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Description:

Develop molecular scale model of mechanoreceptors of the skin. Incorporate biomimetic mechanoreceptor models in synthetic material to be used for artificial skin.

Report on Molecular Scale Mechanism of Mechanoreceptors in Skin

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1. Introduction

Touch is essential to our everyday lives. Most of the physical actions performed during a normal day, from easier tasks such as holding a cup of coffee to a surgeon's dexterous manipulation of tools, requires sensory feedback for successful completion. The sense of touch is facilitated by our somatosensory system, which responds to a numerous mechanical action from our external world.

In mammals and many other animals, the skin serves as the resident site of innervation for the tactile sensors embedded within it[1]. The cell bodies of mammalian cutaneous mechanosensory neurons reside within dorsal root ganglia (DRG) (often known as DRG neurons) and trigeminal ganglia and each gives rise to a single axon that branches to form a distal, cutaneous axonal projection and a centrally projecting axon. It is within the distal, cutaneous endings of mechanosensory neurons that the transformation of mechanical forces into electrical signals occurs[2-5]. To understand the touch mechanism, animal testing on rats and monkeys are carried out all around the world in various labs and industries[3, 6-8]. Also, because of lack of available technology, there is still very little understanding of how skin filters the stress applied over it and activates the various skin mechanoreceptors within it.

In this report, a detailed literature review on structure of skin, its mechanoreceptors, and the mechanotransduction mechanism with special focus on molecular scale mechanism is presented. Additionally, outcomes from few previous work on modelling and simulation of skin mechanoreceptors and their ion channels from literature has also been included in this report.

2. Skin and its mechanoreceptors

In mammals (including humans) and other animal species there are physiologically, morphologically, and functionally distinct regions of skin. These include the hairy skin and non-hairy (glabrous) skin[1, 9]. These regions of skin differ in tactile sensitivity because of the difference in the distribution pattern of tactile sensors present within the skin. The cutaneous sense comes from different types of sensory receptors such as mechanoreceptors (responds to mechanical stimulation), thermoreceptors (responds to thermal stimulation), and nociceptors

(responds to the sensation of pain) embedded in the skin[1, 10]. In this report we will focus more on mechanoreceptors and the touch mechanism. There are several review papers which describes the skin mechanoreceptors, their afferent fibres and the mechanotransduction mechanism in detail[1-6, 9, 11-13]. Below, a summary on these mechanoreceptors and the touch mechanism is presented.

Mechanoreceptor sense mechanical stimuli like force, vibration, or movement at the surface of the skin. They are classified into two types; Slow adapting receptors (SA-I and SA-II), which respond to static and quasi-static stimuli - meaning that they produce a sustained response against a stable and constant stimulus; and fast adapting receptors (FA-I and FA-II) respond to dynamic stimuli such as vibrations[1]. These receptors are innervated by special nerve fibres which have different structure and conduction velocity[4, 10]. Figure 1 shows the skin mechanoreceptors and nerves innervating these receptors. Table 1 shows the characteristics of glabrous skin mechanoreceptors and Table 2 shows the properties of nerves innervating these receptors.

