to determine the strength of the registered records on the basis of the method proposed by Gough (2007). We used the percentage of the number of teams with different quality levels as the quantitative index of the strength of each category. The overall grade for the records was used to reflect a global assessment of the following aspects: the awareness and identification of safety issues in the project, the ability to deal with the related risk, and ideas for future iGEM competition. We used these evaluation categories to determine the degree of safety consideration. The number of teams that discussed safety issues, that provided detailed answers, and that raised safety concerns regarding their project were analyzed from 2008 to 2011. On the basis of the special questions in 2010 and 2011, we also investigated the percentages of teams from these two years that raised different safety issues; that had their own institutional committees, training, and rules; and that had ideas on how to further improve biosafety in future iGEM competitions.

Outcome of our analysis

The result of our analysis is summarized below.

Evolution of the biosafety examination in iGEM. We analyzed the history of safety examination at iGEM from the beginning until 2011. The first iGEM competition, which consisted of only five teams, all from the United States, was held in 2003. Five years later, the number of competing teams had greatly increased, and the involved teams were from around the world. In its early years, the competition was mainly focused on how to improve collaboration and how to foster creativity. In recent years, more attention was paid to the risk associated with standard biological parts. The open-source nature of the iGEM competition; the professionalism, enthusiasm, and creativity of the students; and the students' contributions to the field have brought significant scientific and media attention to the program. Eventually, biosafety concerns emerged. The safety aspect became more obvious to the organizers and was introduced into the mandatory requirements to be addressed by all iGEM teams in 2008. The competition required every team to answer four initial questions on the basis of their own situation. The list of safety questions is recorded in supplemental table S1.

The safety questions of the competitions in both 2008 and 2009 were relatively simple—merely including safety issues raised by the project, the existence of safety regulation, the review of the project by a local biosafety group, and the safety assessment of the submitted BioBrick parts (table 2). The questions in 2009 were slightly different from those of 2008: The teams were asked to document the safety assessment at the Registry for Standard Biological Parts (*http://partsregistry.org*).

The biosafety questions were changed more profoundly for the 2010 competition (table 2). First, they were more specific, and second, a new question was added regarding how to address safety issues that could be useful for future iGEM competitions. On the basis of these changes, further adjustments were made in 2011. The teams were required to provide information about the biosafety provisions, such as whether their institution had a biosafety group or committee, whether they received any biosafety training, and institutional biosafety rules. The question on useful ideas for future iGEM was downgraded to an optional question. These changes indicated that the iGEM organizers realized the need for generalization and standardization of safety supervision and for reducing the workload by making one question optional.

In 2008, when safety questions were included for the first time, 12 of 77 teams (16%) had a safety section on their wiki page. Subsequently, more participants began to address safety issues (74% in 2009, 82% in 2010). All 143 teams in 2011 (100%) established safety content on their own wiki Web page.

Response to safety questions. Although safety reports were submitted, their quality varied considerably (figure 1). The reports were classified into five types: a detailed analysis (figure 1; the teams provided a description in detail on how to use experiment material, reagents, and equipment to address the biosafety concerns), a general answer (the teams mentioned the safety issues in general but not specifically in regard to their projects), only a *yes* or *no* answer (the teams only answered *yes* or *no* on the wiki report), a partial answer (the teams addressed only one or a few problems among those to answer), and no answer to any question but a general mention of safety issues (the teams provided no answer other than to the mandatory safety questions). The number of teams with a detailed safety analysis increased considerably from year to year and reached 48% in 2011. The teams that provided only one simple answer constituted a large percentage in 2009 (25%), but this subsection decreased gradually over the next 2 years (16% in 2010 and 14% in 2011). Moreover, the proportion and absolute number of teams that answered some questions or had no answer to any question showed a noticeable decline. In general, most teams provided general answers or even provided a detailed analysis, which shows that the iGEM teams gradually increased their awareness of safety issues.

