SAND2008-3533C

Modeling Biological Membranes as Complex Nanoscale Fluids

Laura J. Douglas Frink

June 23, 2008

Bath University, UK

Colder Insights Corp

Sandia National Laboratories

Albuquerque, New Mexico USA

Andrew Salinger – software development

Mike Heroux – solver algorithms

Amalie Frischknecht – physics of polymers and membranes

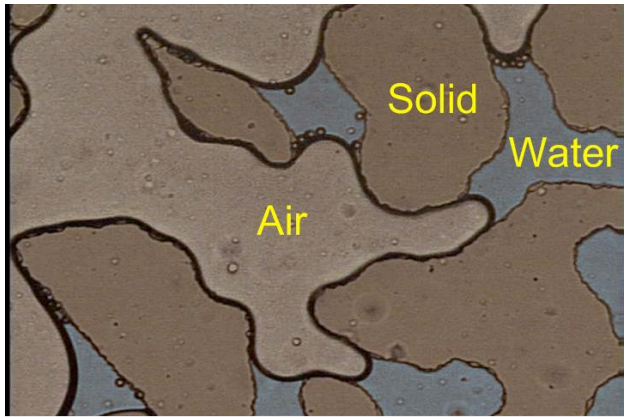
Frank van Swol – physics of surfaces and fluids

Sandia is a multiprogram laboratory operated by Sandia Corporation, a Lockheed Martin Company, for the United States Department of Energy's National Nuclear Security Administration under contract DE-AC04-94AL85000.

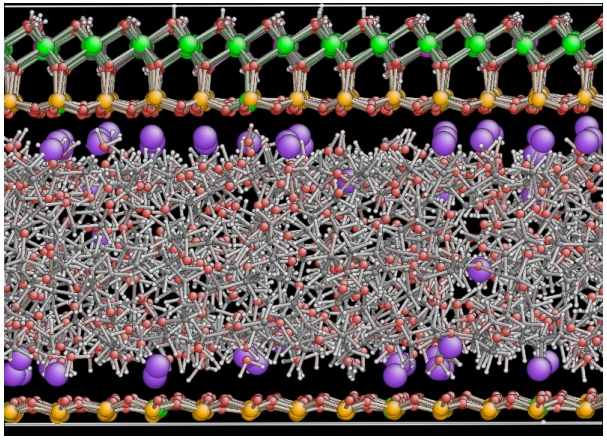
NNSA National Nuclear Security Administration

Sandia National Laboratories

Fluids at Interfaces



Porous Media
(www2.bren.ucsb.edu/~keller/micromodels.html)



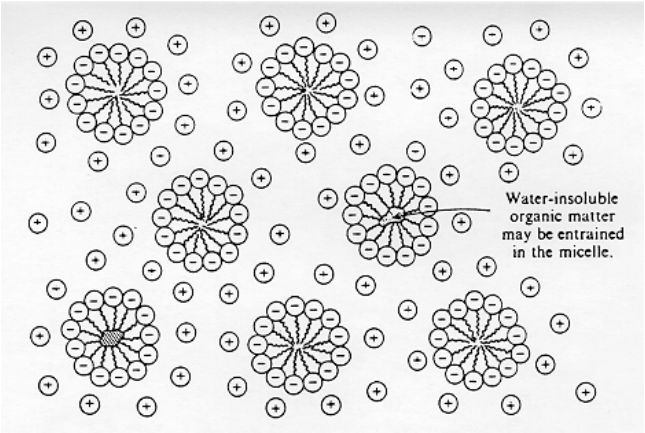
Clay-polymer nanocomposites
(Univ. College London exclaim.org.uk)

- Complex Fluid Structure

- Self-assembly

- Properties differ from bulk
  - *density, diffusion viscosity, etc.*

- Rich phase behavior
  - *wetting, capillary condensation, layering etc*



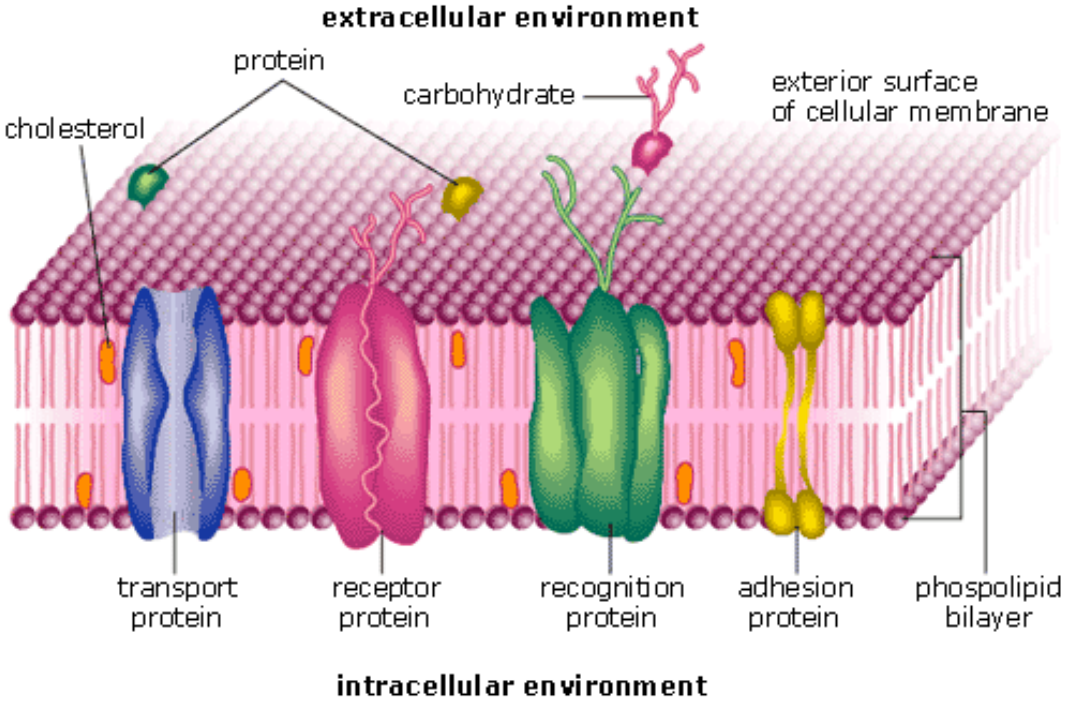
Colloidal/Amphiphilic systems
(www.science.duq.edu)

Biological Membranes

- Complex self-assembled fluid structure

- Properties differ from bulk

- Rich phase behavior - ?
  - *rafts*
  - *pore formation*
  - *protein orientation*
  - *others…*



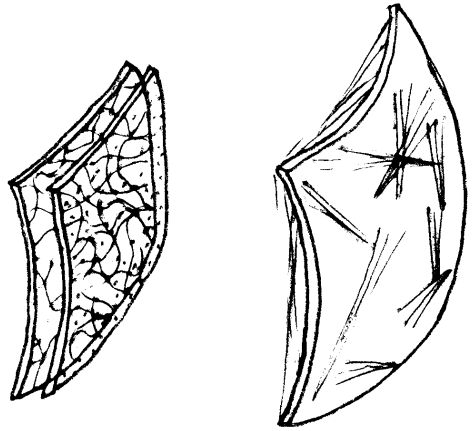
Modeling strategies

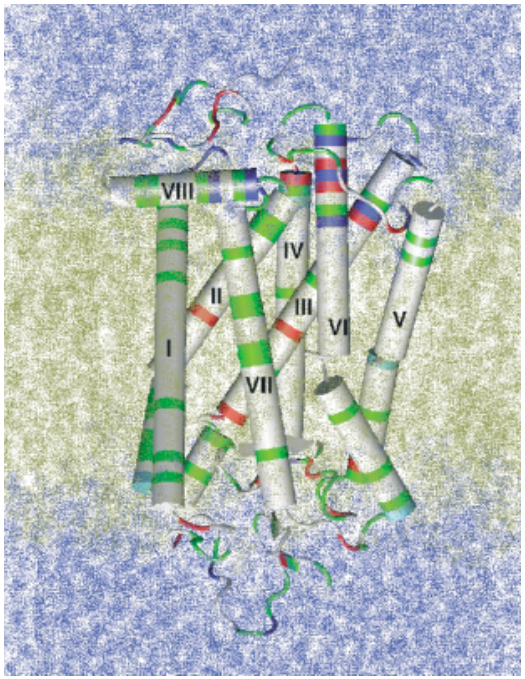
- Continnum elastic membrane (bilayer)

- Landau / Helfrich models (bilayer).
  Free energy functional depends on membrane properties.

- Coarse-grained molecular models.
These models predict bilayer assembly.
(MD and theory)

- Fully atomistic models. (MD)





Crozier et al,
J. Mol. Bio (2003)

40 ns MD simulation
99 DOPC lipids,
7441 waters,
and rhodopsin
(41623 atoms).

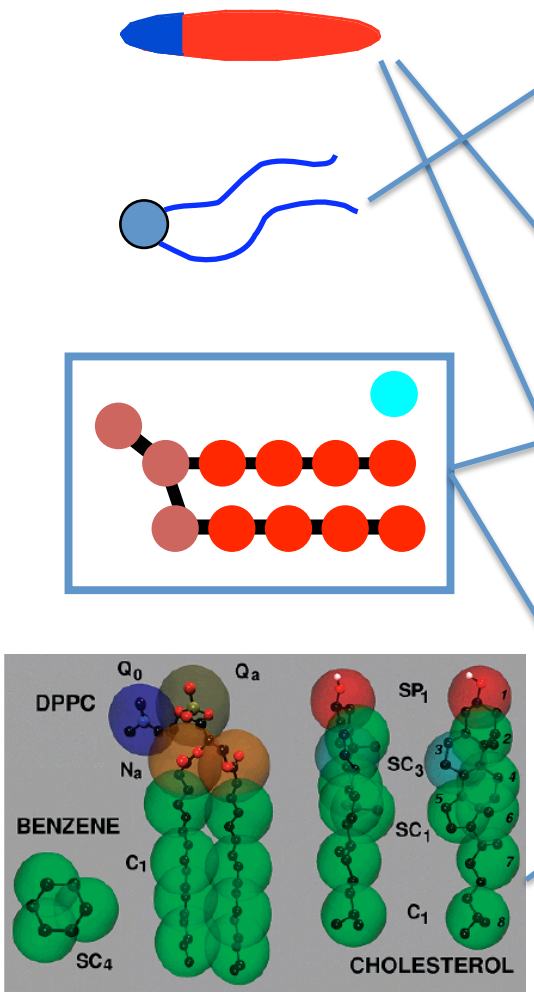
Coarse-Grained models

I. Rigid, anisotropic lipids
(Samoza et al., Brannigan et al.)

II. Thread lipids
(Leermakers et al., Schick et al.)

III. Site model lipids
(Goetz & Lipowsky, Stevens et al., Marrink et.al.)

IV. United Atom lipids
(Shelley et.al.; Marrink et.al.)



I. Self-Consistent Field Theory

II. Density Functional Theory

III. MD / MC

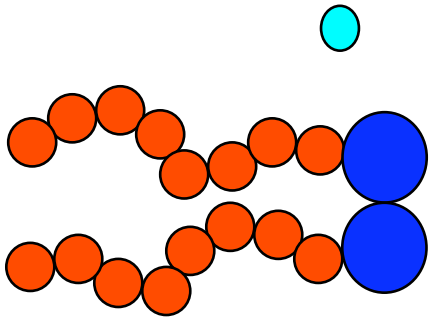
Fluids-DFT

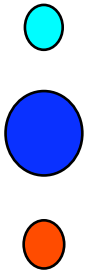
- **Fluids- Density Functional Theories**
  - Van der Waals, Landau and Lifshitz (1935, magnetic domain boundaries), Mitsui and Furuichi (1953, ferroelectric interfaces) Cahn and Hilliard (1958, structure and tension of interfaces), Onsager (1949, liquid crystals).
  - 1976: Ebner, Saam, and Stroud - first application fo a LJ fluid
  - Formulated at the level of the free energy functional.
  - Minimization of free energy leads to equilibrium solutions.
  - Proper DFTs are self-consistent and satisfy sum rules.
  - In most cases, free energy functionals are not exact.
  - Specifics : (WJDC functional) Jain, Dominik, and Chapman – 2008.
    (CMS functional) Chandler, McCoy, Singer.

