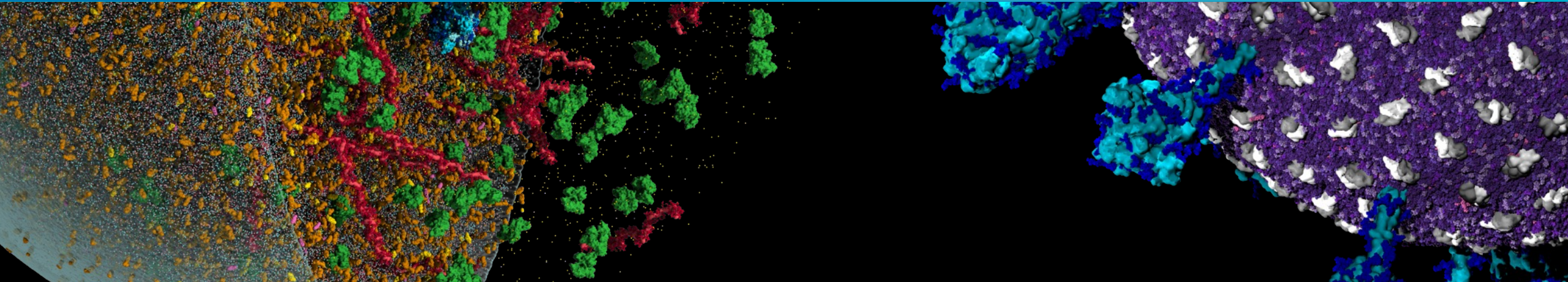


Pushing the boundaries of ultra large-scale molecular simulations and unraveling the mechanisms behind aerosol transmission of SARS-CoV-2

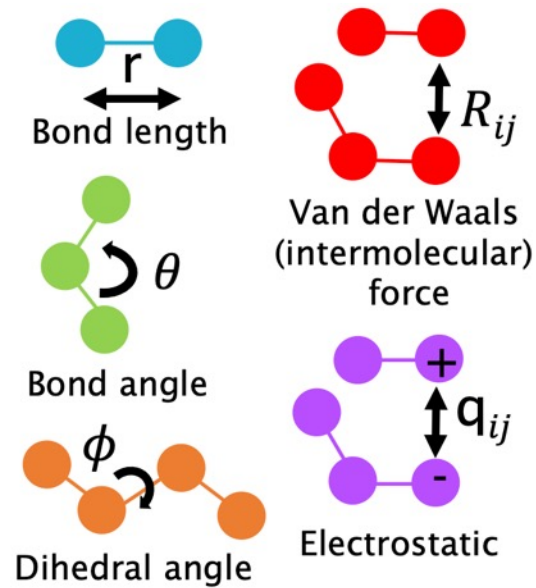
Nicholas Wauer

10/17/2023

Abigail Dommer, Lorenzo Casalino, Fiona Kearns, Mia Rosenfeld, Clare Morris,
Rommie Amaro



Molecular Dynamics simulation as a Computational Microscope

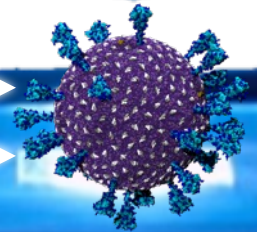


$$U(\vec{R}) = \underbrace{\sum_{bonds} k_i^{bond} (r_i - r_0)^2}_{\text{Bond length}} + \underbrace{\sum_{angles} k_i^{angle} (\theta_i - \theta_0)^2}_{\text{Bond angle}} + \underbrace{\sum_{dihed} k_i^{dihed} [1 + \cos(n_i \phi_i + \delta_i)]}_{\text{Dihedral angle}} + \underbrace{\sum_i \sum_{j \neq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

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



CryoEM / Tomography / X-ray
Glycomics / Lipidomics / Genomic



SARS-CoV-2 has had dreadful consequences

Impacts of COVID

- 6,881,955 deaths globally
- 676,609,955 of cases worldwide
- -3.4% change in world GDP in 2020

Long COVID

- Unknown long-term impacts
- 1 in 5 people who have had COVID

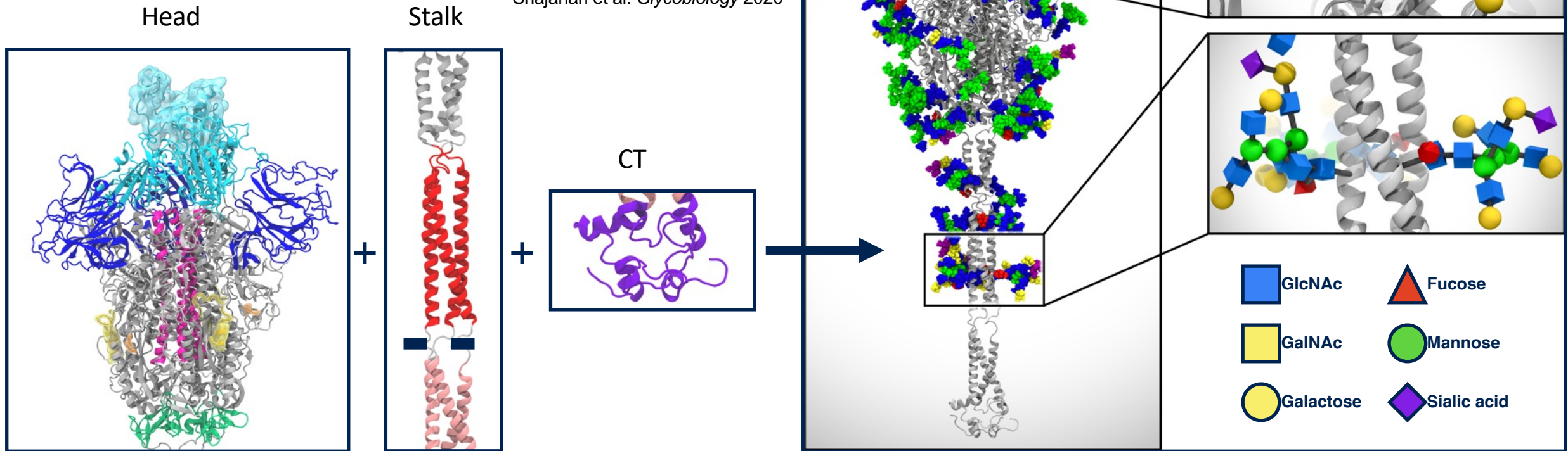
Understanding transmission mechanisms is crucial limiting impacts

- Applicable to future diseases and potential pandemics

Modeling of the full-length, glycosylated SARS-CoV-2 spike

- Starting from available cryo-EM data, we modeled the full-length spike, including missing parts.
- We then modeled glycans according to glycomics data

