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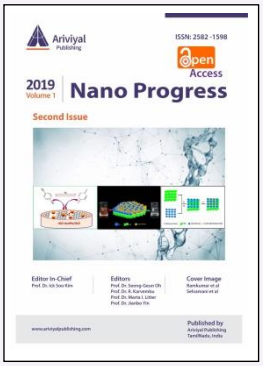

Monte Carlo Simulation for the Investigation of the Transport of Ions through a Gramicidin Ion Channel

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Abstract: Ion channels are the pores through the protein or membrane through which ions can pass. These pores are opened and closed depending on various factors such as change of voltage or binding with ligands. These changes bring some conformational changes to the channel and some selective ions are allowed to pass through the pores. Ion channels are found everywhere in our body, like the nervous system, sperm tail, muscle, etc. Gramicidin is a model membrane protein which when bound with lipid, tells about the protein-lipid interaction and it is suitable for analyzing the structure-function relationship of an ion channel. Here a voltage-gated and lipid-bound gramicidin ion channel is simulated by the Monte Carlo method for a mammalian cell and a squid axon to find the number of ion crossing in both directions across a cell.

Keywords: Ion channel; Monte Carlo simulation; ion transport; voltage gated channel

1. Introduction

The flow of ions maintaining potential gradient in the membrane, signaling in various organs and tissues can be some major factors in cell proliferation and cell migration. The plasma membrane has a potential gradient, formation of which is due to the distribution of positive and negative charge. This gradient of potential is maintained by the choosy passing of ions through the proteins, called ion channels present on the membrane. Cations like K^+, Na^+, Ca^{2+}, and anions like Cl^- are distributed in the intracellular and extracellular parts of the cell. Each ion has its importance in a particular physiological function of our body. Ca^{2+} influx in the cell changes many physiological functions to change. The cause of Ca^{2+} influx is hormonal change and the change of concentration is a major reason for the egg to embryo formation,[1] nerve disorder, and cell death by apoptosis and necrosis, and cancer.[2]

Numerous physical problems and disorders are identified as channelopathies and as time advancing new more diseases are added to the same. Ion channel mutation depends on the genotype of the person and hence can be treated by knowing the genetic information and the drugs that can bind the channel to change its function. Change of genotype means leading to personalized medicine. Neuro problems,[3] epilepsy,[4] diabetes,[5] asthma,[6] heart diseases,[7] and cancer[8] are some of the examples of channelopathy. Reported that mutation of CLCN1 in the chloride channel in the nervous system is the reason for congenital myotonia.[9] Ca^{2+} signaling or Ca^{2+} influx is crucial in determining the hyperactivated motility of spermatozoa. Male fertility depends on the Hyperactivation of sperm cells which is a delicate process and involves the action of different forces, chemical signaling mechanism, and elastic forces in the sperm tail which is very little understood. A vast field of fertility and infertility needs attention for computational knowledge. Though some mathematical modeling on the structure-function relationship of ion channels[10,11] sperm chemotaxis,[12] opening and closing of CatSper1 and CatSper2 channels on ligand binding[13] are reported so far, but the complete knowledge of the signaling mechanism is necessary for future nanomedicine.

Voltage-gated ion channels excite Na^+, Ca^{++} ions and this is the reason for transmitting an electrical signal to the axons. They operate on the change of a specific voltage in the membrane. Voltage-gated ion channels have much influence on the action of neuronal and muscular cells. They are found in viruses as well (Charlton E.W. et.al.).[14] They readily respond to the change of action potential. For example, the passage of sodium ions through the channels is a very important function which, if resisted, changes many physiological functions of our body. Many important characteristics and structure-function relationship of sodium channel were known from the pioneering work of Hodgkin and Huxley.[15,16]

As gramicidin is a model membrane protein, it is deeply studied by the researchers to understand the lipid-protein interaction and its structure-function relationship. Several recent studies are also carried out to get ideas about the channel in different conditions.[17,18]