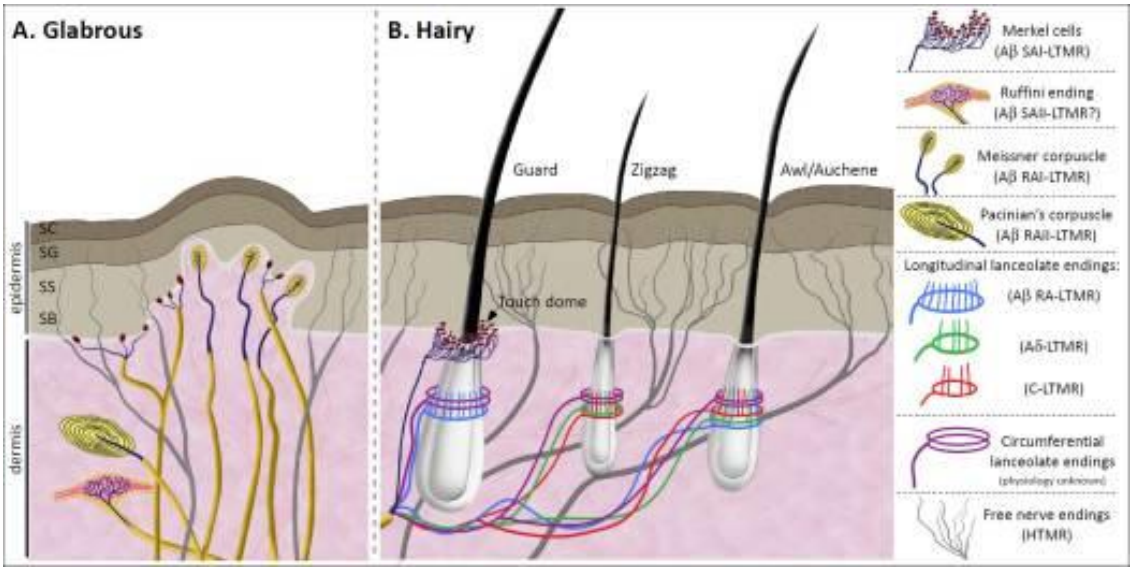


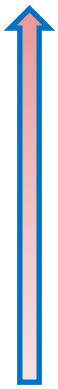
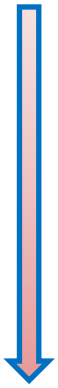
Figure 1: Cutaneous mechanoreceptors in skin[3]

Table 1: Characteristics of glabrous skin mechanoreceptors[9, 10]

	FA I Meissner	**SAI Merkel**	**FAII Pacinian**	**SA II Ruffini**
Receptive Field Diameter (mm)	3-4	3-4	>20	>10
Spatial Acuity (mm)	3-4	0.5	10+	7+
Response Properties	Responsive to dynamic skin deformations at relatively low frequency (~5-50 Hz)	Responsive to dynamic skin deformations at low frequency (~<5 Hz)	Extremely responsive to high frequency vibration (~40-400 Hz)	Low responsiveness to dynamic force but responsive to static force

Density and location	70-140/cm^2 in dermal papillage of the fingertip	70-140/cm^2 in fingertip epidermis	20/cm^2 in dermal and subcutaneous tissue; distributed throughout the hand	50/cm^2 in dermal and subcutaneous tissue; distributed throughout the hand

Table 2: Classification of peripheral nerve afferents[10]

Fiber Type	Sensory Function	Fiber Characteristics	Diameter (µm)	Conduction velocity (m/s)	Sensory Stimulation Threshold
Myelinated				60-120	Low stimulation threshold
Aα	Proprioception	Ia fibres: muscle spindle primary endings to sense muscle stretch (signals change in muscle length and velocity) Ib fibres: Golgi tendon organs to sense muscle tension	12-22		
Aβ	Tactile, proprioception	II fibres: muscle spindle secondary endings (signals static length), touch, joint position	6-12		
Aδ	Pain, Cold	III fibers: sharp pain	2-5		
Unmyelinated C	Pain, thermal, mechanical	IV fibers: dull, burning, poorly localized pain; primary thermal afferent	0.3-1.3	0.5-2.0	High stimulation threshold

2.1 Cutaneous Touch mechanism

Figure 2 shows the flowchart of mechanotransduction mechanism in skin showing how a mechanical stimulus on skin is detected and then converted into electrical signals. Cutaneous mechanoreceptors convey four basic types of information when stimulated— modality (e.g., gentle touch, vibration, stretch, injurious forces), location, intensity, and timing[1, 9, 10]. At the receptive site, mechanical energy is transduced into a change in membrane potential that is

called receptor potential. The receptor potential is then transformed into a neural pulse code, in which the frequency of action potentials reflects to some extent the amplitude of the receptor potential[2-4, 14]. As can be seen from this figure, understanding the biomechanics of skin, its mechanoreceptors and other cells and tissues involved in the filtration of the mechanical stimuli while it passes through the skin, the structure and gating mechanism of ion channels within the receptors (discussed in next section) are essential[3, 4, 7, 12-14].

