

Computational Microscopy of SARS-CoV-2

Rommie Amaro . UC San Diego . April 2021

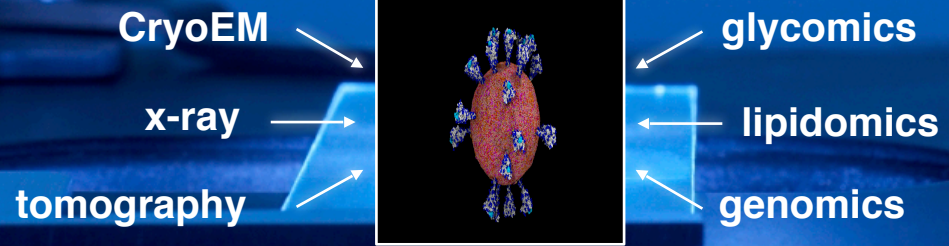
Molecular Dynamics Simulations as a Computational Microscope



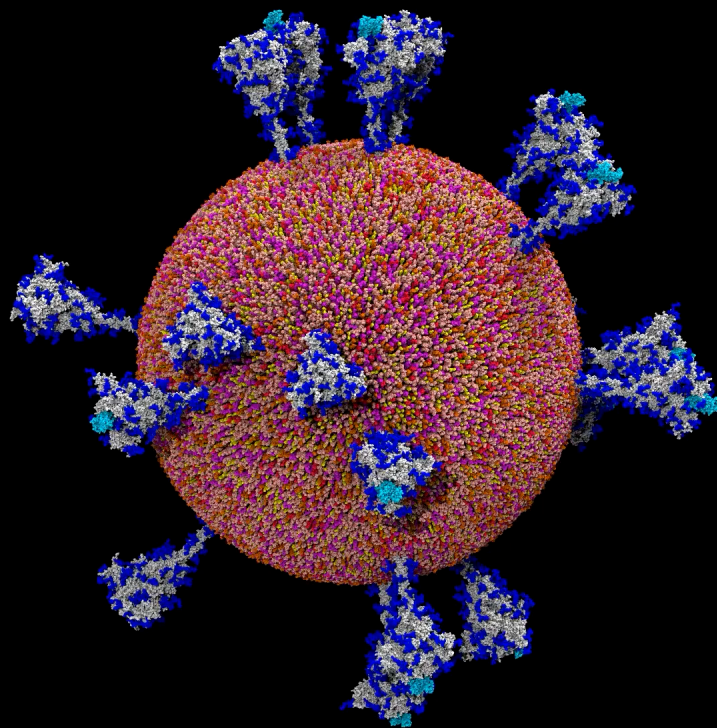
$$U(\vec{R}) = \sum_{bonds} k_i^{bond} (r_i - r_0)^2 + \sum_{angles} k_i^{angle} (\theta_i - \theta_0)^2 +$$

$$\sum_{dihed} k_i^{dihed} [1 + \cos(n_i \phi_i + \delta_i)] + \sum_i \sum_{j \neq i} 4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \sum_i \sum_{j \neq i} \frac{q_i q_j}{\epsilon r_{ij}}$$

$$\vec{F}_i = m a = m_i \frac{d^2 \vec{r}_i}{dt^2} = - \vec{\nabla} U(\vec{R})$$



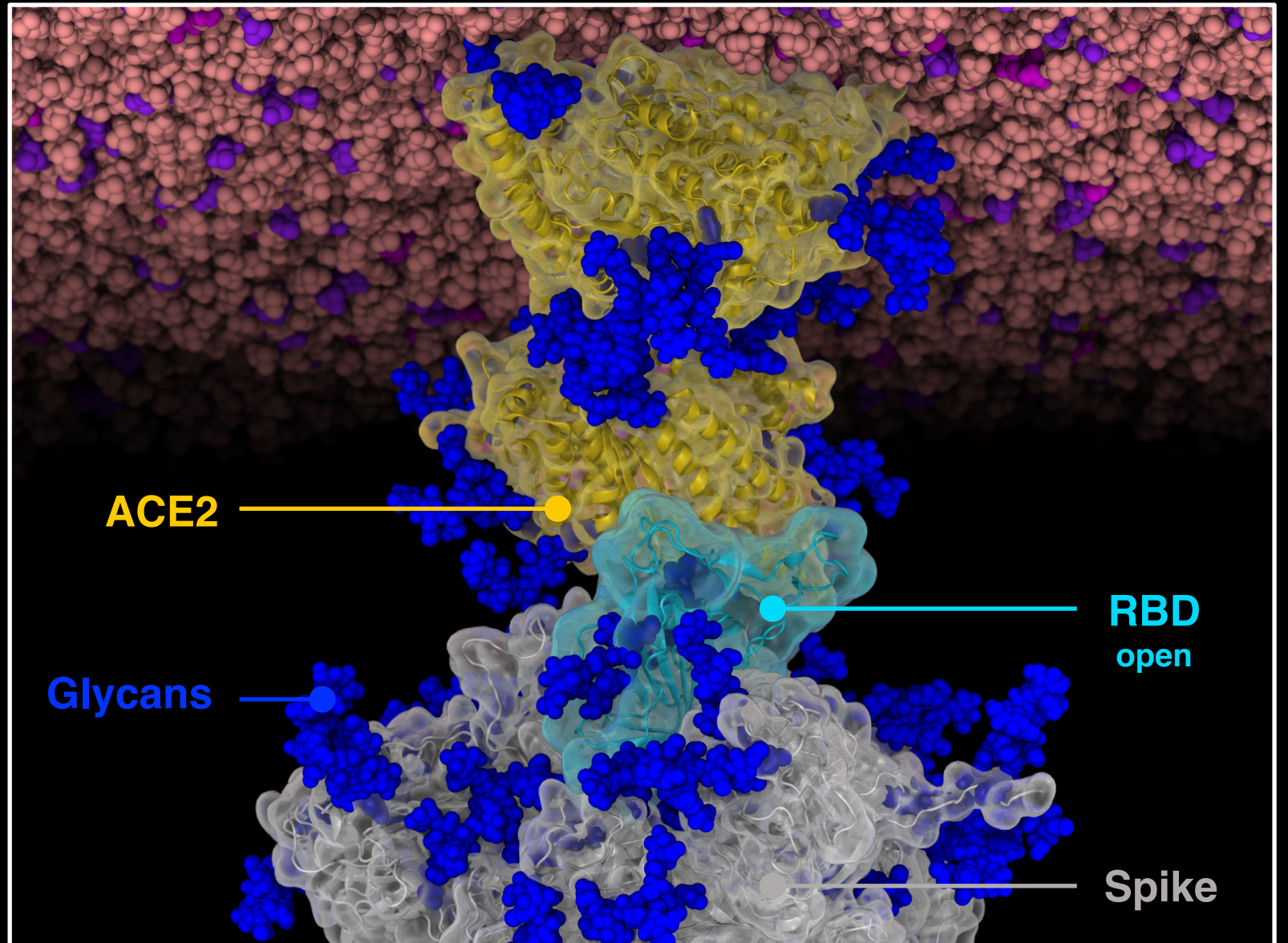
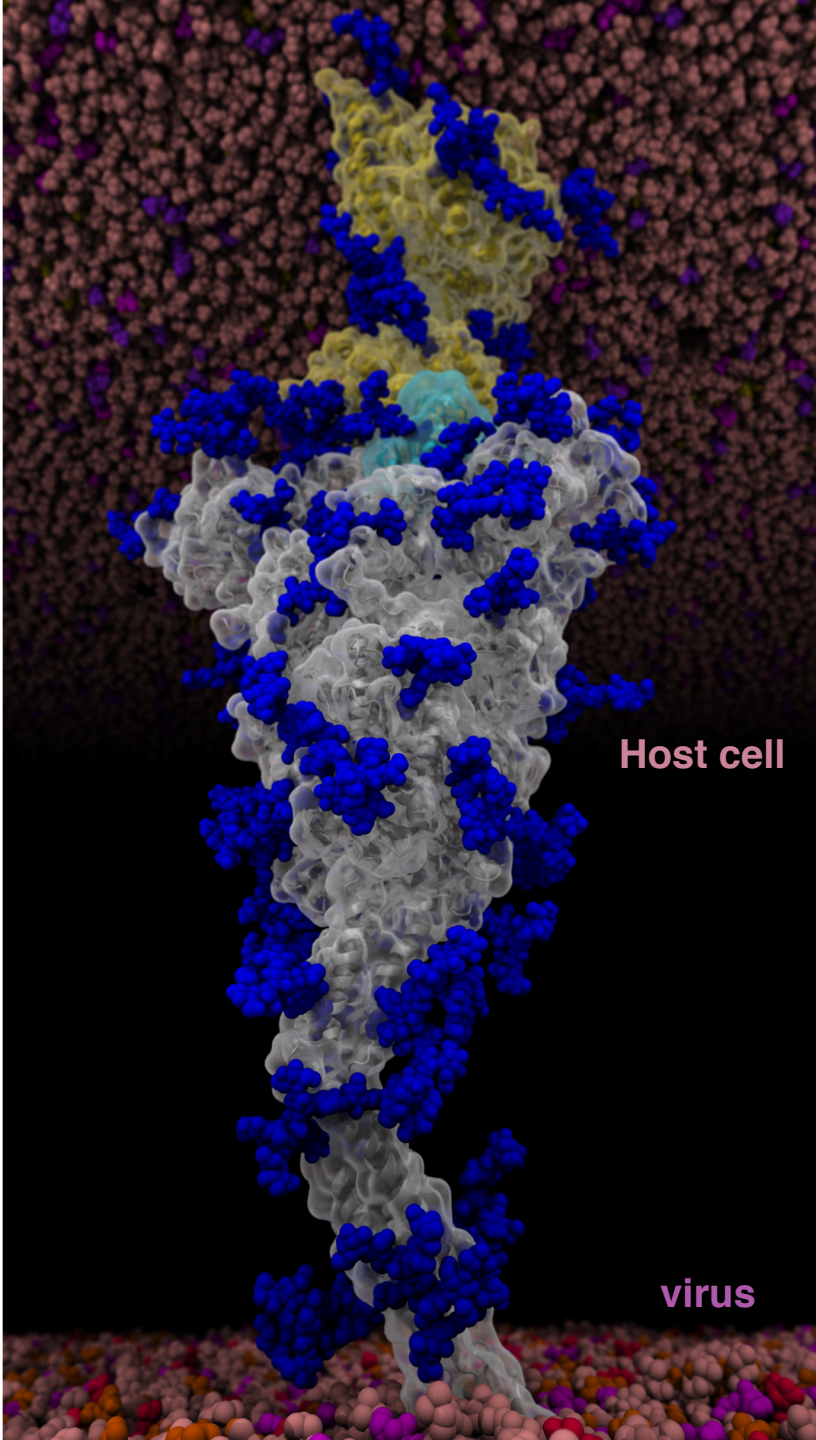
Data centric computational simulations integrate and extend experimental data



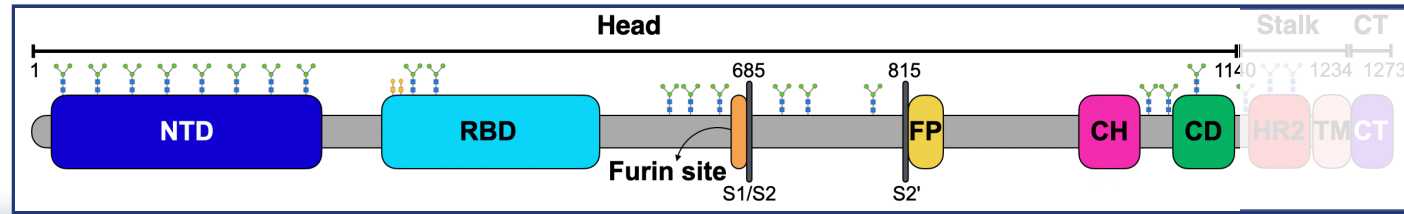
SARS-CoV-2 virus

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. Corbett², Jory A. Goldsmith¹, Ching-Lin Hsieh¹, Olubukola Abiona², Barney S. Graham², Jason S. McLellan^{1,†}