Table 1. Intracellular and extracellular concentration of different ions in mammalian cell[21]

Ion	Intracellular Conc. (mM)	Extracellular Conc. (mM)
K^+	140	5
Na^+	5-15	145
Cl^-	4	110
Ca^{++}	0.0001	2.5-5

Table 2. Intracellular and extracellular concentration of different ions in squid axon[21]

Ion	Intracellular Conc. (mM)	Extracellular Conc. (mM)
K^+	400	10
Na^+	50	440
Cl^-	40-150	560
Ca^{++}	0.0001	10

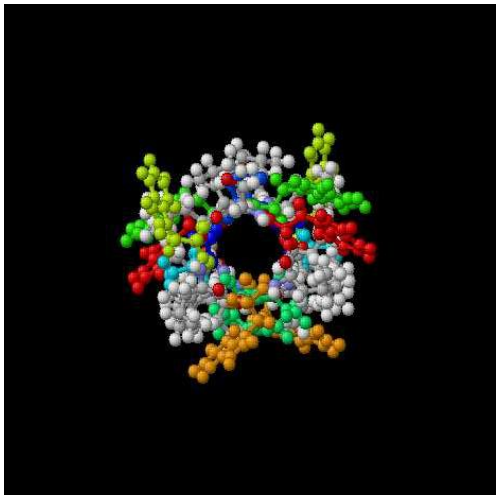

Fig. 1. Gramicidin ion channel structure (open state)

So for its importance, a voltage-gated gramicidin ion channel is investigated to study the transport of different ions through a gramicidin ion channel by Biology Monte Carlo (BioMOCA)[19,20] simulation in a mammalian cell and also in a squid axon.

2. Methods of modeling

Ion channels generally allow the flow of certain ions and disallow other ions from passing through them. It is a kind of switching mechanism which can be used to prepare biosensors.

In the present model, the transport of different ions (sodium, potassium, chlorine, calcium) through a gramicidin ion channel is investigated by Biology Monte Carlo (BioMOCA) simulation.[16] The background method of this simulation is Boltzmann Transport Monte Carlo (BTMC) methodology.

In MC simulation unphysical movement of ions can also be simulated. But here unphysical movements are restricted i.e. no two ions overlap or no ion overlap with protein. So, close-range calculations are performed. Here water and lipid are treated as background dielectric materials but ions and proteins are treated discretely. The lipid is treated like a slab of material having a uniform dielectric constant. The electrostatic potential is given by Poisson's equation.

$$\nabla \cdot \left(\varepsilon(r)\nabla\emptyset(r)\right) = -(\rho(r)_i + \rho(r)_p) \quad (1)$$

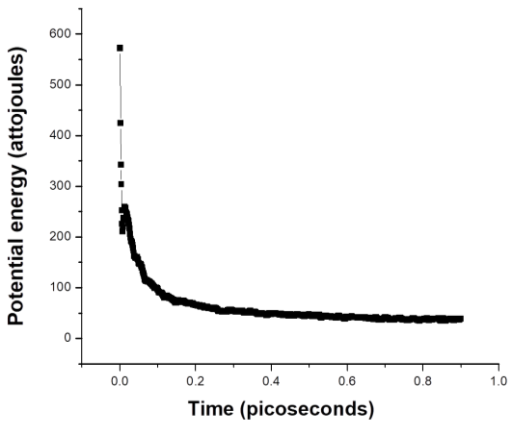

Fig. 2. Time vs. Potential energy curve

Here $\rho(r)_i$and $\rho(r)_p$ are the densities of moving ions and static charges on the protein and $\varepsilon(r)$ is the dielectric constant of the surroundings.

Whereas total energy is calculated as

$$E_i^t = E_i^m + \sum_{i \neq j} E_{ij}^c - E_{ij}^r \quad (2)$$

E_i^m represents the field produced at each grid point or in other words at each ion. In the short range mesh created, E_{ij}^c is the Coulomb force on the i^{th} ion due to other ions j. By introducing the term E_{ij}^r, the influence of j^{th} ions residing in the small domain are excluded from E_i^m.

