Interactions Between and Within Membranes

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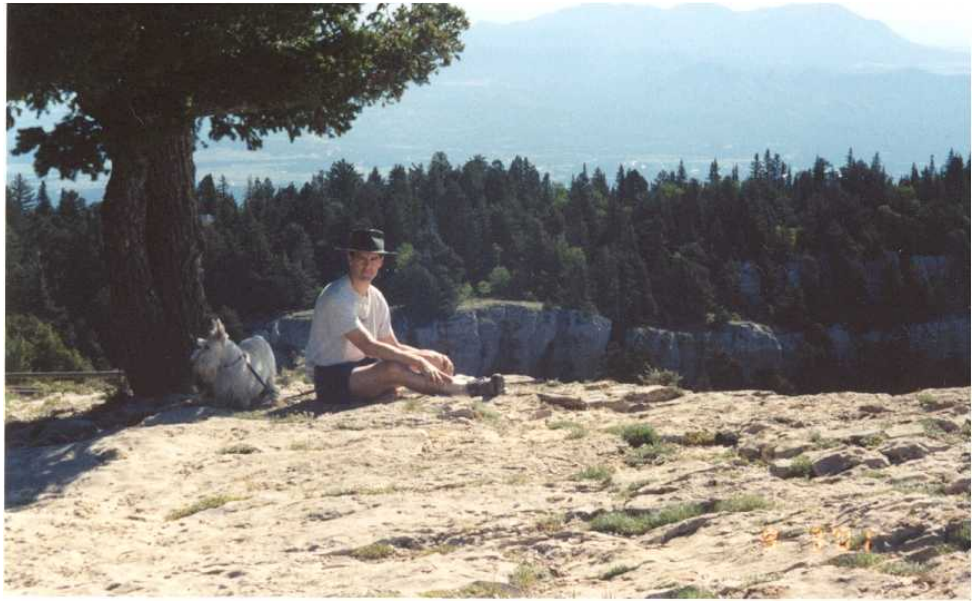

Collaboration:
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Anastacia Gentilcore
Naveen Michaud-Agrawal
JHU Med School
Paul Crozier, Sandia

NIH Grant
5R21GM076443-02

National Institute of General Medical Sciences

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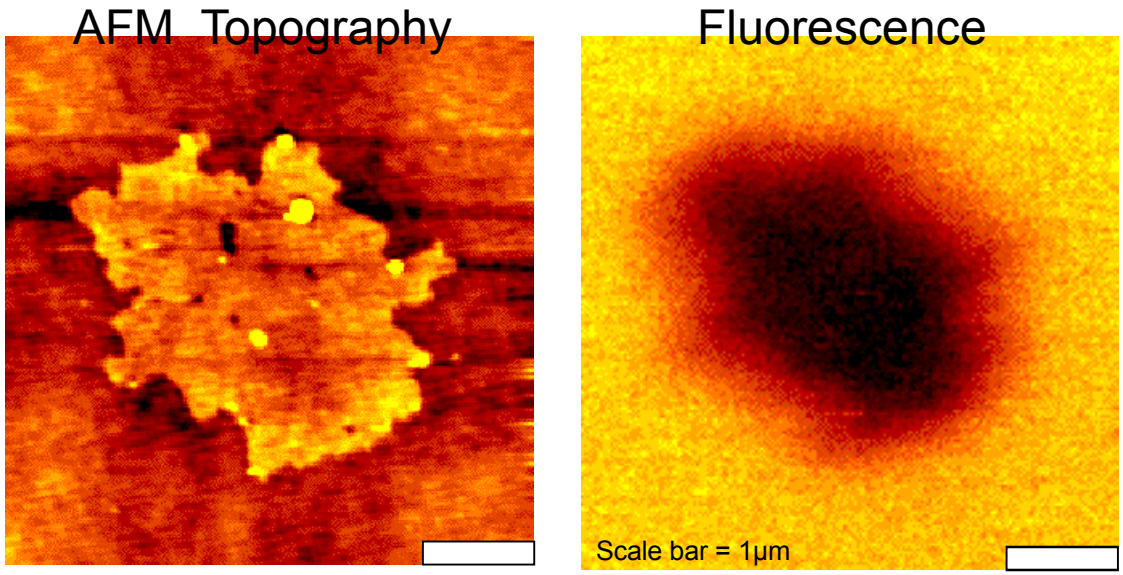
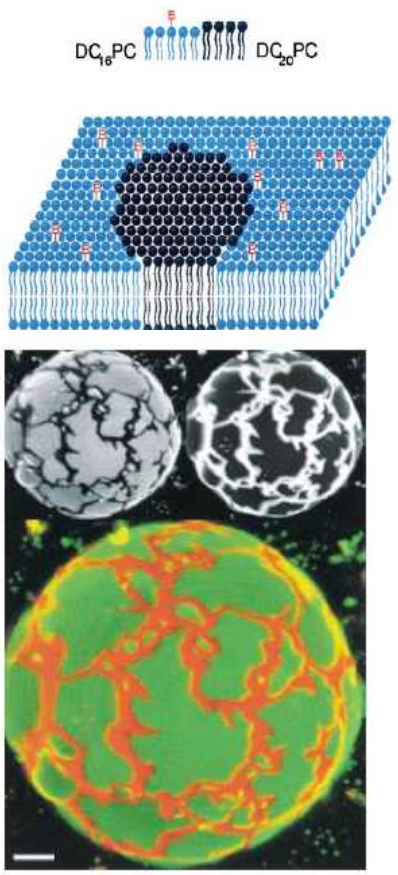
Domains in Biomembranes

- Domains (‘rafts’) in biomembranes have biological function
  - proteins prefer certain domains (‘corrals’)
- Domains form in binary lipid mixtures
  - different chain lengths, saturation levels, ...
  - different phases: e.g. liquid, gel



3:1 DOPC/DPPC with DPPC “rafts”
0.5 % Fluorescent Bodipy-labeled DHPE

Alan Burns, SNL



Feigenson & Buboltz, 2001
DPPC/DLPC 1:1

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?

