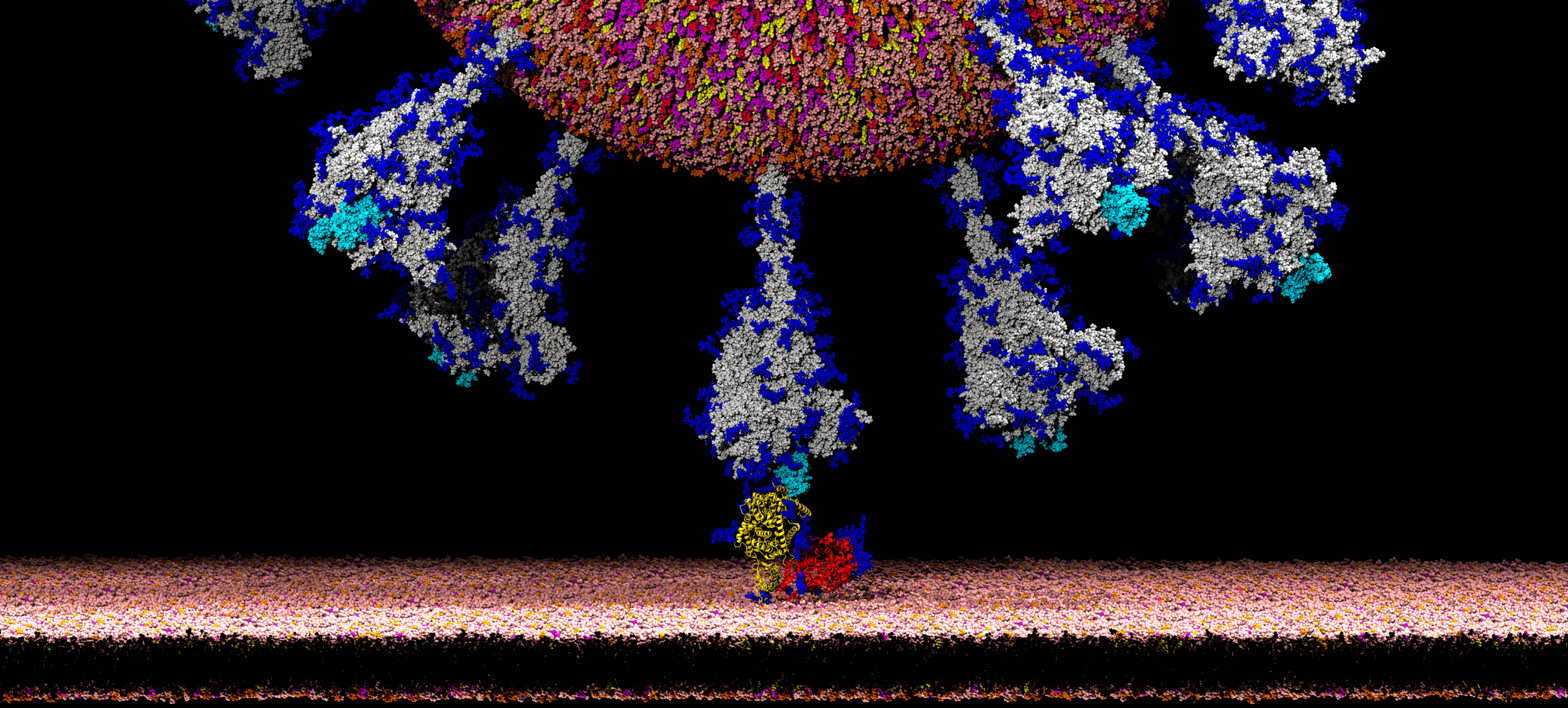
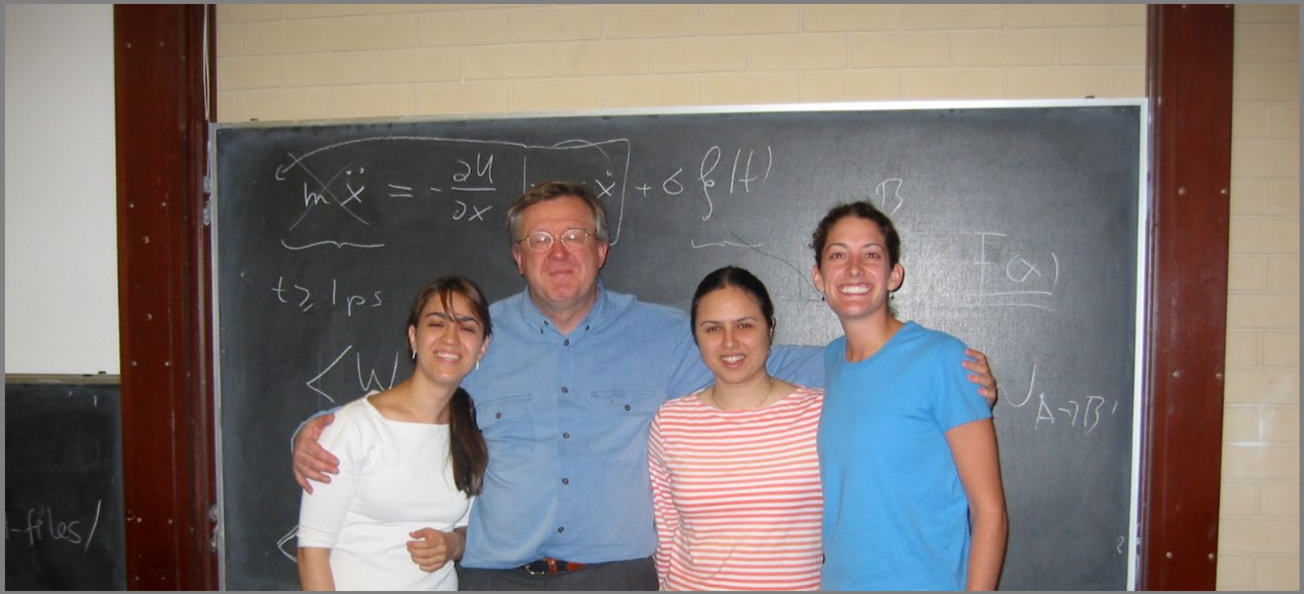


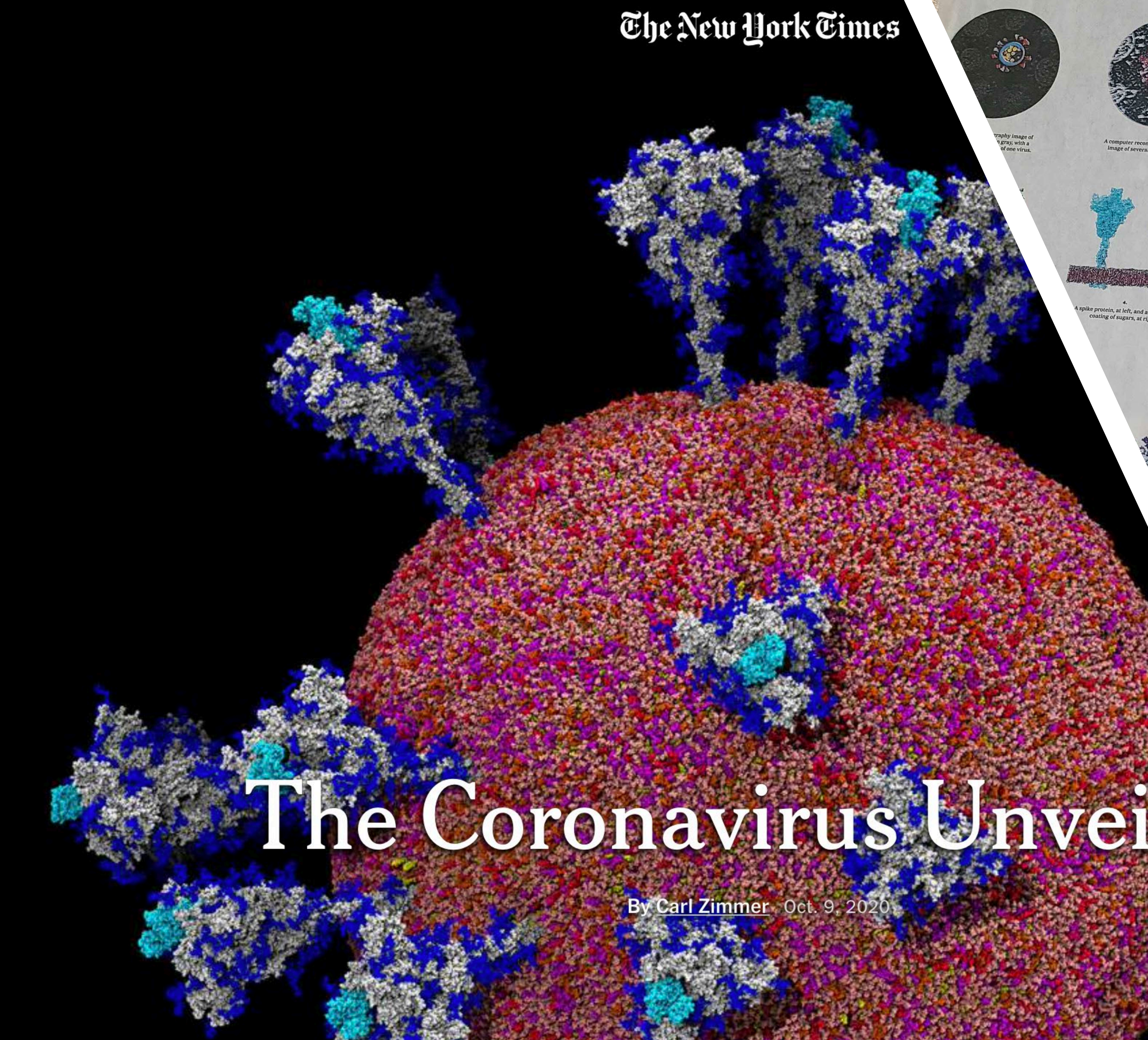
Computational Microscopy of SARS-CoV-2

Rommie Amaro . UC San Diego . March 2021

'… my goal was to look with mathematical and computational means at the inside of cells, one atom at a time, to decipher how living systems work. That is what I strived for and I never deflected from this goal.'

Klaus Schulten





2. A computer reconstruction overlaid on an image of several SARS-CoV-2 viruses.

4. A spike protein, at left, and a protective coating of sugars, at right.

The Coronavirus Is Unveiled Down to Its Blobs and Pores

By CARL ZIMMER

IN FEBRUARY, AS the new coronavirus swept across China and shut down entire cities, a scientist named Sai Li set out to paint its portrait.

At the time, the best pictures anyone had managed to take were low-resolution images, in which the virus looked like a barely discernible smudge.

Dr. Li, a structural biologist at Tsinghua University in Beijing, joined forces with virologists who were rearing the virus in a biosafety lab in the city of Hangzhou. Those researchers doused the viruses with chemicals to render them harmless and then sent them to Dr. Li.

Dr. Li and his colleagues then concentrated the virus-laden fluid from a quart down to a single drop. He could only hope that they had done everything just right, so that the weeks of work to produce that drop would not have been a waste.

"At the time, you don't know what's inside," Dr. Li said. "It's just liquid, right?"

Glimpsing the Structure

Dr. Li carefully froze the drop in a fraction of a second. If he made the slightest mistake, ice crystals could spear the viruses, tearing them apart.

Hoping for the best, Dr. Li placed the smidgen of ice into a cryo-electron microscope. The device fired beams of electrons at the sample. (Figure 1) As they bounced off the atoms inside, Dr. Li's computer reconstructed what the microscope had seen. When the picture formed, he was taken aback.

"I saw a screen full of viruses," Dr. Li recalled.

He could see thousands of coronaviruses packed in the ice like jellybeans in a jar. They were beautifully intact, allowing him to inspect details on the viruses that measured less than a millionth of an inch.

"I thought, I was the first ...

... to see the virus in such good resolution," Dr. Li recalled.

Over the following weeks, Dr. Li and his colleagues pored over the viruses. They inspected the proteins that studded its surface and they dove into its core, where the virus's strand of genes was coiled up with proteins. The pictures reminded Dr. Li of eggs in a nest.

Thanks to the work of scientists like Dr. Li, the new coronavirus, known as SARS-CoV-2, is no longer a cipher. They have come to know it in intimate, atomic detail. They've discovered how it uses some of its proteins to slip into cells and how its intimately twisted genes commandeer our biochemistry. They've observed how some viral proteins throw wrenches into our cellular factories, while others build nurseries for making new viruses. And some researchers are using supercomputers to create complete, virtual viruses that they hope to use to understand how the real viruses have spread with such devastating ease. (Figure 2)

"This time is unlike anything any of us has experienced, just in terms of the bombardment of data," said Rommie Amaro, a computational biologist at the University of California, San Diego.

Probing the Spike

Earlier this year, Dr. Amaro and other researchers directed much of their attention to the proteins, called spikes, that stud the virus's surface. Spike proteins have an essential job to play: They latch onto cells in our airway so the virus can slip inside. But it soon became clear that the name is a misnomer. The spike protein is not sharp, narrow or rigid.

Each spike protein snaps together with two others, forming a structure that has a tulip-like shape. A long stem anchors the proteins to the virus, and their top looks like a three-part flower.

Gerhard Hummer, a computational biophysicist at the Max Planck Institute of Biophysics, and his colleagues used the frozen microscopy method to take pictures of spike proteins embedded in the virus membrane. (Figure 3) Then they calculated how the atoms in the proteins pushed and pulled on each other. The result was a molecular dance: The spike proteins swivel around on three hinges.

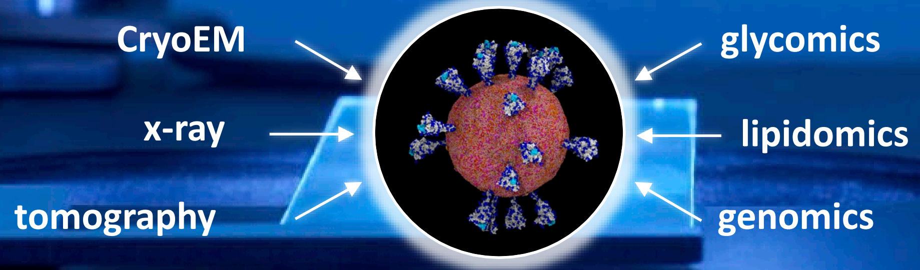
"You can ...

Molecular Dynamics Simulations as a Computational Microscope

Molecular Dynamics Simulations as a Computational Microscope

$$U(\vec{R}) = \sum_{bonds} k_i^{bond}(r_i - r_0)^2 + \sum_{angles} k_i^{angle}(\theta_i - \theta_0)^2 + \sum_{dihed} k_i^{dihed}[1 + \cos(n_i \phi_i + \delta_i)] + \sum_i \sum_{j \neq i} 4\epsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \sum_i \sum_{j \neq i} \frac{q_i q_j}{\epsilon r_{ij}}$$

$$\vec{F_i} = ma = m_i \frac{d^2 \vec{r_i}}{dt^2} = -\vec{\nabla} U(\vec{R})$$



Data centric computational simulations integrate and extend experimental data

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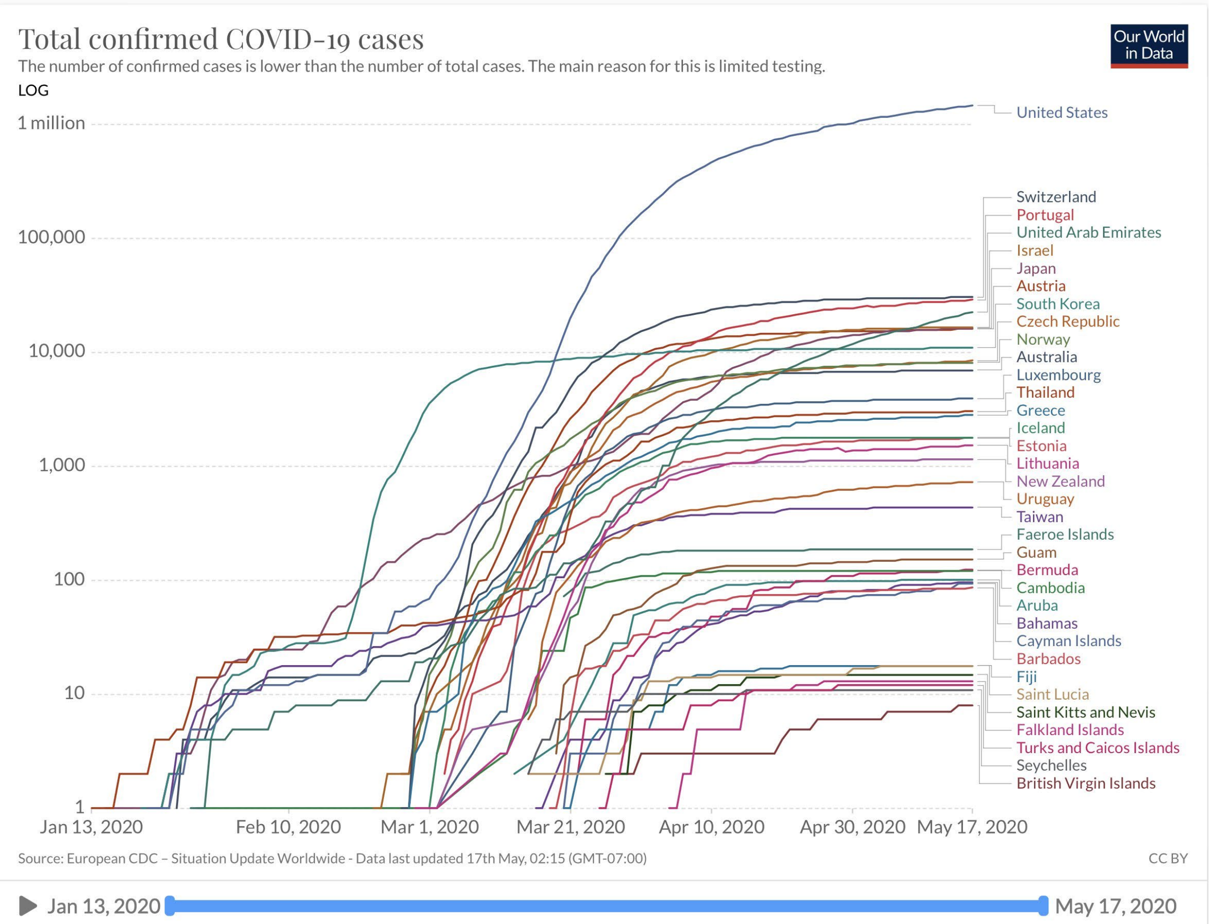
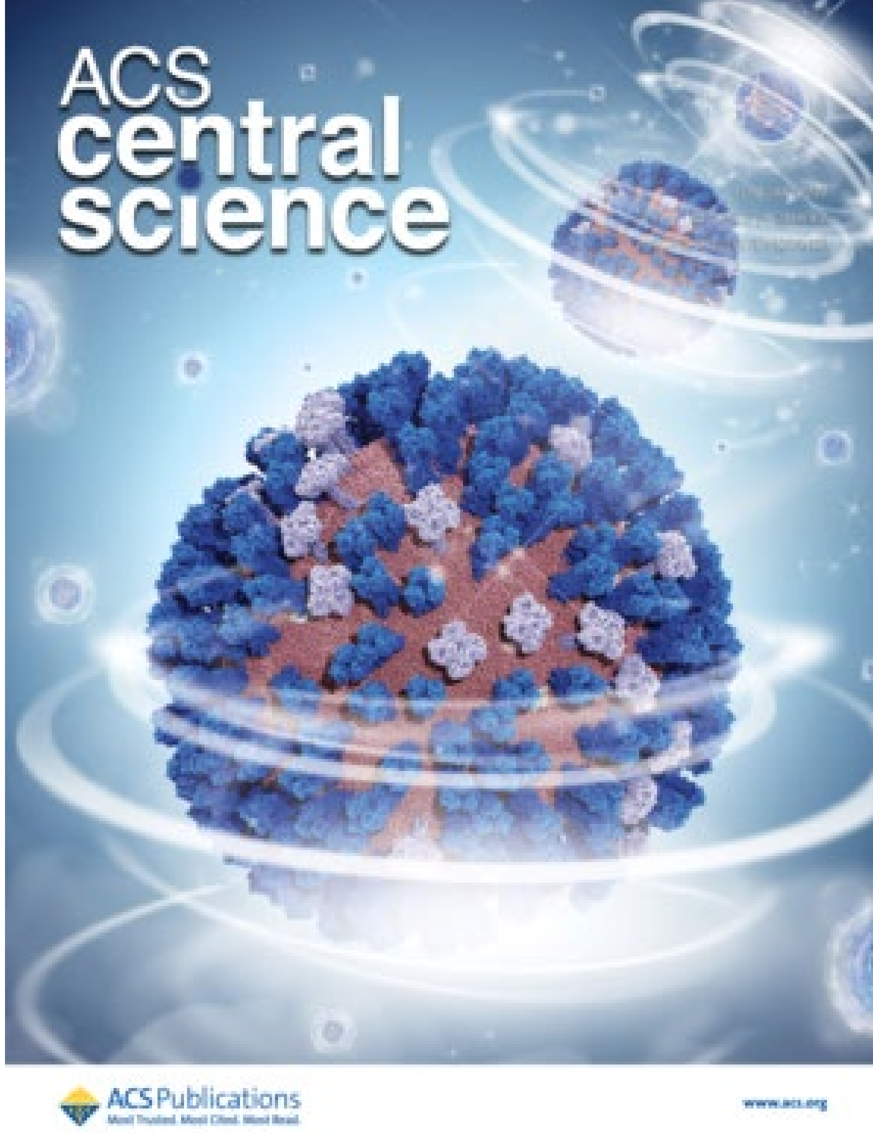
Mesoscale All-Atom Influenza Virus Simulations Suggest New Substrate Binding Mechanism

Jacob D. Durrant, Sarah E. Kochanek, Lorenzo Casalino, Pek U. Ieong, Abigail C. Dommer, and Rommie E. Amaro*

Cite this: *ACS Cent. Sci.* 2020, 6, 2, 189–196
Publication Date: February 19, 2020
https://doi.org/10.1021/acscentsci.9b01071





This was the day we pivoted our efforts towards SARS-CoV-2

New Results

1 comment

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Posted February 15, 2020.

