The Impact of Cholesterol on Lateral Organization in a Three-Species Non-Equilibrium Model of a Biomembrane

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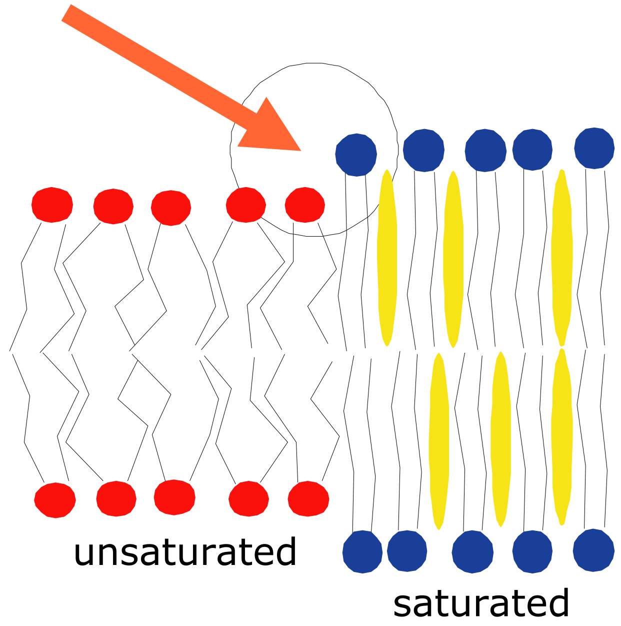
Motivation

- Our goal: to model (describe and predict) biomembrane phase behavior over a wide range of parameters.
  - To what extent does cholesterol affect the distribution of lipid domain sizes?
  - To what extent does cholesterol affect the phase diagram of the biomembrane (e.g., liquid ordered, liquid disordered, etc.)?
  - How do cellular processes keep cell membranes far from equilibrium?

Why Do Biomembranes Laterally Organize?

Exposing hydrophobic region is energetically unfavorable! [Mouritsen & Bloom, 1984]



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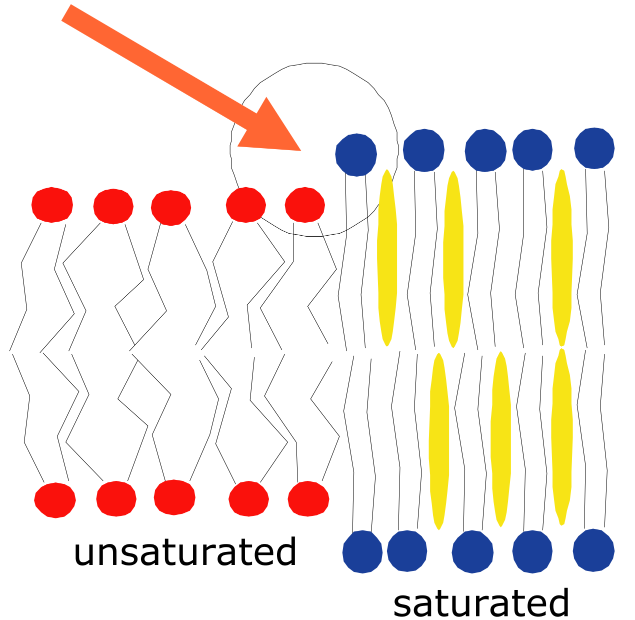


Simulations depend on **J**, the matrix of interaction energies (in units of $k_B T$).

