Critical Points in Biological Membranes

Ben Machta[1,2], Sarah Veatch[3], Stefanos Papanikolaou[1], Jim Sethna[1]

Recent work in plasma membrane vesicles (GPMVs) isolated from living cells demonstrates that these GPMVs can be tuned with a single parameter (temperature) to criticality, not far from in vivo temperatures [1,2]. This suggests that in vivo plasma membranes are near a miscibility critical points and may help explain some of the paradoxes associated with putative lipid rafts. Here we use universal predictions from Ising criticality to predict the shapes and sizes of membrane inhomogeneities as well as the dynamics of anomalous diffusion for components of membranes. In addition, we introduce a minimal model of the cytoskeleton to help understand why cell membranes do not phase separate at macroscopic length scales even at low temperatures. Finally, we explore the functional significance of near critical membranes for cell signaling.

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I. Background

Biological membranes are lipid bilayers composed of thousands of distinct lipids and a host of embedded proteins. In the canonical fluid mosaic model this bilayer is laterally homogeneous, with lipids playing a purely structural role as substrates for embedded proteins.

This 'simple' picture has been challenged by recent experiments suggesting structure in cell plasma membranes at length scales from 20-200nm. Detergent resistance of a reproducible membrane fraction, anomalous diffusion of some membrane components, associations probed by fluorescence techniques, and spatial correlations seen in electron micrographs all suggest that membranes are heterogeneous at length scales much larger than any single component, yet much smaller than the size of the cell. Termed 'lipid rafts,' this structure presents a thermodynamic puzzle- creating inhomogeneities of this size should have an enourmous free energy.

Parallel work in model membranes composed of just two phospholipids and cholesterol show two distinct liquid states and a gel state, with both two and three phase coexistence possible[2,3]. At the boundary of the two liquid coexistence region a critical point can be reached in the 2-d Ising universality class.

Surprisingly, vesicles isolated from living cell plasma membranes are tuned to the close vicinity of an analogous liquid-liquid critical point. Ising criticality requires the fine tuning of two parameters, and this would seem to be the first example of a system tuned to the vicinity of a thermal critical point outside of a laboratory. We propose that critical fluctuations resolve the thermodynamic paradox above and provide the physical basis for the lateral heterogeneities seen in experiments.

[1]Deparment of Physics, Cornell University, Ithaca, NY
[2] E-mail: bbm7@cornell.edu
[3]Department of Chemistry and Chemical Biology, Cornell University, Ithaca, NY

II. Results

A. Actin Cytoskeleton

The membrane is connected to a dense three-dimensional cytosekeletal network which is known to provide structural support to the membrane, and is thought to be involved in many signaling processes. GPMVs which lack this meshwork show macroscopic phase separation, while intact cells do not phase separate at any temperature. We reproduce these results in Ising model simulations by treating the cytoskeleton as an applied field fixing individual spins. We also test the impact of these fields on correlation functions and other observables.

B. Diffusion of Lipids and Proteins

Some evidence for lateral structure in plasma membranes comes from experiments that show anomalous diffusion of membrane components. We can model results from these experiments using an Ising model, by allowing individual ising spins to wander during the evolution of conserved order parameter dynamics or on a fixed Ising background. Even without introducing a cytosekeletal network this model predicts anomalous diffusion, and we compare results with and witout the network to experimental results.

C. Functional Significance of Near Criticality

Why does biology choose to have a critical membrane? Criticality lends thermodynamic plausibility to a host of functions already attributed to lateral organization by biologists. From this perspective, the primary functional significance of criticality is to give the system a large correlation length and susceptibility. Alternatively, we can directly ask what biology gains from criticality. Using techniques from information theory we can make precise the intuition that a protein embedded in a membrane with a large correlation length knows more about the state of the rest of the membrane than it would if it were in a membrane far from criticality. We are applying these ideas towards an understanding of lateral reorganization during cell signaling.

References

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