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

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Acknowledging

- Goal: Predict biological function from jiggling-and-wiggling of atoms

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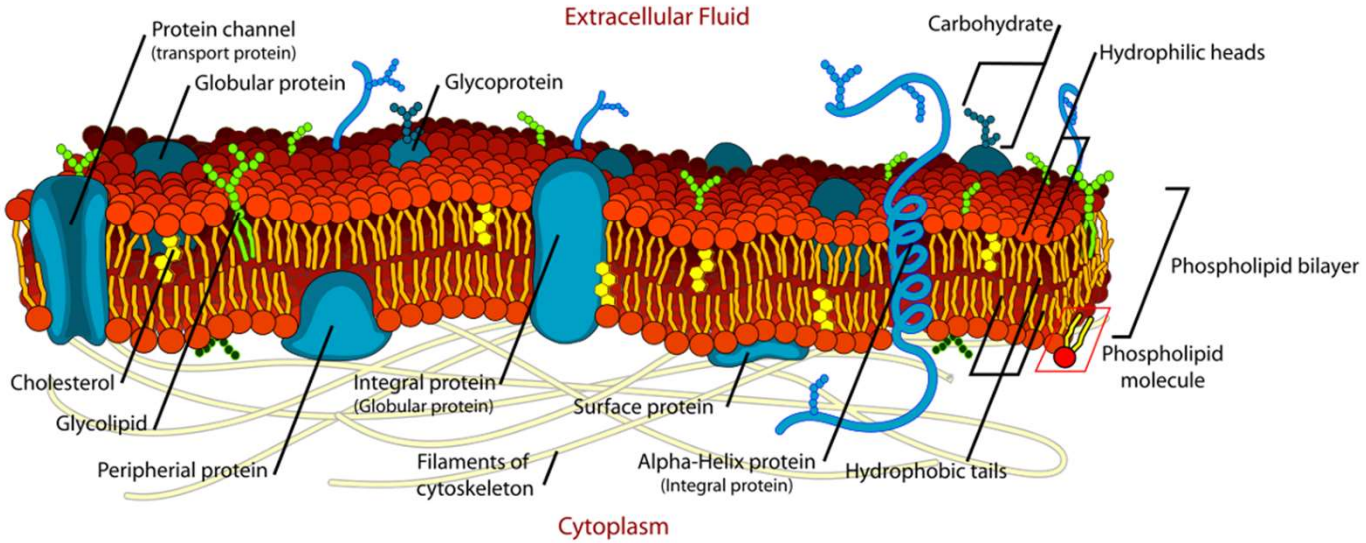
- Obstacle 1: Time scale
- Obstacle 2: Intrinsic and artifactitious fluctuations
- Ways to overcome or circumvent
- Free or biased:
  - brute force *vs* biasing for enhanced sampling
  - down to the root: what drives the processes

~3 trillion water molecules

Cell: separation but not isolation
Membrane with machineries



https://commons.wikimedia.org/wiki/File:Cell_membrane_detailed_diagram_en.svg

Study biological processes in a predictive manner?