- **Integral Equation Theories – cousins to DFT**
  - Ornstein & Zernike – with closure relation
  - Formulated at the level of correlation functions (second functional derivatives of free energy)

- **Quantum mechanical – DFT**
  - Widely applied for electronic structure in a field produced by nucleii.
  - Same theoretical basis as Fluids-DFT.

Coarse-grained molecular model





solvent

Head groups

Tail groups

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

Cut and shifted Lennard-Jones potentials … *cutoffs = 3.5σ*

Define:

state point and

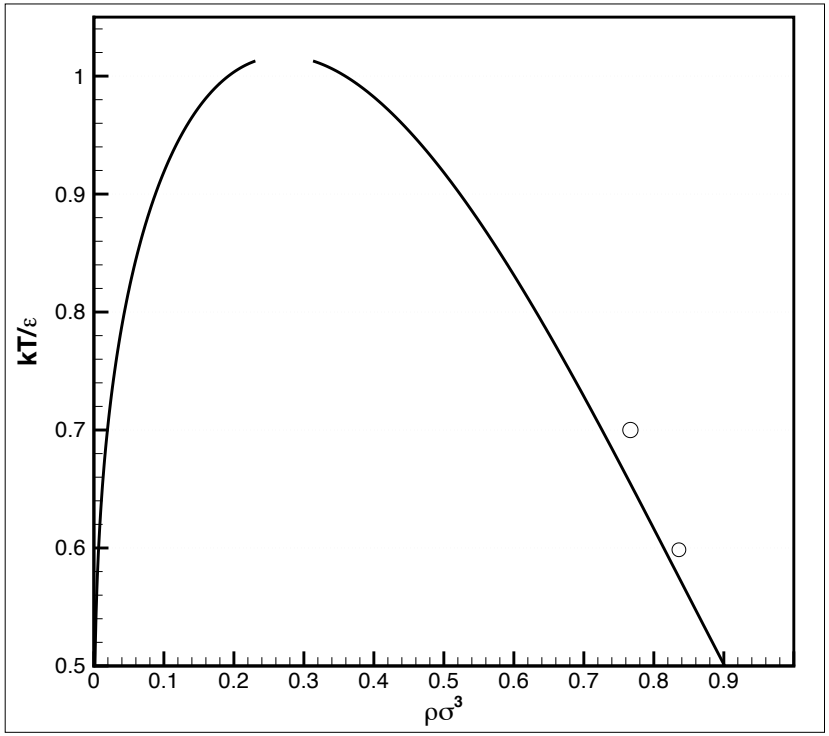
energy parameters, ε

State parameters

Biological membranes are zero tension membranes. The temperature and pressure are set by the bulk solvent (water / physiological electrolyte).

	$T_{critical}$	T_{triple}	T
H_20 (°C)	374	0.01	37
Model (k_BT/ε)	1.015	~0.55	0.6-0.7

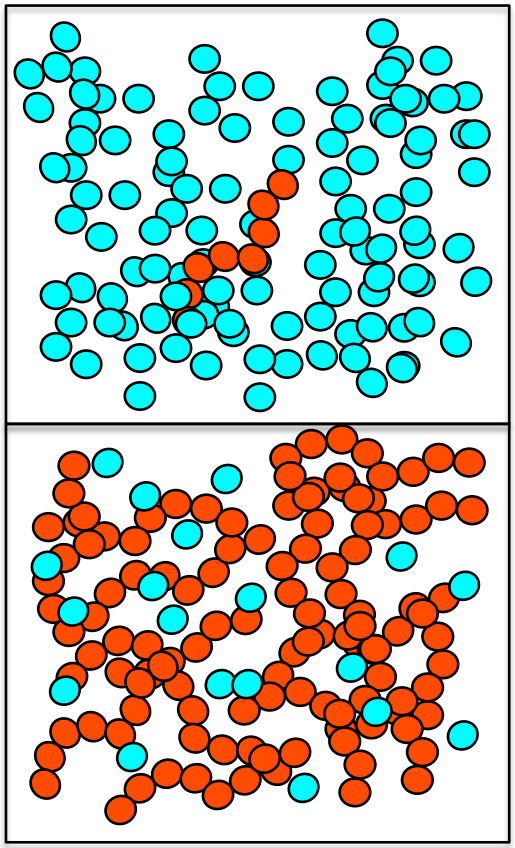
	P	$P_{vap}(T)$	P/Pvap
H_20 (atm)	1	0.0619	16.2
Model ($P\sigma^3/kT$)	0.279	0.00334	16.2



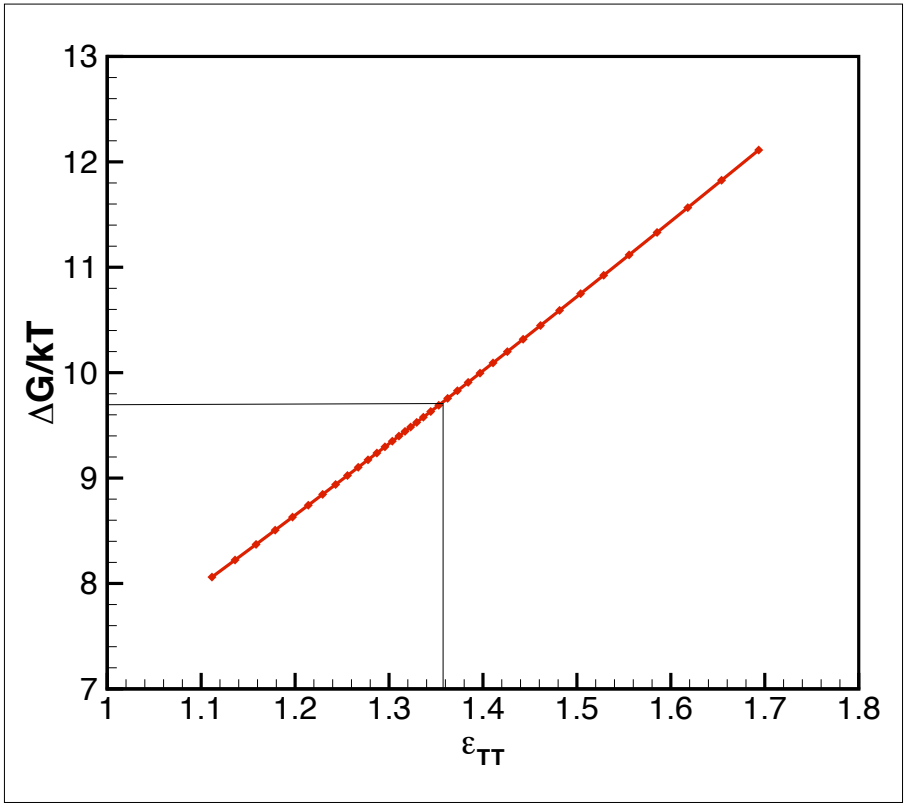
The mappings are not unique because the ***law of corresponding states*** is not true for a comparison of LJ fluids and water.

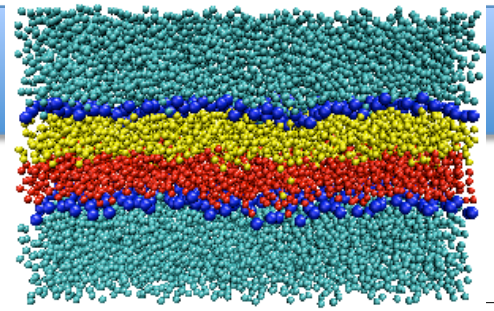
Partitioning Calculations

Energy parameters are set to mimic the interactions of water with hydrocarbon tails of lipid chains. Partitioning studies of the model system were done on water and hexadecane (= 8 "tail" beads). *ΔG/kT=9.69 for water/hexadecane at 40°C*

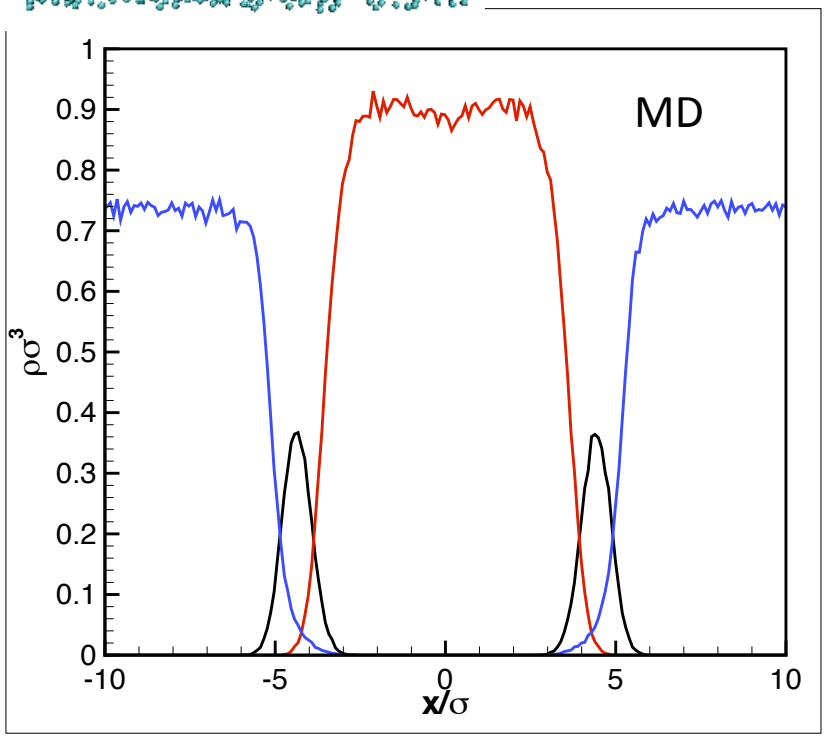


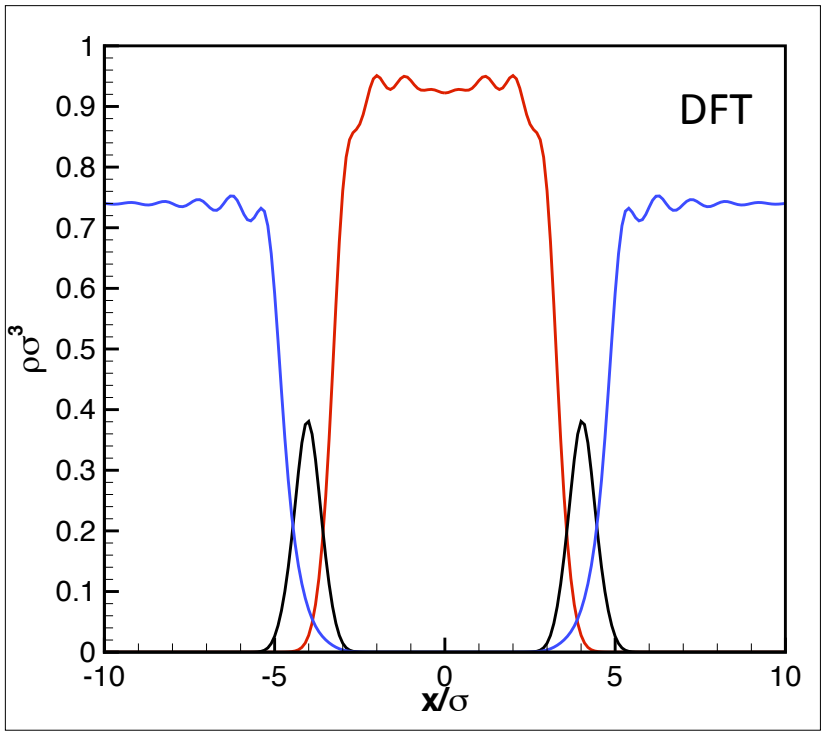
$$\Delta G / kT = -\ln(\rho_w^{oil} / \rho_w^{aq})$$





