Metadynamics Simulations of Antibody and SARS-CoV-2 RBD Complex in MARTINI 3 Force Field

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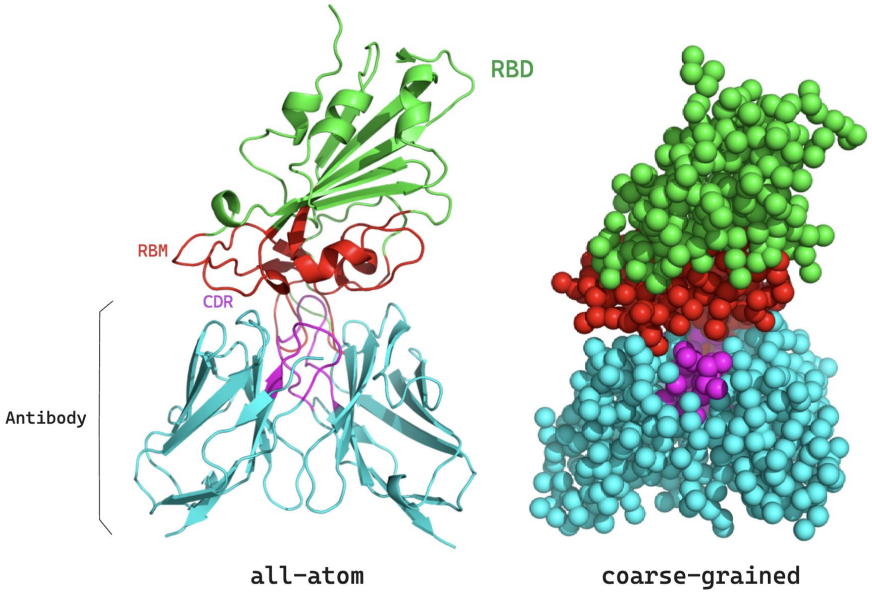
THE OBJECTIVE

❗ Neutralising antibodies are effective in treating viral and autoimmune diseases. For SARS-CoV-2, **rapid antibody design is urgently needed to address emerging variants and maintain efficacy.**

❓ **Generative ML models for protein design are currently gaining popularity.** However, there is a need to develop a rapid method for evaluating and ranging new structures.

✅ **The use of metadynamics in coarse-grained force fields to obtain the free energy surface allows us to evaluate the efficiency of antibody-antigen complex formation.**

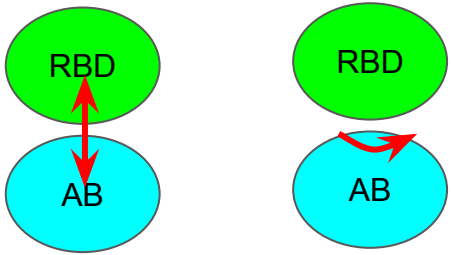


ANTIBODY DESIGN PIPELINE

Metadynamics in MARTINI 3

validation of the method on known complexes

Collective variables



Making the average antibody structure

"average antibody structure" — a starting point for the generation of new antibody CDRs

Method: MODELLER

Materials: structures and CDRs sequences from the CoVAbDab

Redesign of antibody CDRs

(based on “average antibody” complex states)

Methods:

