STUDY OF MIXED LIPID BILAYER SYSTEM USING MOLECULAR DYNAMICS SIMULATION

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STUDY OF MIXED LIPID BILAYER SYSTEM USING MOLECULAR DYNAMICS SIMULATION

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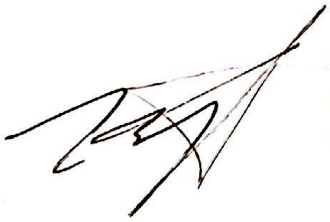

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CHAPTER 1

INTRODUCTION

For most of the pharmaceutical industry's existence, there have been many efforts to develop a cure for treating cancer.[1] However, we are still years away from any possible cure for cancer, and available treatments have many obstacles to overcome.[2] Specifically, chemotherapy has significant issues in delivering the required dosage of drugs to the cancer site. One of the disadvantages is that large amounts of drugs are required to be injected in order to overcome various obstacles including the circulatory system.[3] However, due to toxicity, there is a limitation on the administered dosage allowed.[1, 2, 3, 4, 5]

To solve this problem, smart drug delivery systems have been developed. Encapsulating chemotherapy drugs inside synthesized carriers such as liposomes can reduce toxicity by shielding the drug from contacting healthy cells.[5] One of the goals is to create a type of release mechanism at the cancer site. Releasing a chemotherapy drug at a specific site will make it possible to deliver appropriate doses of drugs without causing high toxicity.[6] To study how carriers act inside the body, Molecular Dynamics (MD) simulation can be incorporated.

Introduction to Molecular Dynamics Simulation

Previous research has shown that finding the proper structure for liposome is one of the profound challenges.[7] The general goal is to run a computer simulation with the desired composition of lipid bilayer. The innovative part of this experiment is to provide the most desired structure and see the data from different structures with set temperature.[8] For this project, a thermal sensitive lipid bilayer system, with DiPalmitoylPhosphatidylCholine (DPPC) and MonoPalmitoylPhoshatidylCholine (MPPC), has been chosen due to the highest specificity of the releasing site by using localized heating methods (ultrasonic or microwave). Because of the

thermal sensitive nature of the lipid bilayer system, the lipid molecule must have an acceptable liquid-crystalline transition temperature with great increase in permeability.[7, 8] Currently, the team has gathered information from the molecular dynamics simulations of DPPC and MPPC. Much research has been done for the DPPC and MPPC models. Validation of this data will prove the data from simulation. For the future, since much research is needed for the mixed system, the study will be conducted using this data to run molecular dynamics simulations on the mixture system.

CHAPTER 2

MATERIALS AND METHODS

Materials for Molecular Dynamics Simulation

For the MD simulation, many of the programs based on Linux system have been used to create models, energy minimize the models, distribute charges to the models, and run multiple simulations. Prior to any steps, molecules should be created by using the program called Cerius 2. Energy minimization is a required step to reduce any future error. In addition, the program called Maestro contains a subprogram called Jaguar where models can be assigned with specific charges.

Methods for Molecular Dynamics Simulation

There are five main steps to perform MD simulation. Figure 1 represents the basic five steps: creating molecules, distributing the charges, calculating molecule-molecule interaction, performing MD study, and creating mixture of the molecules.

Creating Molecule

First, the selected molecule will be drawn in atomic sketch by using Cerius 2. 3D sketcher function in the Cerius 2 can be used to create molecules. Then, desired force field file should be loaded to the specific structure. By using the energy minimization function, it is recommended to reduce energy to reduce any risk of error later on. The energy minimized molecule should be saved as .bgf file to distribute the charge.

Distributing the Charges

The atomic charge of each atom in the molecule will be calculated by Density Functional Theory (DFT) B3LYP with a basis setting of 6-31G** using a program called Jaguar. This will give the total and individual optimization electric charge and geometric configuration for the molecule.

Molecule-Molecule interaction

After the atom has been optimized, the geometric optimization packing between molecules needs to be found in order to create a mega structure. Figure 2 represents the images of molecules and a mega structure. By applying the force field calculations, this procedure can be accomplished by using Cerius 2. This will calculate the molecule-molecule interaction to find the most thermodynamically stable geometric shape and the distance between molecules.

Molecular Dynamics Study

After creating the required structure with Cerius 2, molecular dynamics simulations can be completed by increasing temperature in the system. With various temperatures, the structure shape alteration can be observed. The structure shape alteration at different temperature will discern the transitional temperature that will determine the required temperature for the liposome to release the drugs.