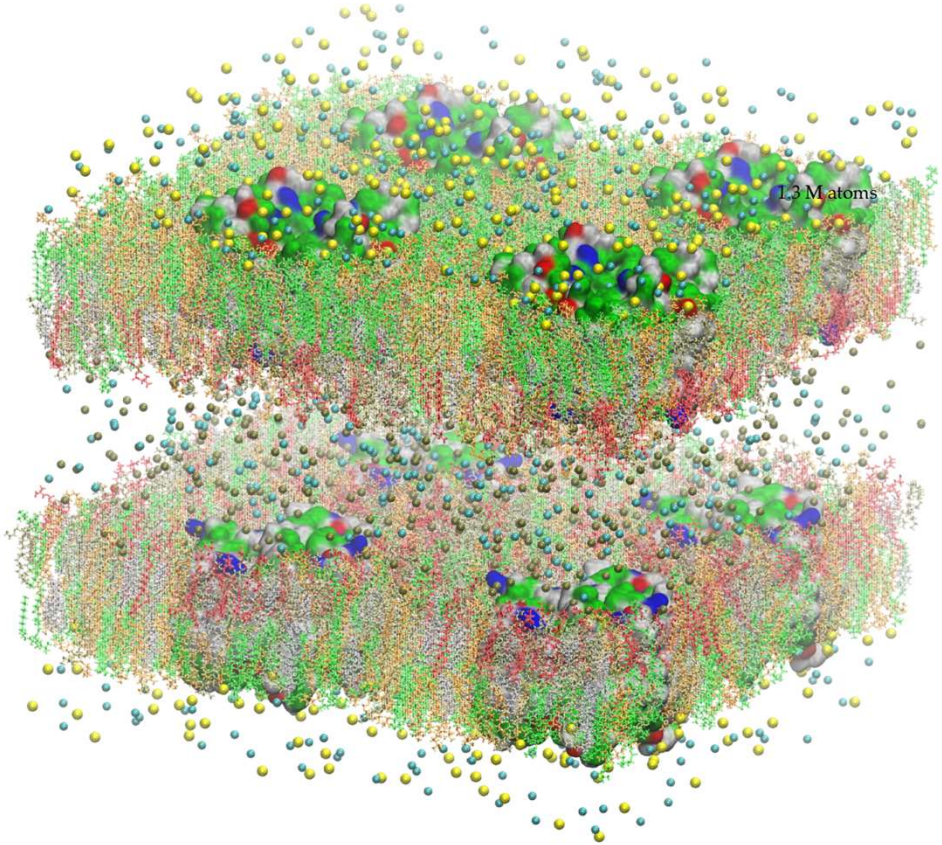
From simplicity to simplicity via complex dynamics

