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Accurate modeling of antibody reach with coarse-grain molecular dynamics simulations

Antibodies are bivalent molecules that recognize and bind antigens on diverse surfaces. Most biophysical methods for studying antibodies, however, can only provide monovalent affinities and binding kinetics. A new method that uses a particle-based bivalent model to fit bivalent SPR data has been developed by Omer Dushek and co-workers. This particle model is able to predict the "molecular reach" of the bivalent antibody, defined as the spatial distance L over which the antibody is able to bind both antigens. The molecular reach values determined for a series of SARS-CoV-2-RBD antibodies were found to be on the order of 30-40 nm, much larger than the ~12-nm value predicted by examining antibody crystal structures. Here, I describe coarse-grain molecular dynamics simulations of six SARS-CoV-2-RBD antibody complexes. These simulations reveal that the molecular reach values from the bivalent particle model correspond to the sum of the maximum reaches of the RBD molecules and the antibody itself. Different epitopes on RBD lead to distinctly different reach values that correlate strongly with experiment. As the reach of an antibody correlates with its ability to neutralize its antigen, these simulations provide a valuable means of predicting antibody effectiveness. In addition, I will describe progress towards a better understanding of how antibodies engineered to mimic the behavior of T-cell receptors bind their antigens, and how we can use this information to design better biotherapeutics.