# Calculating Partition Coefficients of Chain Anchors in Liquid-Ordered and Liquid-Disordered Phases

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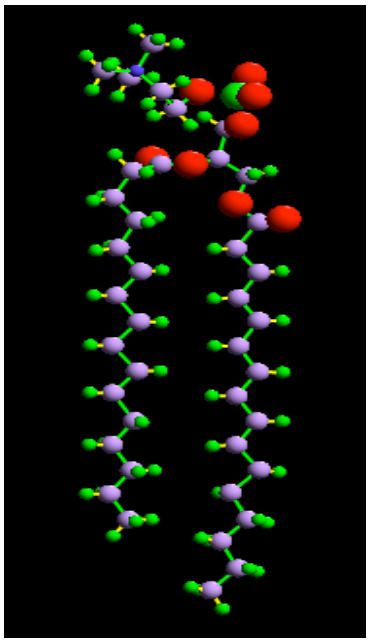
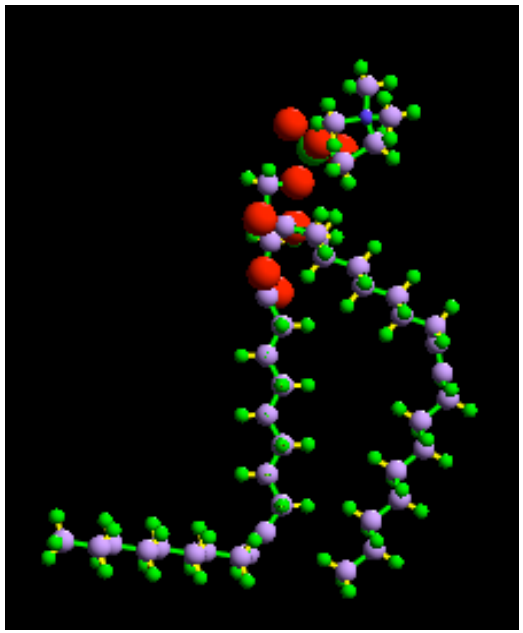
# THE PLAYERS IN MODEL MEMBRANES

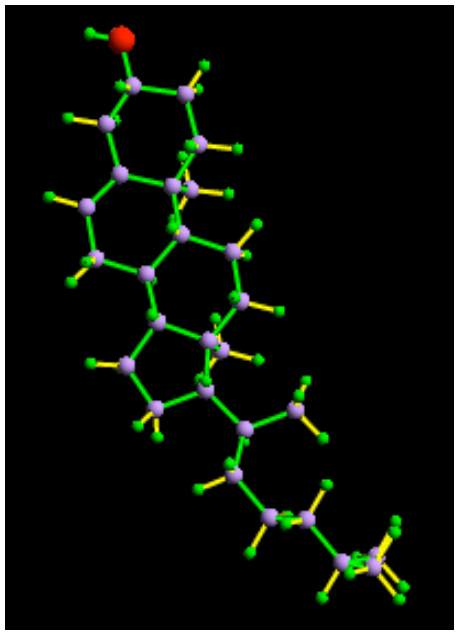
Two representative constituent lipids and cholesterol.



DPPC
di(16:0)pc



DOPC
di(18:1c9)pc



Cholesterol

# Fluid Mosaic Model
(Singer Nicholson 1972)

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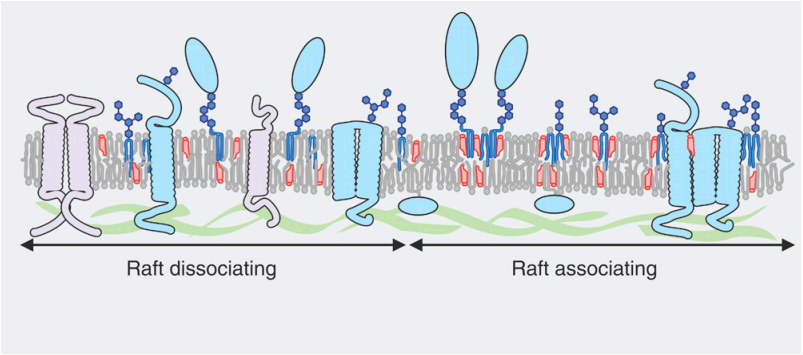
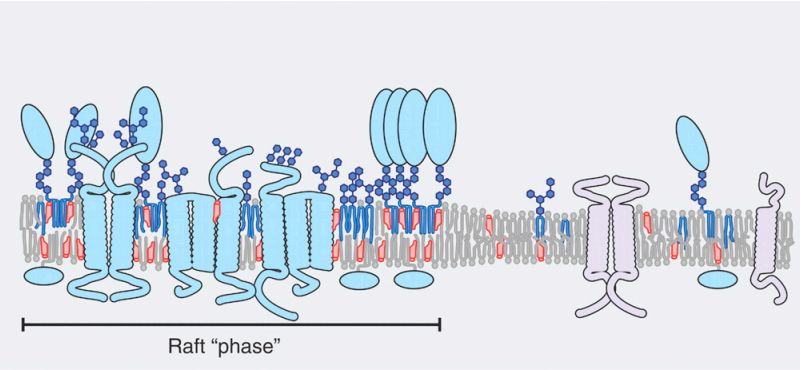


# Raft Hypothesis

- Rafts of saturated lipids and cholesterol; sea of unsaturated lipids

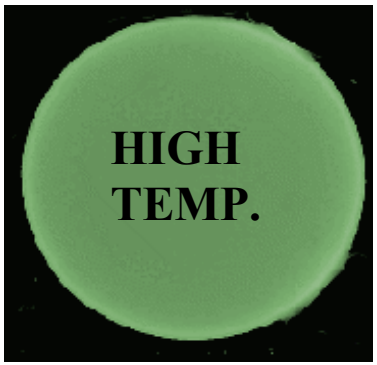


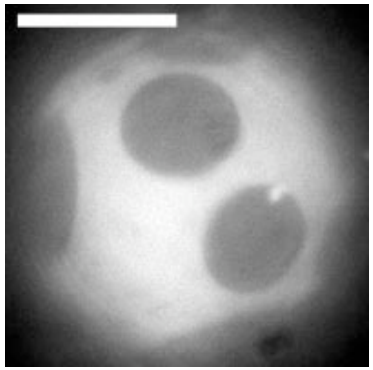

**D. Lingwood et al., Science 327, 46-50 (2010)**

# Raft Hypothesis

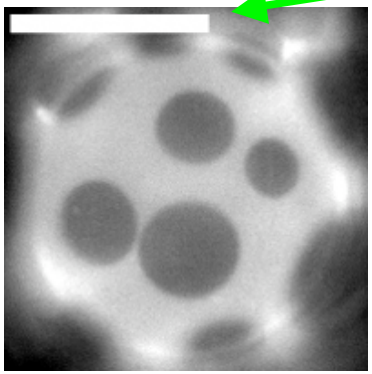
- Rafts of saturated lipids and cholesterol; sea of unsaturated lipids
- Phase separation

Lateral phase separation is readily seen in these membranes with fluorescence microscopy.



