Modeling Cell Signaling Pathways with Spatially Explicit Mobile Agents

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***Short Abstract* — Many activities of cells are controlled by cell surface receptors, which respond to ligands by triggering intracellular signaling reactions. The process of receptor signaling involves highly connected networks of interacting components. Here, an agent-based simulator is under development to study diverse molecular interactions in signaling pathways with spatial resolution and single molecule detail. It permits stochastic modeling of protein clustering, protein motion and biochemical reactions within an idealized cellular geometry. The modularized design confers flexibility. The model is presently being used to determine the impact of spatial proximity and microdomain organization upon EGFR/ErbB receptor signal transduction efficiency and outcome.**

I. Background

THE Erb family of receptors include ErbB1 (EGFR), ErbB2, ErbB3 and ErbB4 and control important cellular processes. ErbBs are composed of an extracellular domain, a transmembrane domain, and a cytoplasmic tyrosine kinase domain. EGFR and ErbB2 overexpression is common in cancers of epithelial origin (cancer, lung, etc.) Signaling by ErbB receptors can be influenced by expression levels, cluster size, location, homo-/heterodimerization, and rates of internalization. The dimer formation is critical for ErbB signaling, since it leads to a transautophosphorylation of a number of cytoplasmic tyrosine residues, providing scaffolds for various cytoplasmic signaling proteins.

II. Introduction

We have developed an agent-based, stochastic, off-lattice modeling framework to model the ligand (EGF) binding and dimerization of the EGFR [1]. We compared our simulation results with various experiments to analyze the dominant mechanism of receptor functional dimerization and tested the hypothesis that membrane rafts govern the duration and efficiency of receptor coupling to specific pathways.

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III. Methods

A simulation iteration is composed of biomolecular reaction, molecular diffusion and dynamic system behavior. At each time step, individual agents check for collision with neighbors and examine if a reaction is possible.

A. Reproduce non-random behavior of receptors

Simulation of ErbB receptor distributions in the membrane is based upon trapping in "Protein Islands" [2]. With this approach, mobile particles cluster in protein islands and clustering persists as particles continue to diffuse**.**

B. Dimerization simulations

Using the experimental data from literature, simulation results suggest that cells expressing clustered or higher level of EGFR have more predimers in the absence of ligand [3].

C. Coarse grain molecular modeling

Using coarse grain modeling of the cytoplasmic domain of EGFR docked with its five signaling molecules [4] to develop a hierarchy of EGFR tail binding partners for future simulations.

IV. Conclusion and Future Directions

Early simulations have considered clustering of individual species, diffusive behavior and dimerization rates. Simulations were used to investigate mechanisms of receptor functional dimerization and activation as functions of time, receptor density and receptor spatial distribution. We are poised to proceed with testing the model for interactions of downstream signaling molecules, based in part on spatial constraints of docking partners and on observed patterns of signaling proteins in membranes.

References

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