Electrostatic interactions explain the higher binding affinity of the CR3022 antibody for SARS-CoV-2 over the 4A8 antibody

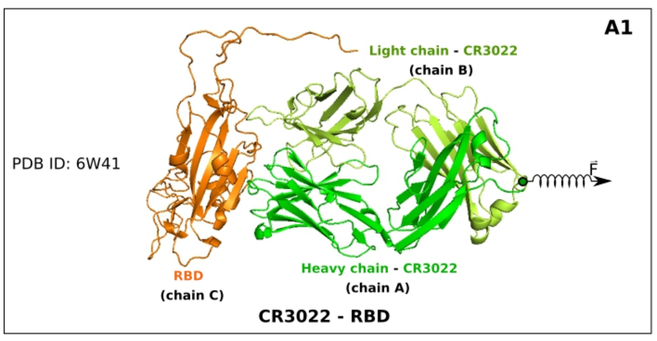
Hung Nguyen[1], Pham Dang Lan[2], Daniel A. Nissley[3], Edward P. O'Brien[4,5,6], and Mai Suan Li[1,*]

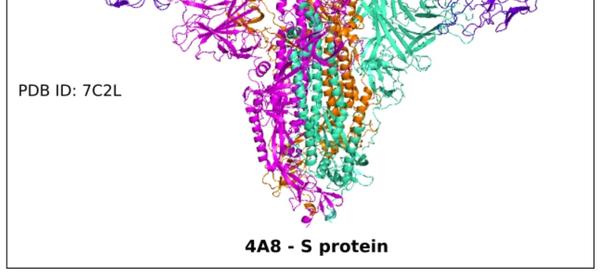
[1]Institute of Physics, Polish Academy of Sciences, al. Lotnikow 32/46, 02-668, Warsaw, Poland. [2]Life Science Lab, Institute for Computational Science and Technology, Quang Trung Software City, Tan Chanh Hiep Ward, District 12, Ho Chi Minh City, Vietnam. [3]Department of Statistics, University of Oxford, Oxford, United Kingdom [4]Department of Chemistry, Penn State University, University Park, Pennsylvania, United States. [5]Bioinformatics and Genomics Graduate Program, The Huck Institutes of the Life Sciences, Penn State University, University Park, Pennsylvania, United States. [6]Institute for Computational and Data Sciences, Penn State University, University Park, Pennsylvania, United States.

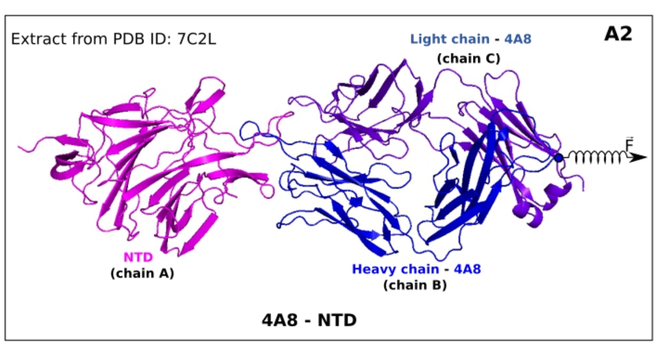
Email me at:
hungnv@ifpan.edu.pl

Introduction and motivation

The first outbreak of coronavirus disease 2019 was known in Wuhan, China in December 2019, then became a global pandemic in March 2020, namely Covid-19. Most of antibodies bind to either NTD or RBD on Spike (S) protein of SARS-CoV-2 structure (Figures A1, A2, B1 and B2) can inhibit SARS-CoV-2's activity, therefore, understanding the interactions of antibodies with these regions of SARS-CoV-2 at the atomic level is important for Covid-19 therapies and vaccinations.