1:1 DPPC/DOPC
+30% Chol.
@30C.(~303K)



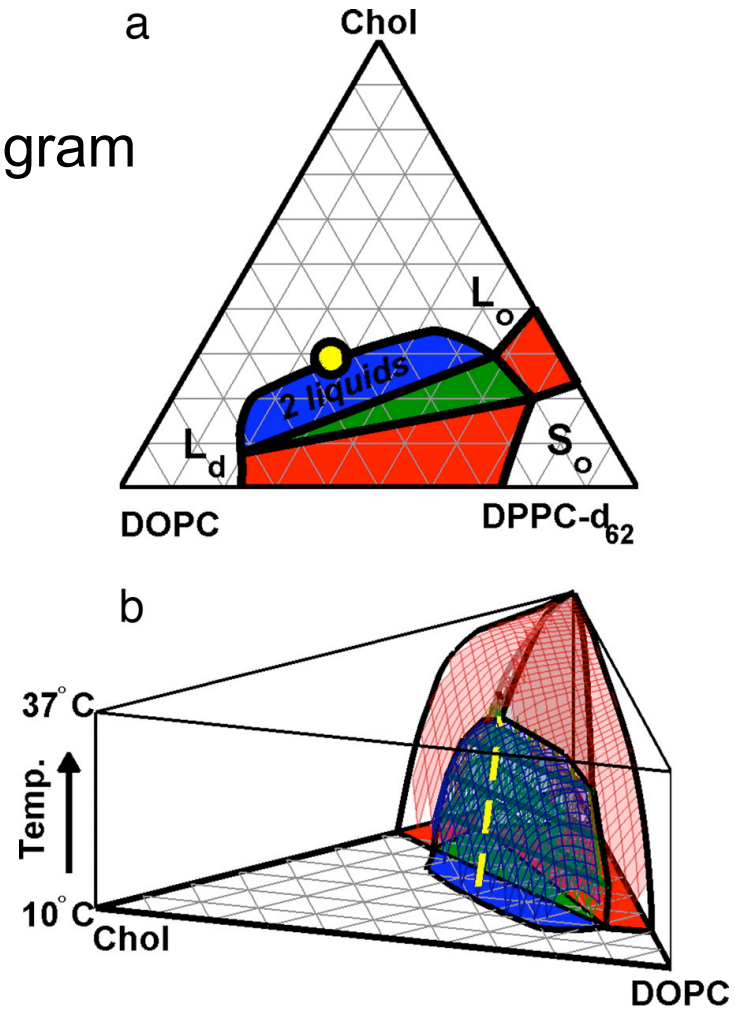

2:1 DPPC/DOPC
+20% Chol.
@30C.(~303K)

Micrographs courtesy of Sarah Veatch.

**-This is fluid/fluid coexistence.**

**Fig. 3. Phase diagrams of DOPC/DPPC-d62/Chol**

Typical Phase Diagram




**Veatch, Sarah L. et al. (2007) Proc. Natl. Acad. Sci. USA 104, 17650-17655**

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# Raft Hypothesis

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- Phase separation
- Preferential partitioning of proteins; efficiency

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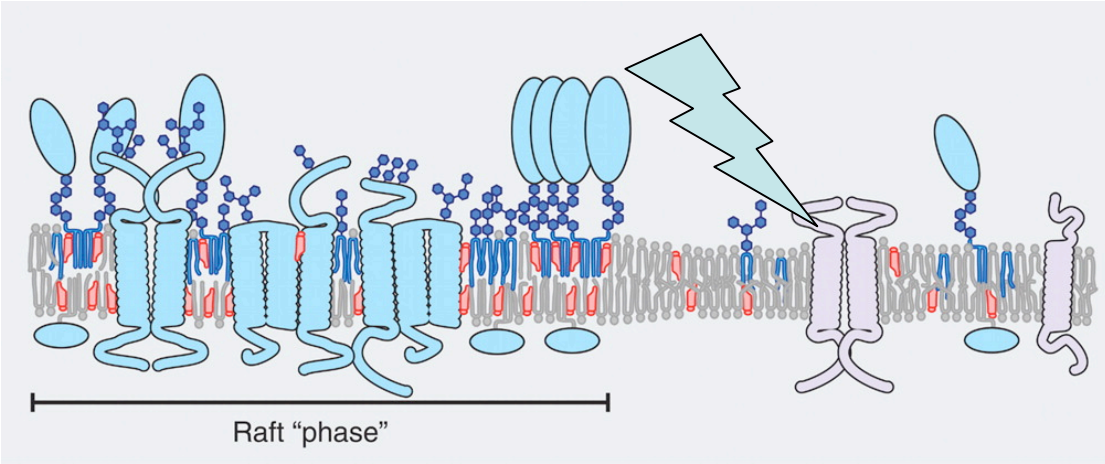
- Rafts of saturated lipids and cholesterol; sea of unsaturated lipids
- Phase separation
- Preferential partitioning of proteins; efficiency
- ***Physical*** organization leads to ***functional*** organization

# How do proteins sense membrane?

- Embed in it (transmembrane proteins)

**Fig. 2 Hierarchy of raft-based heterogeneity in cell membranes**

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# How do proteins sense membrane?

- Embed in it (transmembrane proteins)
- Anchor to it
- Extracellular anchors: glycophosphatidylinositol (GPI) : two acyl chains

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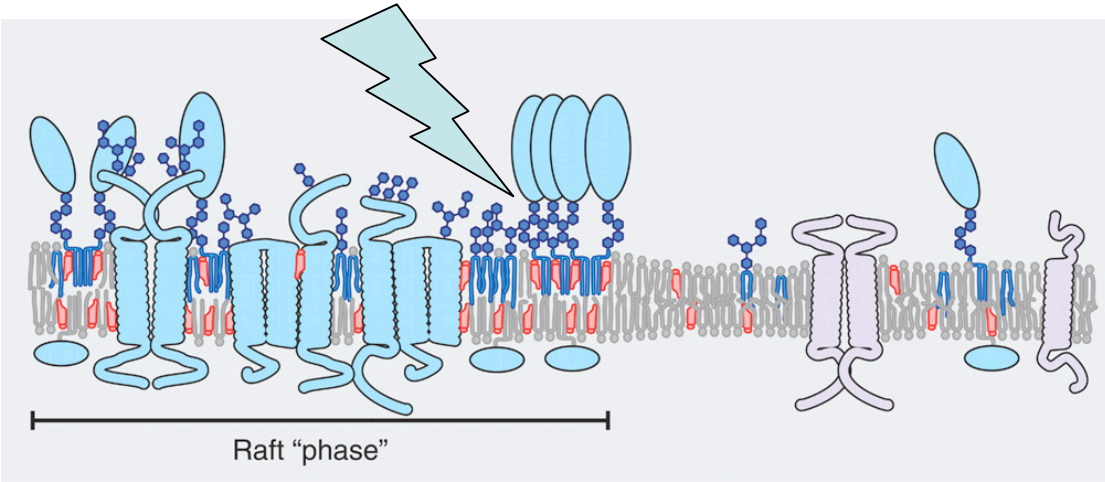