J	S	U	C
S	-10	5	-10
U	5	-5	-5
C	-10	-5	-10

e.g., $J_{SU} = 5$

The Model

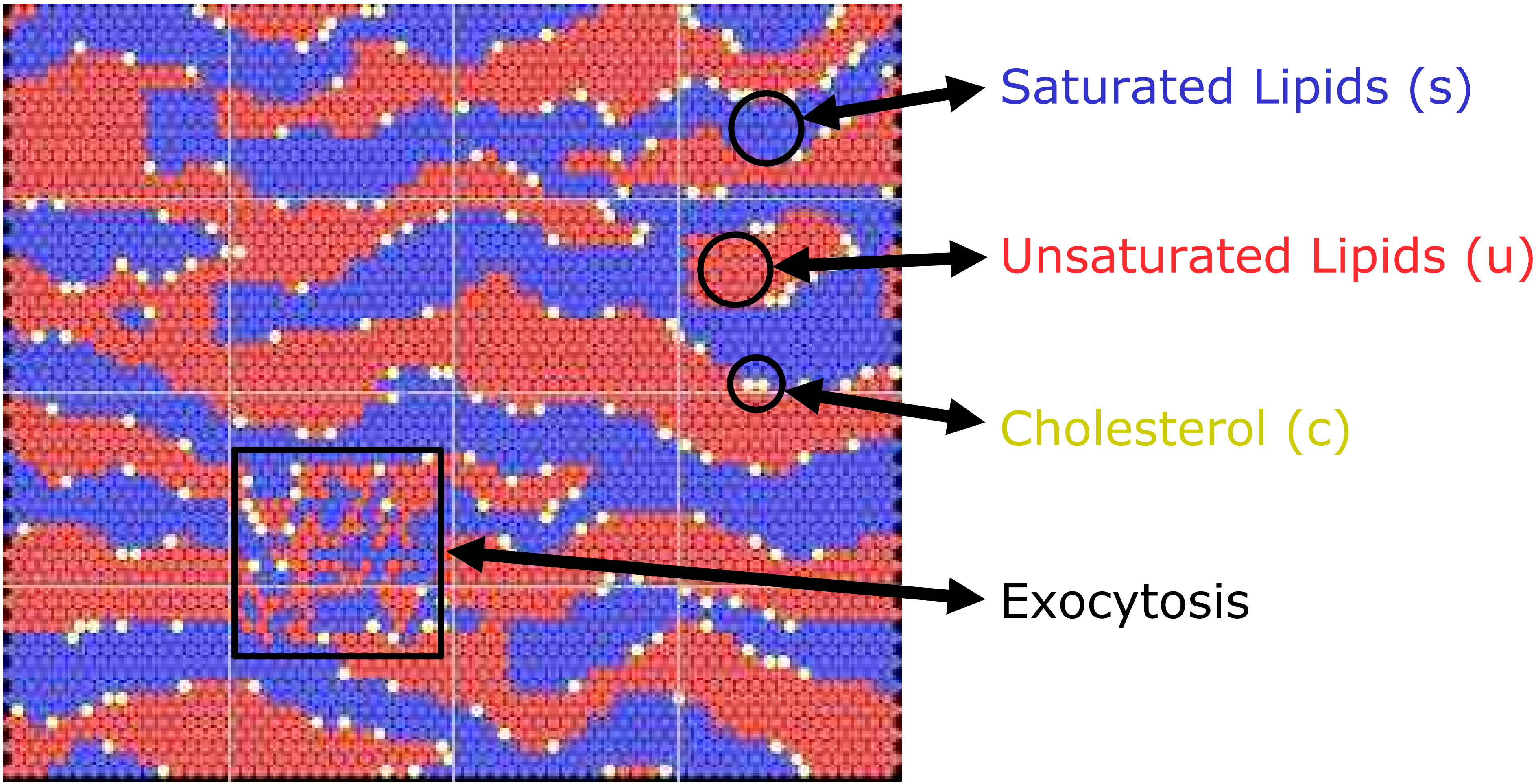
$$E = N_{ss}J_{ss} + N_{uu}J_{uu} + N_{cc}J_{cc} + N_{su}J_{su} + N_{sc}J_{sc} + N_{uc}J_{uc}$$

$$F = E - TS$$

- Monte Carlo 2D triangular lattice
- Three species under periodic boundary conditions
- Nearest neighbor energies
- Simulated with a Metropolis algorithm ($e^{-\beta(\Delta E)}$)

