Bigger, Better, Deeper: HPC as a Computational Microscope to Explore Cell Membranes

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• Membrane: the wall around the building…
• Control: entry/exit of materials & information
• Membrane: lipid bilayer + membrane proteins
• Membrane proteins: 20% of genes; 50% of drug targets
Membranes: Proteins + Lipids

- Lipid bilayer: environment for membrane proteins
- Lipid-like drugs: e.g. fingolimod & MS
- Molecular simulations: proteins in a *complex membrane environment*

Complex *mixtures of lipids* in cell membranes
Asymmetric distribution between leaflets
Membrane Proteins: From PDB to MD

- **X-ray structure**: static, average structure at ~100 K, in crystal
- **MD simulation**: nano to microsecond dynamics at ~300 K, in bilayer
- From structure to dynamic behaviour & function in a model cell membrane

KvAP voltage sensor
Sands & Sansom (2007)
Structure 15:235

• Describe the forces on all atoms: $F = -\frac{dU(x)}{dx}$
• Integrate: $F = ma$ (a few million times…)

Lipid/protein interactions
Simulations as a ‘Computational Microscope’

- MD simulations: transplanting a membrane protein structure back into a lipid bilayer
- **Zoom in**: atomistic simulations, structure/function at the nm & ns scales
- **Zoom out**: coarse-grained simulations, membrane behaviour at the µm & µs scales
- Today: focus on membrane protein/lipid interactions; complex & crowded bilayers

TWIK-1 channel hydrophobic gate

Kir channels in a crowded membrane
Fowler et al. (2016) *Soft Matter*

0.14 µm, 55K lipids, 144 proteins
5 µs CG-MD (Martini)
A Pipeline & a Database: MemProtMD

Membrane protein structure $\rightarrow$ Initial CG system $\rightarrow$ CGMD simulations $\rightarrow$ Atomistic membrane protein system $\rightarrow$ Analysis

http://sbcb.bioch.ox.ac.uk/memprotmd
>2000 structures in bilayers
Phil Stansfeld & Tom Newport

Stansfeld et al. (2015)

MscS: stretch activated
Pliotas et al. (2015) Nature SMB
High Throughput Simulations for Functional Annotation

2015
- \( n = 585 \)
- \( n = \exp(a y) \)
- \( a = 0.220 \)
- \( r^2 = 6.83 \)
- expected growth at year 20 (2005)
  - \( a = 0.244, r^2 = 0.42 \)

2016
- 2000 membrane proteins x 1 µs simulation
- 0.2 PB

2020
- 10,000 structures x 1 ms simulation
- 200 PB
ANT1 transporter: selective interactions with anionic cardiolipin (CDL)
PMF calculations: free energy landscapes of protein/lipid interactions
Predictions: strength & specificity of lipid interactions
Larger Scale Simulations of Biomembranes

• Bacterial outer membrane proteins: OMPs
• Physiological degree of protein crowding slows membrane protein & lipid diffusion
Scaling Up to Experimental Sizes

300,000 particles

1.4M particles

22M particles

1 µm

0.5 µm

simulations

experiment

Matthieu Chavent
Anna Duncan
Bacterial Outer Membrane Protein Islands

- Simulations of crowded membranes: OMP clustering & restricted diffusion
- Imaging *in vivo* & *in vitro*: OMP ‘islands’ in outer membrane biogenesis

Matthieu Chavent  
Anna Duncan  
Colin Kleanthous *et al.*

Dividing *E. coli*: green = new; red = old
Influenza virus: a complex high cholesterol (53%) membrane

- 80 HA + 12 NA + 15 M2; 43000 lipids; microsecond simulations of 5M particles (≡ 20M atoms)
- High cholesterol & glycolipid: diffusion is slow & anomalous ($\alpha = 0.8$) i.e. ‘raft-like’
- Membrane biophysical robustness correlates with virus stability to hostile environments
Combining CryoET & Simulation: HIV-1

- HIV-1 capsid
- Cryo-ET
- Zhao et al. (2013) *Nature*

- Atomistic MD
  - 64M atoms
  - 128,000 cores
  - 5 ns/d

- CG HIV-1
- ~30M particles
- Oxford & UIUC
- Blue Waters, NCSA

- AT-MD
- 120M atoms

- CryoET: overall structure
- X-ray crystallography: protein structures
- Lipidomics: bilayer composition
- MD simulations: integrated model

Tyler Reddy
Juan Perilla (UIUC)
Conclusions & Future Challenges

• Interactions with lipids: simple and complex
• Crowded and complex bilayers: ‘in silico in vivo’
• Simulations to link structural biology of membrane proteins to functional & imaging studies of cell membranes

• Data science challenges: visualization & analysis
• Making simulation data available
• Need for a hierarchy of HPC resources
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