Cryo-EM Structure of the 2019-nCoV Spike in the Prefusion Conformation

Daniel Wrapp, Nianshuang Wang, Kizzmekia S. Corbett, Jory A. Goldsmith, Ching-Lin Hsieh, Olubukola Abiona, Barney S. Graham, Jason S. McLellan

doi: https://doi.org/10.1101/2020.02.11.944462

Now published in *Science* doi: 10.1126/science.abb2507

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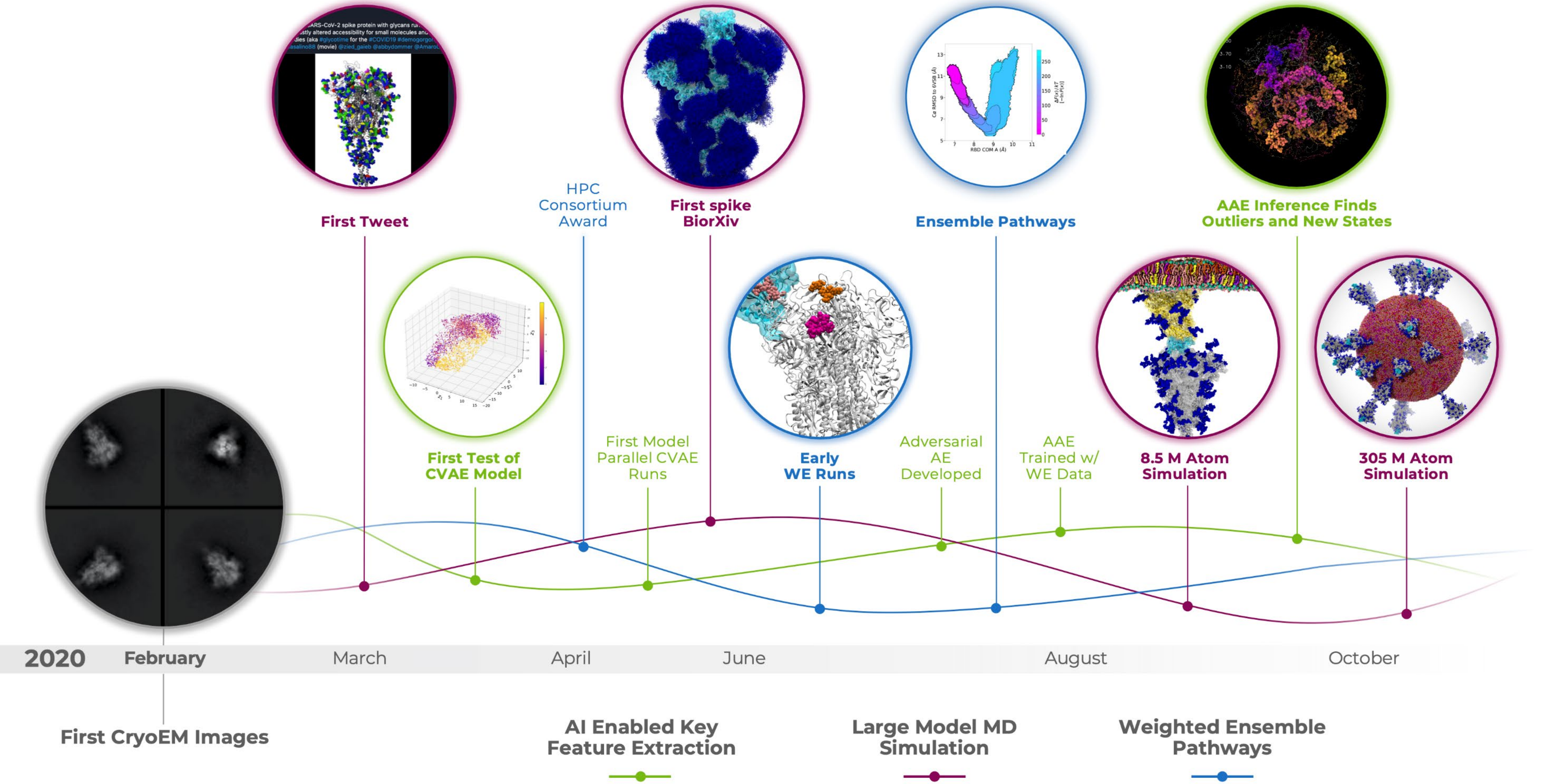
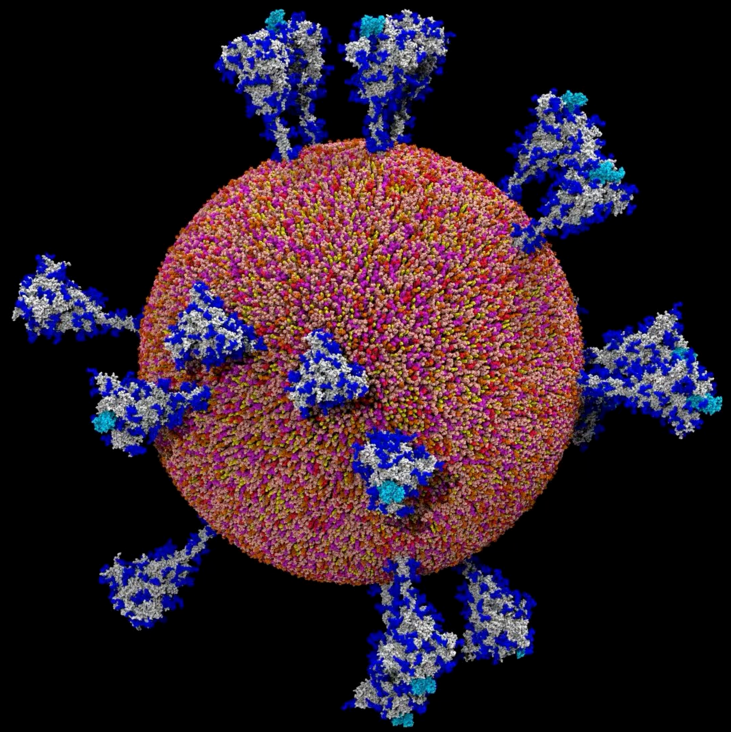
Preprint servers such as bioRxiv have been critical to research in this space



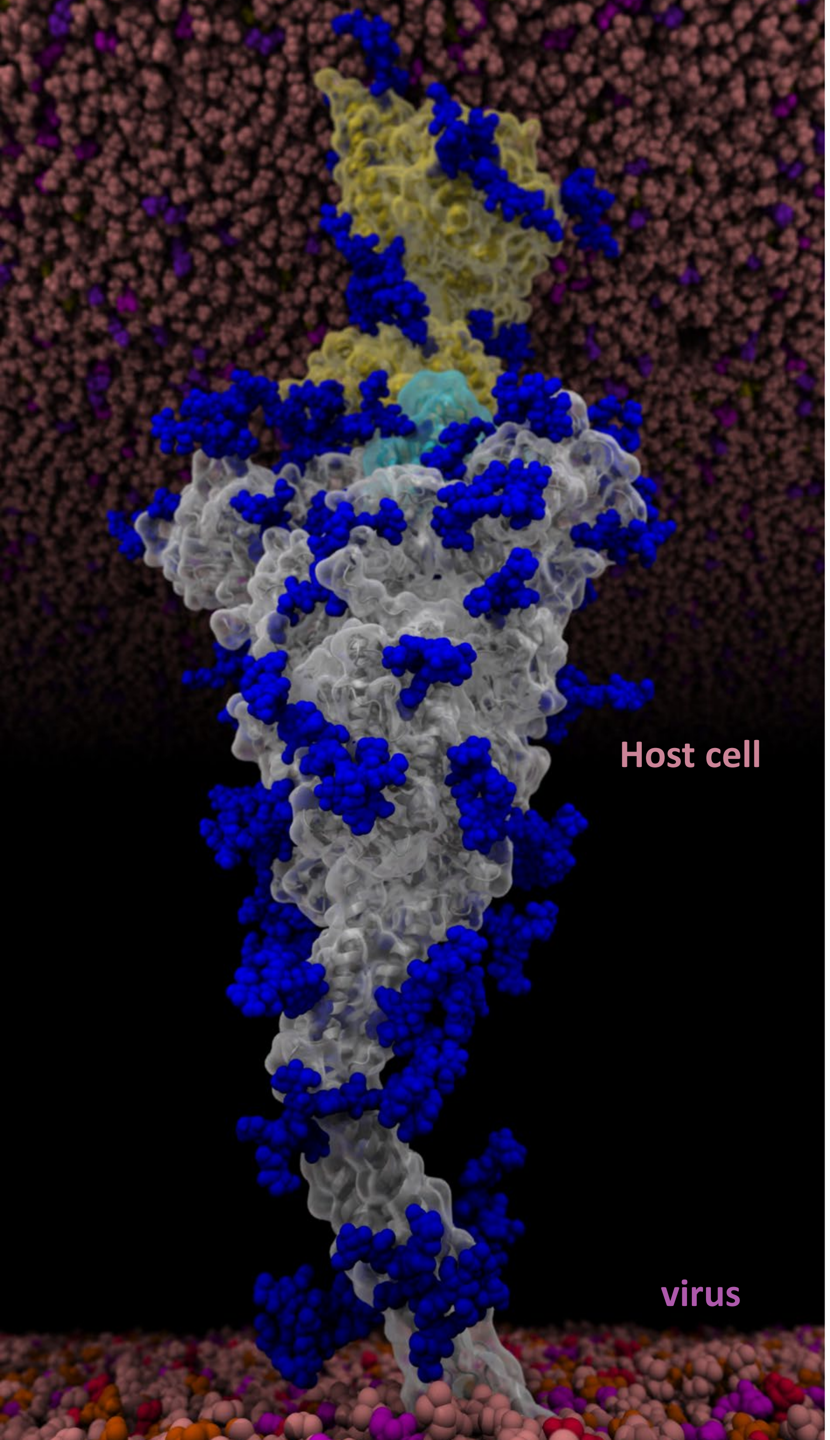
First Tweet
HPC Consortium Award
First spike BiorXiv
Ensemble Pathways
AAE Inference Finds Outliers and New States
First Test of CVAE Model
First Model Parallel CVAE Runs
Early WE Runs
Adversarial AE Developed
AAE Trained w/ WE Data
8.5 M Atom Simulation
305 M Atom Simulation
2020
February
March
April
June
August
October
First CryoEM Images
AI Enabled Key Feature Extraction
Large Model MD Simulation
Weighted Ensemble Pathways

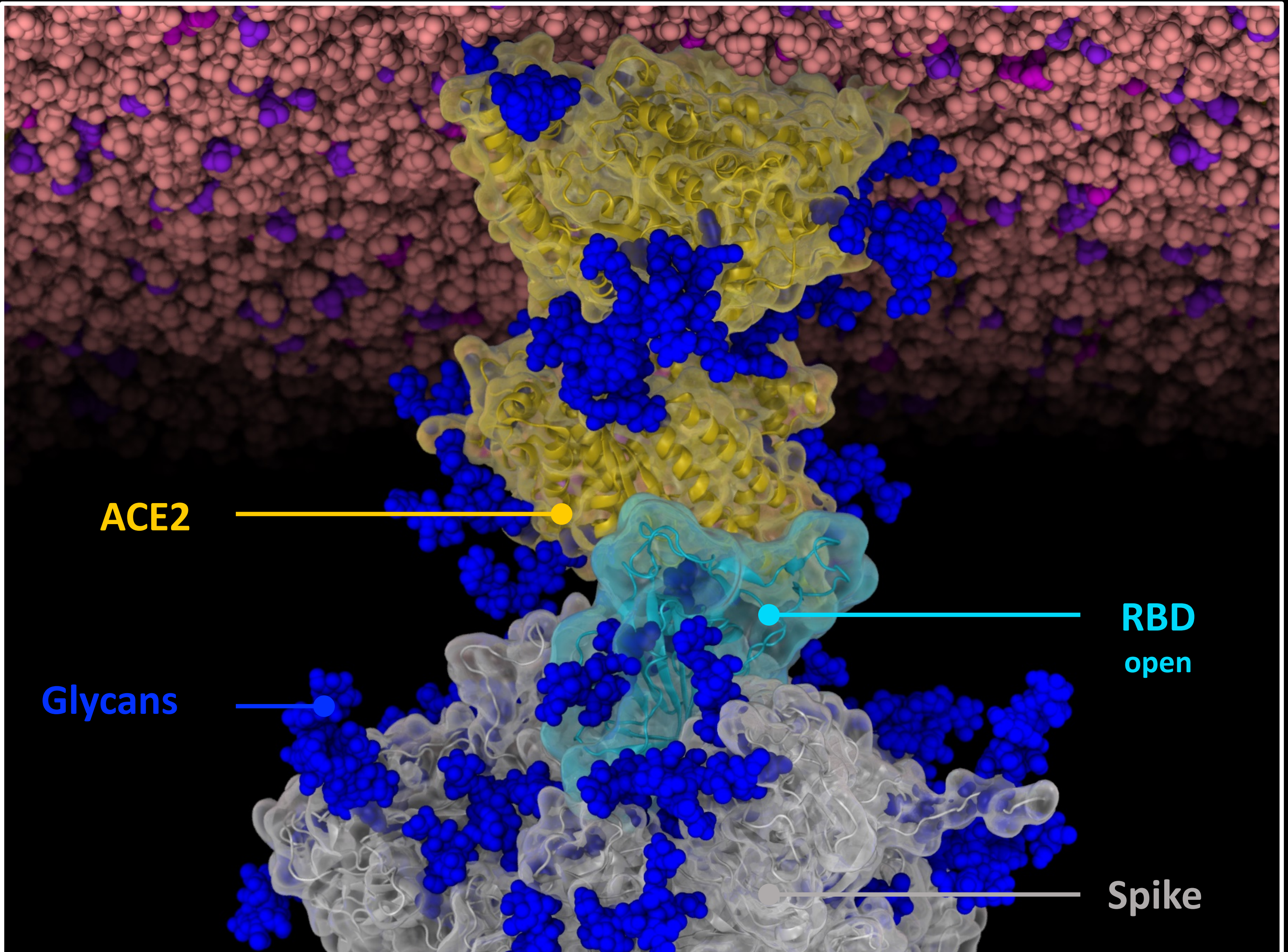


SARS-CoV-2 virus

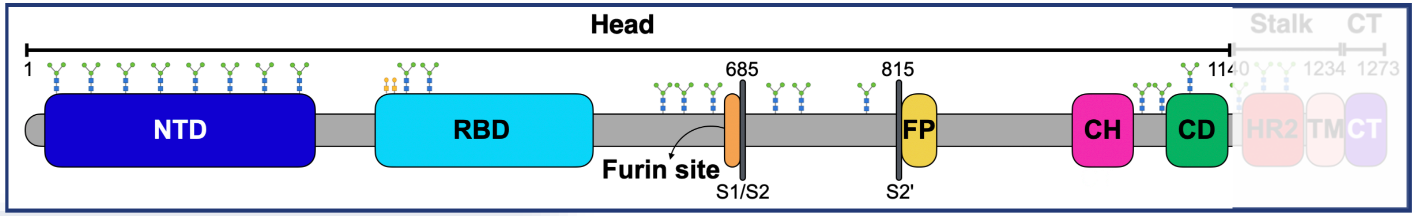
SARS-CoV-2 infection route

The spike protein latches onto ACE2 to infect the host cell





Modeling of the spike’s head



REPORT

Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation

Daniel Wrapp[1,*], Nianshuang Wang[1,*], Kizzmekia S. Corbett[2], Jory A. Goldsmith[1], Ching-Lin Hsieh[1], Olubukola Abiona[2], Barney S. Graham[2], Jason S. McLellan[1,†]

[1]Department of Molecular Biosciences, The University of Texas at Austin, Austin, TX 78712, USA.

[2]Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA.

↵†Corresponding author. Email: jmclellan@austin.utexas.edu

↵* These authors contributed equally to this work.

– Hide authors and affiliations

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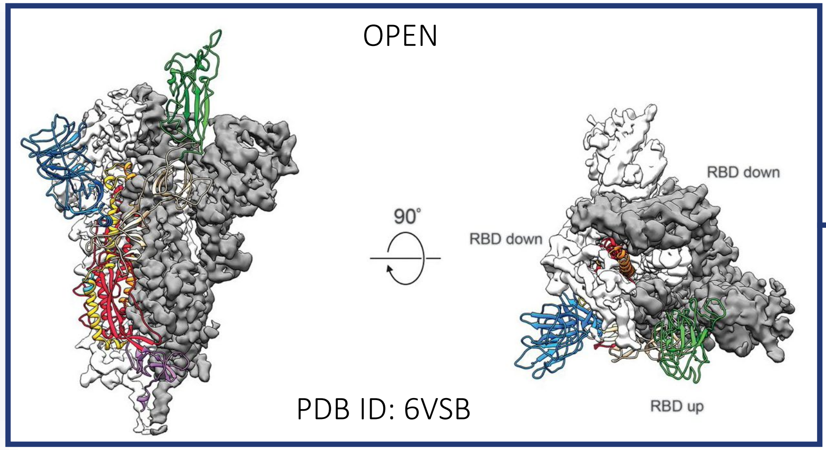
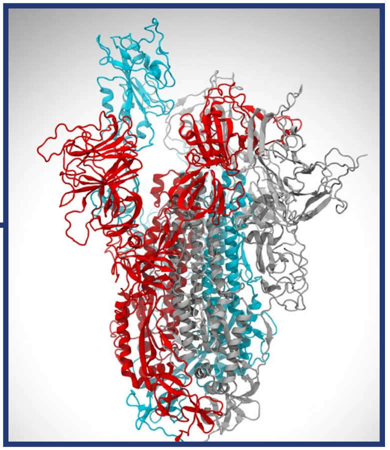
DOI: 10.1126/science.abb2507





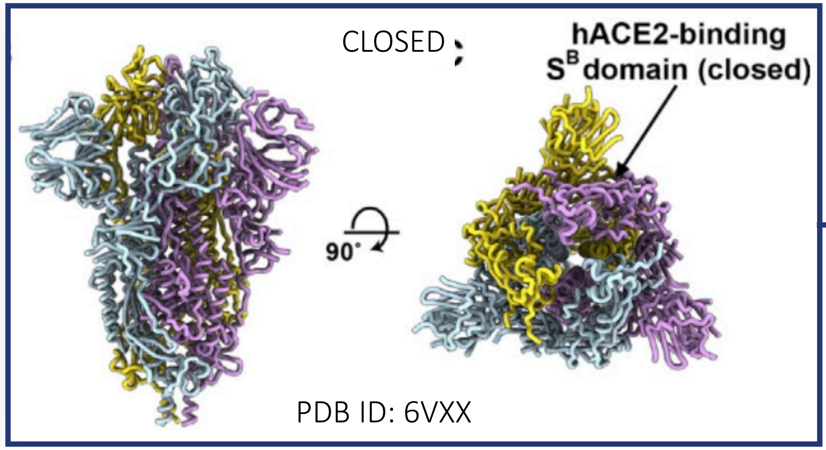
Article

Cell

Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein

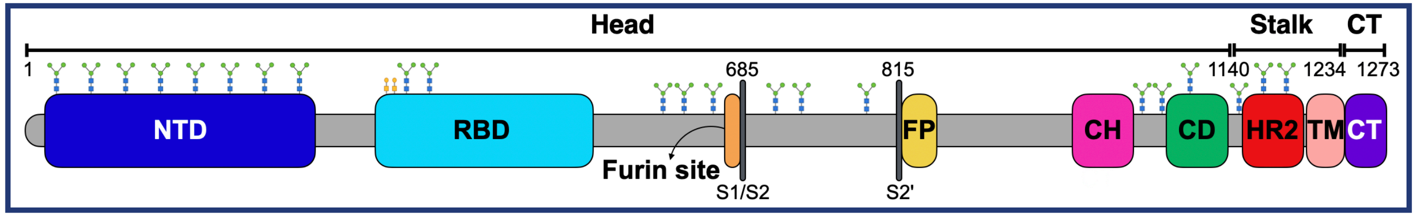
Alexandra C. Walls,[1,5] Young-Jun Park,[1,5] M. Alejandra Tortorici,[1,2] Abigail Wall,[3] Andrew T. McGuire,[3,4] and David Veesler[1,6,*]
[1]Department of Biochemistry, University of Washington, Seattle, WA 98195, USA
[2]Institute Pasteur & CNRS UMR 3569, Unité de Virologie Structurale, Paris 75015, France
[3]Vaccines and Infectious Diseases Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98195, USA
[4]Department of Global Health, University of Washington, Seattle, WA 98195, USA
[5]These authors contributed equally
[6]Lead Contact
*Correspondence: dveesler@uw.edu

https://doi.org/10.1016/j.cell.2020.02.058

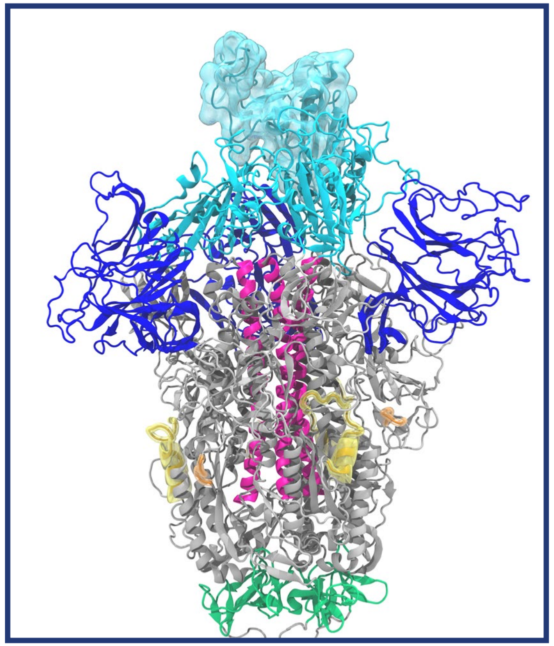


Gaps in the Cryo-EM structures corresponding to flexible loop were modeled using MODELLER

Modeling the spike's stalk and CT



Head



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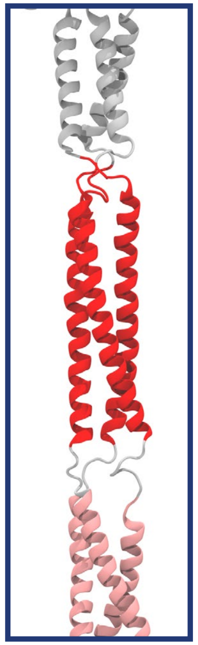
Stalk



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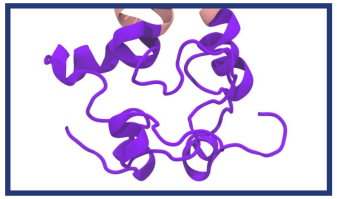
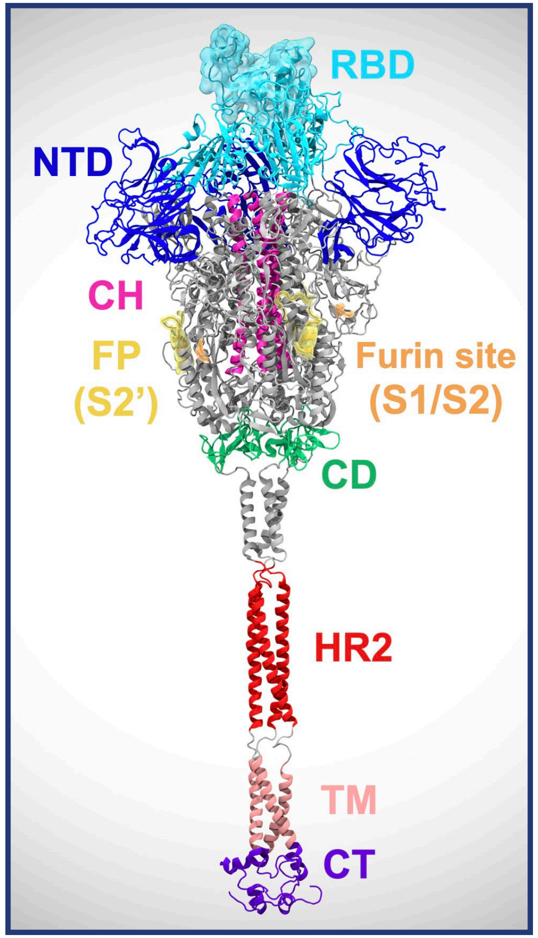
CT





The stalk was modeled as a trimeric coiled-coil helical bundle with MODELLER

The CT was modeled using I-TASSER

N- and O-linked Glycans

Science REPORTS

Cite as: Y. Watanabe *et al.*, *Science* 10.1126/science.abb9983 (2020).

Site-specific glycan analysis of the SARS-CoV-2 spike

Yasunori Watanabe[1,2,3]*, Joel D. Allen[1]*, Daniel Wrapp[4], Jason S. McLellan[4], Max Crispin[1]†

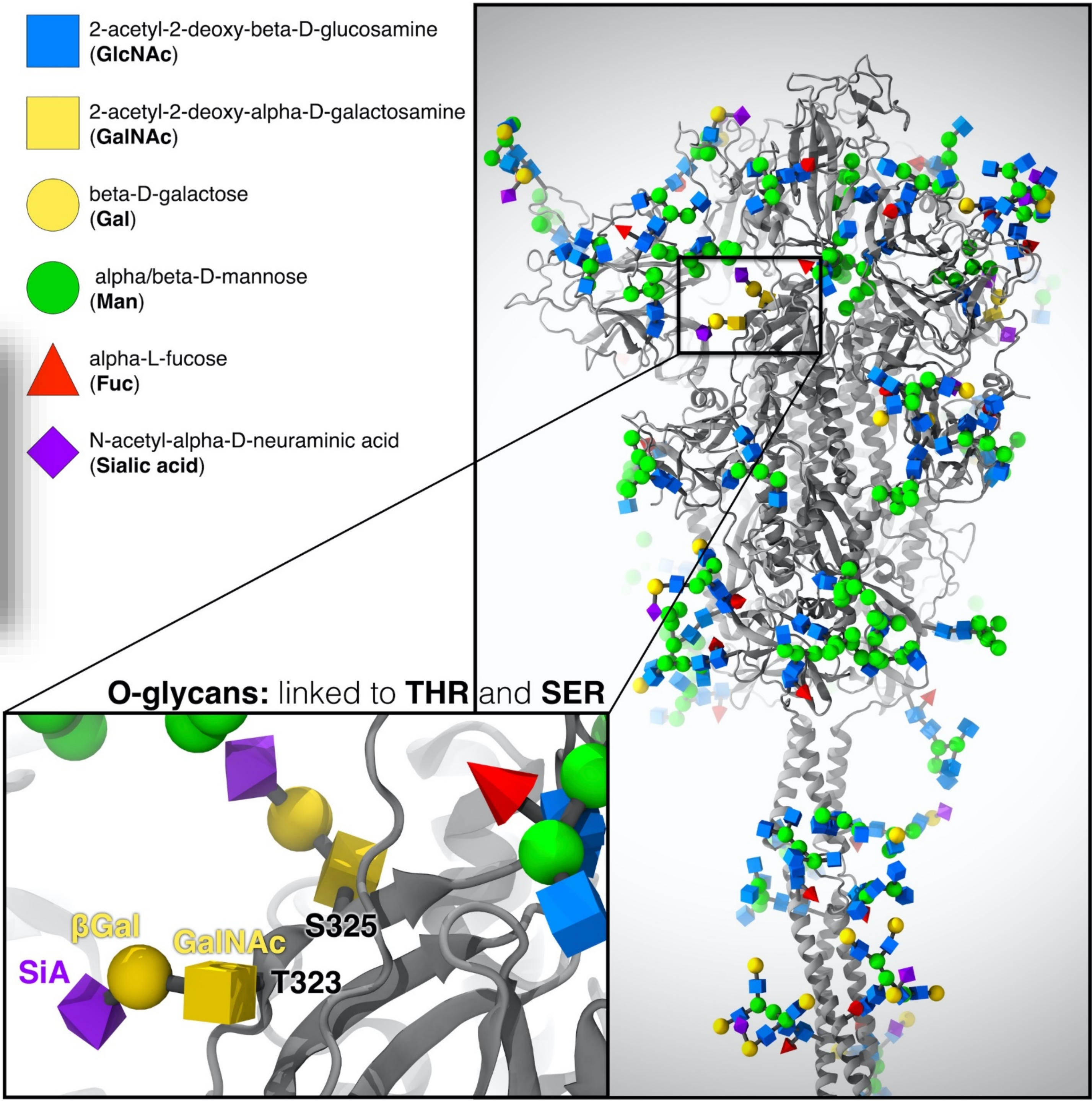
[1]School of Biological Sciences, University of Southampton, Southampton SO17 1BJ, UK. [2]Oxford Glycobiology Institute, Department of Biochemistry, University of Oxford, South Parks Road, Oxford OX1 3QU, UK. [3]Division of Structural Biology, University of Oxford, Wellcome Centre for Human Genetics, Oxford OX3 7BN, UK. [4]Department of Molecular Biosciences, The University of Texas at Austin, Austin, TX 78712, USA.