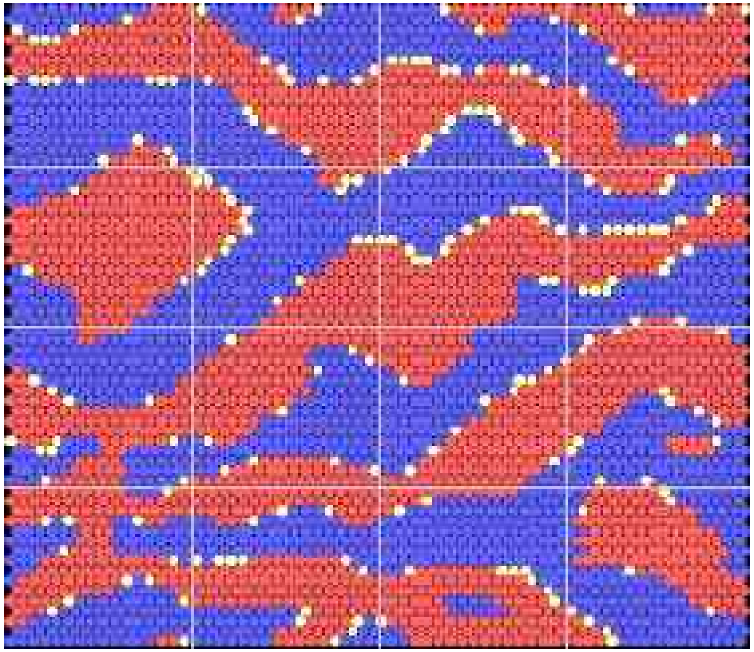
- Endo- and exocytosis events drive the system out of equilibrium.