Comparing MD and DFT





$kT/\varepsilon=1.0$

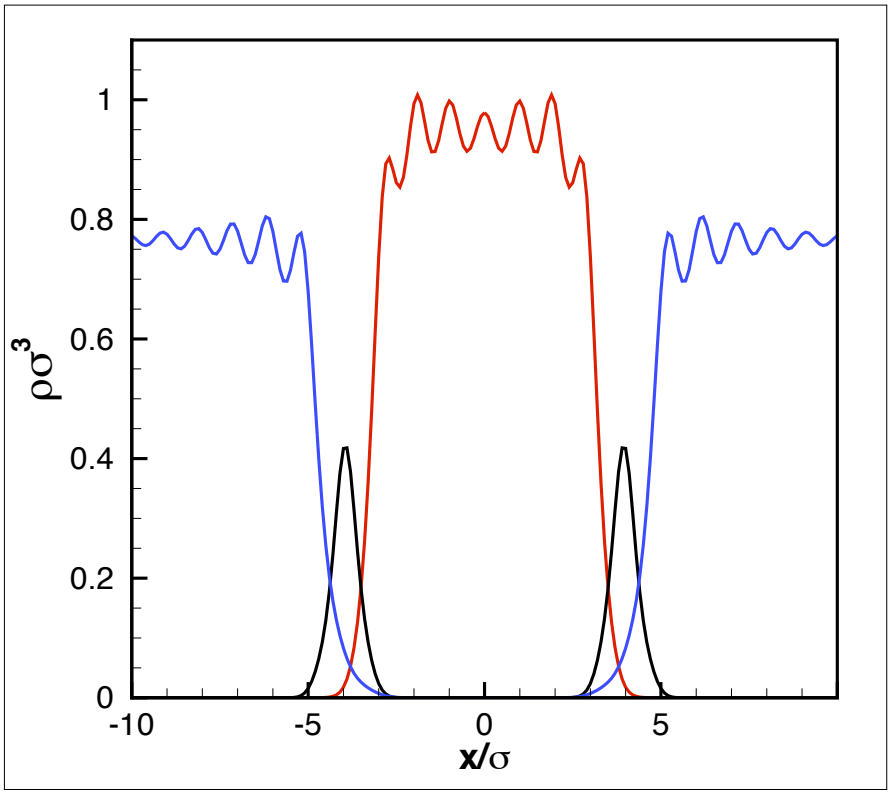
$P\sigma^3/kT=0.5$

	Head	Tail	Solvent
Head	1	0	1
Tail	0	1	0
Solvent	1	0	1

$kT/\varepsilon=0.7$

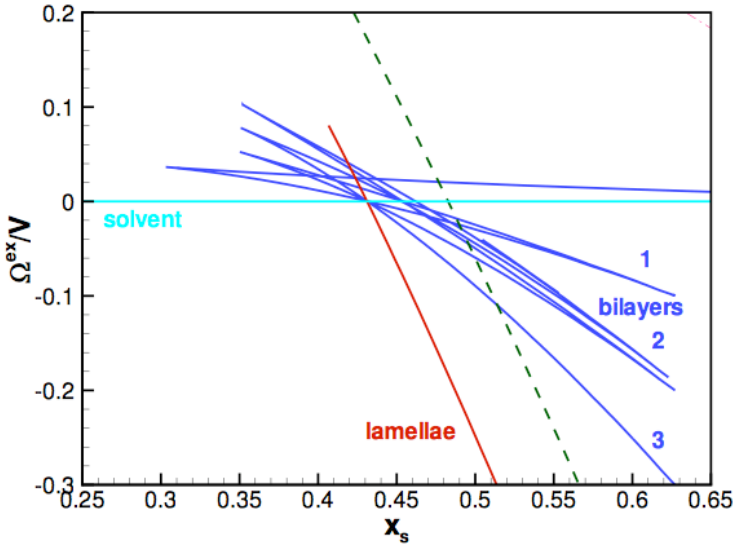
$P\sigma^3/kT=0.28$

	Head	Tail	Solvent
Head	1.42	0.51	1.42
Tail	0.51	1.38	0.51
Solvent	1.42	0.51	1.42



Bilayer Stability

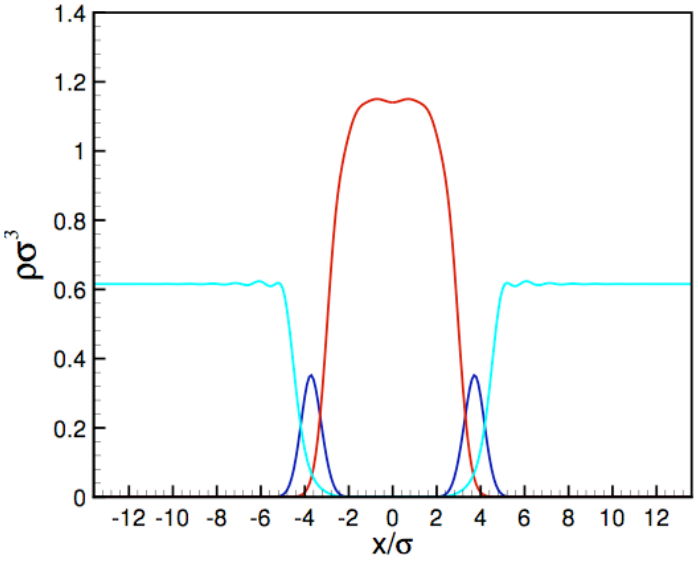
arc-length continuation

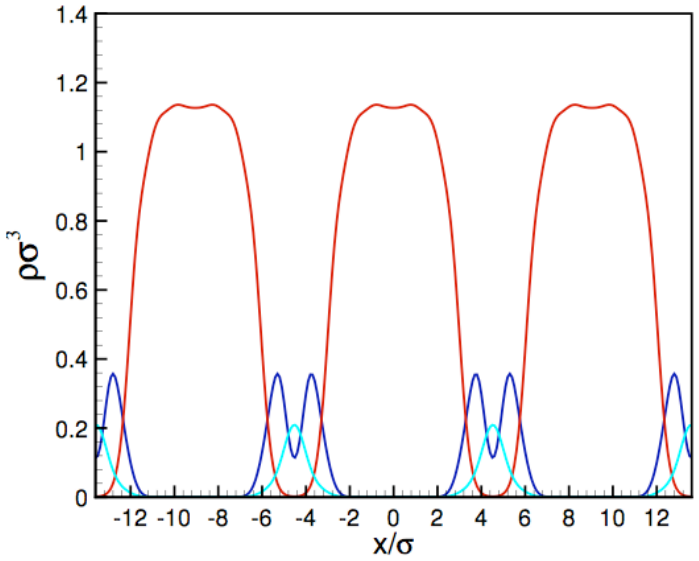


x_s = "bulk" solvent fraction

$$\Omega^{ex}/V = \left(\Omega\left[\rho(r)\right] - \Omega_s\right)/V$$

zero surface tension: $\Omega^{ex}/A = \gamma = 0$

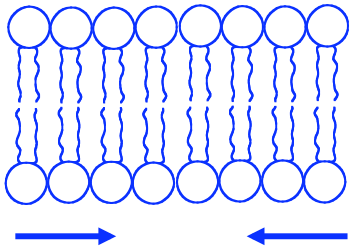




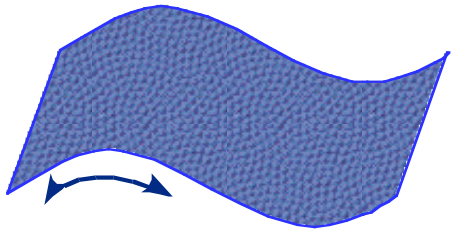
Frink and Frischknecht, Phys. Rev. E, 2005

Bilayer Elasticity

overall elastic properties

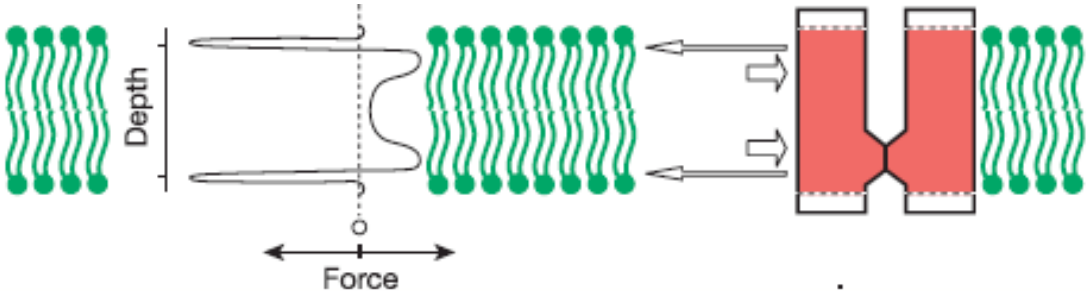


K_A: area compressibility modulus



κ: bending modulus

Lateral pressure profile:



Alcohols in Bilayers

- higher area/per lipid
- lower thickness
- increased permeability

affect mechanical properties

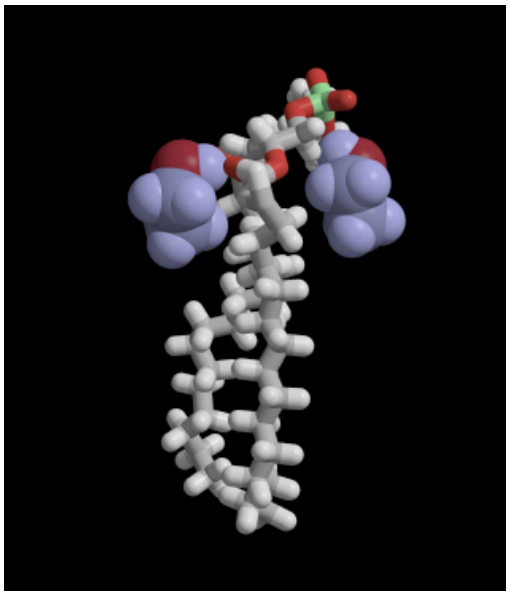
↓

membrane protein function

↓

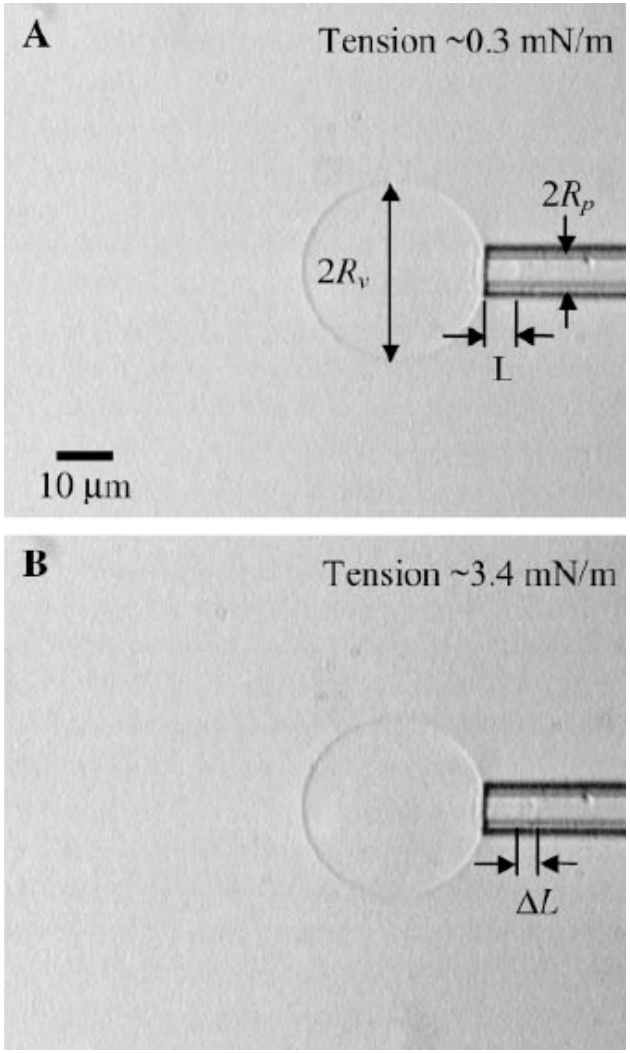
general anesthesia
"stuck" wine fermentation
limits on ethanol production

