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Energy study at different solvents for potassium Channel Protein by Monte Carlo, Molecular and Langevin Dynamics Simulations

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ABSTRACT

Potassium Channels allow potassium flux and are essential for the generation of electric current across excitable membranes. Potassium Channels are also the targets of various intracellular control mechanisms; such that the suboptimal regulation of channel function might be related to pathological conditions. Realistic studies of ion current in biologic channels present a major challenge for computer simulation approaches. Molecular dynamics simulations may be used to probe the interactions of membrane proteins with lipids and with detergents at atomic resolution .Examples of such simulations for ion channels and for bacterial outer membrane has already been studied. In this work, to characterize protein behavior, we observed quantities such as gyration radius and energy average. It was studied the changes of these factors for potassium channel Protein in gas, water, Methanol and Ethanol phases with native conformation by Monte Carlo, Molecular and Langevin Dynamics simulations. Monte Carlo simulation is stochastic method and therefore, is the best method to evaluate the radius of gyration in gas phase. when the temperature is increased the kinetic energy is increased too, and its correlation is linear. All the calculations were carried out By Hyperchem 8.0 program. The radius of gyration for different solvent is calculated by VMD 1.8.7 Software. The determination of gyration radius is a spectacular for configuration of a Macromolecule. It also reflects molecular compactness shape. Monte Carlo simulation is the best method to evaluate gyration radius .

Keywords: Nanomolecular simulation; Channel Protein; Gyration Radius; Protein folding; Monte Carlo; Molecular Dynamics; Langevin Dynamics simulation

INTRODUCTION

All living cells are enclosed by a lipid bilayer, which is virtually impermeable to large-lipid insoluble molecules. Communication between the contents of the cell and the extracellular milieu is achieved by proteins embedded in this lipidous support. Membrane proteins are of considerable biological importance. They account for approx. 25% of genes and for approx. 50% of drug targets, yet they constitute only approx. 0.5% of known syructures.Ion channels are one example of such proteins; they mediate the flow of ions down an electrochemical gradient and share three properties- high conductivity, selective conduction and regulated conduction - that distinguish them from other membrane imbedded structures Knowledge of the protein folding mechanism will result in a huge advance in general bioscience ,especially in the fields of drug design and pharmaceutical chemistry. for example Alzheimer's disease and Prion disease have been found to be caused by miss folding of proteins[9-10].Gyration radius and end to end distance are predict the dimensions of a macromolecule by statistical

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mechanics science. The characterization of the protein folding process represents one of the major challenges in protein chemistry. Large theoretical and experimental research efforts have been devoted to this end [9].capable of facilitating the exchange of solutes between cytoplasmic and extracellular solutions[1-6].

Knowledge of the protein folding mechanism will result in a huge advance in general bioscience, especially in the fields of drug design and pharmaceutical chemistry [7-8].for example Alzheimer's disease and Prion disease have been found to be caused by miss folding of proteins[9-10].Gyration radius and end to end distance are predict the dimensions of a macromolecule by statistical mechanics science. The characterization of the protein folding process represents one of the major challenges in protein chemistry. Large theoretical and experimental research efforts have been devoted to this end [9].

Voltage-gated potassium channels are found in both excitable and non-excitable cell types. They are involved in neuronal and muscular electrical excitability, rhythmicity, of heart rate, as well as modulation of secretion from certain endocrine cells. In the nervous system, the roles of Kv channels are well established as being critical for regulating action potential frequency, membrane potential, and neurotransmitter release. Voltage-gated potassium channels in astrocytes can be sub-classified as delayed rectifiers, transient A-typed and inwardly rectifying channels.

Several methods are available for computational studies of protein-ligand interactions, ranging from the simplest docking methods [2-3] to Langevin dynamics (LD) and the more sophisticated molecular dynamics (MD) simulations [5-7]. The aim of the docking methods is to predict the binding Configurations and energies of large number of ligands for a given receptor with minimal computational effort. This makes them very fast but also limits their accuracy [8]. An accurate and detailed description of the binding unbinding processes requires explicit representation of water molecules, which is possible only in MD simulations. The primary approach used to simulate the dynamical behavior of lipid system is the molecular dynamics simulation technique, in which Newton's equations of motion are integrated numerically for a set of interacting particles to generate the time evolution of the system.