Membrane Snapshot

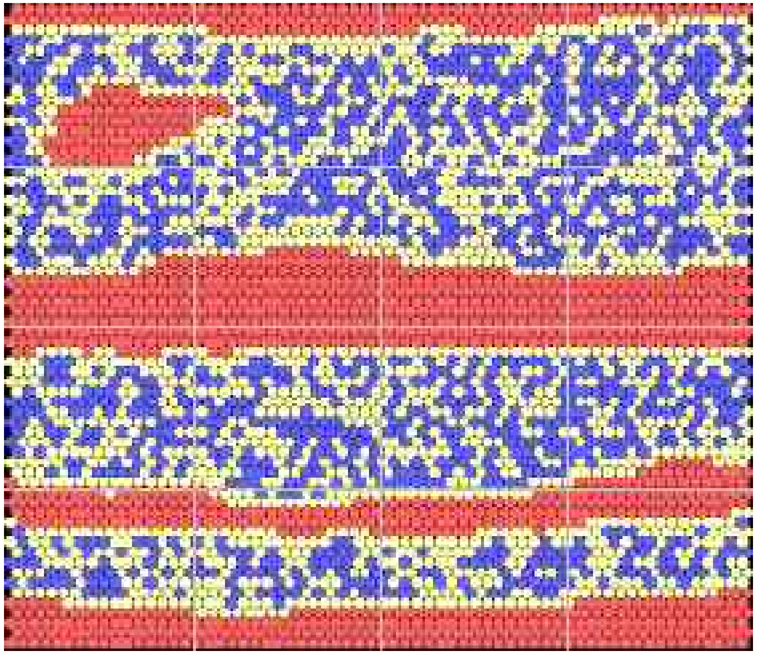


64x64 0.1 kT/J 5% cholesterol mole fraction

Effects of Cholesterol on Lipid Domain Size Distribution: Equilibrium Behavior



5% Cholesterol Mole Fraction
=> Lots of boundaries
=> Higher membrane energy



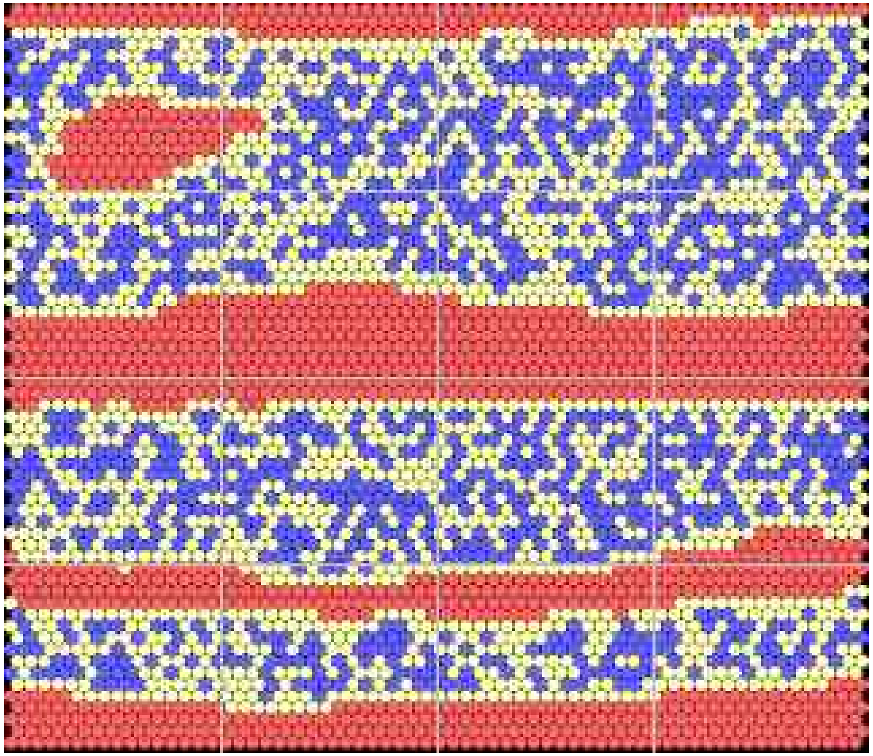
40% Cholesterol Mole Fraction
=> Fewer boundaries
=> Lower membrane energy

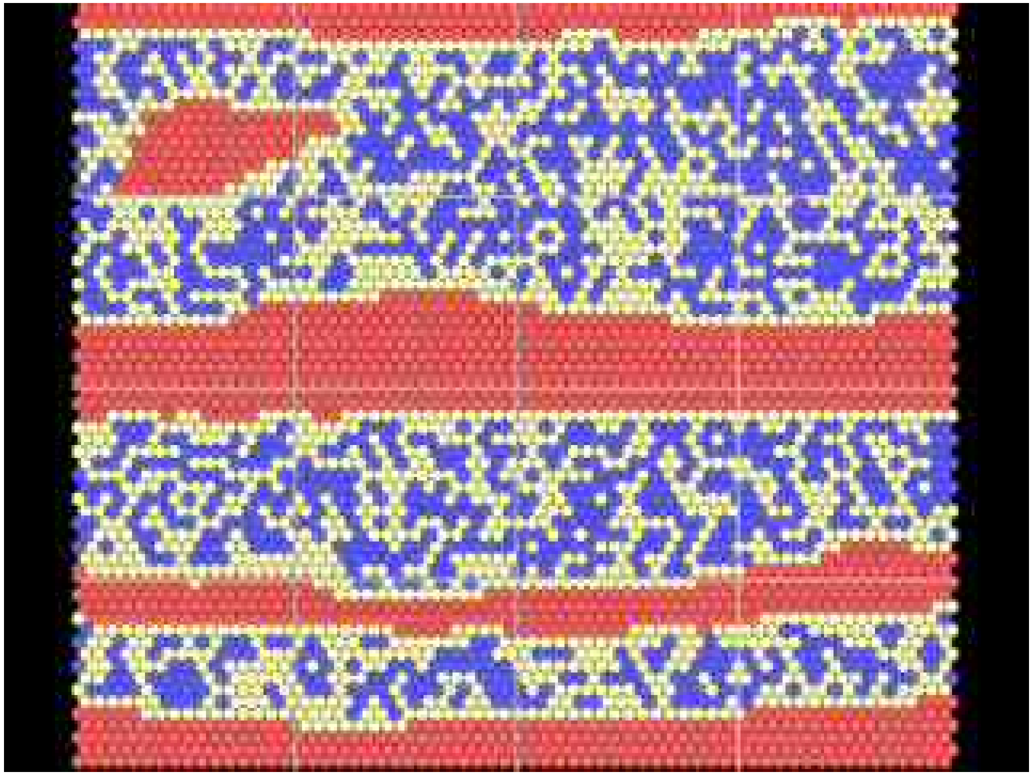
Run at 0.1 kT/J for 100,000 Monte Carlo steps