***These authors contributed equally to this work. †Corresponding author. Email: max.crispin@soton.ac.uk**

Deducing the N- and O- glycosylation profile of the spike protein of novel coronavirus SARS-CoV-2

Asif Shajahan, Nitin T. Supekar, Anne S. Gleinich, and Parastoo Azadi*.

Complex Carbohydrate Research Center, The University of Georgia, Athens, GA 30602



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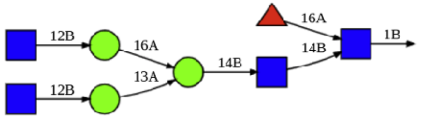
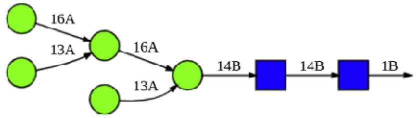
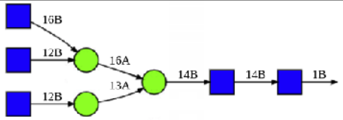
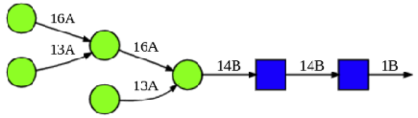
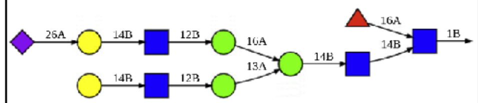
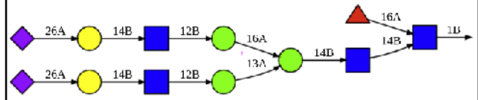
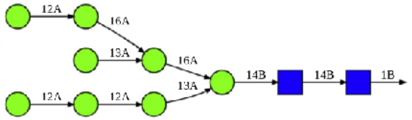
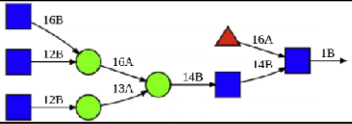
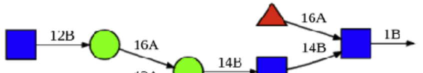
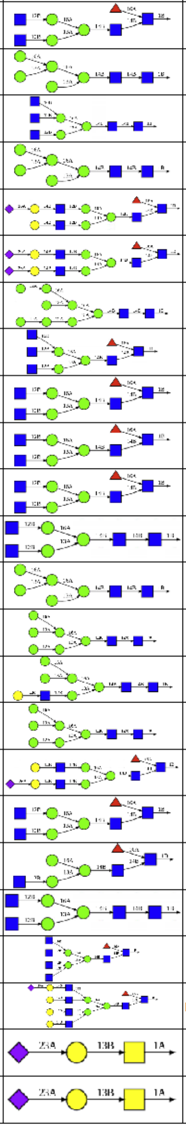
G1	N17	FA2		bDGlcNAc(1→2)aDMan(1→6)[bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)[aLFuc(1→6)]bDGlcNAc(1→)PROA-17
G2	N61	M5		aDMan(1→6)[aDMan(1→3)]aDMan(1→6)[aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROA-61
G3	N74	A3		bDGlcNAc(1→6)[bDGlcNAc(1→2)]aDMan(1→6)[bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROA-74
G4	N122	M5		aDMan(1→6)[aDMan(1→3)]aDMan(1→6)[aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROA-122
G5	N149	FA2G2S1		aDNeu5Ac(2→6)bDGal(1→4)bDGlcNAc(1→2)aDMan(1→6)[bDGal(1→4)bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)[aLFuc(1→6)]bDGlcNAc(1→)PROA-149
G6	N165	FA2G2S2		xaDNeu5Ac(2→6)bDGal(1→4)bDGlcNAc(1→2)aDMan(1→6)[aDNeu5Ac(2→6)bDGal(1→4)bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)[aLFuc(1→6)]bDGlcNAc(1→)PROA-165
G7	N234	M8		aDMan(1→2)aDMan(1→6)[aDMan(1→3)]aDMan(1→6)[aDMan(1→2)aDMan(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROA-234
G8	N282	FA3		bDGlcNAc(1→6)[bDGlcNAc(1→2)]aDMan(1→6)[bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)[aLFuc(1→6)]bDGlcNAc(1→)PROA-282
G9	N331	FA2		bDGlcNAc(1→2)aDMan(1→6)[bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)[aLFuc(1→6)]bDGlcNAc(1→)PROA-331

CHAIN A



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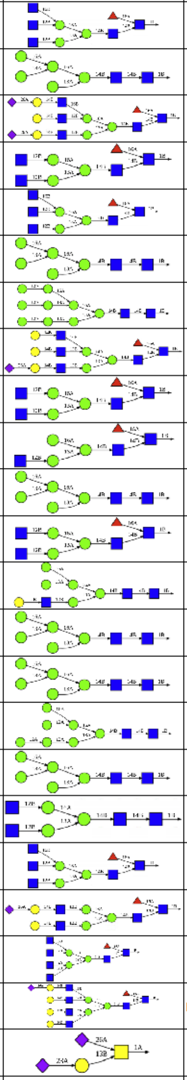
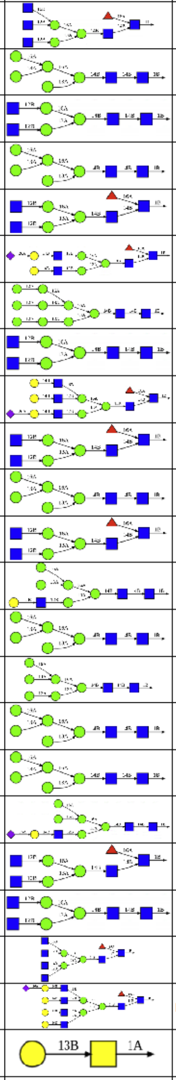
G14	N709	M6		aDMan(1→6)[aDMan(1→3)]aDMan(1→6) [aDMan(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROA-709
G15	N717	Hybrid G1		bDGal(1→4)bDGlcNAc(1→2)aDMan(1→3)[aDMan(1→6) [aDMan(1→3)]aDMan(1→6)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROA-717
G16	N801	M6		aDMan(1→6)[aDMan(1→3)]aDMan(1→6) [aDMan(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROA-801
G17	N1074	FA2G2S1		aDNeu5Ac(2→6)bDGal(1→4)bDGlcNAc(1→2)aDMan(1→3) [bDGal(1→4)bDGlcNAc(1→2)aDMan(1→6)]bDMan(1→4)bDGlcNAc(1→4) [aLFuc(1→6)]bDGlcNAc(1→)PROA-1074
G18	N1098	FA2		bDGlcNAc(1→2)aDMan(1→6)[bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4) [aLFuc(1→6)]bDGlcNAc(1→)PROA-1098
G19	N1134	FA1		bDGlcNAc(1→2)aDMan(1→3)[aDMan(1→6)]bDMan(1→4)bDGlcNAc(1→4) [aLFuc(1→6)]bDGlcNAc(1→)PROA-1134
G20	N1158	A2		bDGlcNAc(1→2)aDMan(1→6) [bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROA-1158
G21	N1173	FA4		bDGlcNAc(1→6)[bDGlcNAc(1→2)]aDMan(1→6)[bDGlcNAc(1→4) [bDGlcNAc(1→2)]aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)[aLFuc(1→6)]bDGlcNAc(1→)PROA-1173
G22	N1194	FA4G4S1		aDNeu5Ac(2→6)bDGal(1→4)bDGlcNAc(1→6)[bDGal(1→4)bDGlcNAc(1→2)]aDMan(1→6) [bDGal(1→4)bDGlcNAc(1→4)[bDGal(1→4)bDGlcNAc(1→2)]aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4) [aLFuc(1→6)]bDGlcNAc(1→)PROA-1194
G23	T323	O-glycan		aDNeu5Ac(2→3)bDGal(1→3)aDGalNAc(1→)PROA-323
G24	S325	O-glycan		aDNeu5Ac(2→3)bDGal(1→3)aDGalNAc(1→)PROA-325

CHAIN B



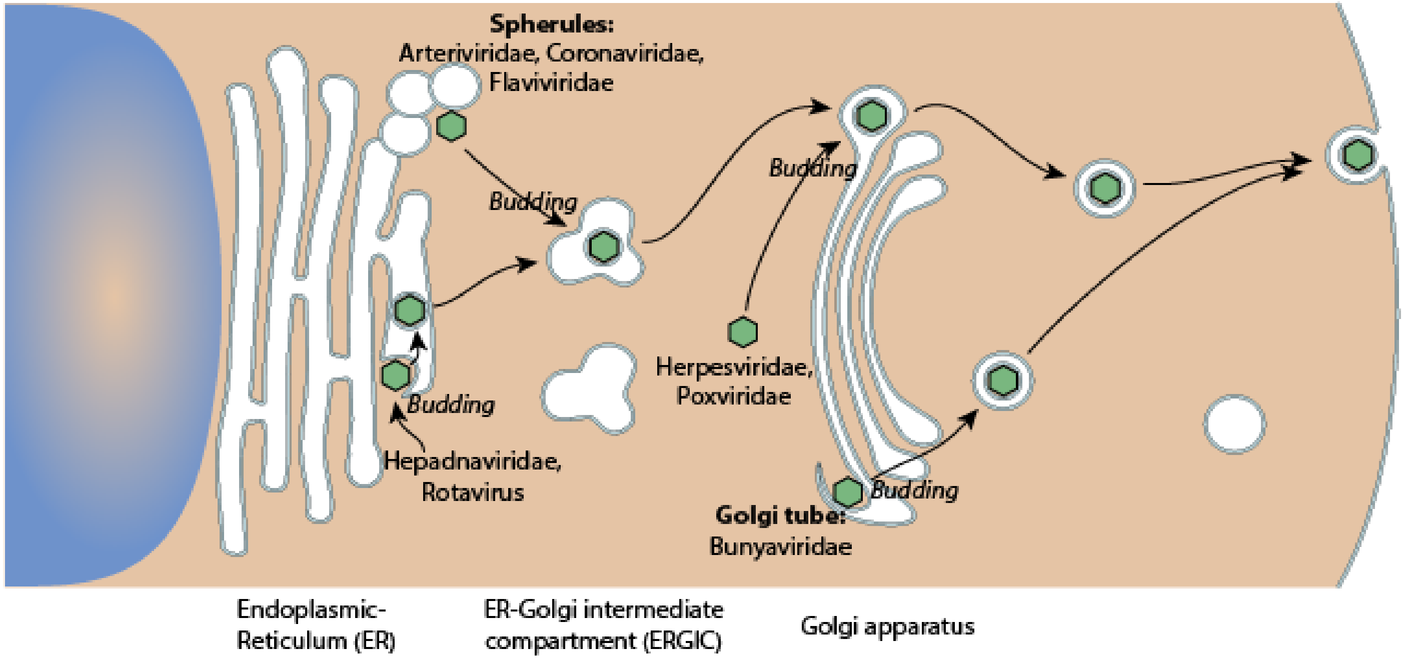
#	SARS-CoV-2 sequon	TYPE	STRUCTURE	SEQUENCE
G25	N17	FA3		bDGlcNAc(1→6)[bDGlcNAc(1→2)]aDMan(1→6) [bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)[aLFuc(1→6)]bDGlcNAc(1→)PROB-17
G26	N61	M5		aDMan(1→6)[aDMan(1→3)]aDMan(1→6) [aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROB-61
G27	N74	FA3G3S2		aDNeu5Ac(2→6)bDGal(1→4)bDGlcNAc(1→6)[bDGal(1→4)bDGlcNAc(1→2)]aDMan(1→6) [aDNeu5Ac(2→6)bDGal(1→4)bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4) [aLFuc(1→6)]bDGlcNAc(1→)PROB-74
G28	N122	FA2		bDGlcNAc(1→2)aDMan(1→6)[bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4) [aLFuc(1→6)]bDGlcNAc(1→)PROB-122
G29	N149	FA3		bDGlcNAc(1→6)[bDGlcNAc(1→2)]aDMan(1→6) [bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)[aLFuc(1→6)]bDGlcNAc(1→)PROB-149
G30	N165	M5		aDMan(1→6)[aDMan(1→3)]aDMan(1→6) [aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROB-165
G31	N234	M9		aDMan(1→2)aDMan(1→6)[aDMan(1→2)aDMan(1→3)]aDMan(1→6) [aDMan(1→2)aDMan(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROB-234
G32	N282	FA3G3S1		aDNeu5Ac(2→6)bDGal(1→4)bDGlcNAc(1→2)aDMan(1→3)[bDGal(1→4)bDGlcNAc(1→6) [bDGal(1→4)bDGlcNAc(1→2)]aDMan(1→6)]bDMan(1→4)bDGlcNAc(1→4) [aLFuc(1→6)]bDGlcNAc(1→)PROB-282
G33	N331	FA2		bDGlcNAc(1→2)aDMan(1→6)[bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4) [aLFuc(1→6)]bDGlcNAc(1→)PROB-331
G34	N343	FA1		bDGlcNAc(1→2)aDMan(1→3)[aDMan(1→6)]bDMan(1→4)bDGlcNAc(1→4) [aLFuc(1→6)]bDGlcNAc(1→)PROB-343
G35	N603	M5		aDMan(1→6)[aDMan(1→3)]aDMan(1→6) [aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROB-603
G36	N616	FA2		bDGlcNAc(1→2)aDMan(1→6)[bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4) [aLFuc(1→6)]bDGlcNAc(1→)PROB-616
G37	N657	Hybrid G1		bDGal(1→4)bDGlcNAc(1→2)aDMan(1→3)[aDMan(1→6) [aDMan(1→3)]aDMan(1→6)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROB-657
G38	N709	M5		aDMan(1→6)[aDMan(1→3)]aDMan(1→6) [aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROB-709
G39	N717	M5		aDMan(1→6)[aDMan(1→3)]aDMan(1→6) [aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROB-717
G40	N801	M7		aDMan(1→2)aDMan(1→2)aDMan(1→3)[aDMan(1→6) [aDMan(1→3)]aDMan(1→6)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROB-801
G41	N1074	M5		aDMan(1→6)[aDMan(1→3)]aDMan(1→6) [aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROB-1074
G42	N1098	A2		bDGlcNAc(1→2)aDMan(1→6) [bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROB-1098
G43	N1134	FA3		bDGlcNAc(1→6)[bDGlcNAc(1→2)]aDMan(1→6) [bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)[aLFuc(1→6)]bDGlcNAc(1→)PROB-1134
G44	N1158	FA2G2S1		aDNeu5Ac(2→6)bDGal(1→4)bDGlcNAc(1→2)aDMan(1→6) [bDGal(1→4)bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4) [aLFuc(1→6)]bDGlcNAc(1→)PROB-1158
G45	N1173	FA4		bDGlcNAc(1→6)[bDGlcNAc(1→2)]aDMan(1→6)[bDGlcNAc(1→4) [bDGlcNAc(1→2)]aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)[aLFuc(1→6)]bDGlcNAc(1→)PROB-1173
G46	N1194	FA4G4S1		aDNeu5Ac(2→6)bDGal(1→4)bDGlcNAc(1→6)[bDGal(1→4)bDGlcNAc(1→2)]aDMan(1→6) [bDGal(1→4)bDGlcNAc(1→4)[bDGal(1→4)bDGlcNAc(1→2)]aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4) [aLFuc(1→6)]bDGlcNAc(1→)PROB-1194
G47	T323	O-glycan		aDNeu5Ac(2→3)bDGal(1→3)[aDNeu5Ac(2→6)]aDGalNAc(1→)PROB-323

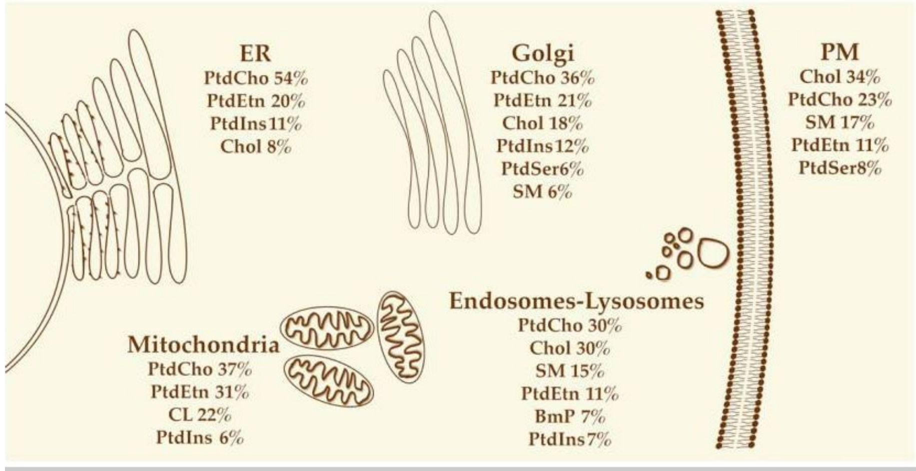
CHAIN C



#	SARS-CoV-2 sequon	TYPE	STRUCTURE	SEQUENCE
G48	N17	FA3		bDGlcNAc(1→6)[bDGlcNAc(1→2)]aDMan(1→6) [bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)[aLFuc(1→6)]bDGlcNAc(1→)PROC-17
G49	N61	M5		aDMan(1→6)[aDMan(1→3)]aDMan(1→6) [aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROC-61
G50	N74	A2		bDGlcNAc(1→2)aDMan(1→6) [bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROC-74
G51	N122	M5		aDMan(1→6)[aDMan(1→3)]aDMan(1→6) [aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROC-122
G52	N149	FA2		bDGlcNAc(1→2)aDMan(1→6)[bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4) [aLFuc(1→6)]bDGlcNAc(1→)PROC-149
G53	N165	FA2G2S1		aDNeu5Ac(2→6)bDGal(1→4)bDGlcNAc(1→2)aDMan(1→6) [bDGal(1→4)bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4) [aLFuc(1→6)]bDGlcNAc(1→)PROC-165
G54	N234	M9		aDMan(1→2)aDMan(1→6)[aDMan(1→2)aDMan(1→3)]aDMan(1→6) [aDMan(1→2)aDMan(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROC-234
G55	N282	A2		bDGlcNAc(1→2)aDMan(1→6) [bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROC-282
G56	N331	FA3G3S1		aDNeu5Ac(2→6)bDGal(1→4)bDGlcNAc(1→2)aDMan(1→3)[bDGal(1→4)bDGlcNAc(1→6) [bDGal(1→4)bDGlcNAc(1→2)]aDMan(1→6)]bDMan(1→4)bDGlcNAc(1→4) [aLFuc(1→6)]bDGlcNAc(1→)PROC-331
G57	N343	FA2		bDGlcNAc(1→2)aDMan(1→6)[bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4) [aLFuc(1→6)]bDGlcNAc(1→)PROC-343
G58	N603	M5		aDMan(1→6)[aDMan(1→3)]aDMan(1→6) [aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROC-603
G59	N616	FA2		bDGlcNAc(1→2)aDMan(1→6)[bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4) [aLFuc(1→6)]bDGlcNAc(1→)PROC-616
G60	N657	Hybrid G1		bDGal(1→4)bDGlcNAc(1→2)aDMan(1→3)[aDMan(1→6) [aDMan(1→3)]aDMan(1→6)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROC-657
G61	N709	M5		aDMan(1→6)[aDMan(1→3)]aDMan(1→6) [aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROC-709
G62	N717	M6		aDMan(1→6)[aDMan(1→3)]aDMan(1→6) [aDMan(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROC-717
G63	N801	M5		aDMan(1→6)[aDMan(1→3)]aDMan(1→6) [aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROC-801
G64	N1074	M5		aDMan(1→6)[aDMan(1→3)]aDMan(1→6) [aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROC-1074
G65	N1098	Hybrid G1S1		aDNeu5Ac(2→6)bDGal(1→4)bDGlcNAc(1→2)aDMan(1→3)[aDMan(1→6) [aDMan(1→3)]aDMan(1→6)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROC-1098
G66	N1134	FA2		bDGlcNAc(1→2)aDMan(1→6)[bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4) [aLFuc(1→6)]bDGlcNAc(1→)PROC-1134
G67	N1158	A2		bDGlcNAc(1→2)aDMan(1→6) [bDGlcNAc(1→2)aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)bDGlcNAc(1→)PROC-1158
G68	N1173	FA4		bDGlcNAc(1→6)[bDGlcNAc(1→2)]aDMan(1→6)[bDGlcNAc(1→4) [bDGlcNAc(1→2)]aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4)[aLFuc(1→6)]bDGlcNAc(1→)PROC-1173
G69	N1194	FA4G4S1		aDNeu5Ac(2→6)bDGal(1→4)bDGlcNAc(1→6)[bDGal(1→4)bDGlcNAc(1→2)]aDMan(1→6) [bDGal(1→4)bDGlcNAc(1→4)[bDGal(1→4)bDGlcNAc(1→2)]aDMan(1→3)]bDMan(1→4)bDGlcNAc(1→4) [aLFuc(1→6)]bDGlcNAc(1→)PROC-1194
G70	T323	O-glycan		bDGal(1→3)aDGalNAc(1→)PROC-323

Now, how about that membrane?





POPC	47%
POPE	20%
CHL	15%
POPI	11%
POPS	7%

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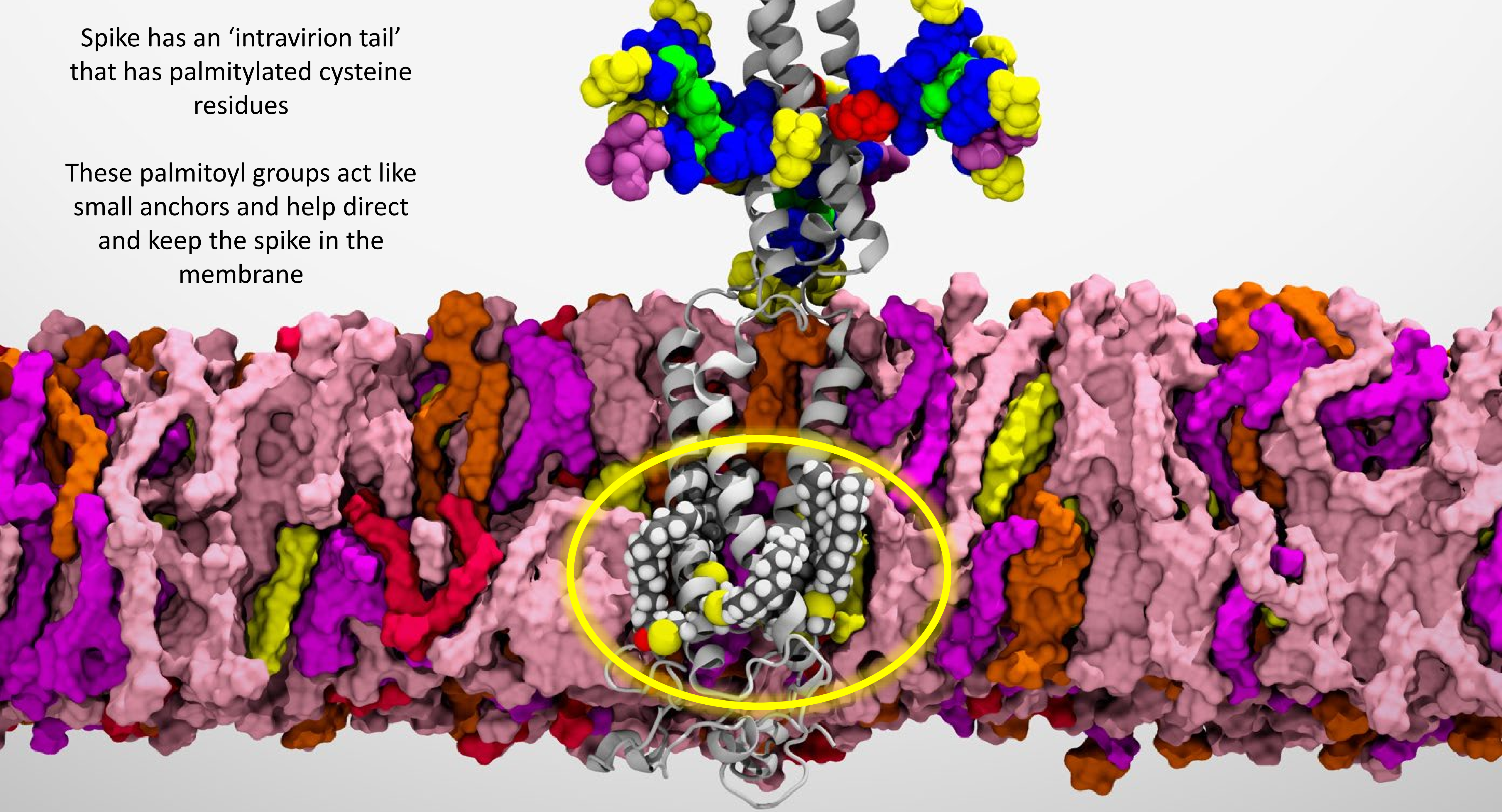
Membrane Lipid Composition: Effect on Membrane and Organelle Structure, Function and Compartmentalization and Therapeutic Avenues

Doralicia Casares,[1,2] Pablo V. Escribá,[1,2] and Catalina Ana Rosselló[1,2,*]

POPC (16:0-18:1): 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine
CHL: cholesterol
POPI (16:0-18:1): 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoinositol
POPE (16:0-18:1): 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoethanolamine
POPS (16:0-18:1): 1-palmitoyl-2-oleoyl-sn-glycero-3-phospho-L-serine

Spike has an ‘intravirion tail’ that has palmitylated cysteine residues

These palmitoyl groups act like small anchors and help direct and keep the spike in the membrane