Mixture of the molecules

After MD simulations, the lipid areas found will be used to compare with other peer-reviewed articles and experimental values to prove that the results are feasible. When the comparison is done, creating the mixture of the two different molecules (DPPC and MPPC) with a certain ratio in a simulation box will be the next step.

CHAPTER 3

RESULTS AND DISCUSSION

From verified models, different compositions and structures of mixed lipid bilayer with water were created. In order to know which geometric configuration for mixed system is appropriate, island structure and dispersed structure were proposed. An island structure is primarily composed of MPPC forming an island surrounded by DPPC, whereas a dispersed structure forms a well-distributed pattern of MPPC and DPPC. Then, for each structure, different compositions of DPPC and MPPC were considered. In addition, for each of the structures, different temperatures composed of 300K, 310K and 320K were selected to see difference among them. First, 50 percent DPPC and 50 percent MPPC structure and 75 percent DPPC and 25 percent MPPC were chosen to study its behavior in 300K temperature.

After running 4 ns of the each structures, data resulting from 75:25 structure were then analyzed using density profile and interfacial tension profile to observe any structural changes. However, from figure 4, some of the data points seemed inaccurate where density was higher than expected along the water section. After running some tests and close observations, the problem occurred in inaccuracy of DPPC model. It is found that previous team members made a mistake when making DPPC model. The team had to create a new DPPC model and validate the structure.

Then, new compositions were selected including 50 percent DPPC and 50 percent MPPC, 80 percent DPPC and 20 percent MPPC, and 90 percent DPPC and 10 percent MPPC. Figure 3 represents different compositions of DPPC and MPPC mixed structures. Each of the compositions will have an island structure and a dispersed structure and three different temperatures composed of 300K, 310K, and 320K. Then, each of the structures were submitted to run simulations. Unfortunately, using full atomistic models is demanding and takes two to three weeks for each of the structures.

CHAPTER 4

CONCLUSION AND FUTURE PLANS

From various results, it is believed that a different structure and different composition are important factors when studying permeability and stability of mixed lipid bilayer. Water molecules are deemed to interact with the lipid bilayer. This creates a hydrophobic and hydrophilic attraction to the lipid heads and tails, respectively. Even though the DPPC model had an incorrect structure issue, the team managed to create structure and run the simulation for each of the structures with water. Each of the models is currently running at temperature of 300K with water. From next semester, results for each of the structures should be ready to be analyzed to show definite structure changes. The results should be agreed with experimental values to validate the findings.