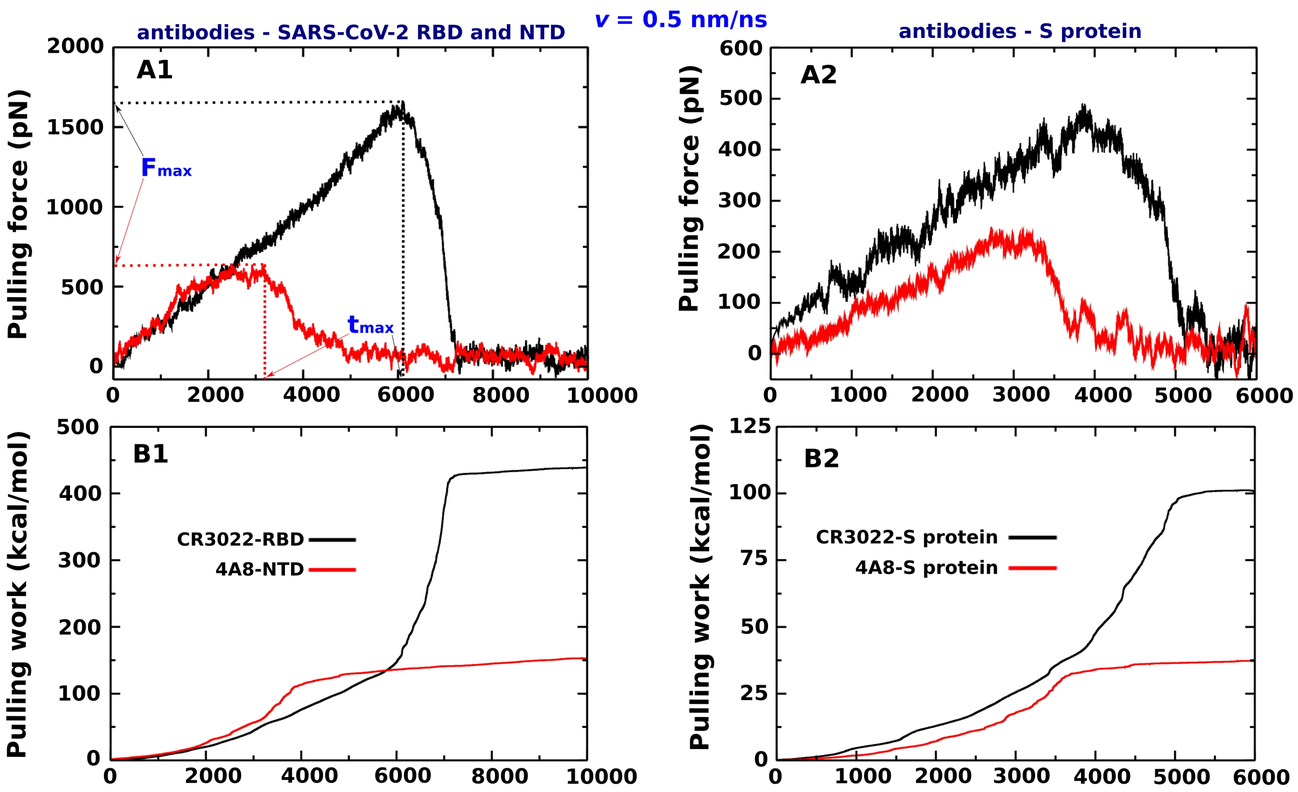




CR3022 and 4A8 are monoclonal antibodies, which target RBD and NTD, respectively (Figure A1, A2, B1 and B2). These antibodies are known as potential antibodies to treat SARS-CoV-2.

We use steered molecular dynamics (SMD) and coarse-grained simulations to estimate the binding affinity of the monoclonal antibodies CR3022 and 4A8 to the SARS-CoV-2 receptor binding domain (RBD) and SARS-CoV-2 N-terminal domain (NTD). This data could lead to a new approach of developing anti-covid-19 antibodies in which good candidates must contain charged amino acids in the area of contact with the virus.