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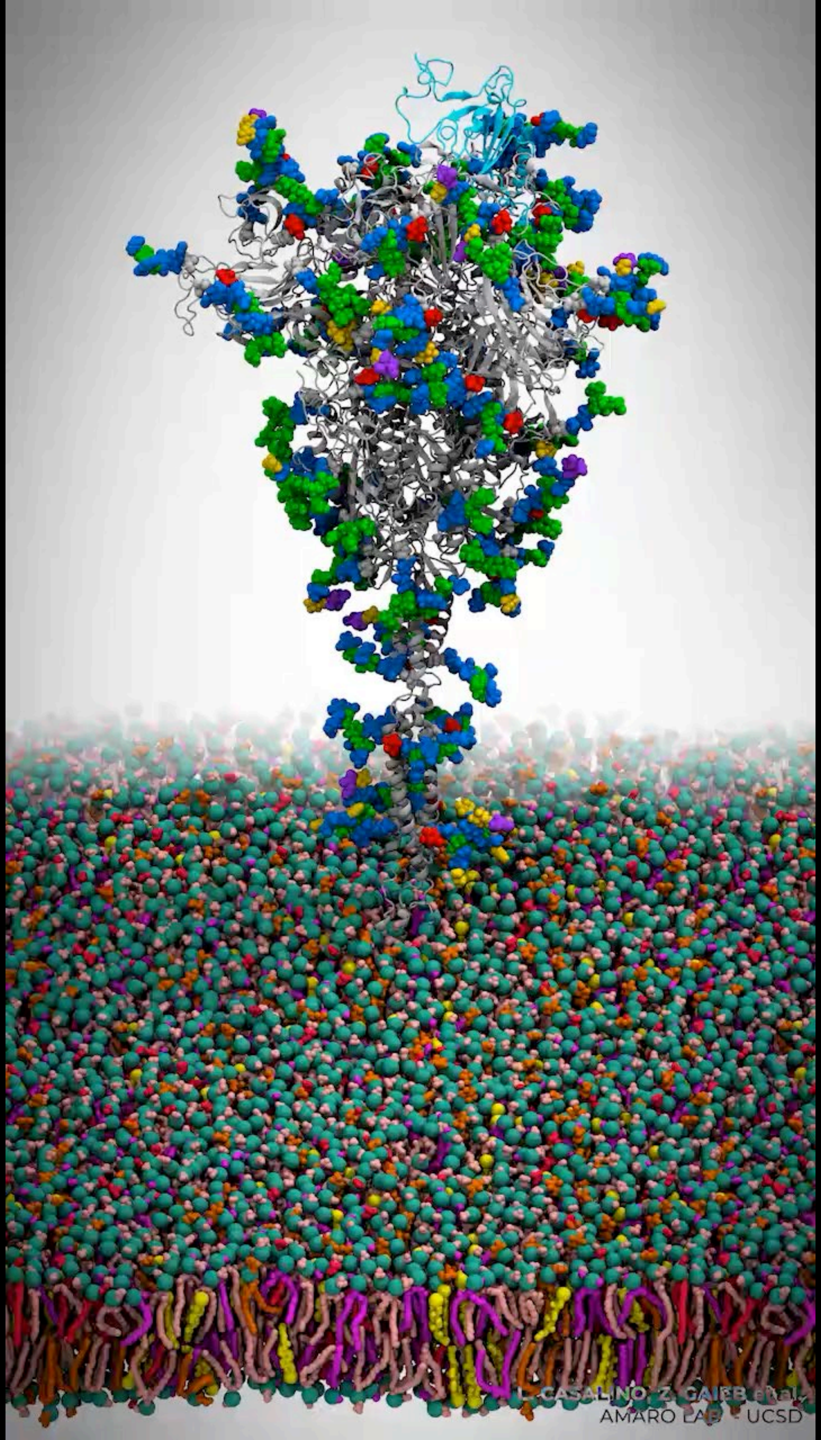
AMARO LAB - UCSD



RBD-up (Open)

RBDs-down (Closed)

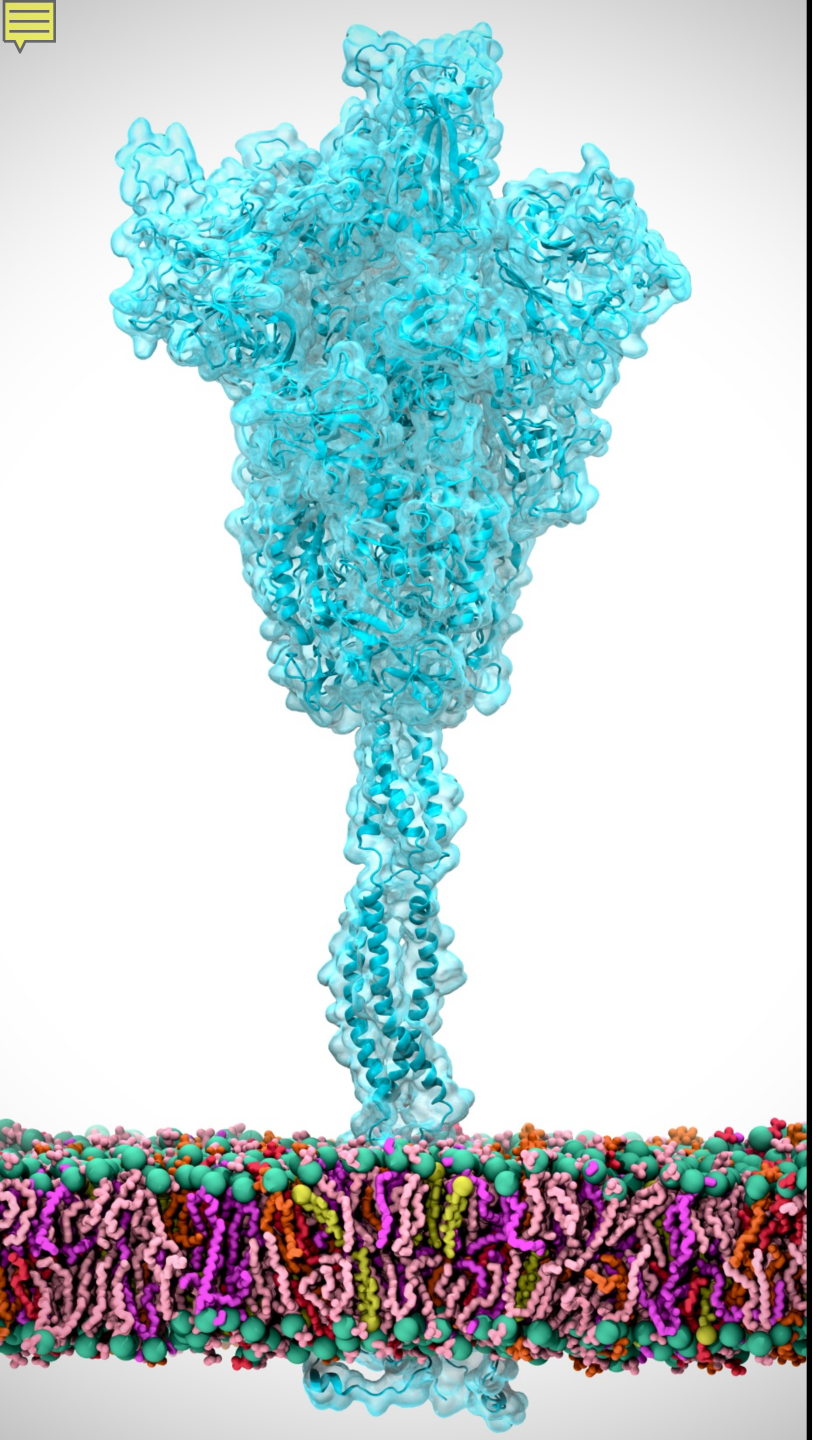
~1.7 million atoms

Charmm36 force field

NAMD2 on TACC Frontera

~ 60 ns/day on 256 nodes

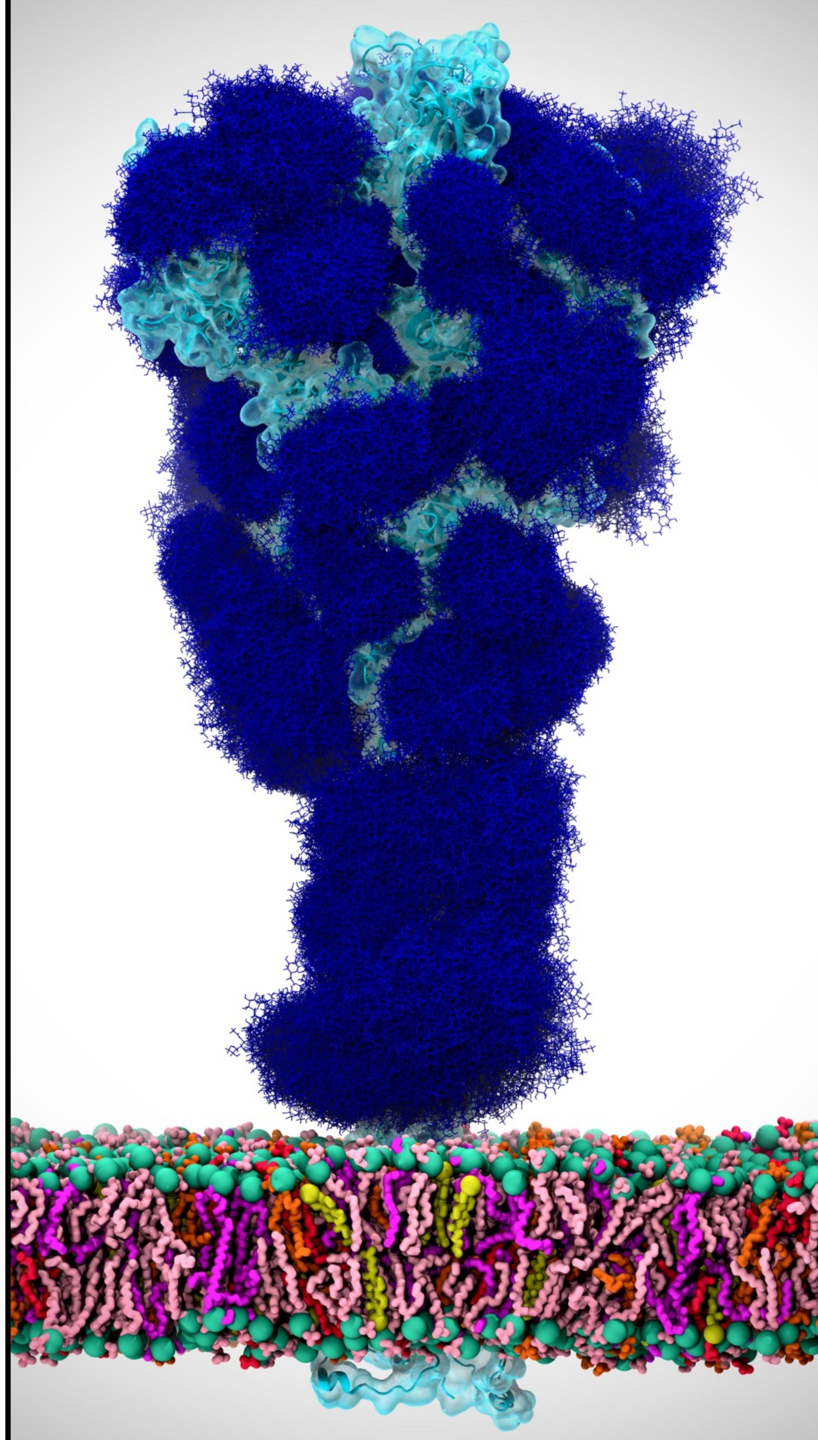
> 4 microseconds for each system



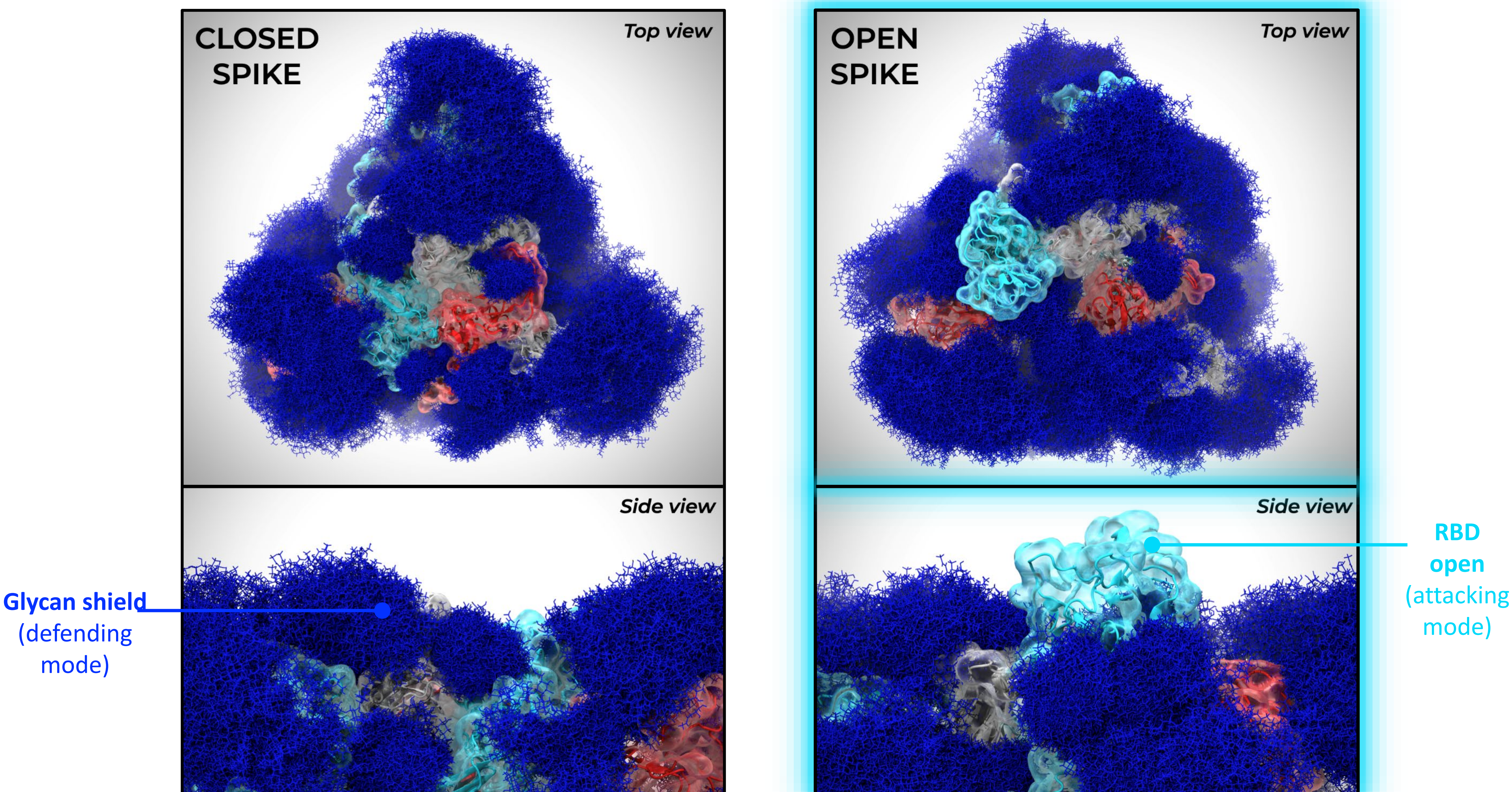
The glycan shield

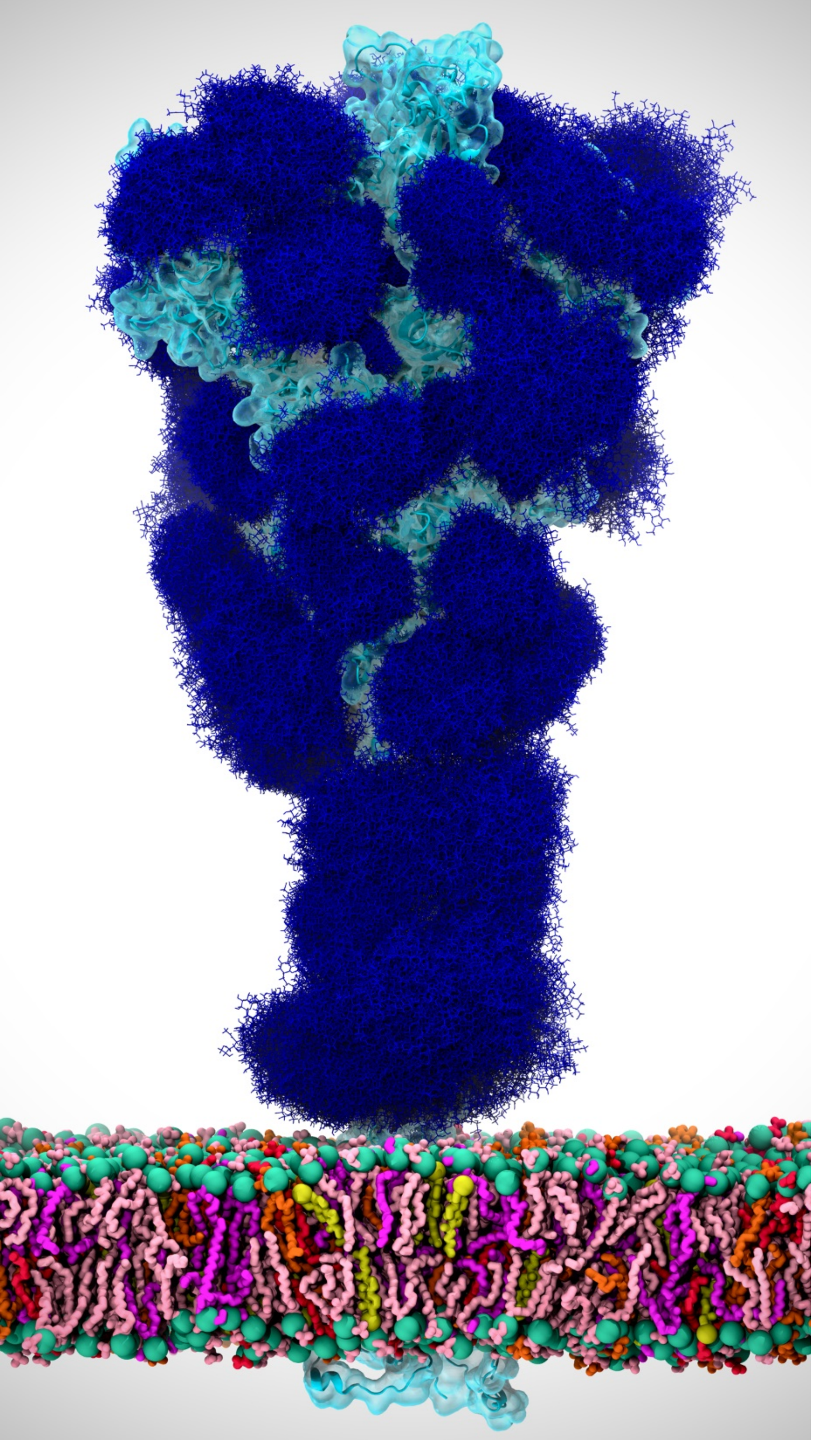
Simulations showed us
the **glycan shield**,
a sugary coat that
experiments cannot see