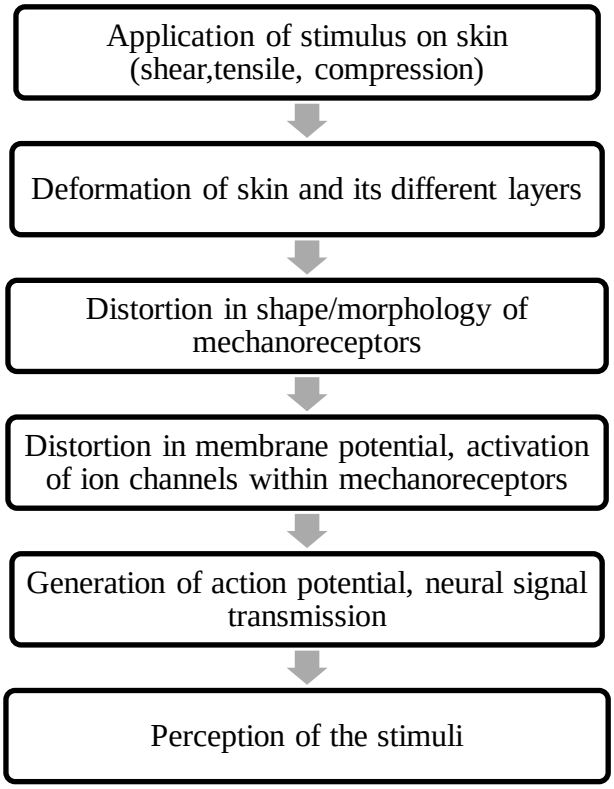


Figure 2: Flowchart of mechanotransduction mechanism in skin[1, 14]

2.2 Ion channels within mechanoreceptors

Ion channels are pore-forming membrane proteins that allow ions to pass through the channel pore. They are present in all the cells of the body. In mechanoreceptors, they are responsible for maintaining a resting membrane potential, regulating action potentials and electrical signals by gating the ion flow across the membrane[14]. These ion channels are composed of special transmembrane proteins surrounded by certain lipid molecules.

Ion channels can be selective allowing only certain ions like Na^+, K^+, Ca^{2+}, Cl^-, etc to pass through the channels while they can be non-selective to ions meaning multiple types of ions can pass through these channels. Based on the gating mechanism, ion channels can be classified[4, 6, 15] as:

- Voltage Gated channels: These channels get activated through changes in the membrane potential. Some examples of these channels include voltage gated sodium channels, voltage gated potassium channels etc. These channels are mostly selective to ions.

- Mechanosensitive channels: These channels get activated by changes in the lipid tension around the transmembrane protein. Some examples are DEG/ENaC channel, piezo channels etc. These channels can both be selective and non-selective in nature.
- Lipid Gated channel: These are activated when certain chemicals are attached to the transmembrane protein. These help in neurotransmission or the synapse process.
- pH Gated channel: These channels get activated through changes in the pH near the membrane protein. Example: ASIC channel

In mechanoreceptors mechanosensitive channels are initially activated as they detect shear, tension, or pressure on skin and then, voltage gated channels get activated to regulate the membrane potential and generation of action potential.