Molecular dynamics simulation is a powerful theoretical approach to gain insight into the structure and dynamics of complex biological macromolecular systems. It consists in calculating the position of all the atoms in a molecular system as a function of time, using detailed models of the microscopic forces operating between them, by integrating numerically Newton's classical equation of motion F = ma. The calculated classical trajectory, though an approximation to the real world, provides ultimate detailed information about the time course of the atomic notions,wich is difficult to access experimentally.

Molecular and Langevin dynamics simulation as well as Monte Carlo simulation have been used to investigate protein folding pathways with some success. The metropolis Monte Carlo was originally developed for calculating equilibrium properties of physical systems [11-14].The metropolis algorithm performs a sample of the configuration space of system starting from a random conformation and repeating a large number of steps. Molecular dynamics simulation is one the most promising. approaches for solving the protein folding problem .in this method we observe the time behavior of atoms of the system .in MD simulation , new positions of atoms are calculated by numerical integration of newton's equation of motion [15-18] (Fig.1).

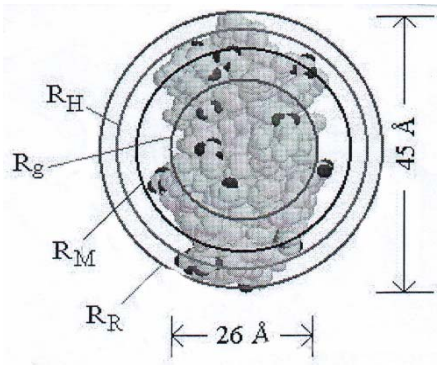

Fig. 1. Comparison of gyration radius (Rg) to other radii for lysozyme

When studying proteins, it important to know how much space a strand takes up at various times. Plotting the radius of gyration for different configurations versus the time interval of the snap shots taken will show you how the radius of

gyration changes over time. The maximum radius of gyration is when the chain is in a perfectly straight line.

METHODS

A small designed protein (PDB cod;1ho2) consisting of only 20 amino acid residues (320 atoms) was selected for this study. By using the VMD software opened this file and by ramachandran plot determined torsion angles (ϕ,ψ) for every amino acid and then in Hyperchem 8.0 program designed this protein with these angles [17].And then optimized voltage gated potassium channel protein by Monte Carlo simulation with amber force field ,at 300 k to 400 k.and by using VMD software gyration radius in gas, water, methanol, ethanol phase determined [18]. It's essential to say that ,Hyperchem uses the Metropolis method. By Monte Carlo simulations Kinetic, potential and total energy calculated. Then by Molecular and Langevin dynamics simulation we optimized protein with MM^+ force field , in 300 k to 400 k and after optimizing determined gyration radius. The present work is limited to simulations of ion flow under Gas , water , Methanol and Ethanol phase conditions that maintain a constant concentration gradient with an efficient way of evaluating the free energy surface of the system, we can turn to the calculation of its time evolution. As stated in the introduction, it is impractical to use direct MD simulations as a general way for evaluating ion current in ion channels. However, the related Langevin dynamics (LD) and Monte Carlo (MC) simulations can be used effectively with our Semimacro scopic free energies (Fig.2).

Fig. 2. Crystal structure of Voltage gated potassium channel from www.pdb.org with code number 1ho2.

RESULTS AND DISCUSSION

Implicit models provide a higher degree of algorithm flexibility. For instance, a Monte Carlo move involving a solvent exposed side chain would require nontrivial rearrangement of the nearby water molecules if they were treated explicitly. With an implicit solvent model thus complication does not arise. Of course all of these attractive features of the implicit solvent methodology come at a price at whose effects are often hard, If not impossible, to estimate. Some familiar descriptors of molecular interaction, Such as solute- solvent hydrogen bonds, are no longer explicitly present in the model; instead, They come in implicitly, in the mean- field way via a linear dielectric response, and contribute to the overall solvation energy. However, despite the fact that the methodology presents an approximation at fundamental level, It has in many cases been successful in calculating various macromolecular properties [21-23].