We examined the general response toward biosafety risks from each team (figure 2). The answers were divided into four distinct categories: (1) the project had no risk, (2) the team encountered some minor problems but solved them,

Table 2. Safety questions addressed in the International Genetically Engineered Machine (iGEM) competition, 2008–2011.

Thematic area	Main question	Year 2008	2009	2010	2011
Raised issues	Would any of your project ideas raise safety issues in terms of researcher safety?	+	+	+	+
	Would any of your project ideas raise safety issues in terms of public safety?	+	+	+	+
	Would any of your project ideas raise safety issues in terms of environmental safety?	+	+	+	+
Local biosafety regulation	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?	–	–	+	+
	What does your local biosafety group think about your project?	+	+	–	–
BioBricks parts	Do any of the new BioBrick parts that you made this year raise any safety issues?	+	+	–	–
	If yes, did you document these issues in the Registry?	+	+	–	–
	Do any of the new BioBrick parts (or devices) that you made this year raise any safety issues?	–	–	+	+
	If yes, did you document these issues in the Registry?	–	–	+	+
	If yes, how did you manage to handle the safety issue?	–	–	+	+
	If yes, how could other teams learn from your experience?	–	–	+	+
Suggestions	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?	–	–	+	+

Note: In 2011, some teams were sent a different, unofficial questionnaire. Those questions are not reflected here.

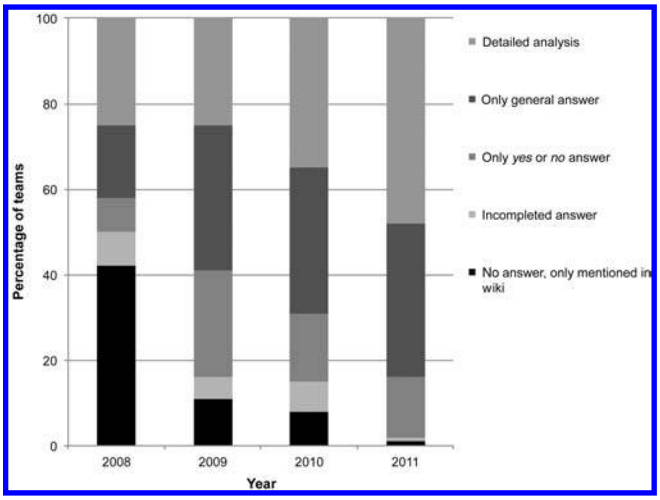

Figure 1. Summary of safety reports in the wikis of the International Genetically Engineered Machine (iGEM) competition teams.

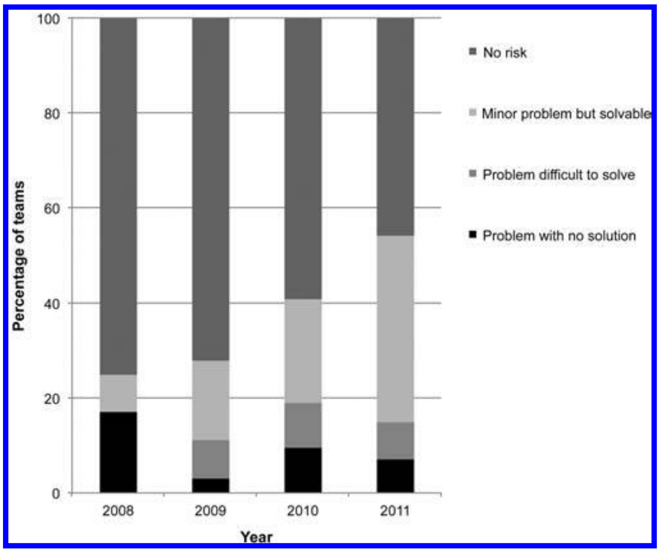

Figure 2. Self-evaluation of their project's biosafety by International Genetically Engineered Machine (iGEM) competition teams.

