Critical fluctuations and membrane proteins

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Recent experiments show that plasma membranes are near a 2D liquid-liquid critical point in the Ising class. This mediates long ranged entropic forces between membrane bound proteins. Proteins embedded in the membrane could use these forces to communicate over large distances, and we compare energetic and information theoretic measures of this communication channel with other channels available to membrane proteins. We propose that these results quantify the underlying physics and biological function of 'lipid rafts' often seen in biochemical assays.

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I. Introduction

Biological membranes are 2D liquid soups made up of many types of lipids and proteins. A wide array of recent evidence (reviewed in [1]) suggests that the plasma membranes of living cells are heterogeneous at lengths from 10-100nm, much larger than the 1nm typical of a lipid. Recent experimental work gives a compelling explanation for this discrepancy in length scales. Giant plasma membrane vesicles (GPMVs) isolated from living cells have compositions which at 37^0C sit just above a critical point in the 2D Ising class[2]. Below a transition temperature T_c~25^0C GPMVs phase separate into two 2D liquid phases with different compositions of protein, lipid and reporter dye. Above T_c equilibrium fluctuations become as large as ~1μm[2]. Intact cells cooled below T_c do not phase separate, likely due to interactions with the cytoskeleton[3]. Still, we expect large (~20nm) fluctuations at 37^0C, giving a quantitative explanation for the commonly observed 'lipid rafts'[3]. This research aims to understand the physical implications and biological role of these critical fluctuations.

II. Long ranged Forces

Liquid-liquid critical points are distinguished by long ranged correlations in an order parameter, $\phi(r)$, which describes deviations from the average composition. A protein which prefers a certain lipid environment interacts with $\phi(r)$ through its boundary, coupling it to spatial composition fluctuations and leading to entropic Casimir forces. We calculate the resulting long-ranged potential of mean force between pairs of proteins. We use a perturbative approach which treats proteins as points, an exact conformal field theory technique which treats proteins as circles and a Monte-Carlo technique on the square-lattice Ising model. We find that proteins with radius ~2nm can interact with a potential of order k_BT out to ~20nm. This is very long ranged in the cellular environment where electrostatics is screened over ~1nm[4].

III. Communication between Membrane Proteins

In signal transduction and other tasks, information distributed over many membrane bound proteins must be integrated before a cell responds with a coherent unified response. Motivated to quantify the usefulness of criticality in the cell membrane we set out to quantify the bandwidth and energetic costs for different physical channels through which membrane bound proteins could communicate.

By changing its coupling to the membrane composition's Ising order parameter a transmitter protein could send a signal to a distant receiving protein that is picked up by that protein's allosteric state. A similar membrane curvature mediated force could also be used. In addition, a protein could control the flow or production of ions or other second messengers either into the cell or into the membrane plane to be detected by a distant receiver protein. Finally, a protein could push on the actin cytoskeleton, and directly exert a force on a distant protein. For each we estimate the bandwidth of such a channel as a means for communication. In addition we bound the energetic cost using simple physical models.

IV. Anesthesia

Despite widespread use the microscopic mechanism of general anesthesia is not well understood. Strikingly, the potency of an anesthetic is well predicted by its partition coefficient in oil, suggesting a membrane based mechanism. We show that the ED50 concentration (at which 50% of tadpoles have lost their righting reflex) of the series of long chain alcohols lowers the critical temperature in membrane derived blebs by approximately 4K. We present a simple model in which such a change is able to reproduce the observed changes in channel conductance seen in GABA sensitive Chloride channels, without the need for a specific anesthetic binding site.

References

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