Modeling multivalent ligand-receptor interactions with constraints on configurations of cell-surface receptor aggregates

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***Short Abstract* — We have developed a rule-based kinetic Monte Carlo method that is illustrated by using it to characterize interactions of multivalent ligands with cell-surface receptors in a well-mixed system. A pseudo-spatial modification of the model accounts for steric effects and constrains binding of multimolecular complexes. We study the effect of receptor aggregate structure on the overall kinetics of aggregation. We demonstrate that at certain conditions, spatial description of receptor aggregates can be avoided and steric effects can be lumped into reaction rate constants that are functions of aggregate sizes.**

***Keywords* — multivalent ligand-receptor binding, steric effects, rule-based modeling, signal transduction, stochastic simulation algorithm, kinetic Monte Carlo**

I. Background

SIGNAL TRANSDUCTION generally involves multivalent protein-protein interactions, which can produce myriad protein complexes and post-translational modifications [1]. Such protein-protein interactions can be represented compactly and precisely using graphical reaction rules, which can be processed automatically, by software tools such as BioNetGen, to obtain a chemical reaction network [2]. However, reaction networks implied by typical sets of rules are so large as to challenge conventional simulation procedures. To address this challenge, we have developed a kinetic Monte Carlo method that can take advantage of a model specification in terms of rules [3]. To our knowledge, no rule-based models that incorporate steric effects have been developed.

II. Method Application

The method is illustrated by using it to characterize interactions of a trivalent ligand with a bivalent cell-surface receptor in a well-mixed system. In this system, a synthetic molecule containing symmetrically arrayed dinitrophenol (DNP) groups interacts with anti-DNP monoclonal IgE antibody bound to FceRI, the high affinity IgE receptor [4]. Efficiency of the simulation method allows for fitting of the experimental binding assays. The fitting procedure involves adjustment of binding rate constants by using the non-linear least squares optimization algorithm combined with the bootstrap method. As an extension to the equivalent site model, we propose a pseudo-spatial modification of the model that accounts for steric effects and constrains binding of multimolecular complexes. Algorithmically, such constraints are included by incorporating null-events into the simulation method. The overall system evolution rate is estimated based on the assumption that there is no dependence on the spatial structure of interacting complexes, and then, for any particular binding reaction, accurate corrections to the rate are made based on the connectivity of molecules in complexes. The model with steric constraints applied to multivalent ligand - receptor interactions reveals the effect of receptor aggregate structure on the overall kinetics of aggregation.

III. Conclusion

We prove the validity of our method by showing that estimated equilibrium constants for free ligand binding and receptor crosslinking reactions lie in a reasonable range. We also demonstrate that at certain conditions, spatial description of receptor aggregates can be avoided and steric effects can be lumped into reaction rate constants that are functions of aggregate sizes.

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