Geometric Analysis of Molecular Assembly

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Antibody Aggregation

IgE antibodies (blue) bind to FcεRI receptors crosslink through the binding of antigens (yellow) on the surface of mast cells (pink) and basophiles (left). This formation of aggregates is what stimulates mast cells to initiate an allergic response (right) by releasing proinflammatory mediators (purple granules).

Our research focuses on the development of novel and computationally efficient methods for the modeling and analysis of large-scale molecular assembly. Molecular assembly processes consist of two or more molecules that bind together in order to perform some function.

One example of a molecular assembly problem is antibody aggregation. Up to 40% of the world’s population suffer from allergies caused by antigen-mediated crosslinking of IgE/FcεRI complexes. Studies suggest the spatial organization of these complexes is what affects transmembrane signaling.

Studying this process using all atom molecular dynamics is computationally prohibitive. To make the computation feasible, we generate 3D models of the molecules, apply Monte Carlo simulation, and analyze the resulting aggregates.

We show that we can capture a detailed look into the geometry of aggregates and can compare our results to experimentally measured properties.

Molecular Model Construction

Rather than directly considering the 13486 atoms in the IgE/FcεRI complexes, we use a 3D polygon based representation of molecular structures. This reduces the $N^2$ cost of simulation, where $N$ is the number of atoms or polygons. Previous models have been created based on thermodynamic and kinetic constraints. Aggregate formations in these models are based strictly on mathematical formulation. These approaches lack geometric structure in the representation of the molecules. We include these important geometric structures using isosurface representations of the molecules. Using a polygon based isosurface model, we can study the impact of model resolution on the simulation runtime and aggregate formation/structure.

We start out with all atom models of the molecules (left) and use that to generate a polygon isosurface (center). We can then use this model in our simulation or reduce the geometric complexity by applying various levels of polygon reduction (right).
Simulation Methods

Our algorithm models the molecular interactions of hundreds of molecules using a Monte Carlo based simulation (a). We formulated a graph-based structure to define the molecular interactions. This structure allows us to encode the molecular structure of aggregates in a representation that is simple to maintain during simulation and to further analyze aggregates and their structures after simulation (b).

At each time interval, a Monte Carlo step is taken and all positions of the molecules in the simulation are updated. Biological constraints of the system such as molecule speed and rates of association and dissociation are included. In terms of graph updates, association and dissociation relate to the creation and removal of edges.

As the molecules move, antigens and receptors begin to bind and form aggregates. Simulations are run for a pre-defined time, chosen to be well beyond the time a stable graph formation is determined. We can then use our simulation results to generate all atom aggregate structures (c) giving us a foundation for analyzing detailed molecular interactions.

Results

For each antigen, we simulate a variety of ratios of antigen to receptor. For these experiments, we kept the receptor count consistent and varied the antigen count. This setup was chosen to match experimental methods that keep consistent receptor concentration and vary antigen concentration.

Using our graph encoding of the simulation, we calculate a wide array of properties such as aggregate size (connected components), stability (edges in graph) and aggregate classifications (cycle-based classification).

The results produced were generated simulating synthetic antigen DF3 (top left/right) and a common shrimp allergen PenA1 (bottom left/right). We determine the stability of the simulation to ensure we generate fully formed aggregates (left top/bottom). We also determine similarities in the geometric properties of the aggregates of different antigen such as distance between receptors (right top/bottom).

References

Website: http://www.cs.unm.edu/amprg/Research/AntibodyAggregation/

[ACMBCB ’12] Kasra Manavi, Bridget S. Wilson, and Lydia Tapia. “Simulation and Analysis of Antibody Aggregation on Cell Surfaces Using Motion Planning and Graph Analysis”.


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