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

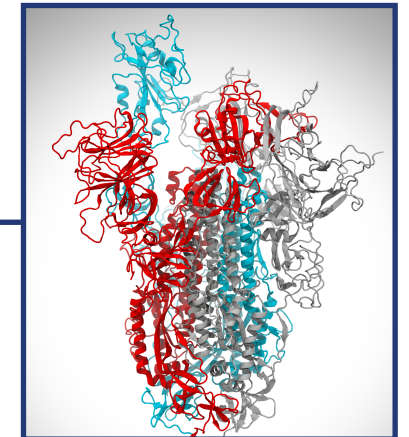
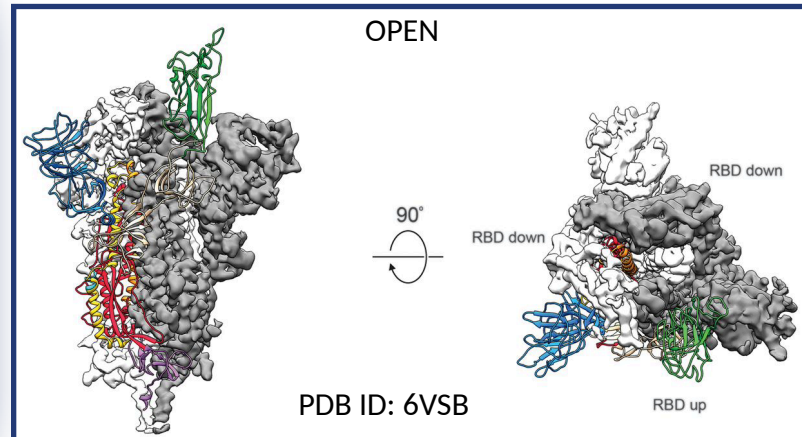
²Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA.

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

* These authors contributed equally to this work.

- Hide authors and affiliations

Science 13 Mar 2020:
 Vol. 367, Issue 6483, pp. 1260-1263
 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 Wall³, Andrew T. McGuire^{3,4}, and David Veesler^{1,6,*}

¹Department of Biochemistry, University of Washington, Seattle, WA 98195, USA

²Institute Pasteur & CNRS UMR 3569, Unité de Virologie Structurale, Paris 75015, France

³Vaccines and Infectious Diseases Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98195, USA

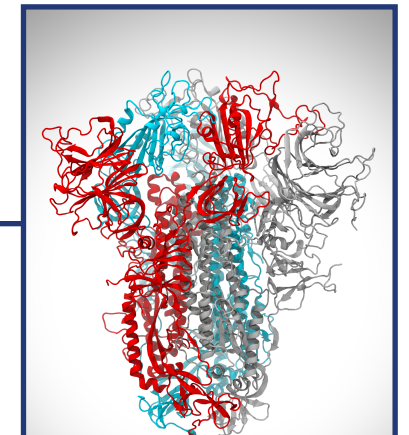
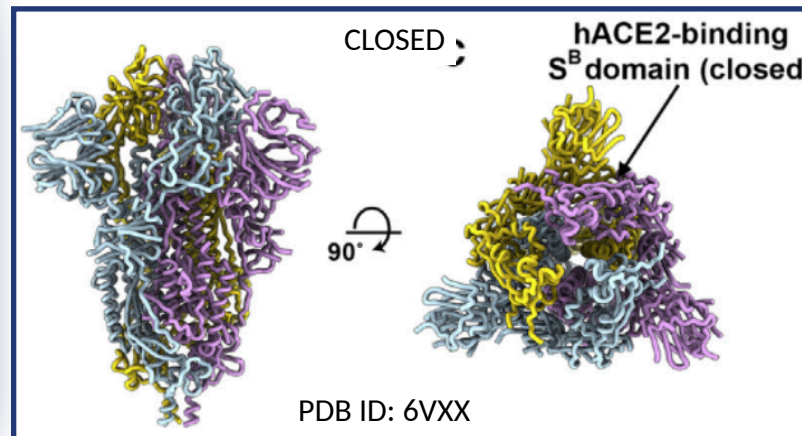
⁴Department of Global Health, University of Washington, Seattle, WA 98195, USA

⁵These authors contributed equally

⁶Lead 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

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 Wrapp⁴, Jason S. McLellan⁴, Max Crispin^{1†}

¹School of Biological Sciences, University of Southampton, Southampton SO17 1BJ, UK. ²Oxford Glycobiology Institute, Department of Biochemistry, University of Oxford, South Parks Road, Oxford OX1 3QU, UK. ³Division of Structural Biology, University of Oxford, Wellcome Centre for Human Genetics, Oxford OX3 7BN, UK. ⁴Department 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

bioRxiv preprint doi: <https://doi.org/10.1101/2020.04.01.020966>; this version posted April 1, 2020. The copyright holder for this preprint (which was not peer-reviewed) is the author/funder. All rights reserved. No reuse allowed without permission.

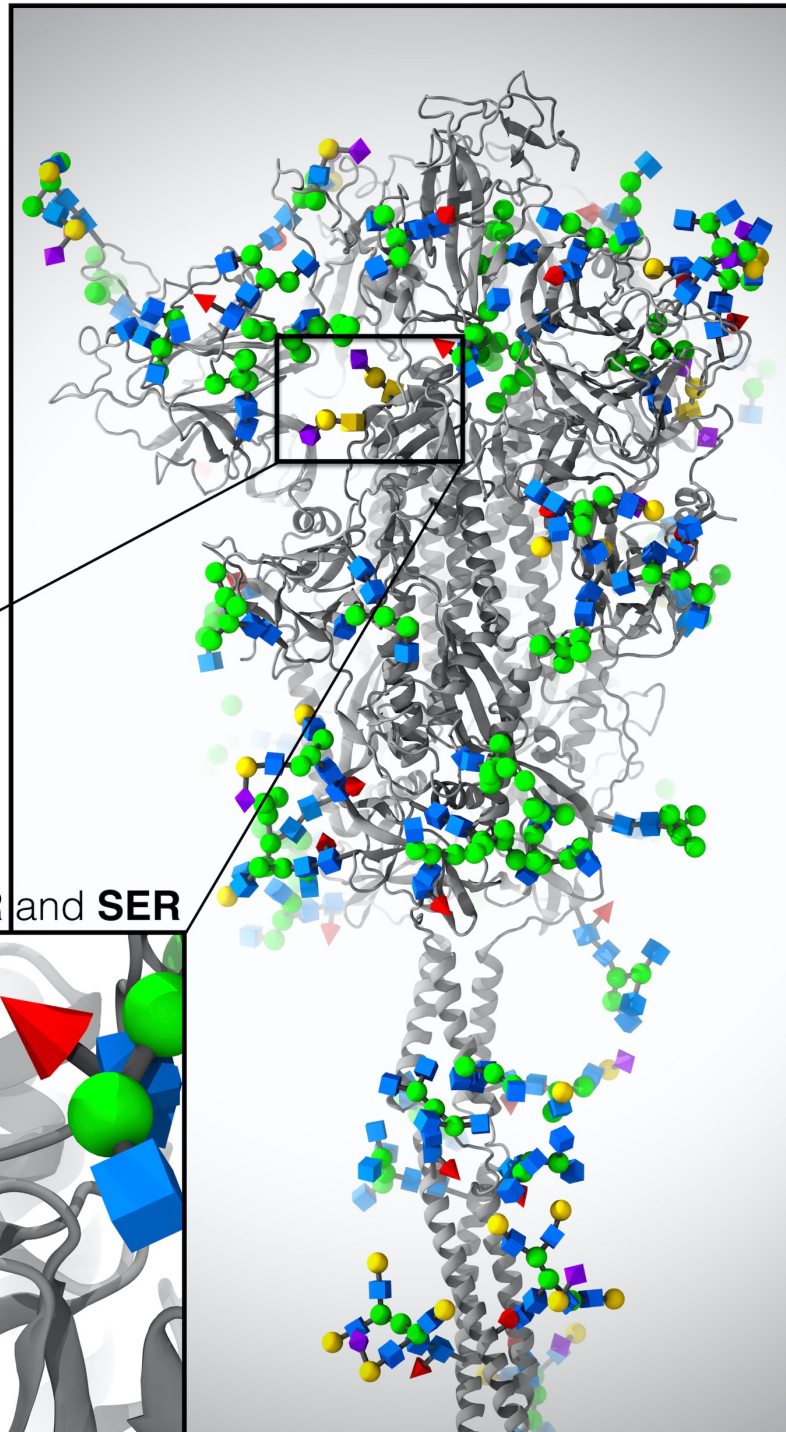
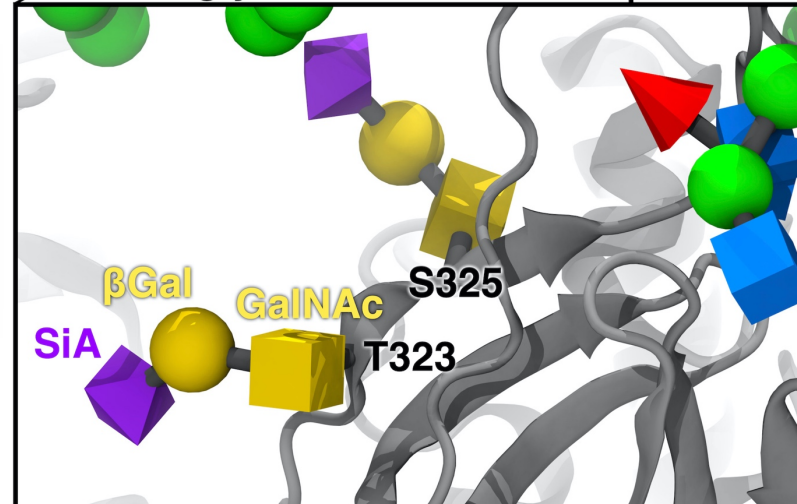
Deducing the N- and O- glycosylation profile of the spike protein of novel coronavirus SARS-CoV-2

