DYNAMICAL EFFECTS OF MULTIMERIC RING FORMATION IN MULTIVALENT ANTIGEN-ANTIBODY INTERACTIONS

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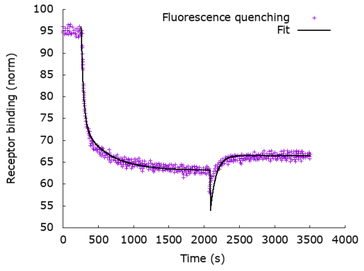
INTRODUCTION

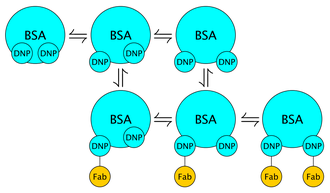
The immune response in mast cells is initialized through the formation of cell-surface receptor aggregates. Aggregation is commonly stimulated using the multivalent ligand DNP-BSA, which causes cross-linking among anti-DNP IgE bound to FcεR1. This process results in intracellular signal transduction driven by a number of well-characterized interactions [1]. The Lyn tyrosine kinase phosphorylates key tyrosine residues (ITAMs) on the FcεR1 γ and β chains, resulting in recruitment and activation of the Syk tyrosine kinase. Active Syk then proceeds to phosphorylate a number of other proteins, propagating the signal. Prior work has aimed to understand the aggregation process formally [2], but constructing equation-based dynamical models that incorporate the complexity of accommodating multivalent molecules can be prohibitive. Here, we employ rule-based modeling techniques [3] in order to develop a mechanistic understanding of receptor aggregation while incorporating complex phenomena into our model. Through inclusion of features such as the size-limited mobility of receptor aggregates and the formation of ring-like structures due to the multivalency and symmetry of DNP-BSA and IgE we can quantitatively predict the aggregation patterns of receptors on the cell surface.

RECEPTOR BINDING KINETICS

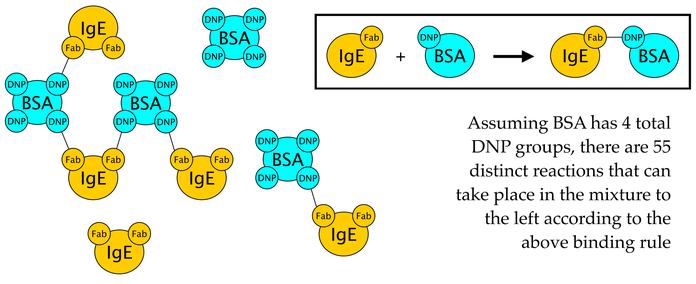


DNP-BSA is a common ligand used for inducing aggregation of IgE-bound FcεR1 transmembrane receptors. The kinetics of binding can be measured with quenching of fluorescently labeled IgE (left, purple) [2].

A simple dynamical model involving transiently exposed haptens and individual Fabs (right) fits the observed data (above, black) [2], but cannot predict receptor aggregation and is not easily extensible.

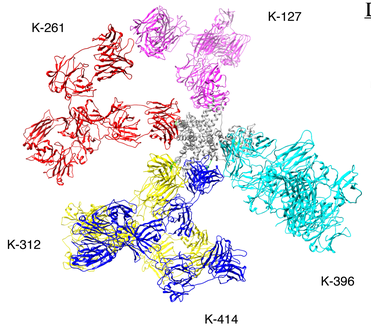


Using rule-based modeling languages we can write simple reaction rules that apply to a set of biochemical species or *agents* [3]. With event-driven simulation, we can iteratively apply these rules to a set of agents or *mixture* to generate arbitrarily complex biochemical species on the fly:



Assuming BSA has 4 total DNP groups, there are 55 distinct reactions that can take place in the mixture to the left according to the above binding rule

STRUCTURAL INFORMATION



DOCKING DNP-BSA WITH ANTI-DNP IGE

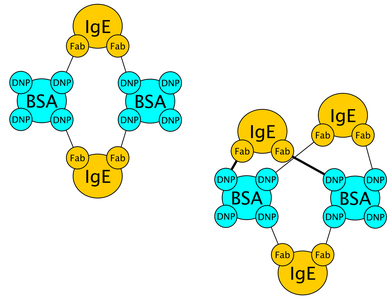
Fully saturated BSA has 5 DNP-conjugated lysine residues capable of binding IgE out of ~25 possible conjugated lysine residues

2 of the sites are sufficiently close to prevent simultaneous IgE binding

Numerical simulation shows that DNP_{15}-BSA has an average of 3 DNP groups available for interaction with IgE