Binding affinity calculated from SMD simulation

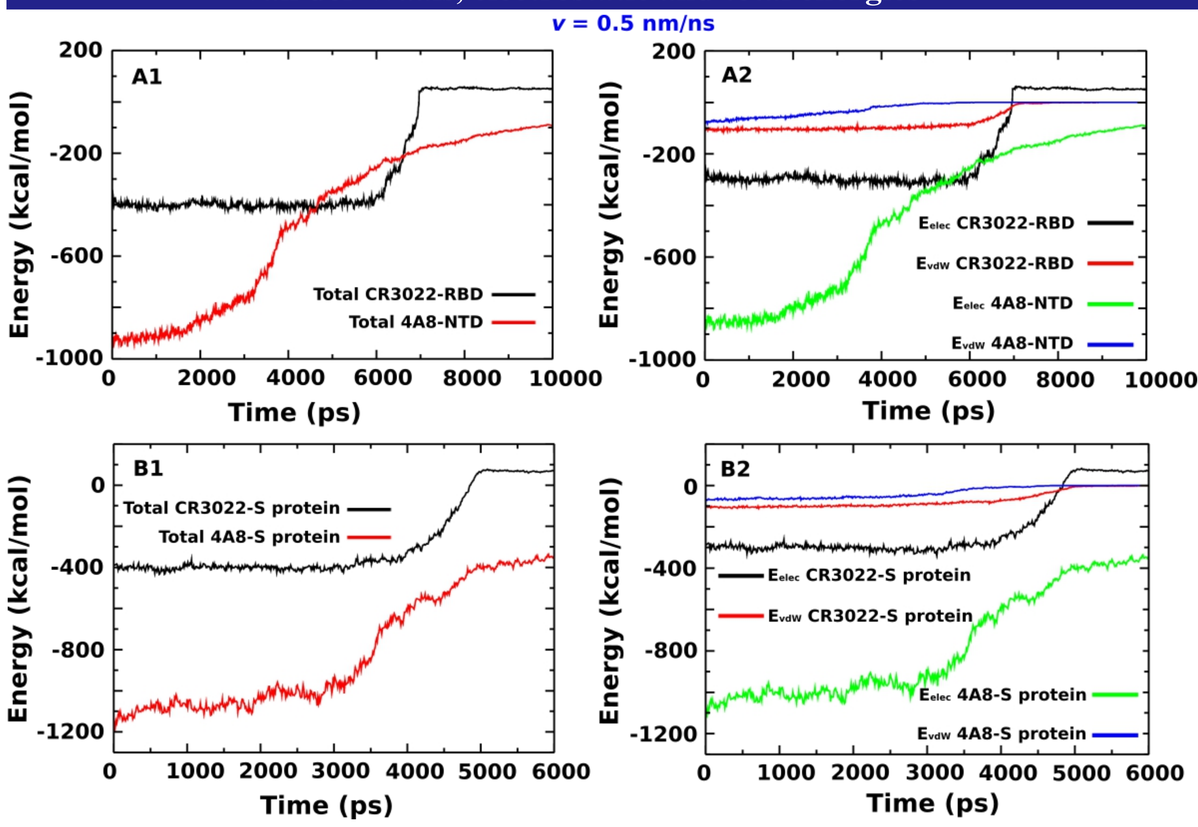


The force-time profiles of four complexes show that CR3022 binds to RBD (or S protein) more strongly than 4A8 to NTD (or S protein) as the corresponding rupture (Figures A1 and A2).

The non-equilibrium work was shown to be a better value for characterizing the relative binding affinity than force. It rapidly increased until CR3022 and 4A8 come out from the binding region and reached a stable value when the antibody ceased to interact with the S protein (Figures B1 and B2).

The binding and unbinding free energy barriers, which are defined as $\Delta\Delta G_{bind} = \Delta G_{TS} - \Delta G_{unbound}$ and $\Delta\Delta G_{unbind} = \Delta G_{TS} - \Delta G_{bound}$ are nearly equal as $\Delta G_{unbound} \approx \Delta G_{unbound} \approx 0$. These obtained results also indicate that CR3022 binds to RBD (or S protein) more tightly than 4A8 to NTD (or S protein) (Figures C1 and C2).

Van der Waals, electrostatic and total energies



The time dependence of vdW, electrostatic and total (vdW+electrostatic) interaction energies of the CR3022-RBD, 4A8-NTD, CR3022-S protein and 4A8-S protein complexes (Figures A1, A2, B1 and B2). There is a small difference in vdW interaction energies of CR3022-RBD and 4A8-NTD, but a much more pronounced difference is observed for the electrostatic interactions. The same is true for CR3022-S protein and 4A8-S protein complexes. It is important to note that for all complexes, the energy of electrostatic interactions is significantly lower than the vdW energy, which means that their stability is primarily determined by electrostatic interactions.