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

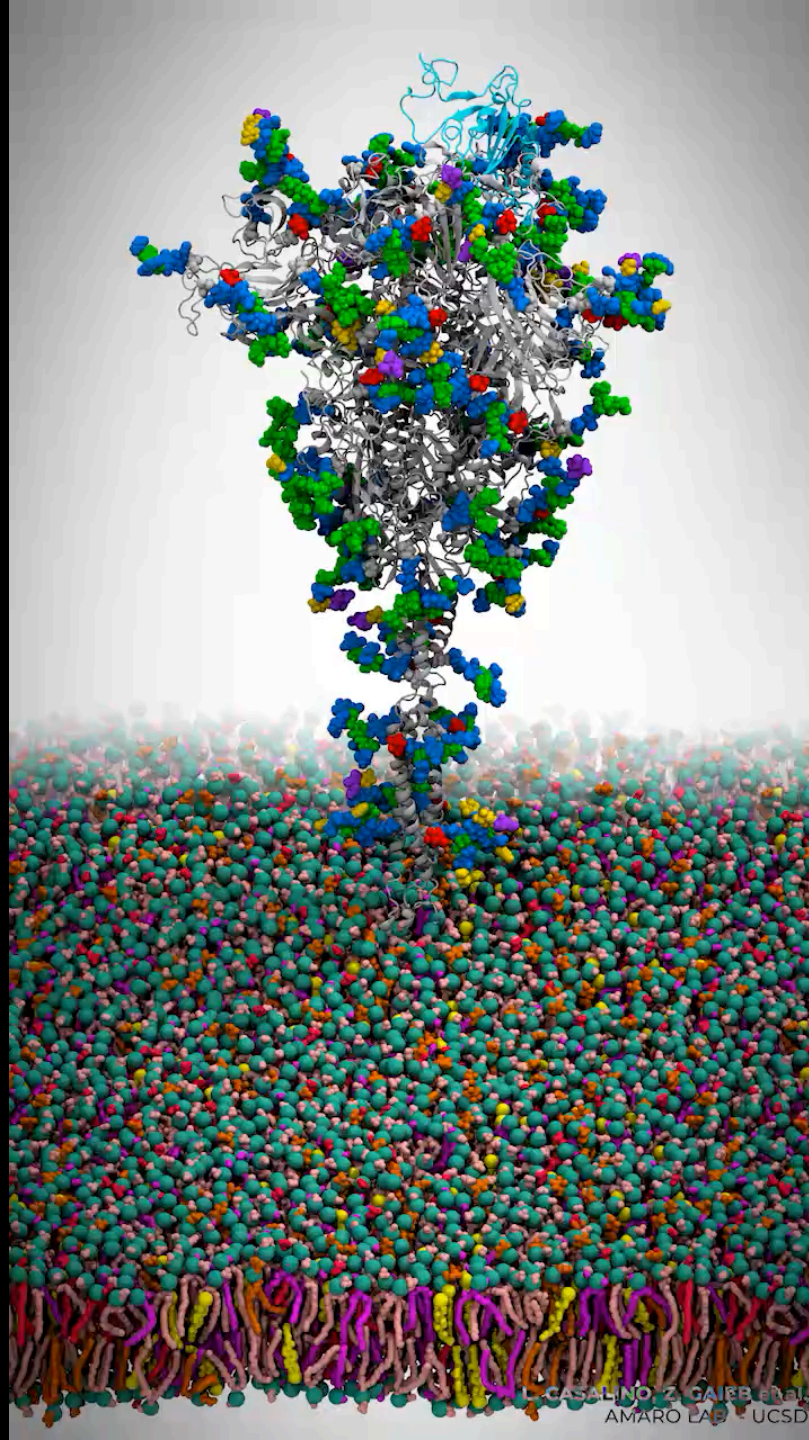
Complex Carbohydrate Research Center, The University of Georgia, Athens, GA 30602

-  2-acetyl-2-deoxy-beta-D-glucosamine (GlcNAc)
-  2-acetyl-2-deoxy-alpha-D-galactosamine (GalNAc)
-  beta-D-galactose (Gal)
-  alpha/beta-D-mannose (Man)
-  alpha-L-fucose (Fuc)
-  N-acetyl-alpha-D-neuraminic acid (Sialic acid)

O-glycans: linked to THR and SER





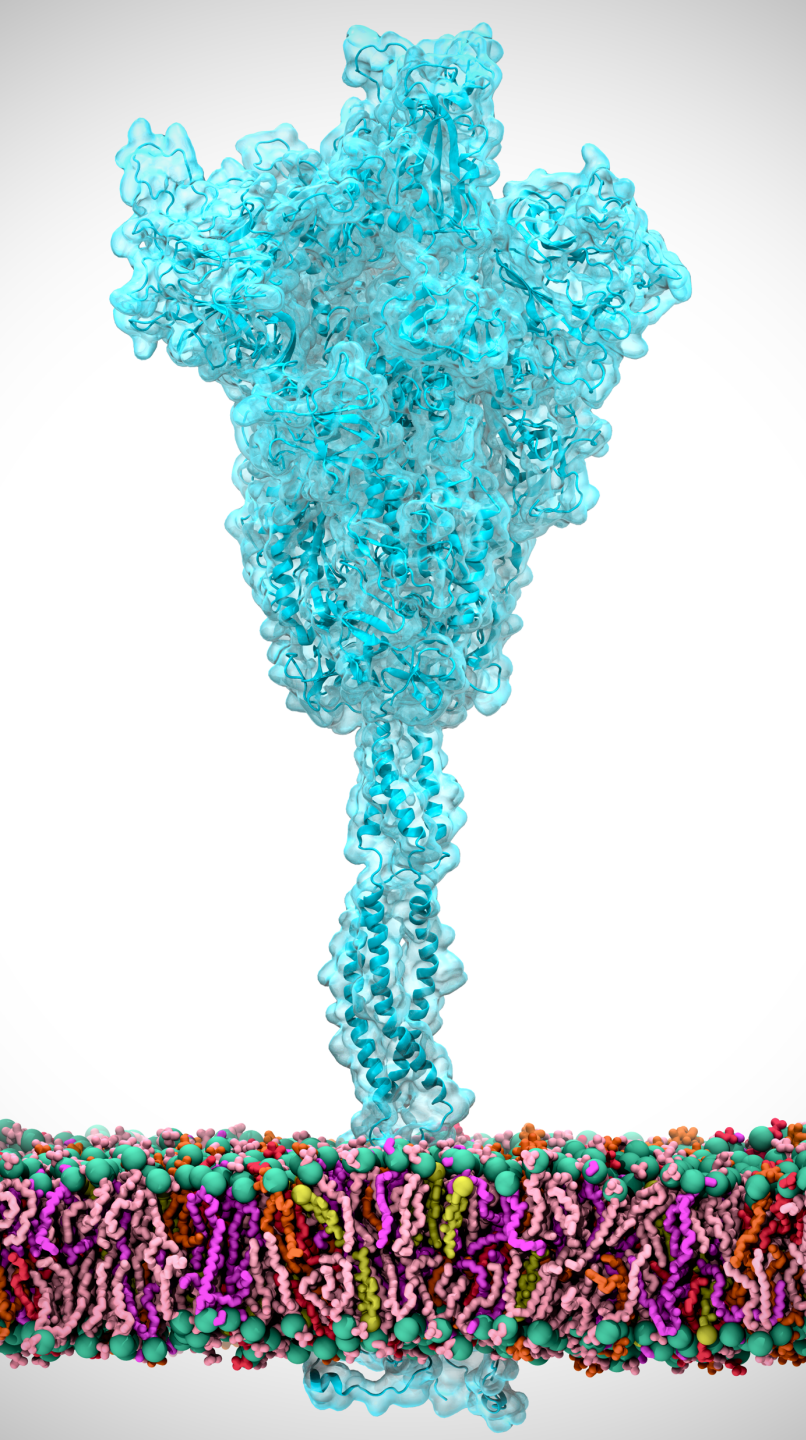


RBD-up (Open)
RBDs-down (Closed)