(3) the team encountered problems that were difficult to solve, and (4) the team encountered problems that could not be solved. The results showed that in 2008, the percentage of teams who thought that everything was fine was at 75%; this number then dropped over the following 3 years to 46% in 2011. To support their positive assessment, the iGEM teams were too optimistic and typically argued that the biological parts were not from pathogenic or toxic sources and, therefore, posed no risk to the safety of the team members, the laboratory, the general public, or environmental quality.

The percentage of teams that encountered some minor problems but solved them rose from year to year (up from 8% in 2008 to 39% in 2011). This increase indicates that the teams began to take safety issues more seriously and attempted to take the appropriate measures to deal with safety. As for the overall trend over all these years, there was an increase in those teams realizing that there were at least some safety risks in their project (the last three categories combined): 25% in 2008, 28% in 2009, 41% in 2010, and 54% in 2011. The common safety problems referred to in teams' answers included the use of known toxic chemical reagents and hazardous physical agents, biological waste disposal, and environmental pollution. At the same time, a small percentage of the teams also mentioned certain insurmountable problems. These included horizontal gene transfer, the mutation of organisms, the (unknown) detailed effects of bacterial modification, the misuse of the products, and antibiotic resistance.

Proposed solutions to safety issues. More detailed and specific questions were introduced in 2010 and 2011. Therefore, we focused on how the teams dealt with safety issues in those years. Two questions concerned mainly whether the materials, parts, or BioBricks in the project raised researcher, public, or environmental safety issues or potential misuse. Our analysis showed that teams varied in recognizing different safety issues (figure 3). Most teams (69% in 2010 and 75% in 2011) thought that the materials used in their projects posed risks to the safety and health of the team's members or others in the lab. These risks mainly involved physical (such as ultraviolet rays) and chemical (e.g., IPTG [isopropyl β-D-1-thiogalactopyranoside], ethidium bromide, phenol,

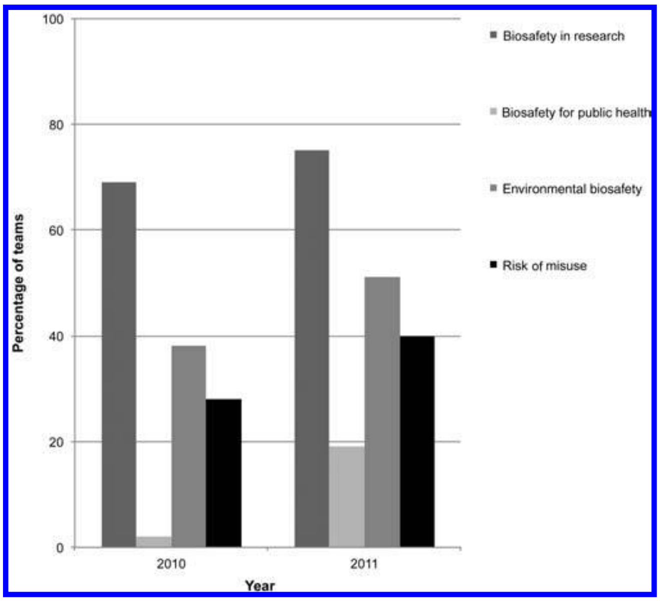

Figure 3. Biosafety-related issues raised by the International Genetically Engineered Machine (iGEM) competition teams in 2010 and 2011. The teams could be counted multiple times, so the total percentage is higher than 100%.

chloroform) risk, and various precautions were implemented to minimize these risks. Some teams (38% in 2010, 51% in 2011) discussed environmental risks. The full review of team wikis revealed that during no project had any microorganisms been released into the environment. All of the projects were conducted in a contained laboratory or were in the virtual world. A number of teams, however, worked on projects that would make sense only if they would at a later date release the engineered organisms for environmental applications. In general, the number of the teams that recognized biosafety issues in the 2011 competition was higher than that in 2010. This indicates that the teams gradually increased their safety awareness and also reported it.

