Information flow in the plasma membrane

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Signaling molecules induce diverse downstream effects. These include the production of membrane bound and bulk diffusing second messengers, changes in membrane conductance and modification of the mechanical properties of the cytoskeleton. Strikingly, they also lead to changes in the spatial organization of membrane bound proteins. Why does the cell use all of these different mechanisms to transmit and process information? We set out to quantify the usefulness of these mechanisms as information channels between spatially separated proteins. In each case, the channels are noisy with shot and/or thermal noise dominating. For each channel we estimate the mutual information rate achievable in a given frequency band, as a function of energetic cost, as a function of separation. Each of these mechanisms are most efficient in particular regimes of frequency and spatial separation, perhaps explaining why all of them are used in actual signaling systems. In particular, the proximity of the membrane to criticality allows for a communication channel that is relatively slow but thermodynamically cheap and relatively long-ranged.

Keywords **— Criticality, Lipid Rafts, Signal transduction, Information theory**

I. Introduction

Biological membranes are 2D liquids made up of many hundreds of types of lipids and proteins. A wide array of recent evidence (reviewed in [1]) suggests that the fluid 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 thermodynamic explanation for this discrepancy in length scales. Giant plasma membrane vesicles (GPMVs) isolated from mammalian immune cells have compositions which, at 37^{o}C sit just above a critical point in the 2D Ising class[2]. Below a transition temperature Tc~25^{0}C 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^{0}C, giving a quantitative explanation for the commonly observed 'lipid rafts'[3]. This research aims in part to understand the physical implications and biological role of these critical fluctuations.

Signaling is often initiated when a receptor embedded in this nearly critical fluid binds a ligand. Many of the early signal processing steps are carried out by membrane bound proteins. These proteins use a surprisingly diverse set of physical mechanisms to communicate with one another over distances ranging from nanometers to microns and at time scales ranging from fractions of milliseconds to minutes. As a typical signal is processed, intermediate steps involve the production of bulk soluble and membrane bound second messengers (like DAG) the release of charged ions into or out of the cytoplasm, the rearrangement of the cytoskeleton, and clustering of components into correlated structures [4-6].

Why do all of these microscopically varied mechanisms see use in signaling cascades? To address this we use minimal models wherein one membrane bound protein sends a signal and a spatially separated one receives it. We calculate the signal to noise ratio as a function of spatial separation and frequency, where noise comes from the shot noise of stochastic particle arrivals and thermal noise. In addition, we estimate the energetic cost of sending a signal. From these two measures, in the linear noise approximation, we can estimate the energetic cost of sending a bit/s at a given frequency.

At high frequency and large spatial separation, the release of charged second messengers is by far the most efficient. However, for shorter distances and lower frequencies, release of second messengers into the membrane can be more effective- these signals spread slower, which means they are less diluted. Release of second messengers into the bulk is intermediate.

Changing coupling to the order parameter of criticality provides a channel that is slower and shorter ranged then both of the above, but which is extremely energetically cheap, allowing it to be optimal at relatively short distances and low frequencies. We make these ideas precise making frequent use of the fluctuation-dissipation theorem.

References

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