This is crucial information
for vaccine & drug design

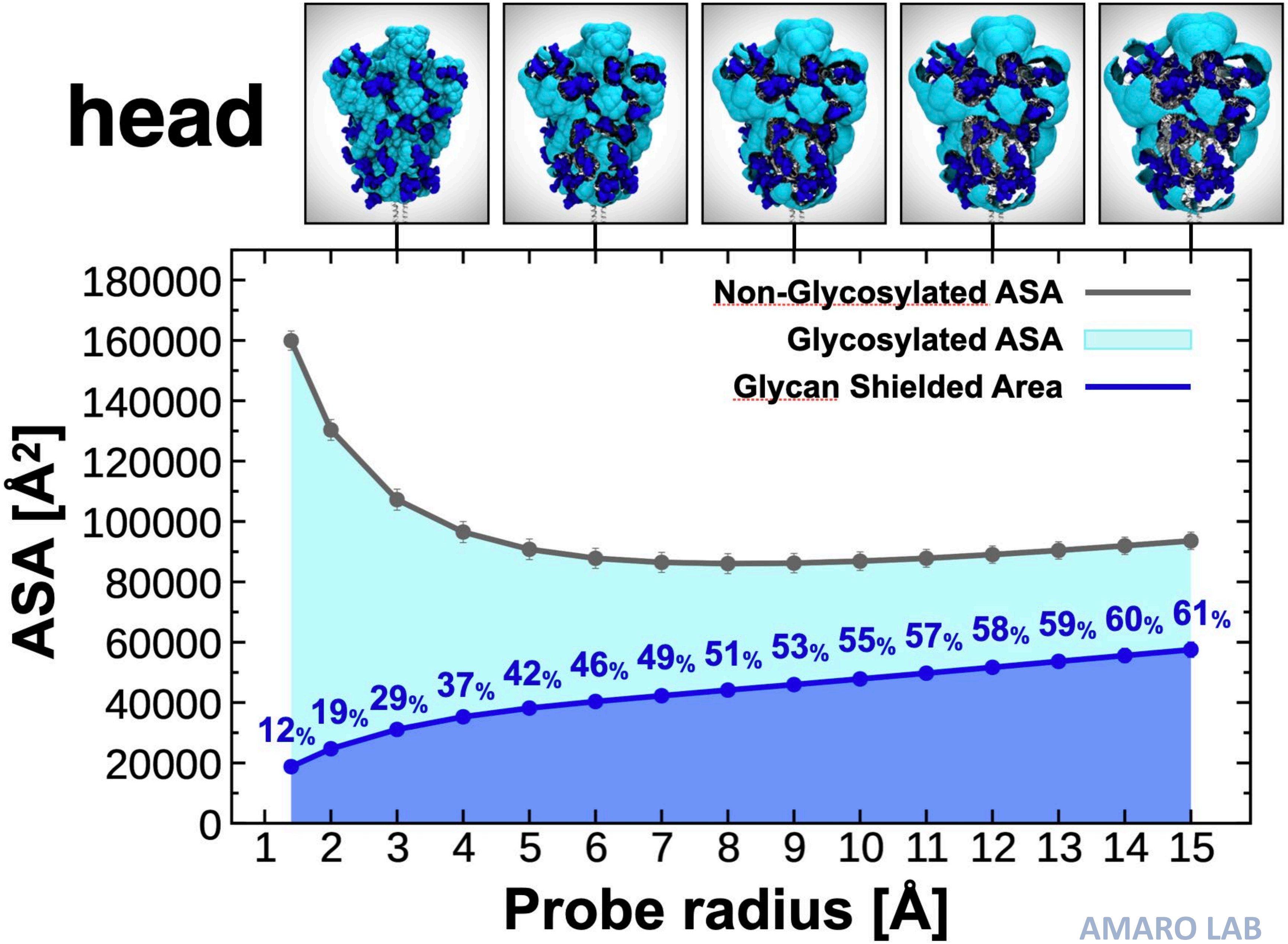


Simulations showed WHY the spike opens and closes





head



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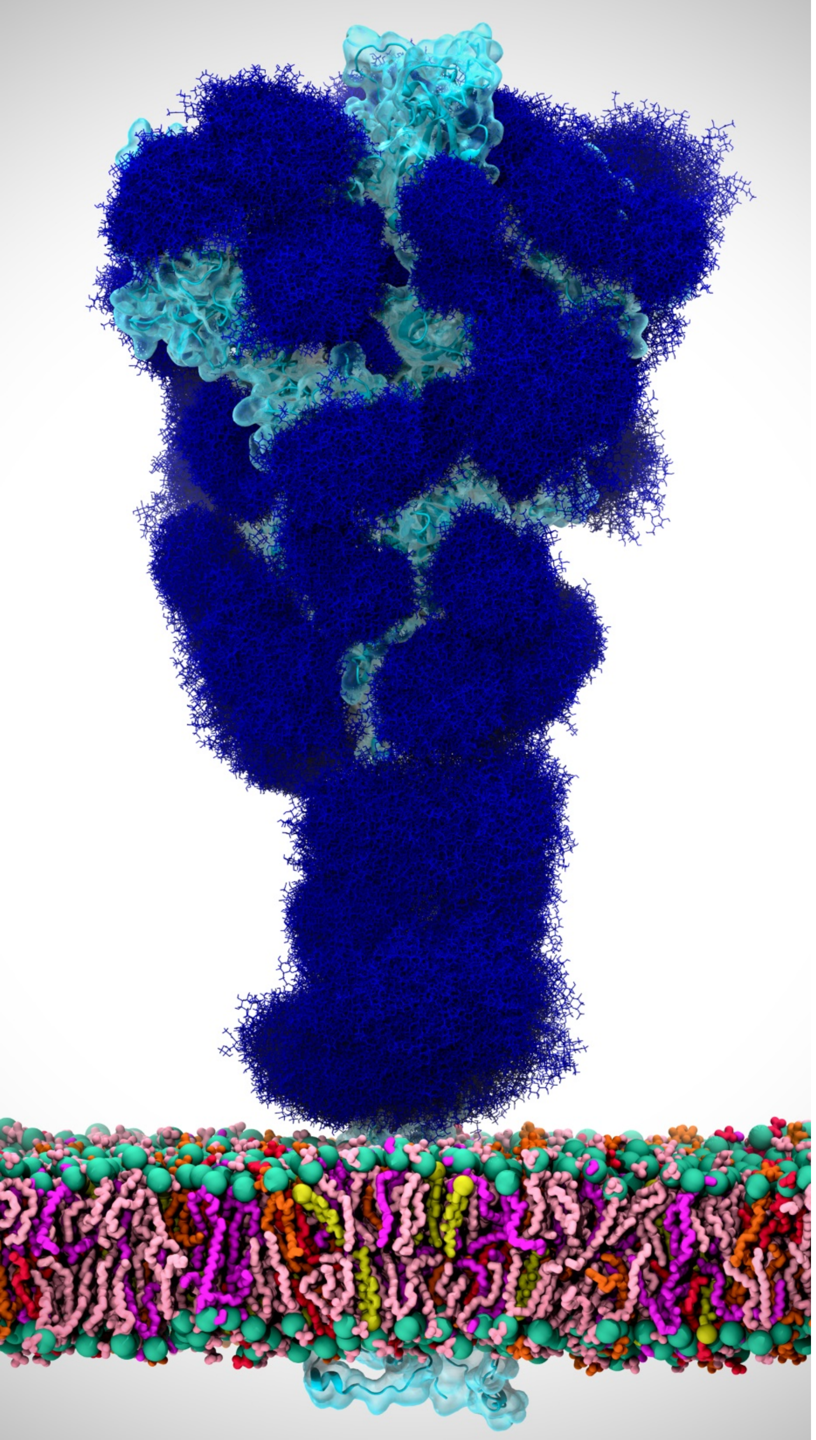
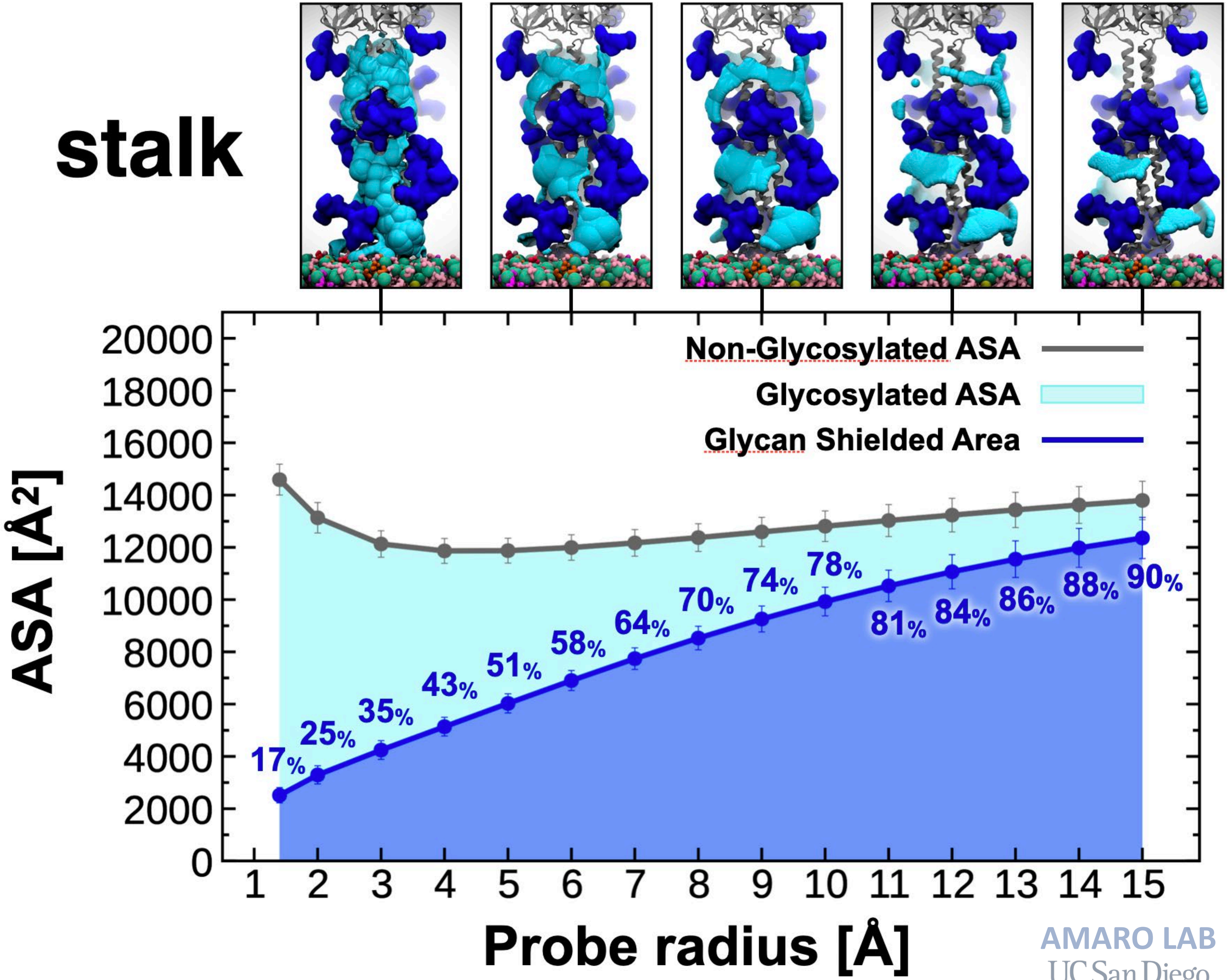


stalk



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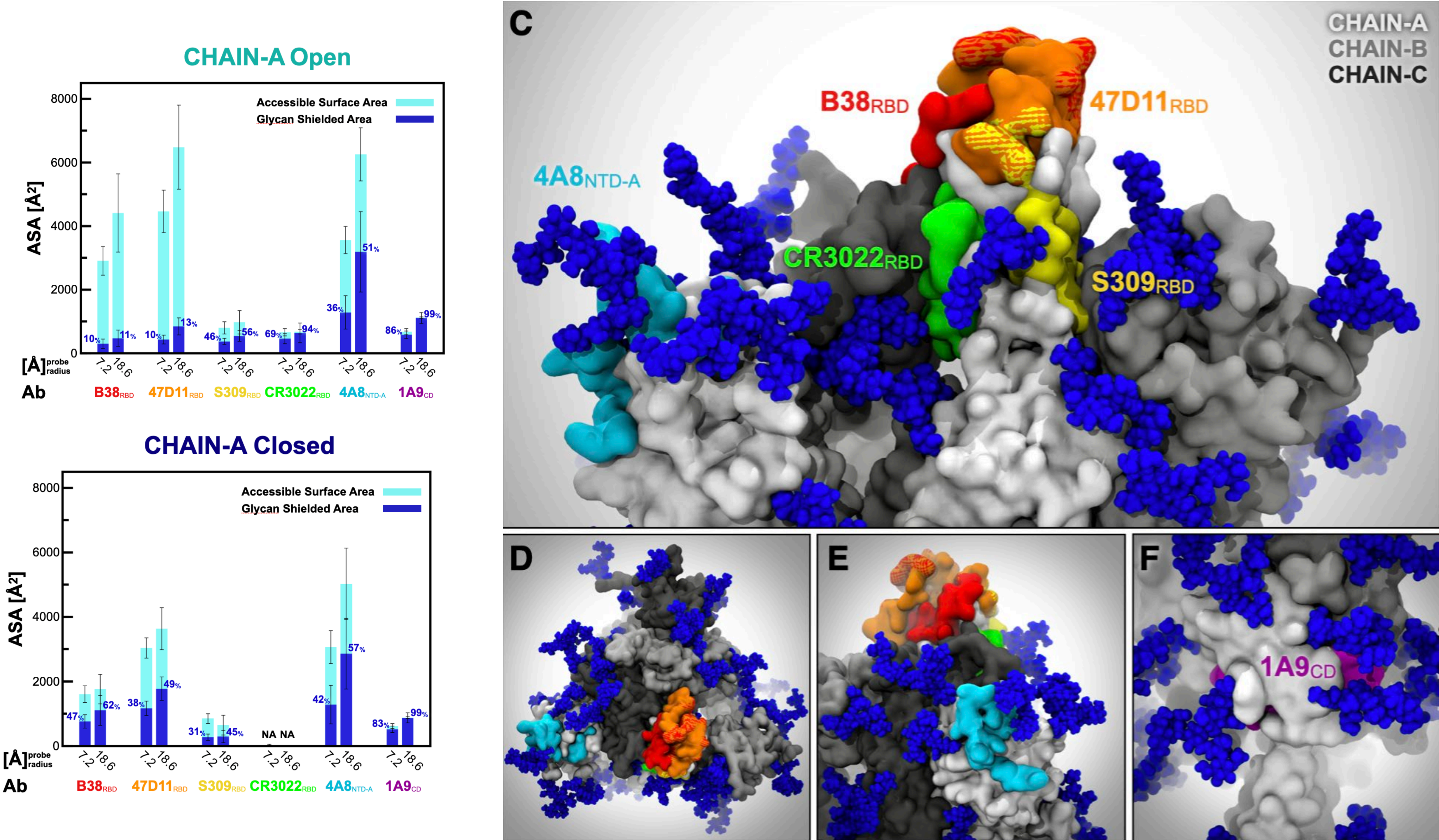
CHAIN-A Open
ASA [Å²]
Accessible Surface Area
Glycan Shielded Area
8000
6000
4000
2000
0
10%
11%
10%
13%
46%
56%
69%
94%
36%
51%
86%
99%
[Å] probe radius
7.2 18.6
Ab
B38RBD
47D11RBD
S309RBD
CR3022RBD
4A8NTD-A
1A9CD
CHAIN-A Closed
ASA [Å²]
Accessible Surface Area
Glycan Shielded Area
8000
6000
4000
2000
0
47%
62%
38%
49%
31%
45%
NA NA
42%
57%
83%
99%
[Å] probe radius
7.2 18.6
Ab
B38RBD
47D11RBD
S309RBD
CR3022RBD
4A8NTD-A
1A9CD
C
CHAIN-A
CHAIN-B
CHAIN-C
B38RBD
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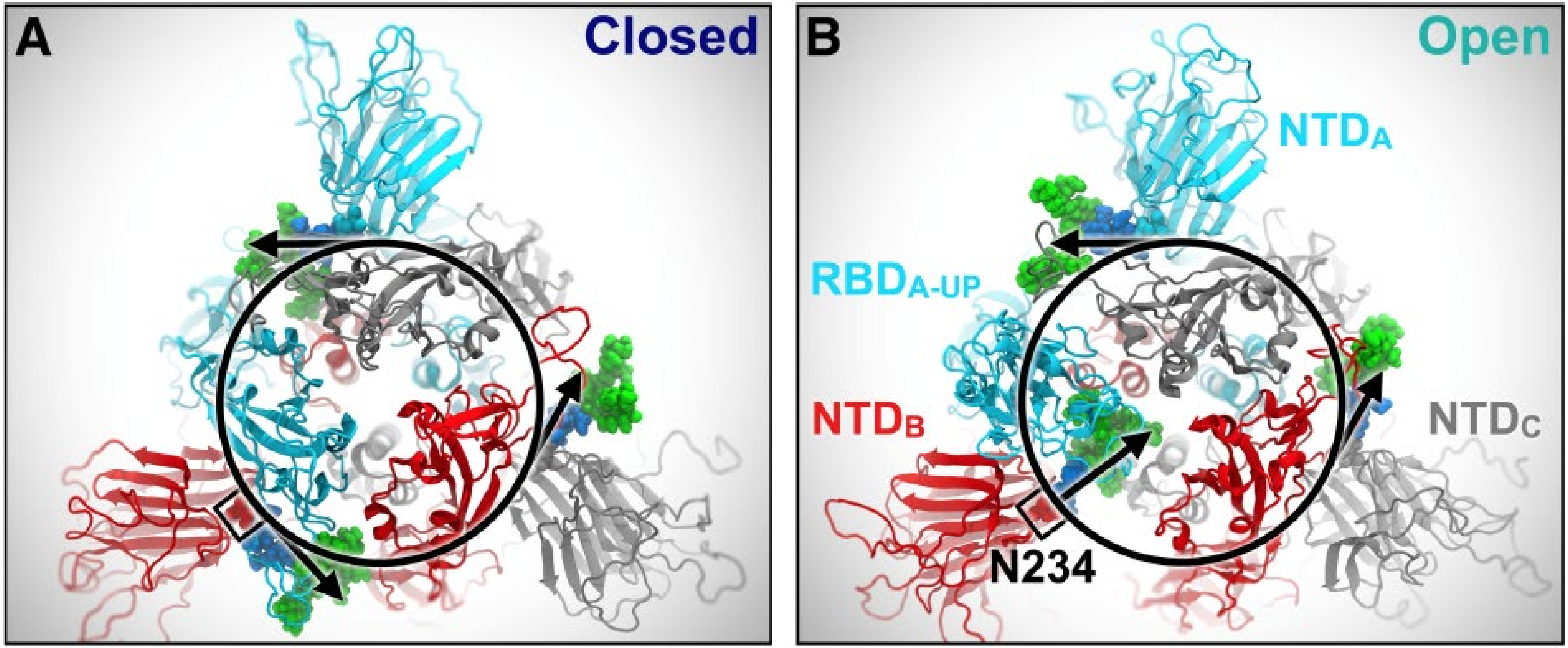
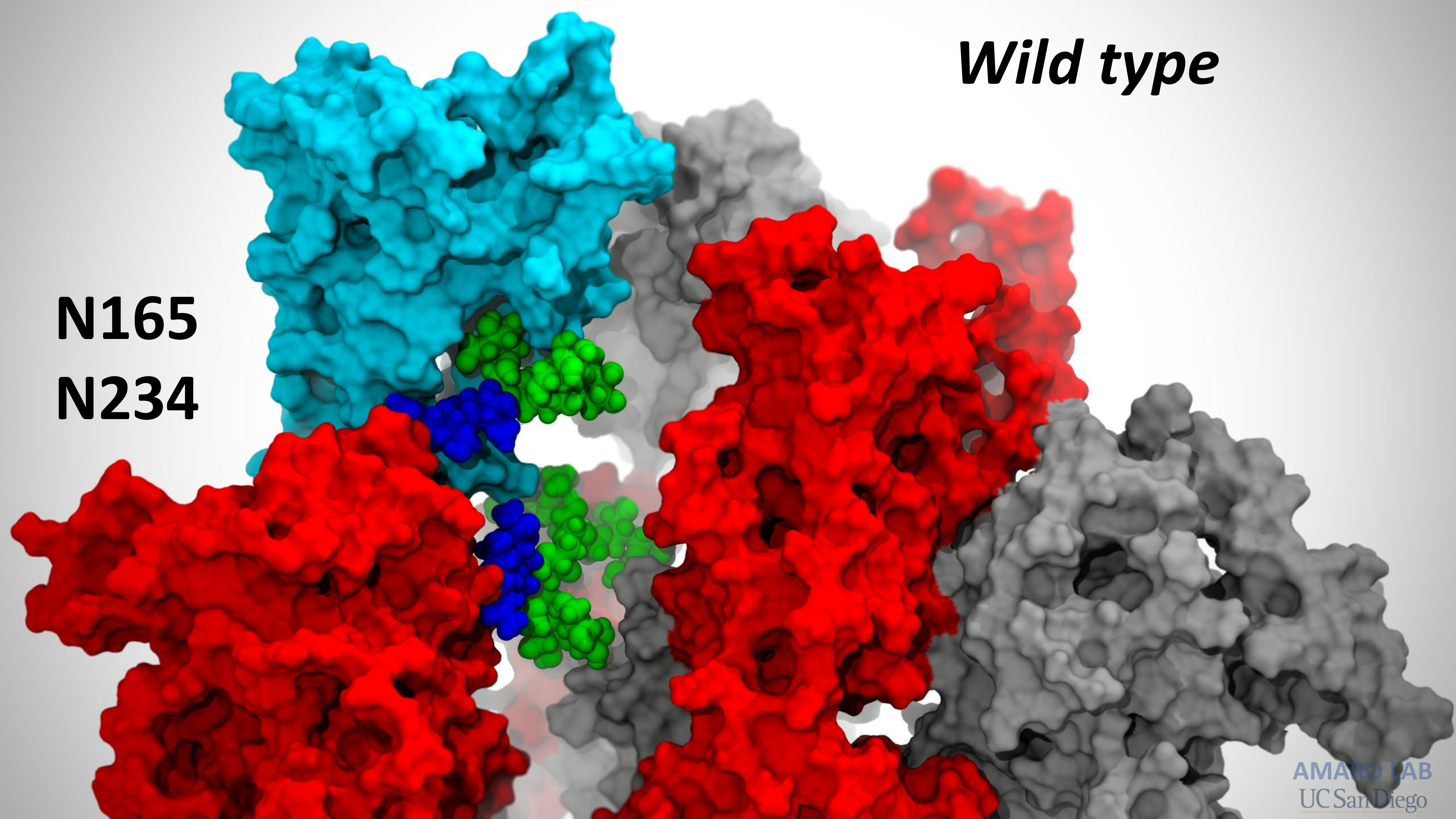
4A8NTD-A
CR3022RBD
S309RBD
D
E
F
1A9CD

Glycans: A Function Beyond Shielding?



Elisa Fadda, Maynooth University

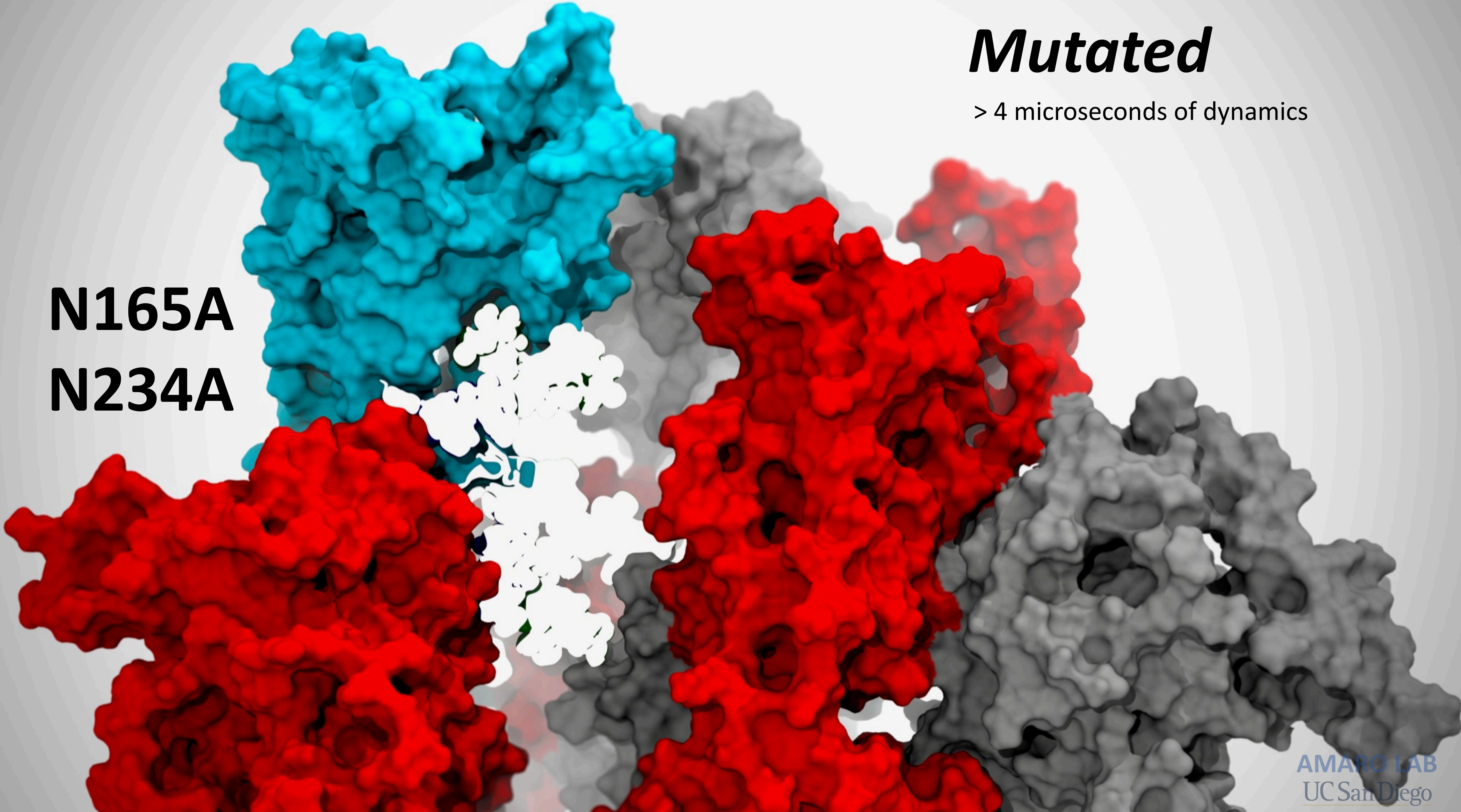


Wild type
N165
N234
AMARO LAB
UC San Diego

Mutated

> 4 microseconds of dynamics

N165A
N234A



AMARO LAB
UC San Diego

McLellan Lab (UT Austin) Collaboration

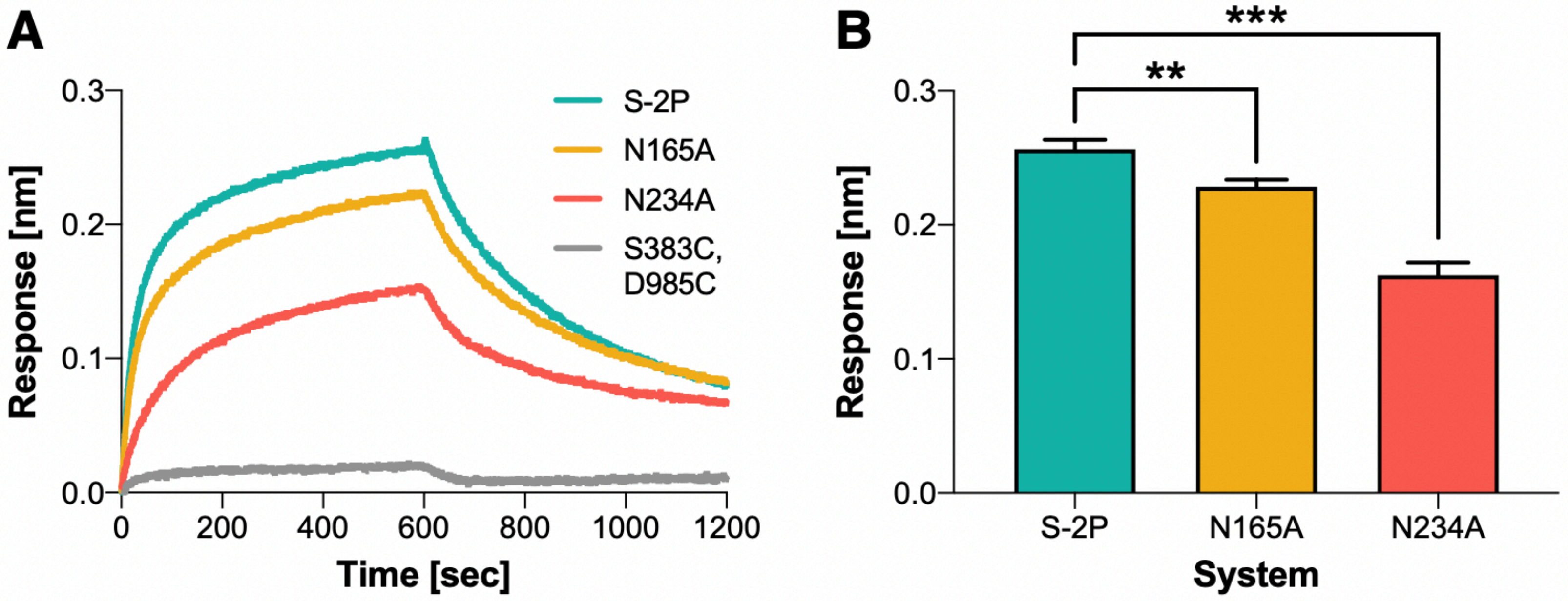
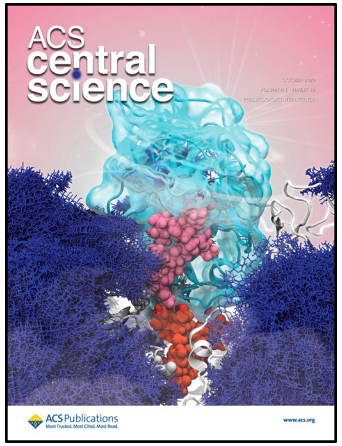


Figure 4. N234A and N165A mutations reduce RBD binding to ACE2. (**A**) Biolayer interferometry sensorgrams showing binding of ACE2 to spike variants. (**B**) Binding responses for biolayer interferometry measurements of ACE2 binding to spike variants. Data are shown as mean ± S.D. from 3 independent experiments. Asterisks represent statistical significance (Student's t test; *0.01<p<0.05, **0.001>p>0.01, ***0.0001<p<0.001).

