Computational Biochemical Simulation

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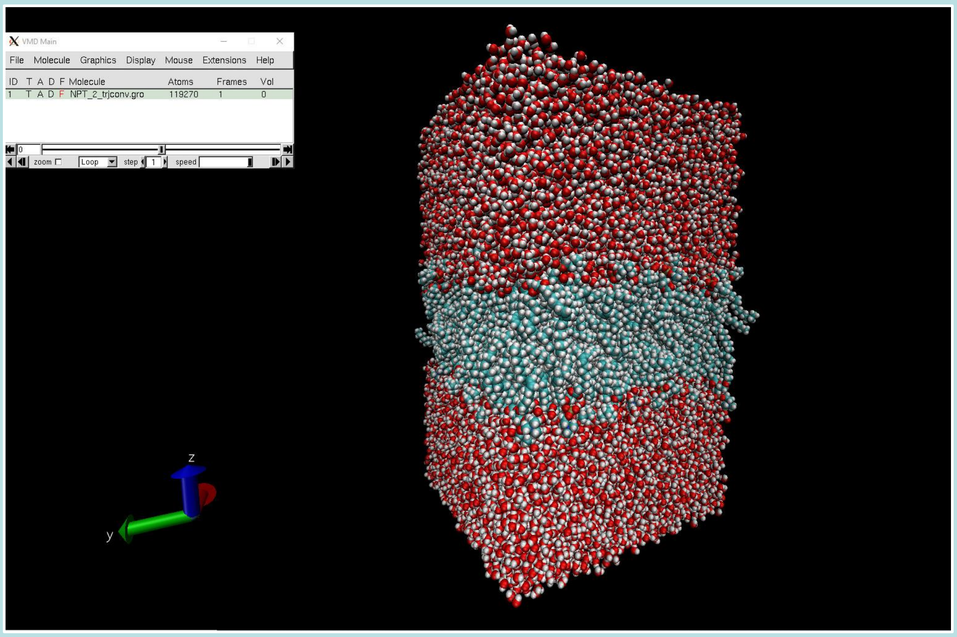
Introduction:

- Undergraduate Research – Dr. Jeffery Klauda (ChemE)

– All about lipids:

Lipids are ubiquitous in biology, playing essential roles at both macro and molecular scales. They form the structural basis of membranes, drive signal transduction, and work alongside proteins and enzymes to regulate molecular transport. Understanding lipid behavior is key to fields ranging from microbiology to disease research and drug delivery.

-What this research does is simulate complex (or simple) lipid systems to better understand their structure, dynamics, and interactions with proteins under different conditions. A combination of computational tools is used: CHARMM for system parameterization, NAMD to perform molecular dynamics calculations, and VMD to visualize the results in 3D space.



CHARMM simple lipid bilayer (in blue) model, with water box (red), rendered in VMD.

Image from https://doku.lrz.de/vmd-10746451.html

More Info:

As you can imagine, running an All-Atom simulation is a computationally intensive process that has its limits in simulations size and length. Alternative model methods can work around this…

- United Atom: Combine certain electrically similar compounds. For example, nonpolar carbon-hydrogen are combined into one unit.

-Coarse Grained: Simplify the system by grouping many atoms into ’bead units’ to maximize scale but loses detail.

Activities:

- Build digital lipid environments with CHARMM membrane builder– generate bilayers by specifying type and ratio of desired lipids, identifying system hydration (waters per lipid), and presence/concentration of ions. All these factors are influenced by differences in cell /organelle type, specialized functions, and chemical environments.
- Through Unix commands, upload files to UMD’s Zaratan High Performance Cluster (HPC). Write scripts to run a ‘job’ on the HPC, then extract and analyze simulation data. Zaratan consists of 360 compute nodes, each with 128 cores and 512 GB memory, that’s A LOT of power!.
- We primarily work with all-atom simulations, meaning every single atom in the system is explicitly modeled by CHARMM’s force field model. The force field accounts for Van Der Waals interactions and electrostatic forces based on charged molecules and ions. Quite a lot to calculate…

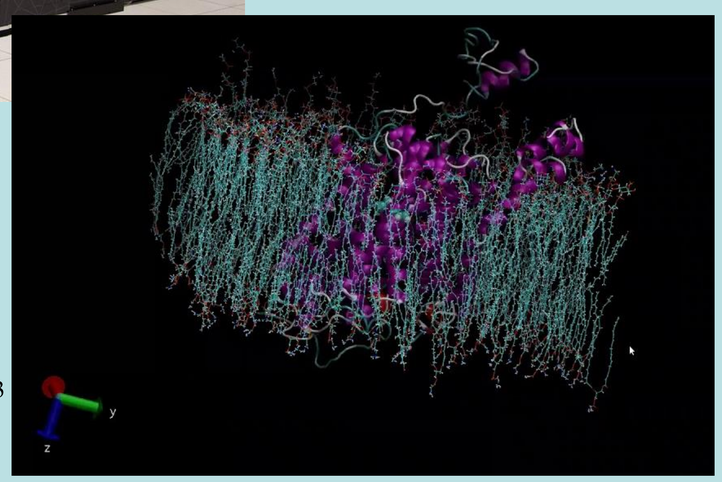
Impact:

As previously mentioned, lipid systems are involved in nearly every biological process. So, there is much to learn from modeling these computationally, studying specific interactions that influence membrane composition, and therefore structure and functionality.

Lipid modeling is critical for designing drug molecules that must interact with membranes. Simulations predict how a drug will embed and diffuse through a lipid bilayer, or how it’s permeation will be rejected.

Understanding how bilayers maintain integrity versus break down is a key factor in neurological diseases like Parkinson’s, Alzheimer’s, and ALS. With further simulative research, we can examine how these disease propagate through membrane disruption that leads to cell death.

UMD Zaratan High Performance Cluster. Image from https://www.maxgigapop.net/umd-introduces-zaratan-the-latest-investment-of-state-of-the-art-high-performance-computing/



Bilayer model including embedded protei, rendered in VMD. Image from https://www.youtube.com/watch?v=Ml7qEkb3wGI

Future Work:

Different extremities of chemical environments (ion concentration, lipid composition, and hydration) can impact simulation accuracy. There are still ways to correct and refine CHARMM parameters to better fit specific biological conditions. We can test and measure simulations by comparing results to experimental data.

SCIENCE AND GLOBAL CHANGE

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TQRCG