Sugar coating locks and loads coronavirus for infection

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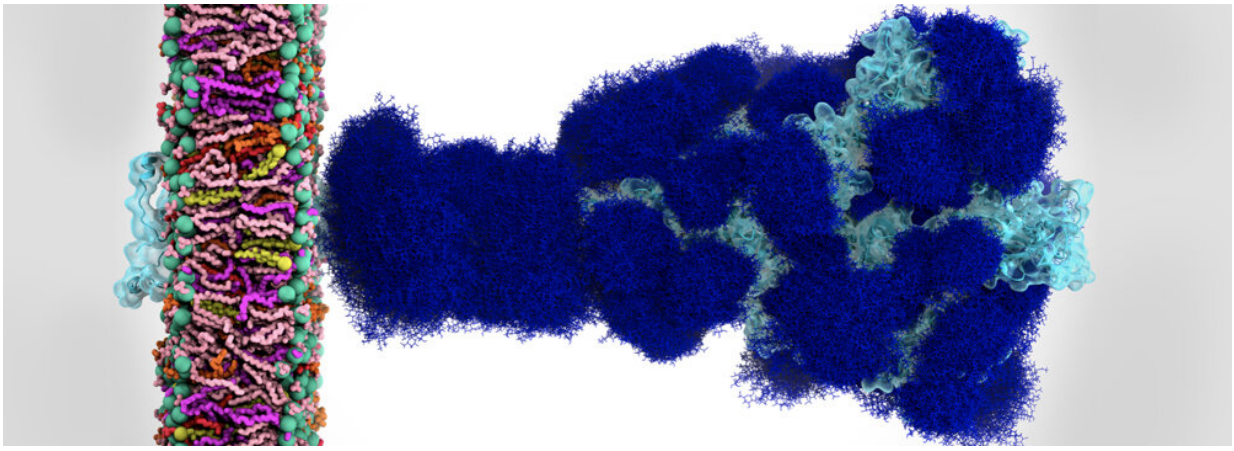

The coronavirus uses a sugary coating of molecules called glycans (deep blue) to camouflage itself as harmless from the defending antibodies. Simulations by the Amaro Lab of UC San Diego on the National Science Foundation (NSF)-funded Frontera supercomputer at the Texas Advanced Computing Center (TACC) have revealed the atomic makeup of the coronavirus's sugary shield. What's more, simulation and modeling show that glycans also prime the coronavirus for infection by changing the shape of its spike protein. Scientists hope this basic research will add to the arsenal of knowledge needed to defeat the COVID-19 virus. Credit: Lorenzo Casalino (UCSD) et al.

They say you can't judge a book by its cover. But the human immune system does just that when it comes to finding and attacking harmful microbes such as the coronavirus. It relies on being able to recognize

foreign intruders and generate antibodies to destroy them. Unfortunately, the coronavirus uses a sugary coating of molecules called glycans to camouflage itself as harmless from the defending antibodies.

Simulations on the National Science Foundation (NSF)-funded Frontera supercomputer at the Texas Advanced Computing Center (TACC) have revealed the atomic makeup of the coronavirus's sugary shield. What's more, simulation and modeling show that glycans also prime the coronavirus for infection by changing the shape of its spike protein. Scientists hope this basic research will add to the arsenal of knowledge needed to defeat the COVID-19 virus.

Sugar-like molecules called glycans coat each of the 65-odd spike proteins that adorn the coronavirus. Glycans account for about 40 percent of the spike protein by weight. The spike proteins are critical to cell infection because they lock onto the cell surface, giving the virus entry into the cell.

"You really see how effective its glycan shield is," said Rommie Amaro, a professor of chemistry and biochemistry at the University of California, San Diego. "That's because you see the glycans covering the surface of the viral spike protein, which is the most exposed bit and the part that's responsible for the initial infection in the human cell," she said.

Amaro is a corresponding author of a study published June 12, 2020 on bioRxiv.org—an open-access repository of electronic preprints—that discovered a potential structural role of the shielding glycans that cover the SARS-CoV-2 spike protein. "You can see very clearly that from the open conformation, the spike protein has to undergo a large structural change to actually get into the human cell," Amaro said.

But even to make an initial connection, she said that one of the pieces of

the spike protein in its receptor binding domain has to lift up. "When that receptor binding domain lifts up into the open conformation, it actually lifts the important bits of the protein up over the glycan shield," Amaro explained.

This is in contrast to the closed conformation, where the shield covers the spike protein. "Our analysis gives a potential reason why it does have to undergo these conformational changes, because if it just stays in the down position those glycans are basically going to block the binding from actually happening," she said.