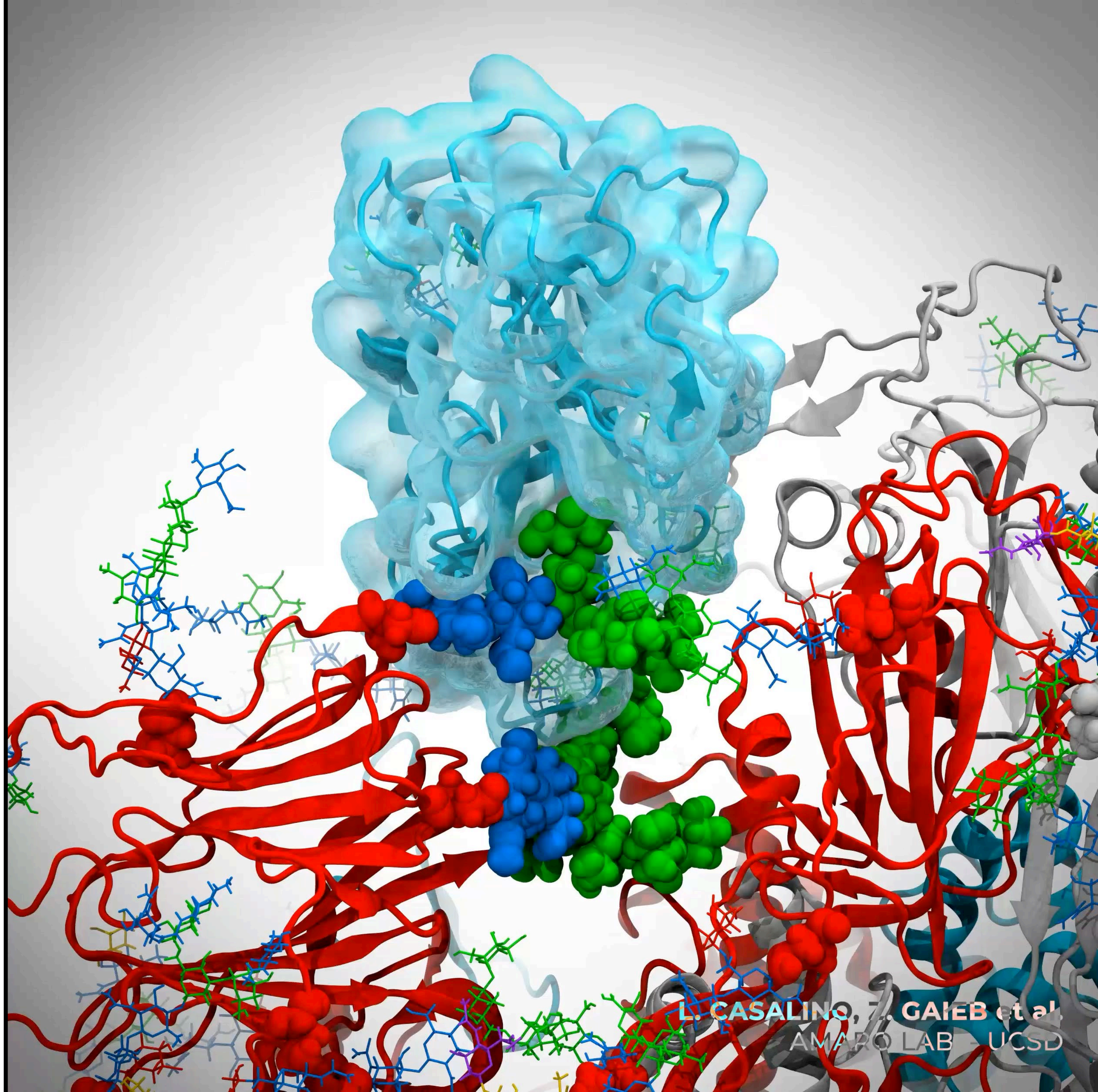
BEYOND shielding...

Simulations established a structural role for glycans

- They act as part of the viral weaponry itself
- They "**lock & load**" the spike for infection



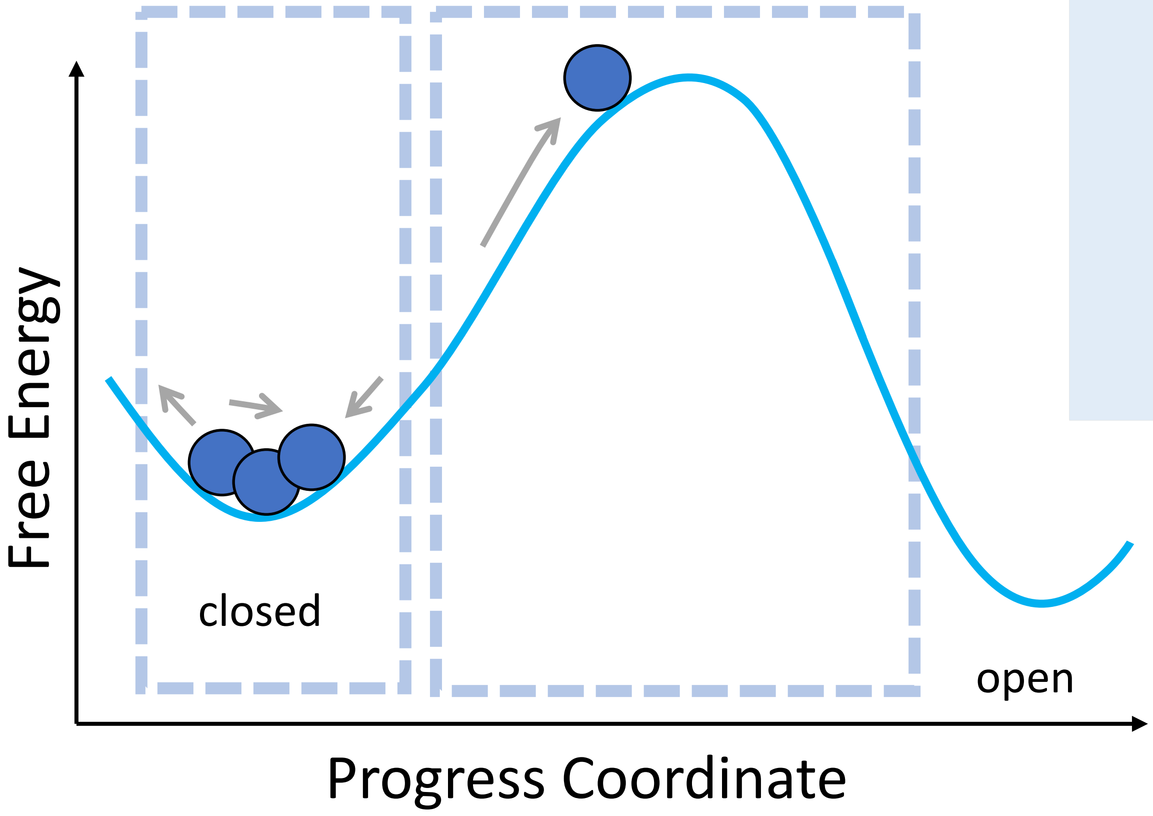
Casalino, Gaieb et al., *ACS Central Science* (2020)



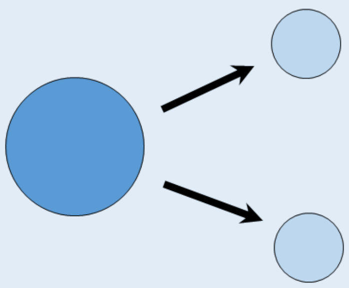
Standard MD simulations of spike opening could take years!

Weighted ensemble MD focuses on functional transitions

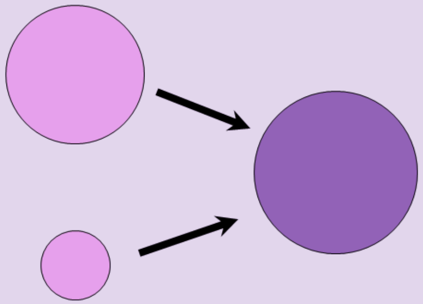
Too much time spent here... **Not enough time spent here.**



To enrich for success...



To save computing power...



Huber and Kim, *Biophys. Journal* (1996)
Zuckerman and Chong, *Ann. Rev. Biophys.* (2017)

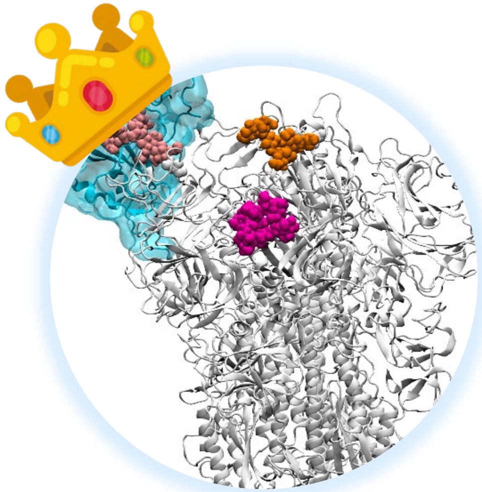
Generates **unbiased, continuous** pathways with **orders of magnitude less computing** than standard MD.

Efficiency scales exponentially with the free energy barrier.

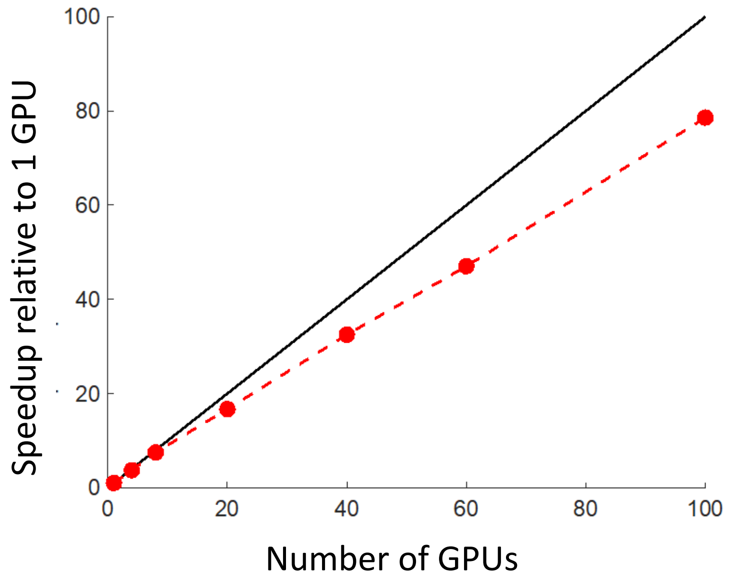
WESTPA

The Weighted Ensemble Simulation Toolkit with Parallelization and Analysis

Weighted ensemble MD is 13x to 127x more efficient than standard MD!



600K atoms



AMBER MD

TACC
TEXAS ADVANCED COMPUTING CENTER

100 NVIDIA V100 GPUs
on Longhorn

Zwier et. Al., *JCTC* (2015)

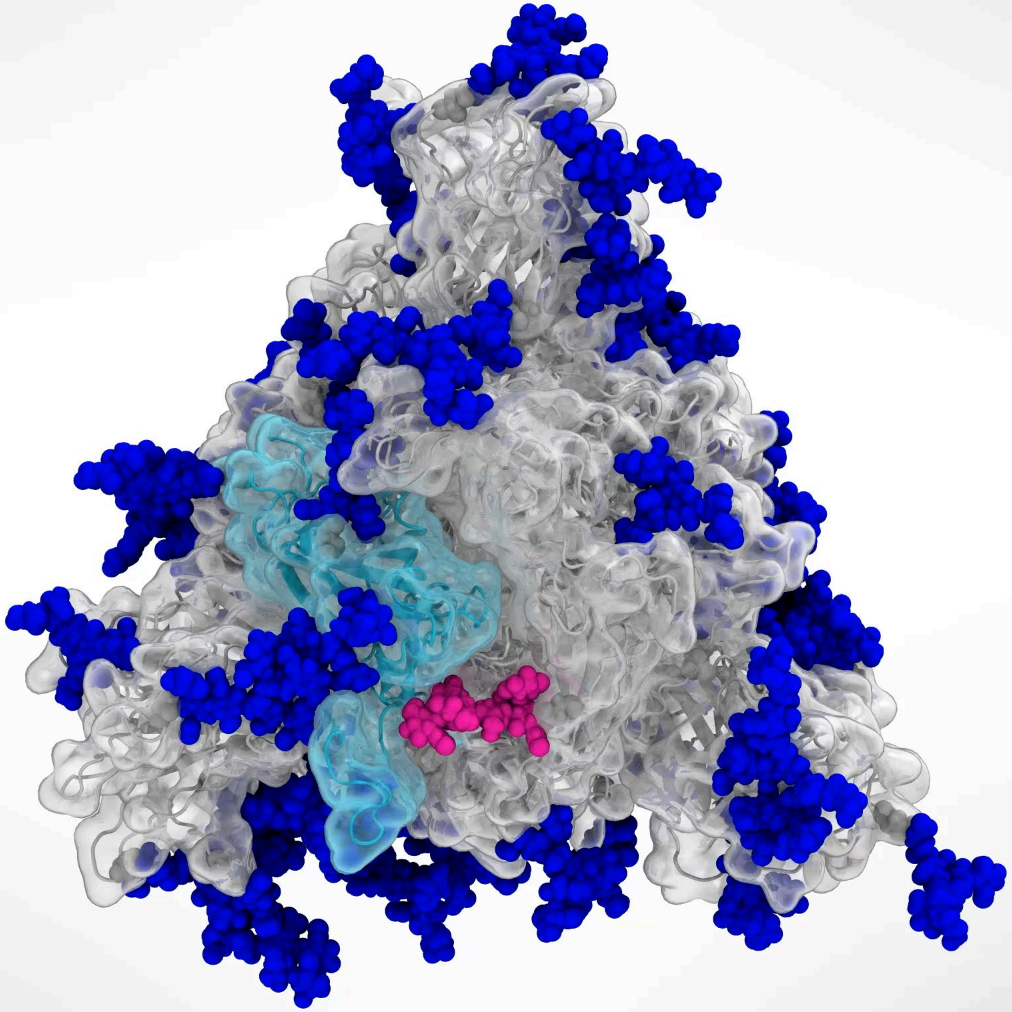
	Weighted Ensemble MD	**Standard MD**
Number of pathways	1193*	100
Wall-clock time	23 days	10 months to 8 years (μs to ms)
Total node-hours	13,800	180,000 to 1,752,000

*133 are independent (uncorrelated in time)

Chong Lab (U Pitt) Collaboration

Closed Spike

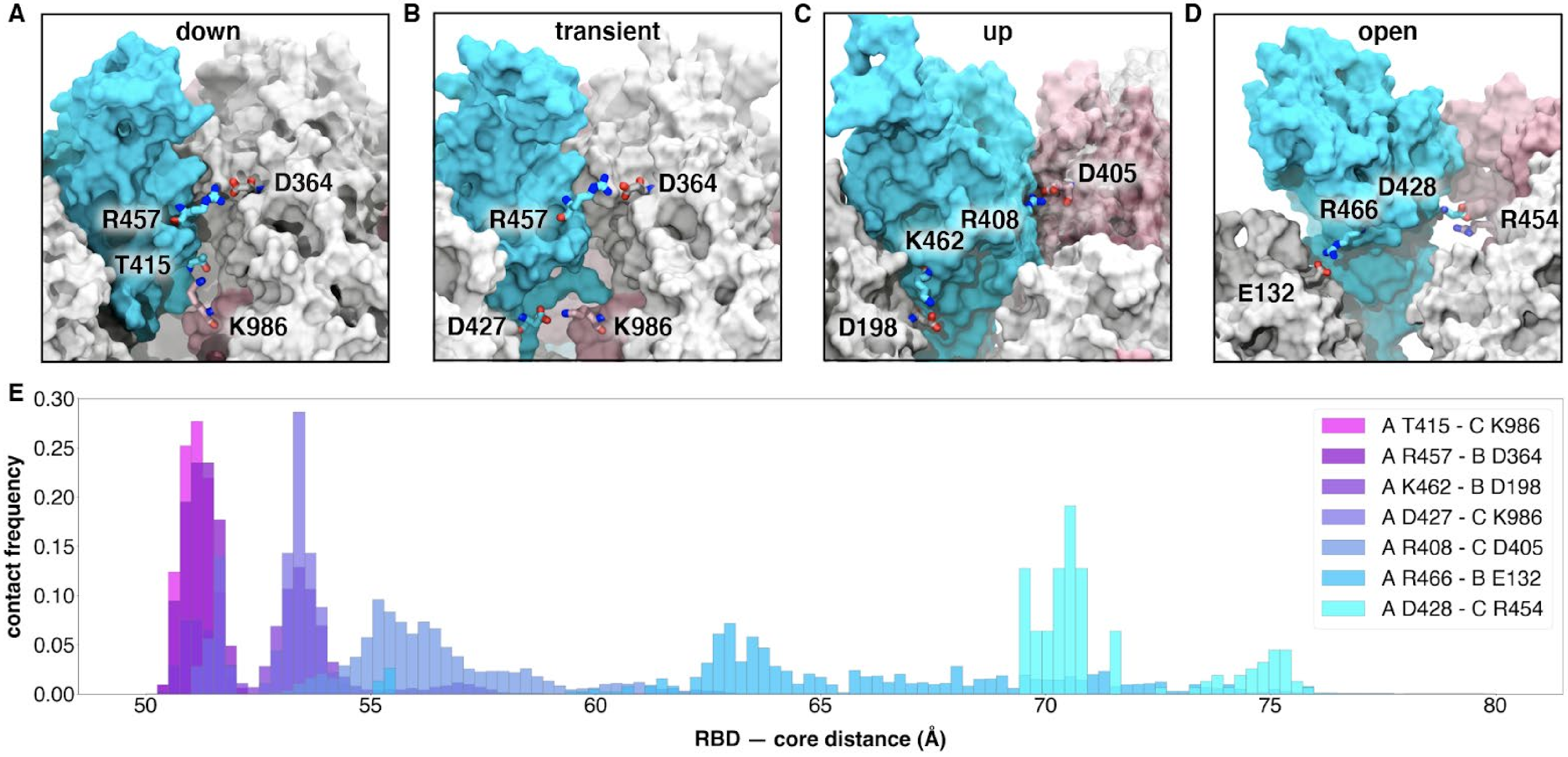
Top view



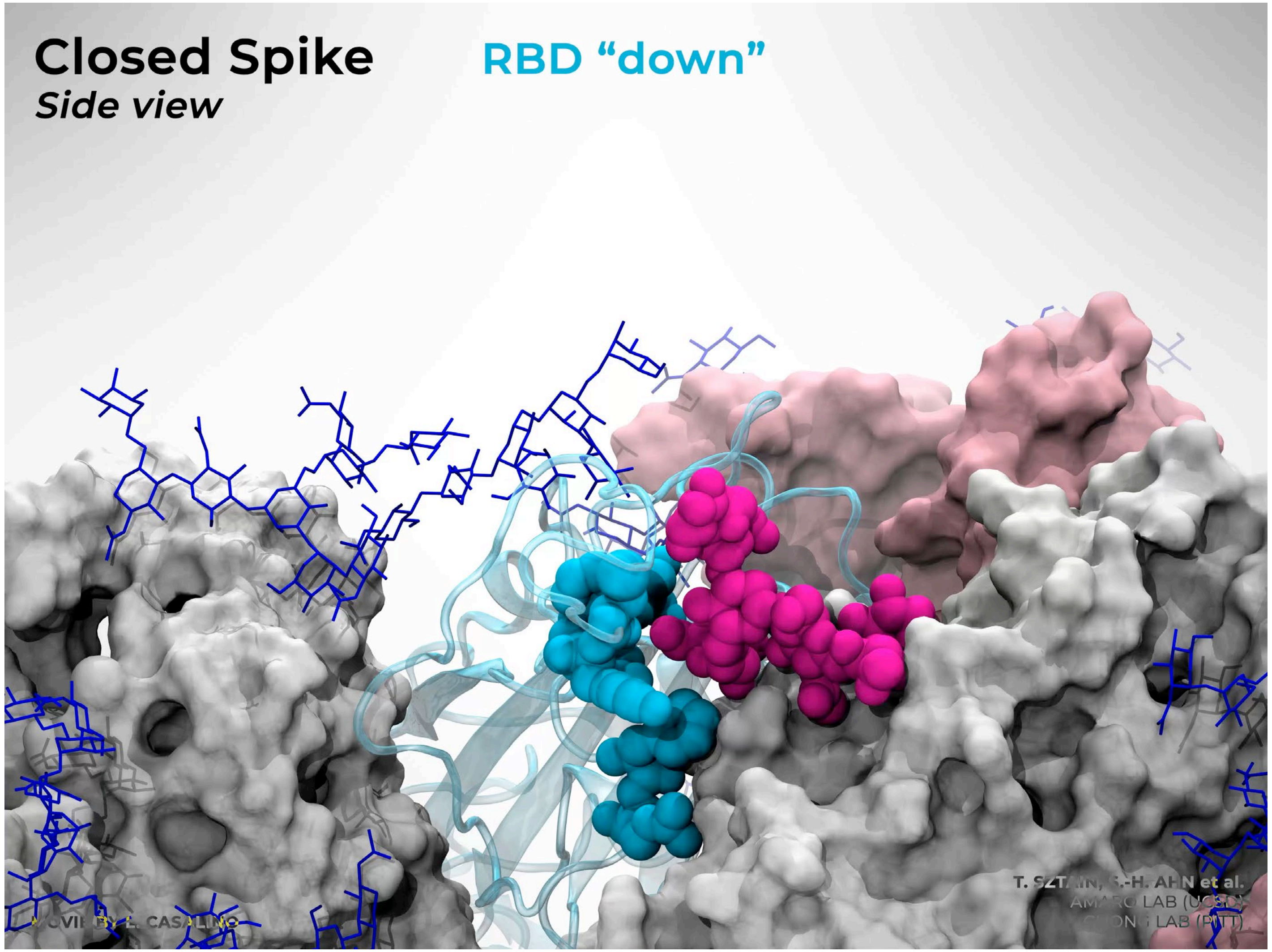
T. SZTAIN, S.-H. AHN et al.
AMARO LAB (UCSD)
CHONG LAB (PITT)

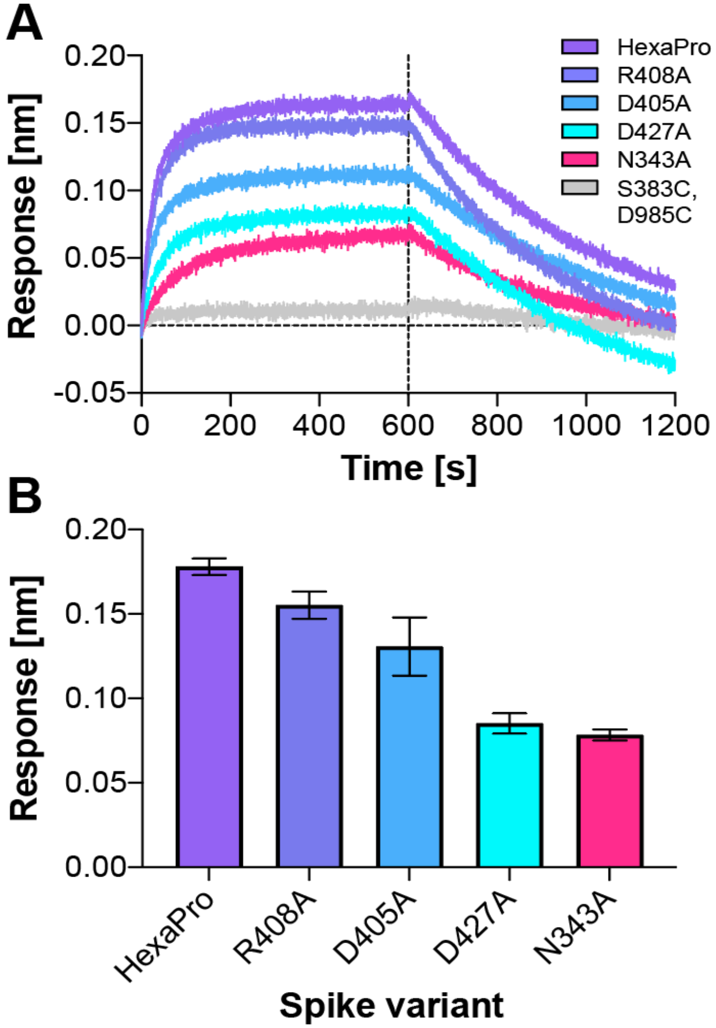
MOVIE BY L. CASALINO

Interactions along the opening pathway



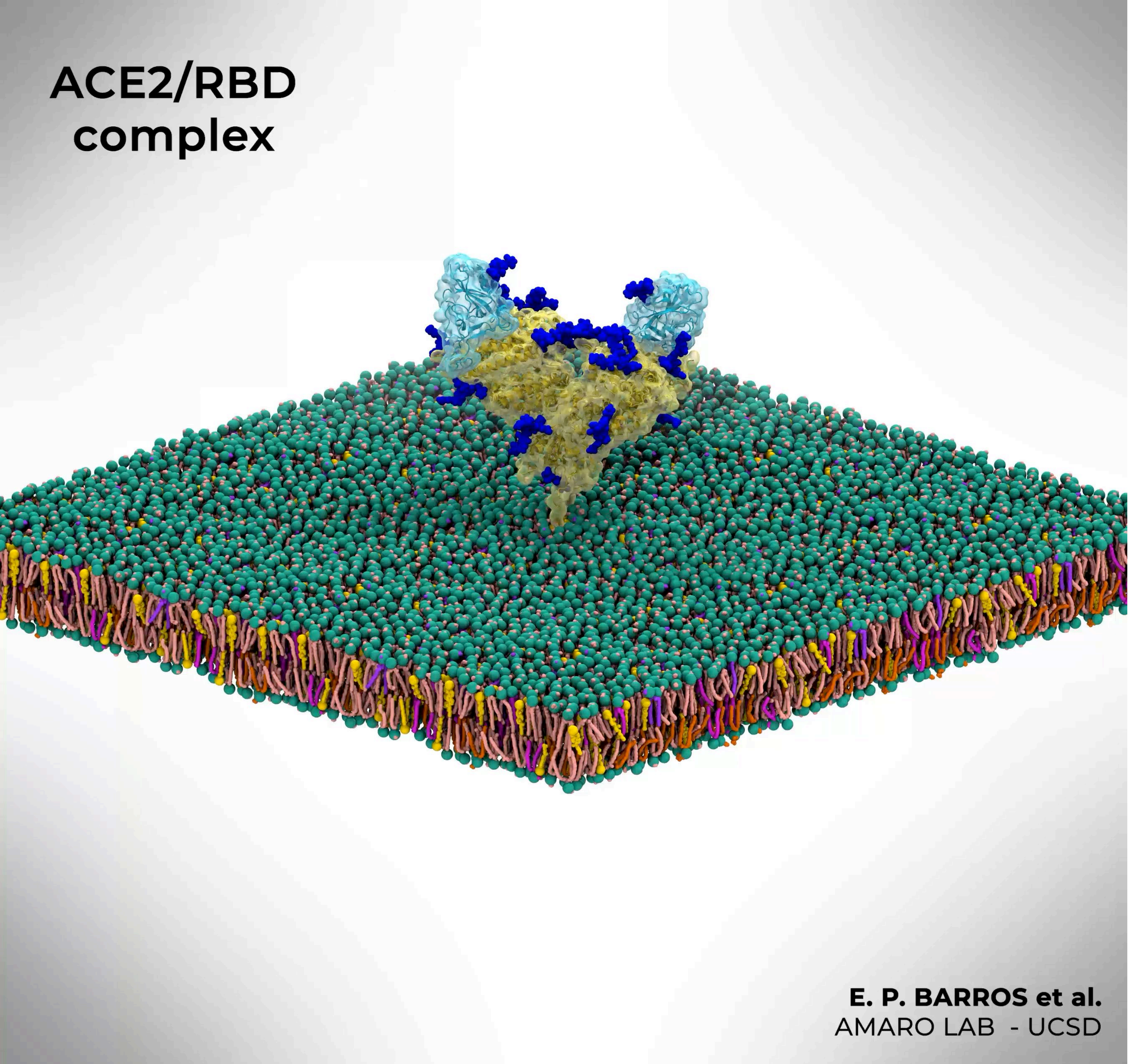
A glycan gate controls opening of SARS-CoV-2 spike