For short range repulsive interaction, modified form of Lennard-Jones potential is used.

The lipid covers the protein very tightly. After a few iterations of optimization, the required conformation of the channel protein is obtained. Hybris LS and CD methods are followed for optimization. A simulation domain is created first by setting spatial grid size and boundaries. A lipid layer with definite thickness is wrapped surrounding the channel. The dielectric constant of protein, lipid, and the channel (i.e. water) is set properly. Boundary force potential is which gives the potential energy profile of a point charge while passing through the channel.

To run the simulation, we have fixed the membrane potential at six different values. The intracellular and extracellular concentrations of different ions are set according to the standard data of a mammalian cell and also for squid axon. Monte Carlo simulation with these values gives a detailed picture of ion transport through the channel.

3. Results and Discussions

The gramicidin ion channel protein is subjected to optimization following LS and CD method. Then MD simulation is carried out taking AMBER94 potential to get the energies of the system. The Channel pore is modeled from the optimized protein structure which is shown in Fig. 1. Figs. 2-4 give the energies of the system on optimization.

Table 3. Results of MC simulation for a mammalian cell (Left- extra cellular part, Right-Intra cellular part)

Ions	Number of ion crossings from left to right	Number of ion crossings from right to left	Number of ion crossings from left to right	Number of ion crossings from right to left
	Membrane potential= -50 mV		Membrane potential= 0 mV	
Na^+:	0	0	No ion crossing is reported at that potential.	
Cl^-:	1	0		
K^+:	0	0		
Ca^{++}:	0	0		
Total current	8.01088 pA			

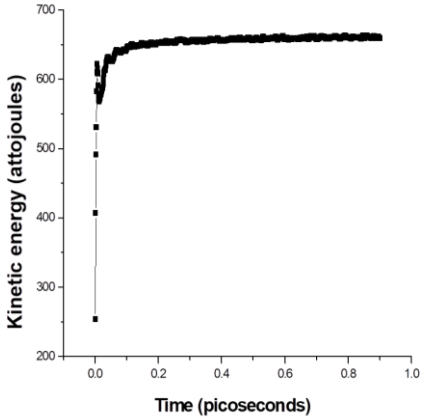

Fig. 3. Time vs. Kinetic energy curve

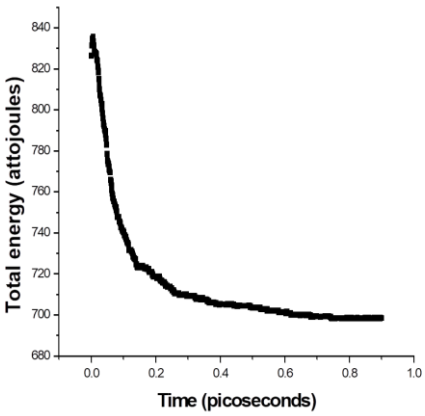

Fig. 4. Time vs. Total energy curve

Table 4. Results of MC simulation for a squid axon (Left- extra cellular part, Right-Intra cellular part)

Ions	Number of ion crossings from left to right	Number of ion crossings from right to left	Number of ion crossings from left to right	Number of ion crossings from right to left
	Membrane potential= -50 mV		Membrane potential= 0 mV	
Na^+:	2	0	1	0
Cl^-:	1	1	9	1
K^+:	1	0	1	2
Ca^{++}:	0	0	0	0
Total current	-24.0326 pA		64.087 pA	

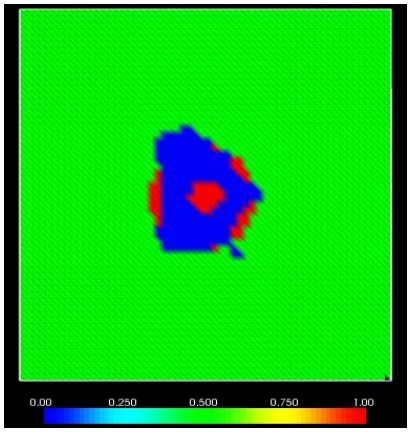

Fig 5. Structure of the ion channel after wrapping the pore with lipid membrane (Green colour shows the lipid wrapping surrounding the pore)

