Implications of criticality in plasma membranes

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Here we present a minimal model of plasma membrane heterogeneity that combines criticality with connectivity to cortical cytoskeleton. Our model is motivated by recent observations of micron-sized critical fluctuations in plasma membrane vesicles that are isolated from cortical cytoskeleton[1]. We incorporate criticality using a conserved order parameter Ising model coupled to a simple actin cytoskeleton interacting through point-like pinning sites. In our model small (r~20nm) and dynamic fluctuations at physiological temperatures arise from criticality. Including connectivity to cortical actin disrupts large fluctuations and macroscopic phase separation at low temperatures (T≤23°C) and provides a template for long lived fluctuations at physiological temperature (T=37°C). More generally, we demonstrate that critical fluctuations provide a physical mechanism to organize and spatially segregate membrane components by providing channels for interaction over large distances.

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I. Background

Biological membranes are two dimensional liquids composed of thousands of distinct lipids arranged in a bilayer along with a host of embedded proteins. It was previously assumed that this bilayer would be laterally homogeneous, with lipids playing a role as substrate for randomly diffusing embedded proteins. Recently, however, wide ranging experimental evidence points to structure at lengths from 10-100nm, commonly referred to as 'lipid rafts'[2]. These structures present a thermodynamic puzzle; how do lengths so much larger (10-100nm) than typical components (1nm in size), emerge in a fluid system? The answer we propose is that these structures are manifestations of critical fluctuations- a claim motivated by experiments in GPMVs extracted from living cells in which liquid-liquid critical fluctuations are seen around 25°C[1]. Here we investigate the predictions of a model for membrane rafts which is based on this observed Ising criticality, estimating the sizes and lifetimes of fluctuations as a function of temperature and lipid composition. In addition we use conformal field theory and information theory to quantify the benefit cells gain by tuning near to criticality.

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II. Results

A. Actin Cytoskeleton

The membrane is connected to a dense three-dimensional cytoskeletal network which is thought to play some role in promoting heterogeneity. Notably, GPMVs which lack this meshwork show macroscopic phase separation below room temperature, 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. In 2D any field providing spatially quenched disorder disrupts phase separation.

B. Why do cells tune to criticality?

Criticality is not generic! Tuning to an Ising critical point requires tuning two parameters; reduced temperature and magnetization[3]. Each of these a cell could tune by varying the concentration of some of its components. Setting aside the question of how cells achieve this fine-tuning we ask the question of what functional significance it might have. We answer this question in several ways. Firstly, near criticality, the free energy cost associated with the formation of a large fluid structure becomes order k_BT, making a wide range of biological processes attributed to rafts thermodynamically plausible[2].

Secondly, embedded proteins experience a composition mediated entropic force- two proteins which prefer a similar lipid environment can lower their free energies by moving close to each other. We show that the range and magnitude of this force is maximized at a critical point, and we bound it using conformal field theory, finding a force much longer ranged than screened electrostatic forces in the cellular environment. Finally, we consider how proteins might make use of this force in cellular processes like signaling. To this end we calculate the mutual information between two circular inclusions in the Ising model. This bounds the amount of information one protein is able to learn about a second distant one simply by measuring the fluctuations in the local order parameter along its border.

References

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