There are no artifacts of periodic boundary conditions: The continuum model corresponds to solvation in an infinite volume of solvent. New and Simpler ways to estimate free energies become feasible, because solvent degree of freedom are taken into account implicitly, estimating free energies of solvent structures is much more straight forward than with explicit water models.

In many molecular modeling applications, and in molecular dynamics (MD), the key quantity that needs to be computed is the total energy of the molecule in the presence of solvent. This energy is a function of molecular configuration, its gradients with respect to atomic positions determine the forces on the atoms. The total energy of a solvated molecule can be written as $E_{tot}= E_{vac}+\Delta G_{solv}$, where E_{vac} rents molecules energy in vaccum (gas phase), and ΔG_{solv} is the free energy of transfering the molecule from vacuum into solvent, that is, Solvation free energy. To estimate the total solvation free energy of a molecule, one typically assumes that it can be decomposed into the electrostatic and nonelectrostatic parts [24,25].

Structural modeling of the K_v channel suggests that the open state conformations of the voltage sensors of these channels are significantly different, whereas the voltage sensors may be similar in conformation in their closed states. This finding potentially explains the difference magnitude of the S4 translational movement observed experimentally for these channels.

Monte Carlo simulation are commonly used to compute the average thermodynamics properties of a molecules, and have been employed extensively in the study of the structure and equilibrium properties of molecules [14] .Monte Carlo calculations evaluate the averages of the ensemble directly by sampling configurations from the statistical ensemble. If the run takes enough time ,Monte Carlo and Molecular Dynamics must give the same average results for the same system, such as rotational frequencies or transitional rates [25] .Monte Carlo is better in sampling the allowed states of a system, thus ,can often calculate the average properties more quickly and accurately. The Run step and delta max for Monte Carlo simulation were 20000 and 0.001, respectively.The Run time and time step for Molecular Dynamics simulation were 30 ps and 10^{-3} ps, respectively. The time step and friction coefficient for Langevin simulation were 10^{-3} ps and 0.1 ps^{-1} , respectively [26,27].All simulations were at different temperatures. The total energy of the system, in these methods, is called Hamiltonian, which is the sum of kinetic and potential energy:

The Total, Potential and Kinetic energy (kcal/mol) potassium channel protein calculated by Monte Carlo, Molecular and Langevin dynamics simulation in Methanol phase respectively in (Fig.3-5).

It was found when the temperature is increased, the kinetic energy is increased too, and its diagram is linear for native structure in each three methods.

The diagram of kinetic and potential energy has been drown as a function of temperature for the native structure of the potassium channel protein. Kinetic energy increases as the temperature rises, and its diagram is linear in each three methods. The total , Potential and Kinetic energy (kcal/mol) potassium channel protein calculated by Monte Carlo, Molecular and Langevin dynamics simulation in Ethanol phase respectively in (Fig.6-8). When the temperature is increased, kinetic energy for biomacromolecules is enhanced.

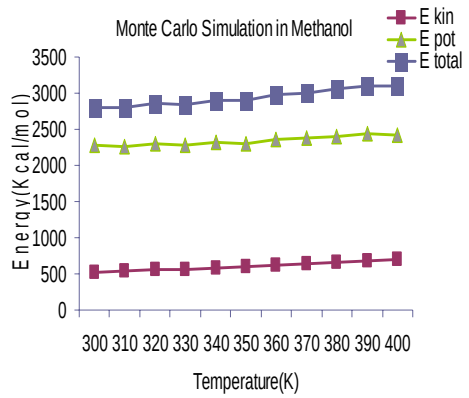

Fig. 3. The Total , Potential and Kinetic energy (kcal/mol) potassium channel protein calculated by Monte Carlo (MC) simulation in Methanol phases (E kin=Kinetic energy,E pot=Potential energy ,E total=Total energy,K=Kelvin temperature) .

