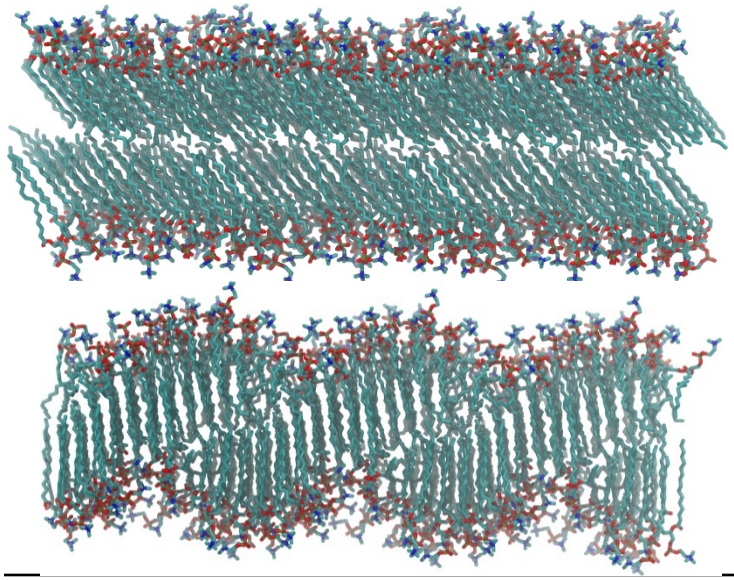
Molecular Modeling of Biomolecules: How can GPUs Advance Research?