APPENDIX: LIST OF FIGURES

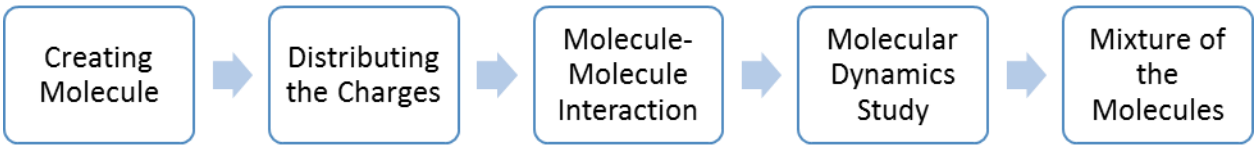

FIGURE 1 | Flowchart for MD Simulation

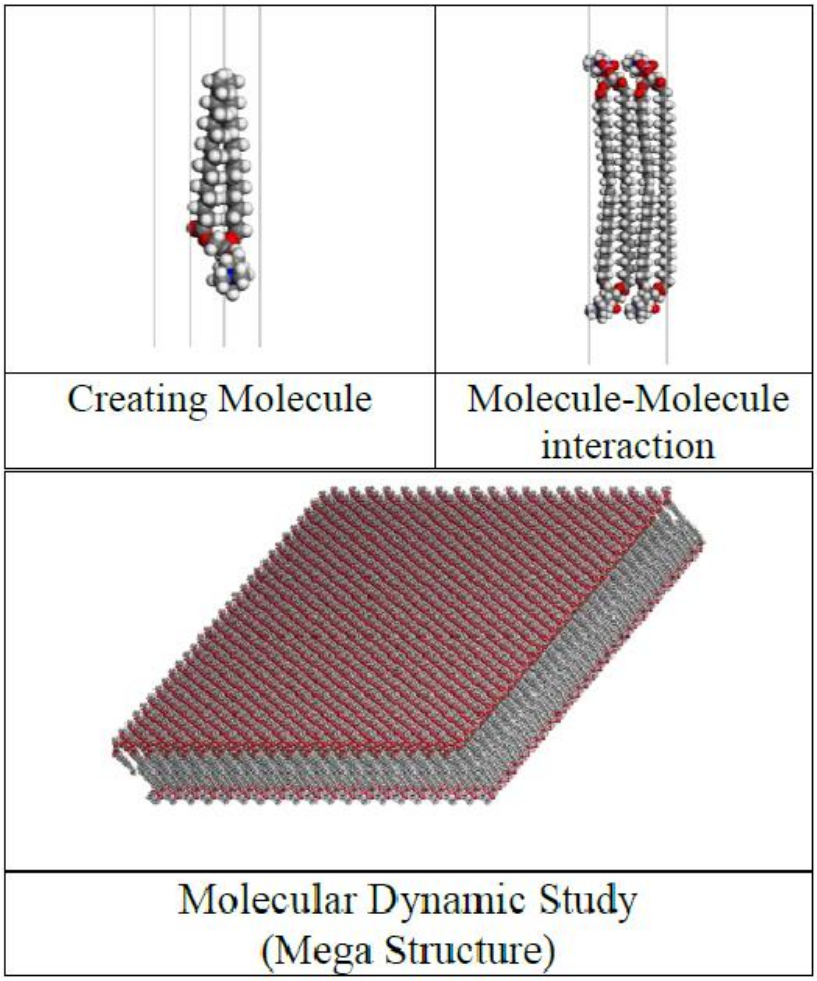

FIGURE 2 | Representative Figure for Making Molecules

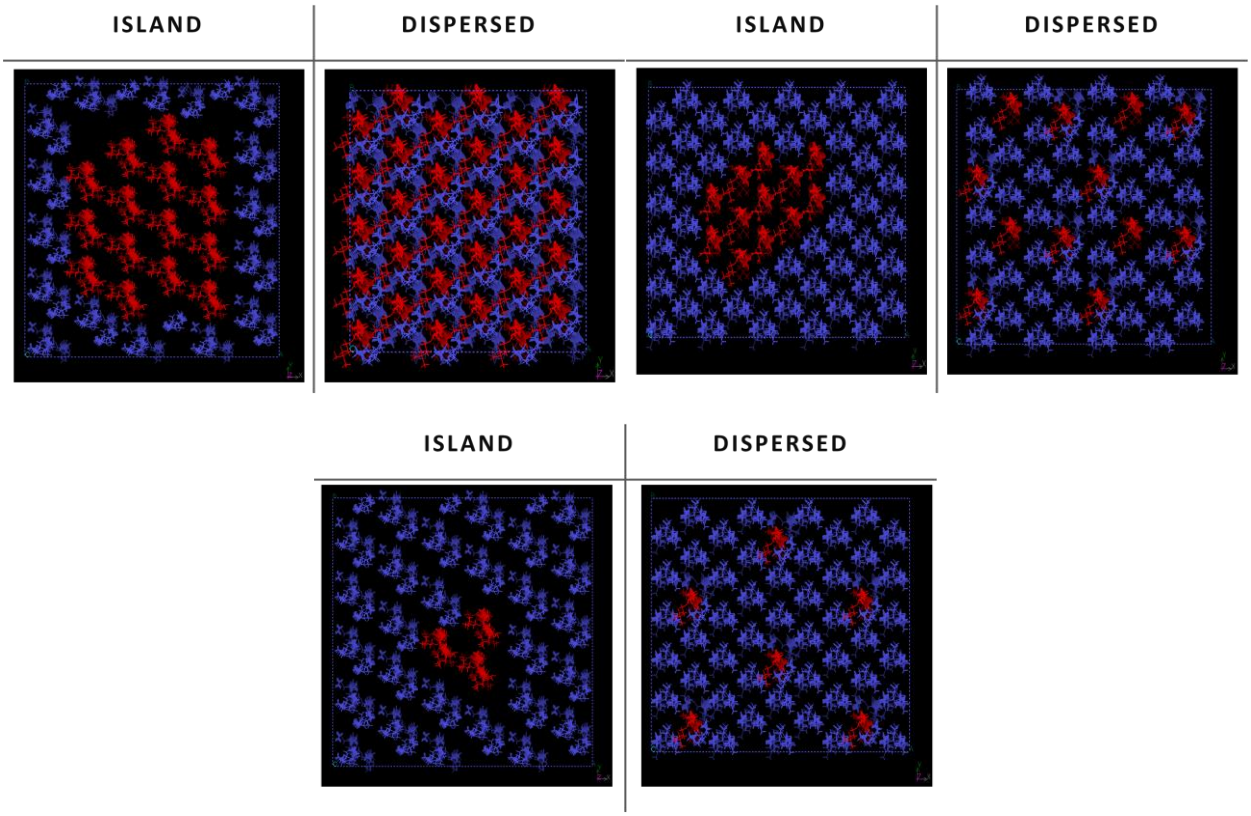

FIGURE 3 | Different Compositions of DPPC and MPPC Mixed Structures Top left pictures are the 50 percent DPPC with 50 percent MPPC island and dispersed structures. Top right pictures are the 80 percent DPPC