McLellan Lab (UT Austin) Collaboration

Sztain, Ahn, et al., bioRxiv (2021)

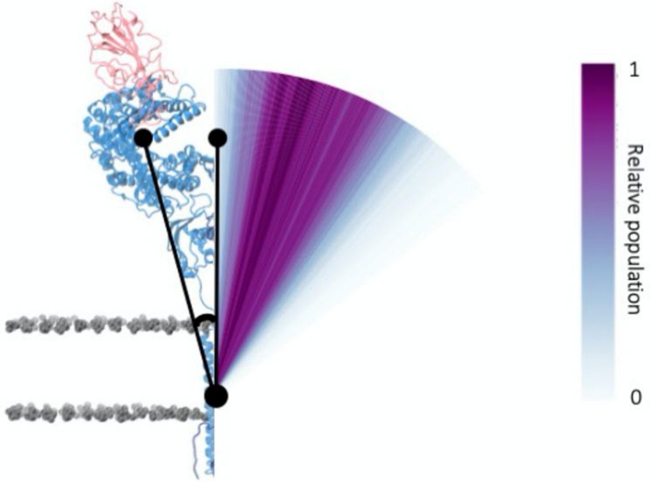


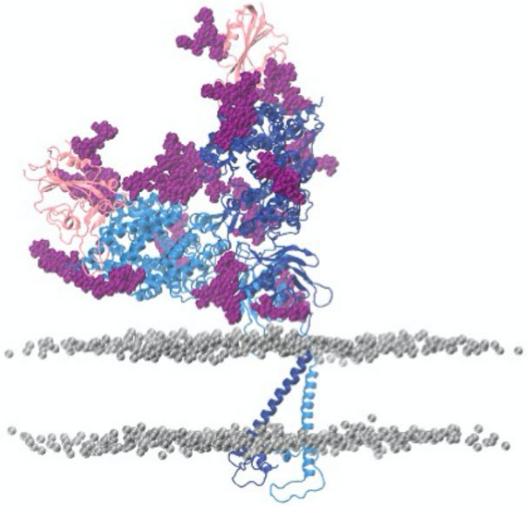
Biophysical Journal
Article

Biophysical Society

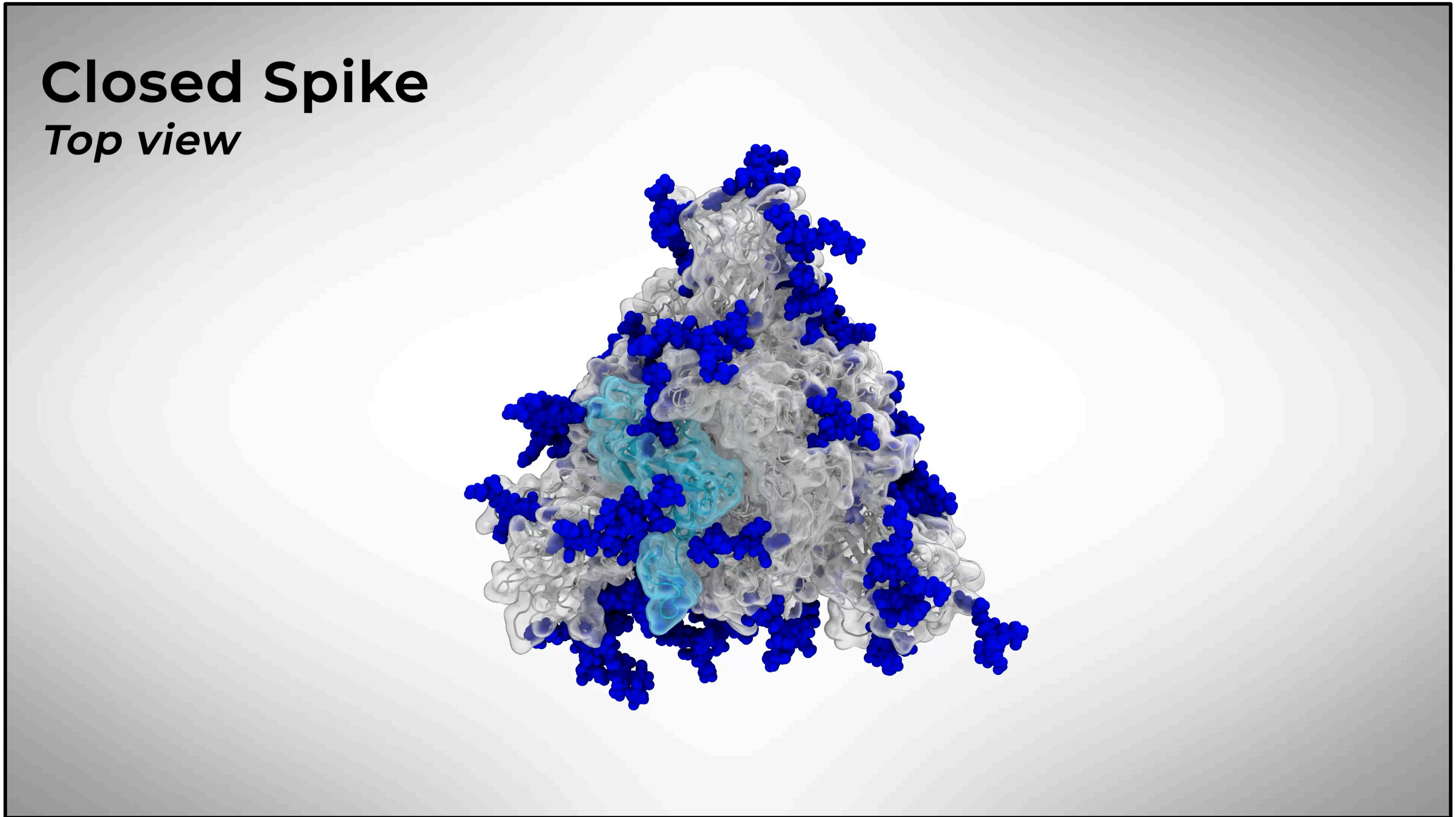
The Flexibility of ACE2 in the Context of SARS-CoV-2 Infection

Emilia P. Barros,[1] Lorenzo Casalino,[1] Zied Gaieb,[1] Abigail C. Dommer,[1] Yuzhang Wang,[2] Lucy Fallon,[2] Lauren Raguette,[2] Kellon Belfon,[2] Carlos Simmerling,[2,3] and Rommie E. Amaro[1,*]
[1]Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, California; [2]Department of Chemistry and [3]Laufer Center for Physical and Quantitative Biology, Stony Brook University, Stony Brook, New York

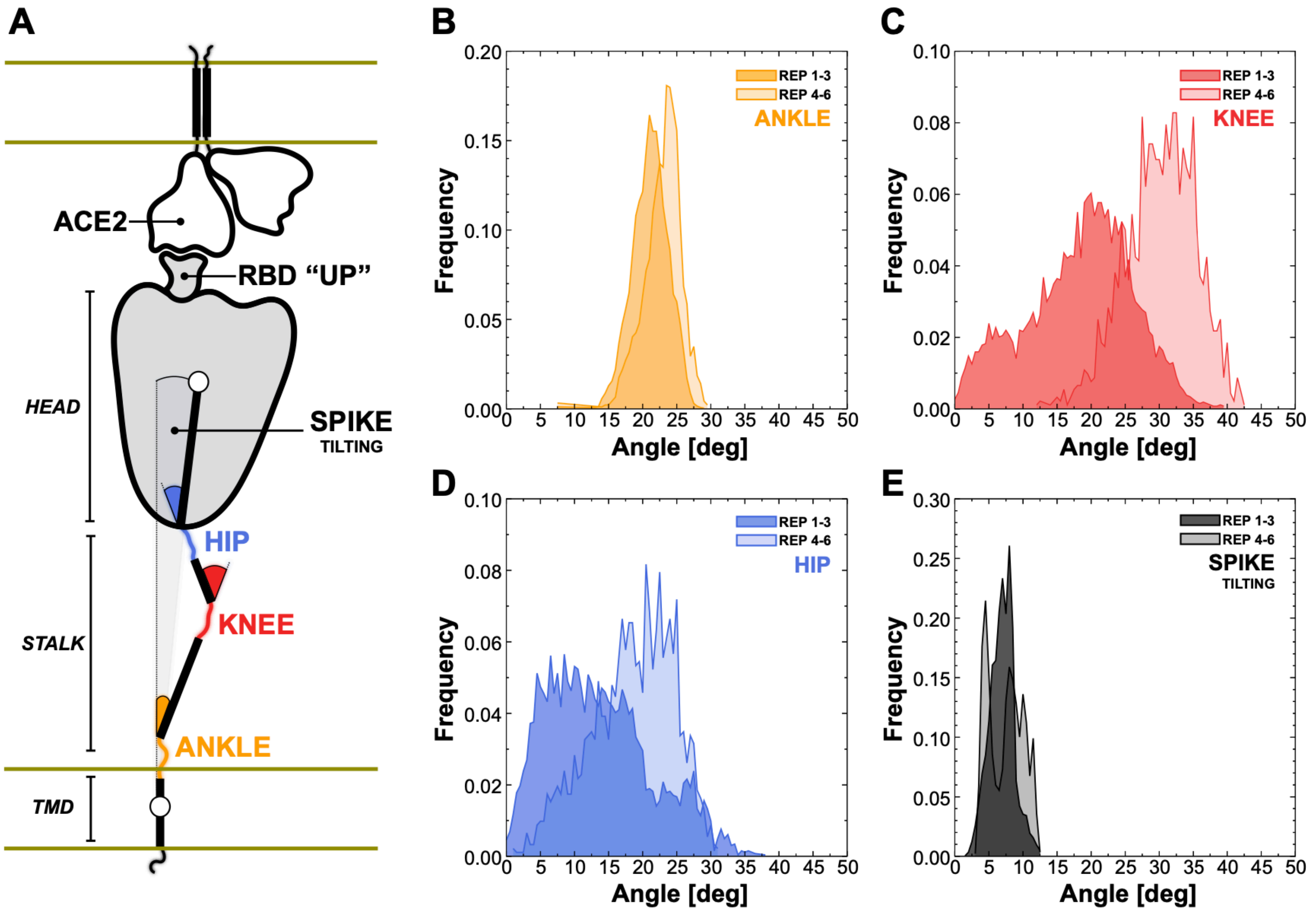




Weighted ensemble simulations show HOW the spike opens & AI acts as a multiscale ‘glue’ to bridge capability gaps

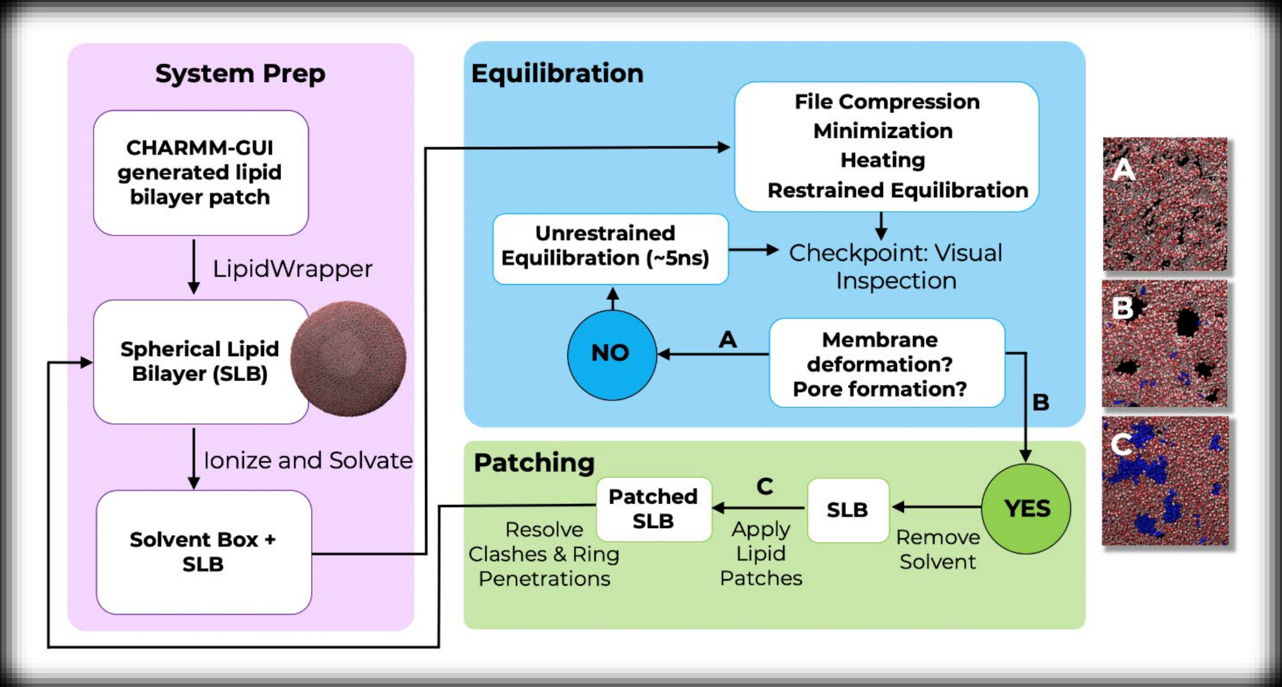


Flexible hinges in spike stalk aid mechanics of binding & cell fusion

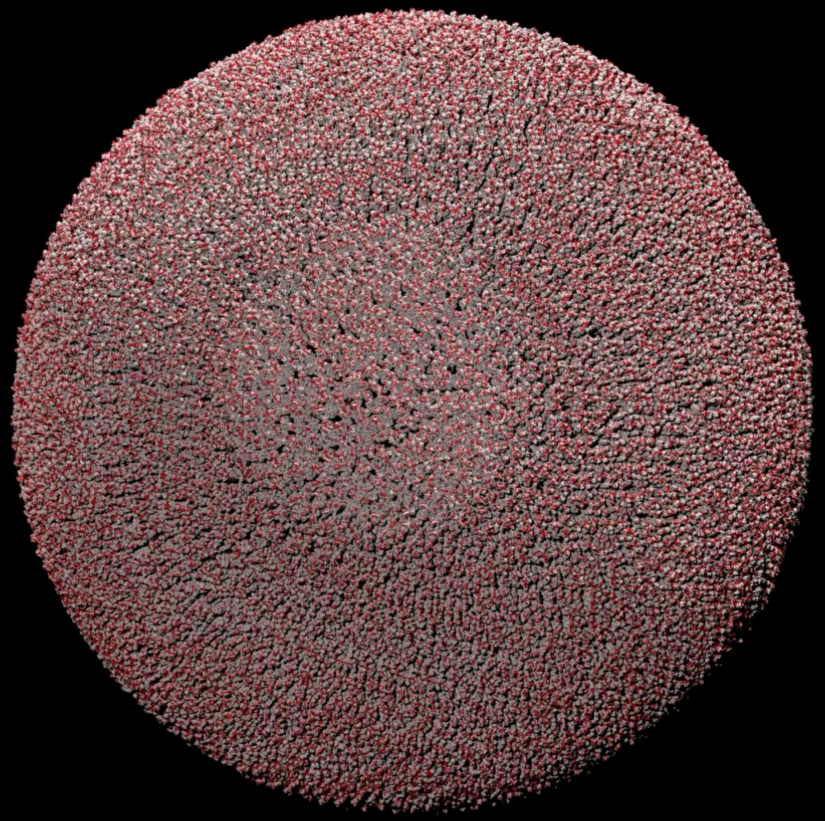


unpublished

Building the entire SARS-CoV-2 viral envelope

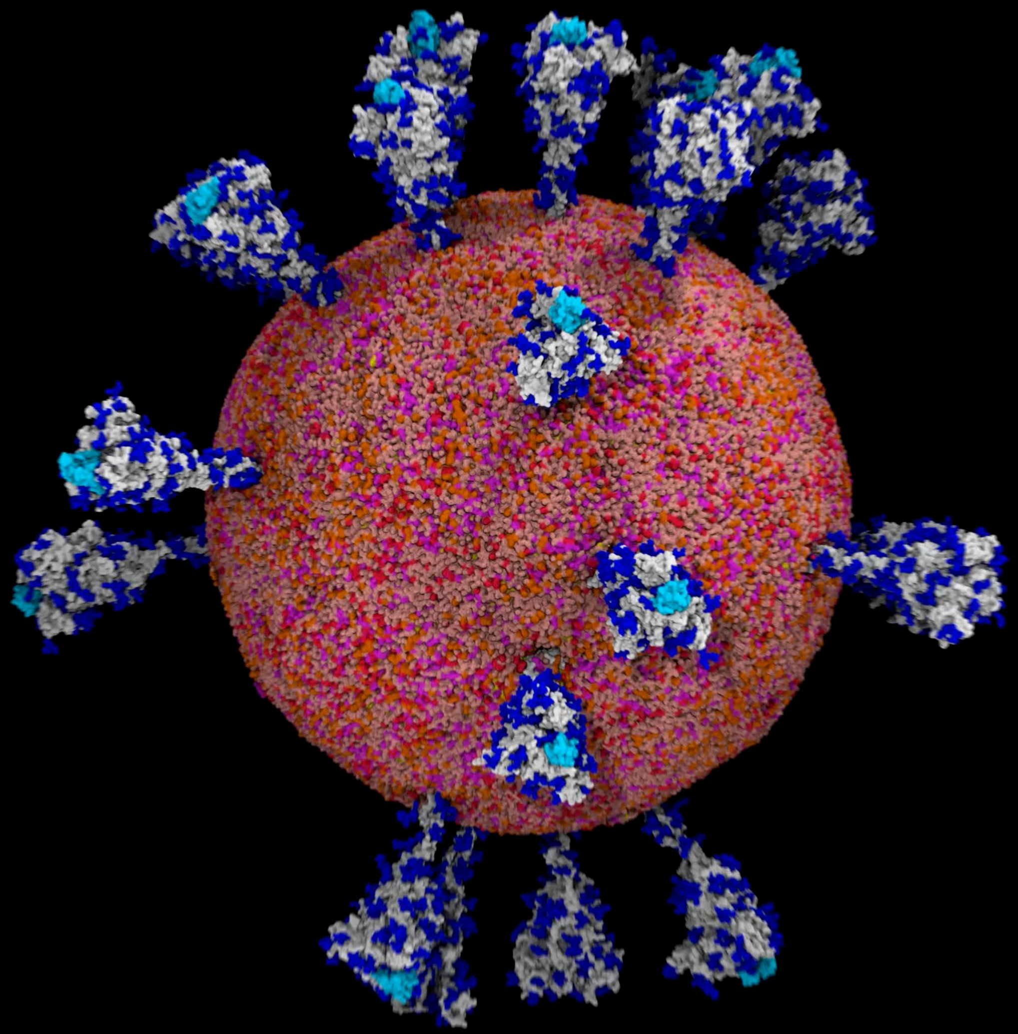


Intensive, iterative remodeling process required



Patch 0

New dimensions for studying viral infection and therapeutics



SHARE

IN DEPTH | COVID-19

New mutations raise specter of 'immune escape'

Kai Kupferschmidt

+ See all authors and affiliations

Science 22 Jan 2021:
Vol. 371, Issue 6527, pp. 329-330
DOI: 10.1126/science.371.6527.329

Rapid assessment of (escape) mutants & Variants of Concern

Cold Spring Harbor Laboratory CSH bioRxiv
THE PREPRINT SERVER FOR BIOLOGY

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Search

bioRxiv is receiving many new papers on coronavirus SARS-CoV-2. A reminder: these are preliminary reports that have not been pee
practice/health-related behavior, or be reported in news media as established information.

New Results

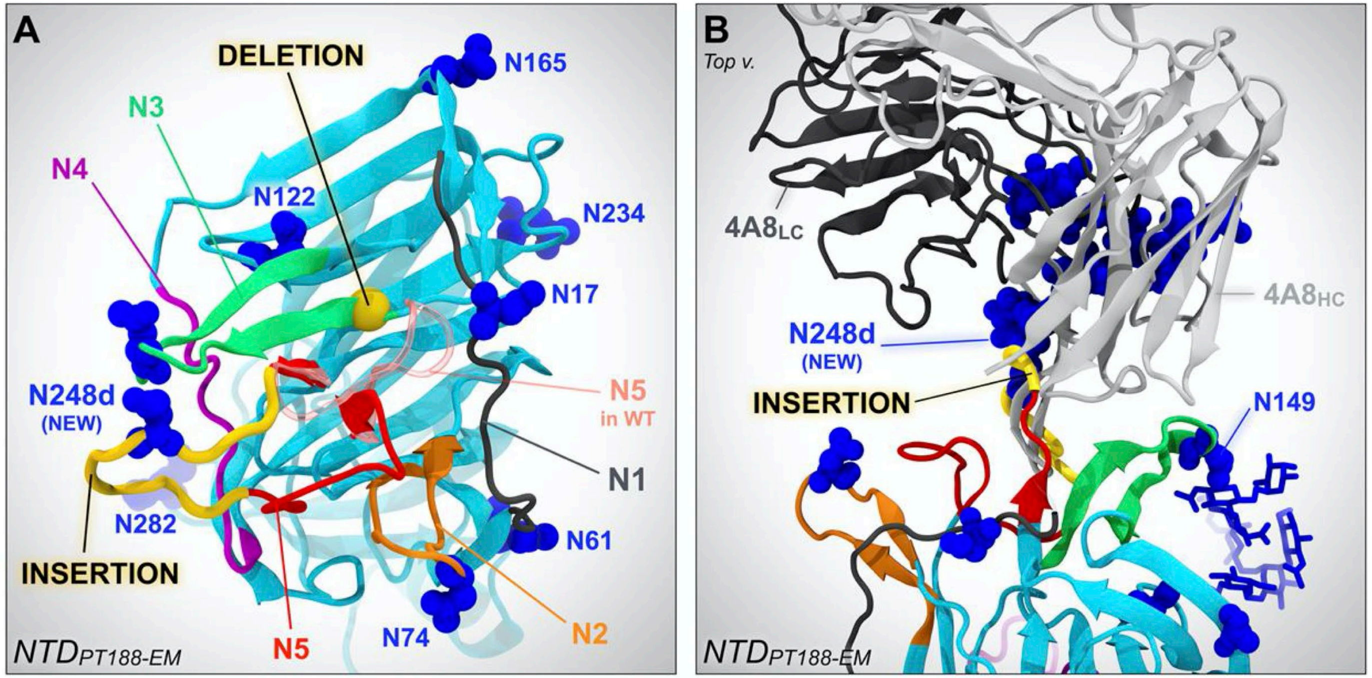
Comments (4)

SARS-CoV-2 escape *in vitro* from a highly neutralizing COVID-19 convalescent plasma

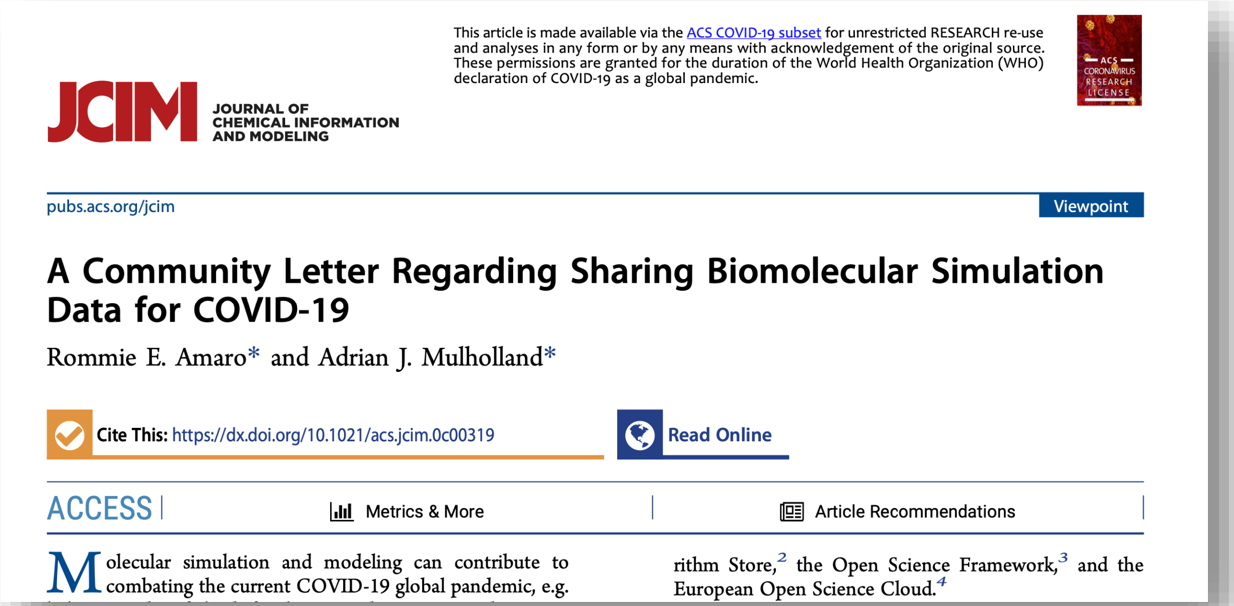
Emanuele Andreano, Giulia Piccini, Danilo Licastro, Lorenzo Casalino, Nicole V. Johnson, Ida Paciello, Simeone Dal Monego, Elisa Pantano, Noemi Manganaro, Alessandro Manenti, Rachele Manna, Elisa Casa, Inesa Hyseni, Linda Benincasa, Emanuele Montomoli, Rommie E. Amaro, Jason S. McLellan, Rino Rappuoli

doi: https://doi.org/10.1101/2020.12.28.424451

This article is a preprint and has not been certified by peer review [what does this mean?].



