Rule-based stochastic model of aggregate formation in systems of multivalent biomolecules

Michael I. Monine[1,2], James R. Faeder[1], and William S. Hlavacek[1,2]

Aggregation of receptors on cell surface by multivalent ligands initiates a variety of cellular responses, which are processed by cytoplasmic signaling molecules in downstream regulatory pathways. We propose an efficient rule-based stochastic algorithm that facilitates understanding the kinetics of aggregation. The kinetic model is originally designed for well-mixed systems, however, in case of diffusion-limited reactions, diffusion effects can be included as corrections to the reaction rates. We apply this method to simulate dynamics of aggregate formation in a system of the high affinity receptor for IgE (bivalent receptors, FcεRI) and antigen (multivalent ligands, DNP_{21}-PE). The simulation results agree very well with recent flow cytometric measurements for this system.

***Keywords*: aggregation of cell surface receptors, FcεRI, stochastic simulations, rule-based models, Monte Carlo, Gillespie algorithm.**

I. Motivation

Aggregation of receptors on cell surface by multivalent ligand is a common mechanism occurring at early stages of signal transduction in cells [1-5]. This process takes place at intrinsic protein tyrosine kinases such as epidermal growth factor receptors (EGFR) [3], platelet derived growth factor receptors (PDGFR) [4], multichain immune recognition receptors [1,2], and in TCR-induced signaling through oligomerization of linker of activated T cells (LAT) [5]. The phenomenon of aggregation is associated with the exponential increase in the number of chemical species and distinct cross-linking interactions, therefore, dynamic simulations of such complex biomolecular systems with the help of conventional methods (such as ODEs, etc.) become intractable. To resolve the complexity of this problem, we propose an efficient stochastic model based on Gillespie method [6] that implements a sequence of binding/dissociation events. Our algorithm is off-lattice "rejection free", i.e., it does not allow null events to occur during the sampling among all possible molecular configurations in the system. To classify individual processes in the system, we have developed a general framework consisting of arrays of molecules and lists of binding sites available for each reaction type. We create dependencies for these lists in such a way that any transformation of the system causes either addition or removal of site addresses in the lists, or shift of addresses between the lists. Such a classification of processes allows to achieve maximum efficiency while sampling individual reactions and sites. It should be noted that the number of classes (and list update rules) increases with the number of species and their valence, and it is equal to the number of distinct reactions in the system.

[1]Theoretical Biology and Biophysics, T-10, Los Alamos National Laboratory, Los Alamos, NM

[2]Center for Nonlinear Studies, Los Alamos National Laboratory, Los Alamos, NM

E-mail: mmonine@lanl.gov

II. Model application

To validate the simulation results, we use a thermodynamic equilibrium theory that quantifies all possible configurations on the surface [7]. In the experimental system, DNP_{21}-PE ligand-induced aggregation of IgE-FcεRI receptors is quantified by the total number of bound receptor sites and the total number of bound ligands [1,2]. Using these quantities, one can extract information about the state of receptor aggregation. However, there is still no way to obtain directly statistics on receptor aggregates in the experiments. Therefore, the simulations, in which dynamics of aggregates can be quantified explicitly, are of great benefit to understanding the kinetics of aggregation. By using the developed model with reasonable values of kinetic parameters, we are able to reproduce quantitatively the experimental data on overall kinetics of ligand-receptor binding and cross-linking both in dynamics and at equilibrium.

III. Conclusion

The developed stochastic algorithm is exact and efficient; it allows to observe dynamics of specified molecular configurations and binding sites, as well as the distribution of aggregates according to their size. We are currently working on generalization of the algorithm and plugging it in to other rule-based software, such as BioNetGen [8].

References

[1] Hlavacek W.S. et al., (1999) Quantifying Aggregation of IgE- FcεRI by Multivalent Antigen. *Biophys. J.*, **76**, 2421 .

[2] Posner R.G., Chemistry and Biology, Northern Arizona University, Flagstaff, AZ, private communication.

[3] Schreiber A.B. et al., (1982) Biological role of epidermal growth factor receptor clustering: investigation with monoclonal anti-receptor antibodies. *J. Biol. Chem.*, **258**, 846.

[4] Heldin C.H. et al., (1989) Dimerization of B-type platelet derived growth factor receptors occurs after ligand binding and is closely associated with receptor kinase activation. *J. Biol. Chem.*, **264**, 8905.

[5] Houtman J.C.D. et al., (2006) Oligomerization of signaling complexes by the multipoint binding of GRB2 to both LAT and SOS1. *Nat. Struct. Mol. Biol.*, **13**, 798.

[6] Gillespie D.T., (2007) *Ann. Rev. Phys. Chem.*, **58**, 35; Gillespie D.T., (1977) *J. Phys. Chem.*, **81**, 2340.

[7] Goldstein B., Perelson A.S., (1984) Equilibrium theory for the clustering of bivalent cell surface receptors by trivalent ligands. *Biophys. J.*, **45**, 1109.

[8] Blinov M.L. et al., (2004) BioNetGen: software for rule-based modeling of signal transduction based on the interactions of molecular domains. *Bioinformatics*, **20**, 3289.