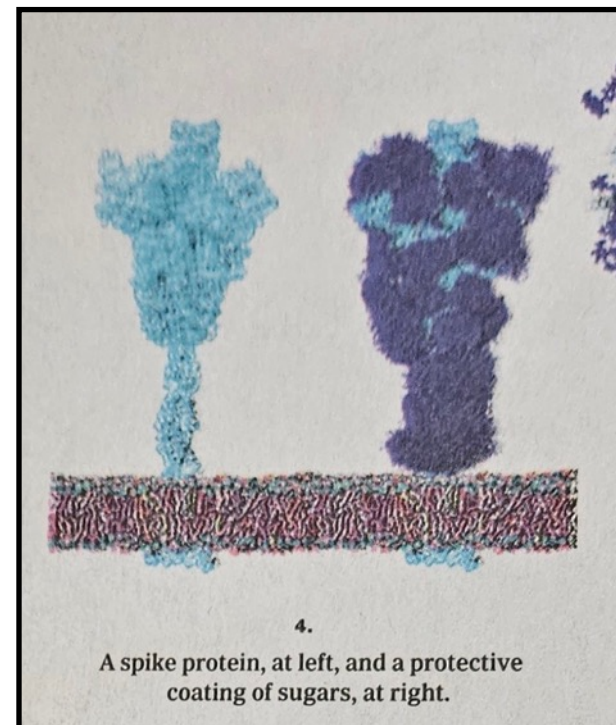
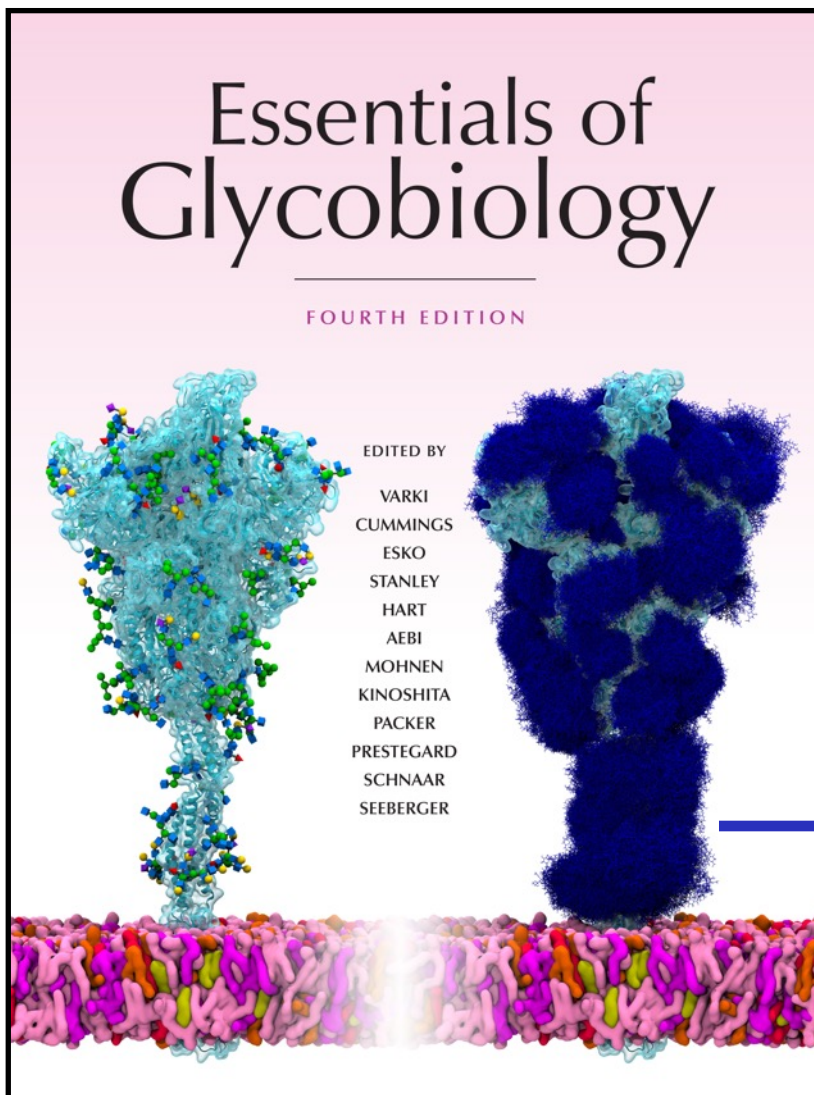
Watanabe et al. *Science* 2020
Shajahan et al. *Glycobiology* 2020



PDB ID: 6VSB

Wrapp et al. *Science* 2020

The look of the glycan shield: The furry spike



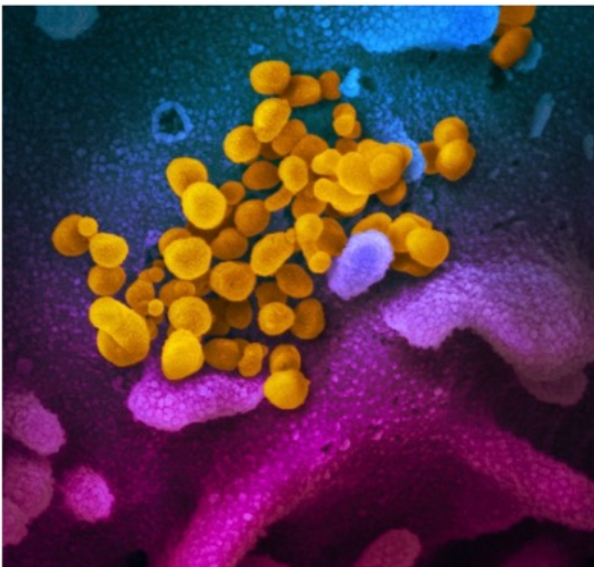
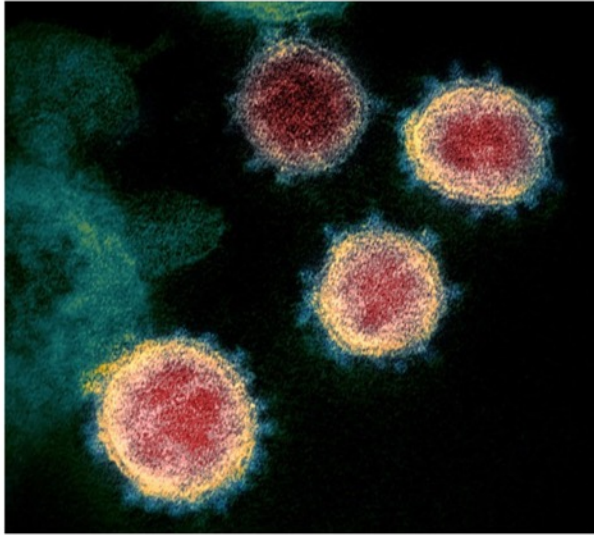
GLYCANS