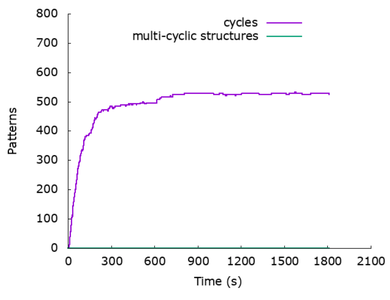
Rings (cycles; right) are thermodynamically stable structures and are thus favored as the system approaches steady-state [5]

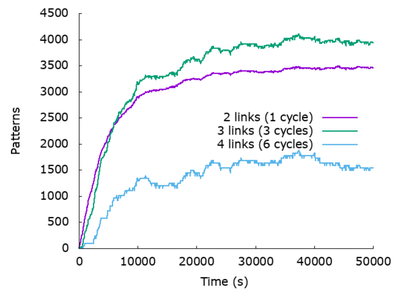
Multi-cyclic structures (bottom right) may form when one of the molecules involved has valency > 2 [6]



DYNAMICS OF RING FORMATION

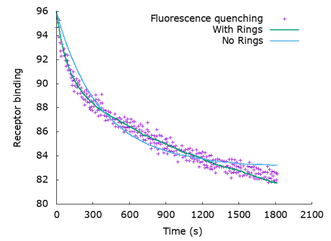
We developed two models to fit experimental data sets for binding kinetics of both cell-surface IgE and soluble IgE [2]. The model for soluble antigen-antibody interaction allows all multi-cyclic ring geometries (right) [6]. The key denotes the number of links between a pair of BSAs



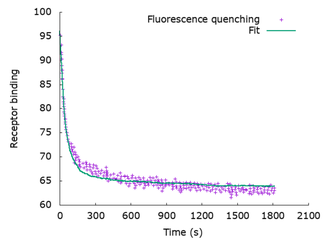


The model for cell-surface IgE (implicitly bound to FcεR1) restricts the formation of multi-cyclic aggregates due to the geometric constraints imposed by the plasma membrane.

MODEL PREDICTIONS

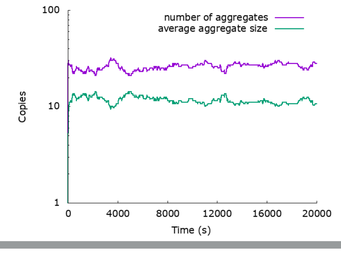


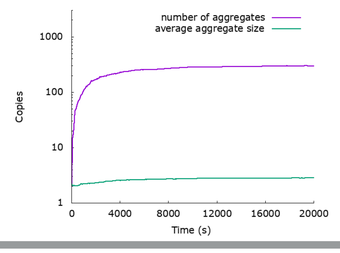
The formation of ring-like structures slows the approach to steady-state and better captures experimentally observed binding dynamics between soluble IgE and DNP-BSA (left)



A preliminary cell-surface model approximates the binding dynamics observed for FcεR1-bound IgE when ring formation and size-limited mobility are considered (right).

The presence of multi-cyclic rings can alter aggregation patterns as seen in comparing the solution (right) and cell surface (left) models:





CONCLUSIONS

With a newly-developed model of receptor aggregation we are able to reproduce the kinetics of interaction between DNP-BSA and IgE-bound FcεR1 in the presence of complex phenomena. Interestingly, the formation of multi-cyclic rings among receptor aggregates in our model contributes to the slow approach to Fab-binding equilibrium in solution observed experimentally. Similar ring- or lattice-like structures are possible when IgE is fixed to the plasma membrane, though the space of potential geometric configurations of these structures is much smaller since the IgE molecules are essentially coplanar. We expect that the formalism present in this model is extensible to other signaling networks involving multivalent ligand-receptor interactions and the resulting aggregation, enabling prediction of aggregation patterns and informing how distinct ligands can influence downstream signaling events.

REFERENCES

1. Chylek, L. A., Holowka, D. A., Baird, B. A., & Hlavacek, W. S. (2014). Frontiers in Immunology, 5(APR), 1–16.
2. Xu, K., Goldstein, B., Holowka, D., & Baird, B. (1998). Journal of Immunology (Baltimore, Md. : 1950), 160(7), 3225–3235.
3. Hlavacek, W. S., Faeder, J. R., Blinov, M. L., Posner, R. G., Hucka, M., & Fontana, W. (2006). Science Signaling, 2006(344), re6-re6.
4. Sneddon, M. W., Faeder, J. R., & Emonet, T. (2011). Nature Methods, 8(2), 177–183. nmeth.1546
5. Deeds, E. J., Bachman, J. A., & Fontana, W. (2012). PNAS, 109(7), 2348–2353
6. Bilgiçer, B., Moustakas, D. T., & Whitesides, G. M. (2007). Journal of the American Chemical Society, 129(12), 3722–3728.

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