alcohols destabilize membranes



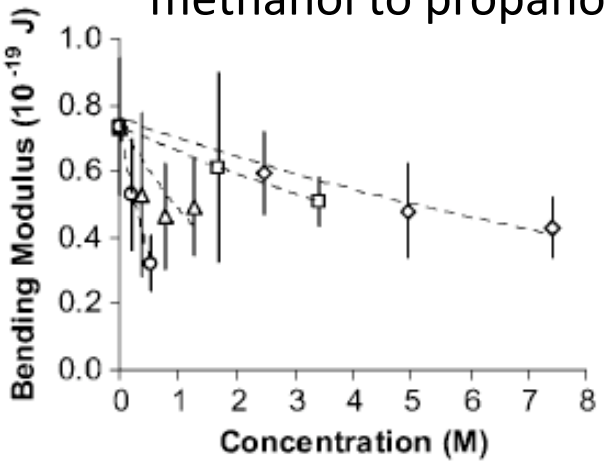
Patra et al, Biophys J (2005)

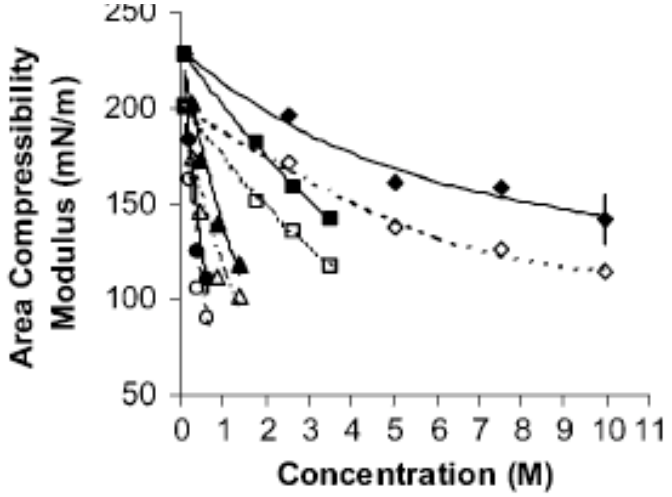
Experimental



Ly and Longo, Biophys. J. (2004)

moduli decrease
methanol to propanol



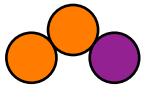


Model Alcohols

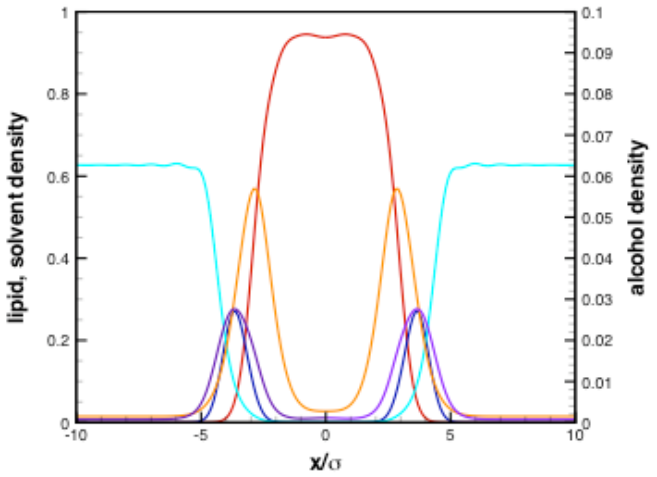
$kT/\varepsilon = 1.3$; $\rho_b\sigma^3 = 0.68$

- 2 CH_2 groups, size σ, likes tails
- OH group, size σ, likes solvent, heads

"butanol"

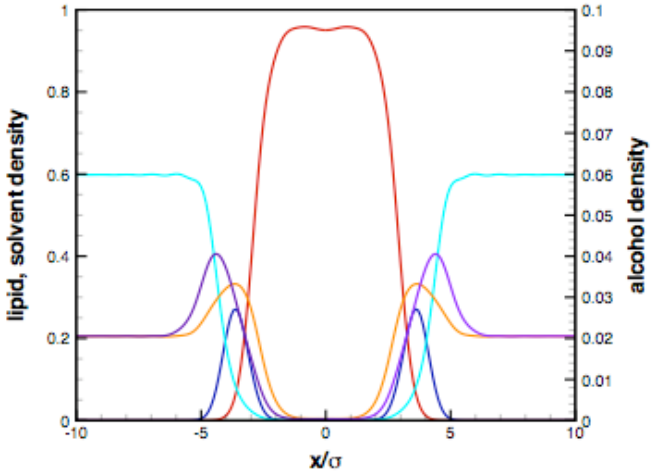


f_{alc} = 0.1%

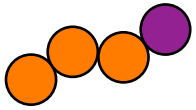


"ethanol"

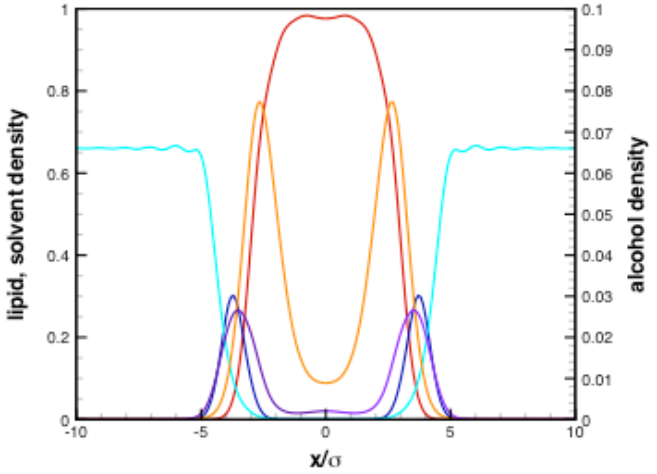
f_{alc} = 3.3%



"hexanol"

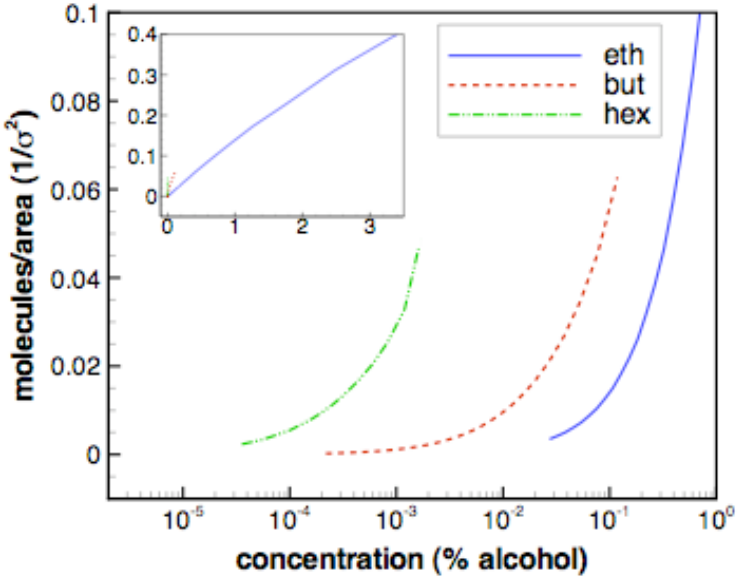


f_{alc} = 0.005%

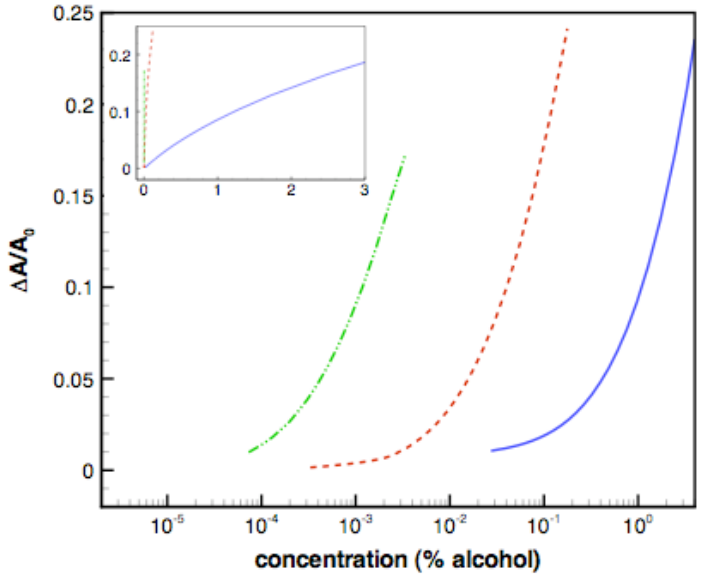


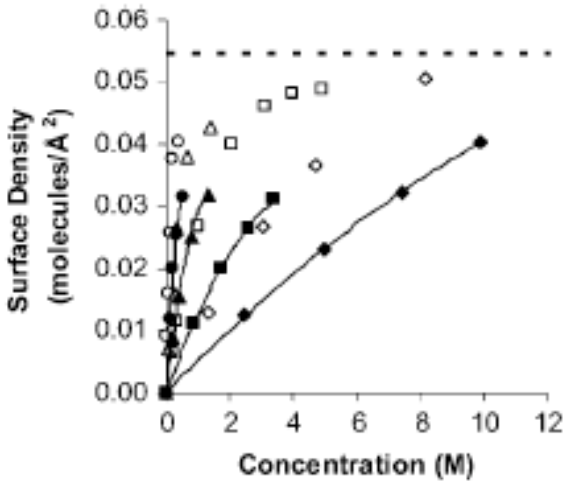
Structural effects

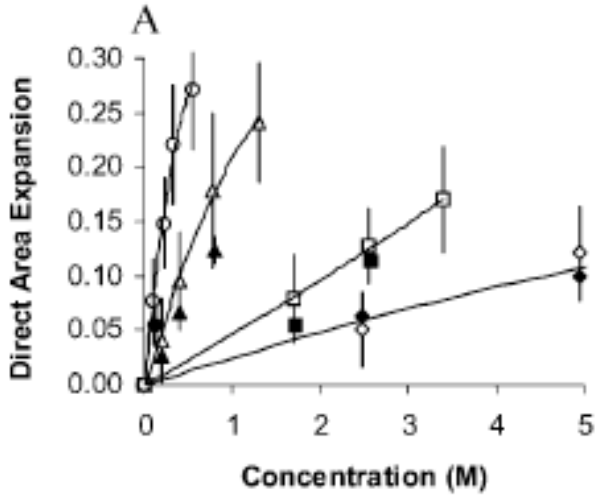
adsorption



area per lipid







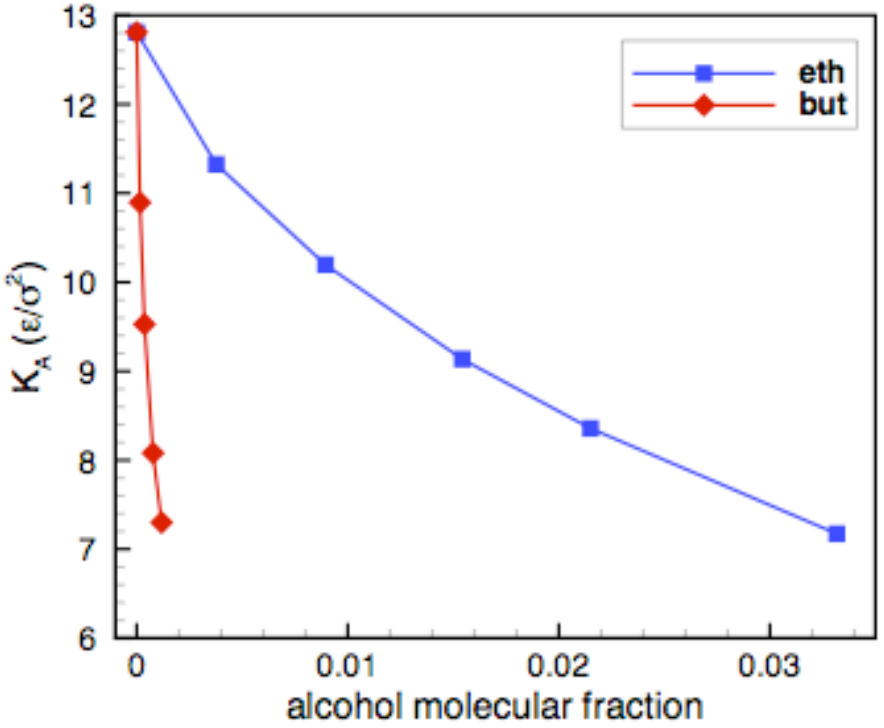
Area compressibility

total surface tension $= \gamma \equiv \Omega^{ex} / A$ $\qquad \gamma \approx K_A (A - A_0)/A_0$

