Early research on existing drug compounds via supercomputing could combat coronavirus

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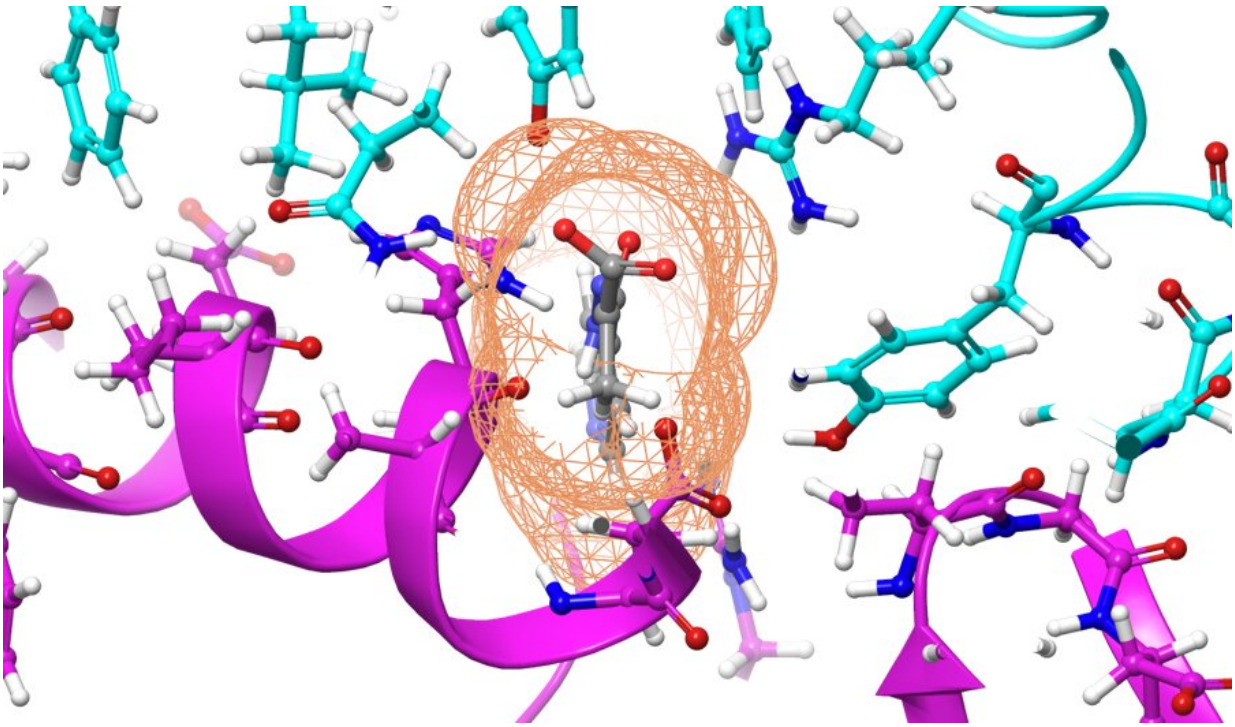

The compound, shown in gray, was calculated to bind to the SARS-CoV-2 spike protein, shown in cyan, to prevent it from docking to the Human Angiotensin-Converting Enzyme 2, or ACE2, receptor, shown in purple. Credit: Micholas Smith/Oak Ridge National Laboratory, U.S. Dept. of Energy

Researchers at the Department of Energy's Oak Ridge National

Laboratory have used Summit, the world's most powerful and smartest supercomputer, to identify 77 small-molecule drug compounds that might warrant further study in the fight against the SARS-CoV-2 coronavirus, which is responsible for the COVID-19 disease outbreak.

The two researchers performed simulations on Summit of more than 8,000 compounds to screen for those that are most likely to bind to the main "spike" protein of the coronavirus, rendering it unable to infect host cells. They ranked compounds of interest that could have value in experimental studies of the virus. They published their results on ChemRxiv.

The idea was born out of an interest in the coronavirus' entry point into a host cell. When Chinese researchers sequenced the virus, they discovered that it infects the body by one of the same mechanisms as the Severe Acute Respiratory Syndrome, or SARS, virus that spread to 26 countries during the SARS epidemic in 2003. The similarity between the two virus structures facilitated the study of the new virus.

Jeremy C. Smith, Governor's Chair at the University of Tennessee and director of the UT/ORNL Center for Molecular Biophysics, worked from the assumption that the two viruses may even "dock" to the cell in the same way.

Team member and UT/ORNL CMB postdoctoral researcher Micholas Smith built a model of the coronavirus' spike protein, also called the S-protein, based on early studies of the structure.

"We were able to design a thorough computational model based on information that has only recently been published in the literature on this virus," Micholas Smith said, referring to a study published in *Science China Life Sciences*.

After being granted computational time on Summit through a Director's Discretionary allocation, Micholas Smith used a chemical simulations code to perform molecular dynamics simulations, which analyze the movements of atoms and particles in the protein. He simulated different compounds docking to the S-protein spike of the coronavirus to determine if any of them might prevent the spike from sticking to human cells.

"Using Summit, we ranked these compounds based on a set of criteria related to how likely they were to bind to the S-protein spike," Micholas Smith said.

The team found 77 small-molecule compounds, such as medications and natural compounds, that they suspect may be of value for experimental testing. In the simulations, the compounds bind to regions of the spike that are important for entry into the human cell, and therefore might interfere with the infection process.

After a highly accurate S-protein model was released in *Science*, the team plans to rapidly run the computational study again with the new version of the S-protein. This may change the ranking of the chemicals likely to be of most use. The researchers emphasized the necessity of testing of the 77 compounds experimentally before any determinations can be made about their usability.

"Summit was needed to rapidly get the simulation results we needed. It took us a day or two whereas it would have taken months on a normal computer," said Jeremy Smith. "Our results don't mean that we have found a cure or treatment for the Wuhan coronavirus. We are very hopeful, though, that our computational findings will both inform future studies and provide a framework that experimentalists will use to further investigate these compounds. Only then will we know whether any of them exhibit the characteristics needed to mitigate this virus."

Computation must be followed by experiment. Computational screening essentially "shines the light" on promising candidates for experimental studies, which are essential for verifying that certain chemicals will combat the virus, according to Jeremy Smith. The use of a supercomputer such as Summit was important to get the results quickly.

More information: Smith, Micholas; Smith, Jeremy C. (2020): Repurposing Therapeutics for COVID-19: Supercomputer-Based Docking to the SARS-CoV-2 Viral Spike Protein and Viral Spike Protein-Human ACE2 Interface. ChemRxiv. Preprint. doi.org/10.26434/chemrxiv.11871402.v3