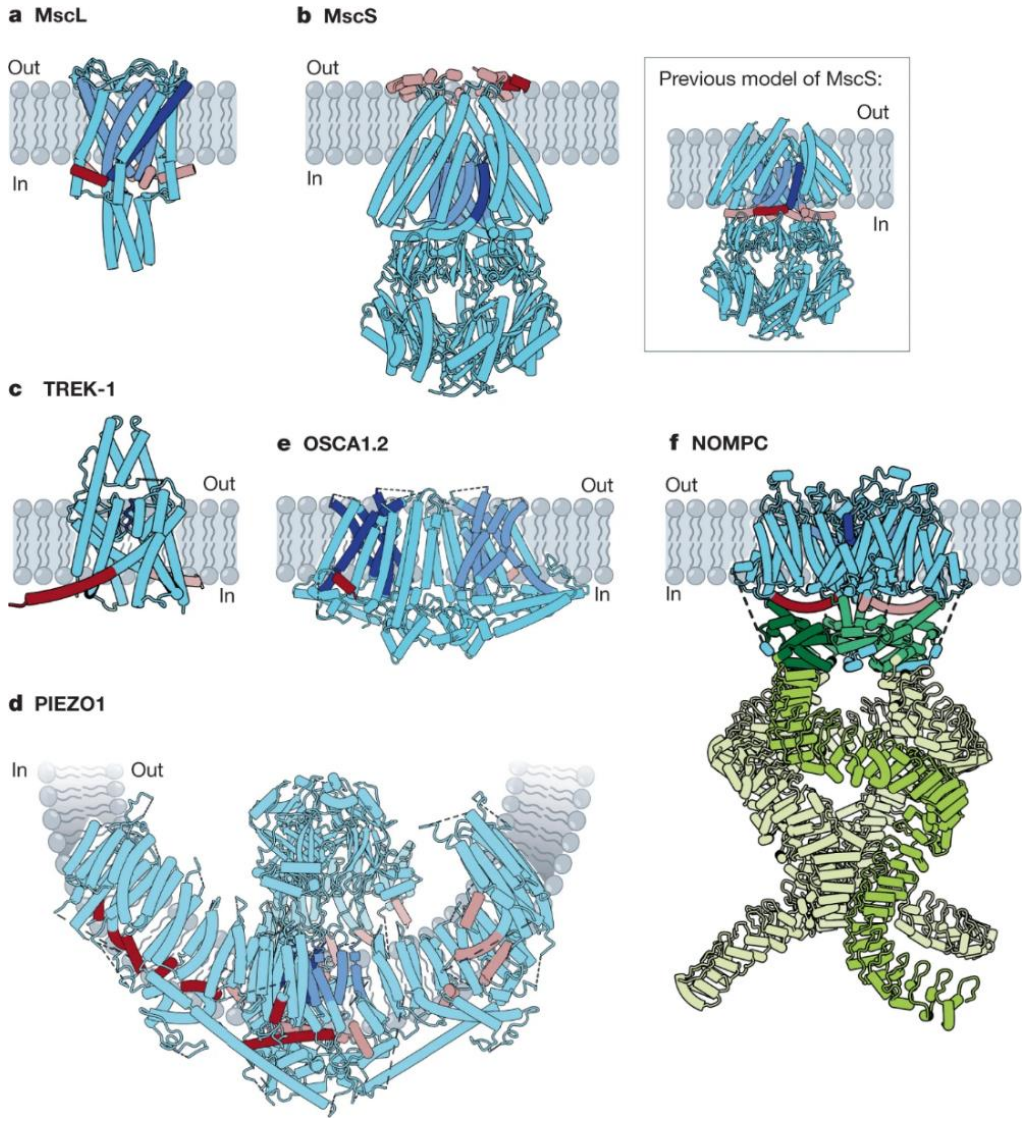


Figure 3: Structures of mechanosensitive ion channels (a) MscL, (b) MscS, (c) TREK-1, (d) Piezo1, (e) OSCA and (f) NOMPC ion channels [6]

Figure 3 shows structure of few of the mechanosensitive ion channels present in mammals and other organisms. Mechanosensitive channel large conductance (MscL) and mechanosensitive channel small conductance (MscS) were the first mechanosenstive channels to be discovered in bacterias[16, 17]. MscL is non-selective and opens its large pore like the iris of a camera in

response to membrane tension. MscS is structurally different from MscL and mainly found in fungi, plants etc. TREK channels can be activated by a variety of mechanical stimuli, including stretching, poking, swelling and fluid jet stimulation, as well as temperature and some chemicals[6]. The PIEZO family is conserved from protozoa to humans and was the first identified class of non-selective cationic mechanotransducers shown to be physiologically relevant in mammals. PIEZOs have roles in a broad and varied set of mechanotransduction processes and are thought to be present in most of the mechanoreceptors in humans[6, 12, 18-20]. Additionally, OSCA and NOMPC channels have been validated as bonafide mechanosensitive channels[6]. Due to advances in cryo-EM techniques, it has led to identification and publication of structures for almost every mechanosensitive ion channels. With the discovery of wide variety of mechanosensitive ion channels and the subsequent structural and biophysical insights, our mechanistic understanding of mechanotransduction is developing rapidly[6, 18]. Till recent times, two models of force transmission to ion channels were mostly recognised: force-from-lipid model (Figure 4a) and the force-from-tether model (Figure 4b) but recently few authors have argued that a hybrid model (Figure 4c) can also play some role[6, 21].