~1.7 million atoms

Charmm36 force field
NAMD2 on TACC Frontera
~ 60 ns/day on 256 nodes

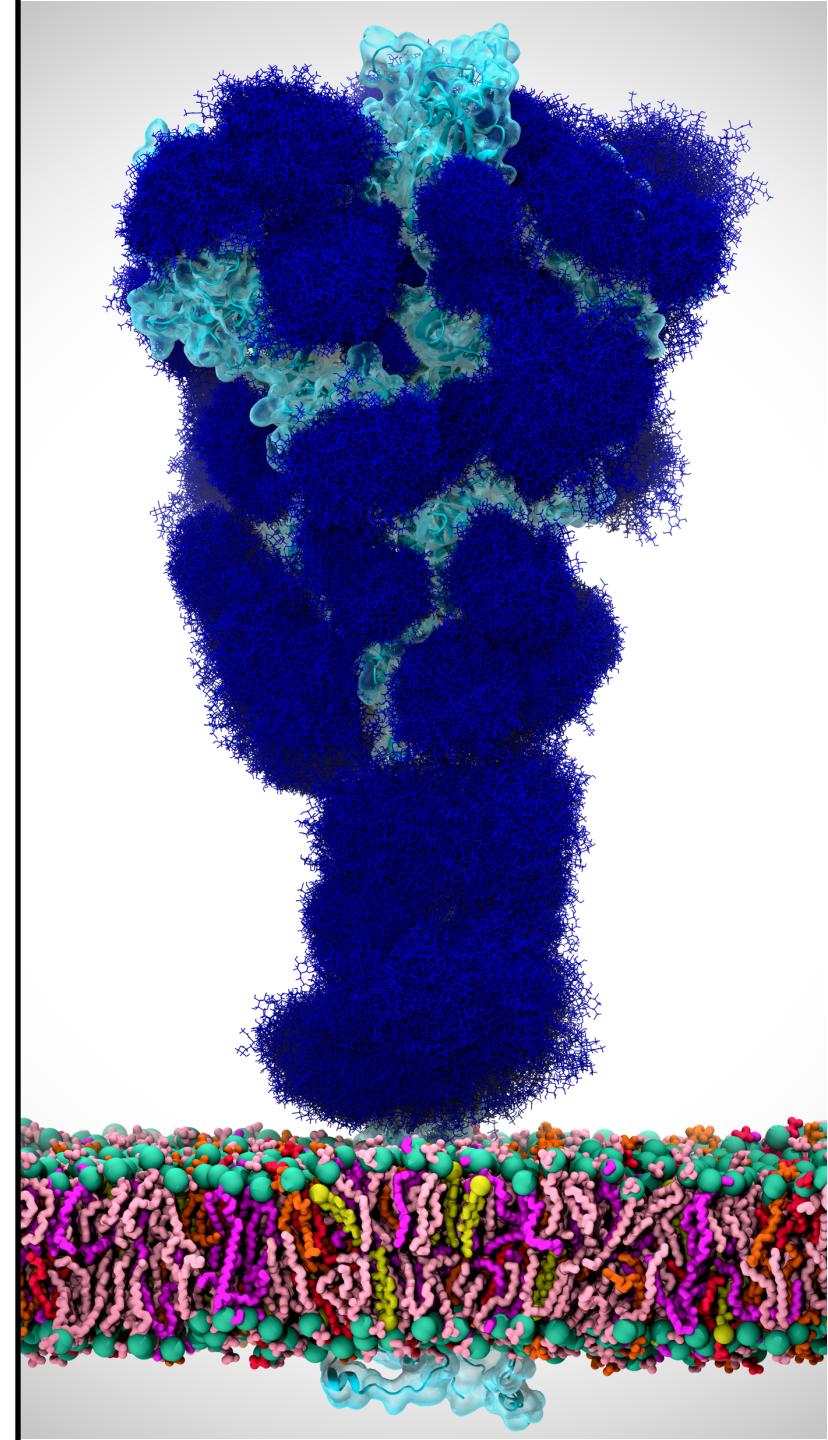
> 4 microseconds for each system



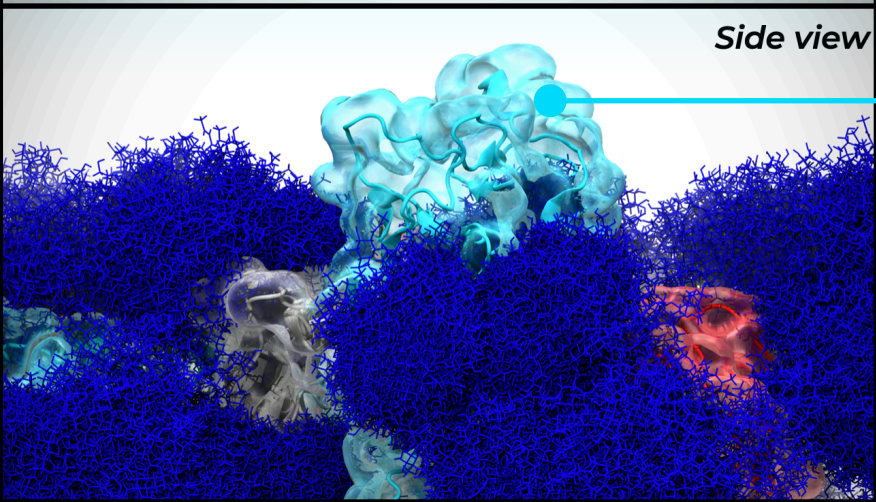
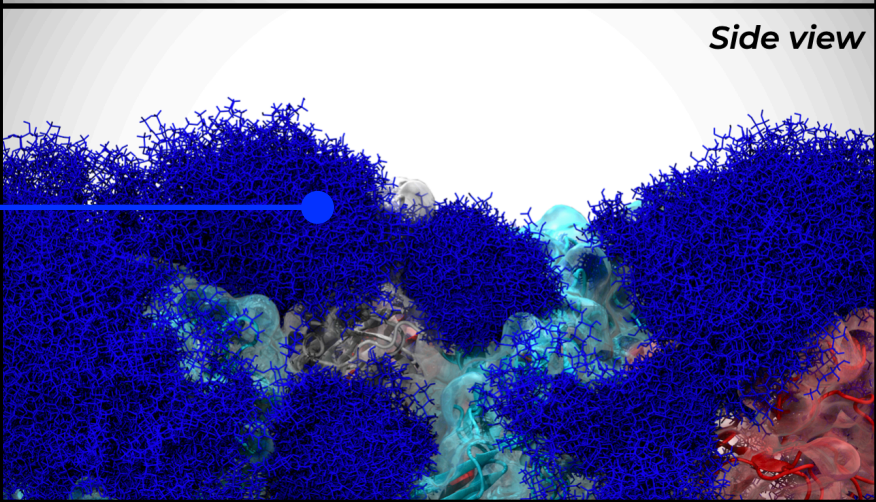
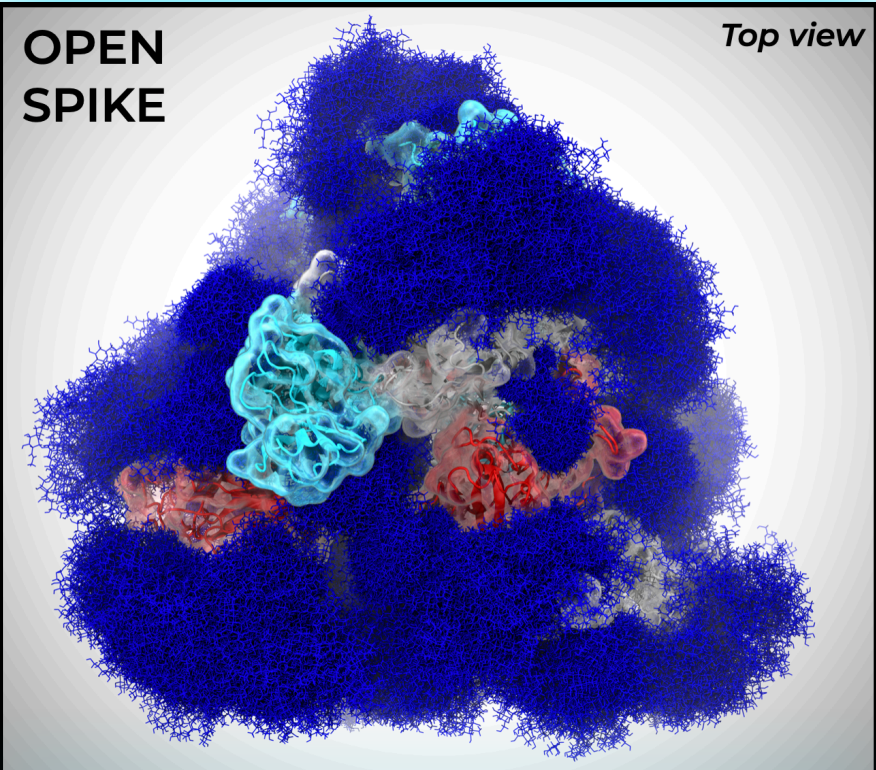
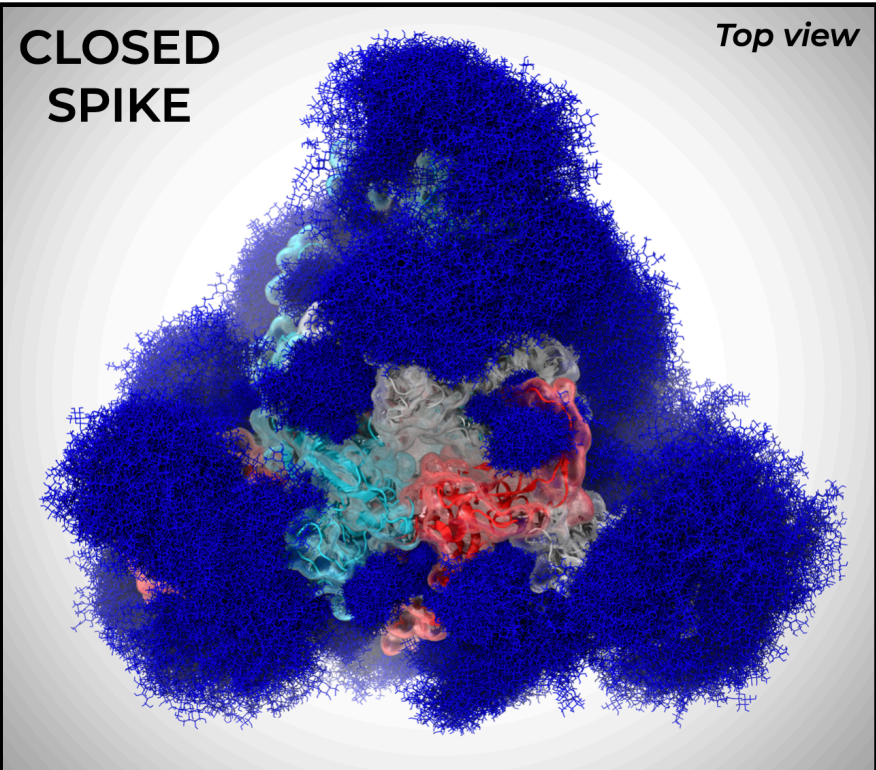
The glycan shield

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

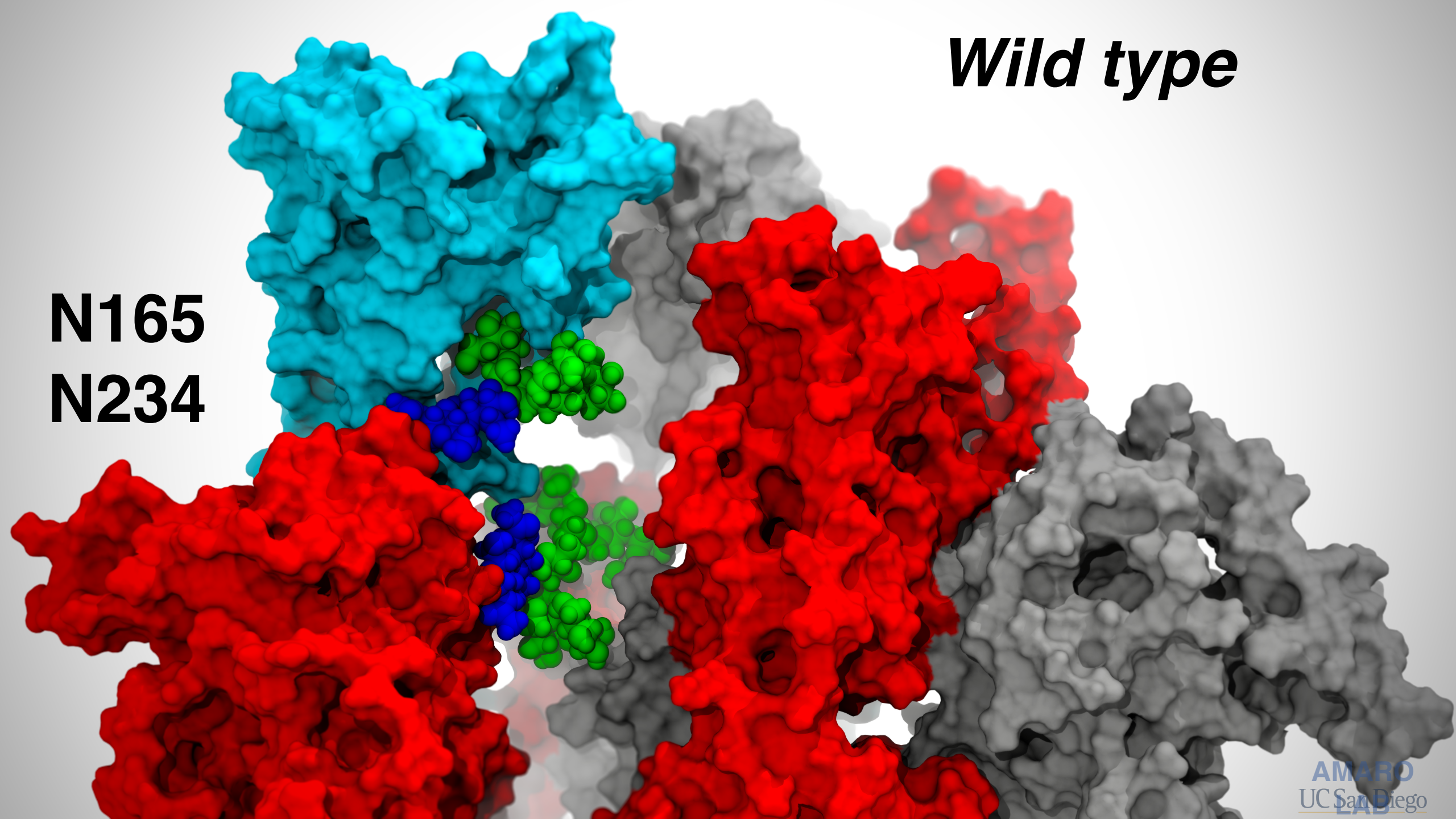


Glycan shield
(defending mode)

RBD open
(attacking mode)