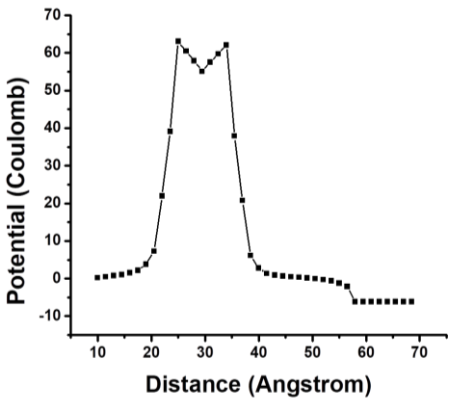

Fig. 6. Boundary force potential

For Monte Carlo simulation, the rectangular simulation domain is created and the channel is wrapped by a lipid layer of thickness 8.5 Å. Simulation is run for different membrane potentials -60 mV, -50 mV, -20 mV, 0 mV, and 30 mV for both mammalian cell and squid axon. The simulation box is generated to wrap the channel protein with lipid. The domain dimensions are -45.323Å and 44.677Å in the x-direction, -45 Å and 45 Å in the y-direction, and -48.421Å and 41.579Å in the z-direction. The dielectric constant of the channel is assumed to be 80, i.e., equal to water. So the channel is filled with water. The dielectric constant of protein and lipid is 2 and 5 respectively. The channel pore is wrapped with a lipid layer where the channel pore radius is set to 8.5. A. The lipid wrapped channel is given in Fig. 5. The boundary force is given by Fig. 6.

To find the number of ions crossing the membrane, MC simulation is performed. Intracellular and extracellular concentration of different ions for mammalian cell and squid axon are considered as given in Table 1 and Table 2.

With the above constants, simulation is run for 20 ns with time step 10 fs. Membrane potential is changed accordingly. Transportation of electrical signal from various parts of the body containing ion channels to the brain and the direction sent by the brain to cells and tissues to perform functions like gene expression,

cell division in non-excitable cells. Voltage-gated ion channels are responsible to perform such actions. The voltage-gated ion channels are active in different regions in the cell membrane and pave the way for the ions through the channel pore. Ions are activated by a particular potential difference created between the cell and outside the cell. After a certain time, the pore is closed due to the difference in the potential gradient in the longitudinal direction and perpendicular direction.

Simulation time is 2e-08s and the time step is 1e-14s. All simulations are carried out at normal temperatures. It is observed that at -50 mV membrane potential only one chlorine ion crosses from extracellular to intracellular part in the mammalian cell. At zero potential no transportation is observed. But for squid axon, several ion crossing is found at two different potentials; hence current flows at the two potentials only. For any other potential the channel current is zero. So the gate is activated at these potentials and for another potential, it remains inactive. As the gramicidin channel is specific for monovalent ions, hence divalent calcium ion shows zero activity under the application of gate potential. Results are given in Table 3 and Table 4.

4. Conclusions

The transport of Na, Cl, K and Ca ions through a gramicidin ion channel is investigated by MC simulation. It was observed that membrane potential has a great influence on the number of ions through the channel pore and hence the total current passing through the channel changes a lot with the potential. For mammalian cells, only one chlorine ion crosses the cell from left to right which produces a current of 8.01.88 pA at -50 mV gate potential but at a potential of 0 mV, no ion crossing is observed hence it contributes zero current. In squid axon, -50 mV potential gives a current of -24.0326 pA which is the combined effect of ion crossings from left to right and right to left. A current of 64.087 pA is reported for a membrane potential of 0 mV. The investigation gives an effective model of studying the ionic transportation and ionic current in a voltage-gated ion channel.

Conflicts of Interest

The authors declare no conflict of interest.

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