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

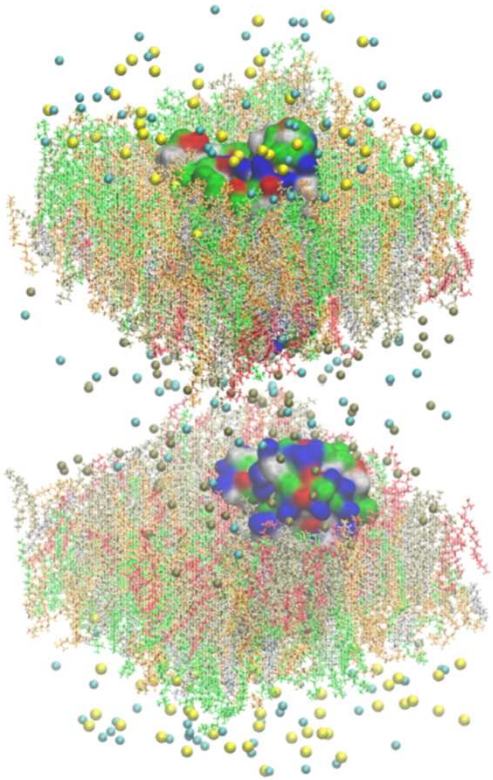
Unbiased, unaccelerated MD

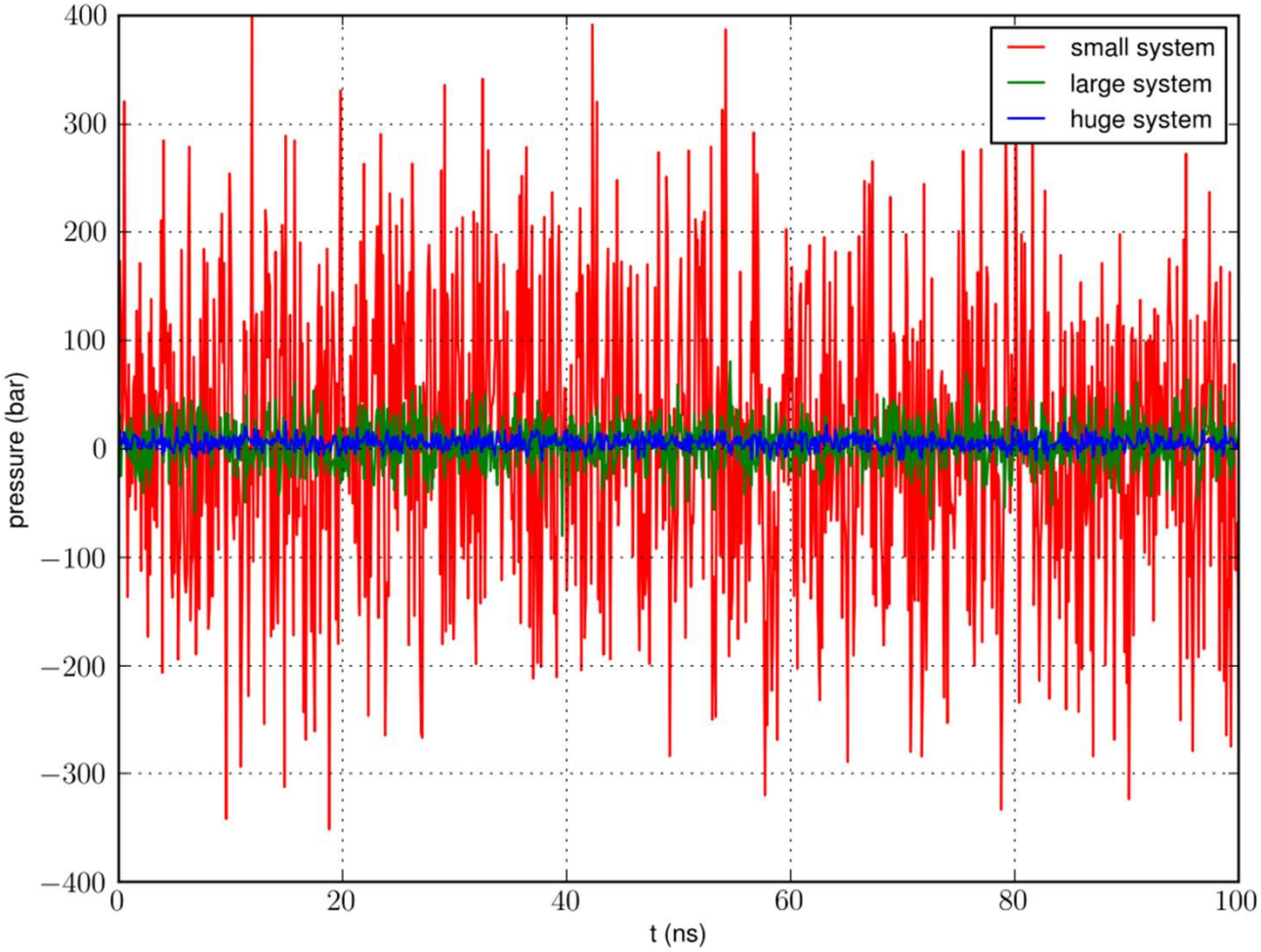
Accelerated MD: REMD, *etc.*

- The driving "force"
  - Free energy gradient
  - "Mechanical" forces
  - Entropic "forces"