Effects of Cholesterol:

- Enhances lateral mobility at lower temperatures
- Alters size distribution of lipid domains (boundaries)

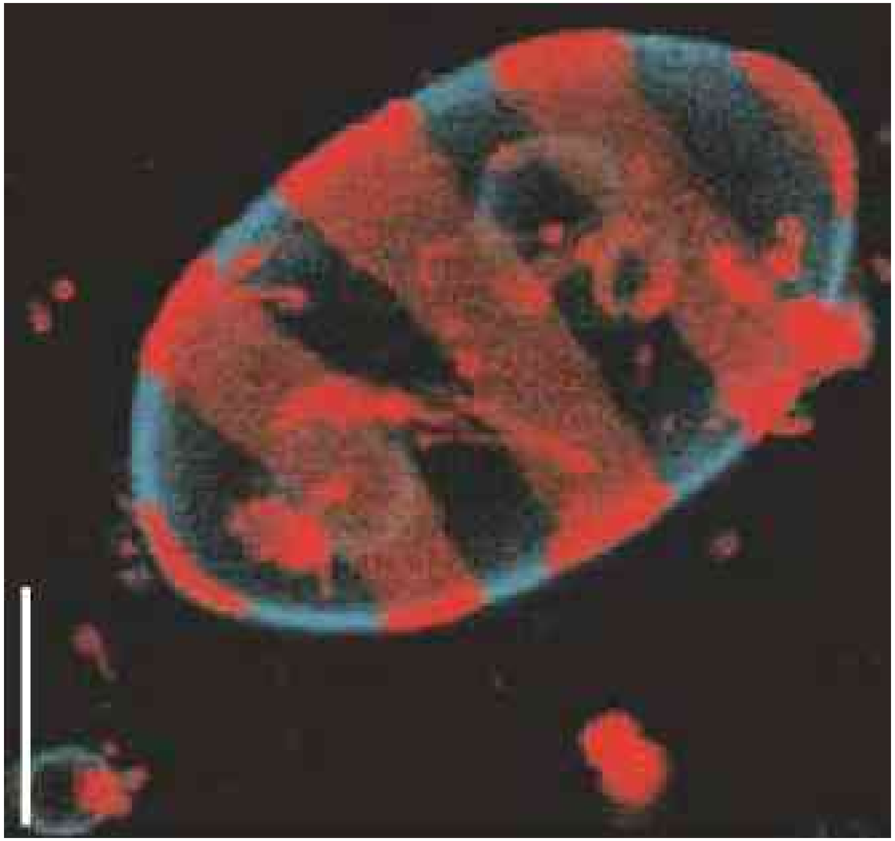
Equilibrium Model Gets Stuck in Local Minima