Wild type

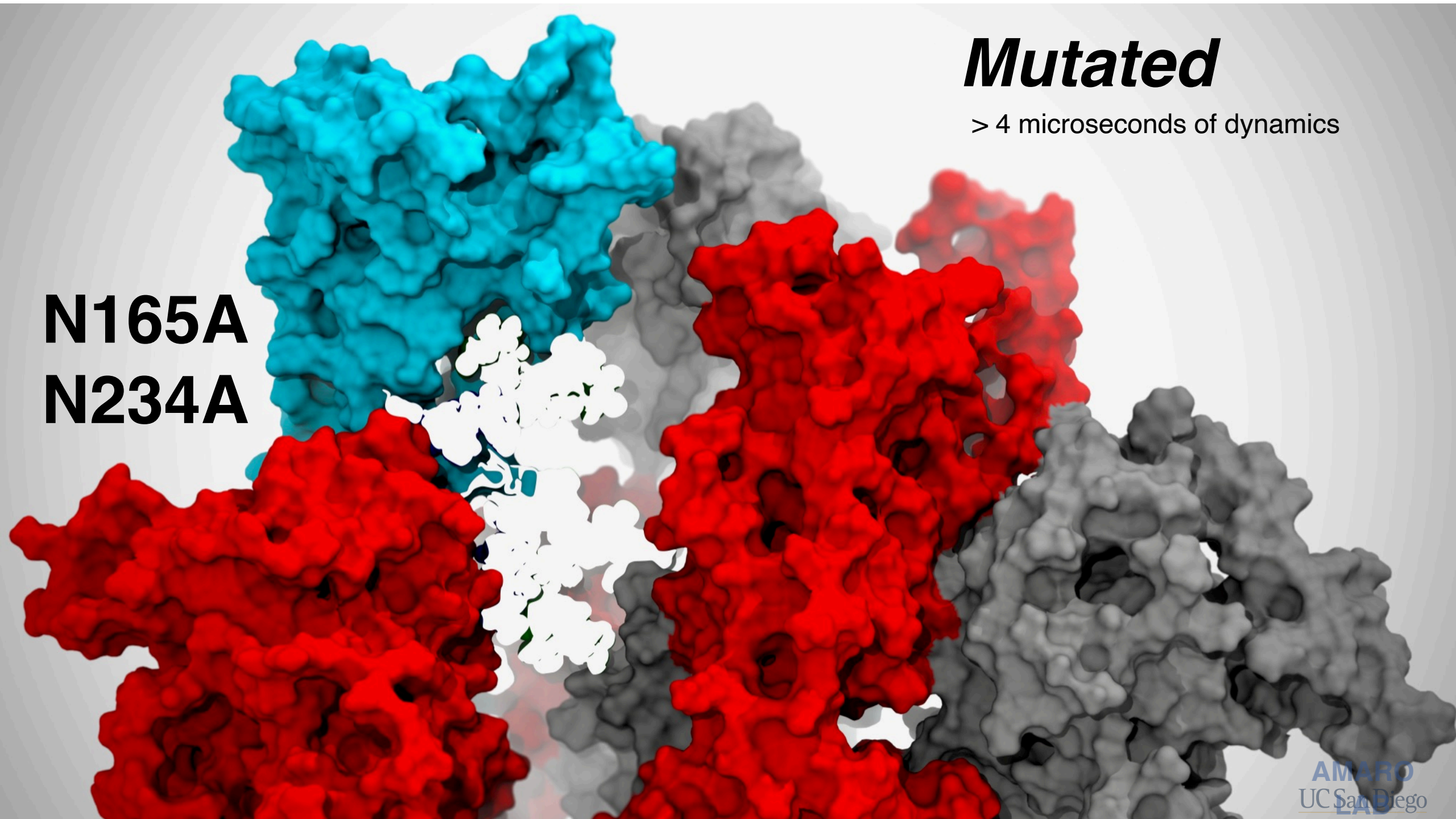
N165
N234



Mutated

> 4 microseconds of dynamics

N165A
N234A



McLellan Lab (UT Austin) Collaboration

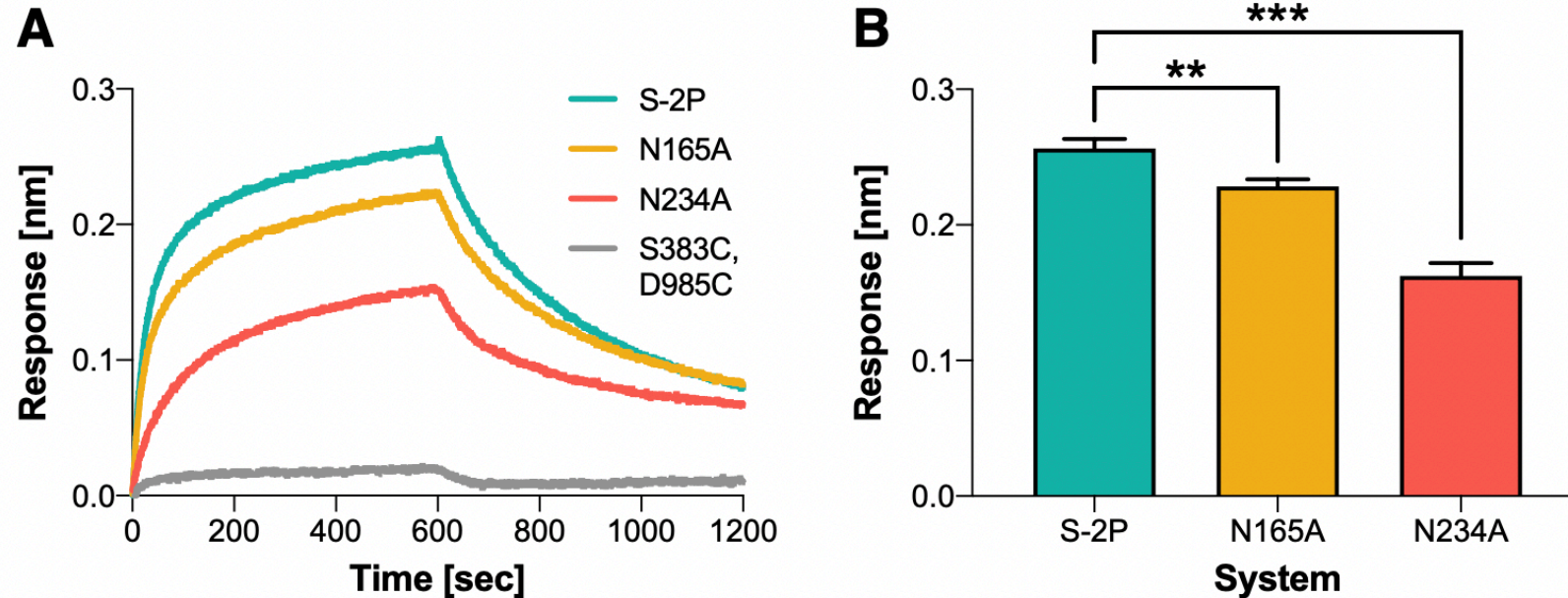
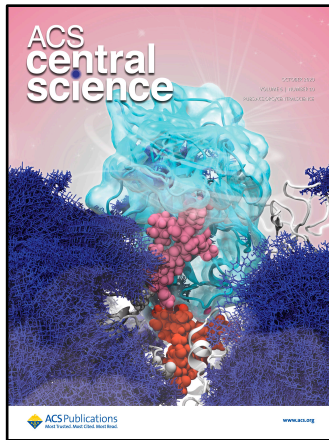


Figure 4. N234A and N165A mutations reduce RBD binding to ACE2. (A) Bi-layer interferometry sensorgrams showing binding of ACE2 to spike variants. (B) Binding responses for bi-layer interferometry measurements of ACE2 binding to spike variants. Data are shown as mean \pm S.D. from 3 independent experiments.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

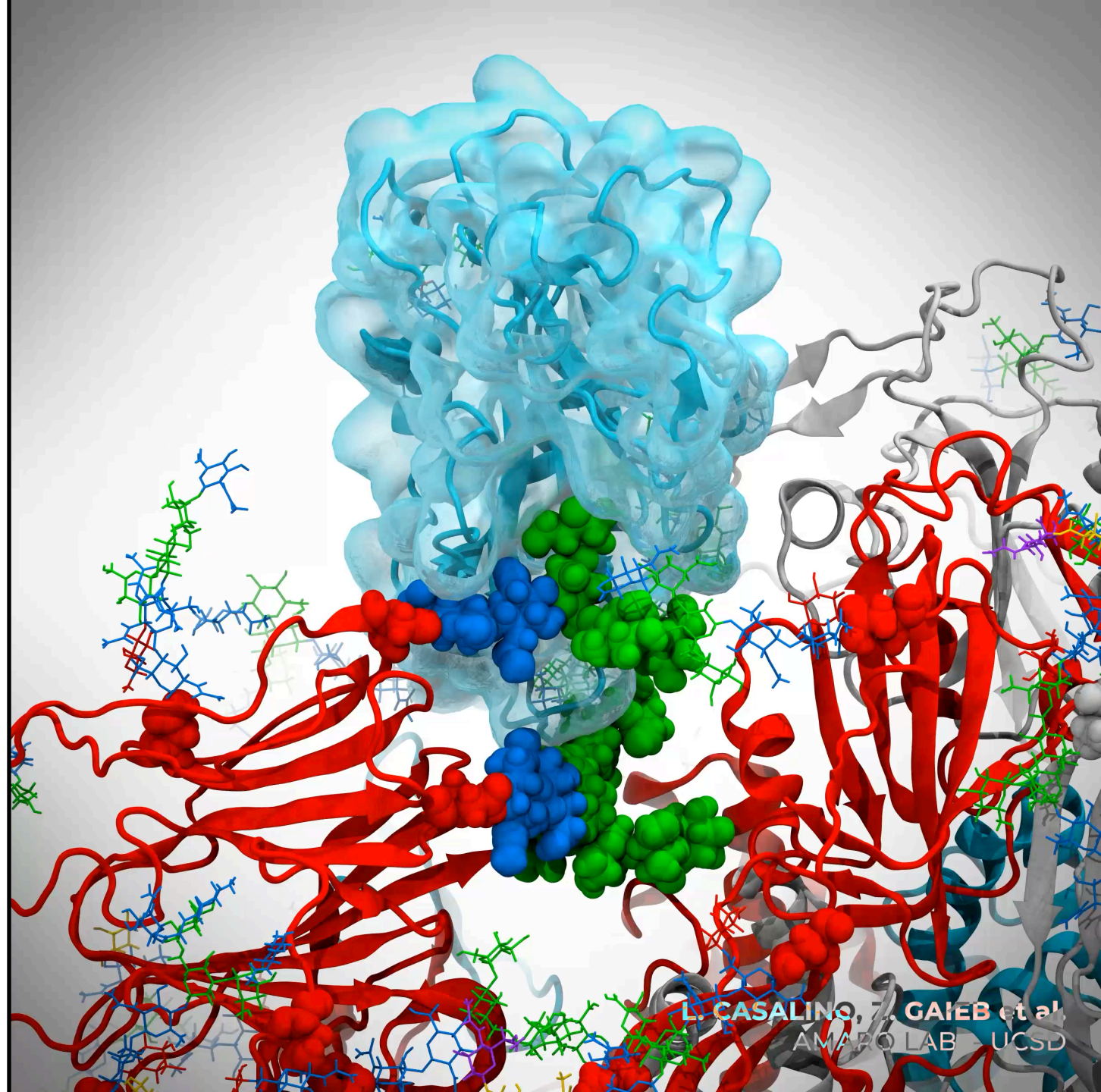
BEYOND shielding...

Simulations established a structural role for glycans

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



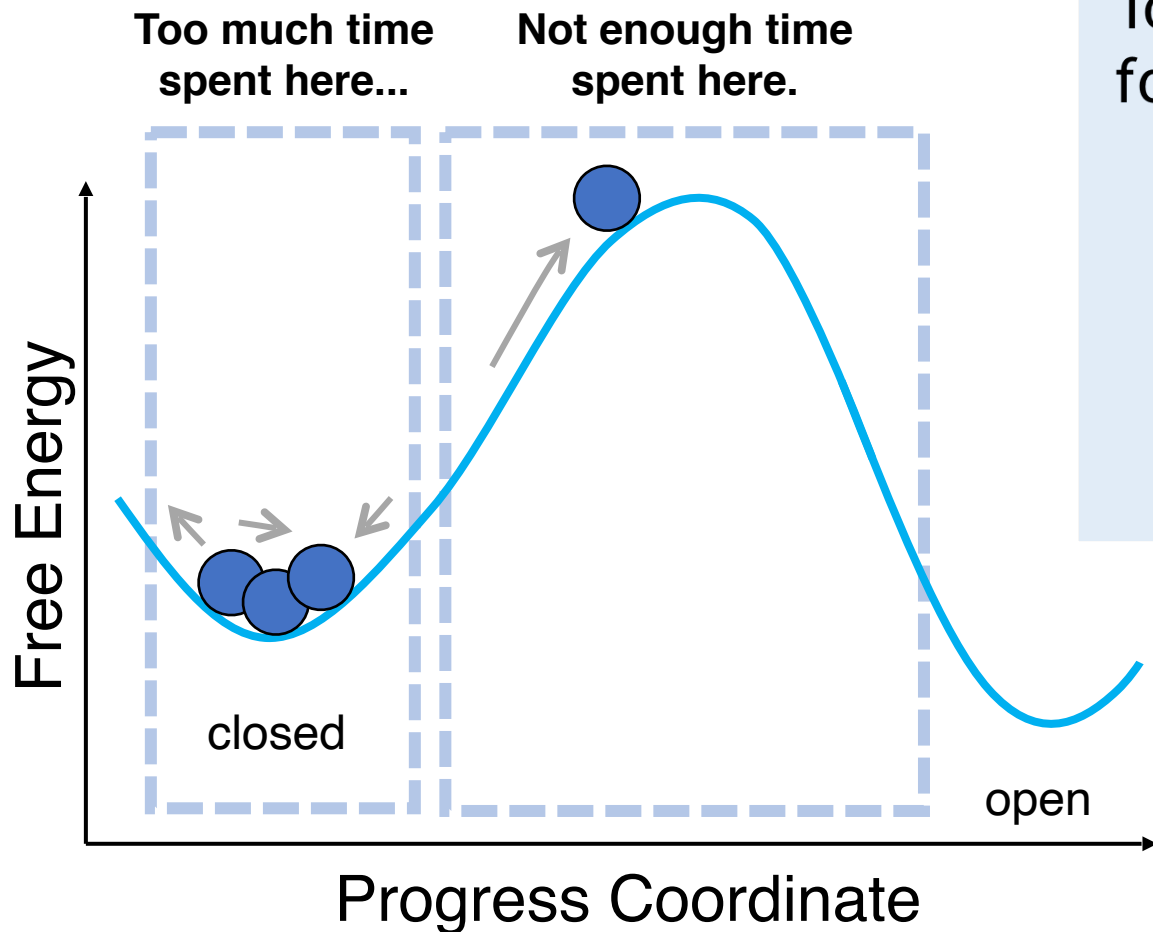
Casalino, Gaieb et al., *ACS Central Science* (2020)



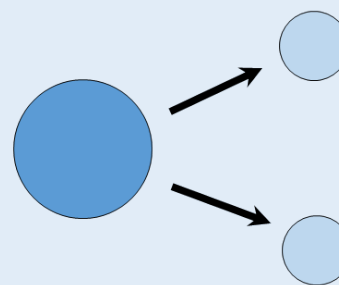
L. CASALINO, Z. GAIEB et al.
AMARO LAB - UCSD

Standard MD simulations of spike opening could take years!