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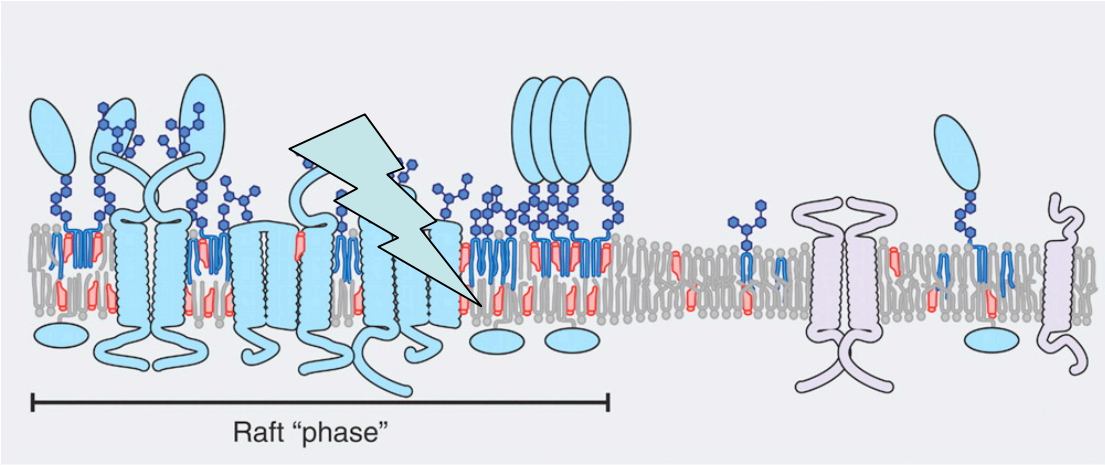
# How do proteins sense membrane?

- Embed in it (transmembrane proteins)
- Anchor to it
- Extracellular anchors: glycophosphatidylinositol (GPI) : two acyl chains
- Intracellular anchors: single acyl chain, (myristol or palmitol) or bulky prenyl group (geranylgeranyl)

**Fig. 2 Hierarchy of raft-based heterogeneity in cell membranes**

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# Presumably

- Saturated anchors prefer the “raft”
- Bulky, prenylated, anchors prefer the “sea”

# Experiment

Silvius, Winter, Schwille

- Partitioning of acyl chains into raft increases with chain length
- Partitioning of acyl chains into raft increases with increasing saturation

# Theory

- Minimal model : ternary mixture of cholesterol, saturated, and unsaturated lipids
- Must produce liquid-ordered, liquid-disordered coexistence; i.e. “raft” and “sea”

# Model-independent statement

## If partition coefficient, $\kappa = x_{lo}/x_{ld}$, is determined primarily by chains

1. Anchor which is identical to membrane lipid tail has
$\kappa$ given by coexisting concentrations from phase diagram

It follows that partition coefficient depends *not only* on the anchor, but on the concentrations as well.

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1. Anchor which is identical to membrane lipid tail has
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It follows that partition coefficient depends *not only* on the anchor, but on the concentrations as well.

2. As a critical point is approached, $\kappa$ goes to 1. Thus, not a good operating point.

# Theory of ben Shaul, Gelbart, Szleifer

Effect of  long-range van der Waals attraction and short-range repulsion is to produce uniform liquid

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Treat chains with realistic Flory Rotational Isomeric States Model

Energy of gauche bonds

Pressure field

$$P(\alpha_i) = \frac{1}{q_i} \exp[-\beta\epsilon(\alpha_i) - \int \beta\pi(z) v_i(\alpha_i, z) dz]$$

$$q_i = \sum_{\alpha_i} \exp[-\beta\epsilon(\alpha_i) - \int \beta\pi(z) v_i(\alpha_i, z) dz]$$

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Sum over $10^8$ configurations (!)

# Problem

- Only one liquid phase, not two
- No gel phase

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- Solution: add a bond-bond orientational interaction. Local bond orientation $\xi(z)$.
- Elliott et al.

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Pressure field

Mean field acting on bonds

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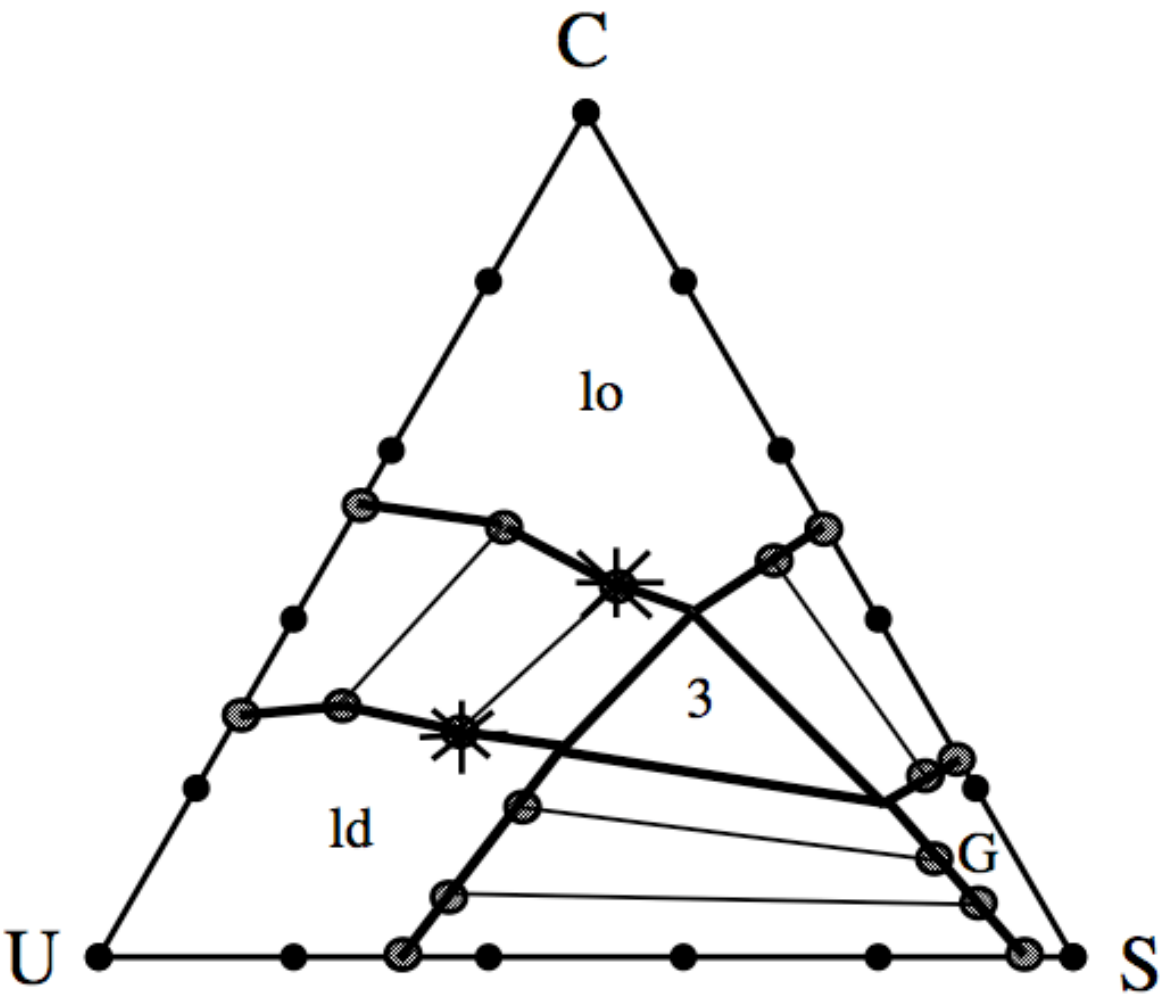
Self-consistent equation