Worldwide Collaboration & Sharing


This article is made available via the ACS COVID-19 subset for unrestricted RESEARCH re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for the duration of the World Health Organization (WHO) declaration of COVID-19 as a global pandemic.

JCIM JOURNAL OF CHEMICAL INFORMATION AND MODELING

pubs.acs.org/jcim Viewpoint

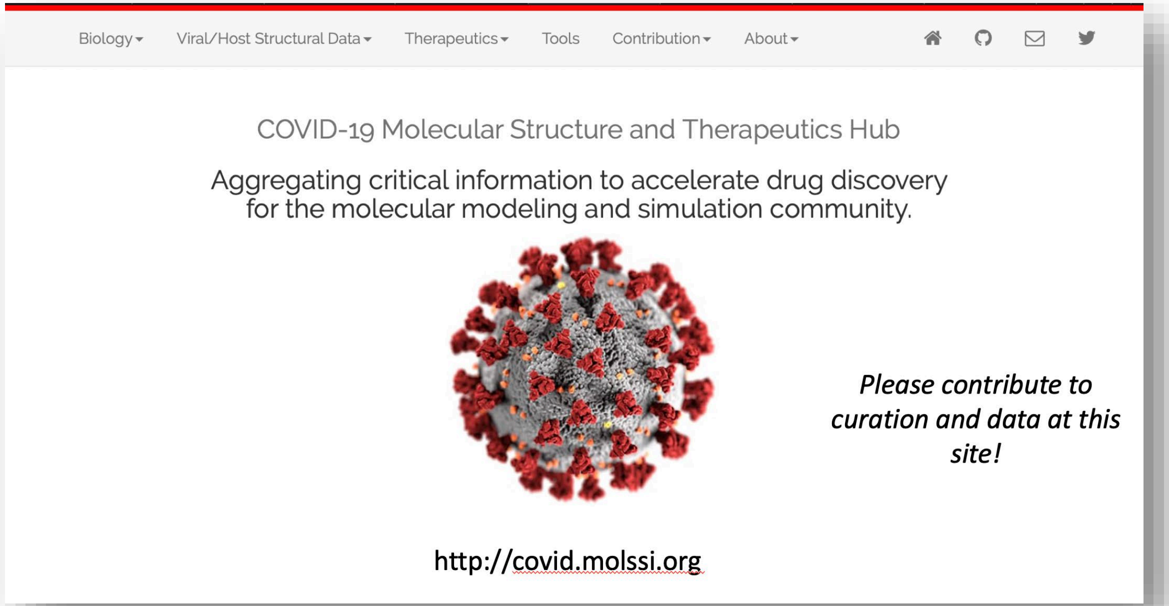
A Community Letter Regarding Sharing Biomolecular Simulation Data for COVID-19

Rommie E. Amaro* and Adrian J. Mulholland*

Cite This: https://dx.doi.org/10.1021/acs.jcim.0c00319 Read Online

ACCESS | Metrics & More | Article Recommendations

Molecular simulation and modeling can contribute to combating the current COVID-19 global pandemic, e.g. ... rithm Store,[2] the Open Science Framework,[3] and the European Open Science Cloud.[4]

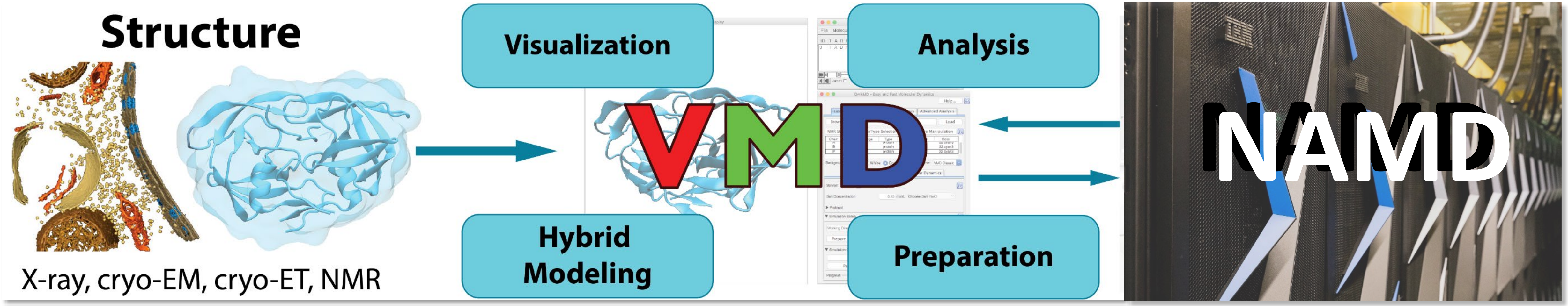


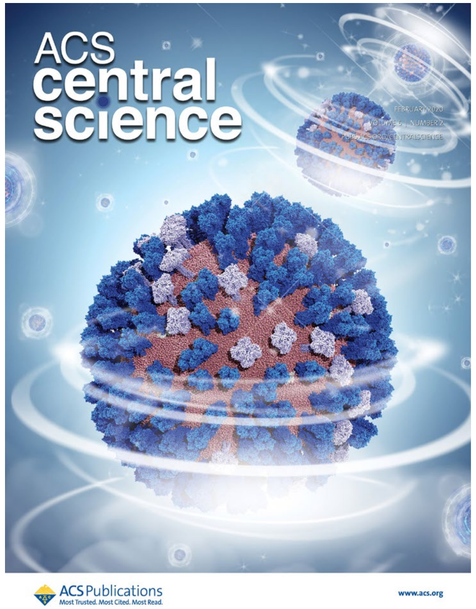
> 200 groups signed on!

Frontera datasets shared > 4k times

Open science (for COVID19) embraced by community, March 2020

NAMD+VMD Molecular Modeling Tools





Weighted Ensembles

AI Driven MD

Collective Variables

...

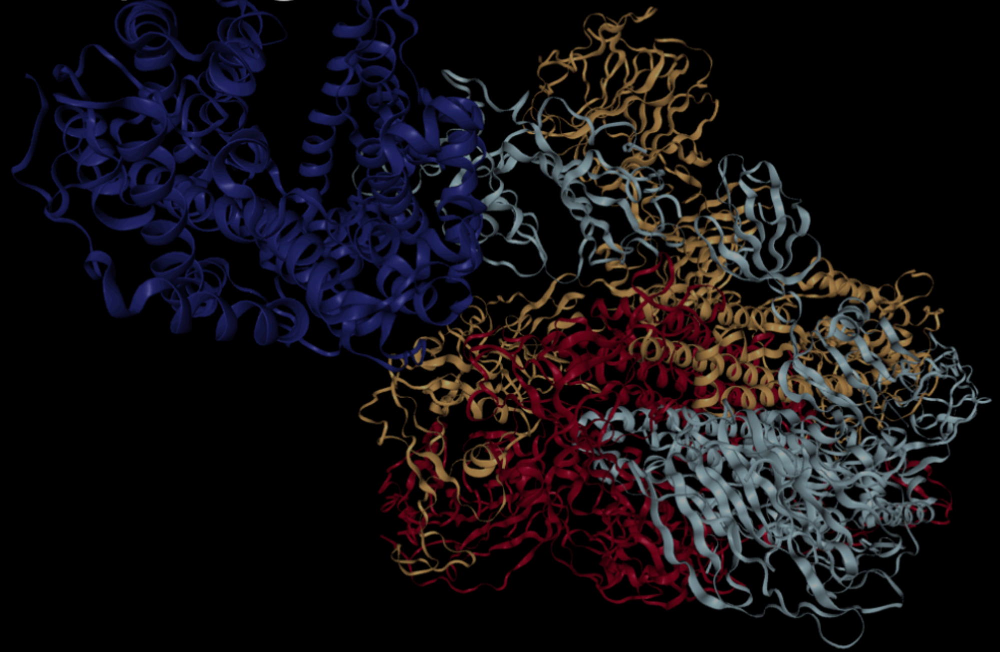
Advanced Methods

Importance of community software, open access

Est. 22 March 2020

COVID-19 HPC Consortium | Who We Are | Collaborations | Projects | News & Press | Blog | Apply

The COVID-19 High Performance Computing Consortium



Bringing together the Federal government, industry, and academic leaders to provide access to the world's most powerful high-performance computing resources in support of COVID-19 research.

43 — Consortium members

50k — GPUs

Making compute cycles rapidly available

Acknowledgements

NSF

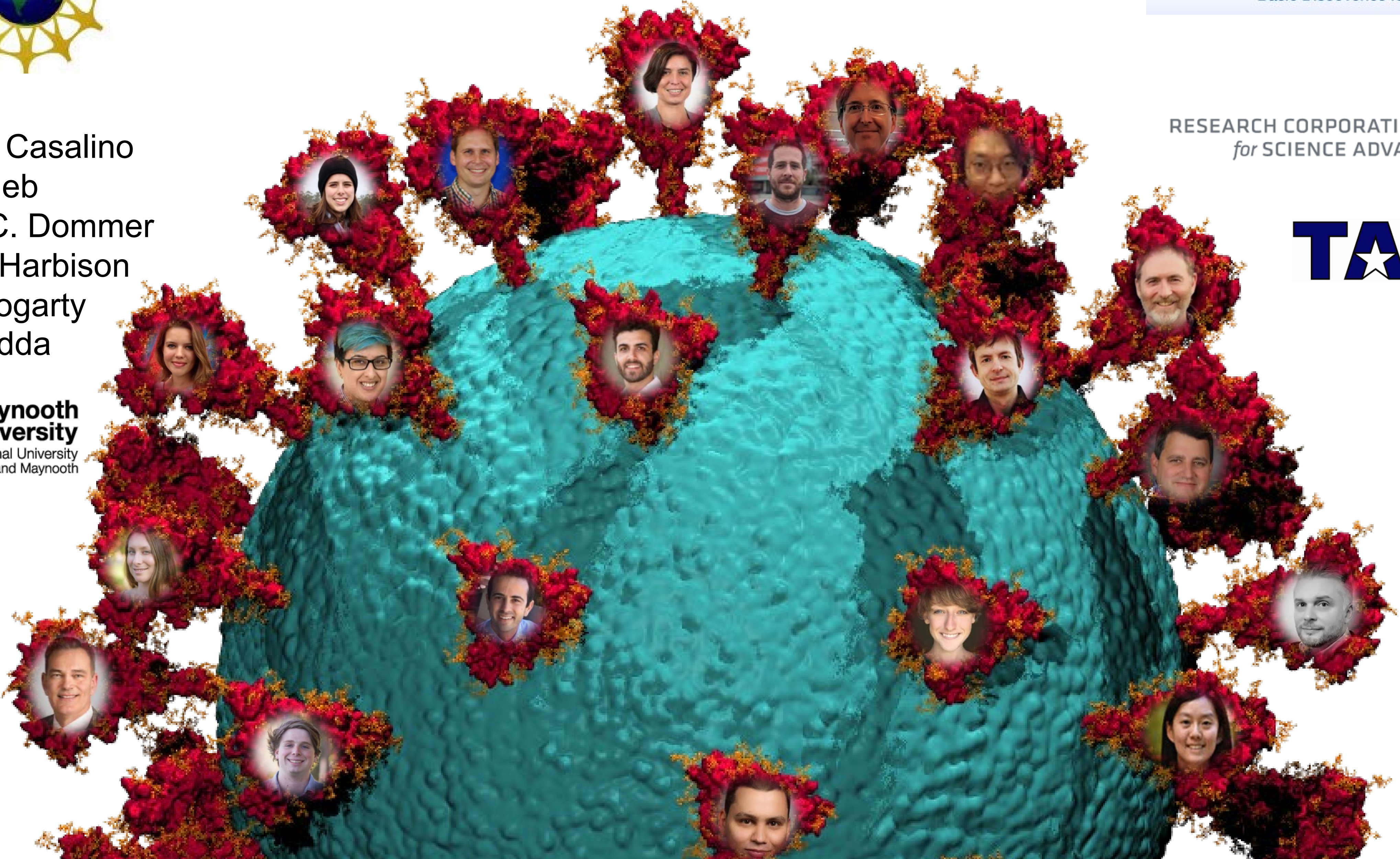
Lorenzo Casalino
Zied Gaieb
Abigail C. Dommer
Aoife M Harbison
Carl A Fogarty
Elisa Fadda

Maynooth University
National University of Ireland Maynooth

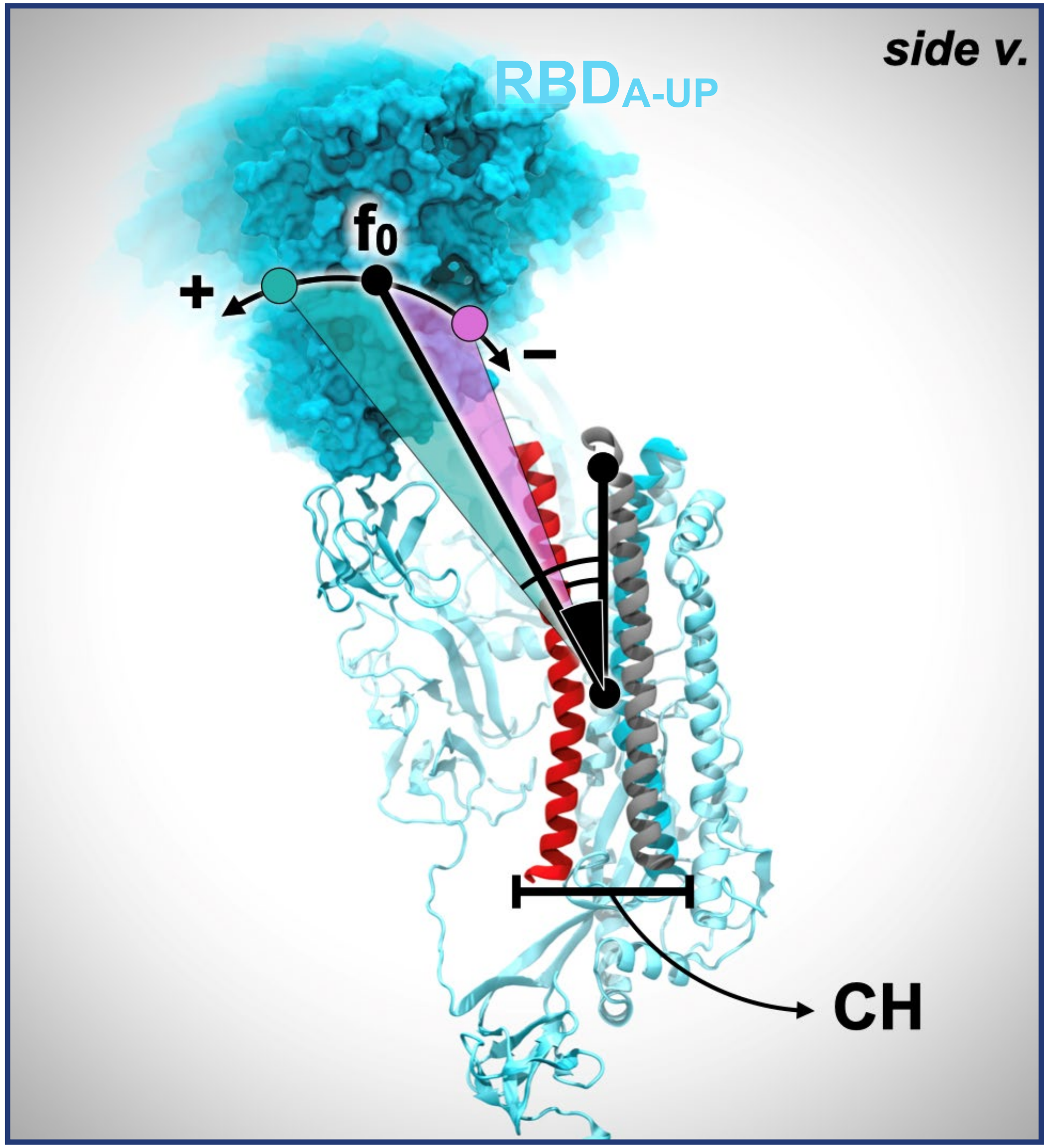
NIH National Institute of General Medical Sciences
Basic Discoveries for Better Health

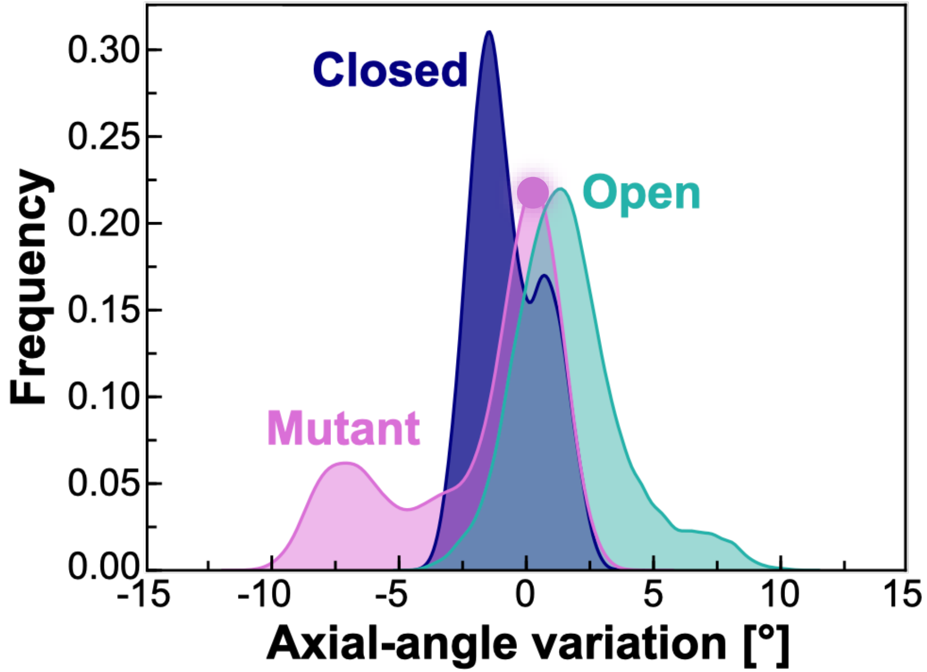
RESEARCH CORPORATION *for* SCIENCE ADVANCEMENT

TACC



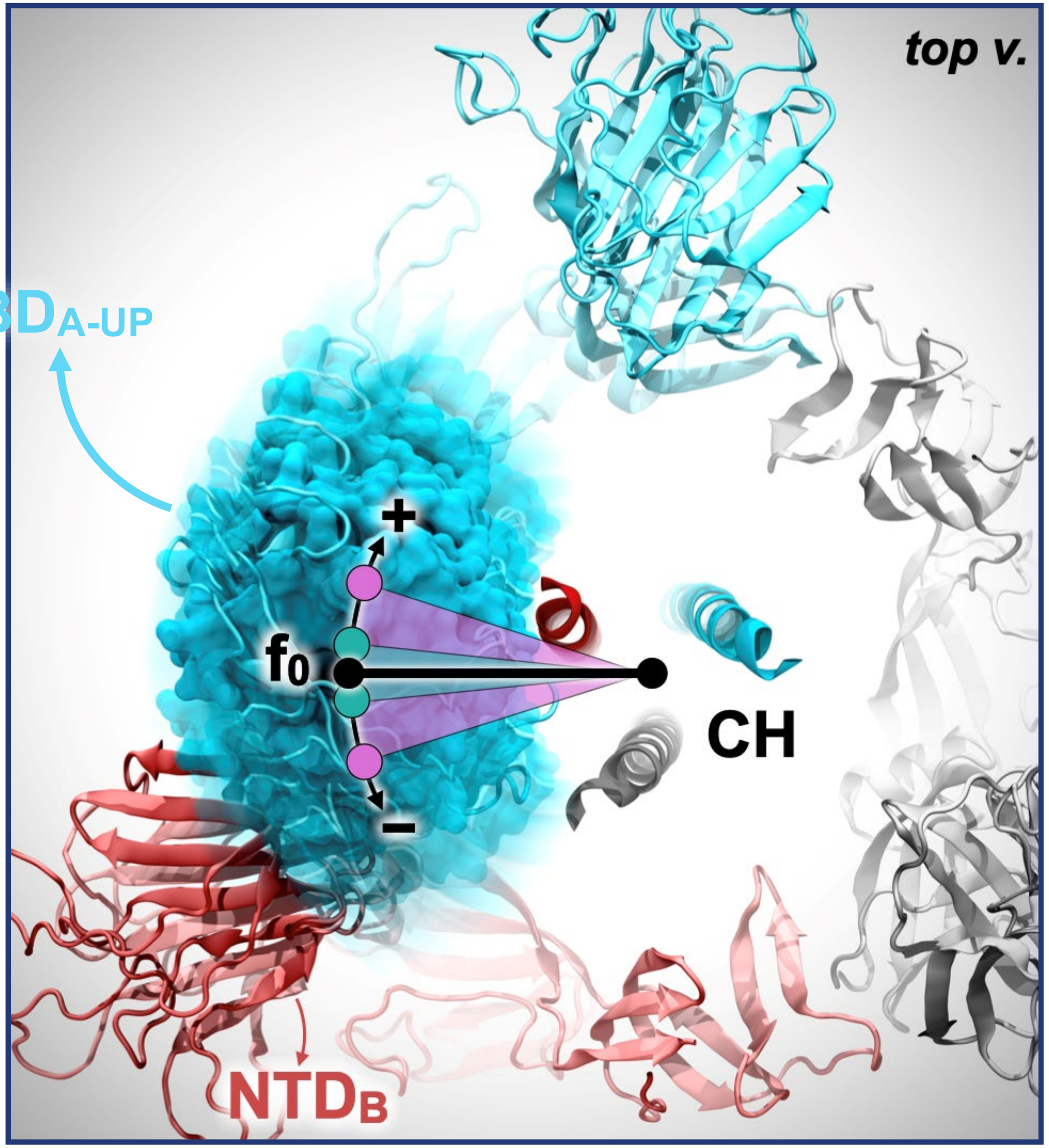
RBD axial tilting

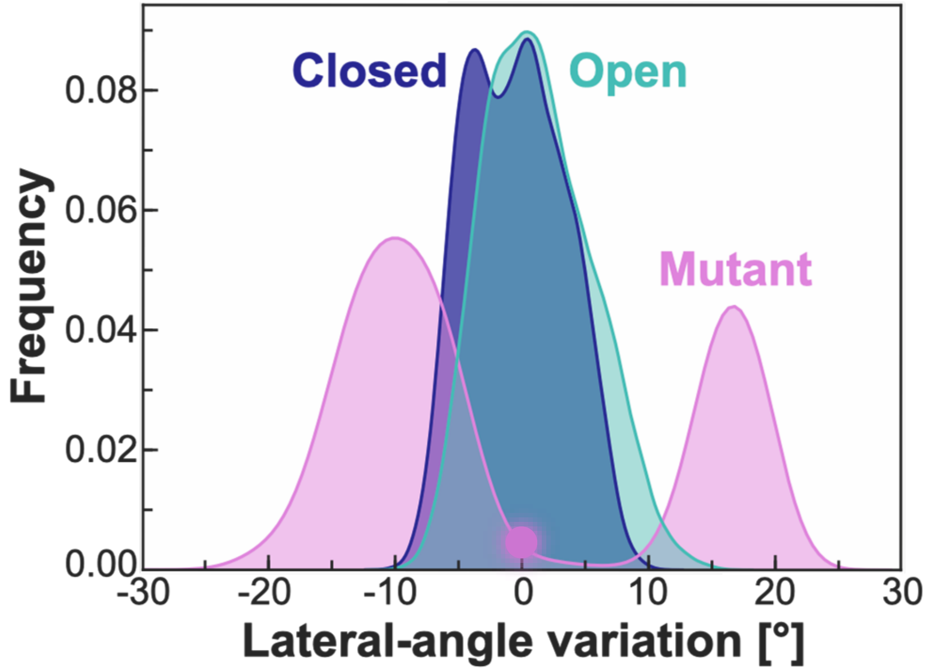




- RBD “down” of CLOSED wild type shows no variation
- RBD “up” of OPEN wild type is overall stable, with a slightly “opening” trend
- RBD “up” of MUTANT exhibits a “closing” trend, showing a negative shoulder

RBD lateral rotation





- RBD “down” of CLOSED wild type shows no variation
- RBD “up” of OPEN wild type is stable
- RBD “up” of MUTANT exhibits large instability, with a bimodal distribution

Our simulation models shared with and vetted by groups worldwide












…. before publication. Many thanks to those who found nits to fix!