

Amino acid binding to nanotube: Simulation of membrane protein channels by computational methods

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ABSTRACT

The importance of ionic channels is due to the passage of ions across the cell membrane which is based on electrochemical gradients. The structure of ionic channels often includes one or several central cores which makes up the pore. The direct electron transfer between the enzyme and unmodified electrode is usually prohibited due to shielding of the redox active sites by the protein shells. Monte Carlo simulation have been used to investigate protein folding pathways with some success. Monte Carlo was originally developed for calculating equilibrium properties of physical systems. In calculations we optimized the geometry and defined Potential Energy of the nanotube structure by performing molecular mechanics calculation using MM+ force field, if too large a time step is used in Monte Carlo simulation, it is possible to have a basic instability in the equations that result in a molecule blowing apart, we need small time steps to preserve integration accuracy, however in the Monte Carlo time step 50 femtoseconds (0.05ps) was appropriate. next step we calculated the Vibrational modes of the tube by applying the semi-empirical molecular orbital method. In this paper, we have studies the stability of CNT-Amino acids clusters using by semi-empirical method and investigation of vibrational frequencies and electrical properties. In the more the potential energy increases the more the conductivity of nanochannels decreases and we chose the least energy among nanotube and amino acid complexes. Also the more energy we use, the more conductivity we will have; therefore, we choose the complex which conducts the most current.

KEY WORDS: AMINO ACIDS- CNT- MEMBRANES PROTEINS- MONTE CARLO- SEMI EMPIRICAL

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INTRODUCTION

Protein helices which make up the pore have consisted of four distinct subunits or one subunit which includes repetitive parts. Any disorder in protein-made channels causes paroxysm attacks. For instance, we can mention neuromuscular diseases as one type of these illnesses. These diseases are called disorders of ionic canals.

The function of channels is to allow selectivity and specificity for a Variety of molecular species transport across the cell membrane (Hornig et al. 2013, Rui et al. 2012). These channels, included: a) ligand-gated channels, b) voltage-gated channels, c) Second messenger gated channels, d) mechanosensitive channels, e) Gap junctions: porins not gated (Mollaamin et al. 2010, Lacroix et al. 2014).

The first step in understanding the physical mechanism of potassium transport through this protein nanopore is the determination of the water molecular distribution along the axial length of the pore Ion channels which are membrane proteins that mediation flux between the outside of the cell through a small, water-filled hole in the membrane-a pore. Ion- Selective pores were originally proposed to explain separate Components of Na^+ , K^+ and leak currents in the classic experiments of Hodgkin and Huxley (Chone 2002 , Lee. AG. 2004). Potassium channels are the most diverse group of the ion channel family (Hornig et al. 2013). The recent determination of the crystallographic structure a bacterial K^+ channel from *Streptomyces lividans* (KcsA) (Syeda et al. 2012) has provided the molecular basic for understanding the physical mechanisms controlling ionic selectivity, permeation, and transport through Various types of K^+ channels. (Mantegazza and Catterall 2012, Rui et al. 2012).

In all cases, the functional K^+ channel is tetramer (Mollaamin et al. 2010), typically of four identical Subunits folded around a central Port (Syeda et al. 2012). Voltage – gated potassium (Kv) channels are members of the voltage – gated ion channel superfamily (Hornig et al. 2013, Syeda et al. 2012), which is important for initiation and propagation of action potentials in excitable cells. They are composed of four identical or homologous Subunits, each containing six transmembrane segments: S1-S6. Segments: S1-S4 form the voltage-sensing domain (VSD), and segments S5 and S6 Connected by the P loop, which is involved in ion selectivity, Comprise the pore- forming domain (PD) S4 has four gating – charge- carrying arginines (R1-R4) spaced at intervals of three amino acid residues, which are highly conserved and are thought to play a key role in coupling changes in membrane Voltage to opening and closing of the pore (Mantegazza and Catterall 2012, Mollaamin et al. 2010). In the K_v channels 13 electronic charges across

the membrane electrical field per channel between the closed and open states (Lacroix et al. 2014, Vladimir et al. 2006). Arginine residues interacting with lipid phosphate groups play an important role in stabilizing the voltage- Sensor domain of the KvAP channel within a bilayer. Simulations of the bacterial potassium channel kcsA reveal specific interactions of phosphatidylglycerol with an acidic lipid-binding site the interface between adjacent protein monomers.

