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Coarse Grained Molecular Dynamic Simulations of the interaction a Carbon Nanotube with a Bilayer Membrane

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ABSTRACT

In coarse grained molecular dynamics (CGMD) simulations, small groups of atoms are treated as single particles (beads) and the forces between these particles are derived from the interatomic forces. The effect of this is to severely reduce the number of particles in a simulation, thereby allowing for the consideration of a larger number of atoms. It has also proven to be a valuable tool in probing time and length scales of systems beyond that used in all-atom molecular dynamics (AAMD) simulations. The down side of this is that the inter-particle interactions are less accurate. However, if these coarse grained particles are chosen carefully, such simulations can provide much useful information. There are different levels of how the coarse grains are constructed. For example, CG systems have been developed using tens or hundreds of atoms per CG bead in some studies of amino acids in biological science. By contrast, for other systems, a single CG bead is used to replace just two or three atoms.

In this paper, the interaction of a carbon nanotube (CNT) with a lipid bilayer membrane is studied using both coarse grained and atomistic MD in an effort to understand the usefulness of the CGMD method for such simulations. Our preliminary studies of the interaction of a CNT with a lipid bilayer points indicates that such nano-tubes inserted into a membrane could be stable. This means that it could be used as an agent in the delivery of drugs. It would be good if these simulations could be repeated using AAMD simulations to confirm the validity of these results.

INTRODUCTION

In recent years there has been much interest in developing drug delivery systems which are both specific in design and localised in delivery. Nanoparticles of various types have been touted as the appropriate agency for such systems. This has resulted in suggestions that CNTs could act as the agency for such applications. In order for this to be successful, it is important to understand the interactions between CNT and the bilipid membrane layers surrounding the biological cell. The penetration of a CNT into biomolecular cells such as a lipid membrane have also been confirmed experimentally, although the mechanism of how they pass through cells still is not well understood [1].

Membrane bilayers can be supported by CNTs in order to increase its structural stability to make for a mechanically strong surface. Carbon nanotubes can penetrate inside mammalian cells without any external help or can be inserted manually into a lipid membrane. Nevertheless, intercalcated carbon nanotubes on a lipid membrane are not yet realizable. Because of this, the interaction between CNT and lipid membranes is a growing area of interest. The complex structure of lipid membranes and its fluidity makes experiments at a molecular or cellular level intensely challenging. This has led to many computer simulation studies aimed at understanding these interactions.

The interactions between lipid bilayers and carbon nanotubes have been studied by computational methods by many researchers [2]. Much of this work has been in the context of developing nano-injectors for drug delivery and gene therapy into cells and for building novel biomaterials [3]. It has been reported in AAMD simulations that open-ended single-walled carbon nanotubes penetrate into a membrane and in so doing, destroy the structure of the lipid bilayer. By contrast, it appears that capped single-walled carbon nanotubes causes less destruction to the lipid structure. The impact of a carbon nanotube on the structure of a cholesterol molecule on a protein has also been investigated [4] where it was found that it forms a layer around the protein.

In this paper, we report on our investigations studying the interactions between a carbon nanotube and a lipid bilayer membrane using CGMD simulations. Specifically, we have studied the energy optimization of the complex system comprising a CNT and a 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) membrane in aqueous solution. The simulations were carried out using the NAMD package [5]. The stability of the CNT was analysed by determining the root-mean-square-deviation (RMSD), the force between lipid bilayer and the CNT throughout the simulations, and the tilt angles of the CNT with respect to the normal axis of bilayer. The resulting data was also analyzed using the Visual Molecular Dynamics (VMD) package [6] to confirm the structural changes seen during MD simulations at finite temperatures. The main purpose of these investigations was to obtain an understanding of the interaction of a CNT with a POPC lipid membrane.

SYSTEM AND COMPUTATIONAL METHOD

The CG structure of the POPC lipid and CNT

In this work, classical CGMD simulations of a system comprising a POPC lipid membrane bilayer and a CNT, all solvated in water at 300 K, were carried out. VMD was used to build the periodic (POPC) membrane bilayer with size 50Å × 50Å. VMD automatically builds a water shell around the lipids in order to properly hydrate the lipid headgroups. The Martini model [7] was used to specify the CG interaction sites of the POPC bilayer with an approximate 4:1 mapping. The beads or particles in the CG structure were characterised by their polarity, hydrophobicity, and charge and were assigned particle types (e.g. P_1, P_2, C_1, C_2, Q_a, Q_d, ..etc). Figure 1 shows an example of the resulting Martini-designed CG lipid. The water molecules were mapped with the ratio of 4 water molecules to 1 CG particle. These particles were assigned a P_4 type as explained in Marrink [7].