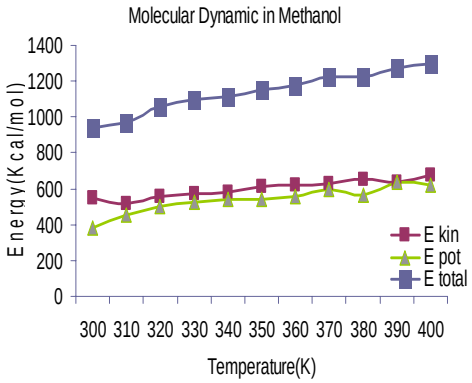

Fig. 4. The Total , Potential and Kinetic energy (kcal/mol) potassium channel protein calculated by Molecular Dynamics (MD) simulation in Methanol phases (E kin=Kinetic energy,E pot=Potential energy ,E total=Total energy,K=Kelvin temperature) .

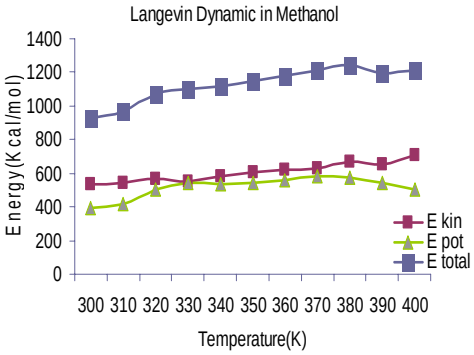

Fig. 5. The Total , Potential and Kinetic energy (kcal/mol) potassium channel protein calculated by Langevin Dynamics (LD) simulation in Methanol phases (E kin=Kinetic energy,E pot=Potential energy, E total=Total energy,K=Kelvin temperature).

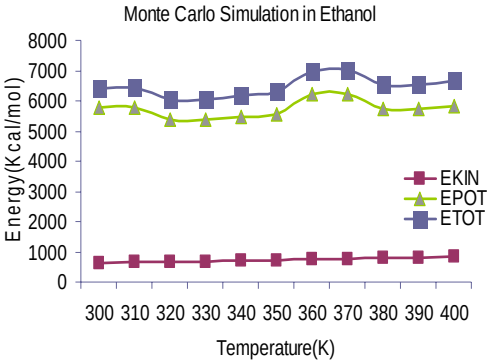

Fig. 6. The Total , Potential and Kinetic energy (kcal/mol) potassium channel protein calculated by Monte Carlo (MC) simulation in Ethanol phases (E kin=Kinetic energy,E pot=Potential energy ,E total=Total energy,K=Kelvin temperature) .

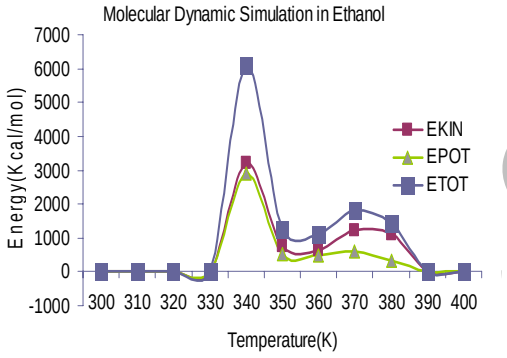

Fig. 7. The Total , Potential and Kinetic energy (kcal/mol) potassium channel protein calculated by Molecular Dynamics (MD) simulation in Ethanol phases (E kin=Kinetic energy,E pot=Potential energy ,E total=Total energy,K=Kelvin temperature) .

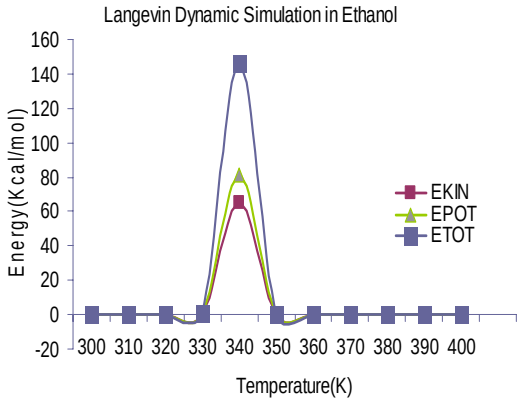

Fig. 8. The Total , Potential and Kinetic energy (kcal/mol) potassium channel protein calculated by Langevin Dynamics (LD) simulation in Ethanol phases (E kin=Kinetic energy,E pot=Potential energy ,E total=Total energy,K=Kelvin temperature).