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 (Sonoda et al. 2011, Sansom et al.2005, Jafari-Dehkordi et al. 2015).

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 (Mollaamin et al. 2011, Cooke and Schiller 2008).

The repentance of the existence of buckminsterfullerene CNT (Kroto et al. 1985), theoretical speculation about carbon clusters (Mollaamin et al. 2011) over 36 years was finally verified. Since then, this beautiful molecule has attracted ever more attention of theoretical and experimental scientists. Some chemists began to focus their research on the chemistry of this molecule, but real fullerene chemistry began only after 1990. described a method for preparing macroscopic quantities of CNT (Oh et al. 2011).

Direct electron transfers between the electrode and the redox enzyme is very important for fundamental studies and construction of biosensors (Liang et al. 2010, Albareda-Sirvent and Hart 2001). However, the direct electron transfer between the enzyme and unmodified electrode is usually prohibited due to shielding of the redox active sites by the protein shells (Wang et al.2008, Mollaamin et al. 2010).

Therefore, several studies have been made to enhance the electron transfer. Mediators are widely used to access the redox center of an enzyme and then to act as the charge carriers. Mediators can minimize the effects of interferences, lower the operating potential of the electrodes, and improve the linear response range and sensitivity of the sensor (Zhang et al. 2005). Use of carbon nanotubes (CNTs) as mediators has attracted increasing attention in recent years. Comparing with traditional carbon electrodes, CNTs show unique properties, such as

good conductivity, high chemical stability, and catalytic activities towards many electrochemical reactions (Mollaamin et al. 2010, Wang et al. 2008, Liang et al. 2010, Manso et al. 2007, Jurkschat et al. 2006). More importantly, it is possible to bring the nanotubes close to the redox centers of the proteins (Gooding et al. 2003, Liu et al. 2003).

MATERIAL AND METHODS

Many studies have shown that the carbon nanotubes possess remarkable mechanical and physical properties leading to many potential applications such as fluid transport, fluid storage at nanoscale, and nanodevices for drug delivery. Since controlled experiments at the nanometer scale are very difficult, the simulation techniques have been widely and successfully used to investigate the mechanical property, wave propagation and resonant frequency (Natsukia et al. 2008). The vibration of molecules is best described using a quantum mechanical approach. A harmonic oscillator does not exactly describe molecular vibrations. Bond stretching is better described by a Morse potential and conformational changes have sine-wave-type behavior. However, the harmonic oscillator description is very useful as an approximate treatment for low vibrational quantum numbers (Youky et al. 2009).

A harmonic oscillator approximation is most widely used for computing molecular vibrational frequencies because more accurate methods require very large amounts of CPU time. Frequencies computed with the Hartree-Fock approximation and a quantum harmonic oscillator approximation tends to be 10% too high due to the harmonic oscillator approximation and lack of electron correlation (Fernandez et al. 2006). The high-frequency oscillations encountered using flexible water models are of the order of 3500 cm^{-1} which are somewhat larger than the CNT vibrational modes of 1500 cm^{-1} (Walther et al. 2001).

Hence, for this case study, the use of the flexible water and solvent model. Vibrational frequencies from semi-empirical calculations tend to be qualitative in (which) they reproduce the general trend mentioned in the Results here. However, the actual values are erratic. Some values will be close, whereas others are often too high. However, PM3 is generally more accurate than AM1.

Since periodic boundary conditions cannot be adopted, first principles calculations of finite-length SWCNTs are only affordable to relatively small systems with C atom number less than 300 within our present computational ability (Ma and Guo (2008).