In order to minimize the risk to researchers in the lab, 92% of the teams in 2011 documented that they had undergone the relevant lab training before the project started. This training covered basic laboratory safety procedures and practices. Most teams (79% in 2010, 86% in 2011) had their own institutional biosafety committees or groups who helped the team members with lab rules and oversaw safety (in various manners) throughout the project. Moreover, 90% of the teams in 2011 had their own institutional biosafety guidelines. The safety procedures to conduct the project were guided by the general regulations of the institution (and country) regarding safety guidelines for laboratory work.

Suggestions for future biosafety improvements. Although the question regarding suggestions for future improvements was "downgraded" to an optional question in the 2011 competition, the number of the teams that responded to it in 2011 (69%) increased over that in 2010 (55%). According to the results from those years, it was clear that in 2011, there were fewer teams with only general suggestions or ideas useful only to the team's own project rather to the whole competition (figure 4). The number of teams, however, with "useful" ideas (i.e., potentially relevant for all future iGEM teams) increased from 2010 (64%) to 2011 (75%), as is shown in figure 4. This indicates that more teams thought about instructive suggestions on how to deal with safety issues that could be useful for future iGEM competitions.

An overview of the data obtained from the teams' wikis provided the relative amount of each category. Interestingly, parts assessment was the most widely discussed theme. This was closely followed by education and safety in the lab. A single team might at some point provide two or more different ideas, which would yield a total number of suggestions greater than the number of teams (table 3).

Specifically, most of the teams suggested that the risk assessment of the biological parts and systems involved in a project should be carefully conducted by each team and by the iGEM committee. They also suggested that a questionnaire indicating the biosafety characteristics and history should be completed for every submitted project. Moreover, 15% of the teams thought that it was very important to increase public awareness of risks and safety issues; this would involve encouraging iGEM teams to give a presentation addressing synthetic biology at schools and in other public forums. Other teams highly recommended that the standardization of biosafety engineering would be very useful for future iGEM competitions. Finally, some teams put forward suggestions on biocontainment—for example, to work on synthetic DNA containing BioBricks below biosafety level 2; not to manipulate any infectious or virulent bacteria; and to integrate suicide circuits into engineered bacteria to ensure the safety of lab researchers, materials, and the environment. (For a real-world discussion of such ideas, and how they were debunked decades ago, see Schmidt and de Lorenzo [2012].) The teams also suggested discussing safety issues in public as part of the human practice activity.

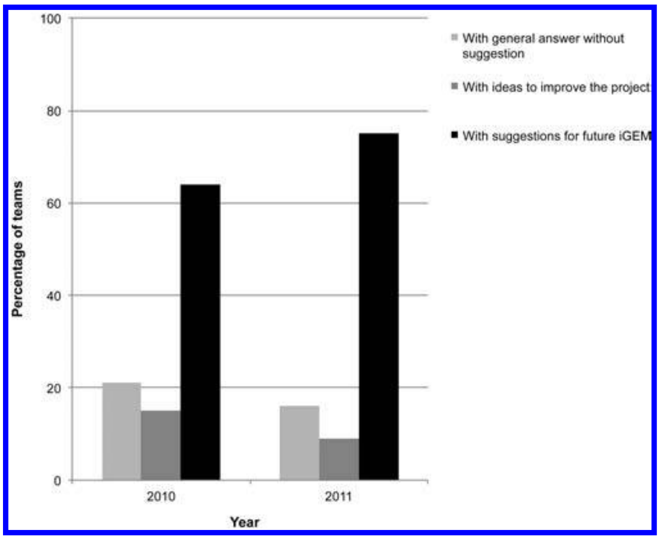

Figure 4. Summary of the ideas on how to improve biosafety for future International Genetically Engineered Machine (iGEM) competitions.

