CBE Live Seminar, May 3, 2023

Topic: Retrovirology through the Lens of the Computational Microscope

Presenter: Prof. Juan Perilla, Department of Chemistry and Biochemistry, University of Delaware, USA

Summary:

In this seminar, a computational biologist showed the application of the molecular dynamics simulations in better understanding the behavior of the HIV virus. The first part of the presentation started with some history of computational biology and then the presenter explained some details about the physics and math behind molecular dynamics simulations.

The next part started with some presentation about the structure of the HIV-1 virus and how it evolves in its early stage. Then, the architecture of the capsid protein cavity was explained in details. The molecular dynamics simulations performed for HIV-1 capsid show the properties of the structure along a reaction coordinate which the presenter and his team considered as in the cavity of the HIV-1 capsid. The properties they generated and plotted was the potential of mean force (Kcal/mol). This curve showed that as they reach to the center of the cavity for the HIV-1 capsid, the potential energy reached to its minimum showing binding sites of the virus. The presenter gave some comparison with experimental studies which was in fact a collaboration with other experimental groups.

Based on the molecular dynamics simulations, their group were able to give more explanation on the assembly of the pentamer in the HIV-a capsid where they analyzed different parts of the capsid protein and generated the architecture of its helix. They have also provided a mechanism for the nucleotide translocation in this virus from the molecular dynamics simulations.

Up to this point, the presenter used only a part of the HIV-1 capsid for simulation and found where binding sites are and what mechanism they have. In the next section, he started to show the main results they generated for the molecular dynamics simulation for the full scale HIV-1 virus which over all is a huge system containing more than sixty four million atoms. In this part, they aim for providing the details for how the ions (such as sodium and chloride) permeate through the virus and how the electrostatic potential of the virus changes in time to provide more explanation for the binding sites of the virus.

First, he explains about the complexity of generating the structure of the virus and how hard it is to make a virus within a proper environment using periodic boundary conditions and explains how some of the structures after months of calculations failed. He did not explain in details on how to generate such structures but it seems that the coordinate generation was coded by themselves since the structure they showed is far more complicated to be made by the current software available in the field of molecular dynamics simulations. The proper structure generation was with the help of another computational biologist from Los Alamos.

After they generated the proper structure for simulations, which was done in a cell of approximately 12 nm x 12 nm x 12 nm, they performed the molecular dynamics simulations where they were able to study the diffusion of the virus lipids and relate it to the its membrane composition asymmetry. In order to show this, they generated maps of the thickness of the virus over the simulation time of 5 microseconds. They also found that the membrane thickness follows a normal distribution.

Another interesting study they have done was simulation of the virus using coarse grain molecular dynamics simulations. This study was done for computing the elasticity of the virus’s surface to see how a drug can penetrate the virus. In order to do this, they put the virus on a flat metallic surface and used a metallic pin which demonstrate the role of an AFM pin and studied the elasticity of the virus from both outside and inside of the molecule. We know that using AFM for understanding the morphology of inside of a structure is not possible but by putting the AFM pin inside the virus, one can also compute the AFM properties from inside.

At the end, I asked a question about the computational cost and time of the simulations. The presenter responded that the simulations took an overall of **4 years**. The first two years simulations were not properly done and they had to redo that for another set of simulations for 2 more years. The disk space they occupied was about 130 TB. They used GPUs with NAMD3 software. For visualization tools they used VMD and implemented some other interesting features inside the VMD software package to be able to analyze the data of the simulations.

At the end, they have provided the molecular dynamics for a full scale HIV virus and provided its properties where it cannot be obtained using the current experimental tools.