The molecular mechanics method using the MM+ force field, and the Austin Model 1 (AM1) (Dewar et al. 1985) and Parameterized Model number 3 (PM3) (Stewart 1989) semi-empirical method within the Restricted

Hartree-Fock (RHF) formalism are sufficient to study carbon systems (Erkoc 2004). In 1989, Stewart improved the techniques of parameterization and published PM3, which gave lower average errors than AM1, are sufficient to study carbon systems, mainly for the enthalpies of formation (Stewart 1989).

Purpose of C60 is nanotube that includes 60 carbons. All calculations presented here were performed with semi-empirical Molecular mechanics (MM+) (Table 2).

In the first step of the calculations we optimized the geometry and defined Potential Energy of the nanotube structure by performing molecular mechanics calculation using MM+ force field, if too large a time step is used in Monte Carlo simulation, it is possible to have a basic instability in the equations that result in a molecule blowing apart, we need small time steps to preserve integration accuracy, however in the Monte Carlo time step 50 femtoseconds (0.05ps) was appropriate (Safi Najafabadi et al. 2015). In the next step we calculated the Vibrational modes of the tube by applying the semi-empirical molecular orbital method by the Hyperchem-7 package program (Hyperchem 7.0 2007).

RESULTS AND DISCUSSION

The resulting method was denoted, and in a sense, it is the best set of parameters (or at least a good local minimum) for the given set of experimental data. The optimization process, however, still requires some human intervention in selecting the experimental data and assigning appropriate weight factors to each set of data. As a reference Table 1 is the result of semi-empirical computation using both method AM1 & PM3. At the first glance in Table 1, it can be observed by increasing dielectrics, normal modes will move to upper normal modes ratio and Vibrational frequencies resulted from semi-empirical Calculations tend to be qualitative. Therefore, by increasing dielectric the higher frequency will be gained in which semi-empirical methods will have the same operating procedure (Mollaamin and Monajjemi 2015).

The PM3 and AM1 methods are also more popular than other semi-empirical methods due to the availability of algorithms for including salvation effects in these calculations. There are also some known strengths and limitations of PM3. Overall heats of formation are more accurate than with AM1. Hypervalent molecules are also predicted more accurately. On average, PM3 predicts energies more accurately than AM1. The heats of formation are more accurate than AM1 or PM3 depending on the nature of the system and information desired, they will often give the most accurate obtainable results for organic molecules with semi-empirical methods. On average, PM3 predicts energies and geometries better than AM1 (Christensen et al. 2016).

Table1a: Calculated Properties of CNT and binding to amino acids. (A) Electric Potential, (B) Electrostatic Properties, (C) Total atomic charges