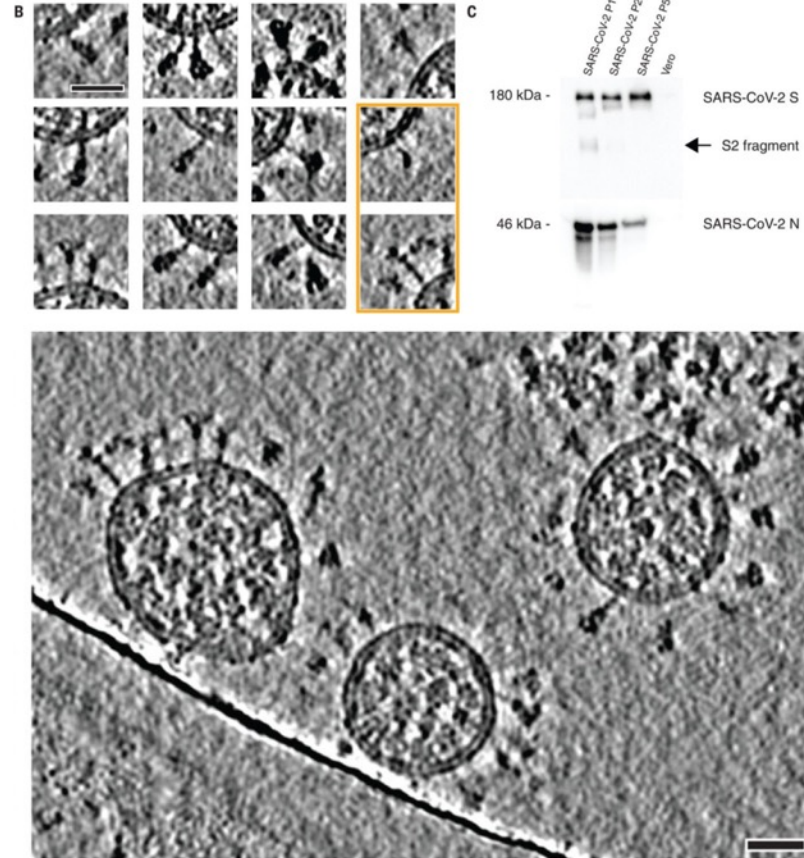
Beyond Shielding: The Roles of Glycans in the SARS-CoV-2 Spike Protein

Lorenzo Casalino,^{*} Zied Gaieb,^{*} Jory A. Goldsmith, Christy K. Hjorth, Abigail C. Dommer, Aoife M. Harbison, Carl A. Fogarty, Emilia P. Barros, Bryn C. Taylor, Jason S. McLellan, Elisa Fadda, and Rommie E. Amaro^{*}

Next scale: SARS-CoV-2 virion morphology

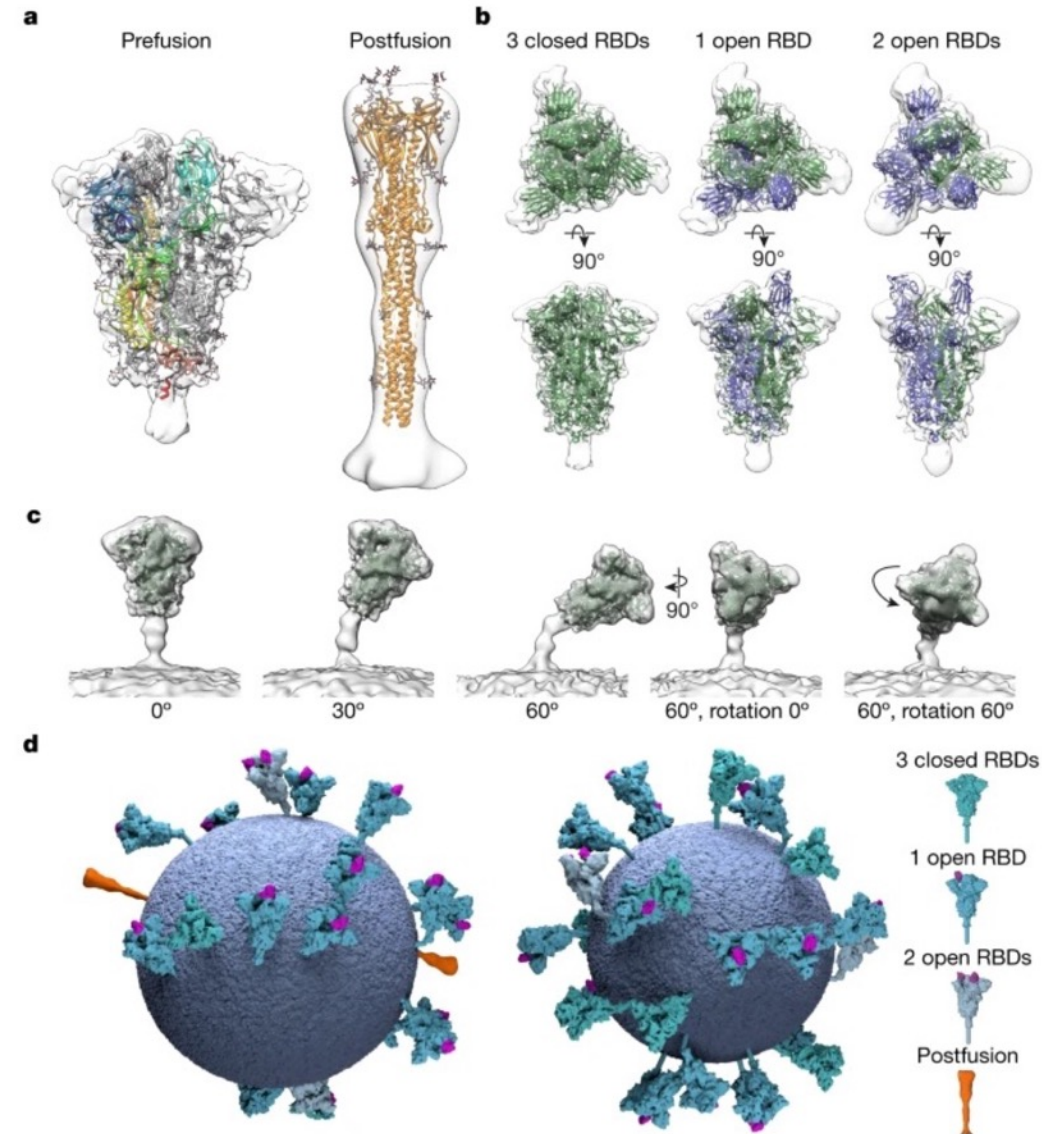


Scanning TEM images of SARS-CoV-2. NIAID Rocky Mountain Labs, February 13, 2020



Cryo-electron tomography of SARS-CoV-2 virions. Turonova, Sikora, and Schürmann, et al. *Science*, **370**, 6513, 203-208 (2020)

Fig. 2: Structural analysis of SARS-CoV-2 S trimers on intact virions.