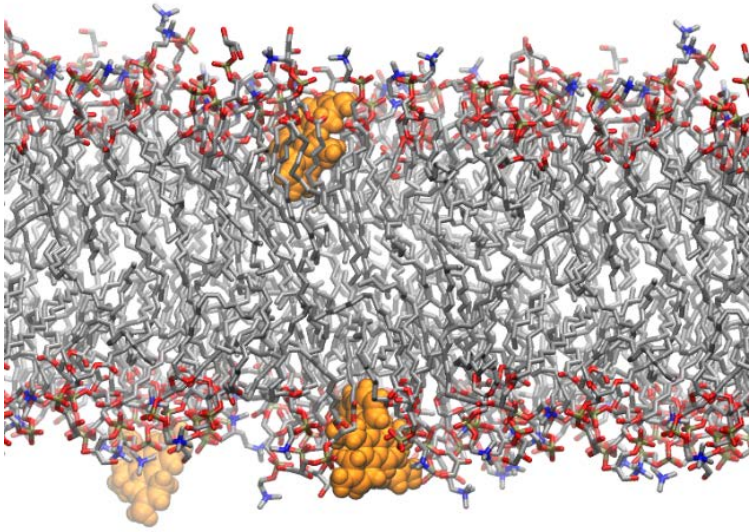
Jeffery B. Klauda

UNIVERSITY OF MARYLAND

Lipid Gel & Ripple Phases

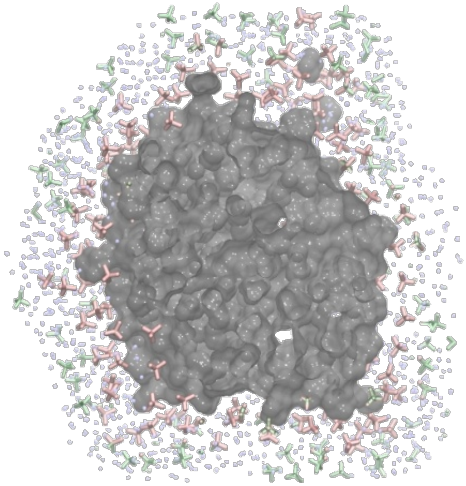


Drug Binding to Lipid Membranes

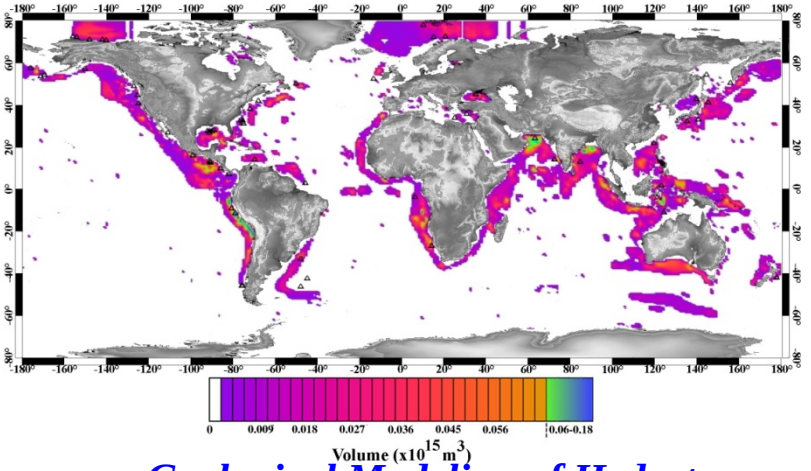


Laboratory of Molecular & Thermodynamic Modeling

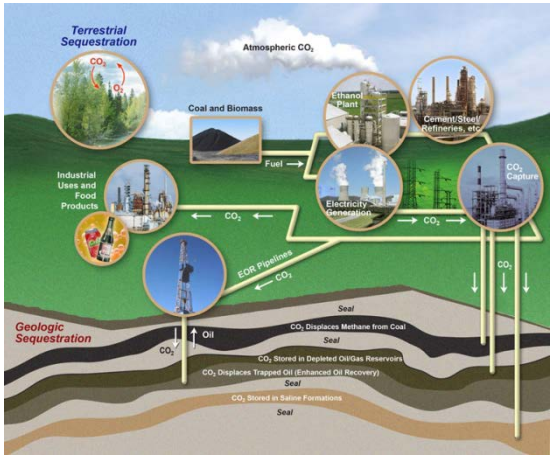
Energy-based Research



Hydrotrope Stabilizing nanodroplet of oil

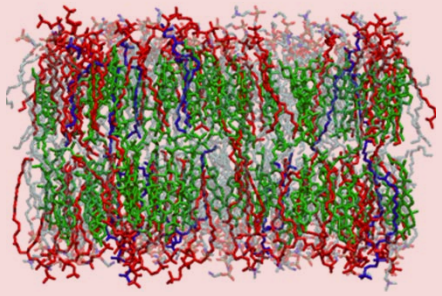


Geological Modeling of Hydrates

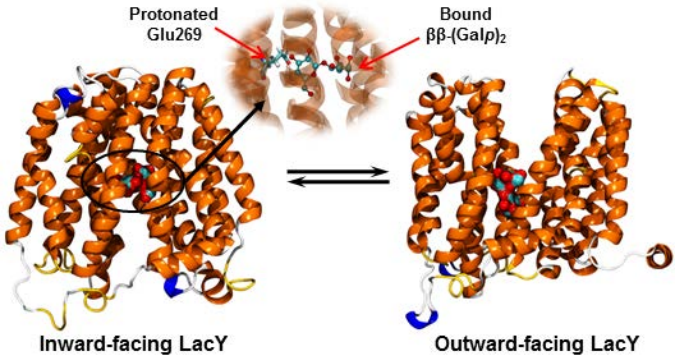


CO_2 Storage DOE-Fossil Energy

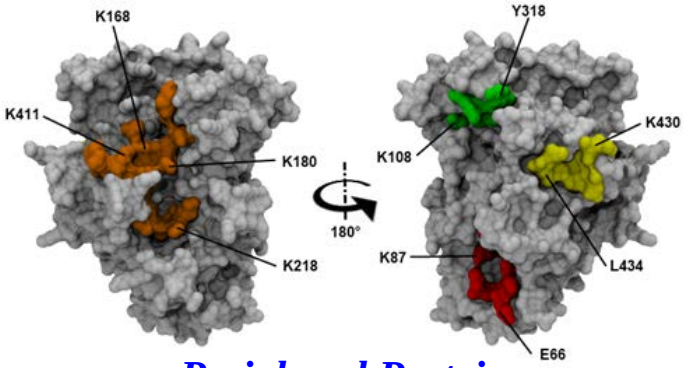
Biomolecular/Membrane Research



Lipid Membranes

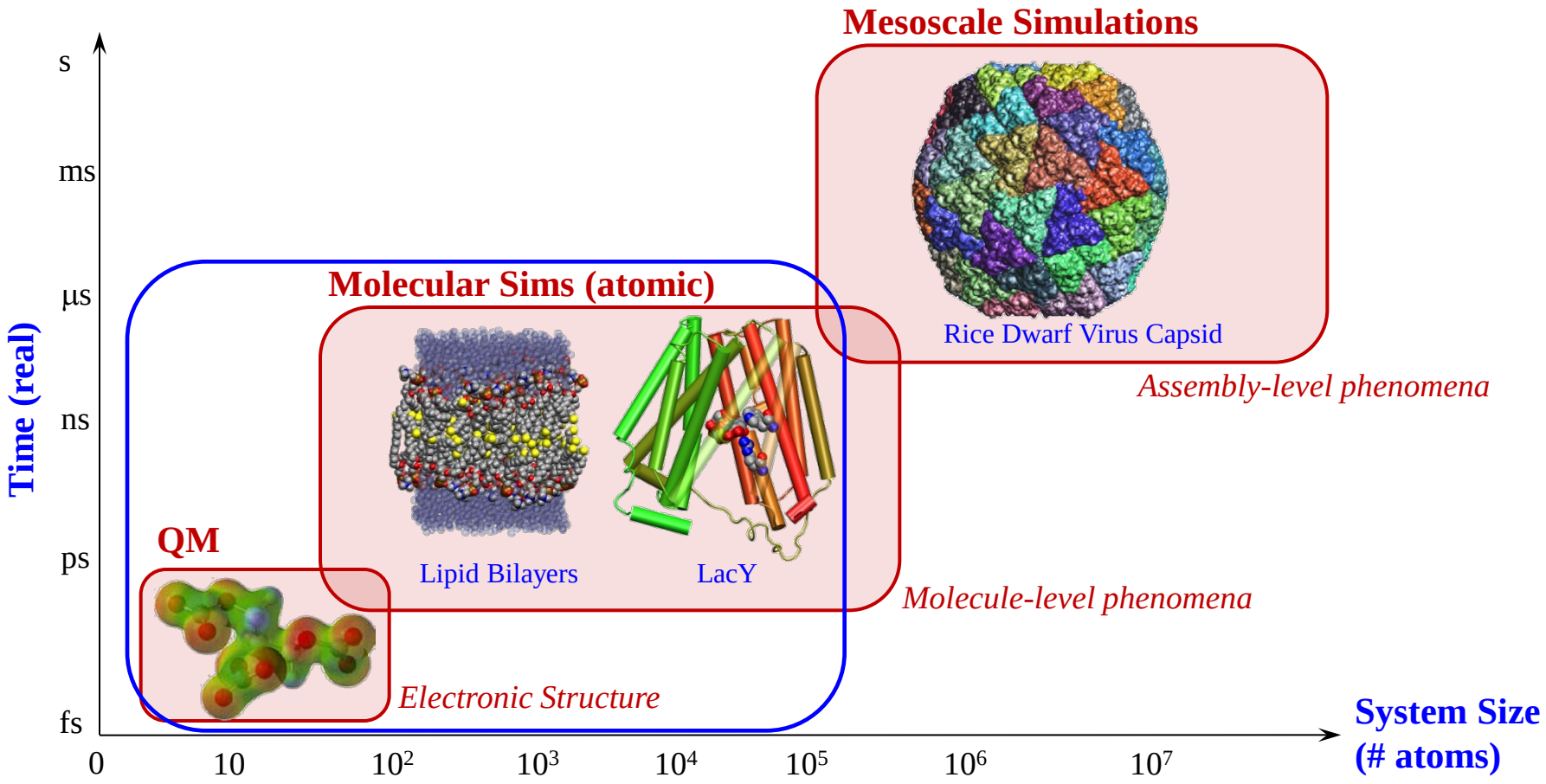


Transmembrane Proteins



Peripheral Proteins

Research Methods & Design

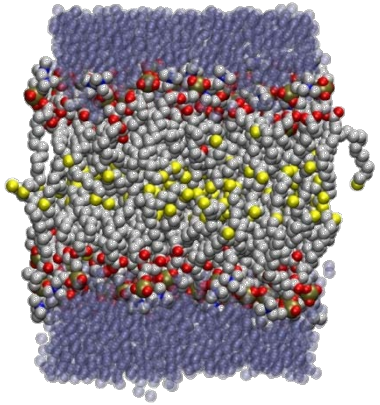


- Research Design

ab initio QM → Molecular Simulations & Models → Macroscopic Properties

QM=Quantum Mechanics

Molecular Dynamics (MD)



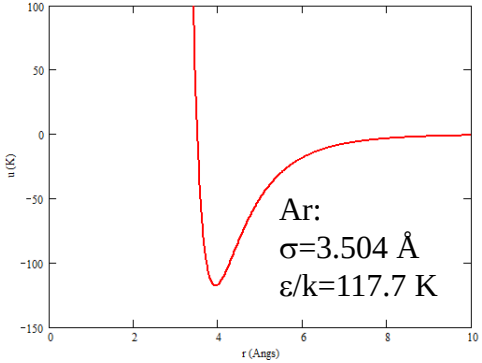
- Governing Equations
  - Newton's Laws of Motion

$$f_i = m_i a_i = m_i \ddot{r}_i$$ where *i* is a molecule or atom

  - Force drives the motion of a system

$$f_{ij} = -\frac{\partial w_{ij}}{\partial \vec{r}_{ij}}$$ where *w* is the inter- and intramolecular potential

    - Accurate force fields are required for realistic simulations



Lennard-Jones Potential (van der Waals/non-bonded forces)

$$w(r) = 4\varepsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right]$$

  - Why use MD?
    - Probe biomolecules at atomic resolution without introduction of artificial labels or expensive equipment
    - Aid experiments (diffraction, NMR, spin labeling) in determining what is measured[1-4]
    - Dynamical understanding of membrane function

[1]Klauda et al. *BJ.* **90**: 2796 (2006).
[2]Klauda et al. *BJ.* **94**: 3074 (2008).
[3]Pendse, Brooks & Klauda. *JMB.* **404**: 506 (2010).
[4]Rogaski & Klauda. *JMB.* **423**: 847 (2012).