≈ 42% decrease as add alcohol

≈ 35-45% decrease in experiment

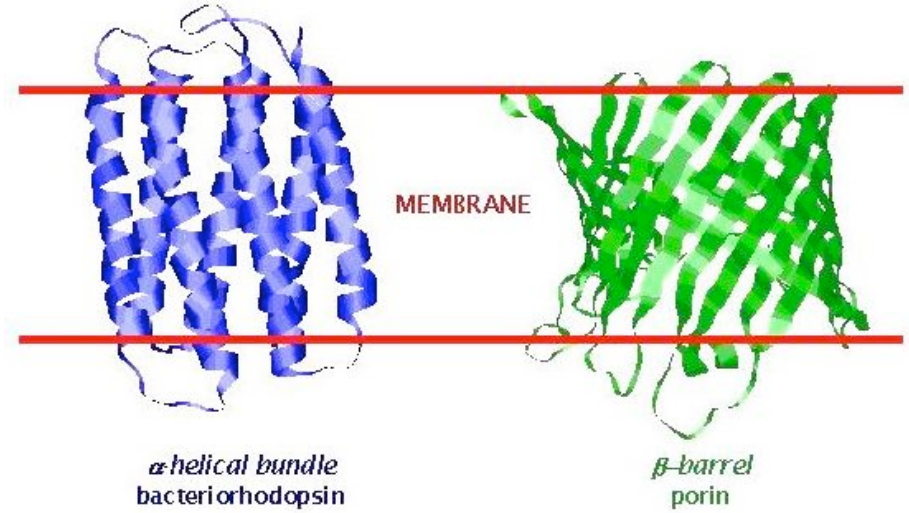
H. V. Ly and M. L. Longo, Biophys. J. (2004)



Peptide Assemblies

Biology

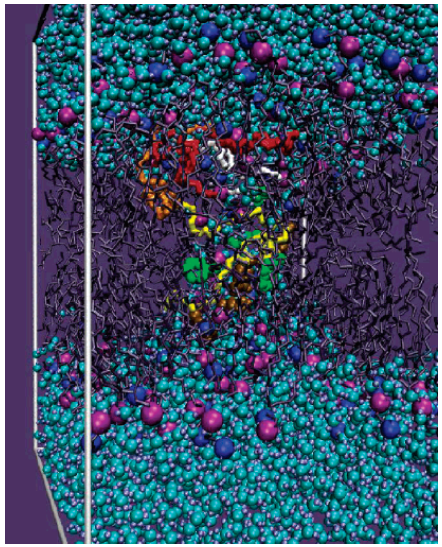
- **Found in bacterial, archaeal, eukaryotic cytoplasmic and organellar membranes**
- **Antibimicrobial peptides**
- **Ion channels**
- **Pore-forming toxins**
- **Viruses**



S. White Lab: http://blanco.biomol.uci.edu/mp_assembly.html

Nanotechnology

- **Sensors**
- **Smart Materials**

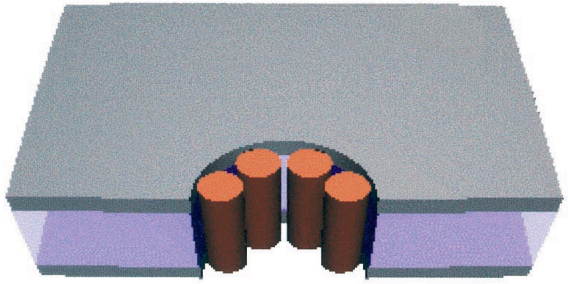


magainin pore

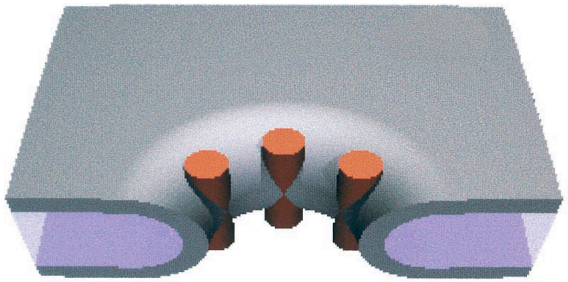
Leontiadou et al., JACS, 128, 12156 (2006)

AMPs in membranes

Barrel-stave structure

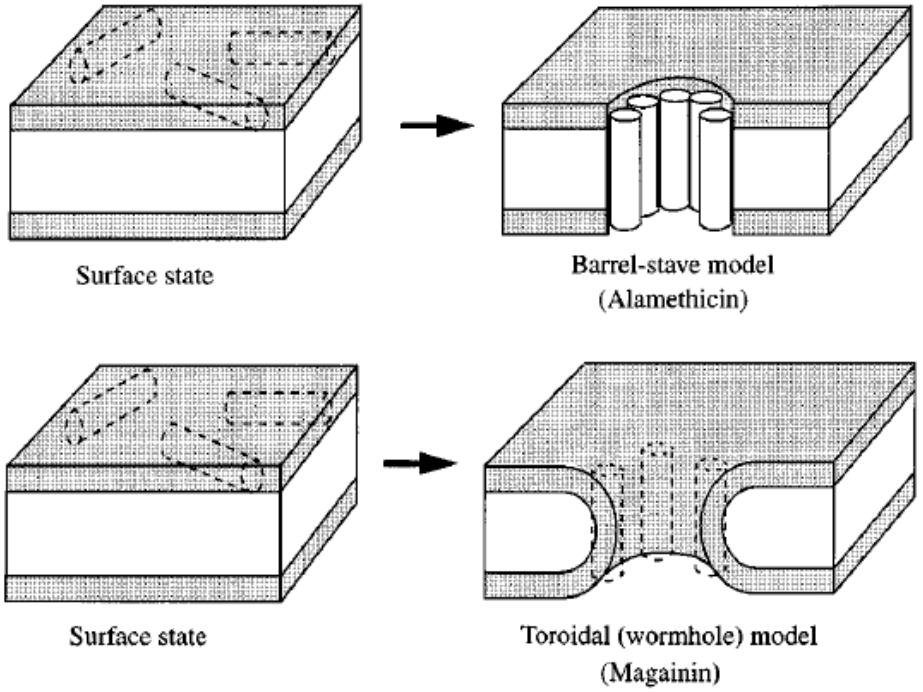


Toroidal structure



Yang et al., Biophys. J. 2001

Protein insertion

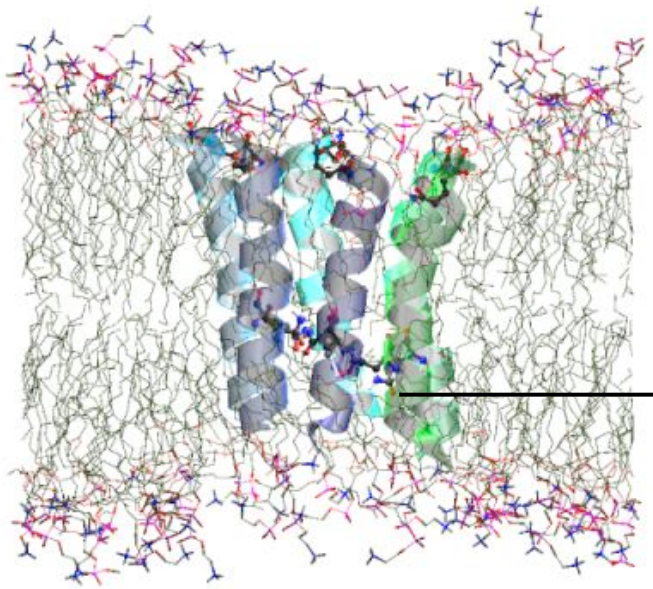


Ludtke et al, Biochemistry, 1996

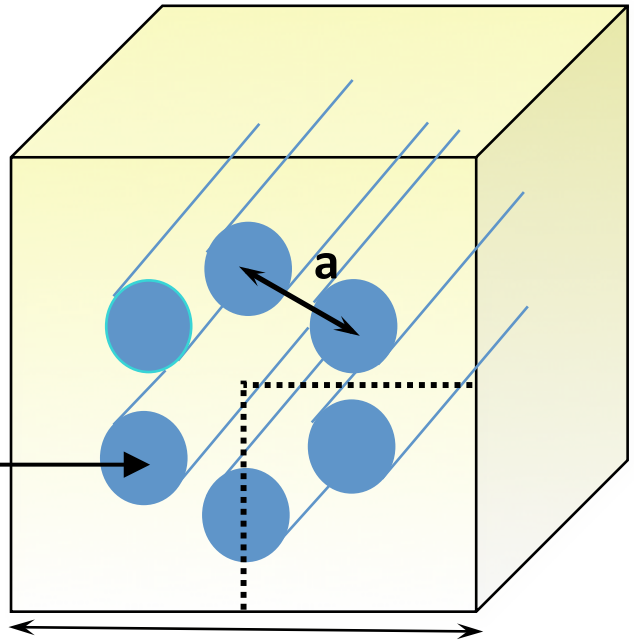
Coarse grained proteins

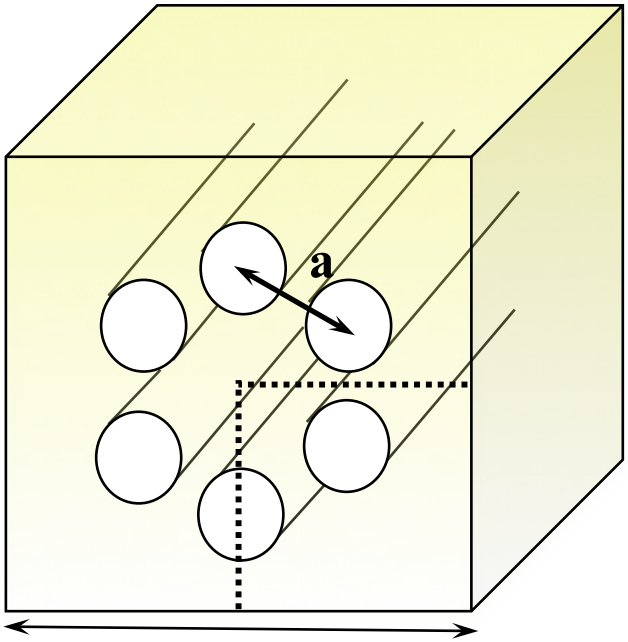
example: 6-helix bundle of alamethicin immersed in lipid bilayer

