PSC

COVID-19 HPC Consortium

With the nation—and the world—disrupted by the COVID-19 pandemic, PSC is answering the call to action. Working with a national alliance of high-performance computing resources called the COVID-19 HPC Consortium, PSC has accelerated urgent and rapid COVID-related research through making ***Bridges***; ***Bridges-AI***; and ***Anton 2***, a special-purpose supercomputer for biomolecular simulation designed and developed by D. E. Shaw Research and hosted at PSC, available to the national research community. By making these resources available at no cost to scientists, PSC has greatly accelerated the development of new treatments to aid people who have contracted the virus and to limit its spread.

The consortium projects are selected from among proposals made by the scientific community via an accelerated review process. Committees of experts in different scientific fields relevant to the pandemic meet daily. They then submit their recommendations to a "matching committee" that determines allocations to each project by that afternoon. The computer can be available as early as the next morning.

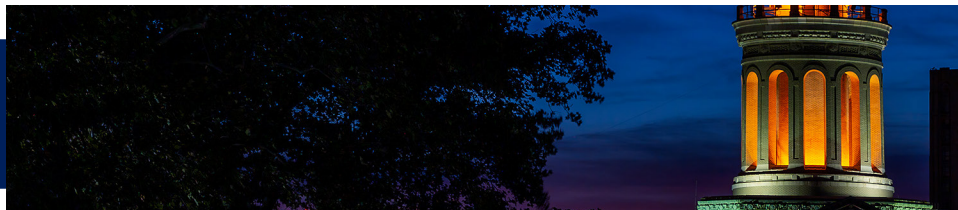
The COVID-19 HPC Consortium encompasses computing capabilities from some of the most powerful and advanced computers in the world. By contributing to this combined effort, PSC hopes to empower researchers around the world to accelerate understanding of the SARS-CoV-2 virus and the development of treatments and vaccines to help address infections. PSC also continues to make time on its systems available for COVID and other research via allocations through XSEDE, the National Science Foundation cyberinfrastructure in which PSC is a leading member.

HPC Consortium Research to-date at PSC

12 projects

18,000,000 cpu hours used

42 users



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PSC Impact

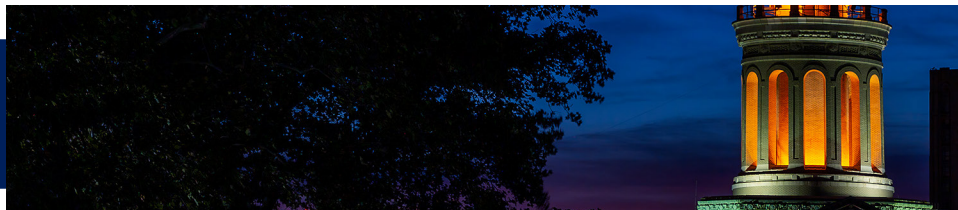
In two separate studies, scientists at Weill-Cornell Medicine have used Bridges to validate and analyze results from a rapid experimental test to identify the presence of SARS-CoV-2 virus and to identify risk factors for bad outcomes in COVID-19 cases.

The 30-minute experimental test, called LAMP, gave results that compared well overall with those of "gold standard" but much slower methods. It tracked how a rare version of SARS-CoV-2 from Europe came to infect over 80 percent of patients in New York City, and helped shed light on the relationship between COVID-19 and high blood pressure and angiotensin-converting-enzyme-(ACE)-inhibitor medications. LAMP was also able to detect the virus at lower levels than current tests, making less-invasive testing possible. The team's paper on the work is in press with a scientific journal. Their results led to an Emergency Use Authorization (EUA) approval for the methods from the FDA, among the EUAs reviewed by the group in correspondence to Nature Biotechnology in August 2020; the LAMP test is now being used in clinical sites around the country.