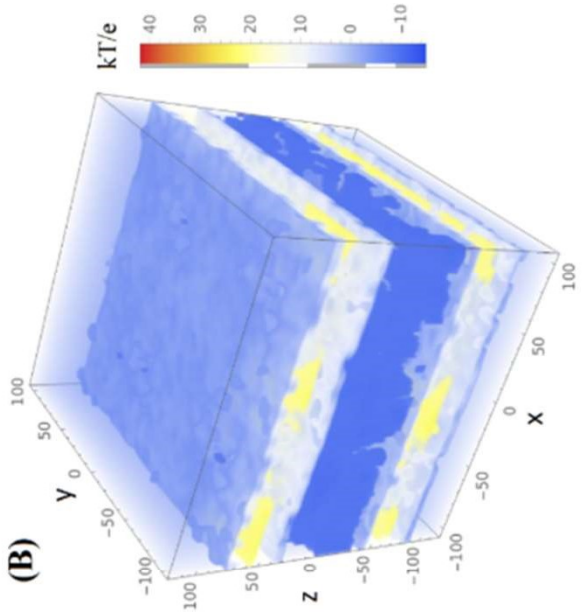
≠ 4X

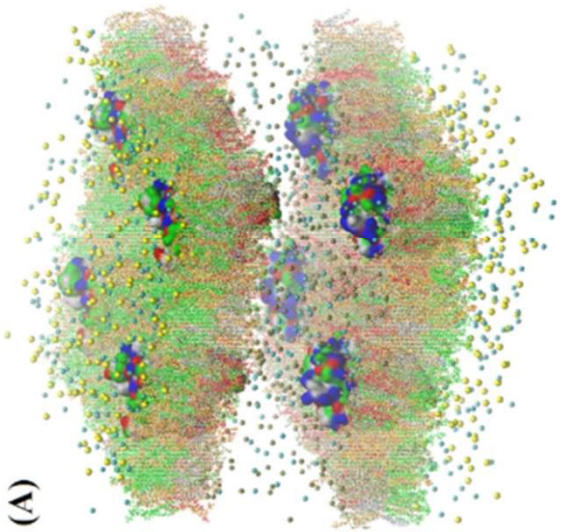


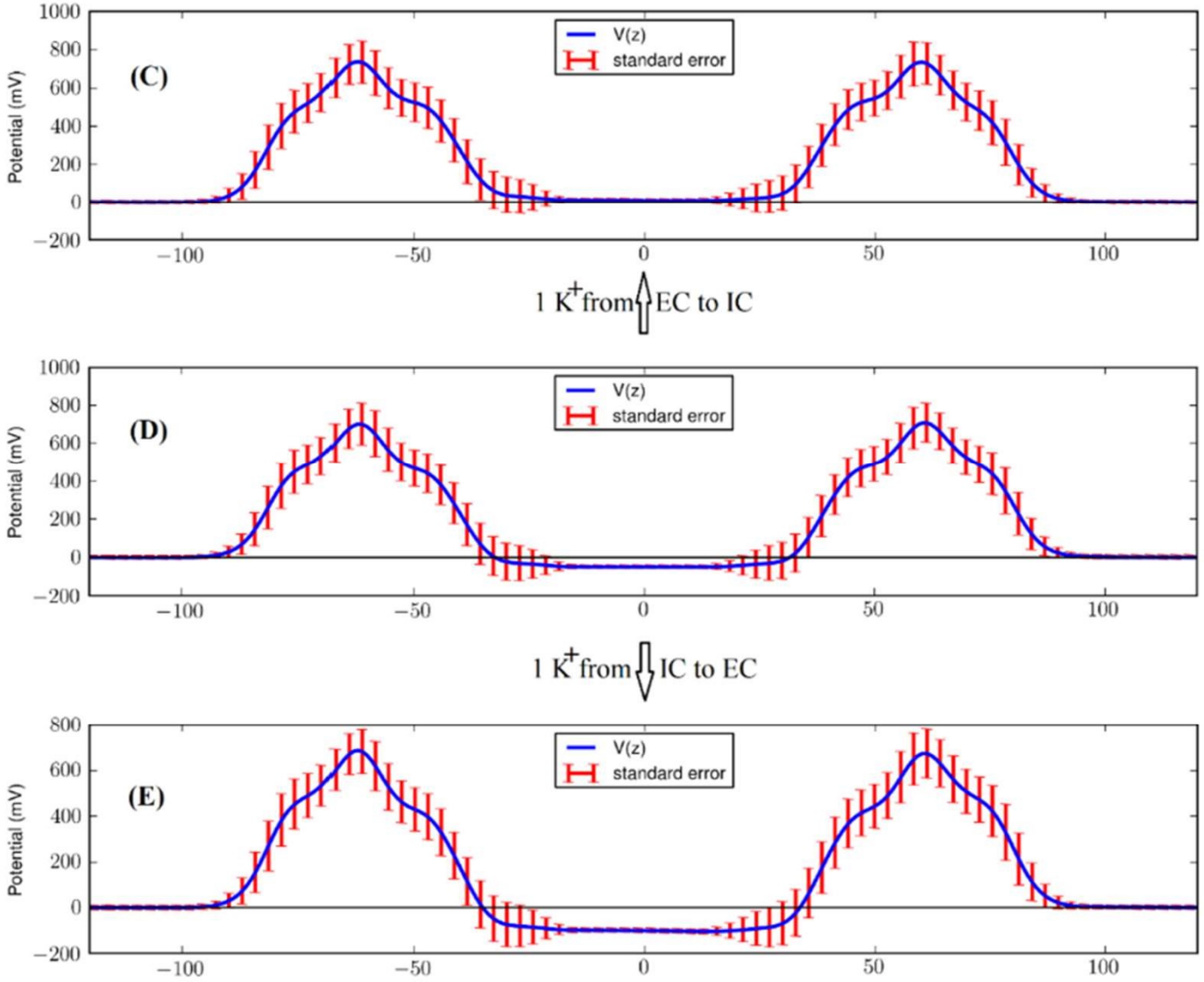