Standard picture:

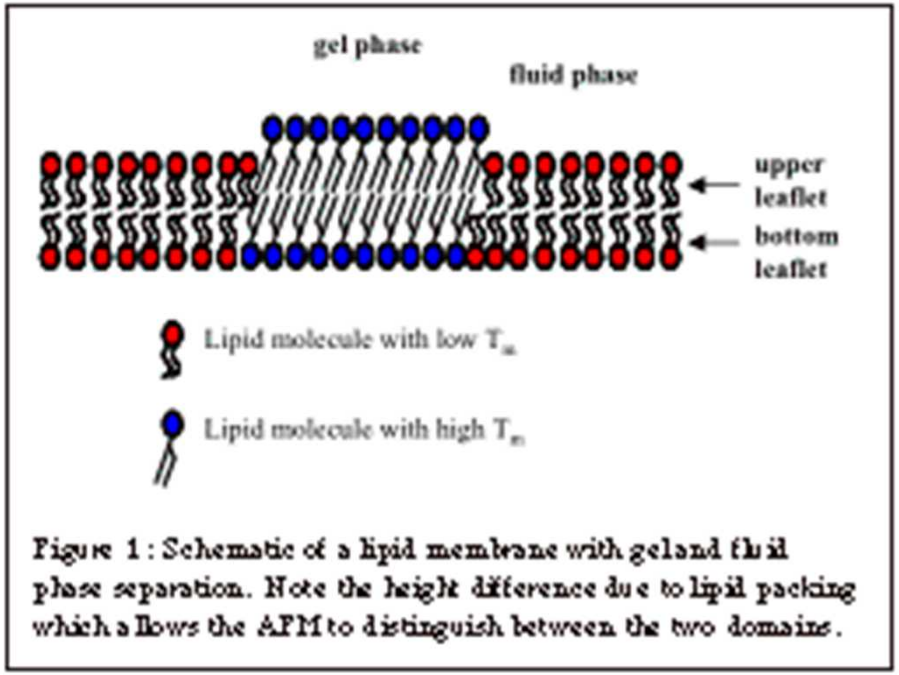
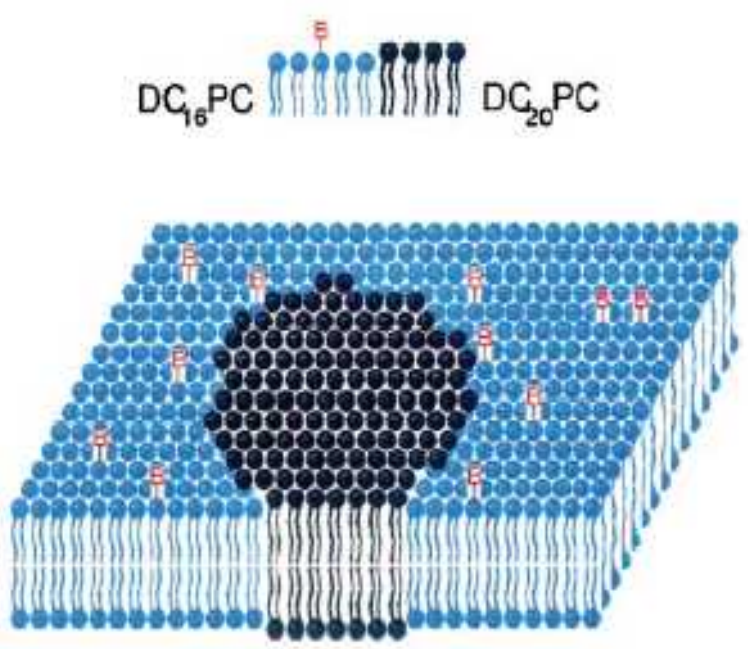


Figure 1: Schematic of a lipid membrane with gel and fluid phase separation. Note the height difference due to lipid packing which allows the AFM to distinguish between the two domains.



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Simulating Lipid Dynamics

Lipid diffusion is 'slow'

- diffusion constant ~ 10^{-8} cm^2/s = 10^{-3} nm^2/ns
- lipid exchange time ~ 100 ns
- too slow for atomistic simulations

$\Rightarrow$ need to use coarse-grained models

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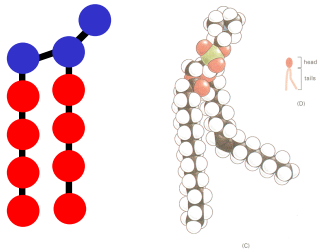
Coarse-grained Models

- Follow successful coarse-grained models in polymer physics
  - bead-spring model
  - hydrophobic/hydrophilic interactions
  - connectivity



- Can treat essential physical features that drive key phenomena
  - self-assembly
  - membrane fluidity

- Expect this is sufficient for more complex phenomena
  - domains
  - fusion
  - membrane-protein interactions

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Lipid Model: Interactions

Lennard-Jones (LJ) potential

The purely repulsive LJ potential u_{RLJ} is cutoff and shifted at $r_c = 2^{1/6}\sigma$.

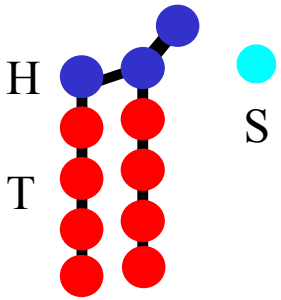
$$4\varepsilon_{\alpha\beta}\left[\left(\frac{\sigma_{\alpha\beta}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{\alpha\beta}}{r_{ij}}\right)^{6}\right]$$

Force field parameters

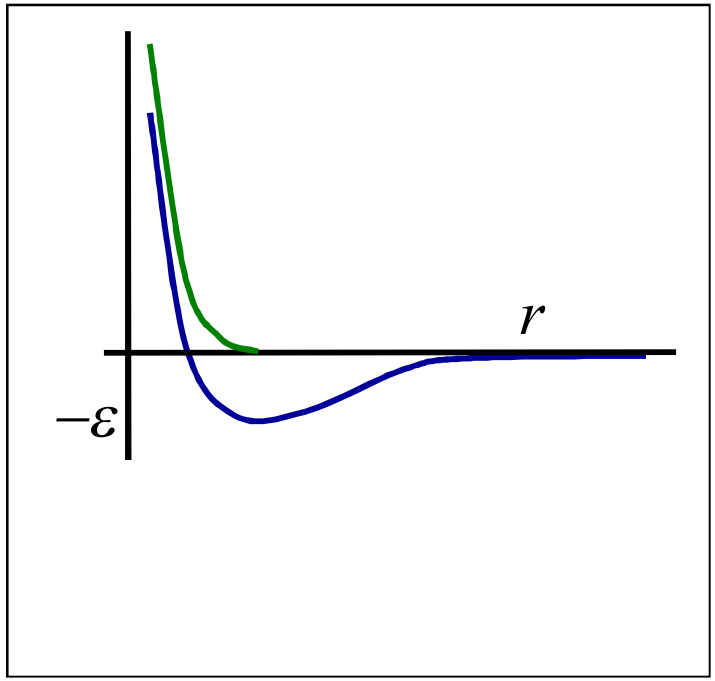
$\varepsilon_{\alpha\beta} = \varepsilon$, and $\sigma_{\alpha\beta} = \sigma$ for all pair types $\alpha\beta$