Force Fields & System Sizes

- Biomolecular Force Field

$$V(\hat{R}) = \sum_{bonds} K_b (b - b_0)^2 + \sum_{angles} K_\theta (\theta - \theta_0)^2 + \sum_{cross\ UB} K_{UB} (r_{1,3} - r_{1,3}^0)^2 + \sum_{improper} K_{im} (1 - \cos(2\phi))$$

$$+ \sum_{dihedrals} \left[\sum_j K_{\varphi,j} (1 + \cos(n_j \varphi - \delta_j)) \right] + \sum_{\substack{nonbonded \\ pairs\, i,j}} \varepsilon_{ij} \left[\left(\frac{R_{\min,ij}}{r_{ij}} \right)^{12} - \left(\frac{R_{\min,ij}}{r_{ij}} \right)^{6} \right] + \sum_{\substack{nonbonded \\ pairs\, i,j}} \frac{q_i q_j}{\varepsilon_D r_{ij}}$$

  - Many terms to describe intra- and intermolecular interactions
  - The r^{-12}, r^{-6} and r^{-1} terms are the most computational demanding terms

- Typical System Sizes Required for Simulations

	Liquid Simulation (small molecule)	Lipid Membrane (lipid only)	Protein with Lipid Membrane
Dimensions	8-10 nm^3	125-700 nm^3	500-1500 nm^3
# atoms	3,000-5,000	20,000-70,000	50,000-150,000

  - Efficient codes that run these large systems is **crucial**

MD Simulation Programs

- CHARMM (Chemistry at HARvard Macromolecular Mechanics)[1]
  - Came out of Prof. Martin Karplus' group at Harvard
  - A comprehensive code that contains many cutting-edge techniques in addition to traditional simulation techniques
  - **GPUs**: CHARMM/OpenMM interface

- NAMD (Scalable Molecular Dynamics)[2]
  - NIH-supported code from Prof. Klaus Schulten's group (UI-UC)
  - Less focus on functionality and more parallel scalability
  - **GPUs & MICs**: directly available in NAMD code

- GROMACS (Groningen University)[3]
  - Development spawned from Prof. Herman Berendsen group
  - European analog to CHARMM
  - **GPUs**: Built-in functionality for GPUs
- Other Commonly Used Programs
  - AMBER, TINKER, DESMOD, and LAMMPS

[1]www.charmm.org
[2]www.ks.uiuc.edu/Research/namd/
[3]www.gromacs.org

Computational Equipment/Resources

- Local UMD Computational Clusters (UMD/IT)

Deepthought: Dell Linux cluster with ~4000 cores

Deepthought2: Dell Linux cluster with 9200 cores and 40 nodes with dual GPUs

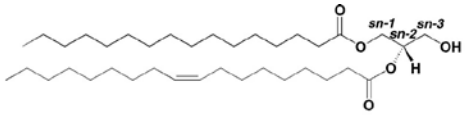
- XSEDE (NSF Supported)

Stampede: Dell Linux cluster with 100,000+ Cores (10 PetaFlops) (All have MIC & some with GPUs)

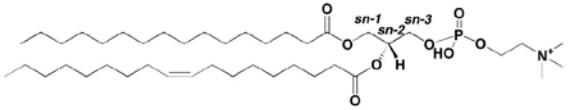
Lipids

- Complex biomolecules
  - Contain a fatty acid chains and head group
- Classified into 8 categories[1]