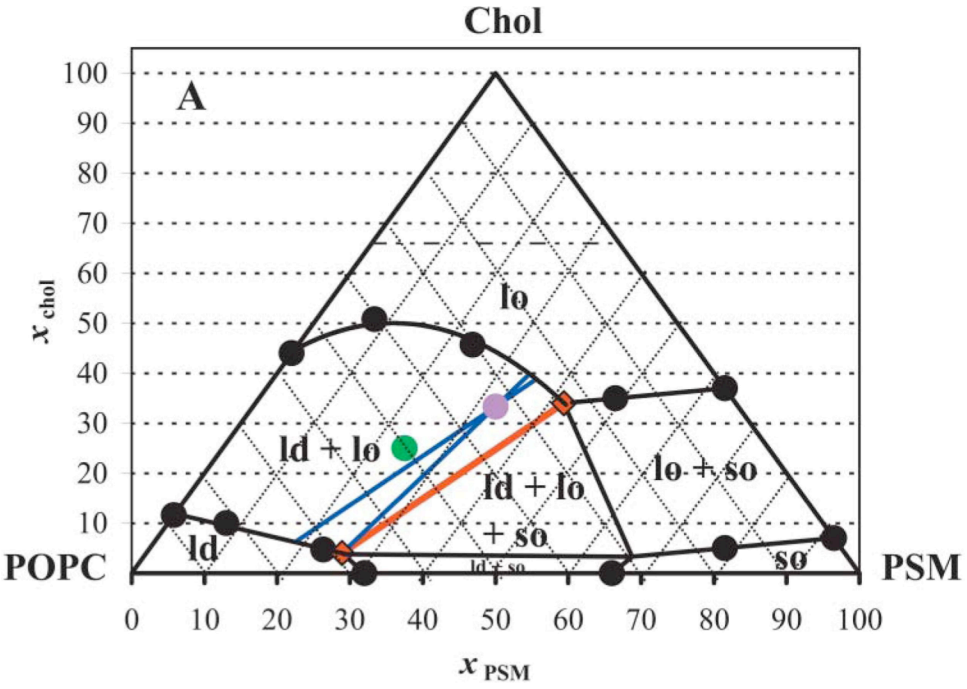
$$\beta b_l(z)\ dz = -\frac{\beta J_{ll}}{a\nu_s}[x_s < \xi_s(z) > + x_u < \xi_u(z) >] - \frac{\beta J_{lc}}{2\nu_s}x_c < \xi_c(z) >$$

# Resulting Phase Diagram



# Phase Diagram of SM, DOPC, Cholesterol

## de Almeida et al. 2003



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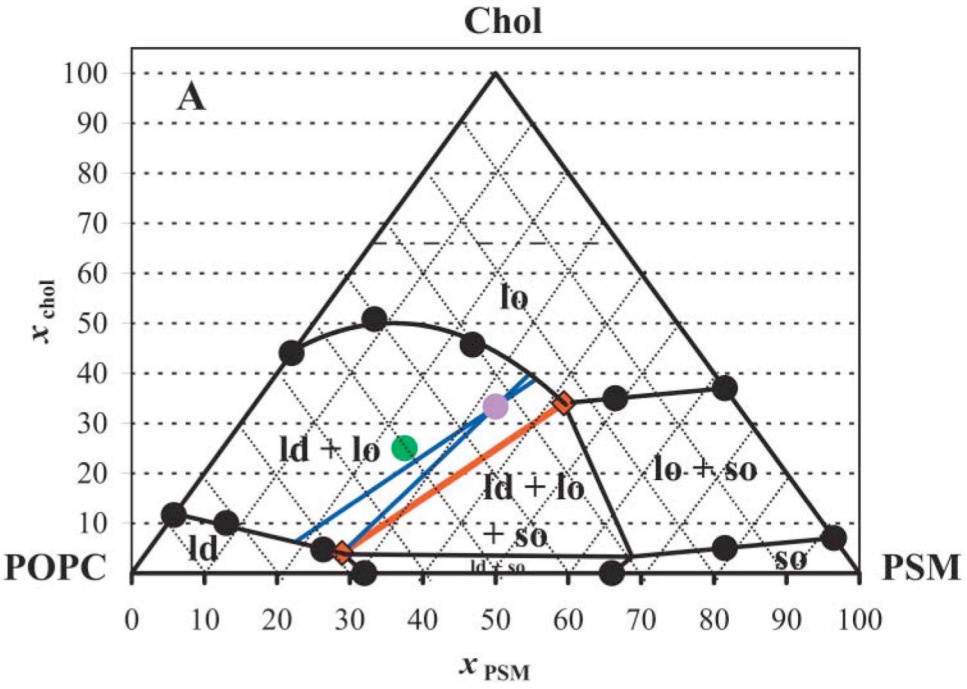


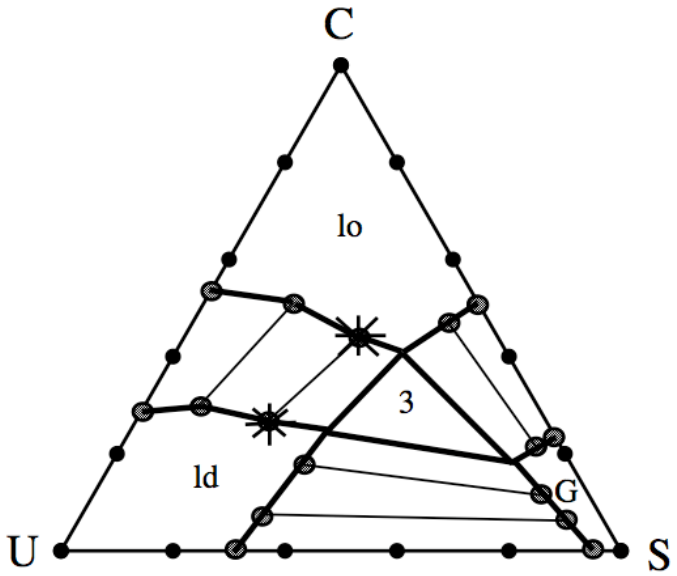

# Calculation of Partition Coefficient

## Add infinitesimal amount of anchor

$$\begin{aligned} \kappa_A &\equiv x_A^{lo}/x_A^{ld} \\ \beta\mu_A &= \ln x_A + \beta\tilde{\mu}_A \end{aligned}$$