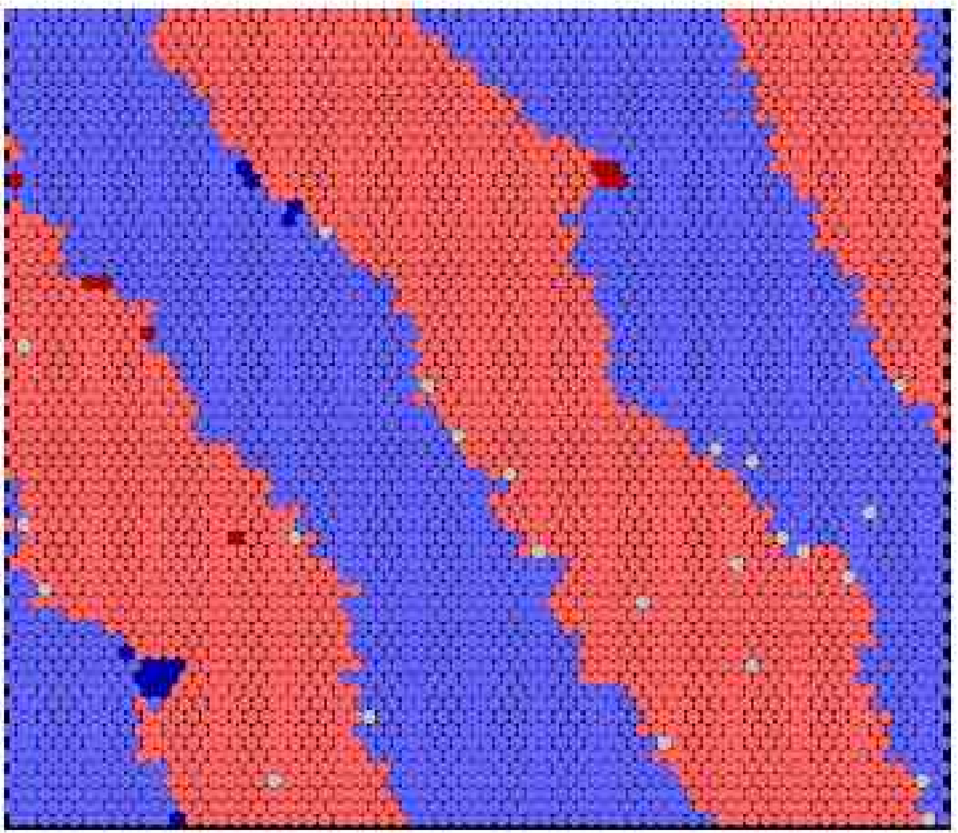




Starting configuration.

Equilibrium Model Predicts Model Membrane Behavior





[Baumgart, Hess, & Webb, 2003.]

Exciting to demonstrate experimentally verified lateral organization, but we’re after cellular membrane behavior. Introduced endo- exocytosis.

Moving from Model to Real

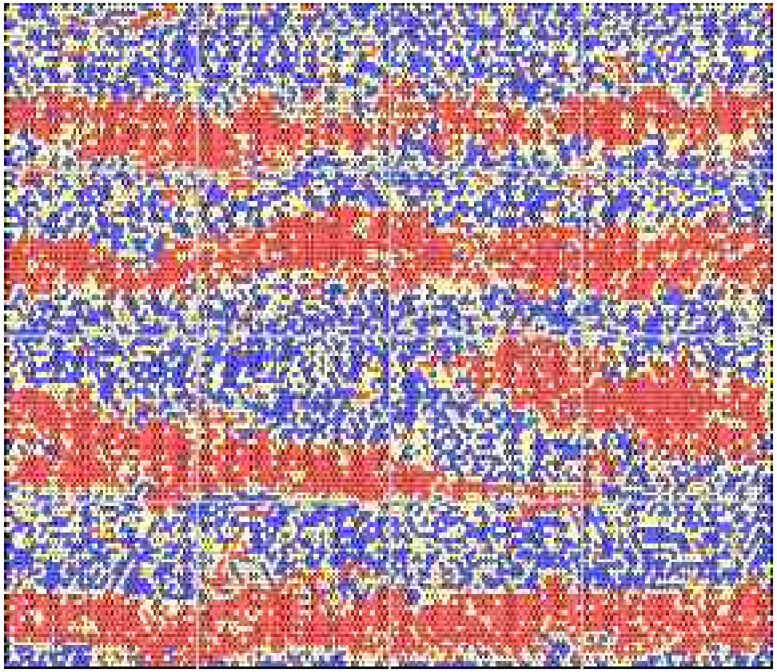
In general, Model Membranes in equilibrium show large (micron sized) lipid domains [Veatch & Keller, 2005], but cellular membranes do not [Anderson & Jacobson, 2002].