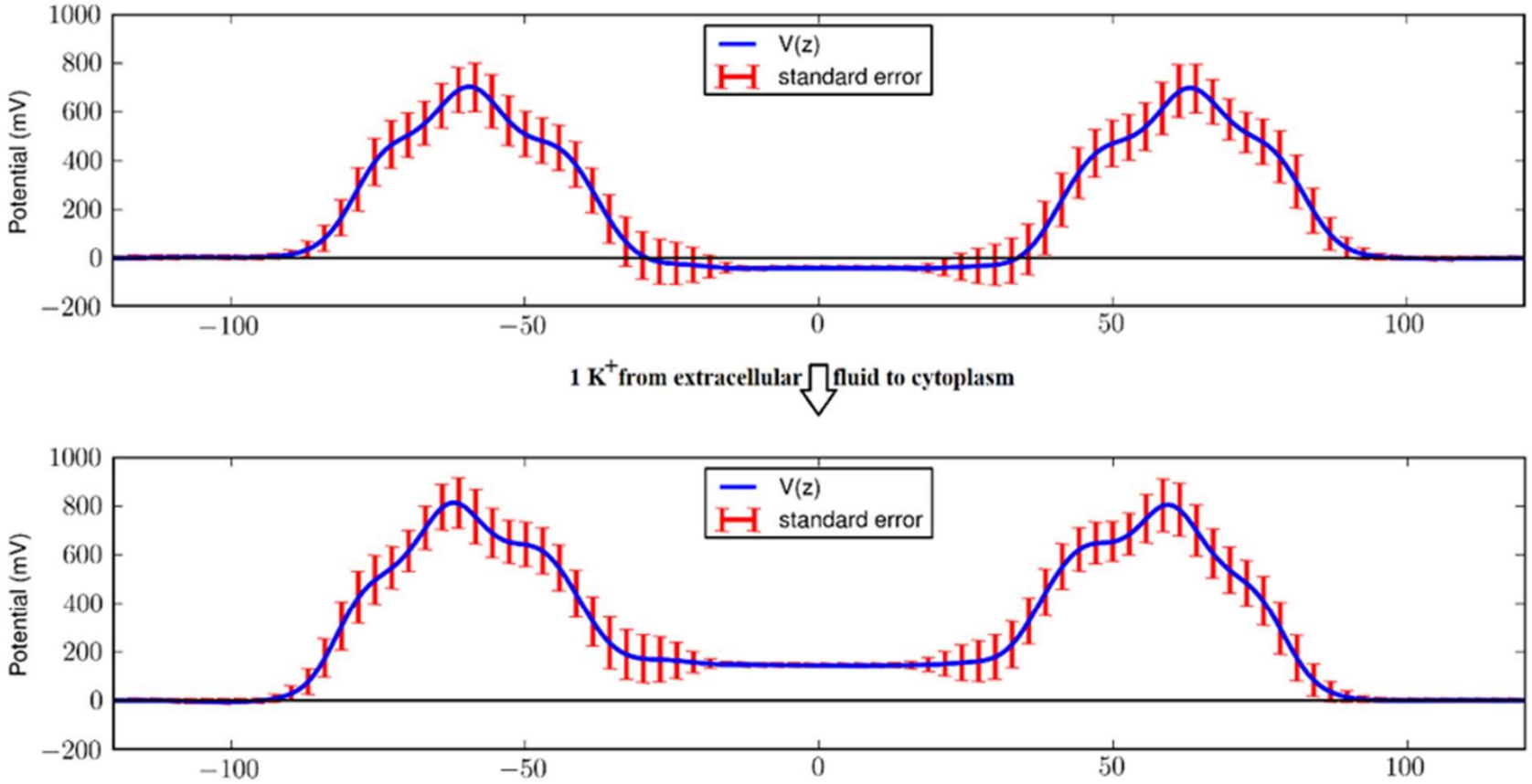
NPT ensemble sampling: N constant, T constant, p constant