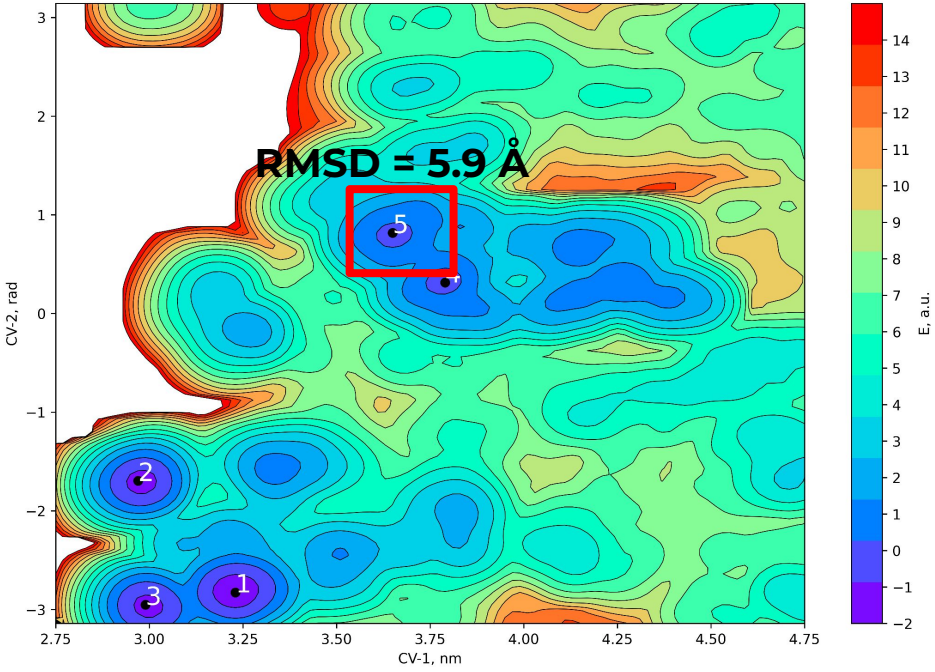
RFDiffusion+ProteinMPNN

Ranging obtained structures

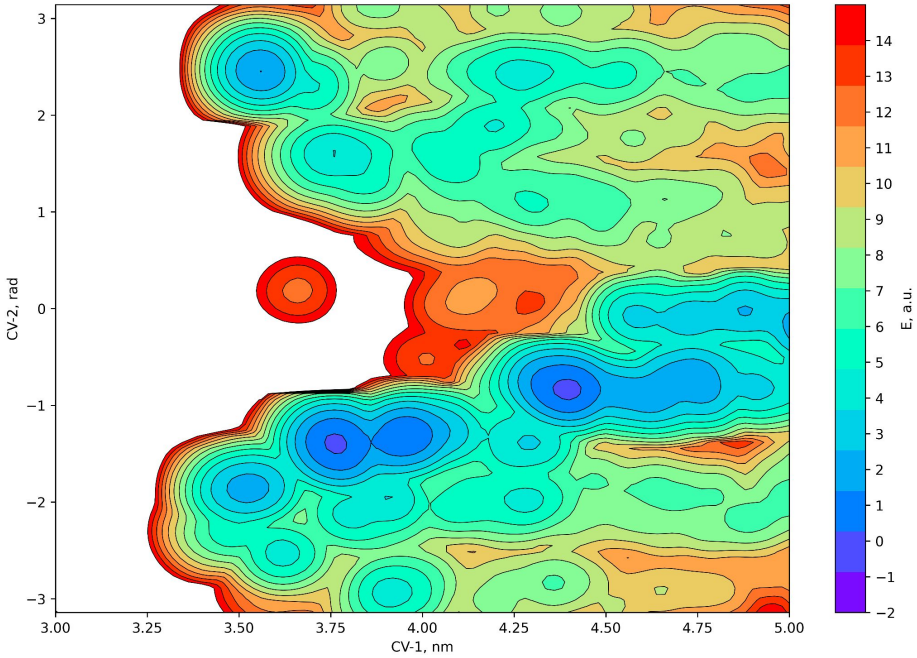
by metadynamics in MARTINI 3

RESULTS: validation of the method

Antibody C102 (PDB ID: 7K8M)