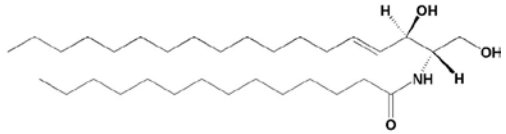
Fatty acyls



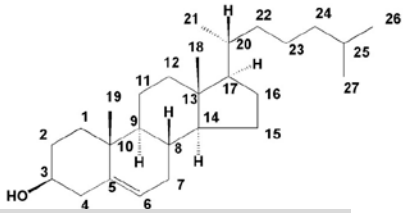
Glycerolipids



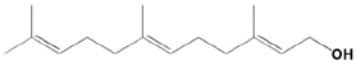
Glycerolphospholipids



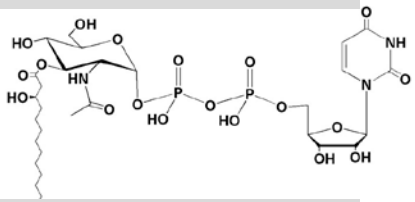
Sphingolipids



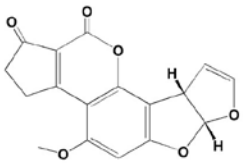
Sterol Lipids



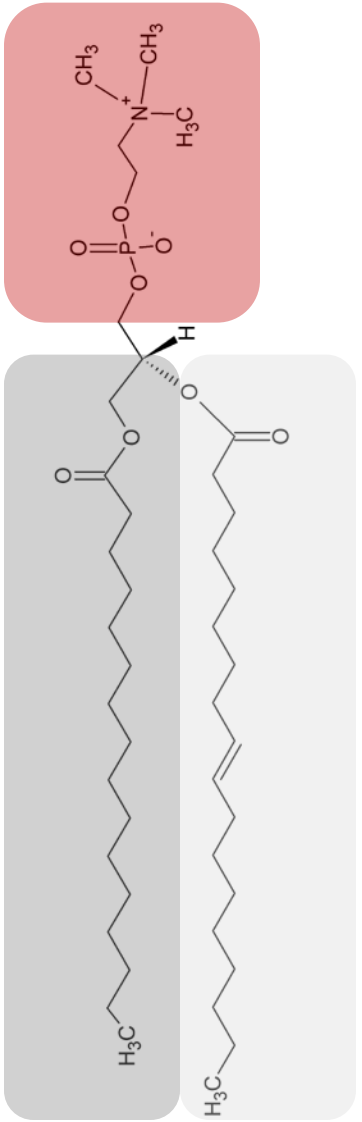
Phenol lipids



Saccharolipids



Polyketides

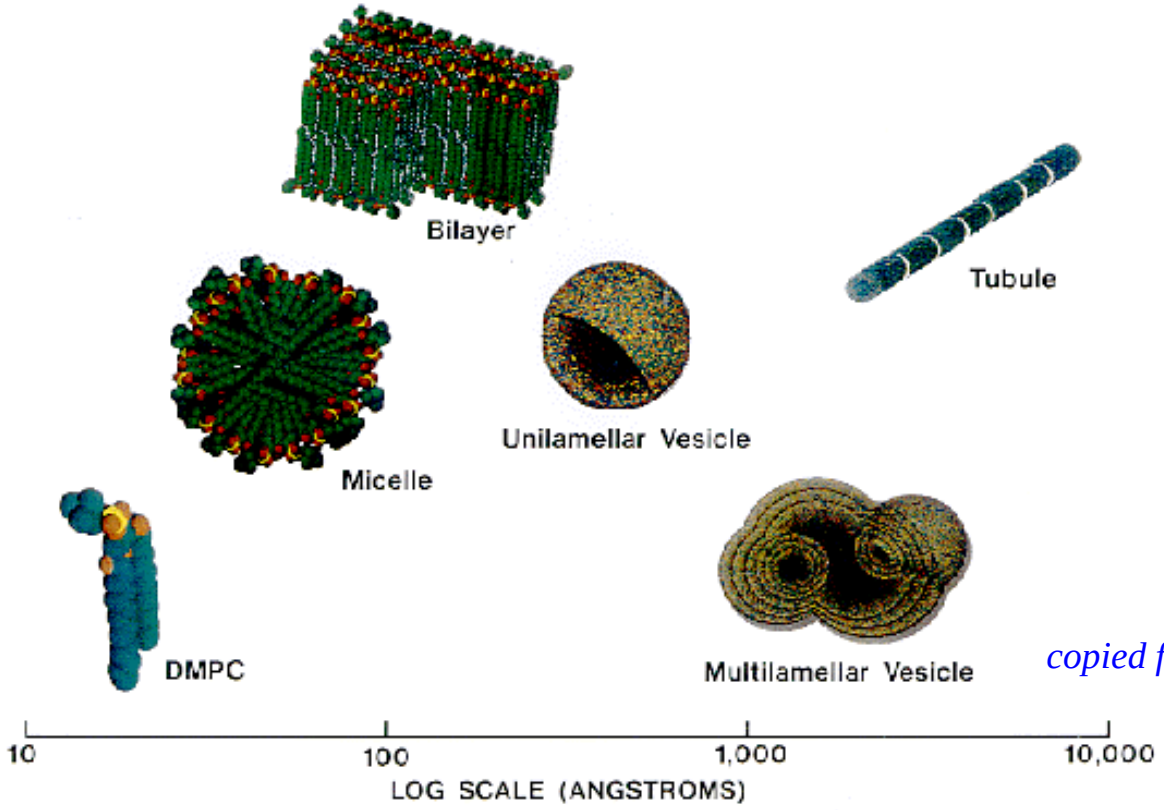


Modified (Fig. 1)[1]

[1]Fahy et al. *J. Lipid. Res.* **46**: 839 (2005).

Lipid Self-Assembly

- Self-assembly into phases depending on water content



copied from ref 1

- Lower concentration of lipid form spherical micelles
- Higher concentrations form bilayer structures (common in cells)

[1]S.A. Sefran. Statistical Thermodynamics of Surfaces, Interfaces and Membranes (Addison-Wesley, NY, 1994).