Another aspect of their study showed how shifts in the conformations of the glycans triggered changes in the spike protein structure. "One thing that really jumped out at us is that in the open conformation there are two glycans that basically prop up the protein in that open conformation," Amaro said.

"That was really surprising to see. It's one of the major results of our study. It suggests that the role of glycans in this case is going beyond shielding to potentially having these chemical groups actually being involved in the dynamics of the spike protein," she added.

She likened the action of the glycan to pulling the trigger of a gun. "When that bit of the spike goes up, the finger is on the trigger of the infection machinery. That's when it's in its most dangerous mode—it is locked and loaded," Amaro said. "When it gets like that, all it has to do is come up against an ACE2 receptor in the human cell, and then it's going to bind super tightly and the cell is basically infected."

The NSF-funded Frontera supercomputer of the Texas Advanced Computing Center at UT Austin is ranked #5 fastest in the world and #1 for academic systems, according to the November 2019 Top500 rankings. Credit: TACC

Amaro and her colleagues use computational methods to build data-centric models of the SARS-CoV-2 virus, and then use computer simulations to explore different scientific questions about the virus.

They started with various experimental datasets that revealed the structure of the virus. This included cryo-EM structures from the Jason McLellan Lab of The University of Texas at Austin; and from the lab of David Veesler at the University of Washington. "Their structures are really amazing because they give researchers a picture of what these important molecular machines actually look like," Amaro said.

Unfortunately, even the most powerful microscopes on Earth still can't

resolve movement of the protein at the atomic scale. "What we do with computers is that we take the beautiful and wonderful and important data that they give us, but then we use methods to build in missing bits of information," Amaro said.

What's more, details of the glycan shielding have been too difficult for experiments to resolve. "What people really want to know, for example vaccine developers and drug developers, is what are the vulnerabilities that are present in this shield," Amaro said.

The computer simulations allowed Amaro and colleagues to create a cohesive picture of the spike protein that includes the glycans. "The reason why the computer resources at TACC are so important is that we can't understand what these glycans look like if we don't use simulation," Amaro said.

Amaro was awarded compute time on the NSF-funded Frontera supercomputer of TACC. Her team has used about 2.3 million node hours for molecular dynamics simulations and modeling , the most among any researchers using the system to study COVID-19. She used up to 4,000 nodes, or about 250,000 processing cores. Frontera—the leadership-class system in NSF's cyberinfrastructure ecosystem—ranks as the fifth most powerful supercomputer in the world and the fastest academic system, according to November 2019 rankings of the Top500 organization.

In order to animate the dynamics of the 1.7 million atom system under study, a lot of computing power was needed, said Amaro. "That's really where Frontera has been fantastic, because we need to sample relatively long dynamics, microsecond to millisecond timescales, to understand how this protein is actually working."

"We've been able to do that with Frontera and the COVID-19 HPC

Consortium," Amaro said. "Now we're trying to share our data with as many people as we can, because people want a dynamical understanding of what's happening—not only with other academic groups but also with different pharmaceutical and biotech companies that are conducting neutralizing antibody development," she said.

Basic research is making a difference in winning the war against the SARS-CoV-2 virus, Amaro explained. "The more we know about it, the more of its abilities that we're going to be able to go after and potentially take out," she added.

Said Amaro: "It's of such great importance that we learn as much as we can about the virus. And then hopefully we can translate those understandings into things that will be useful either in the clinic, or the streets, for example if we're trying to reduce transmission for what we know now about aerosols and wearing masks. All these things will be part of it. Basic research has a huge role to play in the war against COVID-19. And I'm happy to be a part of it. It's a strength that we have Frontera and TACC in our arsenal."

The study, "Shielding and Beyond: The Roles of Glycans in SARS-CoV-2 Spike Protein," was published on bioRxiv.org June 12, 2020. The study authors are Lorenzo Casalino, Zied Gaieb, Abigail C. Dommer, Rommie E. Amaro of the Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, CA; and Aoife M Harbison, Carl A Fogarty, Elisa Fadda of the Department of Chemistry and Hamilton Institute, Maynooth University, Dublin, Ireland. This work was supported by NIH GM132826, NSF RAPID MCB-2032054, an award from the RCSA Research Corp., a UC San Diego Moore's Cancer Center 2020 SARS-COV-2 seed grant, the Visible Molecular Cell Consortium, and the Irish Research Council.

More information: Lorenzo Casalino et al. Shielding and Beyond: The

Roles of Glycans in SARS-CoV-2 Spike Protein, *bioRxiv* (2020). DOI: 10.1101/2020.06.11.146522