Integrating Nanotechnology with Cell Biology and Neuroscience

INCBN IGERT Seminar

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Modeling Multivalent Ligand-Receptor Interactions with Steric Constraints

Modeling of signal-transduction systems is challenging, in part because the molecular interactions occurring in these systems have the potential to generate large numbers of molecular complexes, a feature termed combinatorial complexity. Additional complexity is present in the form of steric constraints on molecular complexes. To address these challenges, we have developed a kinetic Monte Carlo (KMC) method that can take advantage of a model specification in terms of formal reaction rules for molecular interactions. The challenges of combinatorial complexity and steric constraints can arise at any level of a cell signaling cascade. Even at early steps, interactions between multivalent ligands and cell-surface receptors can produce large numbers of distinct chemical species. We have applied our KMC method to study the interaction of a trivalent ligand with a bivalent cell-surface receptor. In our analysis, which was inspired by flow cytometric measurements of trivalent model antigen binding to bivalent IgE-FcεRI complexes on rat basophil leukemia (RBL) cells, we consider the following kinetic models: a model based on the equivalent-site hypothesis, an extension of the equivalent-site model that takes into account steric constraints on the configurations of ligand-induced receptor aggregates, and extensions of these models that account for cyclic receptor aggregates comprised of either two or six receptors. Using these models, we investigate the effects of steric constraints and the formation of cyclic aggregates on the kinetics and equilibria of ligand-induced receptor aggregate formation.