$r_{c,\alpha\beta}$ = 2.5 σ for $\alpha\beta$ = HH, TT, SS, HS

= $2^{1/6}\sigma$ for $\alpha\beta$ = HT, TS



1 bead ≈ 3 C atoms



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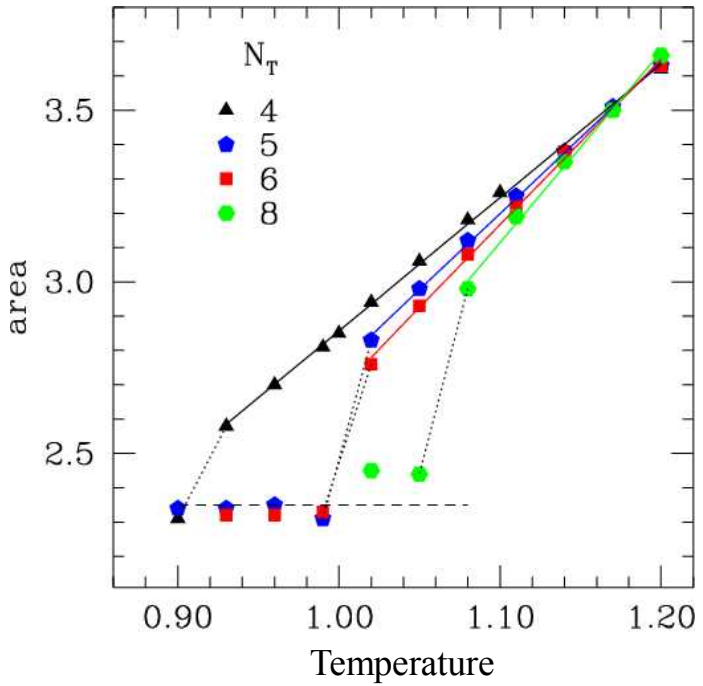
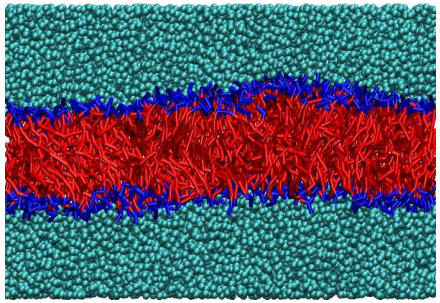
Area per Lipid

Area per lipid A

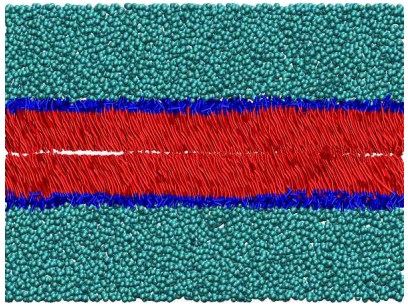
- decreases with temperature T
- has discontinuity at liquid→gel transition
- Phase transition temperature decreases for larger number of tail beads, N_T



At T = 0.95,
N_T = 4 is a liquid
N_T = 8 is a gel



liquid



gel

J. Chem. Phys. 121, 11942 (2004)

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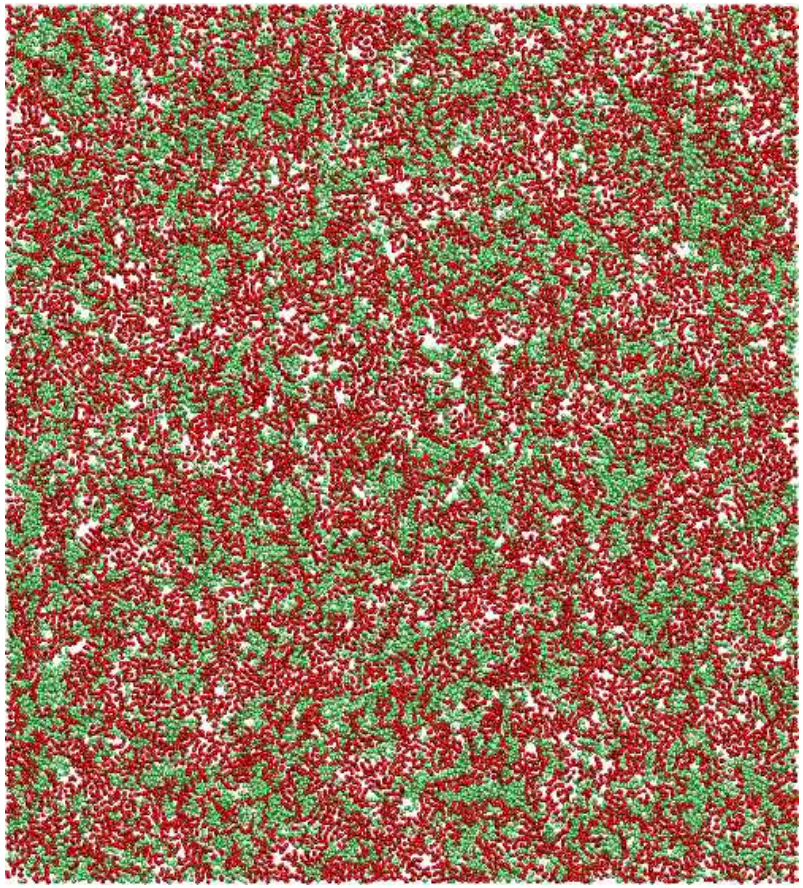
Domain Self-assembly

Start with random configuration of mixed lipids.

Do domains form?