Tieleman et al., Biophys. J. 1999

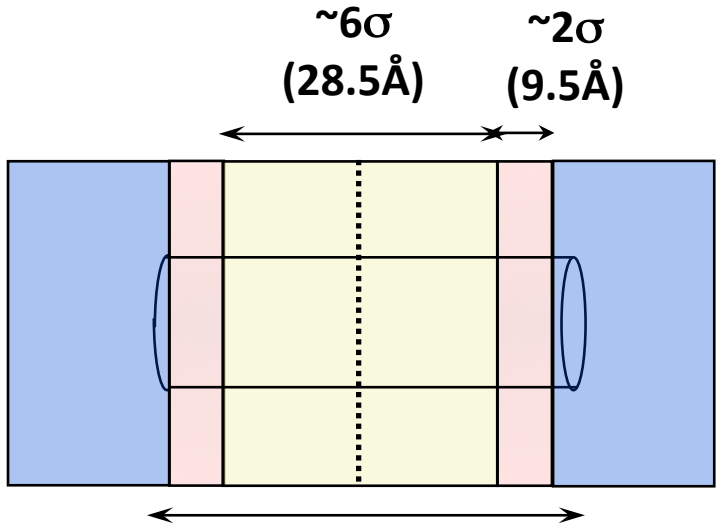


model:
α-helix = cylinder





16-22σ (76-105Å)

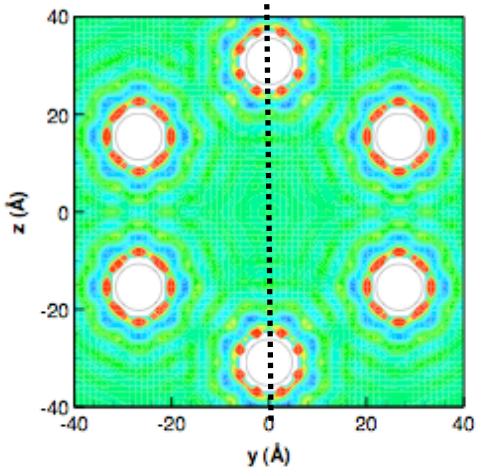


18σ
(85.5Å)

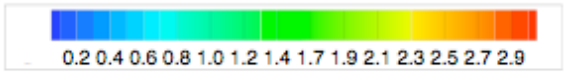
Cylinder-lipid interactions:
- diameter = 2σ = 9.5 Å
- a=lattice constant
- hard (no particular molecular preferences)

3D calculations: Time per solve is ~10-20 minutes on 100 procs

No pore (a = 30.8 Å assembly)

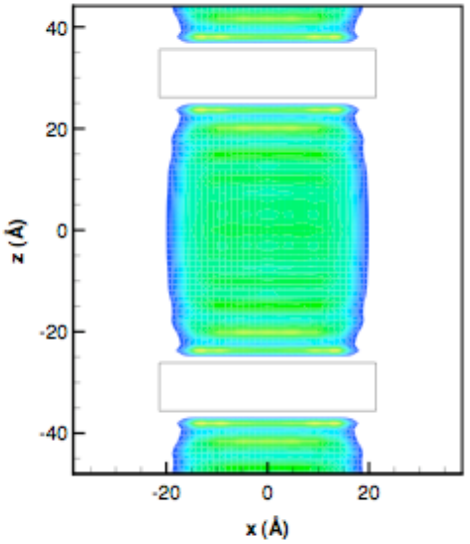


No head groups or solvent in center of bilayer.

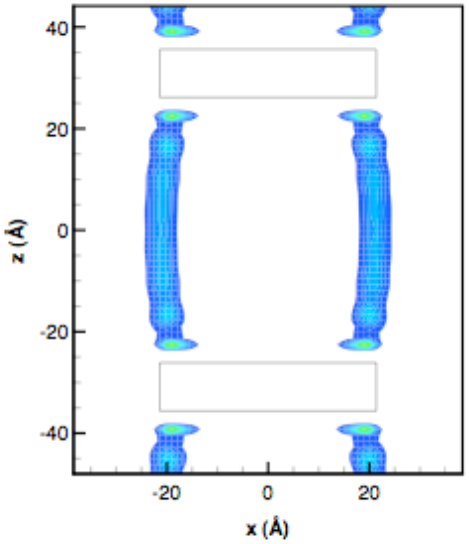


$$\Omega_{mem}^{ex} = \Omega - \Omega_{mem}^{*} = -62kT \approx -37kcal/mole$$

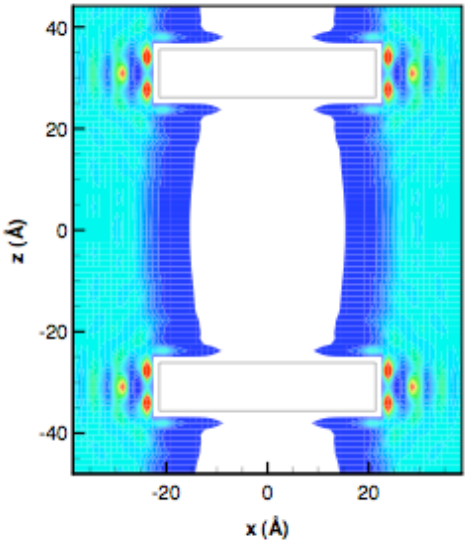
Tails



Heads

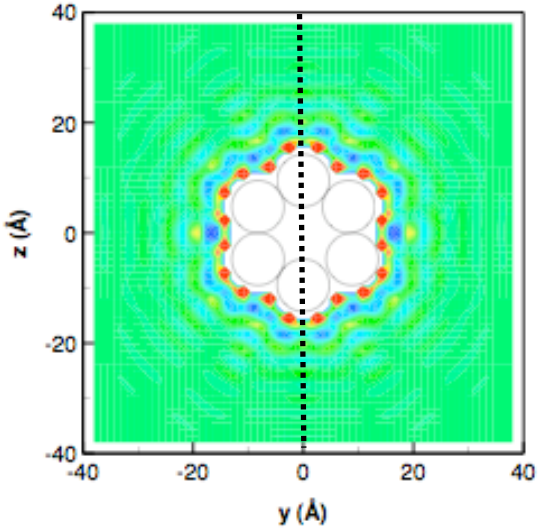


Solvent



Barrel-stave pore (a=9.5Å assembly)

Tails

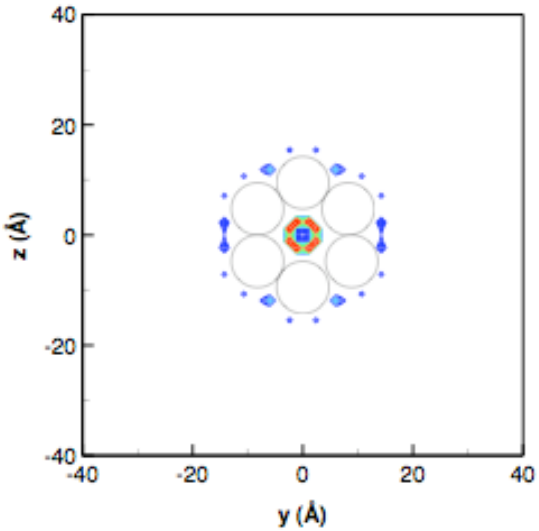


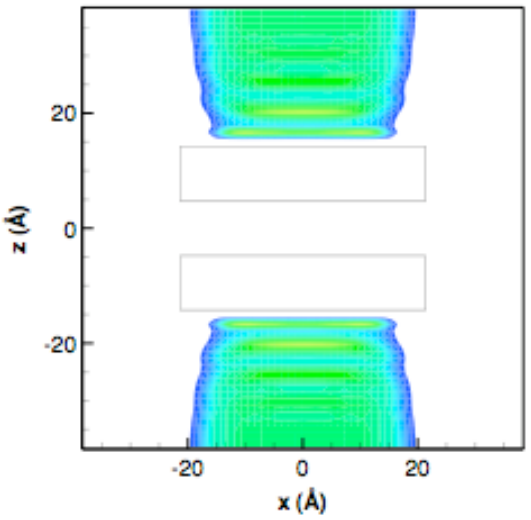
Heads

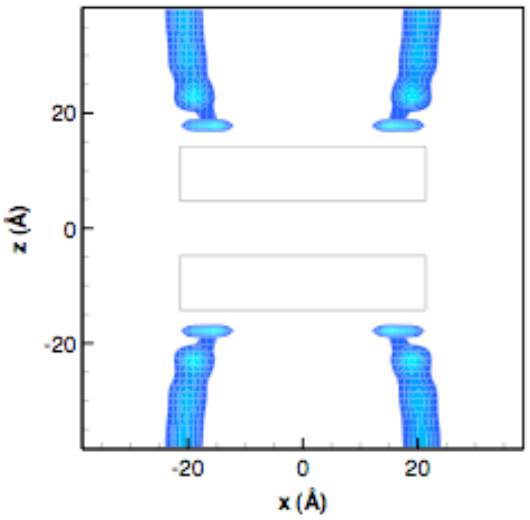
No head groups in center of bilayer.

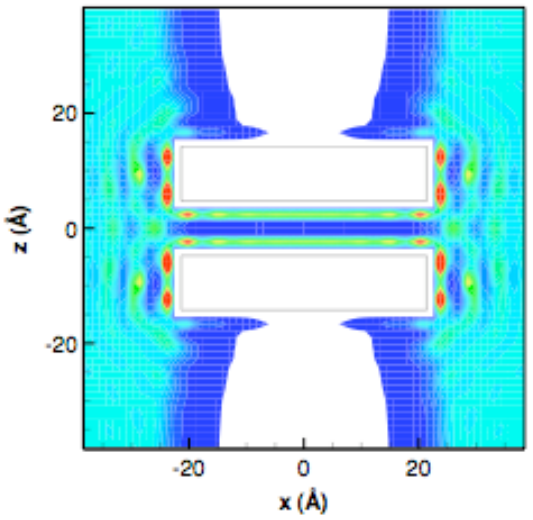
$$\Omega_{mem}^{ex} - 19kT \approx -11kcal/mole$$