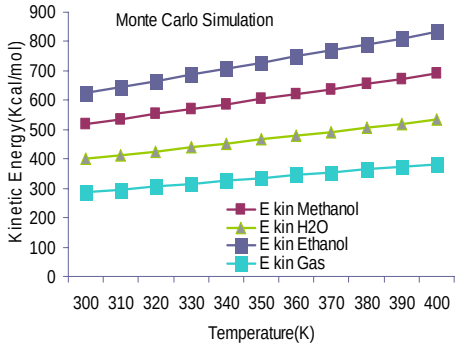

Fig. 9. The Kinetic energy (kcal/mol) potassium channel protein calculated by Monte Carlo (MC) simulation in Gas, H2O, Methanol and Ethanol phases (E kin= Kinetic energy,K=Kelvin temperature).

The Kinetic energy (kcal/mol) potassium channel protein calculated for by Monte Carlo simulation in Gas, H2O, Methanol and Ethanol phase (Table 1, Fig.9).

Table 1. The Kinetic energy (kcal/mol) potassium channel protein calculated in Gas, H2O,Methanol and Ethanol phases by Monte Carlo (MC) simulations (K=Kelvin temperature)

Temperature(K)	Kinetic Energy(kcal/mol)			
MC	Methanol	H2O	Ethanol	Gas
300	517.76	399.72	624.18	287.05
310	535.02	413.05	644.98	296.62
320	552.28	426.3718	665.79	306.19
330	569.54	439.69	686.59	315.75
340	586.79	453.02	707.40	325.32
350	604.06	466.34	728.21	334.89
360	621.31	479.67	749.01	344.46
370	638.57	492.99	769.82	354.03
380	655.83	506.32	790.62	363.59
390	673.09	519.64	811.43	373.16
400	690.35	532.96	832.23	382.73

The Potential energy (kcal/mol) potassium channel protein calculated for by Monte Carlo simulation in Gas, H2O, Methanol and Ethanol phase (Tab. 2, Fig.10).
The Kinetic energy (kcal/mol) potassium channel protein calculated for by Monte Carlo simulation in Gas, H2O, Methanol and Ethanol phase (Fig.11).

Table 2. The Potential energy (kcal/mol) potassium channel protein calculated in Gas, H2O,Methanol and Ethanol phases by Monte Carlo (MC) simulations (K=Kelvin temperature)

Temperature(K) MC	Potential Energy(kcal/mol)			
	Methanol	H2O	Ethanol	Gas
300	2276.71	147.96	5775.56	356.71
310	2267.92	187.28	5783.48	371.74
320	2299.60	181.41	5359.27	361.85
330	2273.48	199.00	5378.03	376.85
340	2320.22	202.70	5458.31	372.21
350	2297.53	200.14	5568.05	386.15
360	2358.26	238.47	6216.59	397.12
370	2371.24	225.71	6243.51	386.34
380	2400.20	260.45	5733.04	383.97
390	2434.06	263.45	5736.88	391.41
400	2414.32	254.88	5837.20	409.51

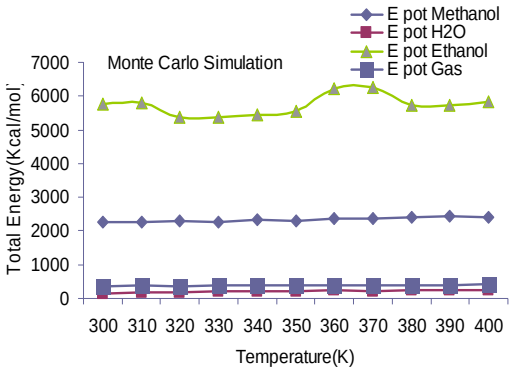

Fig. 10. The Potential energy (kcal/mol) potassium channel protein calculated by Monte Carlo (MC) simulation in Gas, H_2O, Methanol and Ethanol phases (E pot=Potential energy,K=Kelvin temperature).