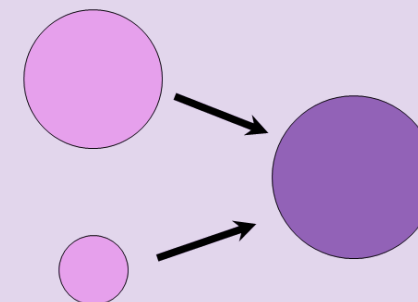
Weighted ensemble MD focuses on functional transitions



To enrich
for success...



To save
computing power...

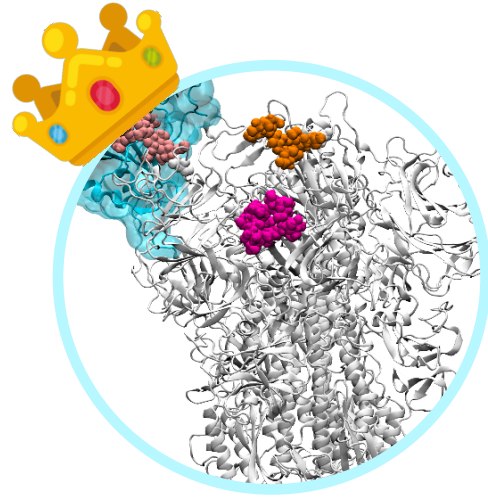


Huber and Kim, *Biophys. Journal* (1996)
Zuckerman and Chong, *Ann. Rev. Biophys.* (2017)

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

Efficiency scales exponentially with the free energy barrier.

Weighted ensemble MD is **>12,000x** more efficient than standard MD!



~500K atoms

AMBER MD

TACC
TEXAS ADVANCED COMPUTING CENTER

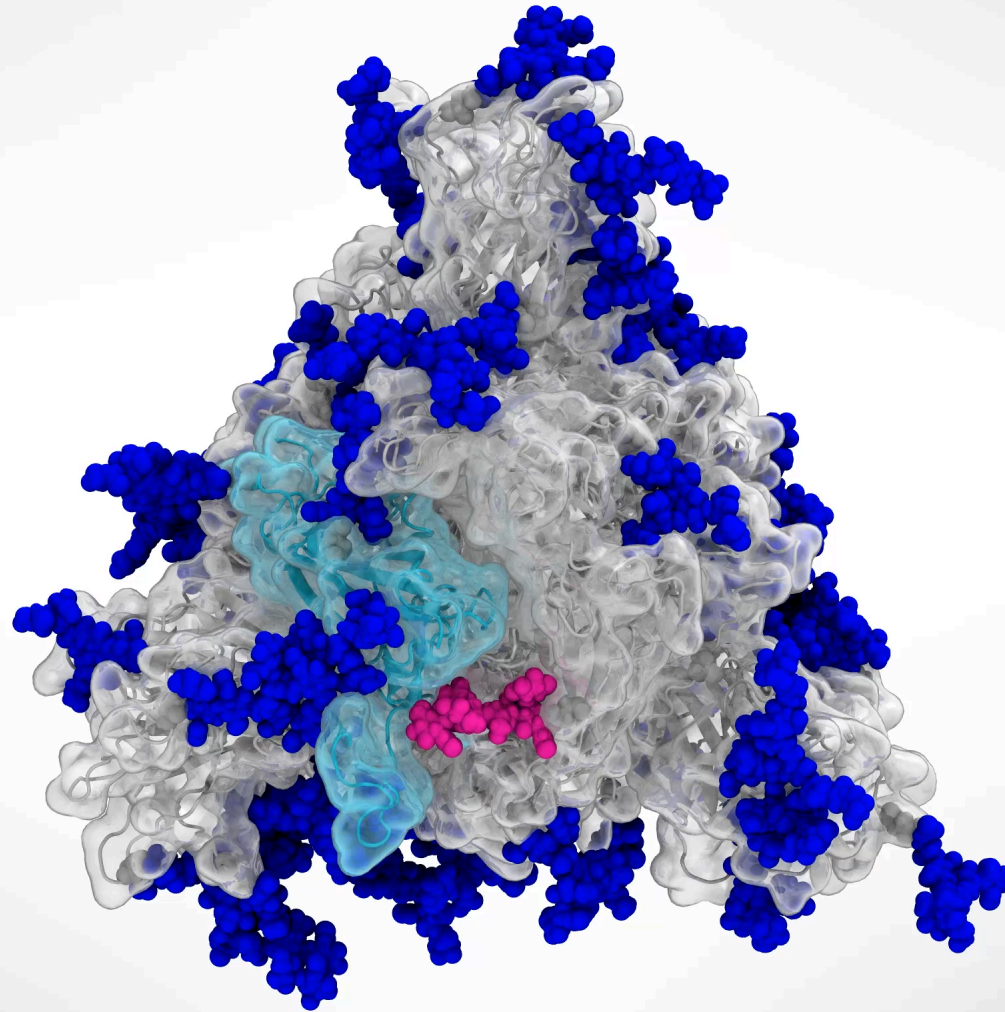
100 NVIDIA V100 GPUs
~100 TB of data

	Weighted Ensemble MD	Standard MD
Number of pathways	310	1
Wall-clock time	23 days	805 years (seconds timescale)*

*Lu *et al.* *Cell Host Microbe*, 28: 880-891 (2020).

Closed Spike

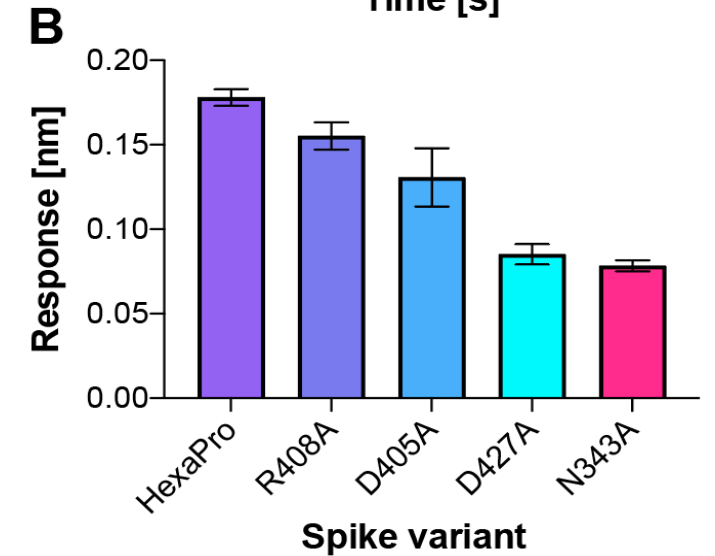
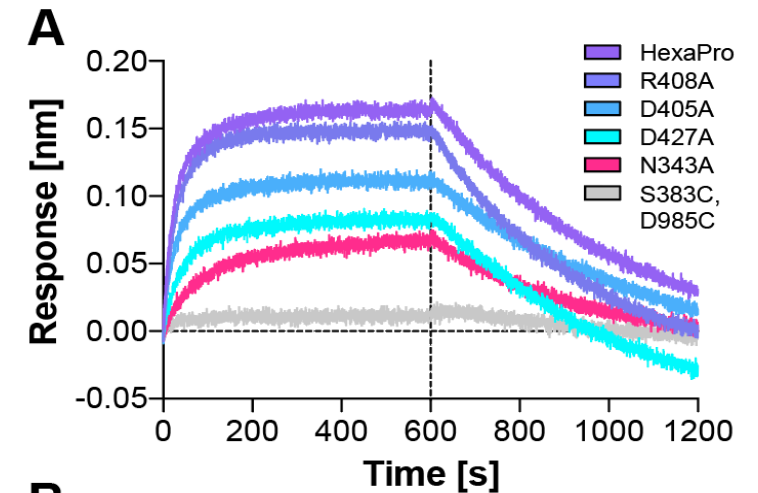
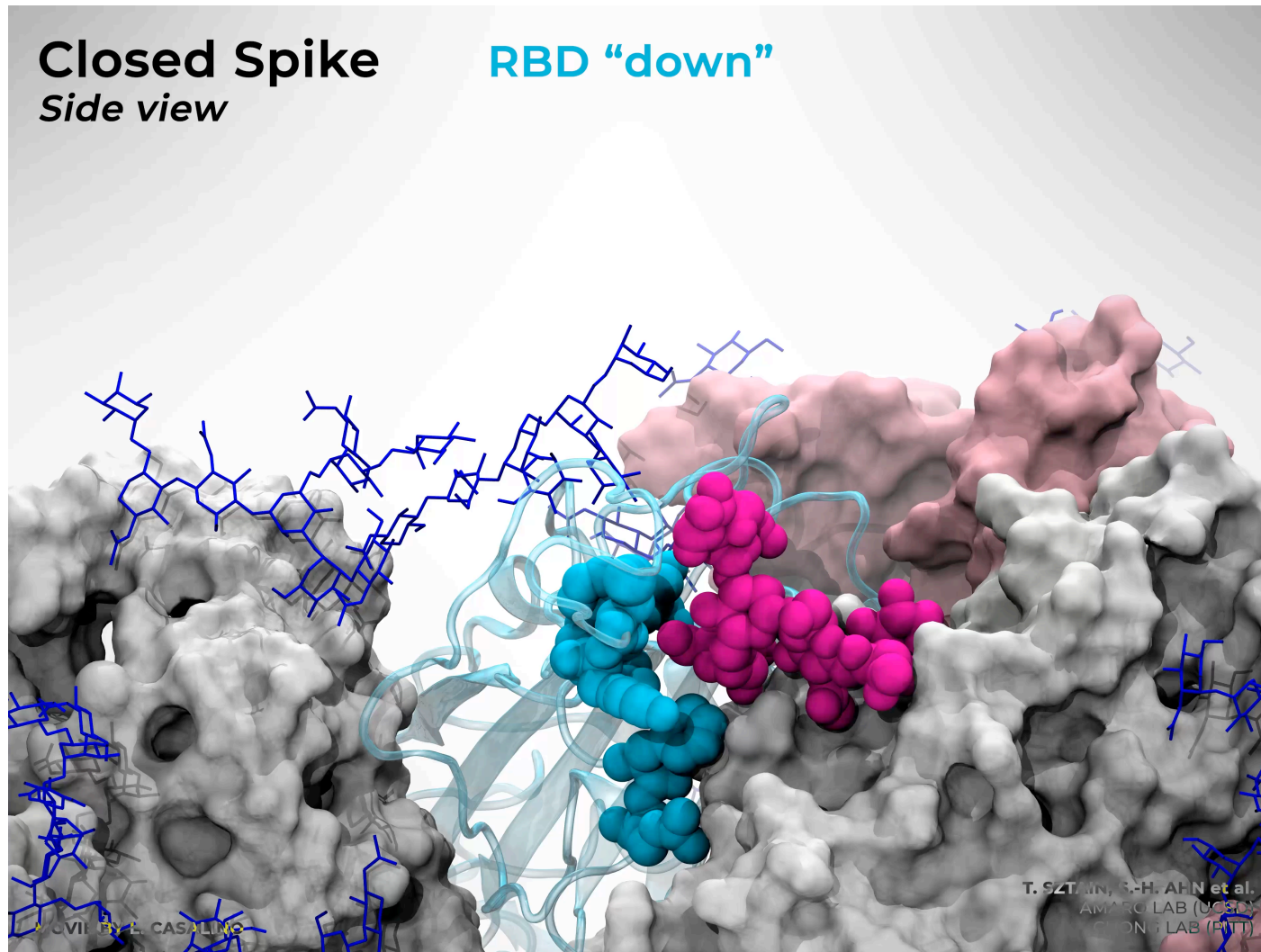
Top view