Solvent

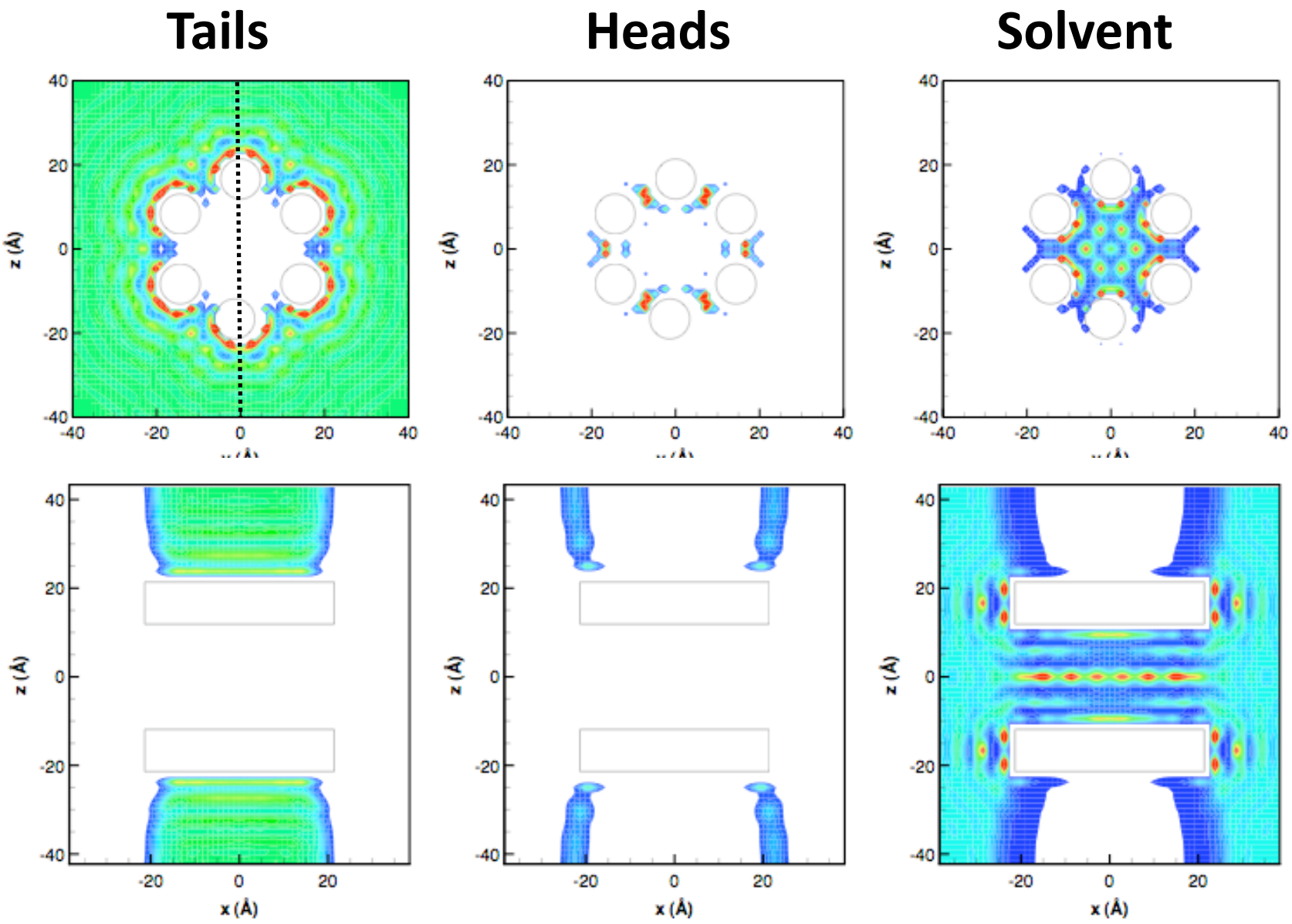




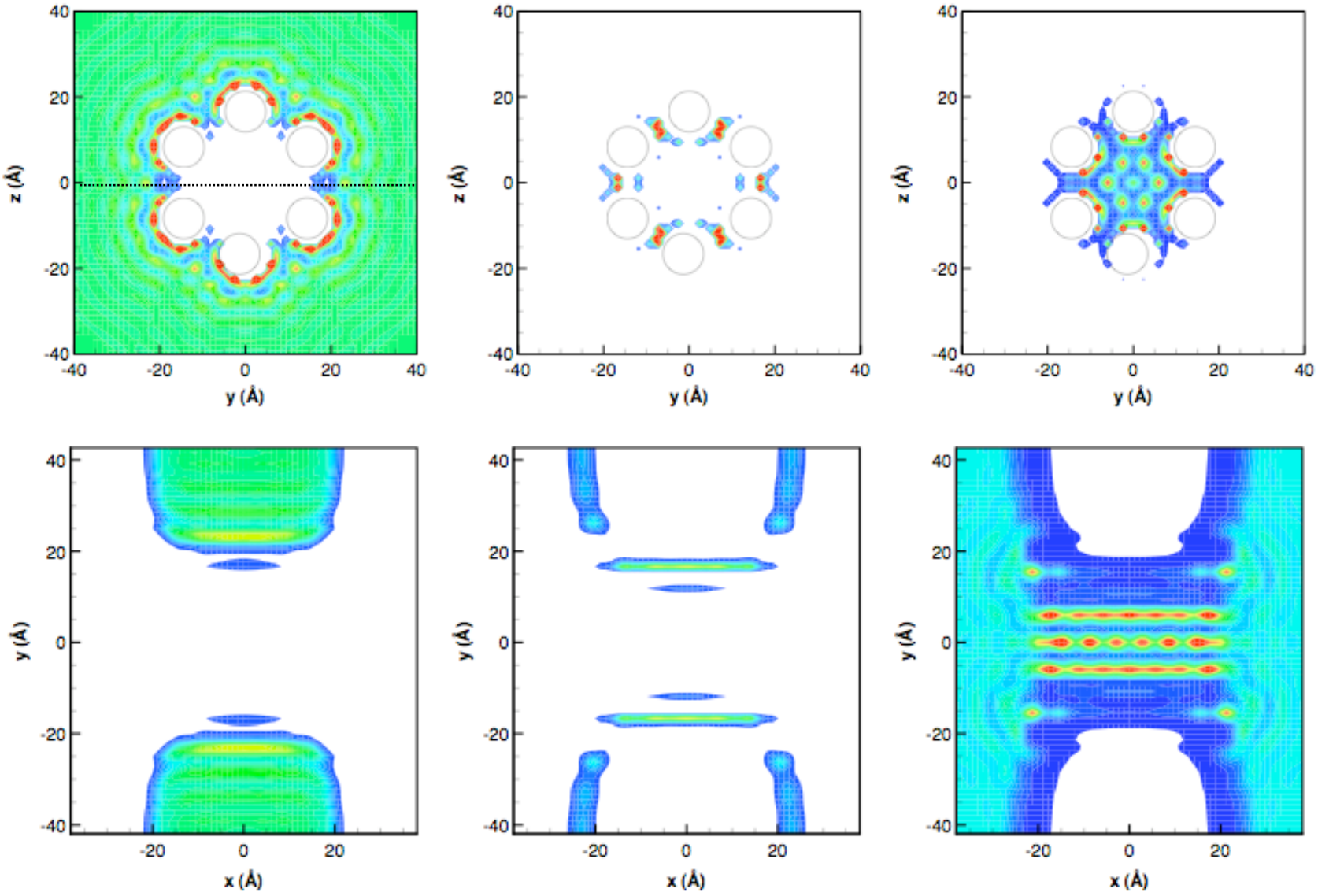


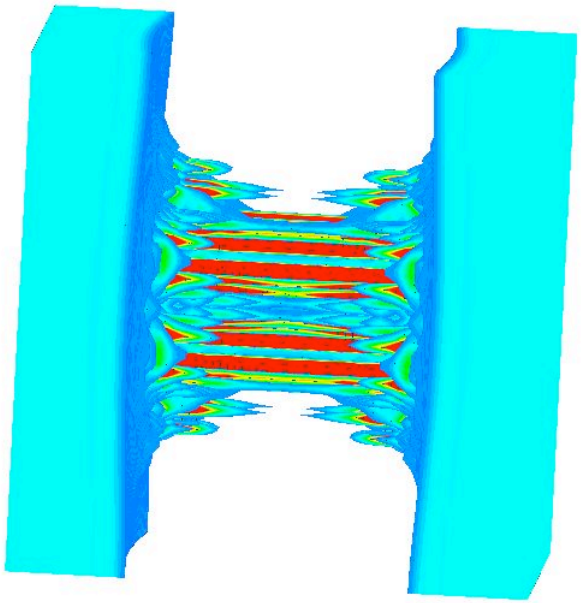


Toroidal pore (a=16.6 Å assembly)