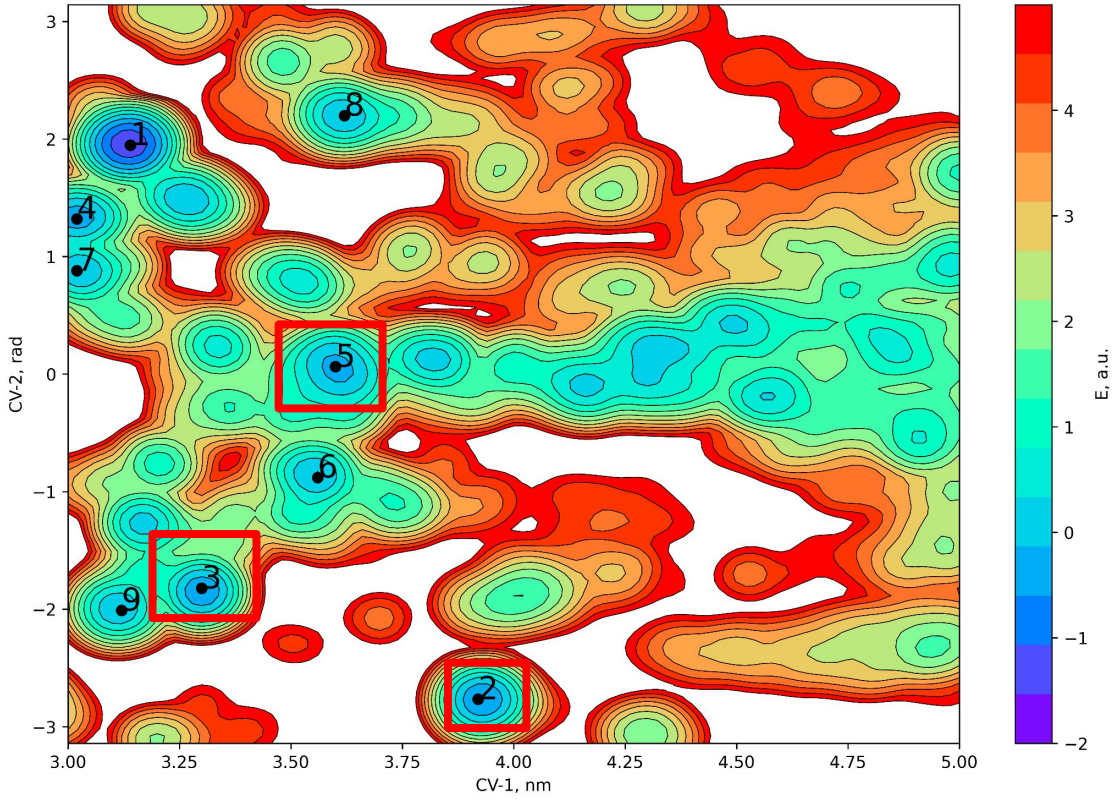
Negative test: antibody to HIV-1



Free energy surface plots.

CV-1 — distance between COMs, CV-2 — dihedral angle.

RESULTS: averaged antibody structure



Free energy surface plot

CV-1 — distance between COMs, CV-2 — dihedral angle.

The highlighted minima were closest in RMSD value to the natural RBD-antibody complexes. They will be the starting point for further design of new antibodies.

CONCLUSIONS

- MARTINI 3 force-field metadynamics is applicable to reproduce antibody-antigen binding states from X-Ray data.

- MARTINI 3 force field metadynamics allows for efficient ranking of antibodies for binding to the RBD domain of the virus.

Further steps:

- method optimization: using data-driven (mlcolvar) collective variables.
- more accurate antibody ranging, comparison with known data.
- design of a variety of new antibodies to the RBD of SARS-CoV-2 and their evaluation by the described method.

References:

1. Ray D., Parrinello M. Kinetics from Metadynamics: Principles, Applications, and Outlook // J. Chem. Theory Comput. 2023. Vol. 19, № 17. P. 5649–5670.
2. Lamprakis C. et al. Evaluating the Efficiency of the Martini Force Field to Study Protein Dimerization in Aqueous and Membrane Environments // J. Chem. Theory Comput. 2021. Vol. 17, № 5. P. 3088–3102.
3. Raybould M.I.J. et al. CoV-AbDab: the coronavirus antibody database // Bioinformatics. 2021. Vol. 37, № 5. P. 734–735.