- $N_T = 4$ red
- $N_T = 8$ green
- 2:1 mixture
- 12096 total lipids
- image shows only tails



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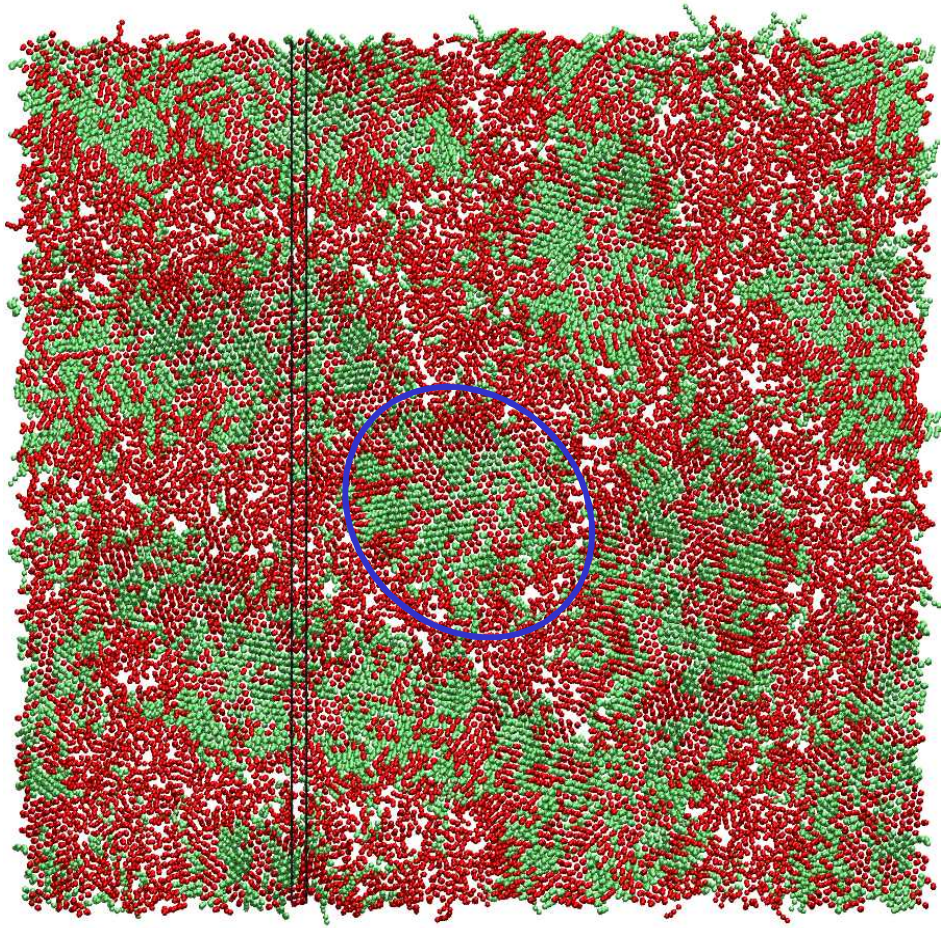
Show Movie



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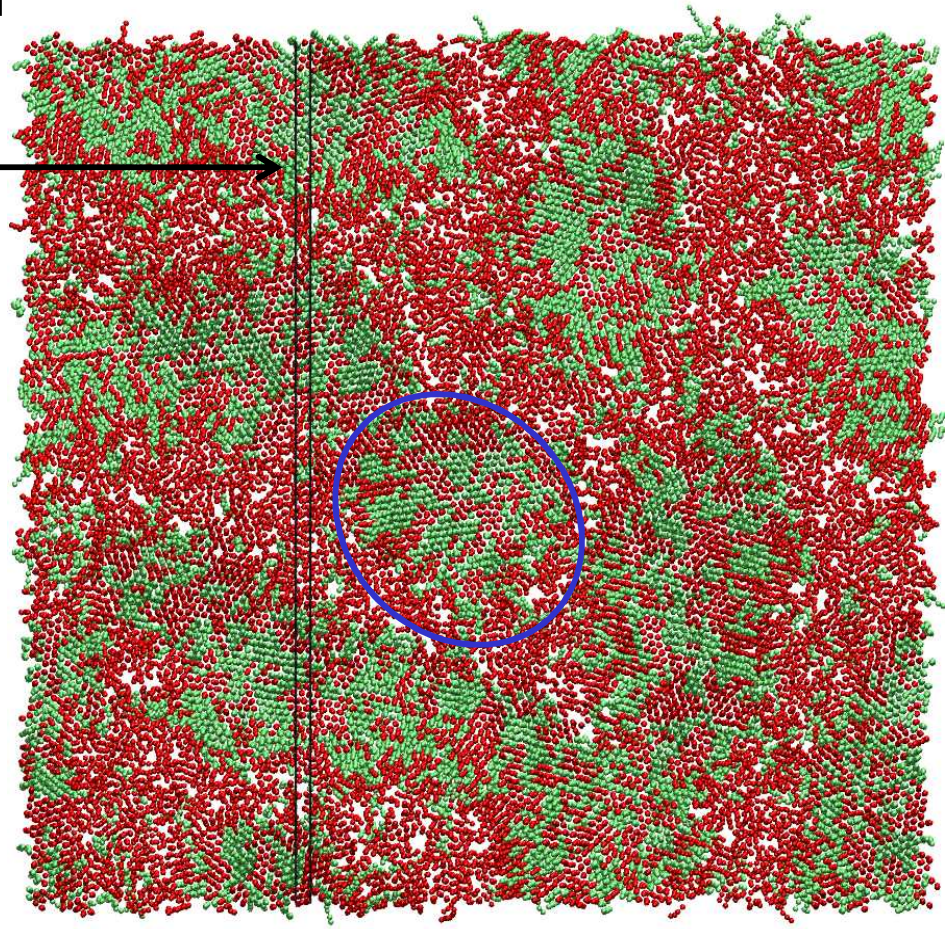
Domains Form

