**Constructing a Bilayer Model of α-tocopherol for Molecular Dynamics Simulation in CHARMM**

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**Introduction**

The method of molecular dynamics (MD) simulations is one of the principal tools in the theoretical study of biological molecules. With the availability of parallel supercomputer clusters, the power of MD simulation has greatly increased to allow the study of complex, dynamic processes in model cell membranes. In this study, we used the program CHARMM to examine specific interactions of α-tocopherol (Vitamin E) in a phospholipid bilayer system. In this paper, we describe the development of force field parameters for CHARMM based on density functional theory (DFT) calculations on isolated α-tocopherol molecules and the development of the CHARMM force field parameters for α-tocopherol in a DPPC bilayer. We have successfully simulated α-tocopherol in a DPPC bilayer. These results provide a baseline for comparison with planned simulations of α-tocopherols in DMPC and DMHPC bilayers containing high amounts of polyunsaturated lipid.

**α-tocopherol**

α-tocopherol, which has the highest bioavailability among all eight forms of vitamin E, is the most important lipid-soluble anti-oxidant. Dr. Herbert Muncin Evans discovered vitamin E in 1932, owing to its significance in rats' fertilization. Many current studies are interested in tocopherol for its noticeable medical impact on heart diseases, cancer, Glaucoma, and age-related diseases, such as macular degeneration and Parkinson’s disease. In a biochemical view, tocopherols protect cell membranes from oxidation by reacting with lipid radicals produced in the lipid peroxidation chain reaction.

**CHARMM**

The CHARMM program is a research program developed at Harvard University for the energy minimization and dynamics simulation of proteins, nucleic acids and lipids in vacuum, solution or crystal environments. The core of the program is based on the empirical potential energy function:

\[ V(R) = \sum E_{\text{bonded}} + \sum E_{\text{non-bonded}} \]

This study was carried out using CHARMM Version 22a6, which was operated via Red NIC Series at 48-prisoner parallel supercomputer.

**Potential Energy Function**

The energy, \( E \), is a function of the atomic positions; \( R \) represents all the atoms in the system. \( E \) is usually expressed in terms of Cartesian coordinates. The value of the energy is calculated as a sum of potential or restrained terms:

\[ E(R) = \sum E_{\text{bond-stretch}} + \sum E_{\text{angle-bend}} + \sum E_{\text{dihedral}} \]

\[ E_{\text{bond-stretch}} = k(R - R_0)^2 \]

\[ E_{\text{angle-bend}} = k(\theta - \theta_0)^2 \]

\[ E_{\text{dihedral}} = n \sum A_i \cos\left(\frac{2\pi}{n} \phi + B_i \right) + C_i \]

**Building α-tocopherol**

Topology and parameter files are two fundamental data structures that contain basic information about the a molecule in CHARMM program. The residue topology file (RTF) contains definitions of the molecular building blocks, such as the names of atoms, masses, partial charges, and connectivity. The parameter file (PDB) is associated with the RTF file as it contains all necessary parameters for energy calculations, including the equilibrium bond distance for stretching, angle bending, and dihedral angles of particular atoms.

**Template with Cholesterol**

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\[ V(R) = \sum E_{\text{bonded}} + \sum E_{\text{non-bonded}} \]

This study was carried out using CHARMM Version 22a6, which was operated via Red NIC Series at 48-prisoner parallel supercomputer.

**Periodic Boundary Conditions**

Periodic boundary condition enables a simulation to be performed using a relatively small number of particles in such a way that the particles experience forces as though they were in a larger system surrounded by eight neighbors. Forces on the primary particles are calculated from particles within the same box as well as in the image box. As a particle moves out of the simulation box, a new image is chosen at random from the set of images that is a shift of the primary particle in the box. A periodic boundary condition is truly implemented if the force is zero on the particle when it moves in to replace it.

**Bilayer with α-tocopherol**

By reading in the topology and parameter files of α-tocopherol, the cholesterol molecules were replaced at the positions located previously. Snapshots below show the movement of α-tocopherols in the DPPC bilayer at different time-dependent stages. The qualitative trend that α-tocopherols were becoming more disordered has been observed.

**Future Work**

Further quantitative analyses of the interactions within this phospholipid bilayer system require a remarkable accumulation of data. Our expected future work is to include the unstructured α-tocopherols in the model, including their random distributed positions in the bilayer.

**References**

2. Feller, S. E.; Pastor, R. W.; Rojnuckarin, A.; Bogusz, S.; Brooks, B. R. Molecular dynamics simulations can be time consuming and computationally expensive, because this method generates microscopic information for each atom. By applying the Ergodic hypothesis, unexpectedly relevant information concerning structural, dynamic and thermodynamic properties may be calculated using a feasible amount of computer resources.
3. \( \dot{\mathbf{x}}(t) = \frac{d\mathbf{p}(t)}{dt} \)
4. \( \mathbf{p}(t) = m \mathbf{x}(t) \) for rigid body with neglectable temperature.
5. \( \mathbf{p}(t) \) is the momentum vector.
6. \( \mathbf{m} \) is the momentum.
7. \( \mathbf{x}(t) \) is the position vector.
8. \( \mathbf{F}(t) \) is the total force.
9. \( \mathbf{F}(t) = \frac{d\mathbf{p}(t)}{dt} \)
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11. \( \mathbf{m} \) is the momentum.
12. \( \mathbf{x}(t) \) is the position vector.
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