with 20 percent MPPC island and dispersed structures. Bottom pictures are 90 percent DPPC with 10 percent MPPC island and dispersed structures.

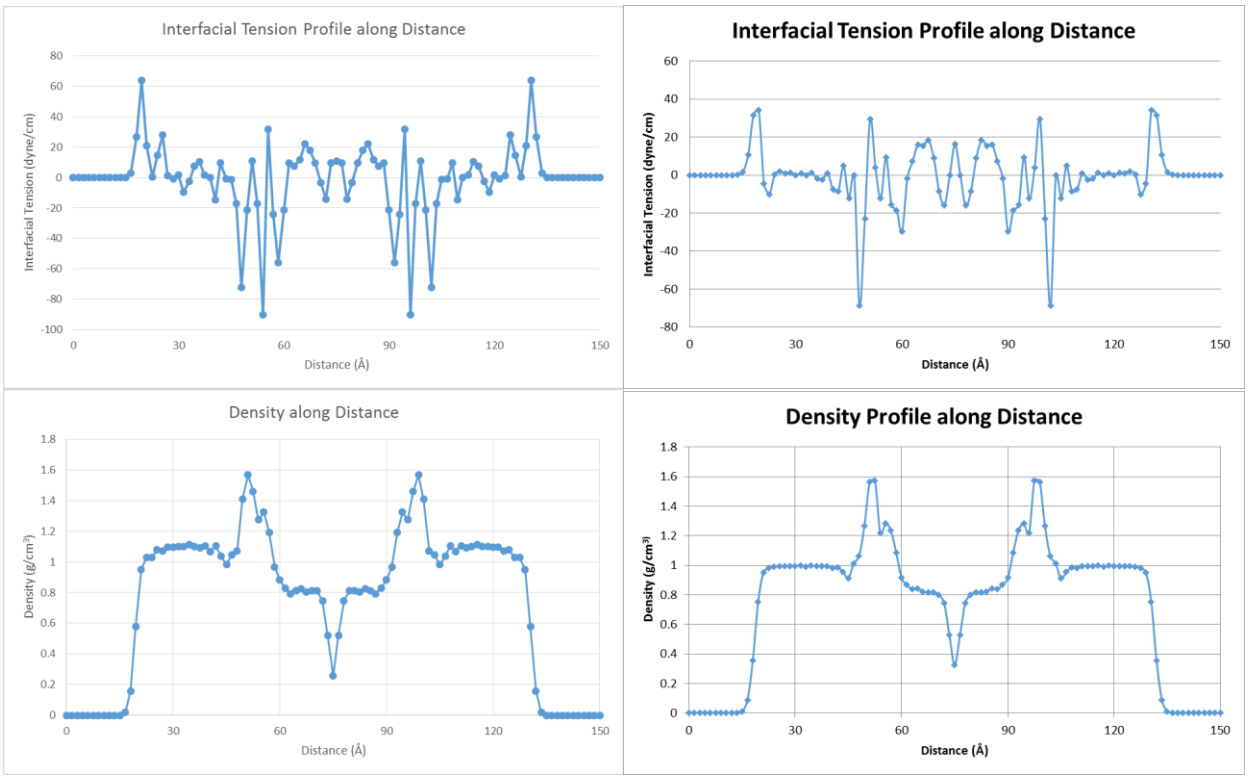

FIGURE 4 | Density Profile and Interfacial Tension Profile along Distance The graph on the left shows the previous structures with incorrect DPPC. The graph on the right shows the structures with modified DPPC.

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