- gel domains are mixture of long and short lipids
- let's look at slice



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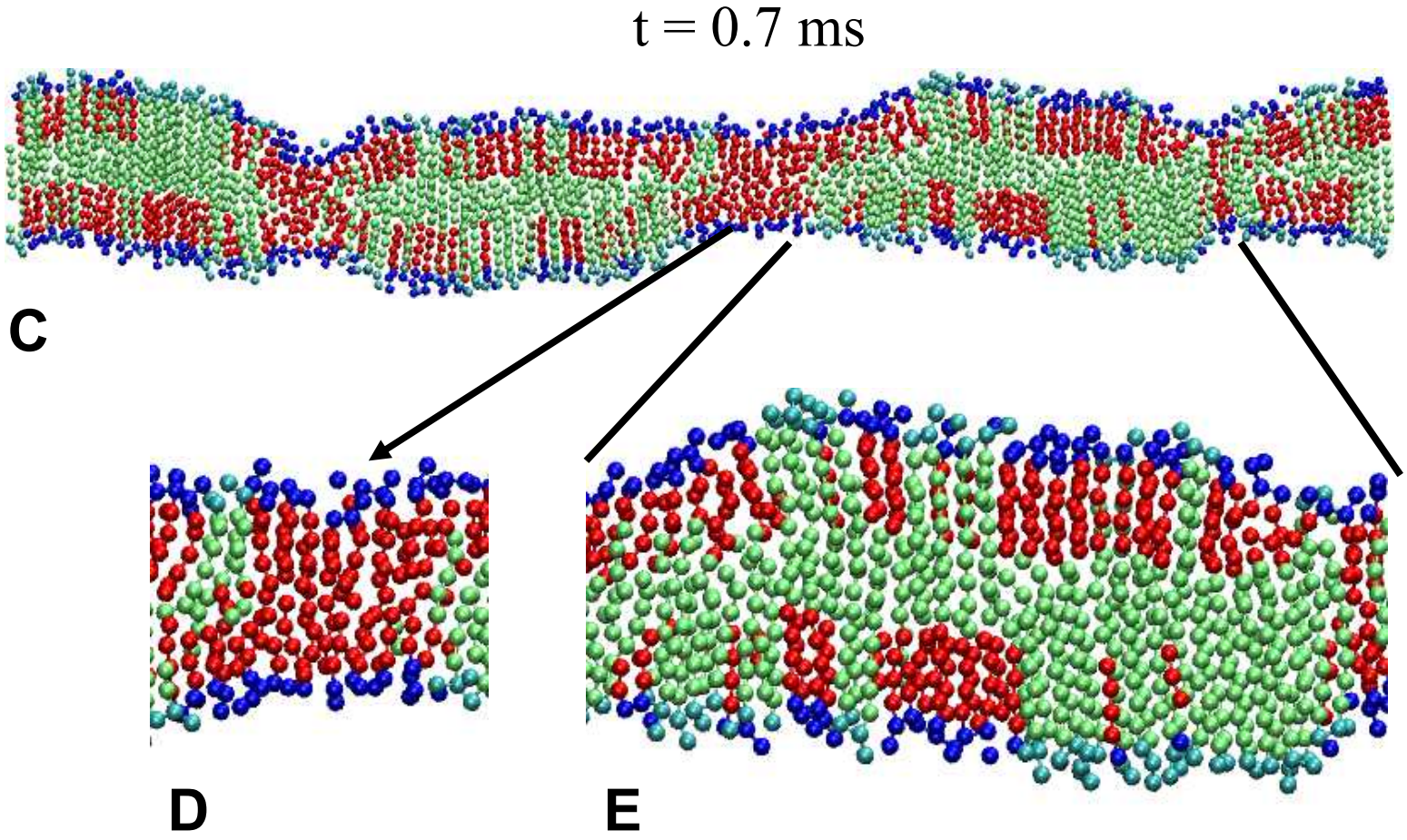
Domain structure: Complementary Matching



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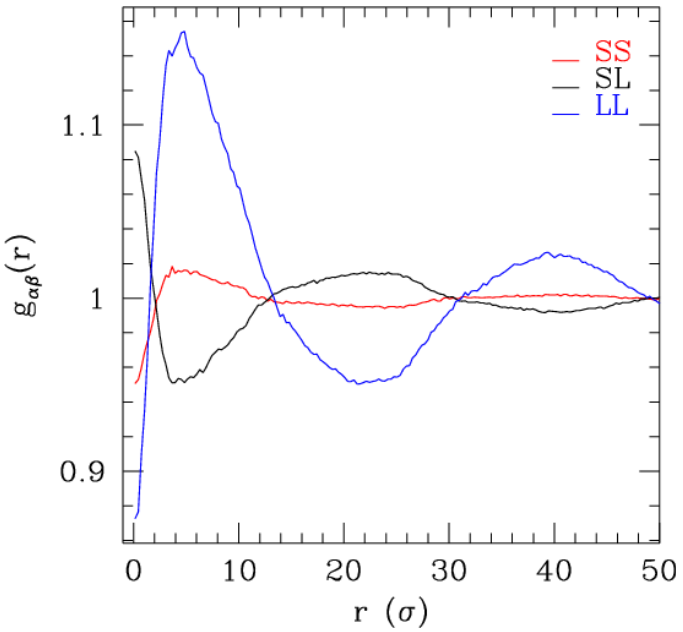
Correlation between Leaflets

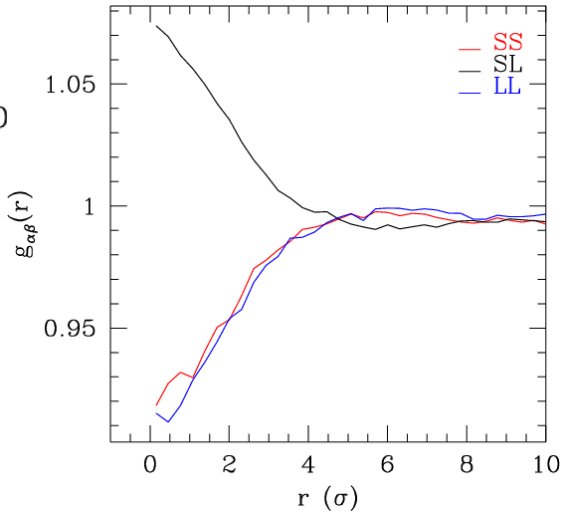
$g_{\alpha\beta}$ is the corr. fn. between type α in one leaflet and type β in the other leaflet

- N_T = 4 & 8
- 2:1 mixture

(note different *r* scales)



- N_T = 4 & 6
- 1:1 mixture



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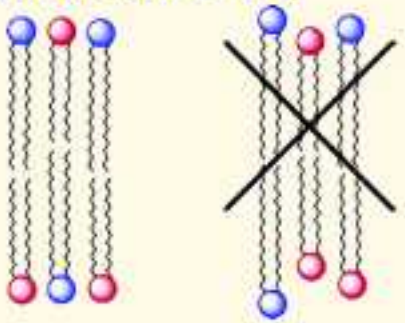
Summary

- See domain formation in binary lipid membrane
- Complementary matching can occur between leaflets
- Similar matching seen in recent experiments
  - Zhang, J.; B.Jing; Tokutake, N.; Regen, S. *J. Am. Chem. Soc.*, **2004**, *126*, 10856.