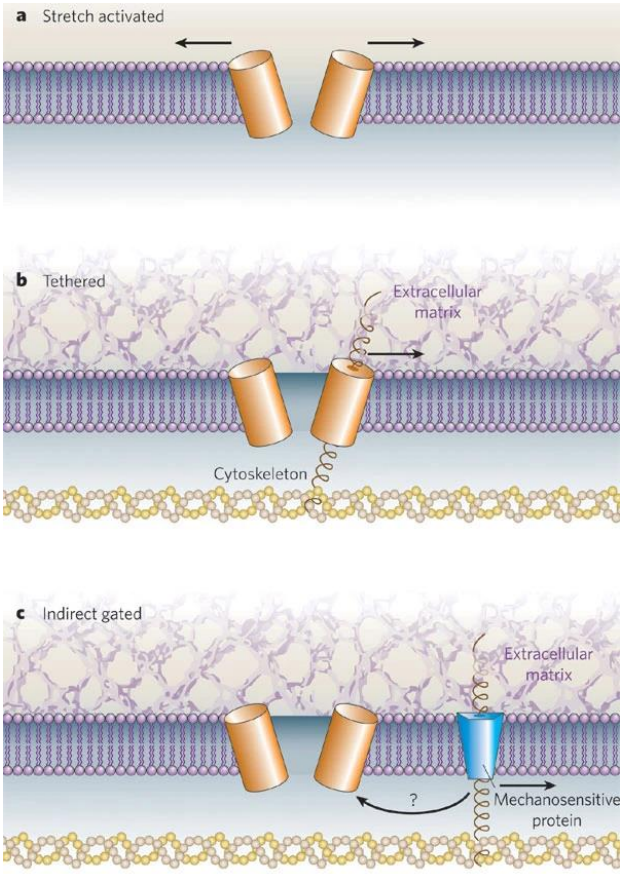


Figure 4: Transmission of force to ion channels (a) Stretch activated, (b) Tethered and (c) Hybrid model of gating mechanisms [21]

2.3 Computational studies

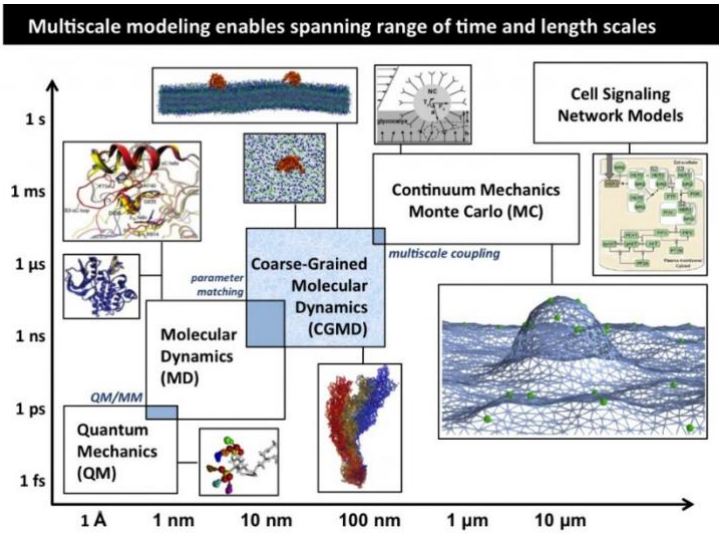


Figure 5: Multiscale simulation approaches for modelling different aspects of touch sensing mechanism in biological skin[22]

The recent advent of various simulation tools and increase in computational power during last two decades have produced quite accurate predictions for virtually most types of biomolecules and biological processes which provided unprecedent views of cells and organs working[23-25]. Within skin, many phenomena take place at different length and time scales due to which it is difficult to model these phenomena using a single computational approach. Thus, different parts of the touch mechanism have been studied computationally using different kinds of modelling and simulation tools. For example, molecular simulations are used to study gating mechanism of ion channels[19, 26, 27] while FEM simulations are used to study the strain energy distribution across different layers of skin when a stimulus is applied over it[28]. There are also some black box models[29-32] where researchers have correlated the input stimulus to the generated action potentials or spikes under stimulus using appropriate mathematical and machine learning models. However, in this report we will focus on molecular models of the mechanoreceptors and their associated ion channels.

2.4 Molecular dynamics and coarse-grained molecular dynamics simulation

Molecular dynamics (MD) simulation tools are used for analyzing physical movements of atoms and molecules under a given condition. Atoms/molecules interact with each other via non-bonded forces (vanderWaals force, electrostatic force, etc) and bonded forces (bonds, angles, dihedrals etc)[26, 33]. Then, Newton's equation of motion is solved for all the atoms/molecules in the system and potential energies are calculated at every timestep of the simulation. The main goal of these simulations is to attain a equilibrium state of potential energy at the given conditions. Because of lower timestep (~1-2 femtoseconds) and requirement of high computational power, the typical simulation time is in the order of few nanoseconds while the length of the system can be maximum upto 1 micrometres. Figure 6 shows the algorithm of a MD simulation.