John Briggs Group: Ke, Z. et al. *Nature*, **588**, 498-502 (2020)

First SARS-CoV-2 full virion model

Special Issue Paper

International Journal of
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COMPUTING APPLICATIONS

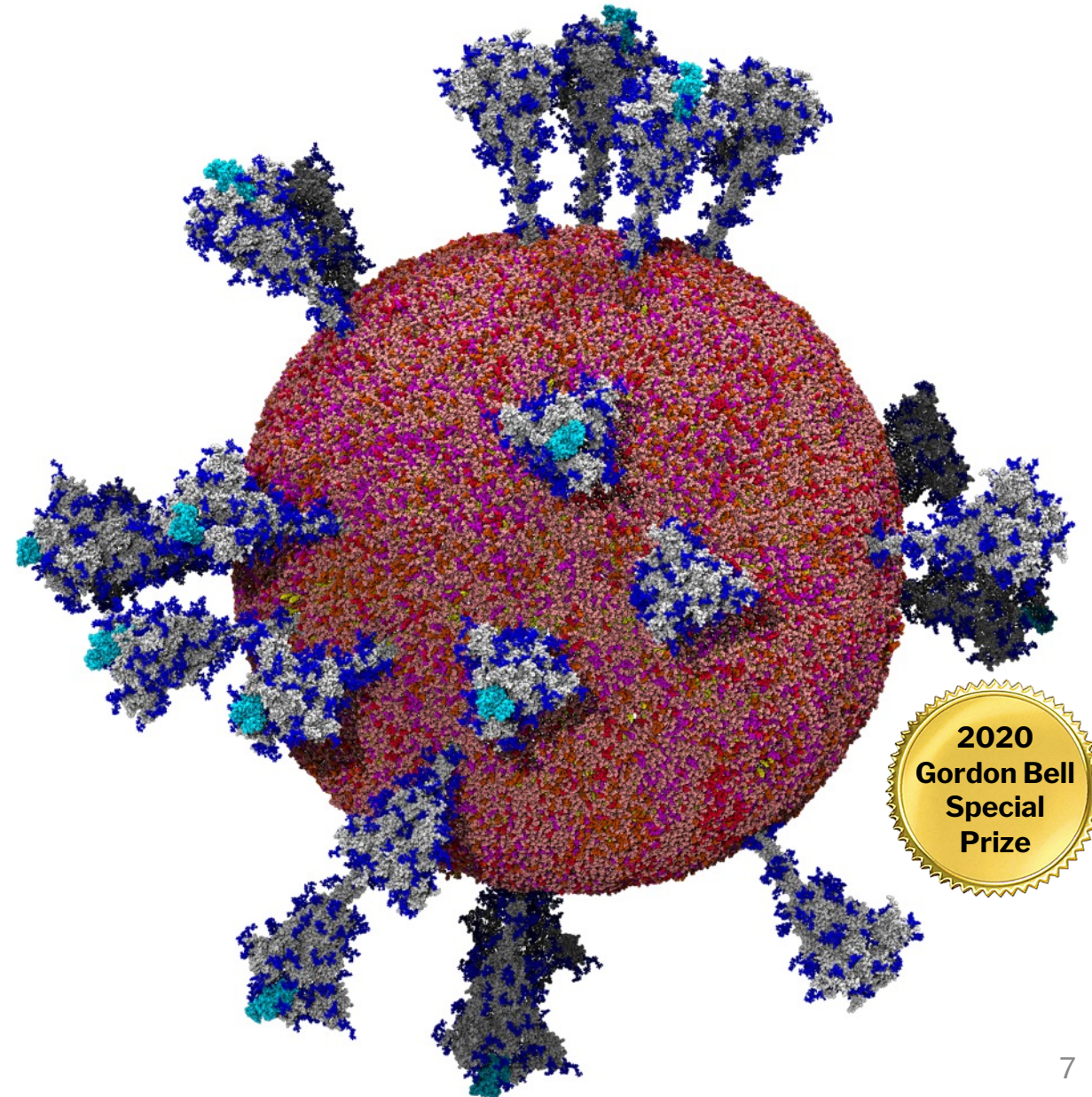
AI-driven multiscale simulations illuminate mechanisms of SARS-CoV-2 spike dynamics

Lorenzo Casalino^{1,†}, Abigail C Dommer^{1,†}, Zied Gaieb^{1,†},
Emilia P Barros¹, Terra Sztain¹, Surl-Hee Ahn¹,
Anda Trifan^{2,3}, Alexander Brace², Anthony T Bogetti⁴,
Austin Clyde^{2,5}, Heng Ma², Hyungro Lee⁶, Matteo Turilli⁶,
Syma Khalid⁸, Lillian T Chong⁴, Carlos Simmerling⁹,
David J Hardy³, Julio DC Maia³, James C Phillips³,
Thorsten Kurth¹⁰, Abraham C Stern¹⁰, Lei Huang¹¹,
John D McCalpin¹¹, Mahidhar Tatineni¹², Tom Gibbs¹⁰,
John E Stone³, Shantenu Jha^{6,7}, Arvind Ramanathan²
and Rommie E Amaro¹

The International Journal of High
Performance Computing Applications
2021, Vol. 35(5) 432–451
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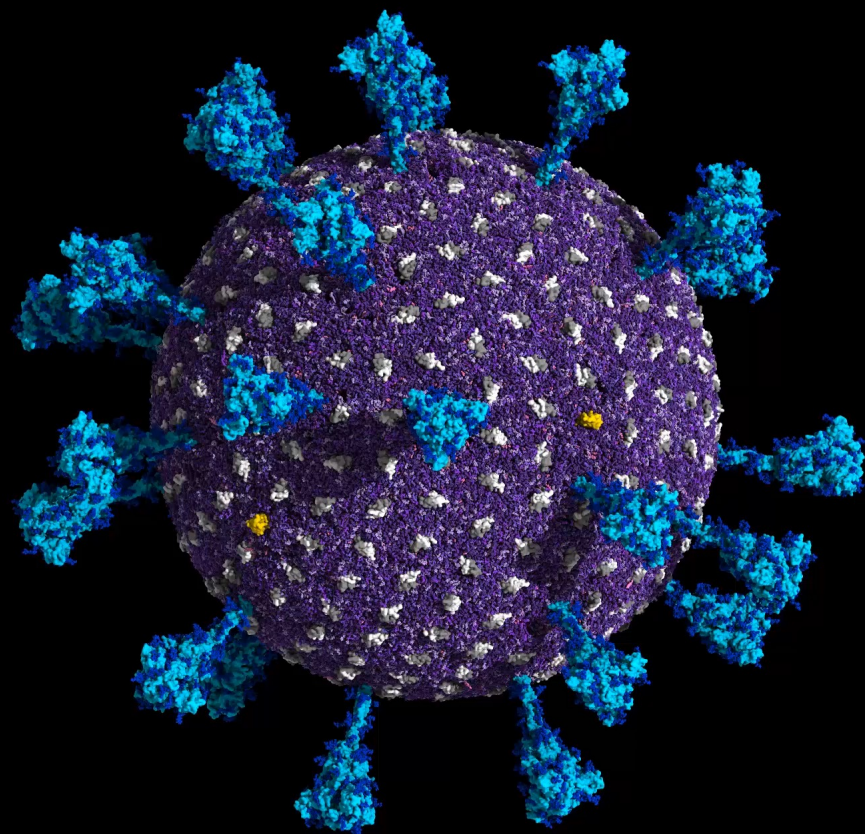