Transbilayer Complementarity of Phospholipids. A Look beyond the Fluid Mosaic Model
Jianbing Zhang, Bingwen Jing, Nobuya Tokutake, and Steven L. Regen
pp 10856 - 10857; **(Communication)** DOI: 10.1021/ja046892a



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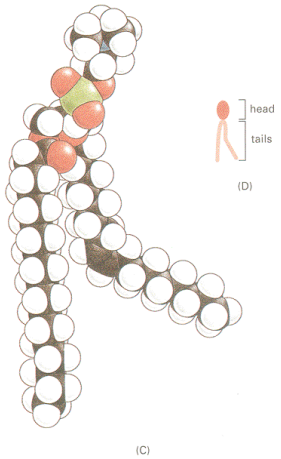
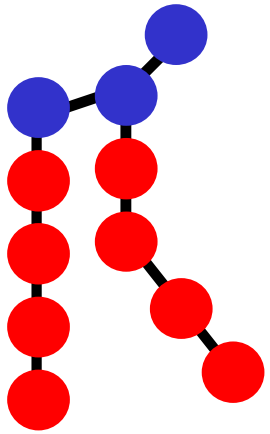
Packing Effect

A double bond in the lipid tail interferes with packing.
The melting temperature is lowered in single lipid system.





What happens in mixtures?
Will the unsaturated lipid in the liquid phase mix with the saturated lipid in the gel phase?

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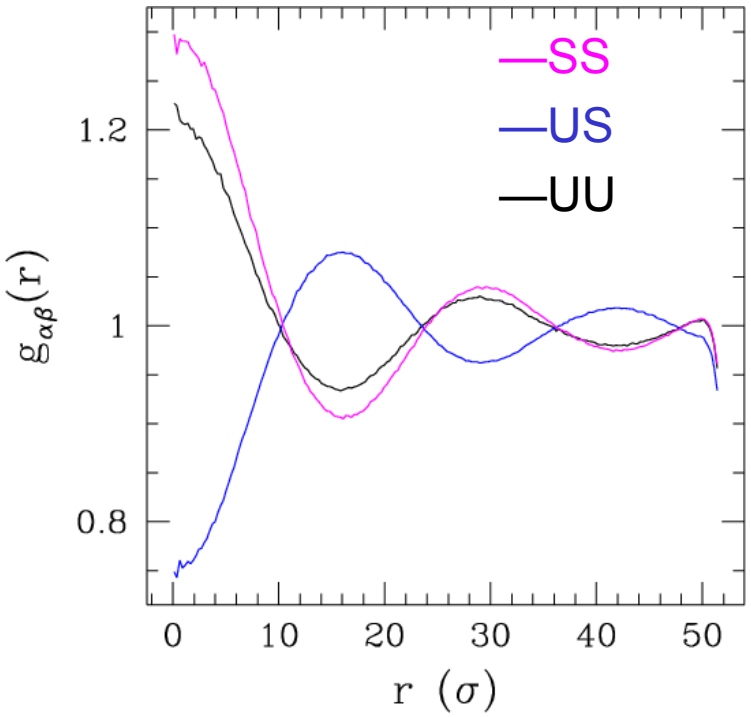
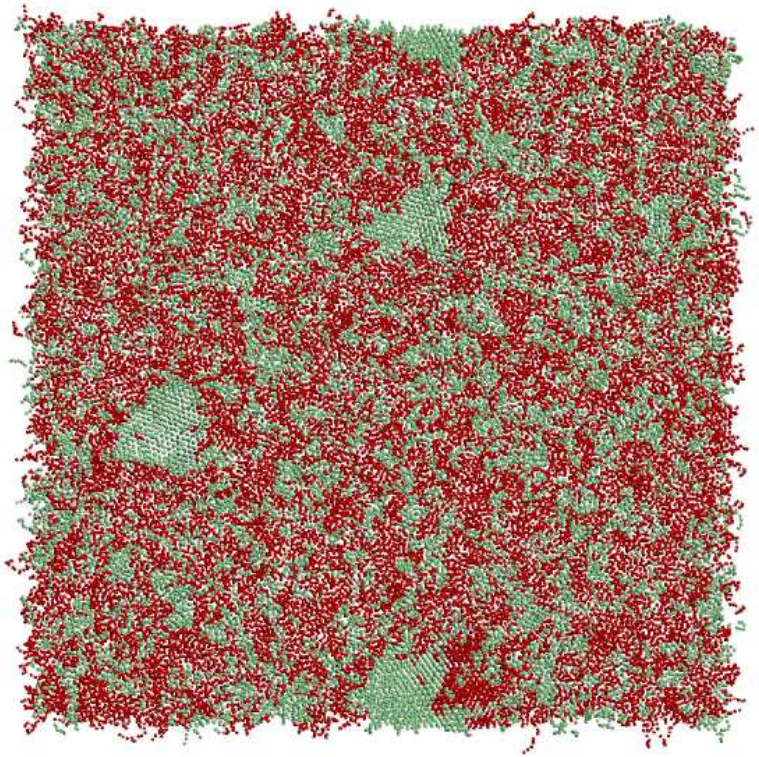
If there is a double bond, then ...

- N_T = 6kk & 6 (U:S)
- 3:2 mixture





See domains of primarily one type.