Binding affinity estimated from REX-US simulation

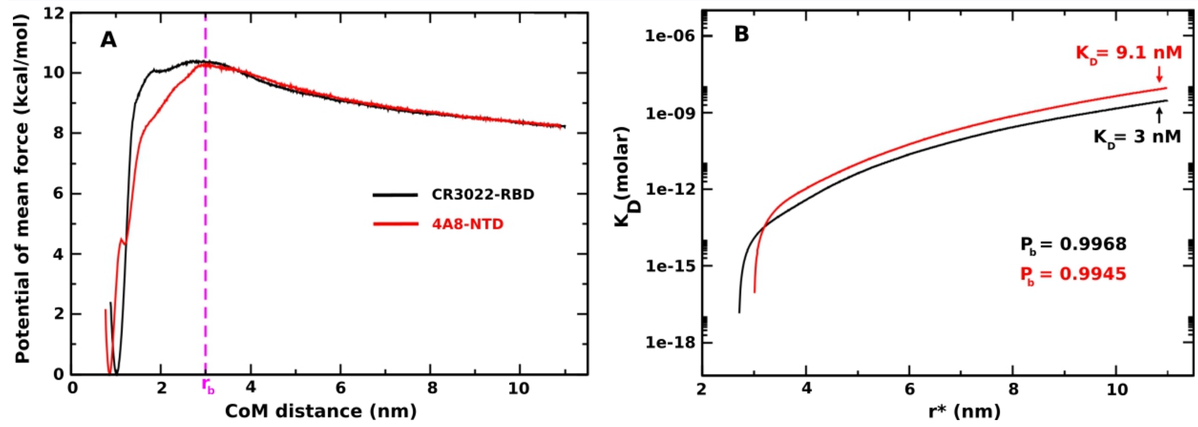


Figure A shows the most stable state locates near the native states with the CoM distance ≈ 1 nm (CR3022-RBD) and ≈ 0.86 nm (4A8-NTD). The barrier of 1D PMF separating the bound and unbound regimes occurs at ≈ 3 nm for both complexes. Figure B plots K_D curves as a function of r*. As expected K_D increases and converges at large radius r* which means K_D physically should not depends on r*. Here we determined r* ≈ 11 nm from which there is no longer interaction between antibody and virus and used this value to calculated KD.

Table: K_D (nM) of CR3022-RBD and 4A8-NTD complexes obtained by experiments and simulations.

Complex	**Experiment results (K_D)**	**Our simulation results (K_D)**
4A8-NTD (ID: 7C2L)	92.7 nM (Chi *et al,*)	9.1 nM
CR3022-RBD (ID: 6W41)	6.3 nM (Tian *et al*) 115.0 nM (Yuan *et al*)	3.0 nM

Both antibodies tightly binds to virus domains with K_D = 9.1 nM for 4A8-NTD and K_D = 3 nM for CR3022-RBD (Table). This means that CR3022 binds to SARS-CoV-2 RBD domain stronger than 4A8 binds to SARS-CoV-2 NTD although the level of about three times in K_D, which shows the difference is not as high as in SMD.

Conclusion

SMD simulations showed that CR3022 displays a higher binding propensity to RBD than 4A8 to NTD, which is consistent with the result obtained by coarse-grained REX-US simulations that the dissociation constant KD of CR3022-RBD is approximately three times smaller than 4A8-NTD. These results are in good agreement with the experimental data of Tian *et al*.[1] and Chi *et al*.,[2] but they are in contrast to the experimental results of Yuan *et al*.[3]

The contribution of electrostatic interactions to the stability of four complexes, including CR3022-RBD, 4A8-NTD, CR3022-S protein, and 4A8-S protein, is more significant compared to vdW interactions. In terms of binding capability, CR3022 is a better candidate for Covid-19 treatment than 4A8.[4]

References

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