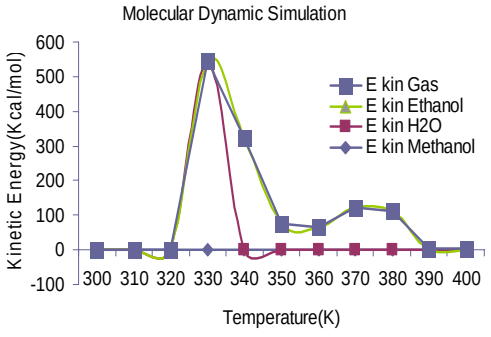

Fig. 11. The Kinetic energy (kcal/mol) potassium channel protein calculated by Molecular Dynamics (MD) simulation in Gas, H2O, Methanol and Ethanol phases (E kin= Kinetic energy, K=Kelvin).

The Kinetic energy (kcal/mol) potassium channel protein calculated for by Monte Carlo simulation in Gas, H2O, Methanol and Ethanol phase (Fig.12).

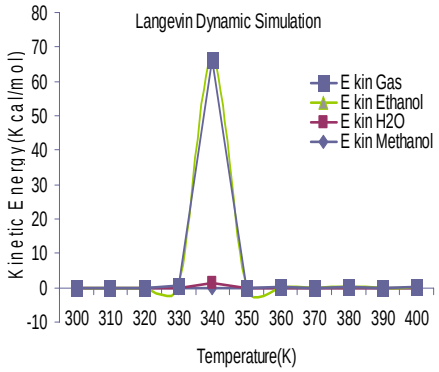

Fig. 12. The Kinetic energy (kcal/mol) potassium channel protein calculated by Langevin Dynamics (LD) simulation in Gas, H2O, Methanol and Ethanol phases (E kin= Kinetic energy,K=Kelvin temperature).

The calculated potential energy by Molecular dynamics approaches Langevin dynamics simulation at 340 K. Molecular dynamics simulation as well as kinetic energy shows some deviations for potential energy at less than 330K and after that proceeds constantly.

Gyration Radius (A^0) of potassium channel protein by Monte Carlo simulation in Gas, water, Methanol, Ethanol phase (Table 3, Fig.13).

Table 3. Gyration Radius (A^0) calculated for potassium channel protein by Monte Carlo(MC) simulation in Gas, water, Methanol, Ethanol phases (K= Kelvin).

Temperature(K) MC	Gyration Radius (A^0)			
	Gas	H2O	Methanol	Ethanol
300	9.4135	21.4818	25.8063	28.1370
310	9.4112	21.5885	25.8058	28.1362
320	9.4185	21.3959	25.8058	28.1364
330	9.4187	21.4649	25.8055	28.1377
340	9.4142	21.5441	25.8046	28.1342
350	9.4113	21.6264	25.8074	28.1319
360	9.4149	21.5091	25.8076	28.1369
370	9.4109	21.4710	25.8044	28.1353
380	9.4186	21.5141	25.8049	28.1337
390	9.4174	21.4939	25.8045	28.1325
400	9.4143	21.5628	25.8069	28.1321

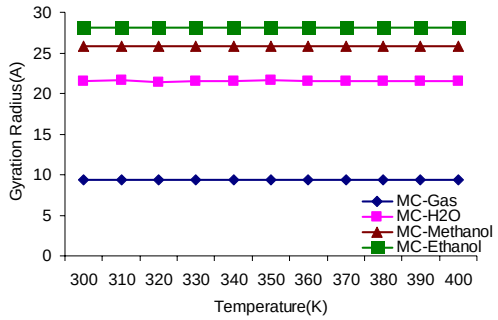

Fig. 13. Gyration Radius (A^0) of potassium channel protein by Monte Carlo simulation in Gas, water, Methanol, Ethanol phases (K= Kelvin).

MC simulation is the best method to evaluate gyration radius for proteins ,because MC is a stochastic method. The calculated values of energy in water, methanol and ethanol solvents are more than those in gas phase in biomacromolecules.Gyration Radius (A^0) of potassium channel protein by Molecular Dynamics simulation in Gas, water, Methanol, Ethanol phase (Tab. 4, Fig.14).