More projects deal with biosafety as their main goal. On the basis of the changes in the iGEM prizes categories since 2008 (table 4), we determined that, initially, the focus of the projects was on the environment, manufacturing, food or energy, and software tools. Subsequently, new types of projects were added, such as those on information processing, health, or medicine and projects specifically designed to address biosafety challenges (table 5). In 2010 and 2011, a number of the iGEM teams had already set their project goals on bioremediation, environmental safety, worker safety and health, or general biosafety issues. A popular idea among those teams was the development of a biosafety tool such as "kill switch" or "suicide circuit" that would cause the bacteria to die should they escape from a controlled environment (either in the lab or in a fermenter). Among other environmental applications, there was a proposed application for using engineered bacteria to detect toxic pollutants. Some teams also aimed to actively decontaminate soil or water in the environment. (See table 5 for a list of examples designed to solve safety issues.) The changes in the iGEM prize categories over the years showed the evolutionary progress of the event. Before 2010, the iGEM organizers established specific awards, such as the best BioBrick, the best model, or the best project in one field (table 4). In 2011, the special project prize was discontinued, and the safety commendation award was added. This may be a bold attempt for the organizer to create incentives for interest in biosafety issues. The winning teams for this award have proposed ideas to

Table 3. Ideas for improving biosafety for the International Genetically Engineered Machine (iGEM) competition and synthetic biology in 2010 and 2011.

Area of concern	Suggested improvement
Safety of biological parts	Mandatory safety review for each submitted part; completion of a safety questionnaire for every submitted part; a list of potential pathogens or environmentally problematic parts; better documentation and standardization of parts; better labels for parts, devices, or systems for better tracking; potentially pathogenic or hazardous BioBricks cloned in a special molecular backbone
Safety education	Increased public awareness of risks and safety issues; a video lecture on workplace safety made for all iGEM teams; an iGEM presentation by the participating teams, open to the school and public; an online, visual introductory course on basic biosafety issues; a customized safety quiz for each team; safety information incorporated for each protocol
Laboratory practices	Clear records of reagents, bacteria, and equipment; use of synthetic DNA containing only BioBricks below biosafety level 2
Principles for engineering	Standardization of biosafety engineering, standard biosafety rules for basic synthetic biology experiments, use of Event Tree Analysis and Fault Tree Analysis
Risk of using the material	Use of purified DNA instead of bacterial cultures, nonvirulent strain of bacteria used as the chassis, no manipulation of any infectious or virulent bacteria
Environmental safety	Suicide genes incorporated into the final constructs, an inactivation mechanism in iGEM plasmid backbone, a suicide system in all engineered bacteria
Self-risk assessments	Risk assessments of the protocols employed to complete the project, a (more) detailed safety report for a minimal medal requirement
Competition organization	A biosafety committee for the iGEM competition, a prize for safety
Other	Harmful genes associated with safety issues, encouragement of collaboration and experience sharing among the teams

improve biosafety, ranging from incorporating a watermark into synthetic DNA (by Team SDU-Denmark) to developing dedicated software for biosafety and biosecurity purpose (by Team VT-ENSIMAG Biosecurity).

To address the biosafety challenges of synthetic biology, some iGEM teams were able to uncover unanticipated safety or security risks. For example, Team Gaston_Day_School's project (2010) was to create a biological iron detector designed to use the limited techniques available in a high school laboratory to replicate techniques developed in well-equipped university research laboratories. Team Harvard iGarden (2010) created a toolkit to cultivate a personalized garden containing safety features introduced through synthetic biology. In addition to a "genetic fence" designed to prevent the spread of introduced genetic circuits, the team envisioned the iGarden as a medium through which nonscientists could see the potential of synthetic biology and apply it to everyday life. Team VIT_Vellore (2011) proposed a novel approach to solving the problem of sustained drug release and controlled the concentrations of the target molecule through synthetic biology. Their project "*In vivo* drug factory" involved using *E. coli* strains colonizing the human gut to produce and deliver drugs in the required concentration, controlled by a promoter. The system could be potentially used to treat a malfunctioning metabolism when it is coupled with the appropriate circuits.

