Geometric Rule-Based Modeling of the Shrimp Allergen Tropomyosin

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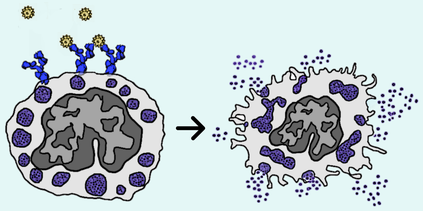
Adaptive Motion Planning Research Group

STMC SpatioTemporal Modeling Center

CETI Center for Evolutionary and Theoretical Immunology
University of New Mexico • Los Alamos National Laboratory • Santa Fe Institute

Problem and Motivation

Mast Cell Biology



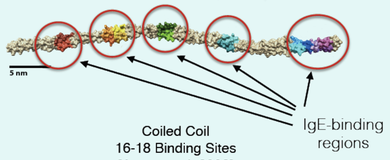
IgE antibodies bound to FcεRI receptors (blue) crosslink through the binding of antigen (yellow) on the cell surface. This formation of aggregates is what stimulates mast cells and basophils to initiate an allergic response.

It has been estimated that up to 40% of the world's population have allergies. The allergic response is caused by the antigen-mediated crosslinking of IgE antibodies bound to FcεRI cell-surface receptors, and is related to the formation of antigen-receptor aggregates on mast cells and basophils.

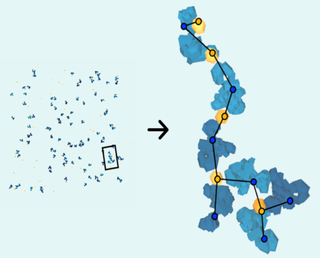
The highly potent shrimp allergen Pen a 1 (tropomyosin) has a linear structure and five major IgE-binding regions. The overall goal of this research is to understand the aggregation of Pen a 1 molecules and receptors by simulating aggregation based on allergen and receptor geometry.

We use a 3D rigid-body Monte Carlo method that explicitly represents geometry, and a spatial rule-based method that implicitly represents geometry through a set of reaction rules. We seek to understand specifically how steric effects, which depend on model resolution, affect the size and structure of aggregates.

Pen a 1



Background and Related Work

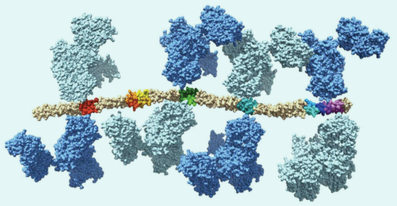


In this graph-based geometric model, receptors (blue vertices) bind to antigens (yellow vertices). The bonds are represented by edges (black lines).

A method for the geometric modeling and simulation of antibody aggregation based on robotic motions has previously been developed [1].

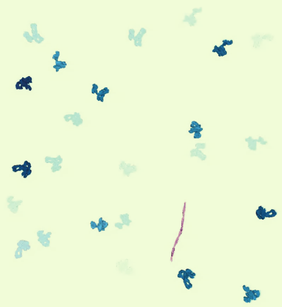
Rule-based modeling is useful for modeling proteins in cellular signaling systems, as it overcomes the problem of combinatorial complexity [2].

The rule-based model has been extended to incorporate spatial information [3].



An all-atom aggregate structure consisting of IgE-FcεRI receptor complexes (blue) bound to a Pen a 1 antigen (tan) at various binding regions (multiple colors).

3D Geometric Model

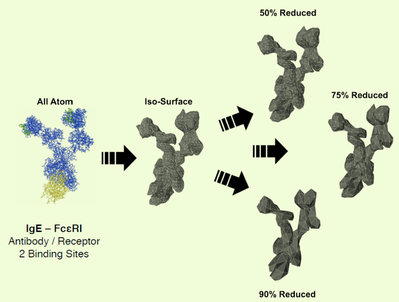


In our 3D geometric model, diffusion and binding of rigid-body models of the antigens and the receptor complexes are simulated using a Monte Carlo method. Molecular binding is tracked using a graph in which the vertices represent antigens and receptors, and edges represent antigen-receptor bonds.

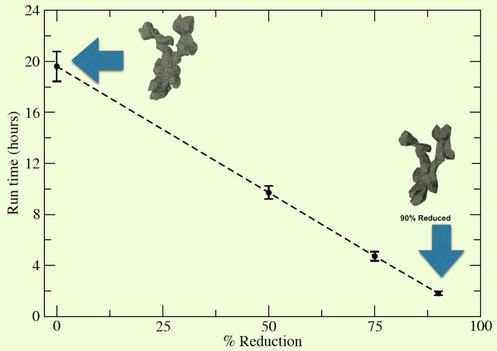
Parameters used such as the association/disassociation rates and diffusion constant were obtained from experiment. An aggregate's speed is inversely proportional to its size.

The probability of binding depends on binding volume overlap and the association rate.

To reduce computational cost, resolution was reduced by first creating isosurface models of the all-atom structures and then using polygon reduction to reduce the model complexity. The models we tested had 0%, 50%, 75%, and 90% polygon reduction.