> *"The ability to process these gigantic datasets so quickly on PSC systems was critical to the success of our studies."*
>
> Christopher Mason, Weill-Cornell Medicine

Another paper by the team, published in Nature Medicine in August 2020, linked variations in the genes responsible for blood coagulation and tissue inflammation to higher risk of severe disease in people infected with the virus. The study connected genetic sequences with the immune-system overreaction and blood clotting in the lungs seen in patients with the worst outcomes, which could help identify which patients will need the most aggressive therapy.

"The ability to process these gigantic datasets so quickly on PSC systems was critical to the success of our studies," said Christopher Mason, who led the work along with Jonathan Foox and Cem Meydan.



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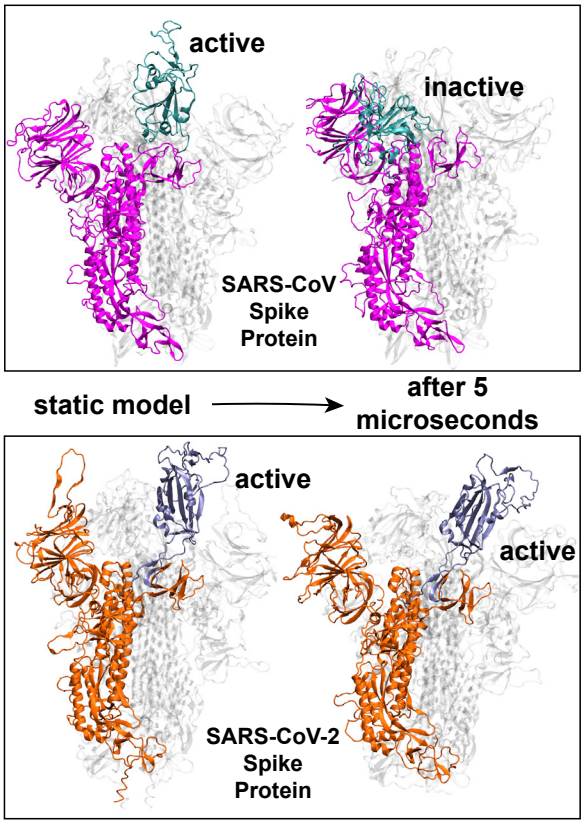
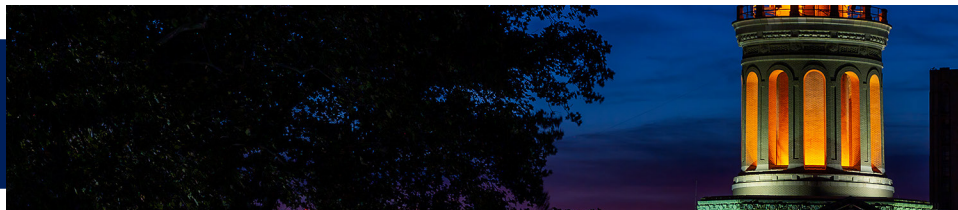
Anton 2 simulations of the SARS-CoV-2 virus's spike protein have provided an explanation for the virus's high infectivity that was not evident in prior, static images of the protein. Virtual spike proteins—the external "nubs" in the virus that first interact with host cells—in SARS-CoV-2 move differently than almost-identical proteins from SARS-CoV, the cause of the SARS epidemic of 2002-2003.

The simulated CoV and CoV-2 spike proteins behaved similarly when in their inactivated states. Once activated by encountering host-cell proteins, the CoV spike protein moved into a second inactive state. But the CoV-2 protein stayed active, helping to explain why SARS-CoV-2 is better able to spread than its earlier relative. The specific differences between the proteins may give doctors far better targets for therapy and vaccine development.

"I do not believe that we could have observed the crucial difference in the behavior of SARS-CoV and SARS-CoV-2 spike proteins using any supercomputer other than Anton 2," said Mahmoud Moradi of the University of Arkansas, who performed the simulations. "Anton 2 at PSC allows [us] to perform microsecond-level simulations of large biomolecular systems such as spike protein within hours rather than months … That is exactly the type of simulations that we needed to run to be able to see the differences that we observed between the two viruses."