Table 4. Gyration Radius (A^0) calculated for potassium channel protein by Molecular Dynamics (LD) simulation in Gas, water, Methanol, Ethanol phases (K= Kelvin).

Temperature(K) MD	Gyration Radius (A^0)			
	Gas	H2O	Methanol	Ethanol
300	9.6670	17.3163	48.3778	45.0976
310	9.9669	16.9159	49.2020	45.6435
320	8.8311	17.5743	52.8095	45.7996
330	9.2525	17.7240	53.8442	45.7742
340	10.5721	17.0378	54.7466	29.6013
350	10.8485	17.0378	55.5309	33.0328
360	8.1510	17.9517	56.7099	63.1202
370	10.1149	16.2780	57.3707	76.0607
380	10.0334	16.5494	58.1642	29.2674
390	10.6953	16.7344	59.4389	49.2500
400	10.6102	16.3387	60.2004	51.9395

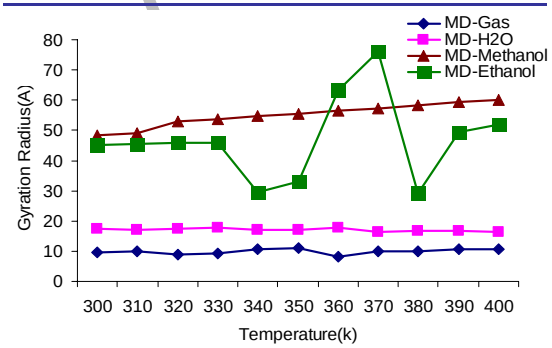

Fig. 14. Gyration Radius (A^0) of potassium channel protein by Molecular Dynamics simulation in Gas, water, Methanol, Ethanol phases (K= Kelvin).

The calculated gyration radius for potassium channel protein in water indicates less difference from that is gas phase, while a great difference is observed in methanol and ethanol solvents. Gyration Radius (A^0) of potassium channel protein by Langevin Dynamics simulation in Gas, water, Methanol, Ethanol phase (Table 5, Fig.15). In general in calculation chemistry , Langevin Dynamics simulation is the same as Molecular Dynamics.

Table 5. Gyration Radius (A^0) calculated for potassium channel protein by Langevin Dynamics (LD) simulation in Gas, water, Methanol, Ethanol phases (K= Kelvin)

Temperature(K) LD	Gyration Radius (A^0)			
	Gas	H2O	Methanol	Ethanol
300	10.0133	17.6520	51.3180	47.5011
310	9.8518	17.5515	52.2539	46.7000
320	10.1088	16.8403	54.3821	29.1663
330	10.1358	17.1895	55.5933	32.2915
340	10.4000	18.0253	56.3590	72.3401
350	9.4348	15.4037	57.0643	44.3314
360	9.4394	16.2258	58.3067	29.3692
370	9.5714	15.6407	59.0030	29.2976
380	8.5493	16.7183	59.9321	29.2674
390	9.9480	16.4275	59.1093	29.3247
400	8.5499	17.9001	59.8098	31.3881

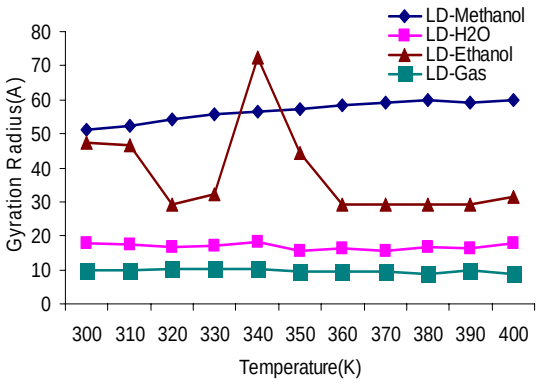

Fig. 15. Gyration Radius (A^0) of potassium channel protein by Langevin Dynamics simulation in Gas, water, Methanol, Ethanol phases (K= Kelvin).

Considering the gained values for gyration radius from each three methods for K+ channel protein, it can be understood that the second

structure of potassium channel protein is the kind in which α-helix is more.