To better model cellular membranes, we introduce **endo- and exocytotic events**:

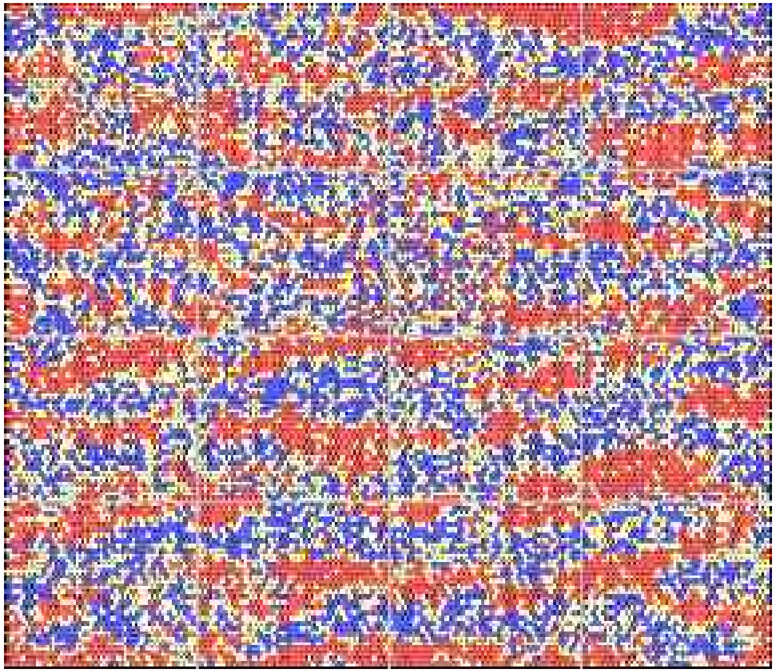
- An endocytotic event removes a patch of membrane material, representing 5% of total membrane
- An exocytotic event inserts randomly generated (according to original concentrations) membrane material into "gap" left by endocytosis

How do these events alter lateral organization?

Comparison of Equilibrium and Non-equilibrium Behavior (1kT/J)