MOVIE BY L. CASALINO

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

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



**McLellan Lab (UT Austin)
Collaboration**

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

CSH Cold Spring Harbor Laboratory
bioRxiv
THE PREPRINT SERVER FOR BIOLOGY

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

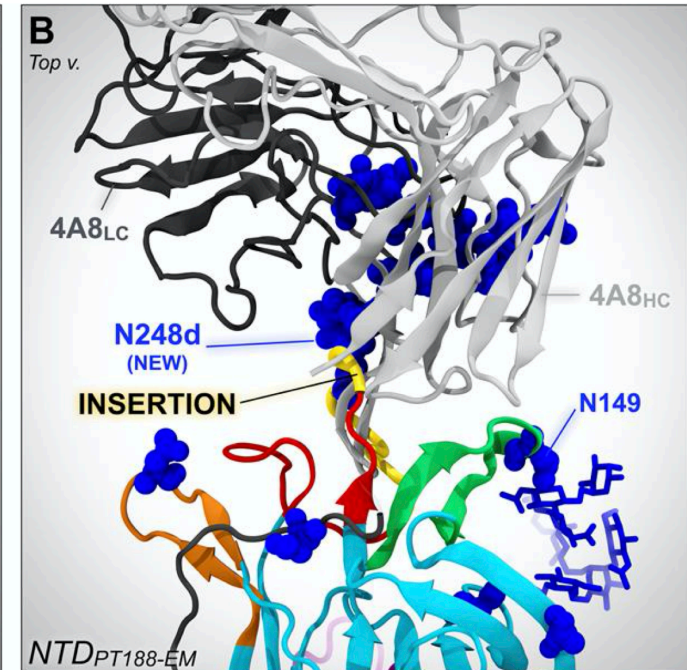
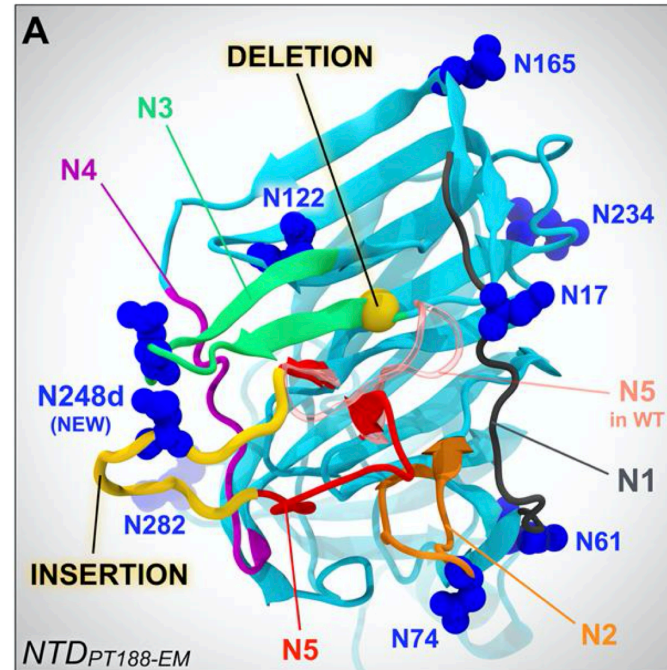
New Results [Comments \(4\)](#)

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

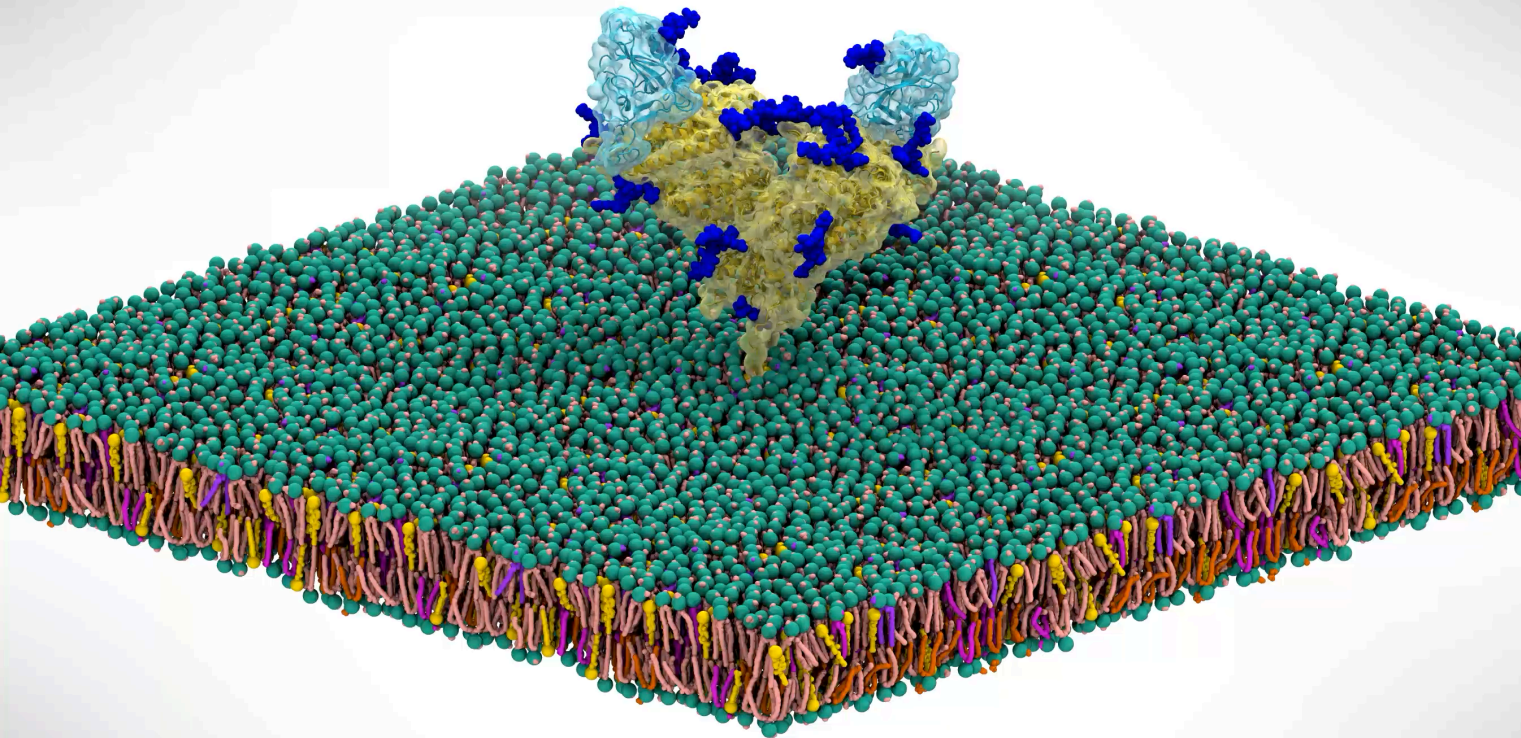
Emanuele Andreano, Giulia Piccini, Danilo Licastro, Lorenzo Casalino, Nicole V. Johnson, Ida Paciello, Simeone Dal Monego, Elisa Pantano, Noemi Manganaro, Alessandro Manenti, Rachele Manna, Elisa Casa, Inesa Hyseni, Linda Benincasa, Emanuele Montomoli, Rommie E. Amaro, Jason S. McLellan, Rino Rappuoli

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?].



ACE2/RBD complex

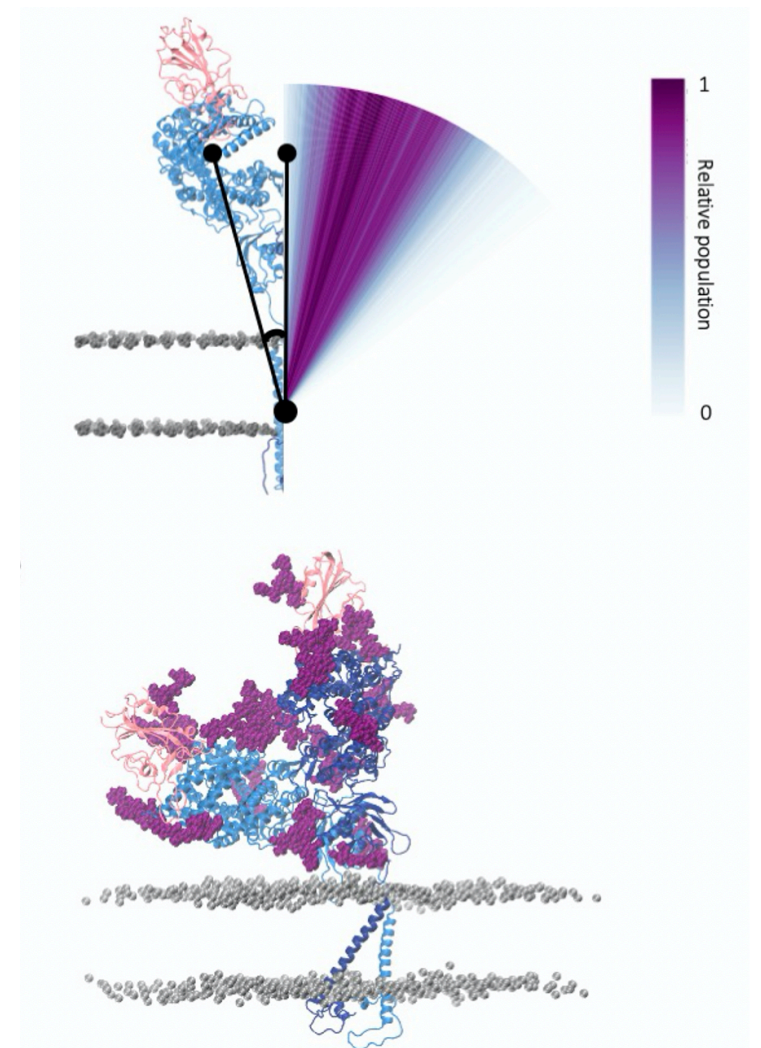


E. P. BARROS et al.
AMARO LAB - UCSD

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,*}

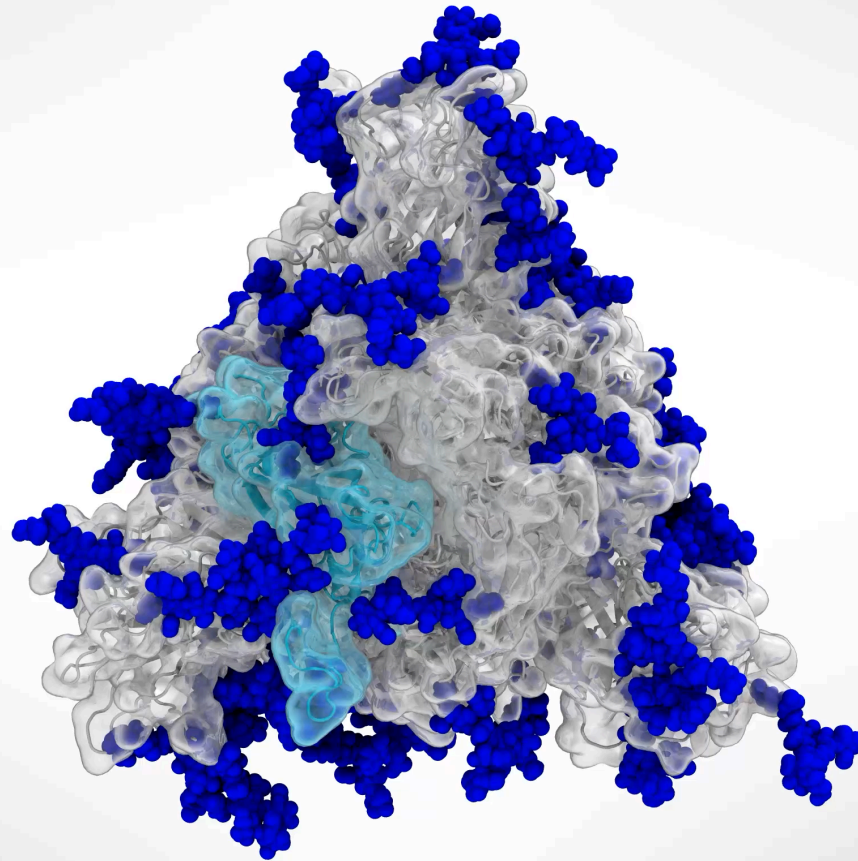
¹Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, California; ²Department of Chemistry and ³Laufer Center for Physical and Quantitative Biology, Stony Brook University, Stony Brook, New York