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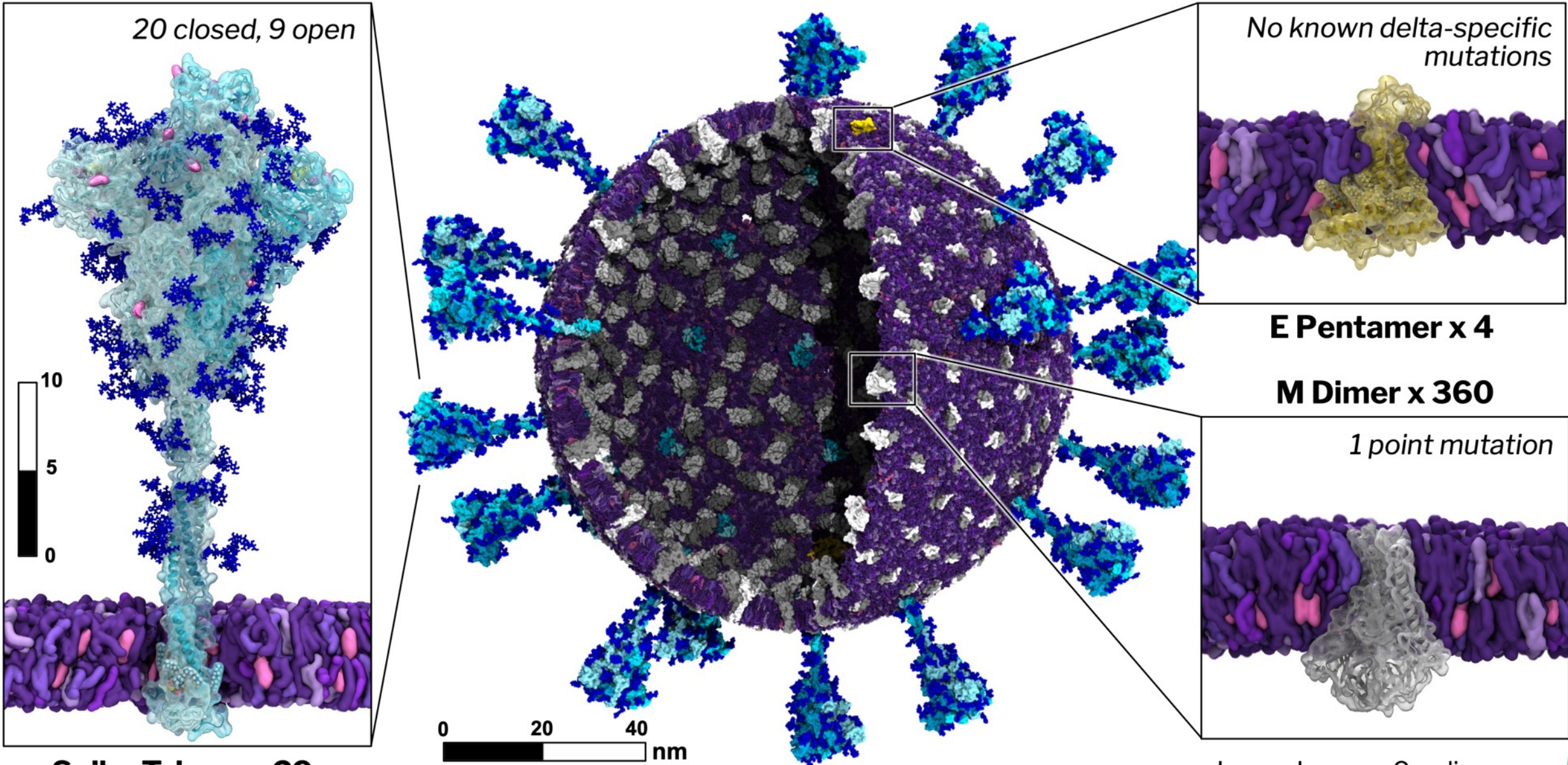
2020
Gordon Bell
Special
Prize





Delta SARS-CoV-2

Building the SARS-CoV-2 Delta Variant virion



COVID-19 is an airborne threat

Int. J. Biol. Sci. 2020, Vol. 16

1678



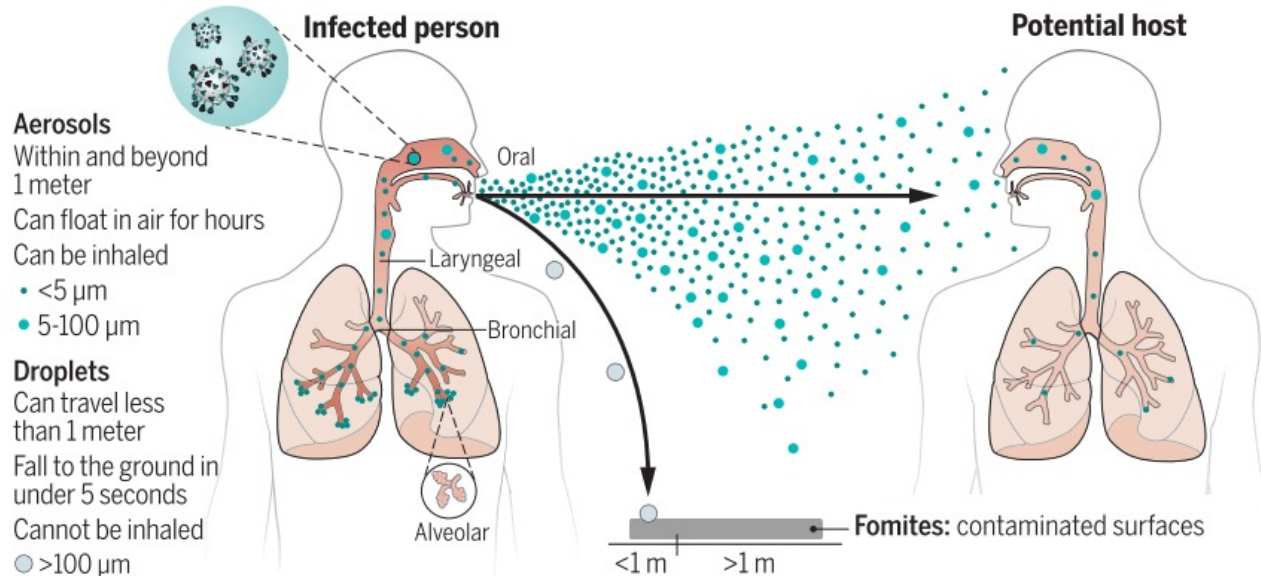
International Journal of Biological Sciences

