Comparing the Binding Interactions in the Receptor Binding Domains of SARS-CoV-2 and SARS-CoV

Muhamed Amin,* Mariam K. Sorour, and Amal Kasry

ABSTRACT: SARS-CoV-2, since emerging in Wuhan, China, has been a major concern because of its high infection rate and has left more than six million infected people around the world. Many studies endeavored to reveal the structure of the SARS-CoV-2 compared to the SARS-CoV, in order to find solutions to suppress this high infection rate. Some of these studies showed that the mutations in the SARS-CoV spike (S) protein might be responsible for its higher affinity to the ACE2 human cell receptor. In this work, we used molecular dynamics simulations and Monte Carlo sampling to compare the binding affinities of the S proteins of SARS-CoV and SARS-CoV-2 to the ACE2. Our results show that the protein surface of the ACE2 at the receptor binding domain (RBD) exhibits negative electrostatic potential, while a positive potential is observed for the S proteins of SARS-CoV/SARS-CoV-2. In addition, the binding energies at the interface are slightly higher for SARS-CoV-2 because of enhanced electrostatic interactions. The major contributions to the electrostatic binding energies result from the salt bridges forming between R426 and ACE-2-E329 in the case of SARS-CoV and K417 and ACE2-D30 in the SARS-CoV-2. In addition, our results indicate that the enhancement in the binding energy is not due to a single mutant but rather because of the sophisticated structural changes induced by all these mutations together. This finding suggests that it is implausible for the SARS-CoV-2 to be a lab-engineered virus.

In this work, we study the binding interaction between the amino acids on the interface between the ACE2 receptor and the S protein of SARS-CoV and SARS-CoV-2 viruses using molecular dynamics (MD) simulations and Monte Carlo (MC) sampling.

The crystal structure PDB ID 2AJF,7 which includes the receptor binding domain RBD of SARS-CoV and the ACE2, was first MD optimized using openMM software,8 followed by running Monte Carlo simulations using MCCE (Multi Conformer Continuum Electrostatic) software,14,15 to sample the protonation states of the amino acids. The electrostatic interactions between the different amino acids’ conformers were calculated by solving the Poisson–Boltzmann equation using DELPHI.16 The generated conformers’ occupancies based on Boltzmann distributions were used to calculate the electrostatic and van der Waals interactions between the amino acids in the SARS-CoV and the ACE2.
To study the interactions between the SARS-CoV-2 and the ACE-2, the mutants V404K, R426N, Y442L, L443F, F460Y, L472F, N479Q, D480S, Y484Q, and T487N were constructed based on the cryoEM structure PDB ID 6M17. The simulations were performed by replacing the side chains in the native structures with the proper side chains of the mutants using MCCE. Several conformations of the side chains were created to avoid van der Waals clashes. The side chain conformers with the highest Boltzmann occupancies were then MD optimized, followed by using MCCE to calculate the binding energies.

The electrostatic potential maps of SARS-CoV, SARS-CoV-2, and ACE2 were calculated using Adaptive Poisson–Boltzmann Solver (APBS). While both SARS-CoV and SARS-CoV-2 showed positive potentials (Figure 1a,b), ACE2 exhibited a negative electrostatic potential at the RBD, as shown in Figure 1c. However, the potential observed for SARS-CoV-2 was more positive, which consequently resulted in a greater electrostatic interaction between ACE2 and SARS-CoV-2. This could be explained by the replacement of the negatively charged amino acid Asp by a neutral Ser (D480S).

The optimized structure of SARS-CoV showed a salt bridge between SARS-CoV-R426 and ACE2-E329 (Figure 2a), which dominated the electrostatic interactions with the ACE2. In the case of SARS-CoV-2, the corresponding salt bridge was shown to be forming between CoV-2-K404 and ACE2-D30 (Figure 2b). However, the latter exhibited a higher electrostatic interaction by 1.4 kcal/mol (Table 1). The contribution in the free energy formation of the salt bridges ($\Delta G$) is dominated by the pairwise acid/base interactions (Table S4).

The total electrostatic interactions between the SARS-CoV-2 and the ACE-2 is 3 kcal/mol higher than SARS-CoV (Table S1). The contribution of a single mutant to the electrostatic binding energies is very small (Table S1). However, these mutants induce structural changes that increase the favorable van der Waals interactions in SARS-CoV-2.