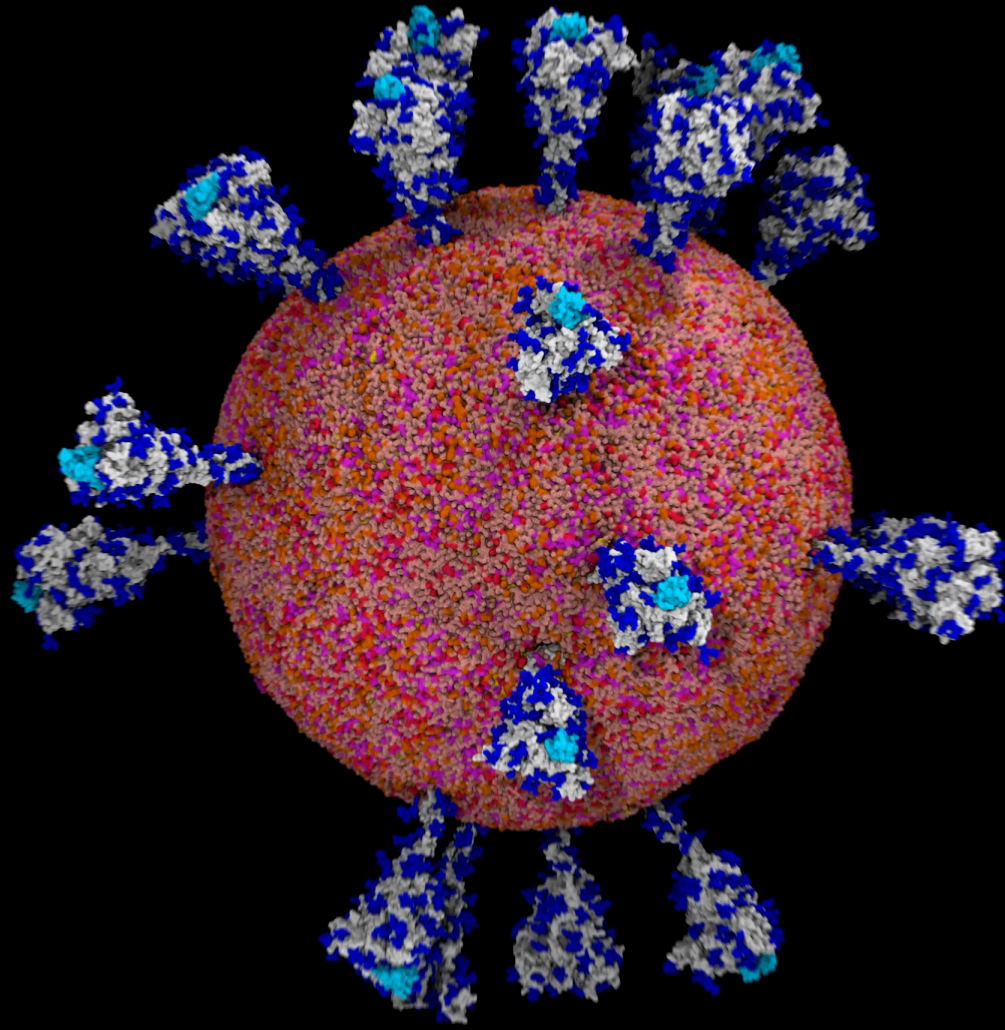
Weighted ensemble simulations show HOW the spike opens & AI acts as a multiscale 'glue' to bridge capability gaps

Closed Spike

Top view



New dimensions for studying viral infection and therapeutics





ACM GORDON BELL SPECIAL PRIZE IN HPC-BASED COVID-19 RESEARCH - WINNER

AI-Driven Multiscale Simulations Illuminate Mechanisms of SARS-CoV-2 Spike Dynamics

University of California San Diego, Argonne National Laboratory, University of Illinois Urbana-Champaign, NVIDIA Corporation, Stony Brook University, Texas Advanced Computing Center, San Diego Supercomputing Center, Rutgers University, Brookhaven National Laboratory




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*

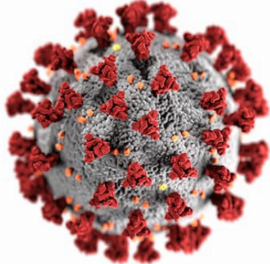
Cite This: <https://dx.doi.org/10.1021/acs.jcim.0c00319> Read Online

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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

COVID-19 Molecular Structure and Therapeutics Hub

Aggregating critical information to accelerate drug discovery for the molecular modeling and simulation community.



Please contribute to curation and data at this site!

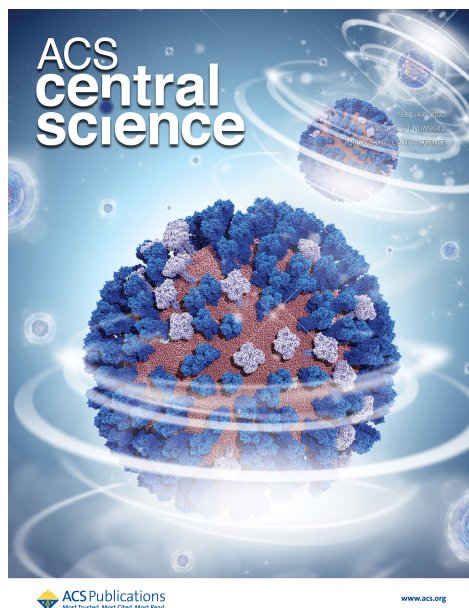
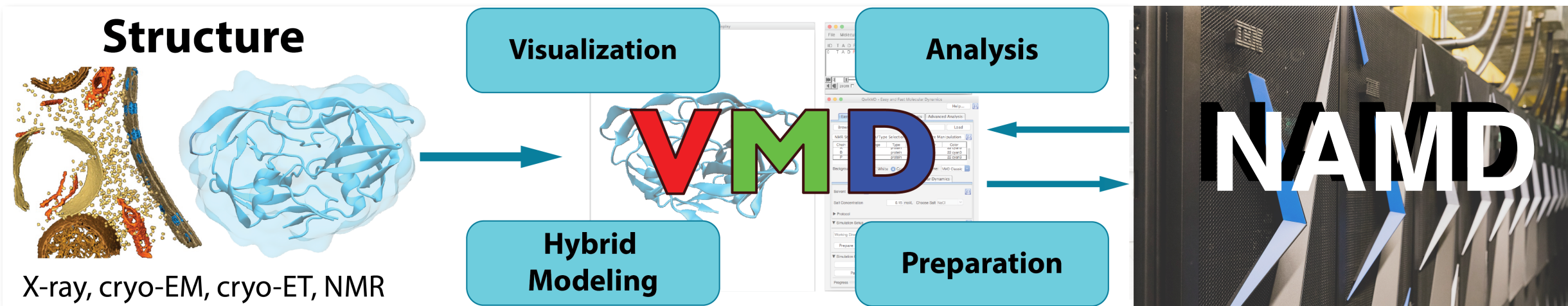
<http://covid.molssi.org>

> 200 groups signed on!

Frontiera datasets shared > 4k times

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

NAMD+VMD Molecular Modeling Tools



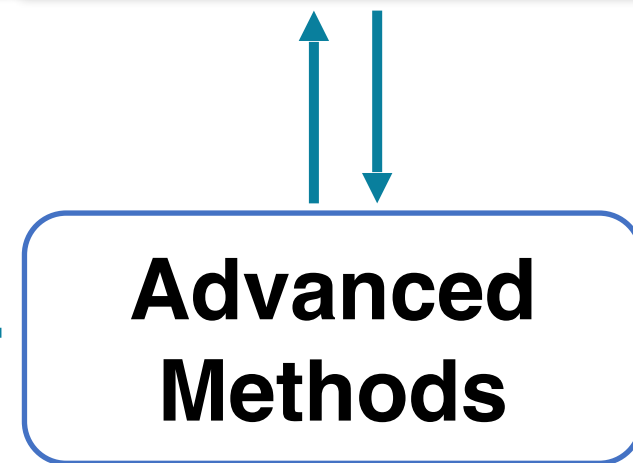
Weighted Ensembles

AI Driven MD

Collective Variables

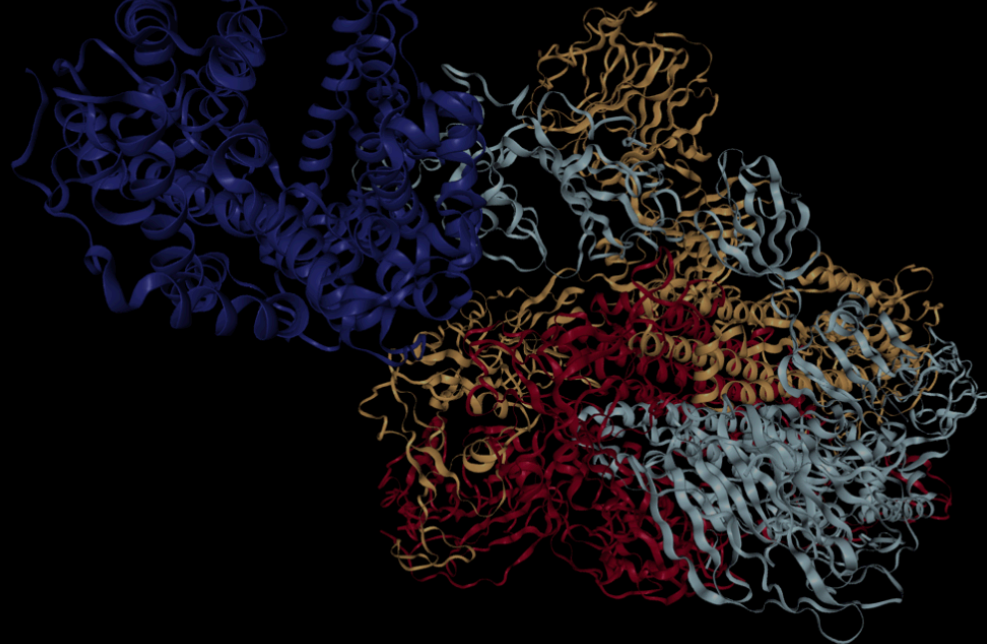
...

Importance of community software, open access



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



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