2020; 16(10): 1678-1685. doi: 10.7150/ijbs.45053

Review

SARS-CoV-2: an Emerging Coronavirus that Causes a Global Threat

Jun Zheng^{1,2}✉



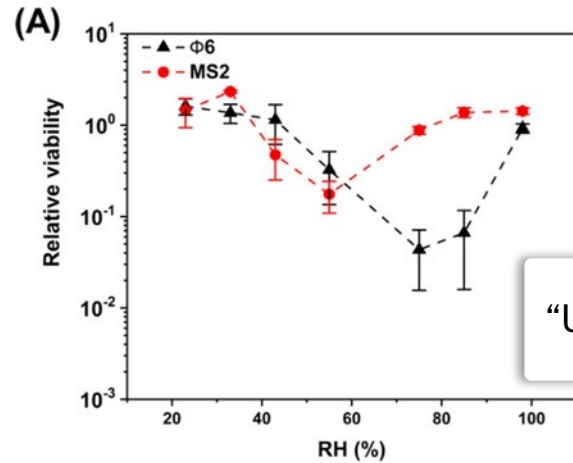
The coronavirus is an airborne threat, the CDC acknowledges.

The new language is a change from the agency's previous position that most infections were acquired through "close contact, not airborne transmission."

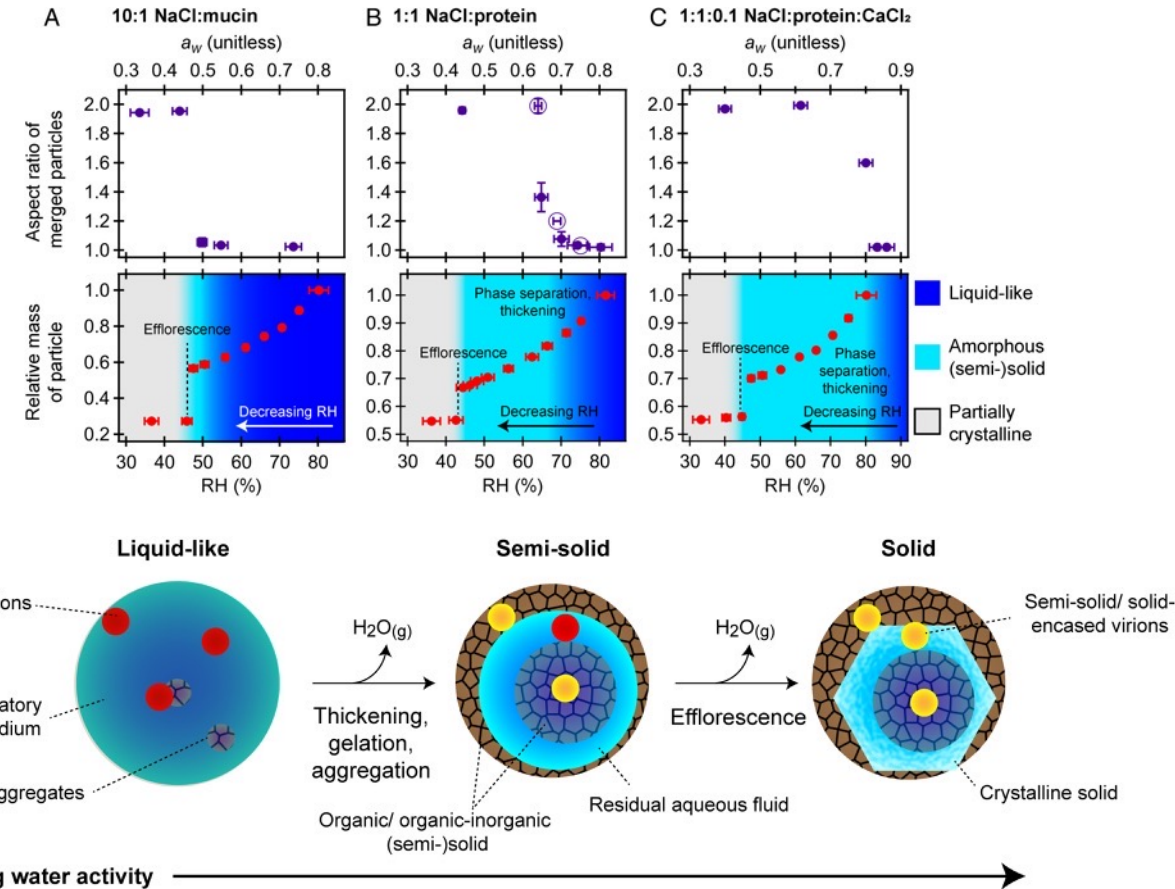
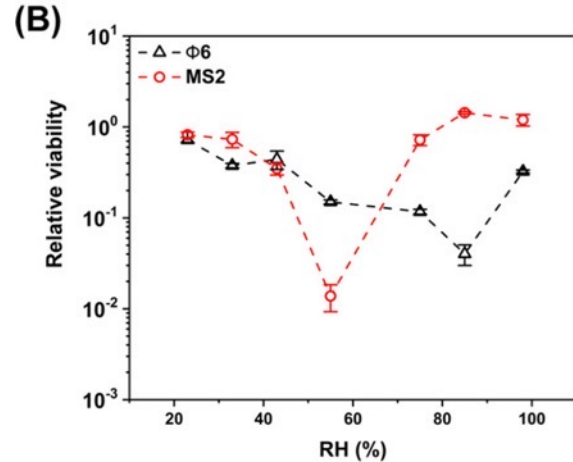
May 7, 2021