CNT				(B) CNT-Ala-Gly				CNT-Val-Ala			
Atomic number	A	B	C	Atomic number	A	B	C	Atomic number	A	B	C
C ₁	-14.562	5.91621	0.049	N ₁	-18.293	6.77	-0.446	N ₁	-18.28	6.52	-0.25
C ₂	-14.562	5.91621	0.050	C ₂	-14.653	7.79	-0.107	C ₂	-14.65	7.76	0.02
C ₅	-14.559	5.91623	0.053	C ₃	-14.621	9.10	0.337	C ₃	-14.64	8.55	0.33
C ₆	-14.560	5.91621	0.051	O ₄	-22.238	9.32	-0.285	O ₄	-22.25	8.26	-0.33
C ₉	-14.56	5.91624	0.052	C ₅	-14.714	8.26	-0.413	C ₅	-14.71	8.78	-0.12
C ₁₀	-14.560	5.91625	0.052	C ₁₄	-14.744	6.07	-0.207	C ₆	-14.73	9.20	-0.42
C ₅₁	-14.567	5.91618	0.068	C ₅₆	-14.657	5.75	0.027	C ₇	-14.74	10.07	-0.40
C ₅₂	-14.568	5.91619	0.061	N ₆₆	-18.404	9.75	-0.406	C ₁₃	-14.69	5.52	-0.24
C ₅₅	-14.592	5.91619	0.040	C ₆₇	-14.735	8.57	-0.240	C ₆₆	-14.73	6.28	-0.10
C ₅₆	-14.588	5.91617	0.045	C ₆₈	-14.690	7.36	0.358	N ₆₈	-18.39	8.64	-0.63
C ₅₉	-14.604	5.91634	0.022	O ₆₉	-22.367	7.65	-0.429	C ₆₉	-14.72	7.89	-0.11
C ₆₀	-14.607	5.91634	0.025					C ₇₀	-14.69	7.51	0.31
								O ₇₁	-22.35	7.89	-0.40
								C ₇₂	-14.77	8.95	-0.37
CNT- Ala-Leu				CNT-Ser-Thr				CNT-Gln-Asn			
Atomic Number	A	B	C	Atomic number	A	B	C	Atomic number	A	B	C
N1	-18.301	7.33	-0.393	N ₁	-18.30	7.14	-0.50	N ₁	-18.264	6.30	-0.469
C ₂	-14.673	7.85	-0.188	C ₂	-14.67	8.09	-0.10	C ₂	-14.664	7.48	-0.047
C ₃	-14.651	9.29	0.322	C ₃	-14.64	8.44	0.36	C ₃	-14.666	7.53	0.339
O ₄	-22.260	9.85	-0.310	O ₄	-22.23	7.99	-0.25	O ₄	-22.257	6.68	-0.386
C ₅	-14.765	7.20	-0.399	C ₅	-14.67	9.46	-0.01	C ₅	-14.728	8.71	-0.236
C ₆	-14.683	7.85	0.135	O ₆	-22.31	10.44	-0.59	C ₆	-14.733	9.94	-0.351
C ₆₀	-14.776	5.48	-0.172	C ₈	-14.71	5.85	0.30	C ₇	-14.733	11.19	0.513
N ₆₆	-18.382	8.94	-0.368	C ₆₁	-14.69	5.97	0.03	O ₈	-22.361	11.23	-0.453
C ₆₇	-14.714	7.86	-0.116	N ₆₇	-18.42	8.89	-0.46	N ₉	-18.329	12.34	-0.718
C ₆₈	-14.729	6.50	0.3 62	N ₆₈	-14.70	8.05	-0.12	C ₁₅	-14.776	6.32	0.020
O ₆₉	-22.364	6.59	-0.452	C ₆₉	-14.68	6.94	0.04	C ₆₉	-14.649	5.53	0.101
C ₇₀	-14.743	8.23	-0.231	O ₇₀	-22.30	6.94	-0.34	N ₇₀	-18.412	9.61	-0.423
C ₇₁	-14.735	7.38	-0.133	C ₇₁	-14.64	7.63	-0.03	C ₇₁	-14.726	8.39	-0.136
C ₇₂	-14.771	7.57	-0.389	O ₇₂	-22.17	6.91	-0.47	C ₇₂	-14.714	7.20	0.175
C ₇₃	-14.756	8.17	-0.395	C ₇₃	-14.74	8.989	-0.38	O ₇₃	-22.346	7.53	-0.320
								C ₇₄	-14.728	8.61	-0.344
								C ₇₅	-14.619	7.57	0.561
								O ₇₆	-22.335	6.55	-0.470
								N ₇₇	-18.309	8.02	-0.711

There is energy of interaction in between solvent and solute. Therefore, the solute properties dependent on energy, such as geometry, total energy and vibrational frequencies depend on the solvent. The presence of a solvent, particularly a polar solvent, can also stabilize charge separation within the molecule. This not only changes the

energy, but also results in a shift in the electron density and associated properties. In reality, these are the result of the quantum mechanical interaction between solvent and solute, which must be averaged over all possible attitudes of solvent molecules consistent with the principles of statistical mechanics. The results of the CNT-amino acids

Table 1b: Calculated Properties of C60 and binding to amino acids.
(A) Electric Potential, (B) Electrostatic Properties, (C) Total atomic charges