VMD was also used to build a zigzag (10, 0) carbon nanotube (CNT) with a diameter 7.82Å with a relatively short length of 30Å. The CNT comprised 320 atoms, 470 bonds, 920 angles and 1800 dihedrals. Then, in order to construct the CG CNT structure, 4 carbon atoms were mapped onto 1 CG bead, as shown in the Figure 2. The CG CNT structure thus comprised 80 particles bonded together through the harmonic potential with a force constant of 5.9752 kcal $mol^{-1}Å^{-2}$ to sustain the geometry of the nanotube. In this study, apolar (C) particle types were used to describe the carbon atoms with hydrophobic properties [7]. Parameters for the Martini force field as applied to the CG CNT were taken from Monticelli et al [8] and Wong-Ekkabut et al [2]. To construct the final combined system, the CNT was manually placed into the center of the POPC bilayer using VMD (Figure 3).

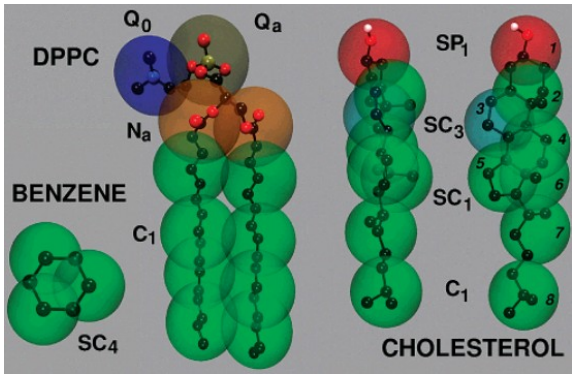

Figure 1: Mapping between the AA and CG model for benzene, the phopholipid Dipalmitoylphosphatidylcholine (DPPC) and the cholesterol molecules.

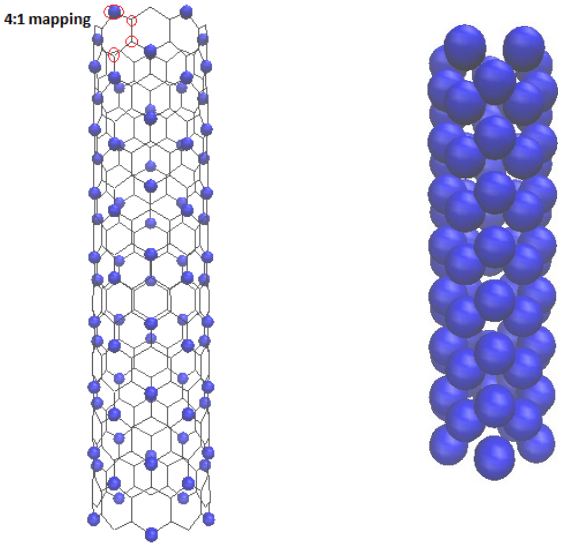

Figure 2: Showing the 4:1 mapping used in constructing the CNT.

Interaction potentials

The interaction potentials between coarse-grained (CG) beads are simplified and do not include bending or torsional interactions. They were allowed to interact with each other via the non-bonded potential functions. The bonded interactions were treated using the same approach as used in atomistic simulations. Electrostatic interactions were taken into account for charged beads. The important point is that CG simulations are used to provide a collective description of observed phenomena using only significant interactions.

Simulation Details

The MD simulations was performed in the NPT ensemble at temperature of 300 K and Langevin dynamics was used to control the temperature. The pressure was set at 1.01325 bar.

The cutoff distance for all non-bonding atom interactions was set to 12Å. The simulation cell was a tetragonal box with axes, x = 50Å, y = 50Å and z = 93Å.

For all the structures an energy minimization (optimization) using the conjugate gradient method was carried out to optimize the structure for 2000 time steps. This was to ensure that any overlap of particle positions were removed. After this, the system was allowed to run for 300 ns with a time step of 10 fs (3×10^8 steps). Finally, the results of the simulation were analyzed using VMD.

The main feature of the CG approach is that it is faster than AAMD simulations. For example, in a simulation of water, 4 water molecules each comprising 3 atoms can be replaced by a single CG water bead. Additionally, the time step in the simulation can be increased by a factor of 10 or 15. So, in this example, a CGMD simulation would give a computational speed-up of the order of about 100 over the AAMD simulation.