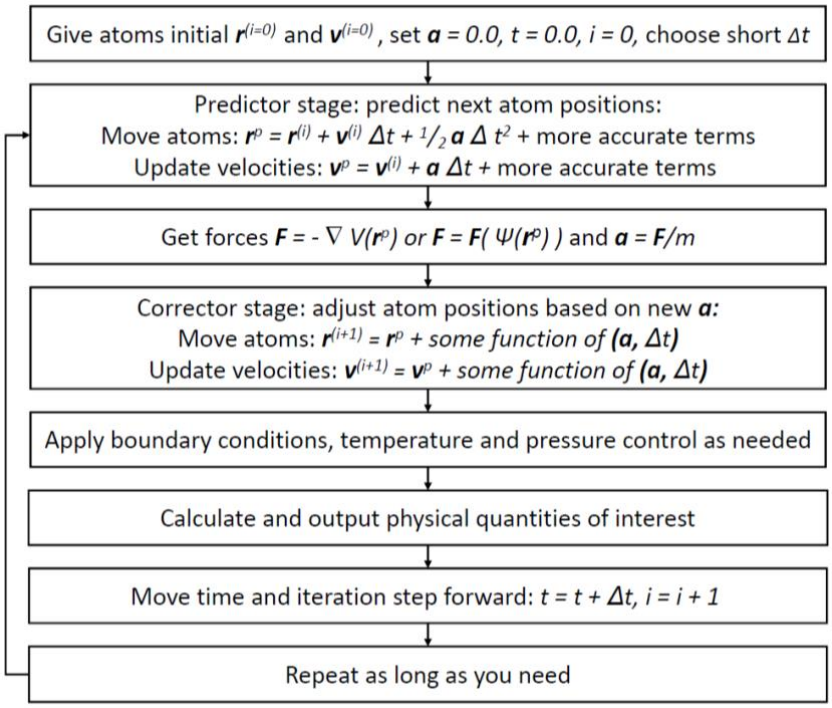


Figure 6: Simplified algorithm of a typical MD simulation[22]

To increase the simulation time and length scale of the system, few atoms are clubbed together as a single entity in coarse-grained molecular dynamics simulation (CGMD)[24, 25]. MD and CGMD simulations are widely used nowadays to simulate the behaviour of biomolecules, proteins, DNA etc under various conditions and have good application in molecular docking and drug design[23].

2.5 MD simulation of mechanoreceptor proteins and ion channels: Previous important outcomes

It is possible to study and investigate the ion channels inserted in the lipid membrane using MD simulations with timescale upto few tens of microseconds in the largest simulations. These simulations are able to capture the biophysics at the very molecular mechanism of mechanotransduction, including effects of mutations and drugs functioning, and can also provide parameters for higher-level or multiscale methods.

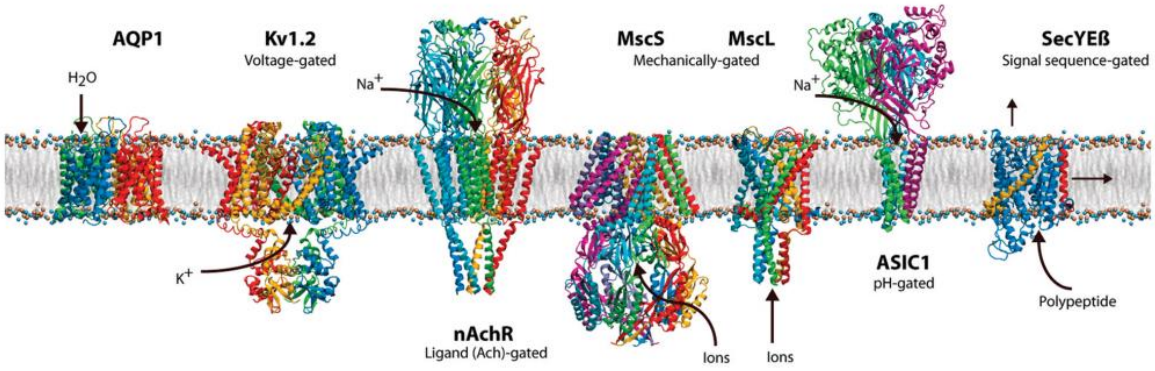


Figure 7: Membrane channels studied recently using MD simulations[33]

Figure 7 shows some of the membrane channels that have been studied using MD simulations. In these simulations, researchers have tried to study the movement of ions across the membrane, gating mechanism, and effect of stress in lipid bilayer of the channels[16, 27, 33-35]. Apart from above channels, Piezo1 protein channel has also been studied[18, 19].

There are several studies where the effect of lipid membrane on regulation of membrane proteins were investigated. In general, lipids may interact with membrane proteins as a whole, i.e., the membrane exerting lateral pressure on the protein transmembrane domain, or instead acting as ligands, binding in protein pockets and exercising allosteric effects. Few simulations have been performed specifically concerning the last point, that are viewed as related to mechanosensing, in the sense that upon concerted motion of channel protein and membrane lipids, isolated lipid chains can occupy specific binding pockets and, therefore, favor or disfavor channel opening. In particular, Kir2 (inward rectifier potassium channels) and PC2 (polycystin-2) have been investigated [36-38], and specific lipid-binding sites have been identified for these channels (Figure 8).

