Receptor binding, membrane deformations, and signal propagation at the cell membrane

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***Short Abstract* — Cell signaling plays a key role in many cellular processes such as immune cell activation by antigen. We investigate two processes important to lymphocyte activation: membrane-mediated interactions between receptor-ligand pairs at cell-cell junctions and subsequent signal propagation by a network with positive feedback. Using spatially resolved, deterministic simulations, we study membrane-mediated interactions between receptor-ligand pairs and characterize the influence of spatial clustering and diffusion on the spread of a chemical signal through space and time in a positive feedback network.**

I. Introduction

CELL communication is vital for biological systems and is often highly dependent upon the interaction between a transmembrane surface receptor and its ligand. Lymphocytes such as T cells and B cells can be stimulated by cell-cell contact, with the ligand being presented on the surface of the other cell. This is an example of juxtacrine signaling, and receptor-ligand binding can couple with membrane mechanics to deform the membrane and locally exclude other surface molecules that are longer than the length of the receptor-ligand complex [1]. This can lead to effective membrane-mediated interactions between receptor-ligand pairs, thus contributing to their spatial organization on the membrane. In many cases, signaling networks downstream of the receptors contain feedback motifs that confer useful dynamical and steady state properties. The spatial organization of surface receptors can significantly influence the dynamics of signaling [2, 3]. Positive feedback networks are interesting because they can support bistability and fast propagation of a signal through space [4,5].

II. Results

We begin by considering a model of receptor-ligand binding at cell-cell interfaces. Drift-diffusion partial differential equations provide a useful framework for describing the concentration profiles of long surface molecules (LSMs) present in the intercellular junction given that a receptor-ligand bond has formed [1]. We have explored the characteristics of LSMs and membrane energetics given that one or more receptor-ligand bonds have formed. The coupling of the drift-diffusion partial differential equations and the Euler-Lagrange equation describing membrane shape and energetics has given insight into the time-dependent evolution of molecular concentrations in the system.

Given that membrane mechanics can promote the spatial clustering of receptor-ligand complexes, we consider the effects of clustering and diffusion on switching to an active state in a bistable positive feedback network. We consider a simple two-component network and seek to understand how diffusion influences various properties of the reaction network. Coupled reaction-diffusion partial differential equations describe the spatiotemporal evolution of molecular concentrations. We obtain numerical solutions for the spread of an "active" chemical signal through space and time, given an initial localized pulse of the active species. The biological motivation includes clustering of receptors at the cell membrane and stochastic fluctuations that could trigger signaling. We find that a slower diffusion coefficient results in a more pronounced interface between active and inactive regions, and that the fastest signal propagation occurs at intermediate diffusion coefficients. It is interesting to note that the diffusion coefficient corresponding to the minimum time for the system to be in the active state over the entire domain is dependent on the ability of the active species to accumulate in a localized region.

III. Conclusion

A general understanding of communication at cell-cell interfaces remains a challenging problem. Methods that couple receptor binding with membrane mechanics and spatial organization have the potential to inform studies of signal transduction networks to give greater insight into receptor-mediated juxtacrine signaling.

References

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