Antibodies as programmable, bipedal walkers

Stochastic modeling of antibody binding dynamics on patterned antigen substrates suggests the separation distance between adjacent antigens could be a control mechanism for the directed bipedal migration of bound antibodies.

The question
Regularly patterned arrays of antigens — molecules or structures that bind to molecular elements of the host immune system such as antibodies — commonly occur on the surfaces of natural pathogens such as viruses and bacteria. This spatial repetitiveness is recognized by the immune system as a marker of foreignness and patterned antigens therefore elicit a stronger response than unorganized antigens. The spacing between patterned antigens occurs on a scale similar to the typical distance between the binding domains of bivalent antibodies. Previous work from our lab investigating antibody—antigen binding using DNA nanostructures to immobilize pairs of antigens at different separation distances revealed that binding stability depends on antigen separation distance. In light of these data, we asked if stochastic modeling of binding dynamics between antibodies and complex antigen patterning scenarios could elucidate the interactions between bivalent antibodies and patterned antigen arrays.

The discovery
We created a stochastic model of antibody binding to monodispersed antigens, based on our previous data on antibody binding dynamics, to predict emergent antibody binding behavior in situations of complex antigen pattern geometry. The model treats antibody binding dynamics as a continuous-time Markov chain, with states based on empty antigen, monovalent antibody—antigen complexes, and bivalent antibody—antigen complexes, where transitions between these states are governed by elementary rates determined by fitting the model to experimental dynamic binding data (Fig. 1).

Using a Markov chain Monte Carlo implementation of the model allowed the prediction of antibody binding trajectories across complex patterns with many adjacent antigens and over long timescales. By simulating regularly spaced arrays of antigens, it was possible to influence relative rates of binding and unbinding by tuning the antigen separation distance. Further, by creating gradients of separation distances between 10–22 nm, we found that antibodies migrate down this gradient towards antigens with smaller separation distances. We predict that this migration occurs owing to a biased random walk, where a bivalently bound antibody dislodges at one antigen and then will show a statistical preference for reassociating with an adjacent antigen with a more favorable binding separation distance. These findings support previous data from Preiner et al. that describe the bipedal movement of antibodies across reconstituted bacterial and viral surfaces with repeating antigen patterns.

The implications
Viral and bacterial pathogens and their host immune systems are in a constant arms race to exploit mechanisms that could lead to a fitness advantage. This work further implicates a relatively overlooked property of antibodies — the spatial reach of antibody binding arms — as an important aspect influencing antibody binding and host–pathogen interactions.

The possibility for programmed antibody migration through the geometric tuning of the energy landscape hints at a complex picture of pathogenic surface molecules in which antigen patterns may have evolved in order to manipulate the spatial distribution of bound antibodies. This could be an important consideration in immunobiology, such as in the design of vaccines or antibody therapies meant to elicit a specific immune response, although further work is needed to demonstrate this in a biological setting.

The next steps will be to validate the predictions made by these stochastic models in natural biological systems and incorporate additional structural aspects of antibodies — for example, the dependence of binding dynamics on antigen angular orientation — in order to improve the model’s realism. Further work should aim to understand what natural constraints have evolved on both the pathogen and immune sides to influence this phenomenon. Finally, we hope that this information can be used to design better vaccines by informing the choice of antigen density and patterning geometry so as to promote a more specific immune response.

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EXPERT OPINION

Hoffecker et al. provide a simple but powerful modeling approach to study antibody binding and movement on defined antigen patterns. The importance of specific antibody binding to repeating patterns of defined spacing has become a hot topic and is certainly relevant not only to basic research, but also clinical biomedical applications, especially with the view of designing new antibody-based therapeutics and vaccine design. "Amelie Heuer-Jungemann, Max Planck Institute of Biochemistry, Germany"

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A work documenting the dependence of the immune response on the spatial repetitiveness of antigens occurring in different viruses and bacteria.

2. Shaw, A. et al. Binding to nano patterned antigens is dominated by the spatial tolerance of antibodies. Nat. Nanotechnol. 14, 184–190 (2019).

Our earlier experimental work on measuring antibody binding in terms of variable binding separations between antigens.

3. Preiner, J. et al. IgGs are made for walking on bacterial and viral surfaces. Nat. Commun. 5, 4394 (2014).

An experimental work that inspired our investigation into the mechanisms of antibody walking.

BEHIND THE PAPER

A provocative experimental work by Preiner et al.1, inspired us to think about antibodies from a new perspective — as walkers rather than simply binders. In their study, high speed atomic force microscopy imaging indicated that antibodies exhibit bipedal walking on patterned substrates. We found this prospect fascinating and, as we had access to precise measurements and models of specific antibody–antigen interactions from our earlier work2, were well positioned to explore this phenomenon having constructed our model pipeline.

This in silico exploration likely would not have happened if not for the extended period of work-from-home caused by the COVID-19 pandemic. Forced away from the bench, we were able to make major advancements in the model that enabled the exploratory investigation into antibody migration. So it seems that, as with our findings, constraints can sometimes set things in motion. I.T.H. & B.H.

Fig. 1 | Modeling antibody binding on antigen patterns. a, Models are based on experimental data measuring the multivalent binding of antibodies to antigens (red spheres) immobilized in precise locations on DNA nanostructures (blue cylinders). b, Model of antibody binding reduced to binding/unbinding and bivalent interconversion. c, An extension of the model to more complex pattern geometries by connecting states with elementary transitions. d, Visualization of the modulation of antigen separation distance to influence antibody binding strength. $k_1$ and $k_\text{off}$ are the on- and off-binding rates, respectively; $k_2$ and $k_\text{on}$ are the monovalent-to-bivalent and bivalent-to-monovalent interconversion rates, respectively; $x$ is the separation distance between adjacent antigens. © 2022, Hoffecker, I. T. et al., CC BY 4.0.

FROM THE EDITOR

"This work stood out to me as the impact of antigen spacing and geometry on antibody movement, modeled as a discrete Markov process, indicates that antigen organization could be under selective pressure during host–pathogen co-evolution. This molecular programmability has extensive applications for designing new vaccines, which is currently a huge challenge." Ananya Rastogi, Associate Editor, Nature Computational Science