Currently available static models of SARS-CoV and SARS-CoV-2 spike proteins (top) are quite similar. However, Anton 2 simulations provide a significantly different dynamic picture of the two proteins (bottom), where SARS-CoV spike protein deactivates within five microseconds of simulations but the SARS-CoV-2 spike protein stays active throughout the simulations.



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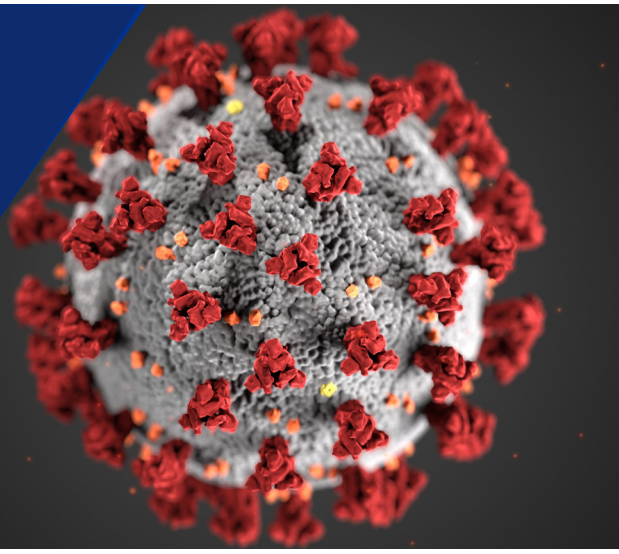

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Antibodies from patients that neutralized the SARS-CoV virus fail to affect the SARS-CoV-2 virus because of relatively small changes in a viral protein, according to a report from the Catholic University of America. Simulations on Bridges's "large-memory" nodes as well as on other supercomputers demonstrated that the old antibodies could be engineered to treat or possibly prevent COVID-19.

"Without supercomputers provided by PSC and XSEDE this research wouldn't be possible," said Victor Padilla-Sanchez, who performed the simulations. "I am glad to hear that PSC supercomputers have gotten renewed NSF funding for the coming years."

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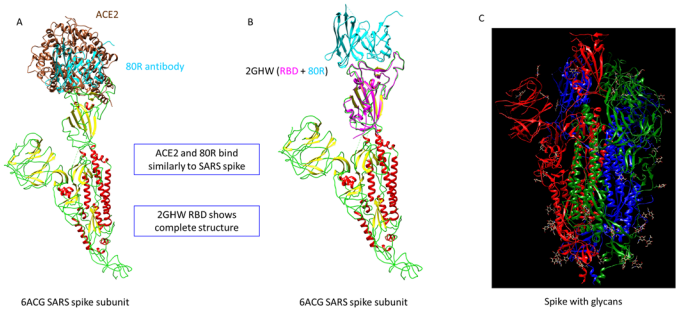
> Victor Padilla-Sanchez, Catholic University of America

Padilla-Sanchez's simulations of the antibodies docking with the SARS-CoV and SARS-CoV-2 spike proteins suggested that changes in the binding site of the SARS-CoV-2 spike protein prevented SARS-CoV antibodies from sticking to the newer virus's protein. Small virtual changes in the antibodies gave them the ability to attach to the COVID-19 pathogen in the simulations, offering possible treatments or preventives for COVID-19 infection.



Structural analysis of SARS-CoV spike glycoprotein. In A the SARS-CoV spike protein (PDB ID: 6ACG) is shown bound to ACE2 (brown) and 80R antibody (cyan), superimposed on the same binding site. In B the spike protein is shown bound only to the 80R antibody (PDB ID: 2GHW), with the structural model of the RBD of the SARS-CoV-2 spike protein (magenta) containing the missing loops. This homology model served as the basis for the docking experiments. In C it is shown a spike colored by subunit and showing the glycans. There are only two possible glycans in the RBD region of the protein, at positions 331 and 343; neither of these sites affect the 80R binding.