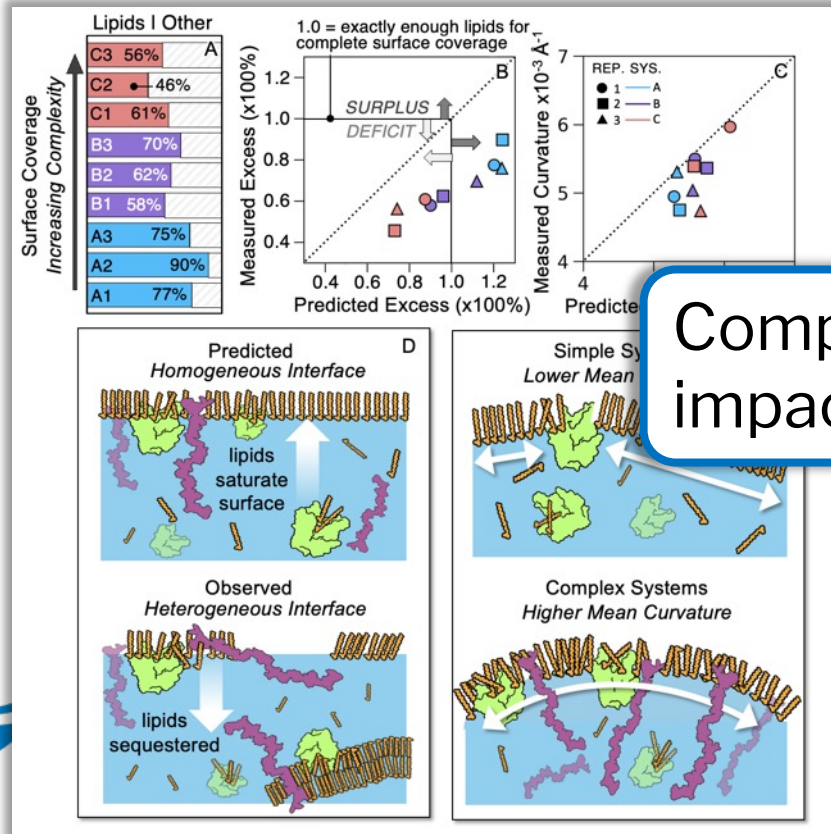
SARS-CoV-2 airborne viability is tricky to study



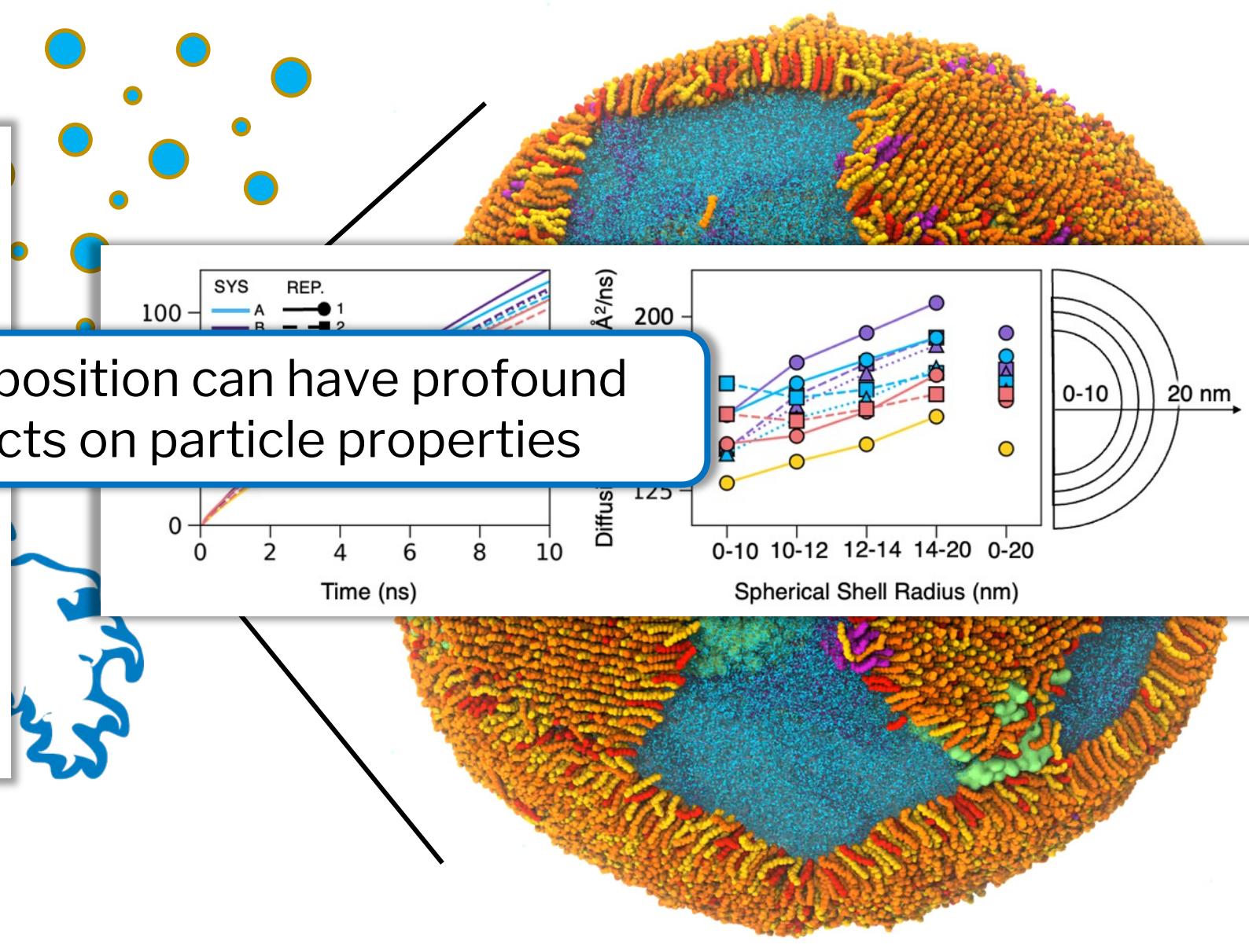
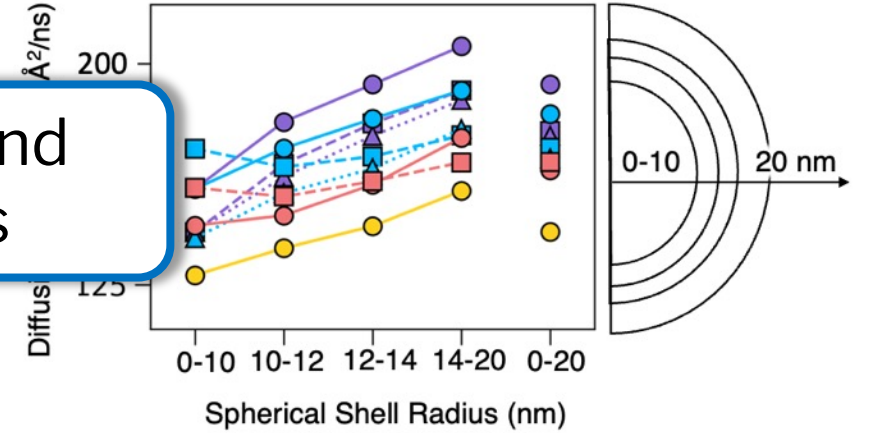
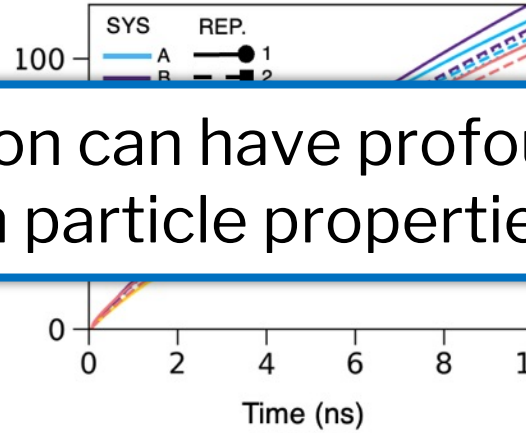
“U” shaped virus viability