A maximum van der Waals interaction of 1.6 kcal/mol was observed between SARS-CoV-Y457 and ACE2-T27, whereas for SARS-CoV-2 the maximum van der Waals interaction observed between CoV2-D491 and ACE2-K353 was 2.1 kcal/mol (Table 1). The total van der Waals contribution to the binding energy was 4 kcal/mol. The total sum of binding...
interactions between the SARS-CoV-2 and the ACE2 receptor was found to be ∼7 kcal/mol, which is higher than the total binding energy in the case of SARS-CoV by a factor of 1.54.

To obtain a better sampling we calculated the electrostatic interactions between SARS-CoV/SARS-CoV-2 and the ACE2 for different MD trajectories at 100, 200, and 300 ps. The binding energies for SARS-CoV/SARS-CoV-2 are comparable. However, on average the SARS-CoV-2 binds stronger than the SARS-CoV (Table S2).

Furthermore, to illustrate the overall structural changes in the S-protein in SARS-CoV-2, we calculated the binding energies starting from the cryo-Em structure resolved for the S-protein of SARS-CoV-2 and the ACE2 (PDB ID: 6M17). We found that the total binding energy in the case of SARS-CoV-2 is stronger, where the electrostatic and van der Waals interactions are 3 and 1 kcal/mol, respectively, higher than in case of the SARS-CoV.

Several studies proposed that the increased virulence of SARS-CoV-2 is due to its higher binding affinity to the ACE2 receptor. Yan et al. proposed that mutation V404→K147 may result in higher binding affinity due to the salt bridge between K417 and D30, whereas the R426→N439 mutation would weaken the interaction with E329. However, our simulations show that the V404→K417 mutation increased the binding affinities because of favorable electrostatic interactions that are greater than the energy losses induced by R426→N439 mutation. Additionally, mutation L472→F486 was proposed to weaken van der Waals contact with Met 82 of ACE2. In contrast, the relaxed structure showed a van der Waals attraction of −1.32 kcal/mol. The structural changes induced by these mutations likely conferred stability to SARS-CoV-2 as it binds to ACE2. This agrees with the study of Ortega et al., in which they found that two main residues (479 and 487) have been associated with human ACE2 recognition. They further found a higher number of residues in the SARS-CoV-2 capping loops and attributed the more favorable binding affinity of −15.7 kcal/mol as opposed to −14.1 kcal/mol for SARS-CoV. Our results also agree with the experimental work of Wallas et al, where they studied the binding kinetics and affinity of the purified human ACE2 to both SARS-CoV-2 and SARS-CoV. They found that the equilibrium dissociation constant in the case of the first is ∼4 times lower than the second, indicating much higher affinity between SARS-CoV-2 and ACE2.

In summary, we show that the total binding energy between ACE2 and SARS-CoV-2 is higher than in the case of SARS-CoV, because of enhanced electrostatic interactions induced by the SARS-CoV-2 mutations. Based on our calculations, there is no significant contribution from a single mutant to the binding energies; however, these mutations induce sophisticated structural changes that enhance the electrostatic and van der Waals binding energies. These results might also support the idea that it is unlikely that the SARS-CoV-2 is lab engineered, but rather a result of a biological evolution.19

**ASSOCIATED CONTENT**

1. Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jpcllett.0c01064.

Detailed description of the MCCE and MD calculations, Table S1 of interactions between amino acids within the RBD, Table S2 of the electrostatic and van der Waals interaction for different MD trajectories, and Table S3 of the surface exposure of key amino acids, Table S4 of the ΔG’s of the ACE2-D30/SARS-CoV-R426 and ACE2-E329/SARS-CoV-2-K404 salt bridges and the coordinates of the relaxed SARS-CoV-2 structures (PDF)

**AUTHOR INFORMATION**

**Corresponding Author**

Muhamed Amin — Department of Sciences, University College Groningen, University of Groningen, 9718 BG Groningen, The Netherlands; Center for Free-Electron Laser Science, Deutsches Elektronen-Synchroten DESY, 22607 Hamburg, Germany; Centre for Theoretical Physics, The British University in Egypt, 11837 Cairo, Egypt; Email: m.a.amin@rug.nl

**Author Contributions**

M.A. proposed the idea and ran the MC and MD simulations. M.K.S. and A.K. worked on collecting the recent work published related to CoV-19 to find out the relevant differences between SARS-CoV and SARS-CoV-2, in order to define the mutations. All authors contributed to different aspects of the work, including writing and reviewing the Letter.

