Quantitative Studies of Membrane Transport in the Dawn Light of Exascale Computing

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Acknowledging

NIH NIGMS

FRONTERA

39 petaFLOP/s

- Goal: Predict biological function from jiggling-and-wiggling of atoms
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• Obstacle 1: Time scale
• Obstacle 2: Intrinsic and artifactitious fluctuations
• Ways to overcome or circumvent
• Free or biased:
  • brute force vs biasing for enhanced sampling
  • down to the root: what drives the processes
Cell: separation but not isolation
Membrane with machineries

~3 trillion water molecules

https://commons.wikimedia.org/wiki/File:Cell_membrane_detailed_diagram_en.svg
Study biological processes in a predictive manner?

From simplicity to simplicity via complex dynamics

- Brute force molecular dynamics
  - Milliseconds by steps of femtoseconds?
  - Accuracy of force fields
  - Millions of degrees of freedom

Unbiased, unaccelerated MD
Accelerated MD: REMD, etc.

- The driving “force”
  - Free energy gradient
  - “Mechanical” forces
  - Entropic “forces”
NPT ensemble sampling: N constant, T constant, p constant

Pressure fluctuations in an NPT simulation of a small system consisting of 183,508 atoms vs. that of a large system consisting of 1,447,456 atoms vs. that of a huge system consisting of 23,186,176 atoms.
All-atom model system of eight GLUT1 in asymmetric environments mimicking the membrane of a human erythrocyte. The system consists of 290,776 atoms. The membrane potential of this model system is $-30$ mV, which will increase to $+168$ mV when a single cation is moved across the membrane along the EC-to-IC direction.
Fig. 3 A. Eight states of the glycerol-AQP3 complex and transitions between them. The three wells on a red curve indicate the binding sites of glycerol inside the AQP3 channel. Each green nut indicates the presence of a glycerol molecule at the binding site. B. An IC-to-EC transport event. The protein AQP3 monomer is shown in ribbons and the ar/R sf residues (Phe63, Tyr212, Arg218) in ball-and-sticks, all colored by residue types (hydrophobic, white; hydrophilic, green; negatively charged, red; positively charged, blue). Water molecules inside and near the AQP3 channel are shown in space-filling spheres colored by atoms (O, red; H, white). Two glycerol molecules are shown in space-filling spheres: GOL661 colored purple and GOL102 colored gold.
Two fundamental problems in typical MD studies of "small system":
1. NPT ensemble but pressure is hardly constant
2. Membrane potential fluctuates too wildly

Good news: By Going larger!