MD simulations of mechanosensing channels for modelling of mebrane tension and its effect on membrane channel proteins have been proved succesful recently for two main reasons. Firstly, the X-rays or cryo-EM structure of eukaryotes mechanosensing channels became available only in recent days [39-41]. Furthermore, because of improvement in computational facilities, large simulation size could be simulated till few microseconds during recent times.

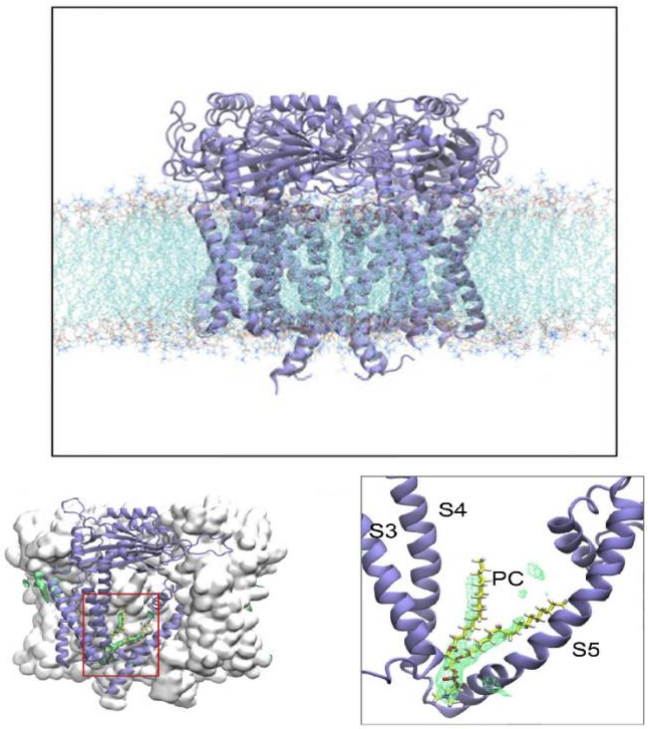


Figure 8: Identification of lipid-binding sites using MD simulations in PC2 channel[36]

TREK-2 channel, a member of the K2P family, has been studied in detail [42-45] via a combination of experimental and modeling tools. The increasing symmetric membrane tension is simulated by increasing the lateral dimensions of the lipid bilayer. For various lateral pressure values, down to -50 bar (that is, at increasing tensions), all-atom MD simulations were performed on the TREK-2 channel in down (closed) conformation, embedded in a 1,2-palmitoyl-oleoyl-sn-glycero-3-phosphocholine (POPC) bilayer. The TREK-2 channel, subjected to increasing membrane tension, in particular to a symmetric stretch of the bilayer, undergoes a large conformational change, from the so-called 'down' conformation to the 'up' conformation, with an overall expansion of the protein section. Notably, the selectivity filter is the putative location of gating in TREK-2 and TRAAK channels. Indeed, when the asymmetric stretch is applied, the increasing tension within the inner leaflet is able to induce the down-up conformational transition, similarly to the symmetric protocol, while tension applied to the outer face does not induce conformational rearrangements [44].

When similar MD simulation protocol was applied to non-mechanosensitive K2P channel TWIK-1, no conformational changes were observed, proving the mechanosensitivity of the TREK-2 channel as well as significance of the molecular modeling [42] (Figure 9). A striking difference between MscL and TREK-2, concerning the channel pore behavior upon membrane tension, is that the protein expansion drives the direct pore opening in MscL, while the mechanism related to the channel conductivity is more complex in TREK-2 and it retains the K+ selectivity [43]. Indeed, the TREK-2 selectivity filter is partially affected by membrane stretch [42] because ion occupancy changes depending on applied tension, while the ionic selectivity, interestingly, is not altered by membrane stretch [43]. Overall, the MD results for TREK-2 confirm that the model force-from-lipid can successfully explain the TREK-2

behavior, that the direct lipid occlusion has a non-prevalent role in the gating mechanism, that the ionic selectivity is retained at the selectivity filter, and that the asymmetric sensitivity of TREK-2 helps in maintaining the filter structure [42-44]. Further investigations have been devoted to the relationship between conformational and conductive states of the channel by simulating TREK-2 up and down states with physiological membrane potential, together with applied membrane tension [45]. Apart from gaining even more details of the gating mechanisms, those last MD simulations could identify the down conformation as a state most probably non-conductive, the up conformation as mostly conductive, and verify that membrane tension increases conductivity by favoring the up conformation.