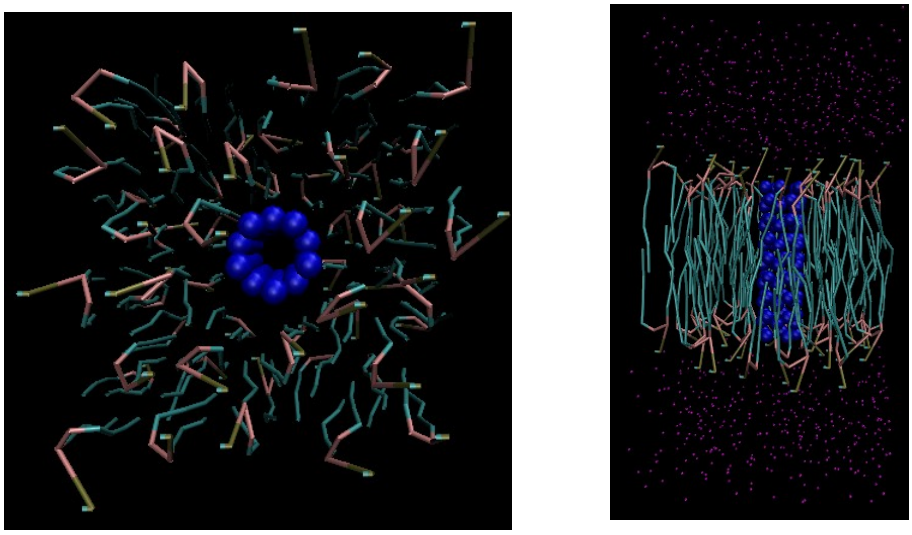

Figure 3. The CNT (coloured blue) inside the bilipid membrane (head groups coloured pink and tail groups coloured cyan) as seen in the *x*-*y* plane (left) and from the *x*-*z* plane (right).

RESULTS

Test results on the protein Ubiquitin (UBQ)

Before carrying out the CGMD simulations on the CNT-POPC membrane system, we tested the usefulness of the potential parameters by simulating the equilibrium structure of the UBQ protein molecule using both CGMD and AAMD. In doing this we found that the speed up was of the order of 100. In comparing the two resulting equilibrium structures using VMD, we found that both structures were very similar, giving confidence in the usefulness of the CGMD simulations for such systems. More interestingly, the CG structure equilibrated far more quickly than the AA structure.

Structure of the CNT in the POPC bilayer

The CGMD simulations of the system consisting of the POPC membrane and a

single CNT in a CG water solution were carried on the initial structure as shown in Figure 3. This structure was allowed to relax so as to minimize its energy which also removes any steric interactions between the particles. Then, CGMD simulations were carried out as described above and by monitoring the average temperature of the system during the simulation run, we confirmed that the temperature was stable around the initial temperature of 300 K.

The structure of the molecules at four different time steps during the course of the simulation are shown in the Figure 4. It can be seen that the impact between biological membrane and the CNT results in an initial movement of the latter. After 5 ns into the simulation, the CNT is seen to move and tilt away from its vertical starting position. However, this does not affect the stability of the CNT in the bilayer. Instead of forcing itself out, the CNT does remain intact within the membrane. That the CNT was stable in the membrane for the remainder of the simulation points to the stability of the system and suggests that such a system could be used for drug delivery as suggested by other researchers.

