Computational (Bio)Molecular Physics Group
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RESEARCH UPDATE
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Identification of Important Molecular-level Interactions between SARS-CoV-1 Spike Proteins and Human ACE2 Receptors

Understanding molecular-level physico-chemical interactions between pathogenic coronaviruses, such as SARS-CoV-1 and SARS-CoV-2, with human ACE2 (hACE2) host receptors is essential for developing countermeasures, such as therapeutic antiviral drugs, or predicting the potential efficacy of neutralizing antibodies.

The severe acute respiratory syndrome coronavirus, SARS-CoV-1, is a potentially reemerging health threat that was identified in late 2002. Recently, much emphasis has been placed on understanding infection mechanisms of SARS-CoV-2 even as key details about corresponding mechanisms of the, structurally related but not identical, SARS-CoV-1 coronavirus remain unclear.

SARS-CoV-1 viruses interact with host receptors *via* the *receptor binding domains* (RBD) of their spike (s) proteins. Structural characterization techniques such as X-ray crystallography (XRC) and cryogenic electron microscopy (cryo-EM) can identify the contact residues at the hACE2...S-RBM interface. However, these techniques cannot unequivocally determine which S-RBM residue fragments are *attractive* and which are *repulsive* relative to hACE2. By contrast, such information, helpful for antiviral or vaccine development, can be obtained *via* rigorous quantum-biochemical calculations as shown by recent work done in our laboratory. Our present computational studies are consistent with and, at the same time, complementary to those based on structural probes such as XRC and cryo-EM.

We have implemented fragment-based quantum-biochemical computational methods to uniquely identify and quantify (in units of kcal/mol) which specific SARS-CoV-1 residue fragments, at the hACE2...S-RBM interface, are *attractive* or *repulsive*. We have uncovered the specific viral S-RBD residue fragments that dominate the attractive interactions with hACE2 and, thus, promote viral-host binding. This new information can aid the faster development of antiviral drugs which attempt to block spike protein binding to human receptors. In addition, our results may identify key viral epitopes and potentially explain the efficacy, or lack thereof, of certain antibodies towards the SARS-CoV-1 S-RBM.

A manuscript, written by Prof. Jorge H. Rodriguez with graduate student Akshita Gupta, entitled *"Contact residue contributions to interaction energies between SARS-CoV-1 spike proteins and human ACE2 receptors"* has been submitted for peer-reviewed publication. In addition the manuscript has been submitted as a pre-print to *Research Square*:
https://doi.org/10.21203/rs.3.rs-95153/v1

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