40% Cholesterol Mole Fraction
=> Equilibrium model
=> Large regular structures



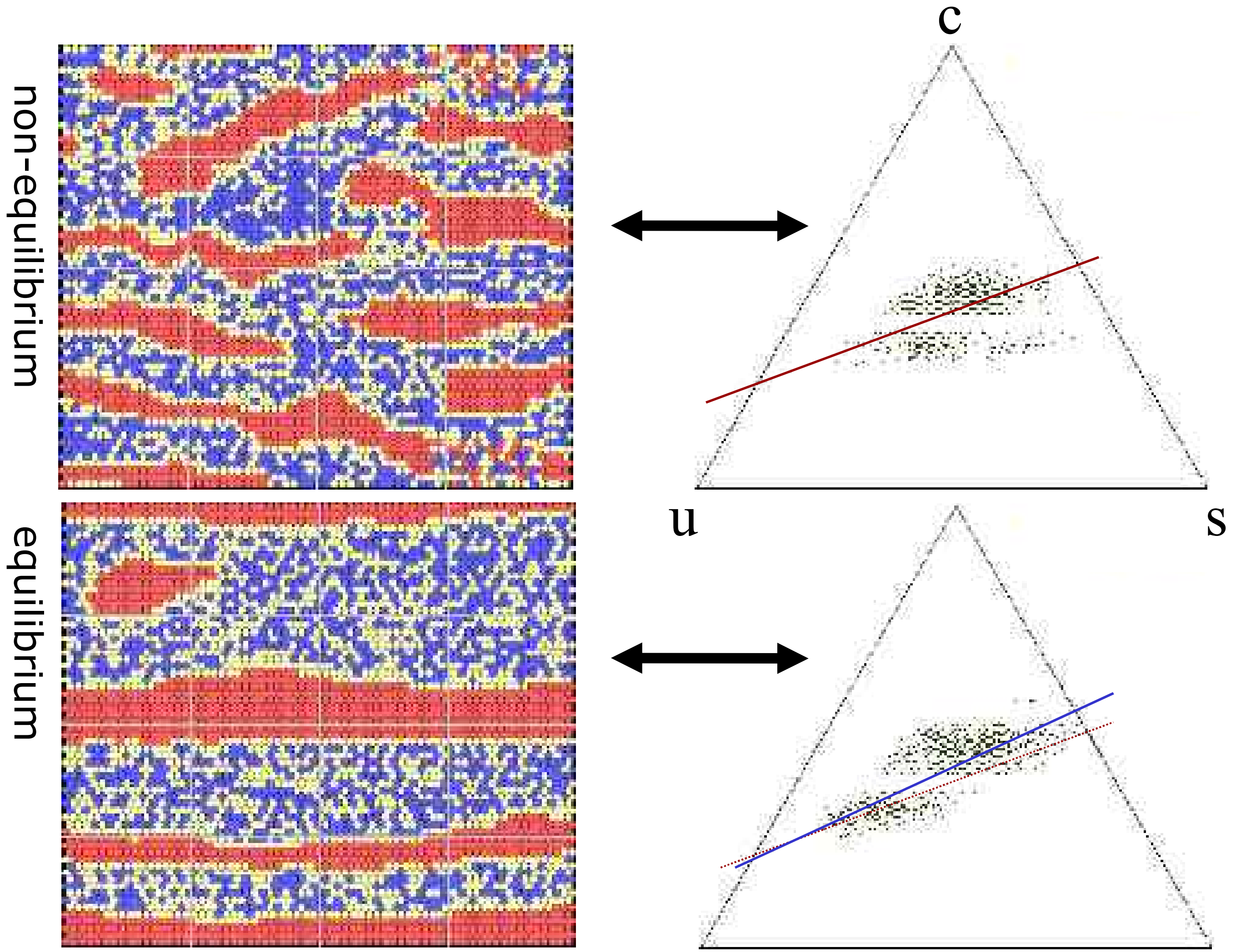
40% Cholesterol Mole Fraction
=> Non-equilibrium model
=> Domains with Irregular, Elongated Boundaries

The model shows 2-phase coexistence

- one phase with saturated and cholesterol
- one phase with unsaturated

Analysis of Local Composition

We can also look at the membrane organization on a three-species triangular map (similar to a Gibbs triangle) .



Future Work

Investigation of Power Law Dependence

- Characteristic size distribution of lipid domains
- Separation of T from some T_c
- Related, perhaps, by $L \sim |T - T_c|^{\lambda}$

Larger lattice sizes

- Robustness of results
- More accurately model endo and exocytosis

Determination of the full phase diagram, including tie lines

Conclusions

Distribution of lipid domain sizes affected by the cholesterol mole fraction

Lateral mobility at low kT/J increases with cholesterol mole fraction

Endo and exocytosis events drive system far from equilibrium

Triangular concentration maps provide more information about coexisting phases

References

Mouritsen and Bloom. 1984. Mattress model of lipid-protein interactions in membranes. *Biophys. J.* **46**: 141-153.

Veatch and Keller. 2005. Seeing spots: Complex phase behavior in simple membranes. *Biochimica et Biophysica Acta*. In press.

Anderson and Jacobson. 2002. A role for lipid shells in targeting proteins to caveolae, rafts, and other lipid domains. *Science*. **296**: 1821-1825.

Baumgart, Hess, and Webb. 2003. Imaging coexisting fluid domains in biomembrane models coupling curvature and line tension. *Nature*. **425**: 821-824.

Heerklotz. 2005. Personal communication.

Unfavorable J_{cc}

$J_{cc} = 2$