Lipid Bilayer Phases

Phase Transitions

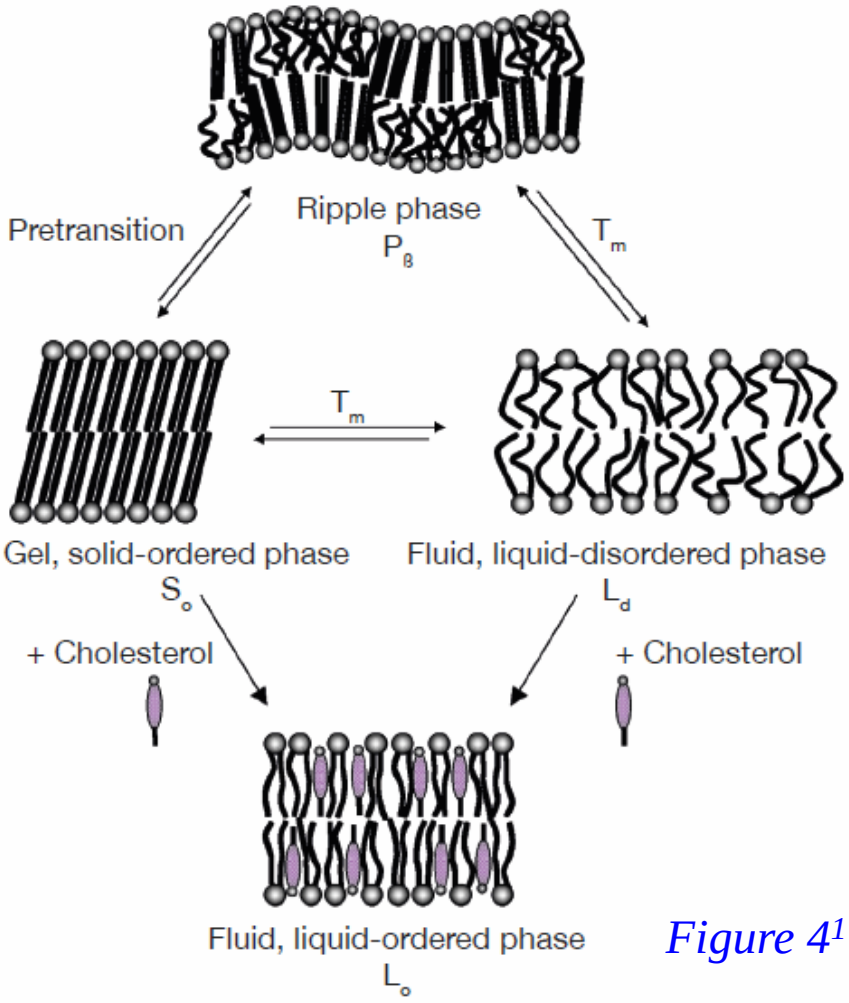


Figure 4[1]

- Fluid or liquid crystalline (L_α) bilayer phases are most common and have high chain disorder.
- Certain lipids go through a pretransition as the temperature is lowered to a ripple phase with interdigitation.
- This short pretransition (~10°C) leads to a ordered gel phase (L_β)
- Introduction of cholesterol leads to a liquid ordered phase (sometimes existing as a lipid raft).
- Can MD simulations on all-atom force fields see this? Requires a significant amount of computational time.

[1]Eeman & Deleu. *Biotechnol. Agron. Soc. Environ.* **14**: 719 (2010).

MD Simulations of DMPC/DPPC Bilayers

- Details of the Simulation
  - Force field and composition: CHARMM36[1] and 50% DMPC
  - Program & #atoms: NAMD with 16,704
  - Deepthought2 with GPUs for 300ns of simulation time

- Benchmarks

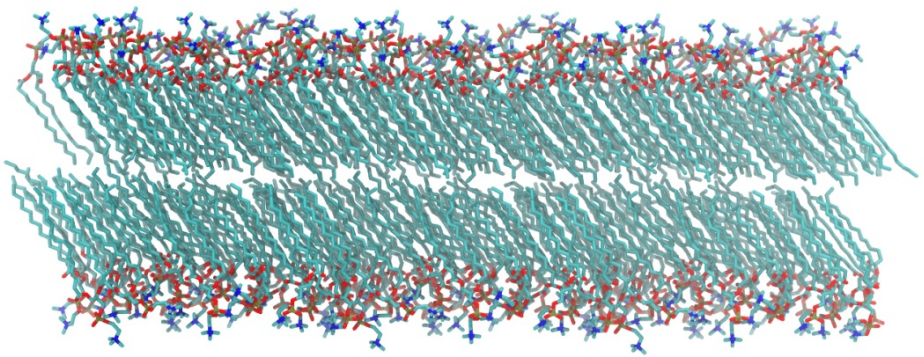
CPU-only

#Cores	hr/ns	ns/day	%Eff
20	1.99	12.1	
40	1.06	22.7	94.0
60	0.74	32.4	89.7
80	0.63	38.4	79.6

- Two weeks to get 300ns with GPUs and this took over two months on older generation HPC.

- Two K20m GPUs on a single node results in 1.24 hr/ns or 19.4 ns per day!
- More significant speedup for larger systems

DMPC/DPPC at 20°C



[1]Klauda, J.B. et al. *JPCB.* **114**: 7830 (2010).

Gel Phase DMPC/DPPC Bilayers Formation

50/50% of DMPC/DPPC at 20oC (300ns)

- Starts with a L_α phase that shortly transitions to a ripple-like phase before gelling
- Chain alignment and tilt between leaflets exists in agreement with experiment