CNT-His-Pro				CNT-Lys-Arg			
Atomic number	A	B	C	Atomic number	A	B	C
N ₁	-18.421	10.12	-0.502	N ₁	-18.340	6.28	-0.593
C ₂	-14.757	8.93	-0.054	C ₂	-14.753	7.43	-0.065
C ₃	-14.713	7.67	0.321	C ₃	-14.769	7.96	0.178
O ₄	-22.380	7.92	-0.414	O ₄	-22.375	7.54	-0.398
C ₅	-14.800	9.29	-0.253	C ₅	-14.751	8.66	-0.255
C ₆	-14.798	10.82	-0.276	C ₆	-14.732	9.86	-0.282
C ₇	-14.769	11.22	-0.140	C ₇	-14.652	11.10	-0.120
N ₈	-18.322	6.66	-0.608	N ₈	-18.228	12.30	-0.649
C ₉	-14.690	7.78	-0.063	C ₉	-14.496	13.51	0.863
C ₁₀	-14.702	9.04	0.182	N ₁₀	-18.215	13.80	-0.728
O ₁₁	-22.316	9.14	-0.392	N ₁₁	-18.218	14.54	-0.741
C ₁₂	-14.694	8.25	-0.288	C ₁₇	-14.771	6.44	-0.159
C ₁₃	14.619	9.55	0.276	C ₇₀	-14.761	5.38	0.052
N ₁₄	-18.192	10.31	-0.679	N ₇₂	-18.513	9.18	-0.514
C ₁₅	-14.633	10.36	0.149	C ₇₃	-14.797	8.59	-0.123
C ₁₆	-14.564	11.42	0.411	C ₇₄	-14.728	7.48	0.371
N ₁₇	-18.187	11.46	-0.679	O ₇₅	-22.350	7.22	-0.447
C ₁₉	-14.698	5.48	0.186	C ₇₆	-14.795	9.74	-0.236
C ₇₃	-14.774	6.36	-0.217	C ₇₇	-14.778	9.46	-0.234
				C ₇₈	-14.718	10.81	-0.271
				C ₇₉	-14.637	10.84	-0.207
				N ₈₀	-18.155	12.24	-0.680

cluster simulation can be used to analyze the energetic aspects which are associated with the process of introducing a CNT fullerene from the gas phase into different amino acids (Table 2 and Fig 1).

The net result clearly indicates that the process of introducing a CNT to different amino acids energetically is remarkable. Whereas a molecular mechanics potential used to characterize the response of a SWCNT which allows long

Table 2: Semi empirical Calculations for CNT and conjunction to amino acids.

	C60 Nanotube	C60- Ala-Gly	C60- Ala-Leu	C60- Val-Ala	C60- Gln-Asn	C60- His-Pro	C60- Lys-Arg	C60- Phe-Tyr	C60- Ser-Thr	C60- Trp-Pro
Total Energy (kcal/mol)	-207257	-254702	-273475	-188038	-298292	-291066	739779.4	789947	573814.9	831669.4
Binding Energy (kcal/mol)	-37784.3	-45141.8	-50207.3	32104.26	-52071.7	-52672.9	993483.9	1046278	804308.2	1083965
Electronic Energy (kcal/mol)	-2069240	-2722240	-3106366	-2914485	-3373457	-3256055	-2520644	-2590608	-2239658	-2639509
Rotation Frequency	352.31	361.96	358.71	3773.92	352.64	369.47	251.51	1816.71	-3825.72	1864.92
Rotation Intensity	0.064	1.285	0.347	8.368	0.315	1.969	1.6	2.669	2.892	5.153
ΔE	-2283.99	-2739.14	-2895.54	-2857.42	-3154.71	-3082.21	-3235.42	-3315.58	-2967.73	-3226.15
Dipole moment	4.1475	11.759	3.2852	8.2113	14.002	32.3063	33.2251	6.3174	6.7668	8.1059

