doi 10.18699/bgrs2024-3.1-31

Calculating of SARS-CoV-2 RBD and antibody complex energy by metadynamics in MARTINI 3 for evaluating complex free energy

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Key words: antibody design; generative models; molecular dynamics; metadynamics

Motivation and Aim: Neutralizing monoclonal antibodies (MAbs) have been found to be effective therapeutic agents in the treatment of a host of viral and autoimmune diseases. This has been particularly highlighted since the outbreak of the 2019 coronavirus infection (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In response to this global health crisis, the Food and Drug Administration (FDA) has given its approval to several drugs that are based on MAbs [1]. The emergence of new variants of the virus has presented a significant hurdle in the ongoing fight against COVID-19. Some of these variants have shown resistance to the existing neutralizing MAbs, reducing their overall efficacy [2]. There's an urgent need for new strategies for rapid antibody design to respond to emerging variants and maintain our therapeutic effectiveness.

Nowadays, there is a rising trend towards the utilization of diffusion machine learning models in the field of the design of innovative protein sequences [3]. These advanced models allow for the intricate redesigning of the antibody constant determining regions (CDR) loops. This is a significant step in the field as it enables us to specifically tailor these CDR loops to correspond with the antigen epitope we require.

To improve the design results and antibody affinity to antigen, we must have initial stable structures of the antigen antibody complex, in which the antibody will target different epitopes. These states can be obtained by the methods of molecular dynamics. One of them, rapid and effective metadynamics, allows one to quickly and efficiently scan different states of a system by adding Gaussian potentials to local free energy minima during a trajectory [4]. Adding to this, representation of structures in the Martini force field together with the use of metadynamics speeds up FES calculations for protein-protein complexes [5]. Therefore, using the metadynamics method in MARTINI 3 atoms representation can allow us to estimate and range hundreds of results of structures obtained from generative diffusion models.

In this report, we detail the application of metadynamics to the most common antibody and SARS-CoV-2 RBD in the Martini 3 force field. We initially created two complexes where the antibody targets the two most likely neutralizing receptor binding domain epitopes. We then performed metadynamics on each complex and identified the states corresponding to the free energy minima.

Methods and Algorithms: SARS-Cov-2 neutralizing MAbs targeted to SARS-CoV-2 S-protein RBD data were downloaded from The Coronavirus Antibody Database CoV-AbDab [6]. Based on them, two antibody-antigen complexes were constructed, in which

the antibody targets the two most common epitopes. Antibodies were constructed with the most common CDR lengths and amino acid sequences by MODELLER [7]. All-atom structures of constructed complexes were presented in coarse grained resolution structures according to the Martini 3.0.beta.3.2 force field (Martini 3) [8 (12)]. Coarse grained structures of two complexes were solvated in triclinic water boxes with ions and were minimized by the steepest descent algorithm. Metadynamics simulations were run under NPT ensemble by GROMACS software with PLUMED. The distance between the antibody and RBD centers of mass (COM) and the dihedral angle characterizing the rotation of the antibody relative RBD were selected as CV. The final minimum structures complexes were back-mapped to the all atom resolution by the 'backward.py' script [8]. *Results*: After conversion to CG-structures and its preparation metadynamics in two CVs was performed. Reweighted free energy surfaces for epitope-A and epitope-B complexes are shown in Figure 1. First five free energy minima (values less than 0) are pointed out with numbers from 1 to 5. Time frames according to states of complexes for these free energy minima were extracted from the trajectory and clustered.

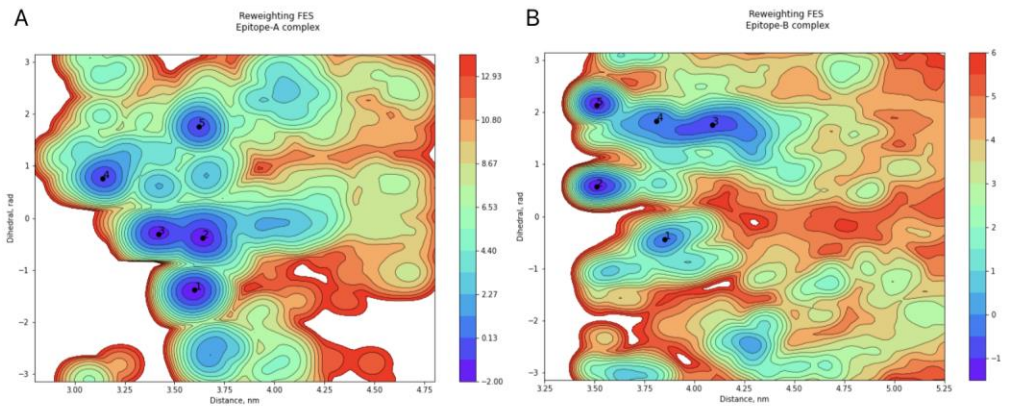

Fig. 1. Reweighting FES plot for epitope-A complex (A) and epitope-B complex (B)

Figure 2 provides an illustrative map detailing the contact residues of the Receptor Binding Domain (RBD) for each minimal state that has been obtained through the process of metadynamics. In the context of the epitope-B complex, the antibody specifically targets the cryptic epitopes site when in minimal states in addition to the main observed epitopes.

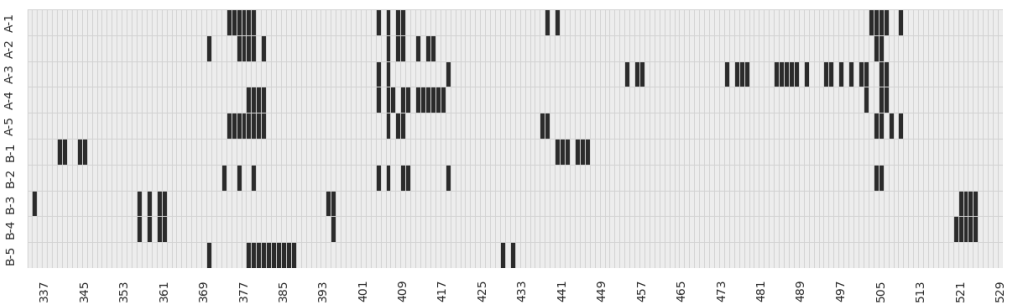

Fig. 2. Representation of RBD residues involved in binding to the antibody for minimal states from epitope-A and epitope-B complexes

Conclusions: According to the values of the collective variables and the obtained conformations of the complexes, the antibody can be targeted to different epitopes during metadynamics, which gives a wide variety of structures on the basis of which new antibodies can be obtained using generative diffusion models. Also, given the high speed of metadynamics in the Martini 3 force field and at the same time effective sampling of the energy space, this approach can be used to evaluate the generated designs.

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