Conclusions

The engagement of the scientific community in implementing biosafety measures is essential (NRC 2009). Without the cooperation of the scientific community, governments will have difficulty preventing accidents that could have possible public health repercussions (de Lorenzo 2010). Indeed, the best time to prevent potential harm is at the beginning of a project. This would cultivate the research responsibility of the scientific personnel working directly in the field.

There has been an effort to streamline the process of manipulating genes to create synthetic organisms and biological systems. New tools, such as the Registry for Standard Biological Parts, have made it possible for scientists and engineers without a high degree of specialization (such as undergraduate students from a variety of scientific fields) to develop new and innovative applications. This has led to a series of biosafety challenges that must be addressed immediately, because an increasing number of people outside the traditional scientific community will begin to create self-replicating organisms (Schmidt 2008). The situation has become even more critical with the emergence of the so-called *amateur biology* (or *biohacker*) community—a group that has begun to conduct biological projects in their own garages and in homemade molecular biology laboratories (Ledford 2010).

The international community has responded to the new challenges of genetically modified organisms by signing treaties such as the Cartagena Protocol on Biosafety, which has enabled regulation of the transfers of living genetically modified organisms across borders. This treaty, signed by many nations, was applied for the first time in 2003 (Gupta and Falkner 2006).

On the basis of our analysis of the iGEM team reports, we detected a clear increase over the years in the awareness of biosafety concerns. This was valid both for the iGEM organizers, who made safety questions a mandatory requirement for winning medals or other prizes at the competition (and refining these questions every other year), and for the iGEM teams. Furthermore, not only has the number of teams increased, but the quality and detail with which the teams dealt with safety issues has improved over the years. We also noted that a greater number of teams began to realize the

Table 4. The changes in the design prizes and categories from 2008 to 2011 for the International Genetically Engineered Machine (iGEM) competition.

Design prizes and categories	2008	2009	2010	2011
Best new BioBrick part or device, engineered	+	+	+	+
Best new BioBrick part, natural	+	+	+	+
Best model	+	+	+	+
Best experimental measurement	+	+	+	–
Best experimental measurement approach	–	–	–	+
Best foundational advance	+	+	+	–
Best new application area	+	+	+	–
Best environment project	+	+	+	–
Best manufacturing project	+	+	+	–
Best food or energy project	+	+	+	–
Best information processing project	–	+	+	–
Best health or medicine project	–	+	+	–
Best software tool	+	+	+	–
Best new standard	–	+	+	–
Best wiki	–	+	+	+
Best presentation	+	+	+	+
Best poster	–	+	+	+
Best human practices advance	+	+	+	+
iGEMers prize	–	–	+	–
Safety commendation	–	–	+	+

Note: The plus and minus signs indicate whether the prize category was present in the given year. The prizes listed here are those given for the final competition; those prizes given in the regional competitions (since 2011) are not listed.

Table 5. The list of International Genetically Engineered Machine (iGEM) competition projects designed to address biosafety challenges.