Equality of chemical potential in coexisting phases implies

$$\begin{aligned} \kappa_A &= \exp(\beta\tilde{\mu}_A^{ld} - \beta\tilde{\mu}_A^{lo}) \\ &= \frac{a^{lo}}{a^{ld}} \frac{\Pi_{k=1}^{n_A^{tails}} q_k(T, a^{lo}, x_s^{lo}, x_u^{lo}, x_c^{lo})}{\Pi_{k=1}^{n_{tails}} q_k(T, a^{ld}, x_s^{ld}, x_u^{ld}, x_c^{ld})} \end{aligned}$$

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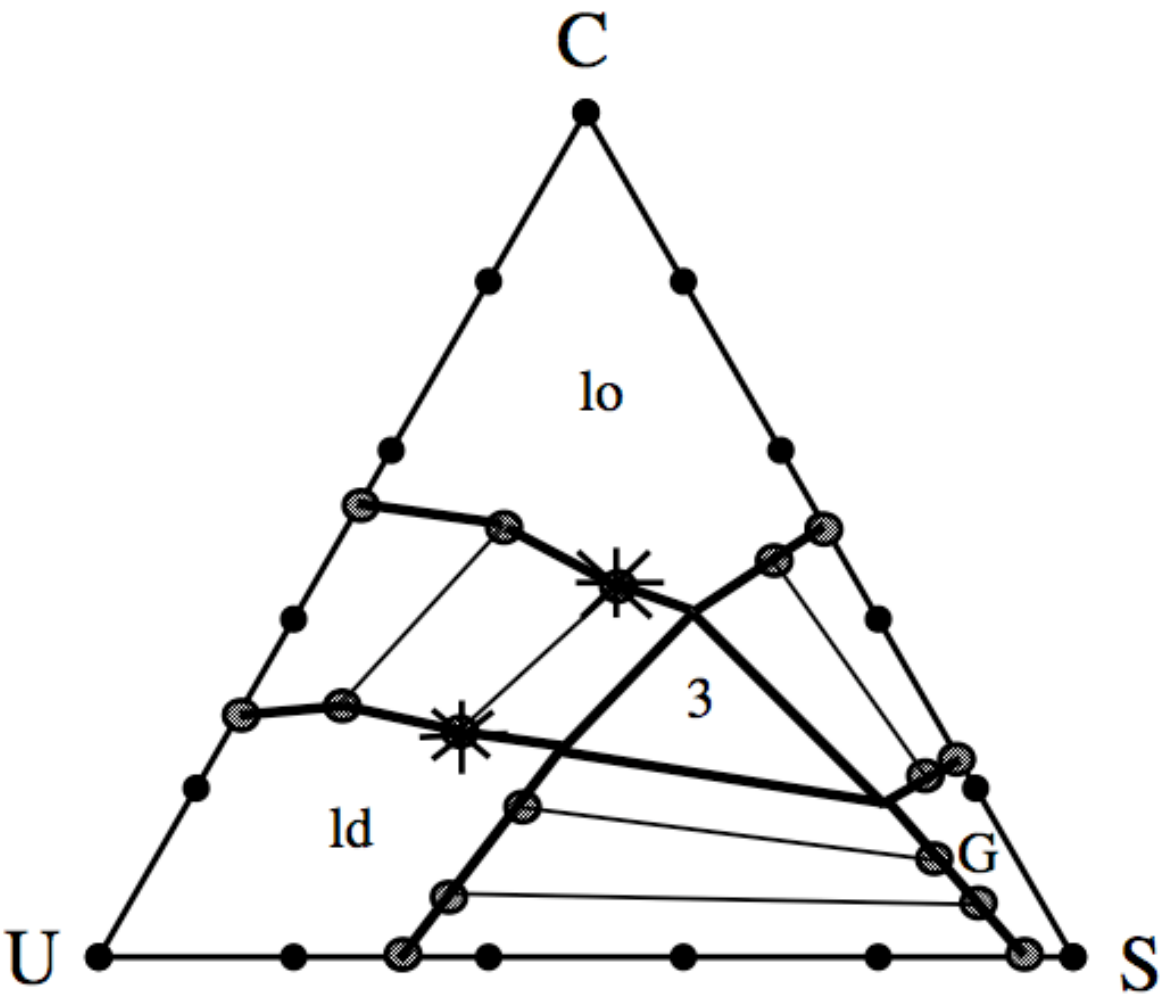
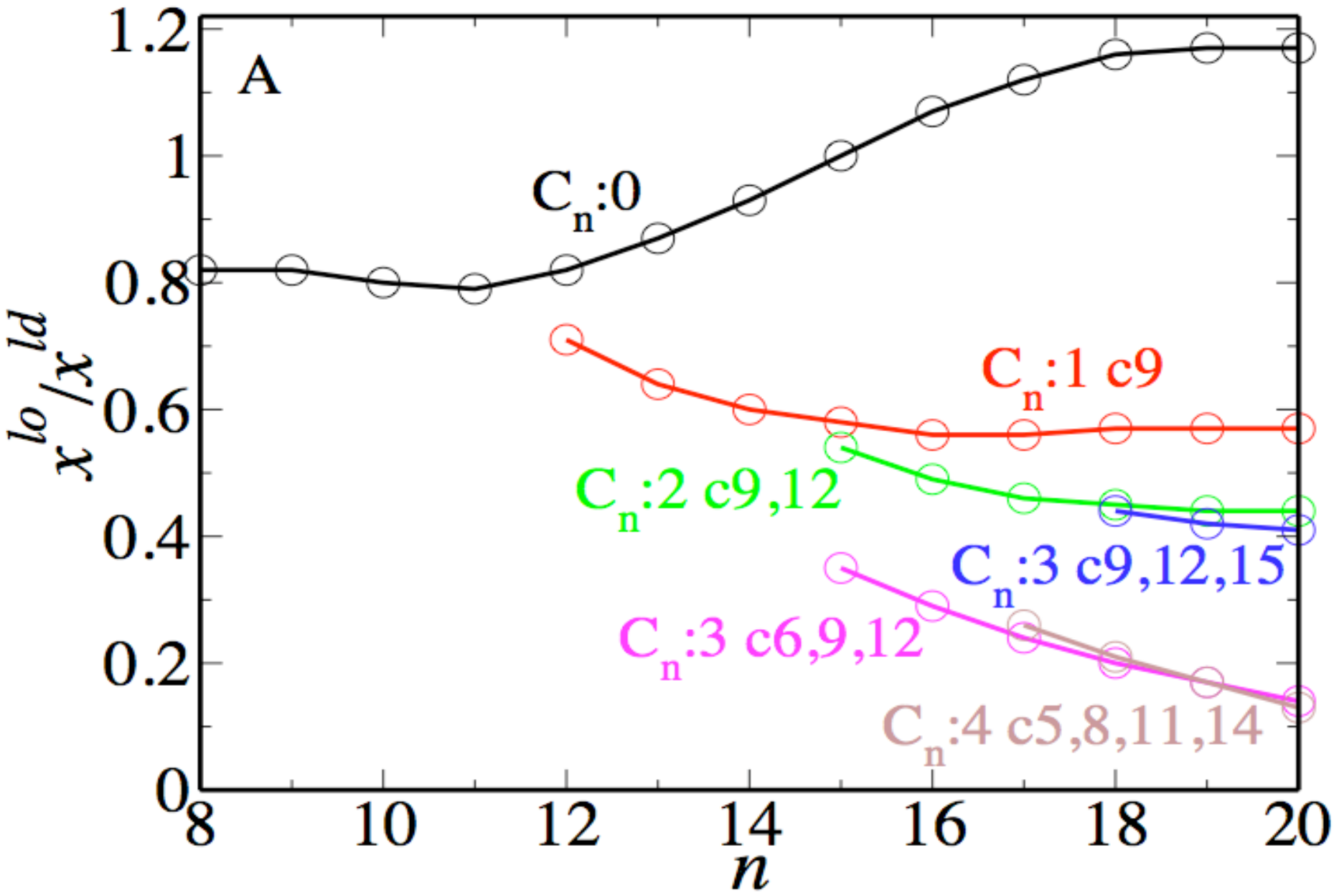
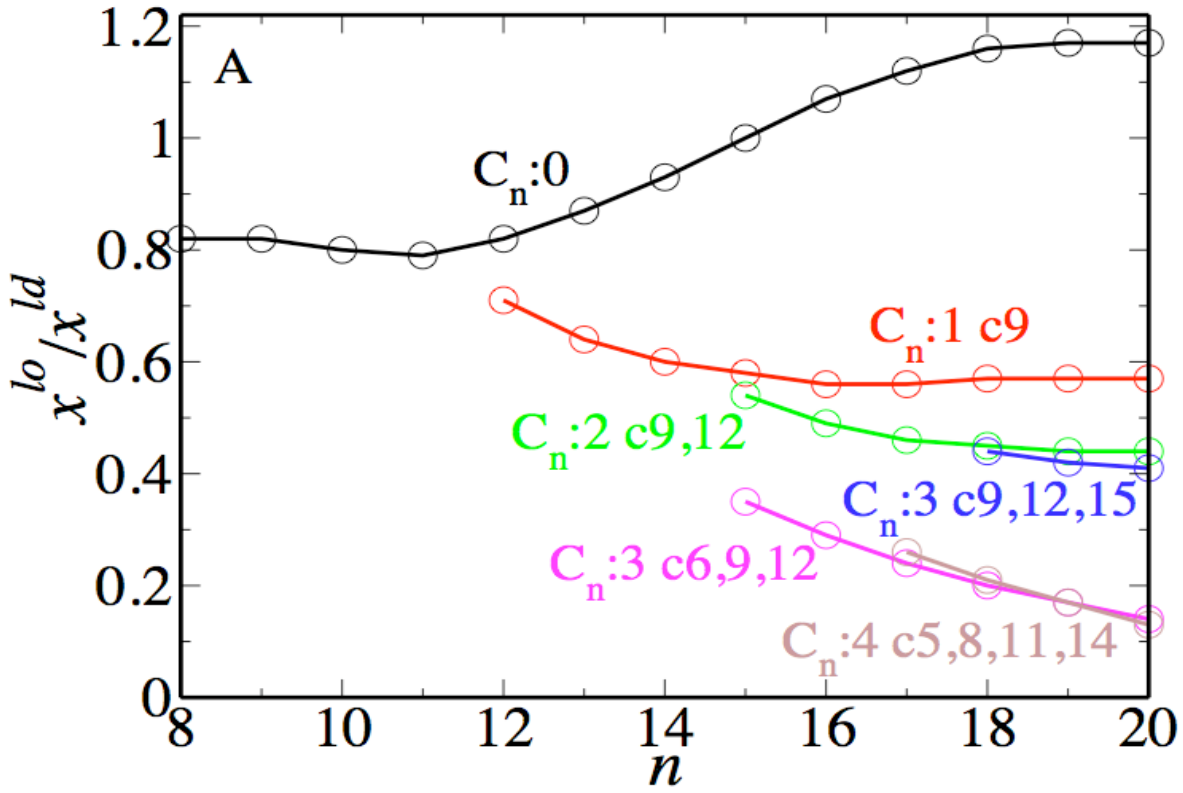
As amount of anchor is infinitesimal, do not need to calculate fields $\Pi$ or b again. (But do generate $10^8$ anchor configurations)