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Bilayer-Bilayer inteactions

- ion channel simulations
- stacks of bilayers
- confinement effects
- fusion

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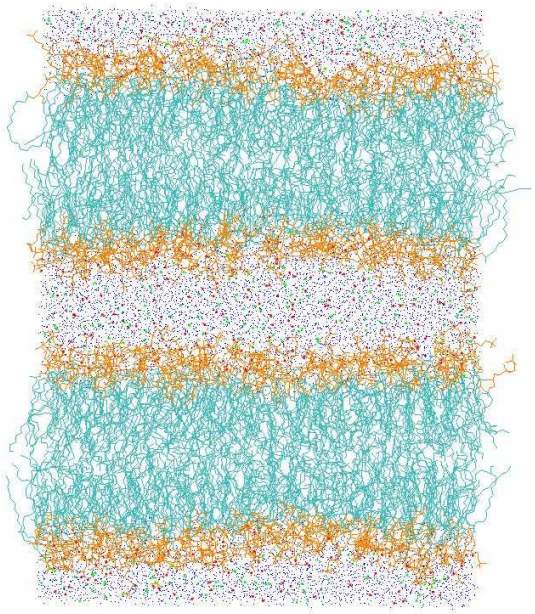
Interactions Between Membranes

- Double bilayer system
- 256 DPPC lipids/bilayer
- Marrink FF

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

coarse-grained model

- Double bilayer system
- 256 POPC lipids/bilayer
- CHARMM FF



atomistic model

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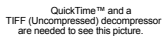
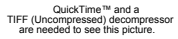
Interactions between lipid bilayers

Potential of mean force calculation

•Weighted histogram method





Successive separations obtained by removing solvent (water & ions).

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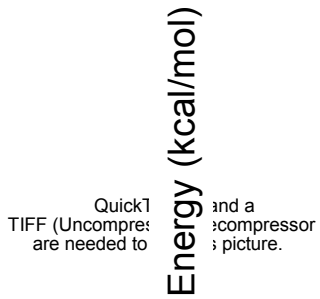
Interactions between lipid bilayers



Surface tension increases as separation decreases

Interaction energies

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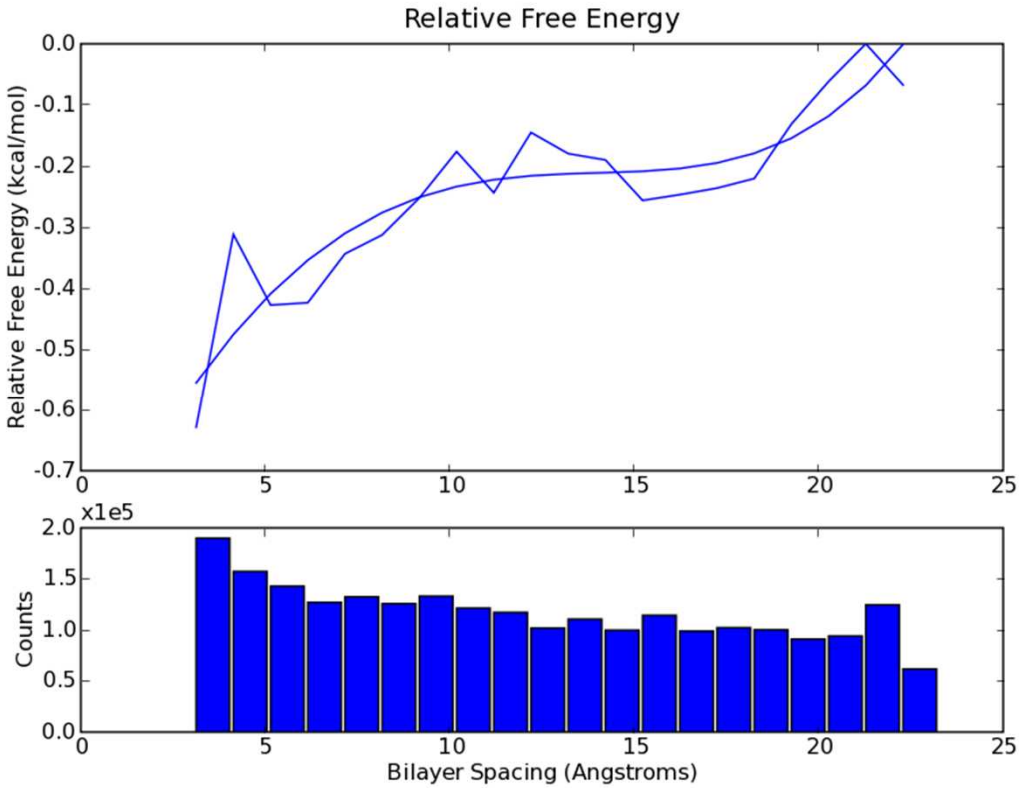
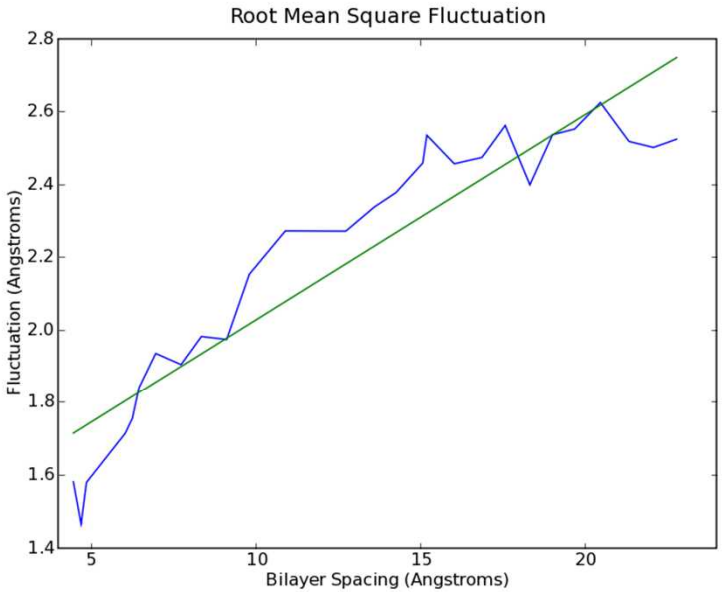
Atomistic PMF