Safety theme	Team	Project objective
Biosafety software	HKU-Hong_Kong_2010	Biosafety net
Containment strategy	Harvard_2010	An open source toolkit for plant engineering, including a "genetic fence"
Containment strategy	BCCS-Bristol_2010	Smarter farming through bacterial soil fertility sensors
Safety device	Chiba_2010	Construction of a genetic double-click system
Environment safety detector	Gaston_Day_School_2010	Construction of a biological iron detector in a secondary school environment
Bacteria safety detector	IvyTech-South_Bend_2010	The development of a handheld monitor that uses this iGEM biosensor
Bioremediation	Lethbridge_2010	A synthetic-biology-based approach for bioremediation of tailings ponds
Bioremediation	Michigan_2010	Bioremediation of oil sands tailings water
Bioremediation	Tokyo-NoKoGen_2010	An ecotanker for the easy collection and delivery of target compounds
Environmental biosensor	UTDallas_2010	A modular whole-cell biosensor to detect environmental pollutants
Biosecurity software	VT-ENSIMAG_Biosecurity_2010	Development of the GenoTHREAT gene sequence screening software
Bioremediation	Caltech_2011	Bioremediation of endocrine disruptors using genetically modified *Escherichia coli*
Bioremediation	NYC_Wetware_2011	Engineering of radiation-resistant organisms
Environmental safety	Penn_State_2011	Bacterial dosimeter for detecting levels of harmful radiation
Bioremediation	Queens_Canada_2011	Engineering *Caenorhabditis elegans* into a toolkit for soil bioremediation
Bioremediation	SYSU-China_2011	Building nuclear-leakage rescuers
Bioremediation	UT-Tokyo_2011	Smart *E. coli*: self-mustering with aspartate-responsive taxis
Human health safety	VIT_Vellore_2011	*In vivo* drug factory
Human health safety	UNIST_Korea_2011	Engineering a synthetic self-killing system for *E. coli*
Bioremediation	Lyon-INSA-ENS_2011	Use of microorganisms to remove pollutants from a contaminated environment
Biosafety tool	St_Andrews_2011	Creation of an intracellular *E. coli* "kill switch"
Environmental safety	Copenhagen_2011	Expression and standardizion of cytochrome p450 in *E. coli* to create the oxime-producing cyperman
Human health safety	Fatih_Turkey_2011	An innovative model to prevent Gram-negative growth and infection
Environmental safety	Imperial_College_London_2011	A novel containment switch

Note: See supplemental table S2, available online at *http://dx.doi.org/10.1525/bio.2013.63.1.7*.

safety risks in their project, in contrast to the more ignorant or optimistic attitude of previous years. The teams identified safety risks that mainly involved lab safety for the researchers, but they also identified issues involving environmental risks.

The 2010 competition included for the first time an open-ended, future-oriented question specifically asking the teams what they thought would improve future biosafety challenges in iGEM and synthetic biology. Although this question was downgraded to an optional question in 2011, more teams responded to it than had previously done so. The suggestions centered on further improving biosafety challenges, as well as helping to identify current gaps and shortcomings in the use of the Registry of Standard Biological Parts and thus promoting the safety of synthetic biology in general. One-quarter of the suggestions were for a mandatory safety evaluation for the biological parts in the Registry, which would provide future users with substantial safety documentation. This indicates a clear mandate for the Registry of Standard Biological Parts and for iGEM to include and improve the currently inadequate practices in order to document safety-relevant characteristics of the registered parts. An example is part BBa_J07009 in the Registry, which is a toxicity-gene activator (*http://partsregistry.org/cgi/partsdb/part_info.cgi?part_name=BBa%20J07009*) from *Vibrio cholerae*. Although it is not toxic itself, it can be used to control toxicity—a characteristic that would merit at least a short comment about its safety implications. The part's description, however, has no biosafety description, reference, or other information that would help users identify and understand the biosafety risks of using this part. A search for the term *toxic* yields more than 180 entries in the Registry, with only a few of them containing explicit warnings (*http://partsregistry.org/wiki/index.php?title=Part:BBa_J07009*).

The safety issues go beyond single parts to encompass higher-order constructs (Schmidt 2009). This includes descriptions of the context dependency of parts in devices or systems, which are completely lacking from the Registry. The iGEM competition has prompted thousands of iGEM students to add and improve parts for the Registry. However, so far, it has largely forgone their suggestions on how to make BioBricks safer for researchers, engineers, the public, and the environment.