Resolution Study – 3D Geometric Model

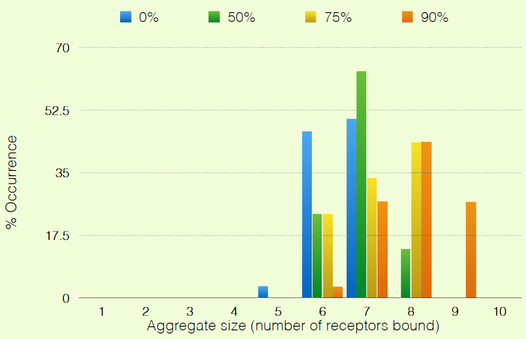


The effect of resolution on the run time of one Monte Carlo simulation is significant. One run at 0% reduction takes about 20 hours.

In addition, the resolution of the model affects the aggregate size distribution.

We prefer to run the low resolution models, as they take much less time to run. However, the effect of lower resolution on the results poses a problem.

We therefore use a rule-based model to characterize the difference in results.



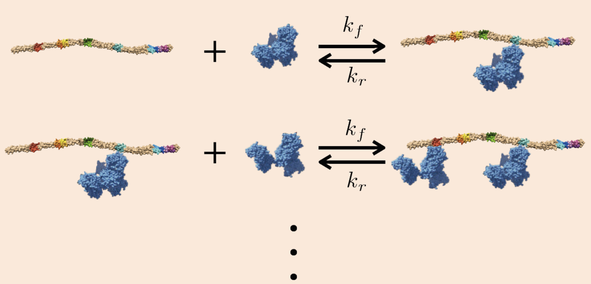
Rule-Based Modeling

A rule-based model that implicitly represents molecular geometry is implemented with RuleBender using the BioNetGen software.

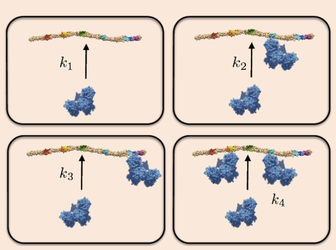
Each rule corresponds with an ODE that represents a possible binding event of one IgE antibody to one of six specified binding regions of the Pen a 1 allergen. The rule specifies the conditions under which the event can occur.

In our model, we specify the rules according to the curvature of the native-conformation Pen a 1 molecule and the occupation states of neighboring binding regions.

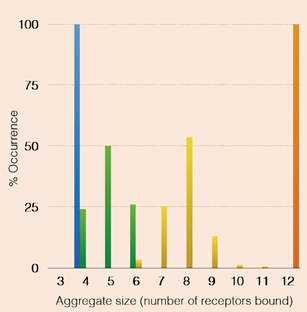
The curvature affects the steric hindrances between binding regions.



Rate Constants



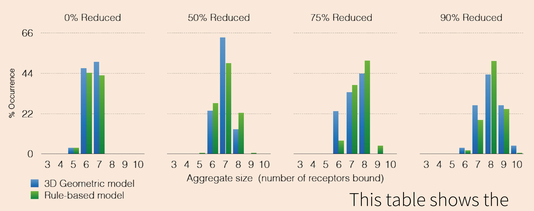
In our model, each rule corresponds with one of four forward rate constants. The rate constants are specified according to the occupation states of the nearest and next-nearest neighbors of a binding region.



This histogram shows how the aggregate size distribution changes as each of the four rate constants are set to zero.

Resolution Study - RBM

For each Monte Carlo model resolution, parameter scanning of the forward rate constants was used to fit the RBM aggregate size distributions to the Monte Carlo aggregate size distributions.



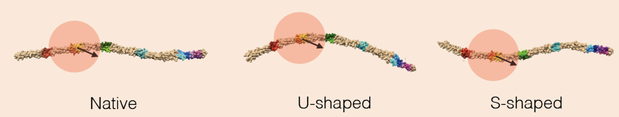
Rate Value	Model Percent Reduction 0%	50%	75%	90%
k_{f1} (mol^{-1}s^{-1})	1.00	1.00	1.00	1.00
k_{f2} (mol^{-1}s^{-1})	0.07	0.12	0.50	1.00
k_{f3} (mol^{-1}s^{-1})	1.00	1.00	1.00	1.00
k_{f4} (mol^{-1}s^{-1})	0.00	0.00	0.00	0.006

This table shows the forward rate constants that correspond to the RBM fit for each resolution. An increase in the rate constant k_{f2} with a reduction in resolution is noted.

Correlations of RBM rate constants with Monte Carlo model resolution may be used to predict Monte Carlo results at high resolution without performing the computationally costly high-resolution runs.

Future Work

Future work will involve the construction of rule sets based directly on the linear distances between binding regions. A steric hindrance between two regions will be specified only if the linear distance between the two regions is less than or equal to the cutoff distance.



The optimal cutoff distance and its correlation with the Monte Carlo model resolution, and with the real system, will be studied. Various conformations of Pen a 1 will also be studied.

Acknowledgments and References

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[1] Kasra Manavi, Bruna Jacobson, Brittany Hoard, Lydia Tapia. Influence of model resolution on geometric simulations of antibody aggregation. Submitted to *Robotica*.

[2] Jin Yang, Michael I. Monine, James R. Faeder, and William S. Hlavacek. Kinetic Monte Carlo method for rule-based modeling of biochemical networks. *Phys Rev E Stat Nonlin Soft Matter Phys*. 2008 September; 78(3 Pt 1): 031910.

[3] Michael I. Monine, Richard G. Posner, Paul B. Savage, James R. Faeder, and William S. Hlavacek. Modeling multivalent ligand-receptor interactions with steric constraints on configurations of cell-surface receptor aggregates. *Biophys J*. 2010 January; 98(1): 48-56.