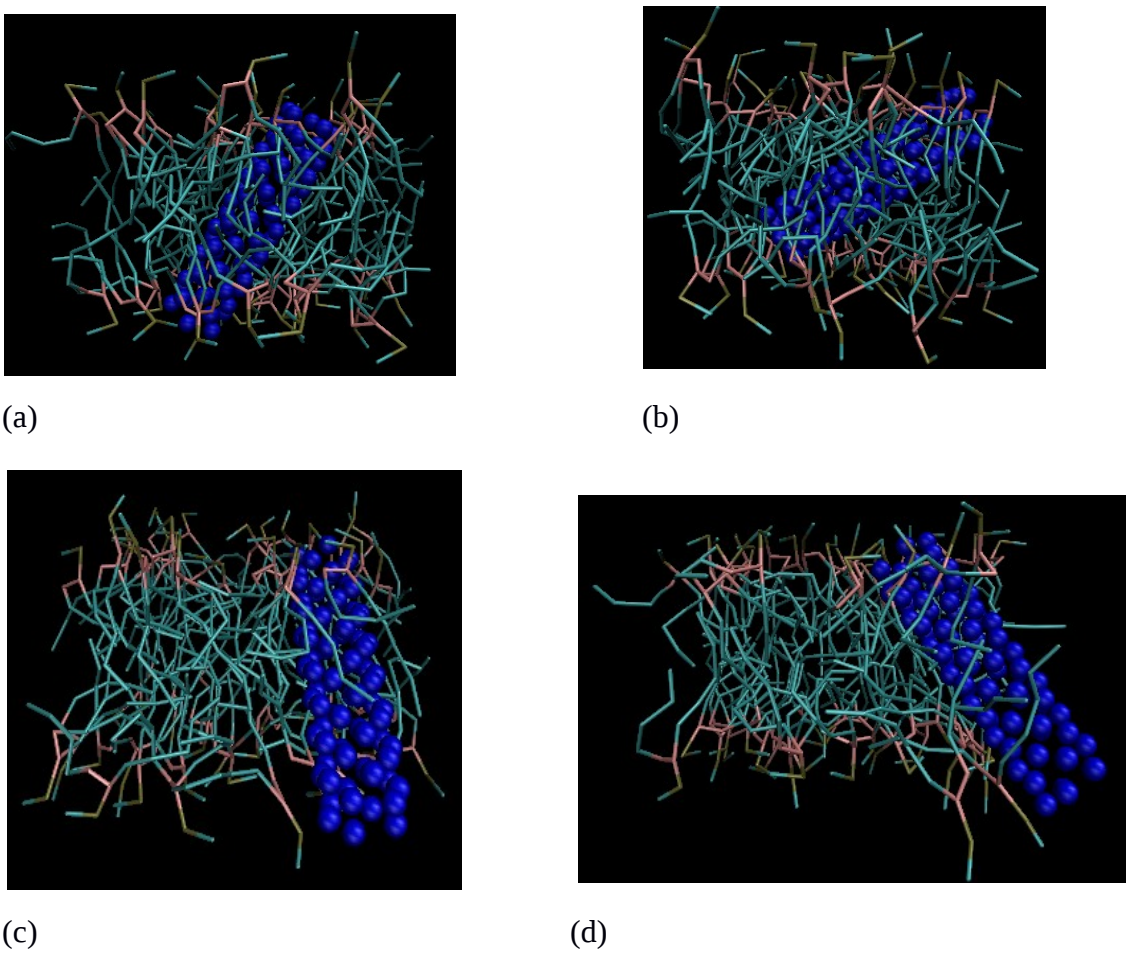

Figure 4: The structure of the CNT inside the POPC membrane (side view as in Figure 3) after (a) 5 ns, (b) 20 ns, (c) 200 ns and (d) 300 ns .

It is also of interest to see what happens to the the thickness of the lipid bilayer as this provides a test of the robustness of the lipid bilayer [9] . Because the temperature of the

simulation was set to be 300 K, any increase in energy resulting from the initial placement of the CNT could lead to a local melting of bilayer and could be manifest in the thickness measurement. The initial thickness of the lipid bilayer was taken to be 35.5 ± 0.4 Å which is in agreement with the experimental values of Kucerka et al [10] and consistent with the value used in other MD simulations. We also find that the bilayer thickness varies very little with MD simulation time. We have also monitored the RMSD values which are a measure of the robustness of the structure and the root mean square fluctuations (RMSF) which gives information on the relative stability of the residues in biological molecules. The RMSD confirms that the CNT embedded in the membrane is a stable structure and similarly the RMSF values point to the relative stability of the residues. The tilt angle between the CNT and the normal axis of lipid bilayer membrane was calculated to be 50^0 . Interestingly the CNT appears to oscillate with small amplitude during the course of the simulations.

CONCLUSIONS

We have used both AAMD and CGMD to simulate UBQ protein. A comparison of the results in structures are similar enough to give confidence that CGMD is a useful tool in carrying out simulations of large bio-molecular systems. Based on the results of the UBQ protein, it is clear that CGMD is computationally much faster than AAMD allowing for the simulation of large systems for longer time scales.

CGMD was used to simulate the interaction of a CNT embedded in a POPC bilayer cell membrane. The results of our preliminary studies suggests that such nano-tubes inserted into the membrane could form a stable structure. This means that such a system could be used as an agent in the delivery of drugs. We are currently carrying out AAMD simulations to confirm the validity of these results for the CNT in bilayer membranes.

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