Experimentally gyration radius for the Voltage – gated potassium channel protein is 9.409 A^0. The radius of gyration for different solvent is calculated by VMD Software. Gyration radius diagram as a function of temperature for each three method shows that Monte Carlo simulation in gas phase is the best method to evaluate gyration radius as well. Considering the gained values from Monte Carlo, Molecular and Langevin dynamics simulation calculations for α–helix conformation and little deviations from the experimental values it can be understood that the second structure of mentioned protein is α–helix folding.

In this research, to characterize the behavior of the protein we observed quantities such as the radius of gyration and the average energy. We studied the changes of these factors as a function of temperature for potassium channel protein in gas phase with native structure, α-helix and β - sheet conformations by Monte Carlo, Molecular and Langevin dynamics simulations. Considering the gained values for gyration radius from Monte Carlo, Molecular and Langevin dynamics simulations for α-helix conformation and little deviations from the experimental value, it can be understood that the second structure of this protein is the kind in which α-helix is more. It is studied the changes of these factors as a function of temperature in water, ethanol and methanol solvents by Monte Carlo, Molecular and Langevin dynamics simulations. The calculated values of energy in these solvents are more than those in gas phase. The calculated gyration radius in water indicates no difference from that is gas phase, while a great difference was observed in methanol and ethanol because the protein in two solvents is denatured. It was found that Monte Carlo simulation calculates more values of kinetic and potential energy for protein in water while Molecular dynamics simulation shows such condition for protein in methanol. Langevin dynamic simulation calculates kinetic and potential energy for protein in methanol with great fluctuation.

An accurate description of the aqueous environment is essential for realistic biomolecular simulation, but may become very expensive computationally. For example, an adequate representation of the solvation of a medium-size protein typically requires thousands of discrete water molecules to be placed around it.

CONCLUSION

Recently discovered interactions of Kv channels with cytoskeletal elements provide insight into channel targeting and localization mechanisms. Disruption of the action cytoskeleton appears to disrupt many different ion channels. More specific studies now demonstrate that Kv channels interact with the cytoskeleton in synaptic terminals through post synaptic density protein, 95 kDa or even the exocytotic apparatus protein syntax in 1A. Many of these interactions alter channel density and targeting of the respective channels.

In general Langevin dynamics simulation are the same as molecular dynamics simulation .There are differences due to the presence of additional forces. Most of the earlier discussion on simulation parameters and strategies for Molecular Dynamic had been applied to Langevin dynamics. We found that Monte Carlo simulation is the best method to assess and find the value of gyration radius, because Monte Carlo is a stochastic method. Our results show that kinetic energy is enhanced when the temperature is increased and kinetic energy plot is linear. Monte Carlo calculations evaluate the averages of the ensemble directly by sampling configurations from the statistical ensemble Molecular Dynamics is the key quantity that need to be computed is the total energy of the molecule in the presence of solvent.

The resolution of the atomic structure of the ion-conduction pathway of potassium channel protein has served as a spring-board from which we have gained a clear understanding of the underlying principles of ion selectivity and permeation. A huge challenge for the field will now be to understand the structural mechanisms of voltage gating and inactivation, In this regard, examples of conformational coupling between the pore and the cytoplasmic domains of potassium channels are already helping to gain new insight into the fundamental mechanisms of channel regulation. A nanomolecular understanding of these processes will be instrumental in elucidating the mechanisms that underlie the higher-order activity of neural

networks. The structure and function of the membrane proteins are central problems in molecular biology and are attracting tremendous interest. However, the cooperative process of lipids and proteins occurring within the membrane is still very difficult to understand. Recent advances in computer technology have proved the molecular simulation approach to be very promising in various fields of research.

PERSPECTIVE

Investigation of ion channels is interesting from several perspectives. Foremost it is important to investigate their structure function relationships to better understand channel dysfunction in disease related mechanisms counting CNS disorders, cardiac attythmias. Diabetes and epilepsy.

It is evident that MD simulations are able to reveal both specific and non-specific interactions of membrane protein components with their lipid bilayer environment. Future simulations will extend such studies to a wider range of membrane proteins, including those peripheral membrane proteins that from strong interactions with specific lipids. This will help us to arrive a detailed understanding of lipid-protein interactions at atomic resolution.

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