Fluctuations decrease $\Rightarrow$ entropy repulsion decreases

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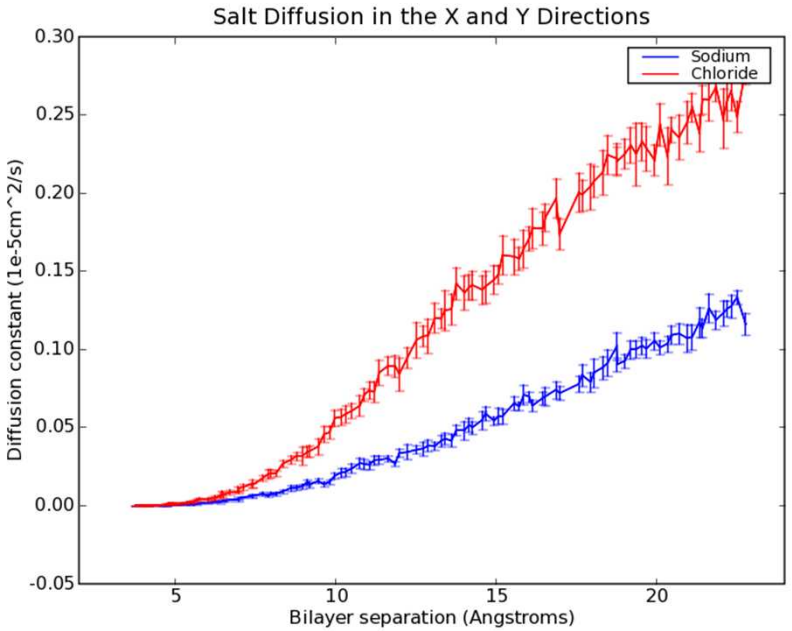
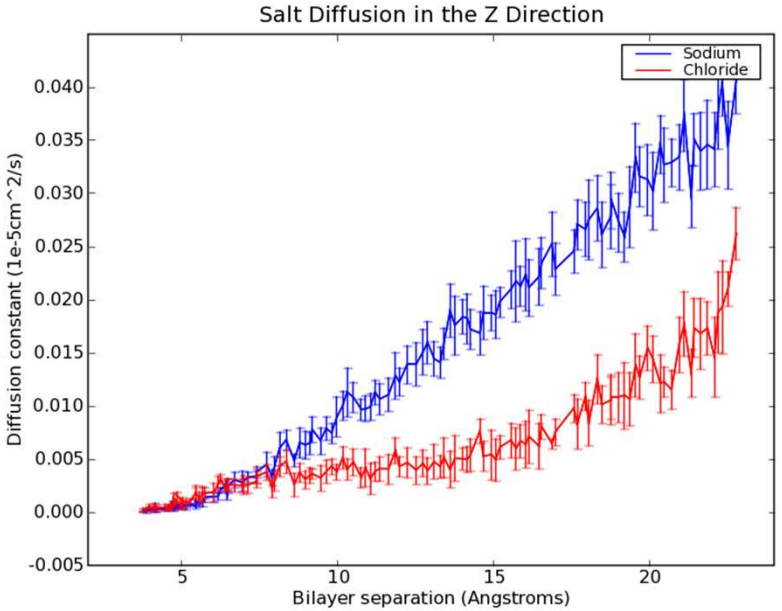
Salt Diffusion





For D > 45Å

- Cl faster in *xy*-plane
- Na faster in *z*-direction
- *z*-diffusion ~ 10x slower

Na closer to lipids: follows slower lateral, lipid motion?

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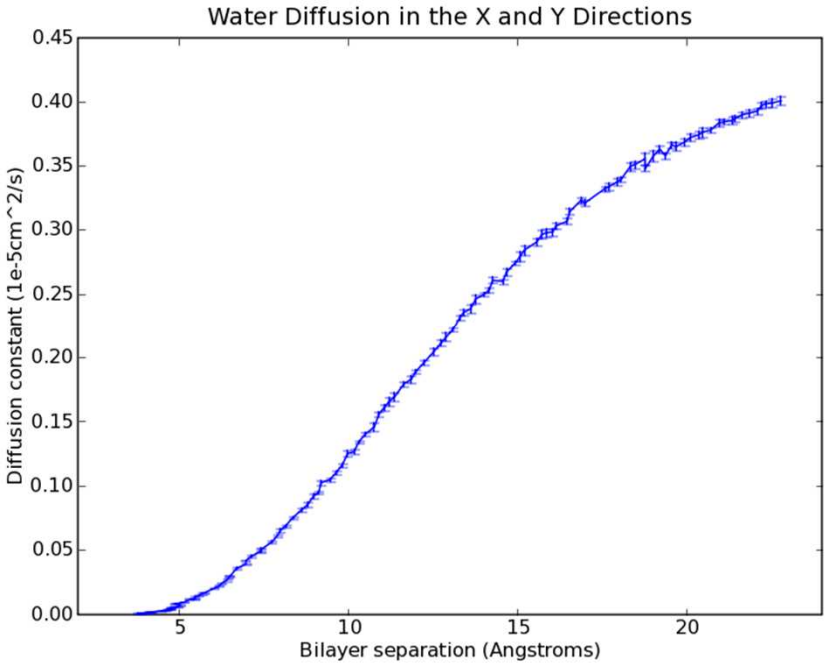
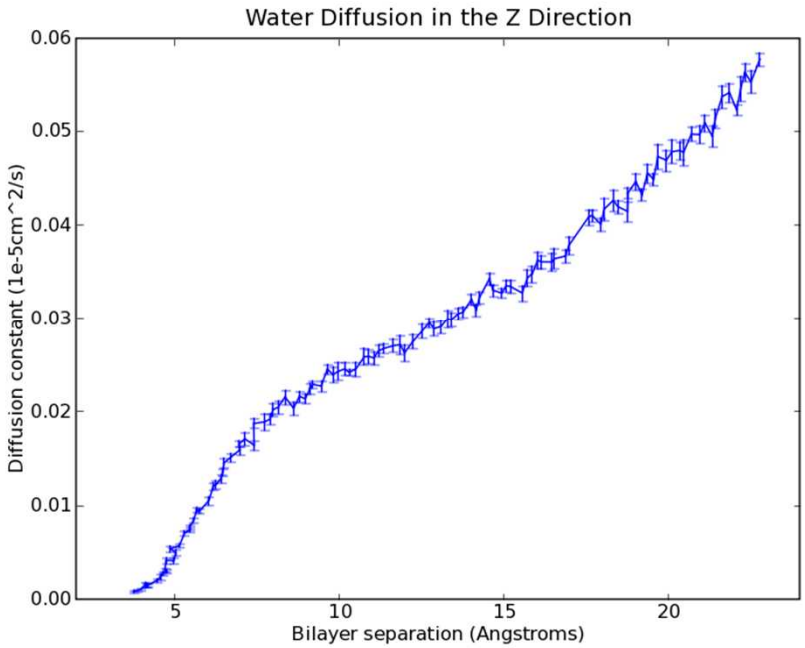
Water Diffusion





z-diffusion ~ 10x slower

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