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.


kT/e
40
30
20
10
0
−10
(B)
x
y
z


(A)


(C)
V(z)
standard error
Potential (mV)
1 K+ from EC to IC
(D)
1 K+ from IC to EC
(E)



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.

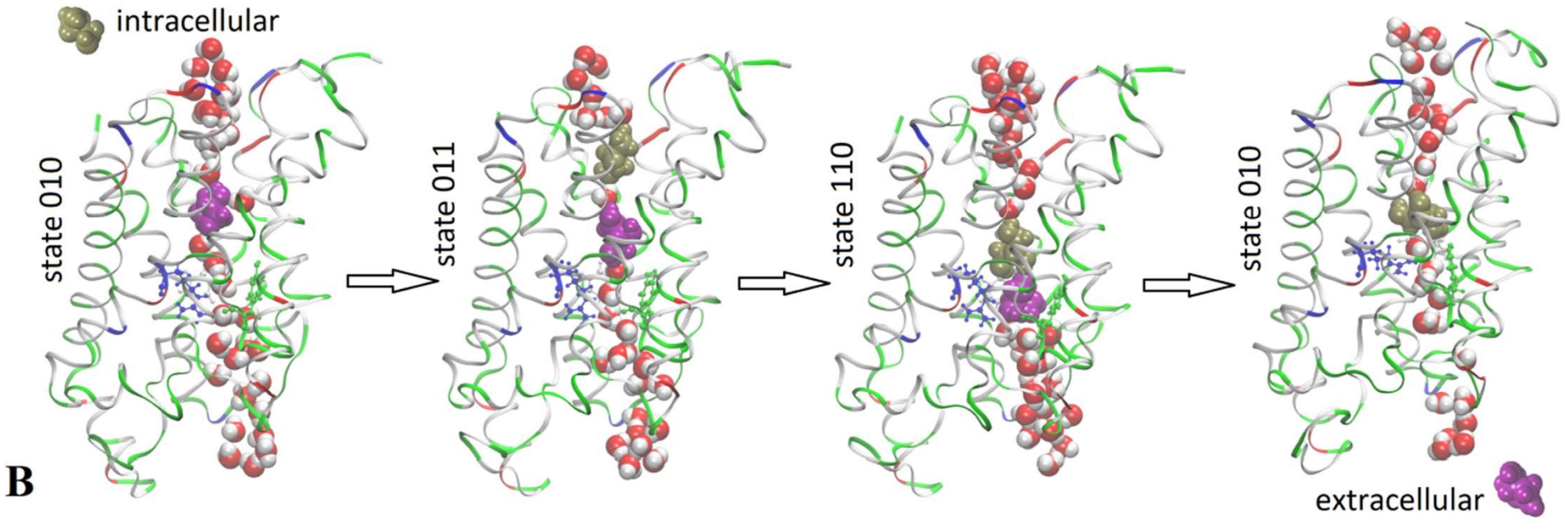
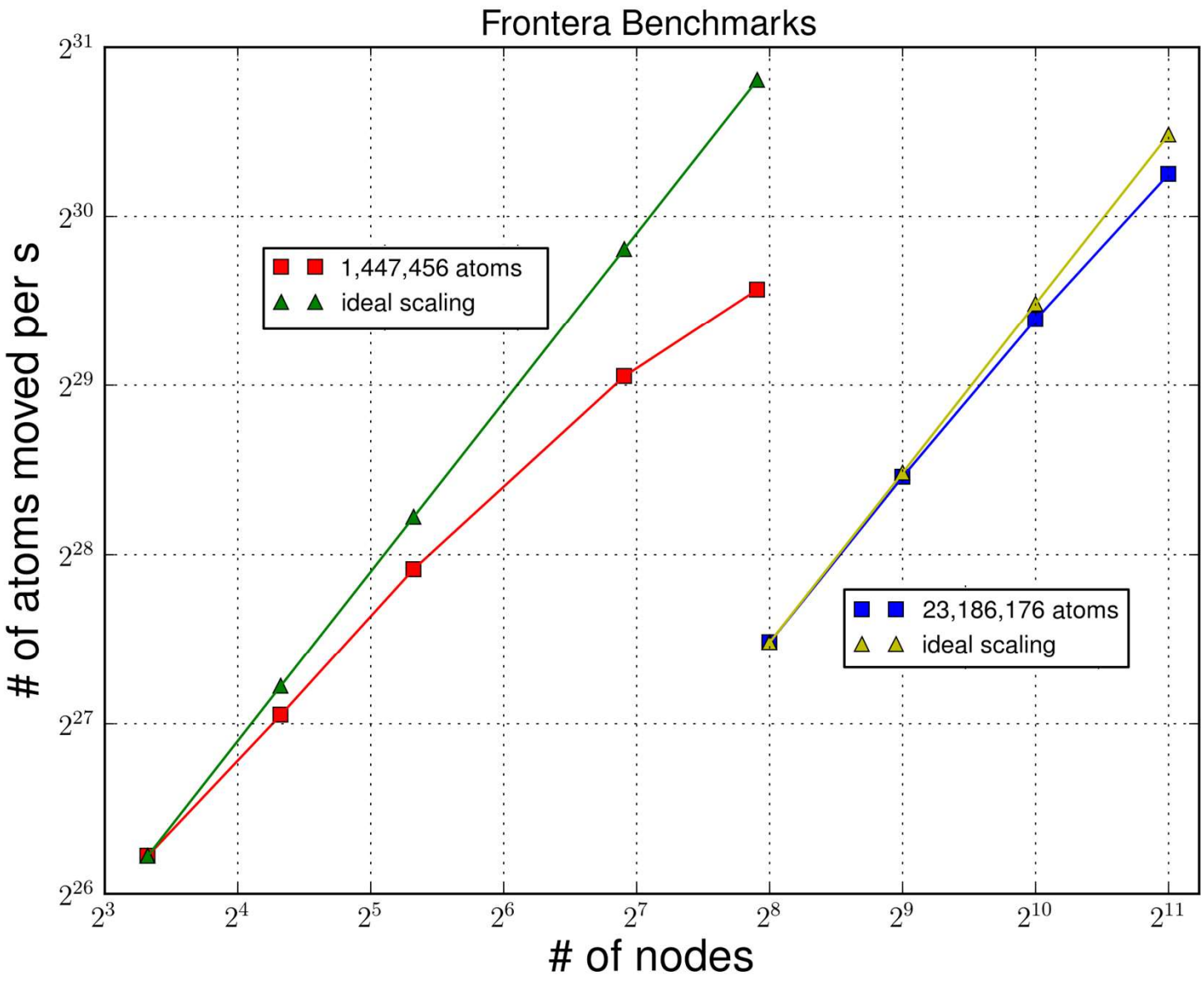


Fig. 3 A. Eight states of the glycerol-AQP3 complex and transitions between them. The three wells on a red curve indicate the binding sites of glycerol inside the AQP3 channel. Each green nut indicates the presence of a glycerol molecule at the binding site. **B.** An IC-to-EC transport event. The protein 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!


Frontera Benchmarks
# of atoms moved per s
# of nodes
1,447,456 atoms
ideal scaling
23,186,176 atoms
ideal scaling
2^{31}
2^{30}
2^{29}
2^{28}
2^{27}
2^{26}
2^{3}
2^{4}
2^{5}
2^{6}
2^{7}
2^{8}
2^{9}
2^{10}
2^{11}