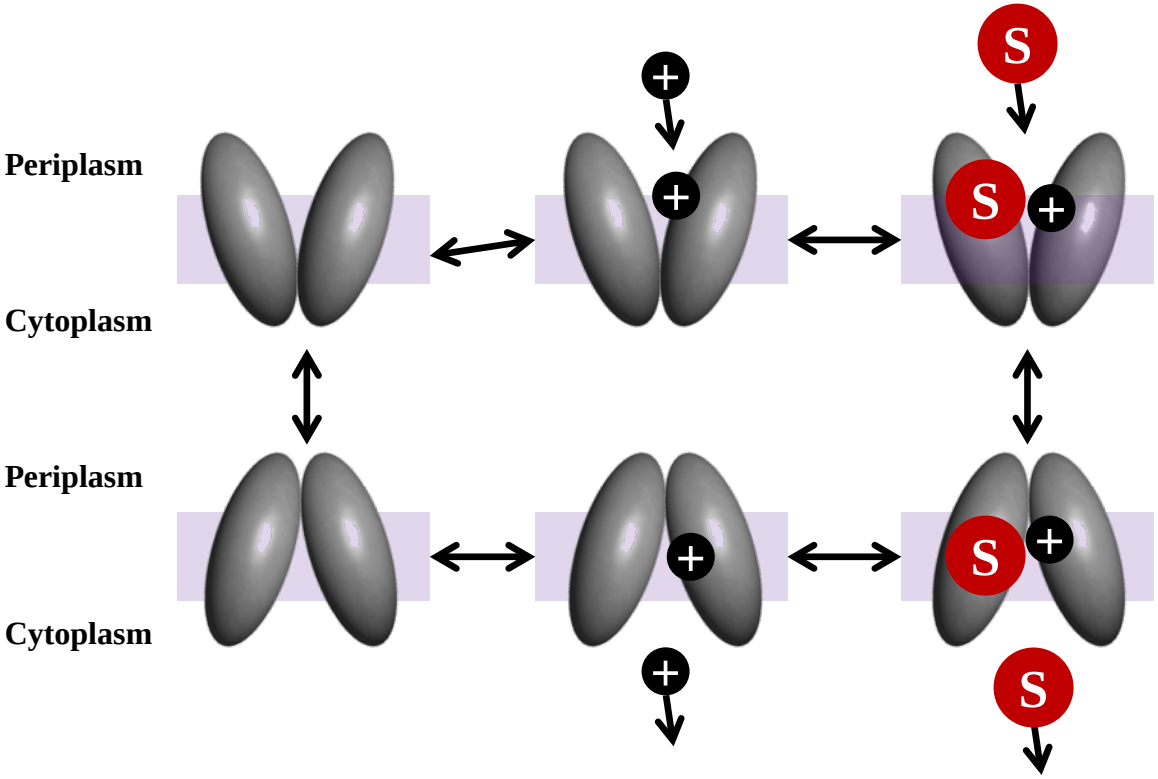
Ripple Phase DMPC/DPPC Bilayers Formation

25/75% of DMPC/DPPC at 25°C (300ns)

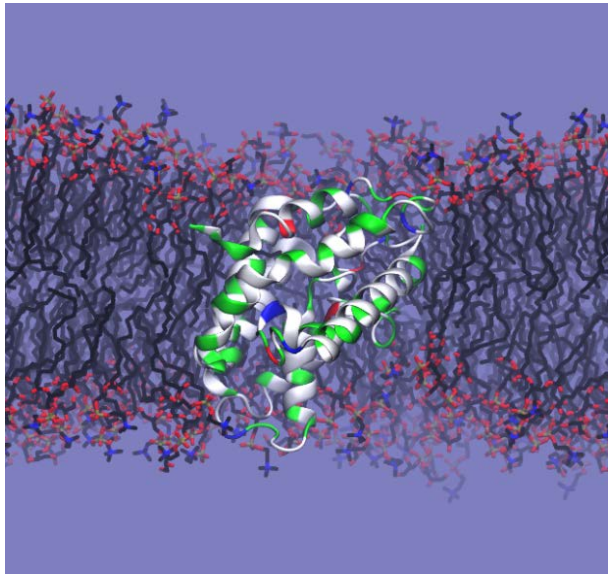
- Starts with a L_α phase that slowly transitions to a ripple-like phase
- Leaflet interdigitation and lipid buckling promotes the ripple-like phase.

Drug Binding to Lipid Bilayers

- Drug Partitioning in Lipids
  - Many drugs and toxins are lipophilic that is they like lipids over water phases
  - Precursor to full transport into/out of cell via membrane transport proteins
  - Alternating Access Model of substrate transport with transmembrane proteins[1]



EmrE Efflux Protein

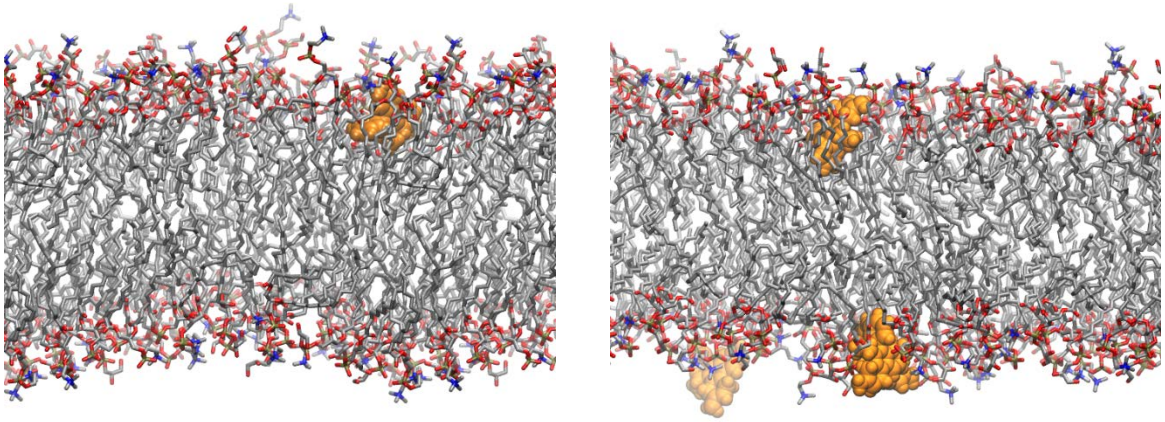


[1]Kaback et al. *PNAS.* **104**: 491 (2007).