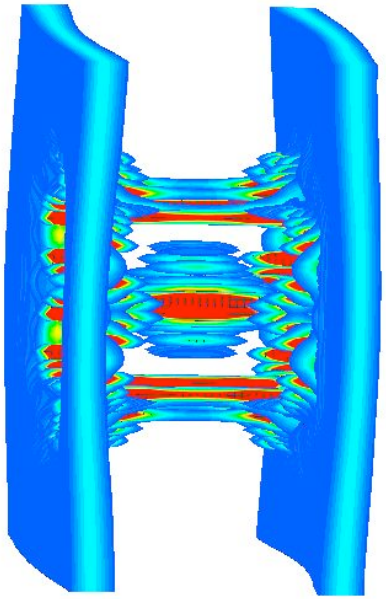


Toroidal Pore (a=16.6 Å) - cut 2

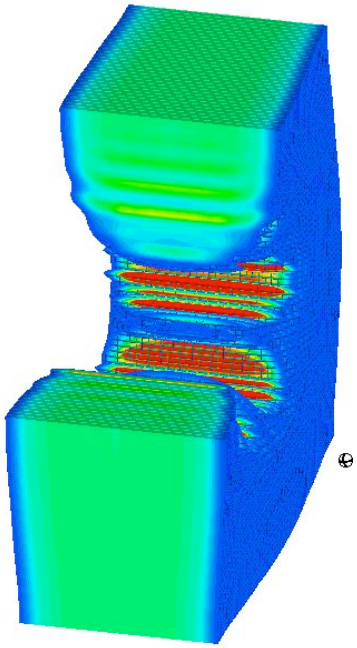




solvent

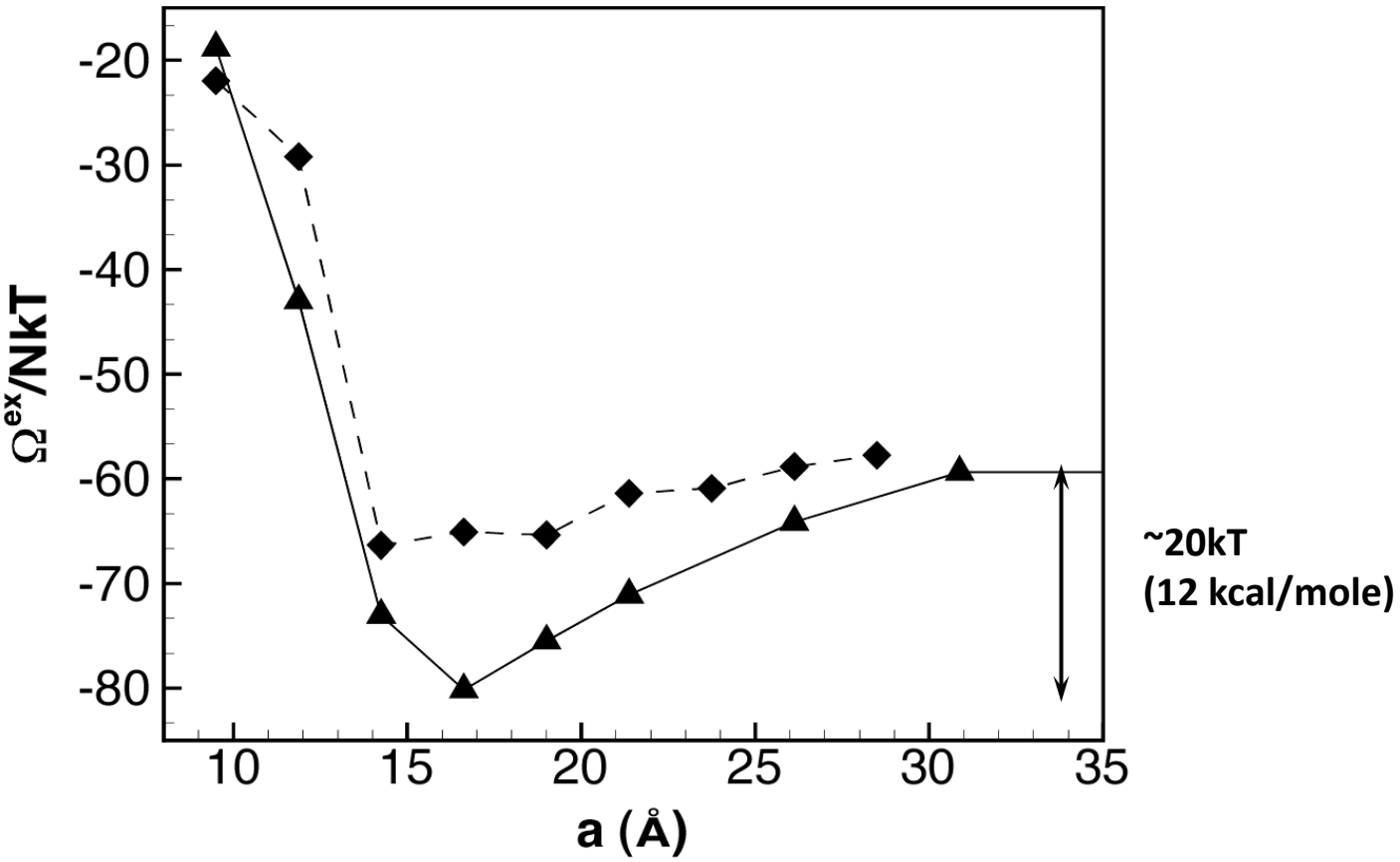


heads



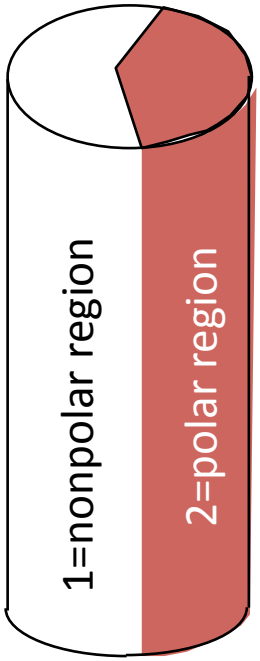
tails

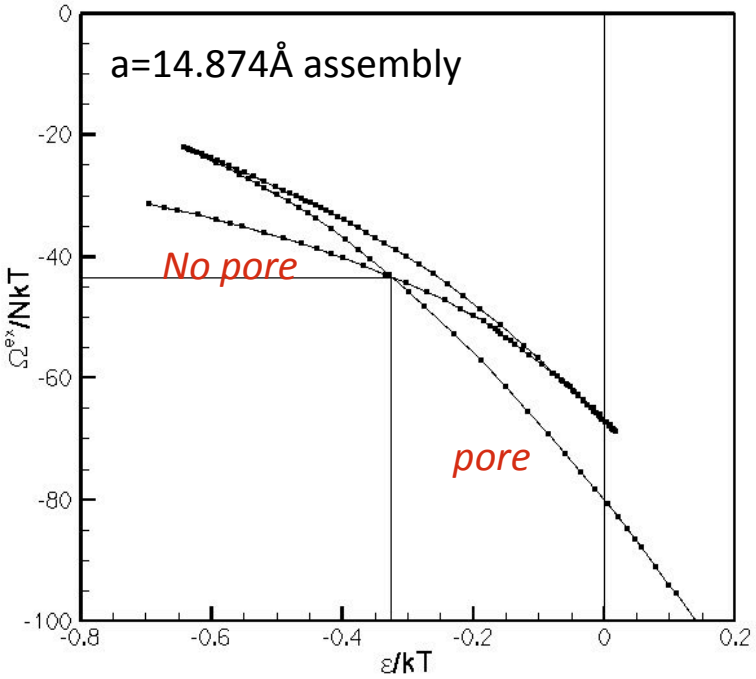
Free energies of the assemblies

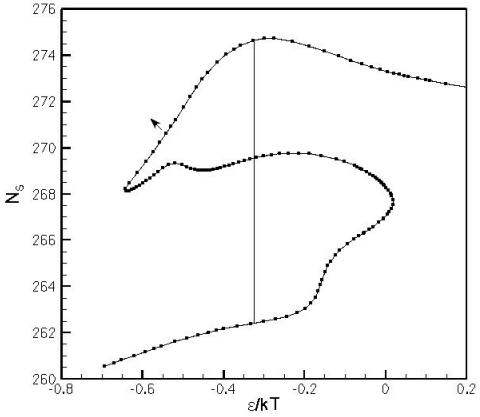


Frink and Frischknecht, Phys. Rev. Lett., 2006

Amphipathic helices





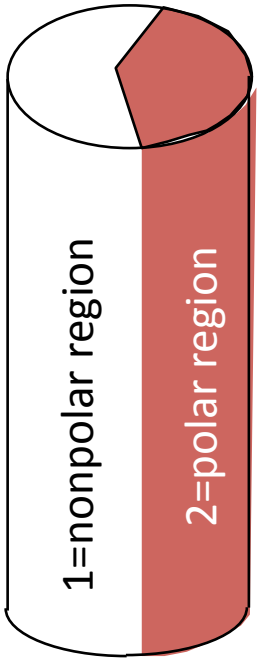


Varying ε_{2s} and ε_{2h}

with $\varepsilon_{1t}=0$

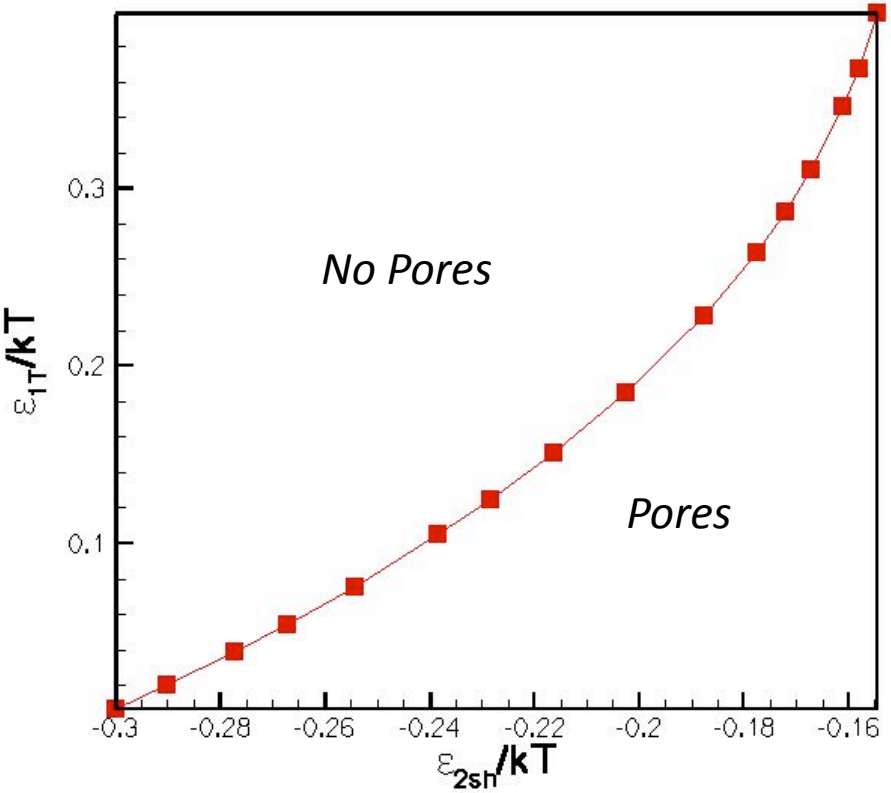
- *a=14.875Å assembly*
- *Found a first order phase transition.*
- *The first converged solution was the metastable solution.*
- *162 data points*

Phase Diagrams



Varying ε_{2s},ε_{2h} AND ε_{1t}

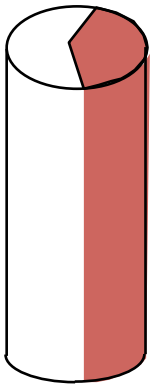
with the constraint that the solutions are at the phase transition (equal free energy).



a=17Å assembly

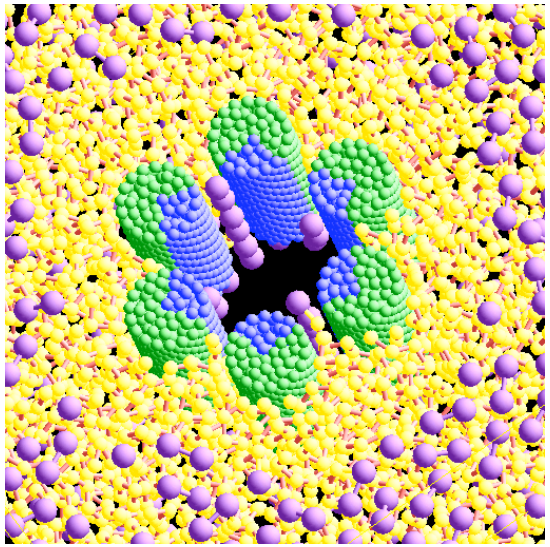
Tuning Molecular Parameters changes Equilibrium state of system.

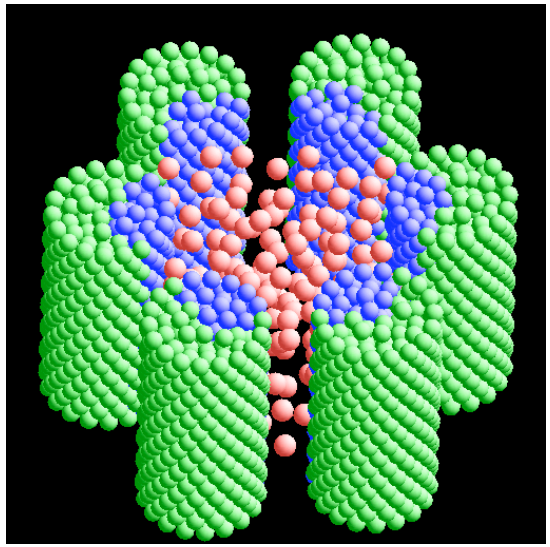
Amphipathic AMPs



- most AMPs: amphipathic a-helices
- angle = 140°
- potential: hard core + LJ attractions

MD simulations: form pore
compare to DFT (ongoing)



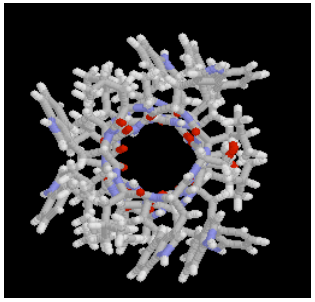


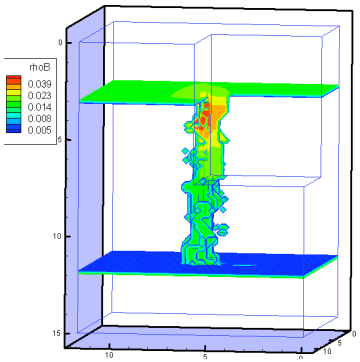
S.J. Plimpton

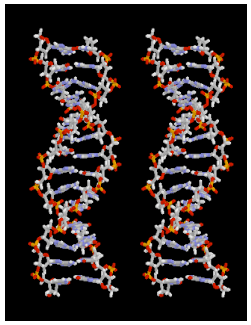
- **Conclusions**
  - Biological membranes are a particularly rich system from a physics perspective.
  - Fluids-DFTs are feasible for studying membrane proteins at a coarse-grained level.
  - These are the first fully consistent 3D molecular theory treatment of peptide assemblies in bilayers. Results from these calculations could be used to construct parameters of phenomenological theories.
  - Method predicts toroidal membrane structures in all cases except when the peptides are tightly packed.
  - Phase diagrams linked to molecular characteristics provide a new physical basis for screening large numbers of peptides (e.g. antimicrobial peptides).
  - Discovering and quantifying the key thermodynamic switches that control biological function will facilitate design of biomimetic nanosystems.

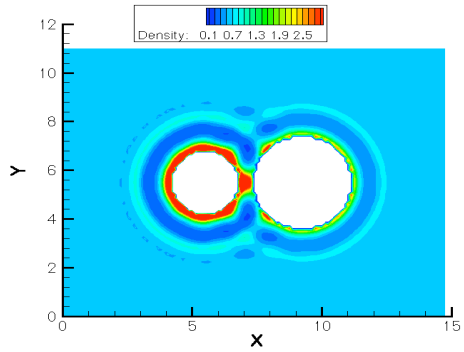
Tramonto

http://www.software.sandia.gov/tramonto









Frink and Salinger, Langmuir 2003