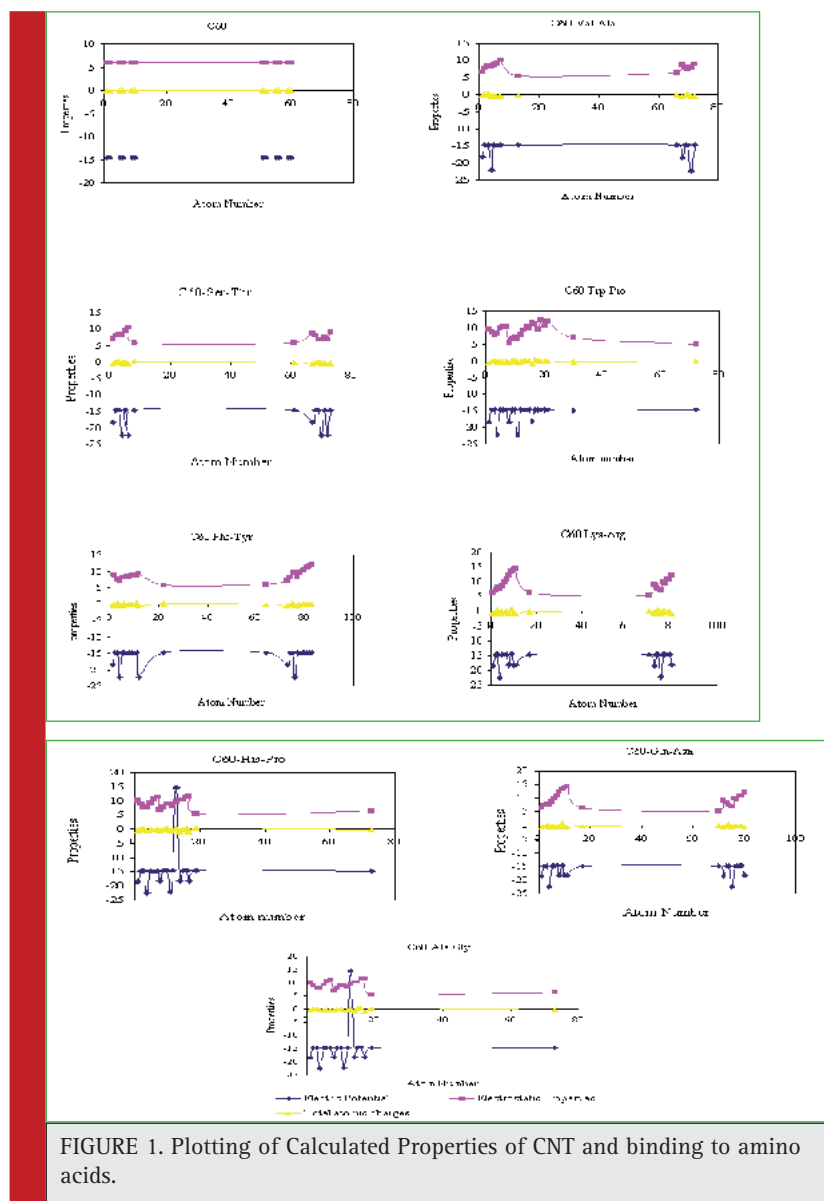


FIGURE 1. Plotting of Calculated Properties of CNT and binding to amino acids.

range interactions between atoms, results in Molecular Mechanics force field which indicates that potential energy is maximum and also the potential energy will increase.

CONCLUSION

To reconstruct membranous proteins, we used simulated nanotubes in order to transfer ions across the membrane and transfer of ions was done successfully. In this study the more the potential energy increases the more the conductivity of nanochannels decreases and we chose the least energy among nanotube and amino acid complexes. And also the more energy we use, the more conductivity we will have; therefore, we choose the complex which conducts the most current. was observed most

changes of Rotation Intensity and Rotation Frequency in the CNT-ALA-VAL and CNT-SER-THR complexes. Also we found maximum of Dipole moment (Debye) in the CNT-LYS-ARG and CNT-HIS-PRO complexes. Minimum of ΔE for the CNT-PHE-TYR obtained. This way we can simulate the channels which have hereditary defects and are not efficiently and can observe the fundamental cure of the diseases.

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