Molecular basis for higher affinity of SARS-CoV-2 spike RBD for human ACE2 receptor

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Abstract

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused substantially more infections, deaths, and economic disruptions than the 2002-2003 SARS-CoV. The key to understanding SARS-CoV-2's higher infectivity lies partly in its host receptor recognition mechanism. Experiments show that the human ACE2 protein, which serves as the primary receptor for both CoVs, binds to the receptor binding domain (RBD) of CoV-2's spike protein stronger than SARS-CoV's spike RBD. The molecular basis for this difference in binding affinity, however, remains unexplained from X-ray structures. To go beyond insights gained from X-ray structures and investigate the role of thermal fluctuations in structure, we employ all-atom molecular dynamics simulations. Microseconds-long simulations reveal that while CoV and CoV-2 spike-ACE2 interfaces have similar conformational binding modes, CoV-2 spike interacts with ACE2 via a larger combinatorics of polar contacts, and on average, makes 45\% more polar contacts. Correlation analysis and thermodynamic calculations indicate that these differences in the density and dynamics of polar contacts arise from differences in spatial arrangements of interfacial residues, and dynamical coupling between interfacial and non-interfacial residues. These results recommend that ongoing efforts to design spike-ACE2 peptide blockers will benefit from incorporating dynamical information as well as allosteric coupling effects.

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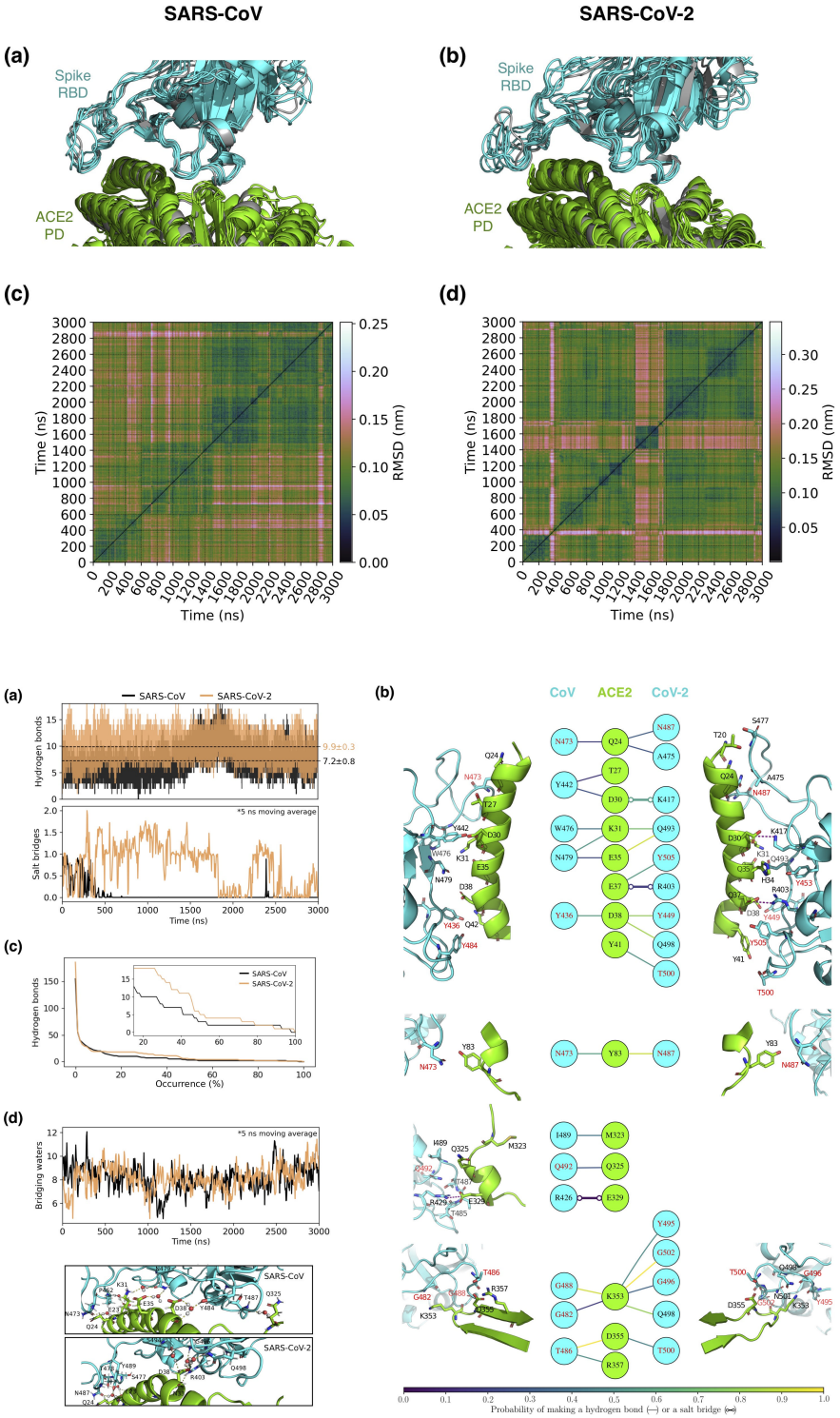
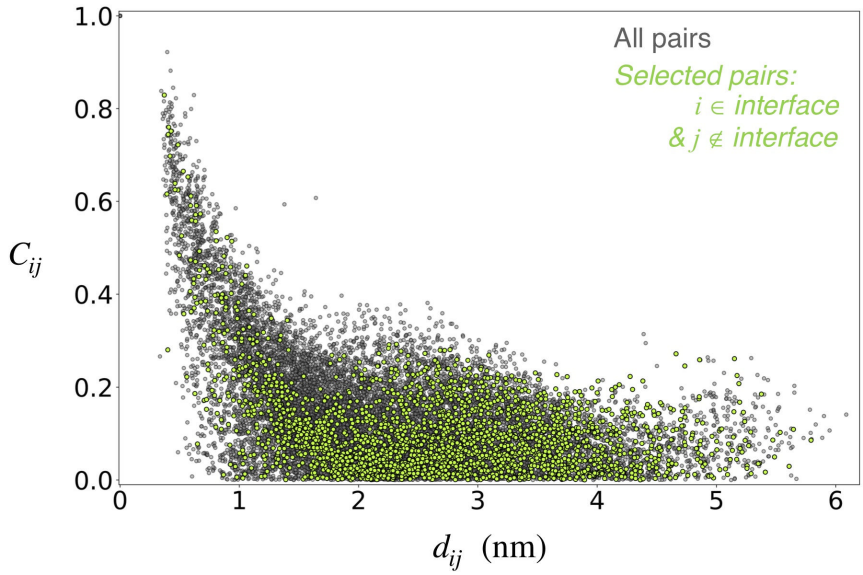


(a) CoV spike RBD



(b) CoV-2 spike RBD