**Notes**

The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

This work is supported by the University of Groningen and the Nanotechnology Research Centre (NTRC), the British University in Egypt (BUE). We acknowledge the funding from NSF MCB 1519640 grant to M.R.G.. We thank Prof. Marilyn Gunner and Prof. Jochen Kupper for useful discussions.

**REFERENCES**

1. Rolling updates on coronavirus disease (COVID-19), Events as They Happen, World Health Organization Website.
2. Li, F.; Li, W.; Farzan, M.; Harrison, S. C. Structure of SARS Coronavirus spike Receptor-Binding Domain Complexed with Receptor. *Science* 2005, 309, 1864–1868.
3. Walls, A. C.; Park, Y. J.; Tortorici, M. A.; Wall, A.; McGuire, A. T.; Veesler, D. Structure, Function, and Antigenicity of the SARS-CoV-2 spike Glycoprotein. *Cell* 2020, 181, 281–292.
4. Wrapp, D.; Wang, N.; Corbett, K. S.; Goldsmith, J. A.; Hsieh, C. L.; et al. Cryo-EM Structure of the 2019-nCoV spike in the Prefusion Conformation. *Science* 2020, 367, 1260–1263.
5. Ou, X.; Liu, Y.; Lei, X.; Li, L.; Mi, D.; et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. *Nat. Commun.* 2020, 11, 1620.
6. Wan, Y.; Shang, J.; Graham, R.; Baric, R. S.; Li, F. Receptor Recognition by the Novel Coronavirus from Wuhan: An Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. *J. Virol.* 2020, 94, e00127–20.
(7) Yan, R.; Zhang, Y.; Li, Y.; Xia, L.; Guo, Y.; Zhou, Q. Structural Basis for the Recognition of SARS-CoV-2 by Full-Length Human ACE2. Science 2020, 367, 1444–1448.

(8) Friedrichs, M. S.; Eastman, P.; Vaidyanathan, W.; Houston, M.; LeGrand, S.; et al. Accelerating Molecular Dynamic Simulation on Graphics Processing Units. J. Comput. Chem. 2009, 30, 864–872.

(9) Eastman, P.; Pande, V. S. OpenMM: A Hardware-Independent Framework for Molecular Simulations. Comput. Sci. Eng. 2010, 12, 34–39.

(10) Eastman, P.; Pande, V. S. Constant Constraint Matrix Approximation: A Robust, Parallelizable Constraint Method for Molecular Simulations. J. Chem. Theory Comput. 2010, 6, 434–437.

(11) Eastman, P.; Pande, V. S. Efficient Nonbonded Interactions for Molecular Dynamics on a Graphics Processing Unit. J. Comput. Chem. 2010, 31, 1268–1272.

(12) Eastman, P.; Friedrichs, M. S.; Chodera, J. D.; Radmer, R. J.; Buss, C. M.; et al. OpenMM 4: A Reusable, Extensible, Hardware Independent Library for High Performance Molecular Simulation. J. Chem. Theory Comput. 2013, 9, 461–469.

(13) Eastman, P.; Swails, J.; Chodera, J. D.; McGibbon, R. T.; Zhao, Y.; et al. OpenMM 7: Rapid development of high-performance algorithms for molecular dynamics. PLoS Comput. Biol. 2017, 13, e1005659.

(14) Song, Y.; Mao, J.; Gunner, M. R. MCCE2: Improving protein pKa calculations with extensive side chain rotamer sampling. J. Comput. Chem. 2009, 30, 2231–2247.

(15) Jurrus, E.; Engel, D.; Star, K.; Monson, K.; Brandi, J.; et al. Improvements to the APBS biomolecular solvation software suite. Protein Sci. 2018, 27, 112–128.

(16) Teixeira, S.; Pacheco, X.; Borland Delphi 6 developer’s guide; Sams Publishing, 2002.

(17) Ortega, J. T.; Serrano, M. L.; Pujol, F. H.; Rangel, H. R. Role of changes in SARS-CoV-2 spike protein in the interaction with the human ACE2 receptor: An insilico analysis. EXCLI J. 2020, 19, 410–417.

(18) Walls, A. C.; Park, Y. J.; Tortorici, M. A.; Wall, A.; McGuire, A. T.; Yeele, D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell 2020, 181, 281–292.

(19) Andersen, K. G.; Rambaut, A.; Lipkin, W. I.; Holmes, E. C.; Garry, R. F. The proximal origin of SARS-CoV-2. Nat. Med. 2020, 26, 450–452.