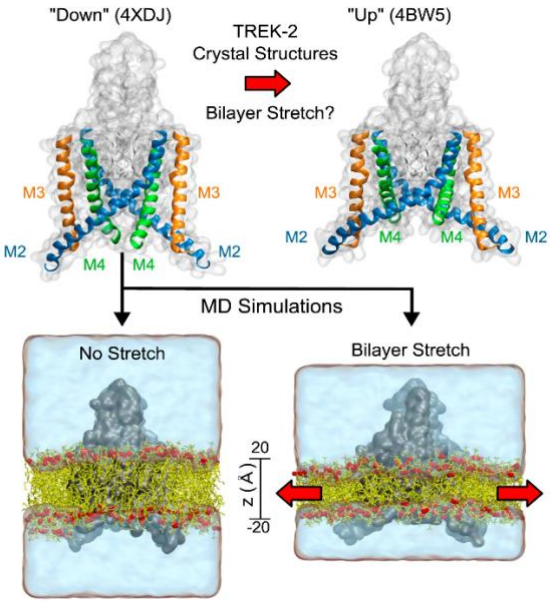


Figure 9: Membrane tension applied to the TREK-2 channel via MD simulations[42]

The TRAAK channel, member to the same K2P family, has also been modeled and studied via similar simulations [46,47]. The steric occlusion of the channel produced by lipids has been in this channel related to the loss of conduction in the closed conformation. Similarly, Piezo proteins have also been modelled using similar simulation protocols. Figure 10 shows the flattening behaviour of Piezo1 protein under various membrane tension[19]. Upon membrane stretching, both membrane and Piezo1 flatten, and Piezo1 expands, remaining embedded in the lipid bilayer. The extracellular domain becomes more exposed upon Piezo1 flattening, and the water-filled region inside the pore increases. Therefore, the applied membrane tension drives the channel opening. Due to the structural similarities between Piezo1 and Piezo2, it is hypothesized that the same mechanism holds for Piezo2 [47].

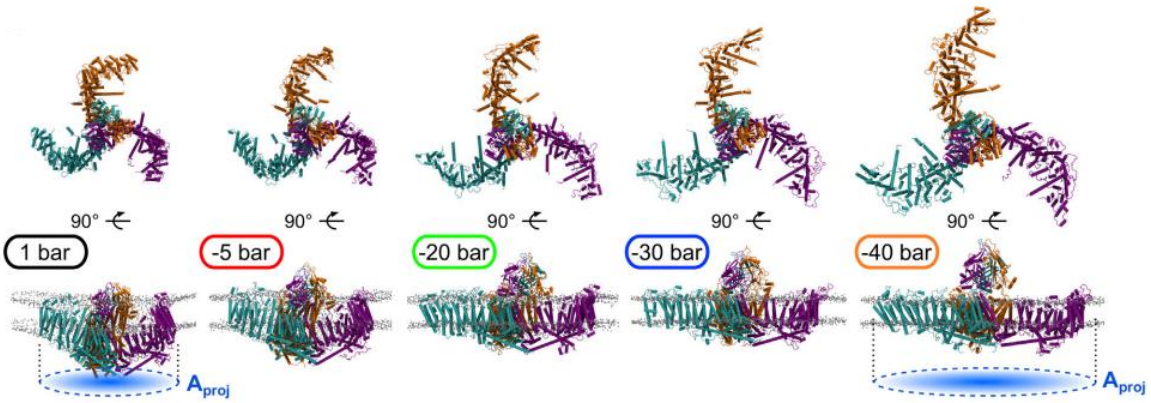


Figure 10: Flattening of Piezo1 protein in response to membrane tension[19]

The described simulations help to gain much better understanding of the ion channels in the mechanoreceptors which is difficult to investigate using experimental methods as the time scale of the opening/closing of these channels is in few nanoseconds and thus it is difficult to observe the process under traditional microscopy processes. Thus, molecular simulations act as powerful tool to describe and understand the functioning of mechanosensing channels at the molecular level.

3. Conclusions

In this report, the molecular scale mechanism of skin touch sensation process has been described. Details and role of various ion channels directly involved in mechanosensation process has been provided. For modelling and simulation of these ion channels, the algorithm of MD simulations has been described while some of the crucial outcomes from the previous simulations has been discussed.

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