MD Simulations of Ethidium Binding to a Lipid Bilayer

- Details of the Simulation
  - Force field and composition: CHARMM36[1] and POPC/POPG bilayer (simple bacterial model)
  - Program & #atoms: NAMD with 30,000
  - Deepthought2 with GPUs for 200ns of simulation time
- Partitioning into Membrane

0.012% Ethidium ***0.047% Ethidium***



  - Benchmark: 18 ns per day with GPU+CPU
  - Quickly sample partitioning and dynamics of antibiotic binding to lipid membranes with the use of GPU+CPU

[1]Klauda, J.B. et al. *JPCB.* **114**: 7830 (2010).

Movie of Ethidium Binding

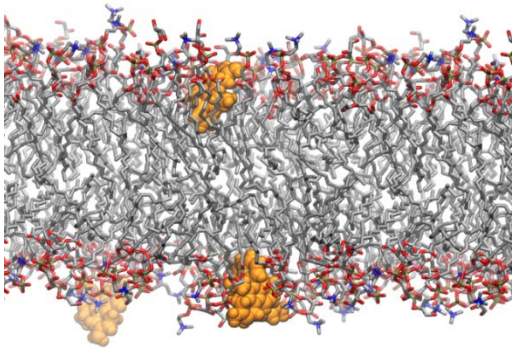
0.047% Ethidium in water with POPC/POPG Bilayer (200ns)

- Quickly determine the extent of drug binding to the membrane
- Ethidium binds to the hydrophobic/philic interface but cannot easily go across the bilayer without the aid of a transport protein

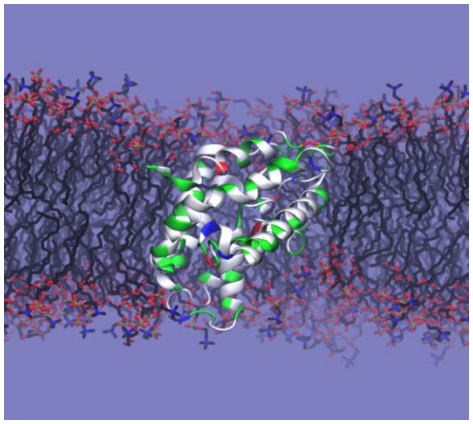
Summary

- MD simulations at the atomic level can probe a wide range of self-assembly and biological problems
- MD simulations require a high amount of computational resources that benefit from GPUs
- Most MD software has been optimized with CUDA programming
- Lipid phase changes are complex but our use of CPU+GPU on DT2 has allowed us to probe gel and ripple phase formation
- Our C36 lipid force field[1] accurately represents the phase transition temperature of PC lipid mixtures
- Many drugs and toxin partition into lipid membranes and fat cells of the body
- The use of GPU nodes has allowed us to quickly determine the tendency of drugs to bind to membranes and their location
- All of these projects are currently being applied to protein-related research in drug transport and understanding of diseases

Ethidium in BIlayer



EmrE



[1]Klauda, J.B. et al. *JPCB.* **114**: 7830 (2010).

Acknowledgments

Outside University of Maryland

Richard Pastor (NIH/NHLBI)
Rick Venable (NIH/NHLBI)
Will Prinz (NIH/NIDDK)
Klaus Gawrisch (NIH/NIAAA)
Mary Roberts (Boston College)
Wonpil Im (University of Kansas)
Alex MacKerell (UMB)
Katie Henzler-Wildman (WU-St. Luis)
Bryan Berger (Lehigh U.)
Hirsh Nanda (NIST)
Yuji Sugita (Riken/Japan)
Cor Peters (TU-Delft/Petroleum Institute)

University of Maryland

Brent Rogaski (M.S. 2010/Industry)
Pushkar Pendse (Ph.D./Postdoc)
Viviana Monje (Ph.D. Student)
Pouyan Khakbaz (Ph.D. Student)
Xiaohong Zhuang (Ph.D. Student)
Joe Lim (undergrad/MIT)
Diana Villanueva (undergrad/GSK)
Chris Boughter (undergrad-phys)
Sylvia Kang (undergrad-BioE)
John Daristotle (undergrad)
Sook Wong (undergrad)
Ryan Konas (undergrad)
Connor Welch (undergrad)
Francis Bacarisas (undergrad-BioE)

Prof. Mikhail Anisimov (ChBE/IPST)
Dr. Ella Mihailescu (IBBR)

Funding and Computational Resources

NSF CAREER (MCB-1149187)
NSF/BIO (DBI-1145652)
National Institutes of Health (intramural)
Anton at NRBSC/PSC [PSCA00009P]
XSEDE [TG-MCB100139]/OIT (UMD)