The lack of safety descriptions in the Registry, however, does not prevent iGEM teams from conceiving projects that directly tackle biosafety problems, such as environmental contamination and horizontal gene transfer. In 2011, more than 10 teams had projects dedicated explicitly to biosafety challenges. Among those, Team Imperial College London (in 2011) developed a sophisticated containment switch as a contribution to environmental biosafety; it not only won the regional European competition but was also among the world finalists and grand-prize winners.

When looking at safety-relevant projects—especially from the point of view of the general public—it must be noted that these projects are nowhere near a real-life application. Although the teams have good ideas and work enthusiastically on completing their goals, it would be difficult for any team to gain real-world biosafety approval for their applications (e.g., for medical use or environmental release). It would take a long time to turn an iGEM project on kill switches, genetic suicide circuits, or bioremediation into a product on the market with all of the liabilities and responsibilities that the market entails. In addition, some of these projects posed some dual-use (biosecurity) research concerns: They may reduce the dependence on sophisticated research facilities, lower the technical barrier to conducting biotech research, or create microbes that colonize the human digestive tract (Schmidt 2009). For example, projects designed to address the protein misfolding issues would have the potential for dual use if the same technologies were to be used to produce toxins or other lethal chemicals (e.g., Team Calgary_2010). Some software tools for synthetic biology may have possible malicious uses (e.g., that of Team METU_Turkey_Software_2010). There is also the potential to misuse any genetic-modification experiment in developing a CRISPR (Clustered Regularly Interspaced Short Palindromic Repeat) mechanism, which could block the genetic exchange of *Bacillus subtilis* and grant the engineered bacteria a resistance to phage (e.g., Team GeorgiaTech_2011's project).

The increase in the number of teams with safety issues on their wiki pages implies that the teams complied with the rules set forth by the iGEM competition. Meanwhile, there has been an increase in the number of projects with some safety elements included. For example, the detailed safety protocols of Team IIT Madras were mentioned on their wiki page, including standard microbiological practices, safety equipment, and laboratory facilities (*http://2011.igem.org/Team:IIT_Madras/Safety*). Team SYSU-China carefully reported their general safety measures for experiment material and reagents, the use of safety equipment, and the standard operation as defined by the Biosafety Committee of the Sun Yat-Sen University (*http://2011.igem.org/Team:SYSU-China/page_project_safety*). However, it would require further investigations on how these measures and guidelines had been implemented by the teams or institutions as a routine procedure to improve the safety assessment, to improve safety standards, and to promote public awareness and scientific responsibility. It is useful to investigate how teams are coordinated and educated about safety issues and whether more effort should be placed in designing and enforcing the regulations or guidelines to ensure that safety measures can be properly introduced into this educational process.

After all, iGEM is still an educational undertaking; it gives students the opportunity to learn, gain experience, develop creative ideas, and—most important—learn more about (synthetic) biology. The iGEM organizers encouraged the participants to pay attention to biosafety issues by making answers to safety questions mandatory for teams that aimed for a main prize. Detailed criteria to address a broader spectrum of biosafety issues should be provided in future iGEM competitions to guide good biosafety practices (Schmidt 2009). Many unknown potential risks related to synthetic biology should be considered and assessed in a case-by-case manner. The increasing awareness of safety issues of the iGEM teams and the increased knowledge of the issues, together with the greater number of dedicated biosafety projects, are positive indicators that the next generation of synthetic biologists (of which many will be iGEM alumni) will keep biosafety issues in mind in an era when it will be easier to engineer biology. Much, however, remains to be done to make biological engineering not only easier but also safer. The iGEM organizers and the Registry of Standard Biological Parts would be well advised to listen to the suggestions raised by the iGEM teams and to start producing a mandatory safety report for each biological part submitted to the Registry; to indicate potential pathogens or environmentally problematic parts; to require better documentation and standardization of parts; to supply parts, devices, or systems with a label to better track them; and so on. Although those measures should be further evaluated for their effectiveness, they would be an important step forward in fully harvesting the intelligence of thousands of iGEM participants who want to make biological engineering easier and safer.

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