# Resulting Phase Diagram



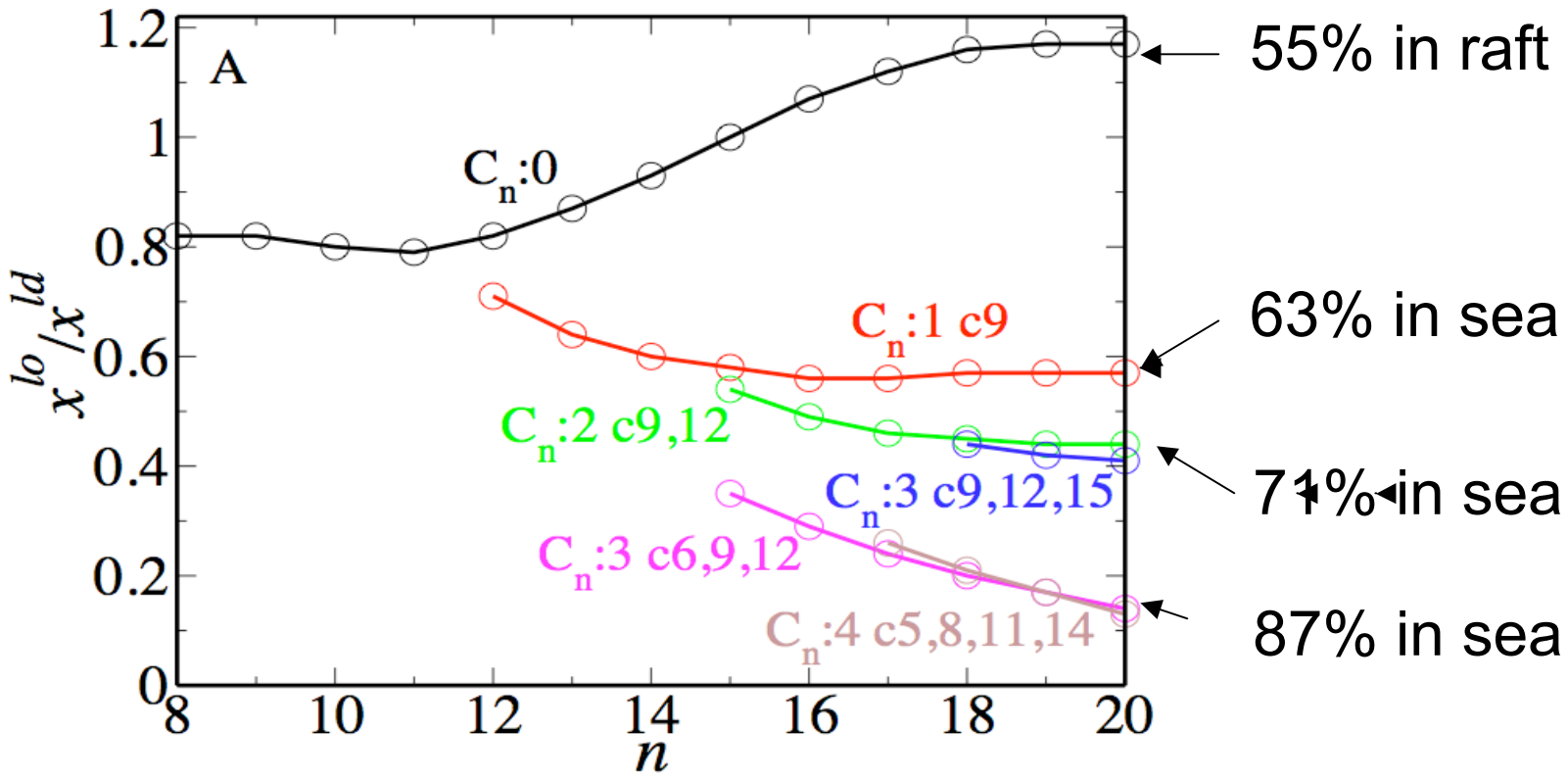
# Results: single chain anchors, T=300





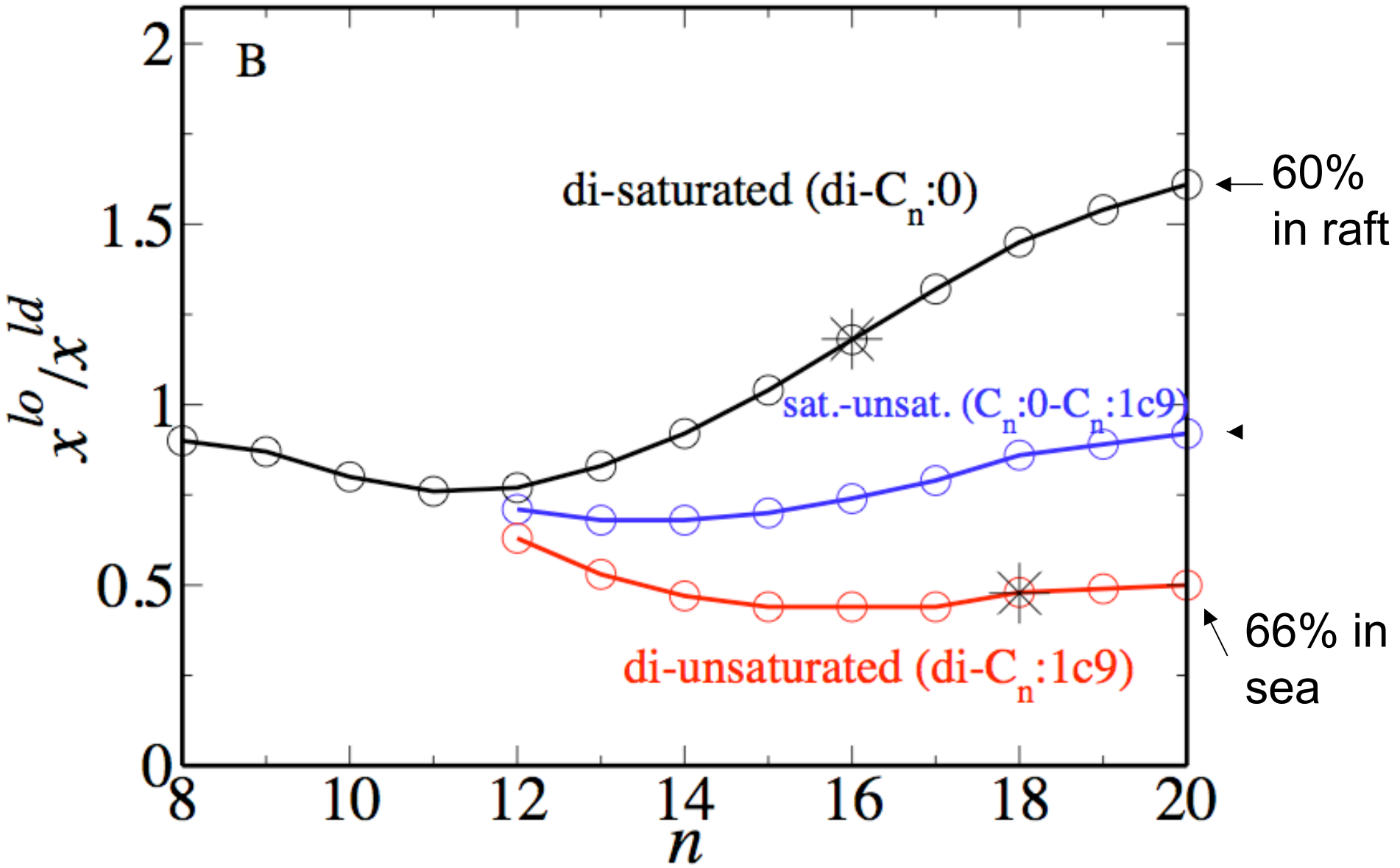

Note: Partition coefficient of saturated chain increases with length for n>12

Partition coefficient of unsaturated chain decreases with increasing length

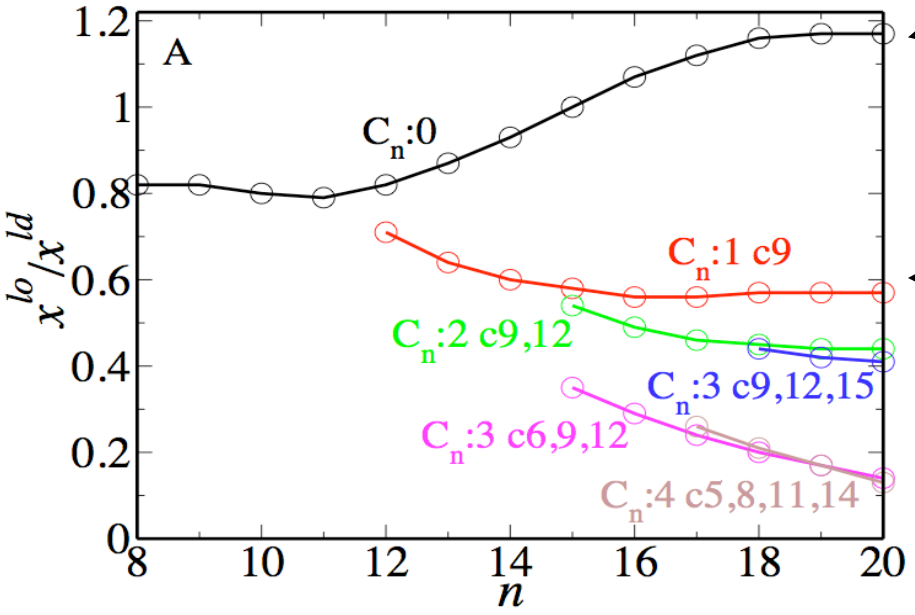



Note: Increased partitioning into sea with increased unsaturation

# Results: double chain anchors, T=300

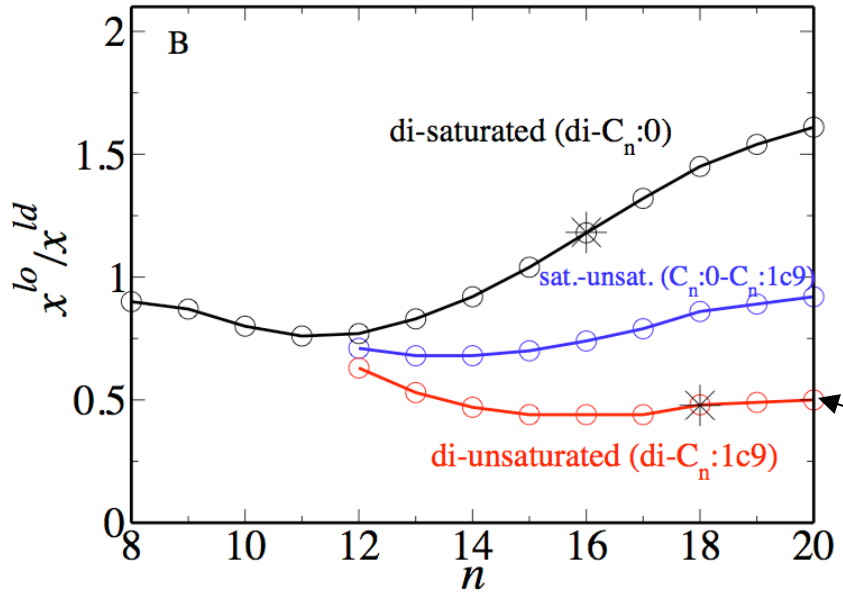


# Partition coefficient increases with number of anchors




55% in raft

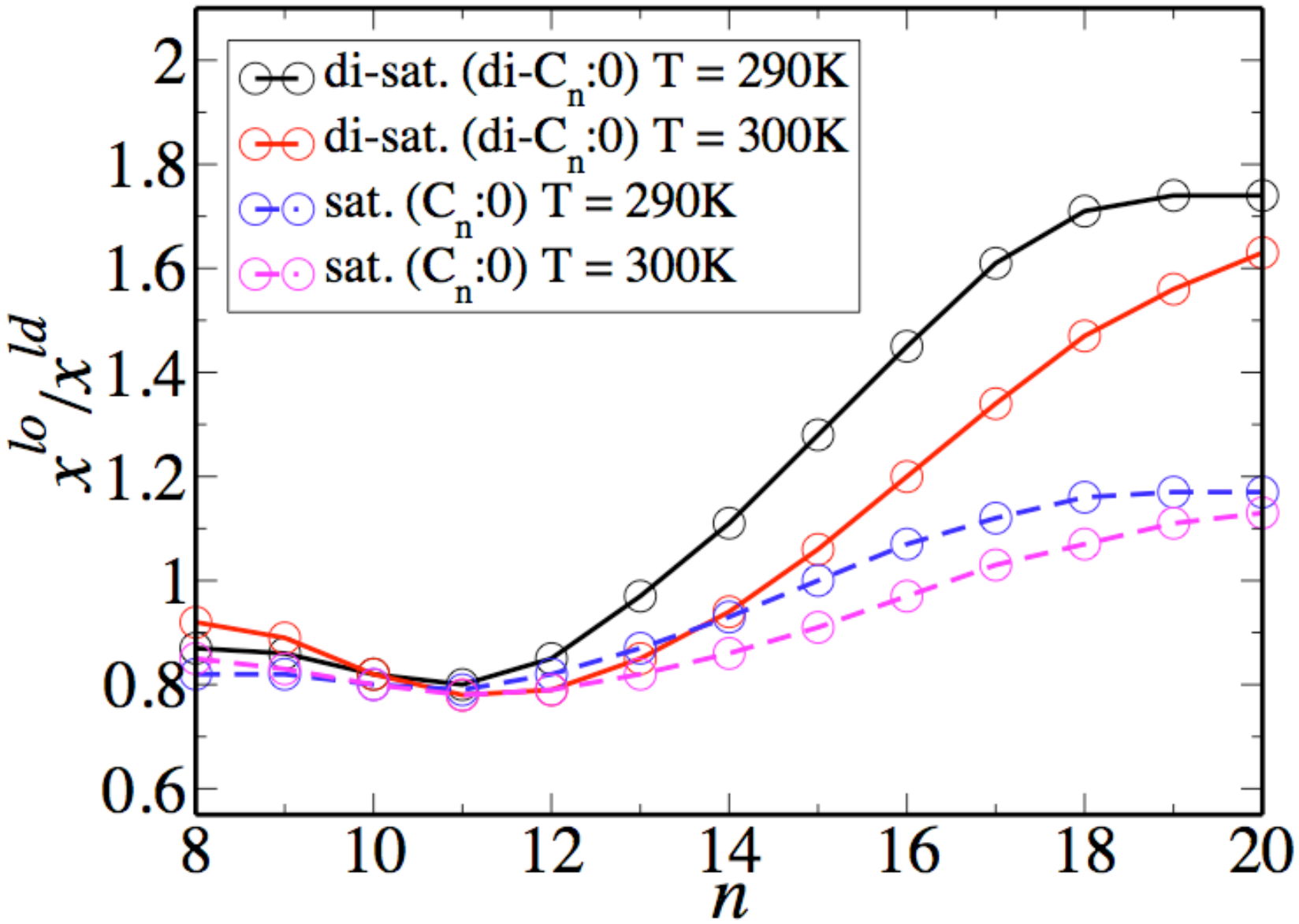
63% in sea




60% in raft

66% in sea

# Effect of Temperature



# Effect of temperature

- For most chains, partition coefficient increases with decreasing T (simple effect of concentration)
- For short chains (n<12) coefficient increases with increasing T (entropic effect)

# Conclusions

- Partition coefficient depends not only on kind of anchor, but also on concentrations

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- First calculation of partition coefficients
- Good agreement with experiments
- Understand dependence on parameters
- Bulky anchors very effective in sea
- Increased understanding of how rafts could function

# Acknowledgments


- National Science Foundation
- National Institutes of Health