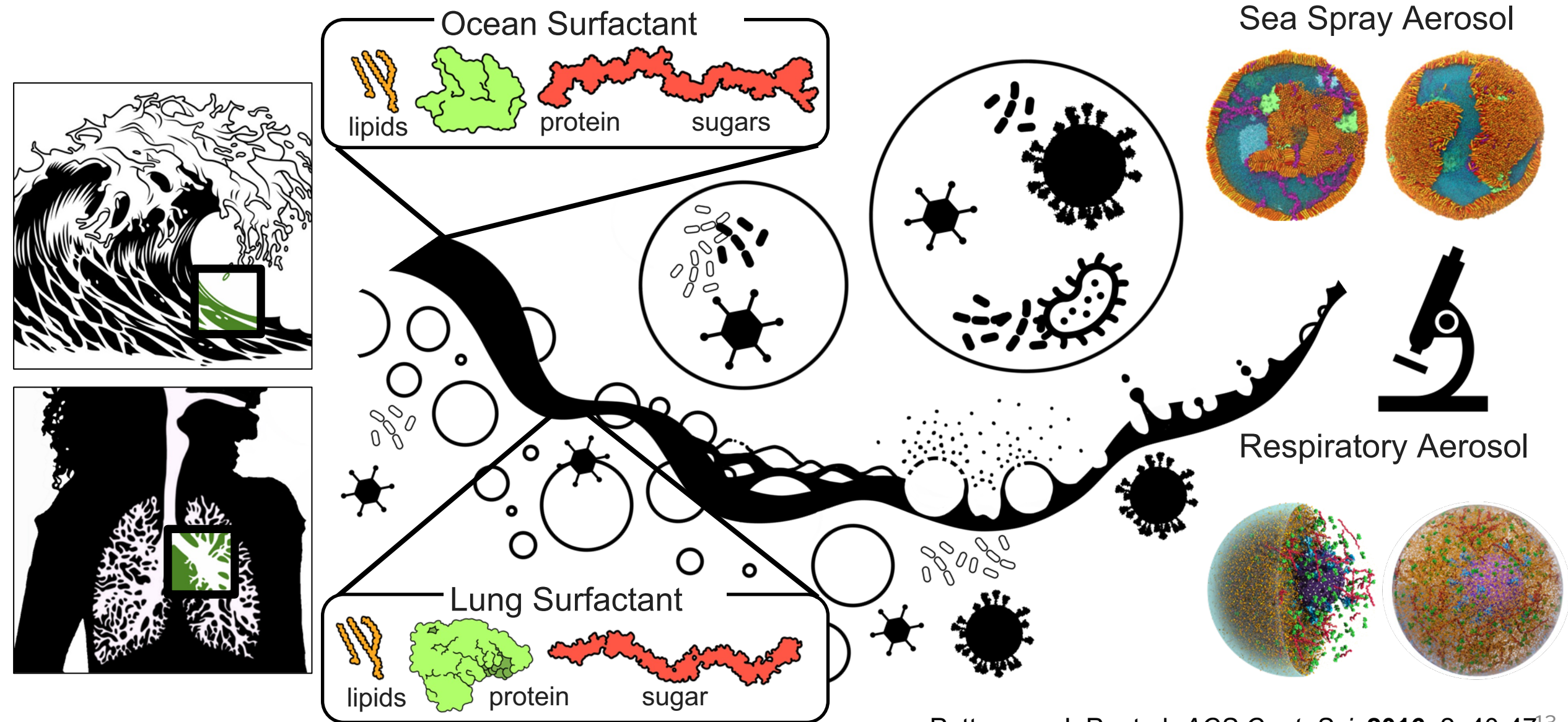
Modeling sea spray aerosols



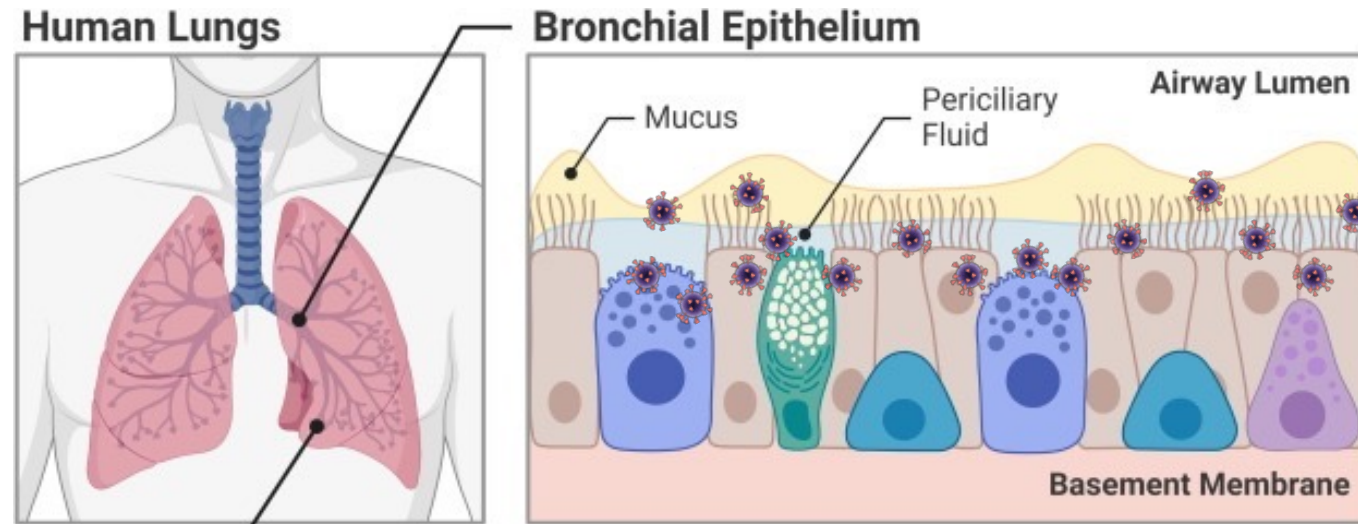
Composition can have profound impacts on particle properties



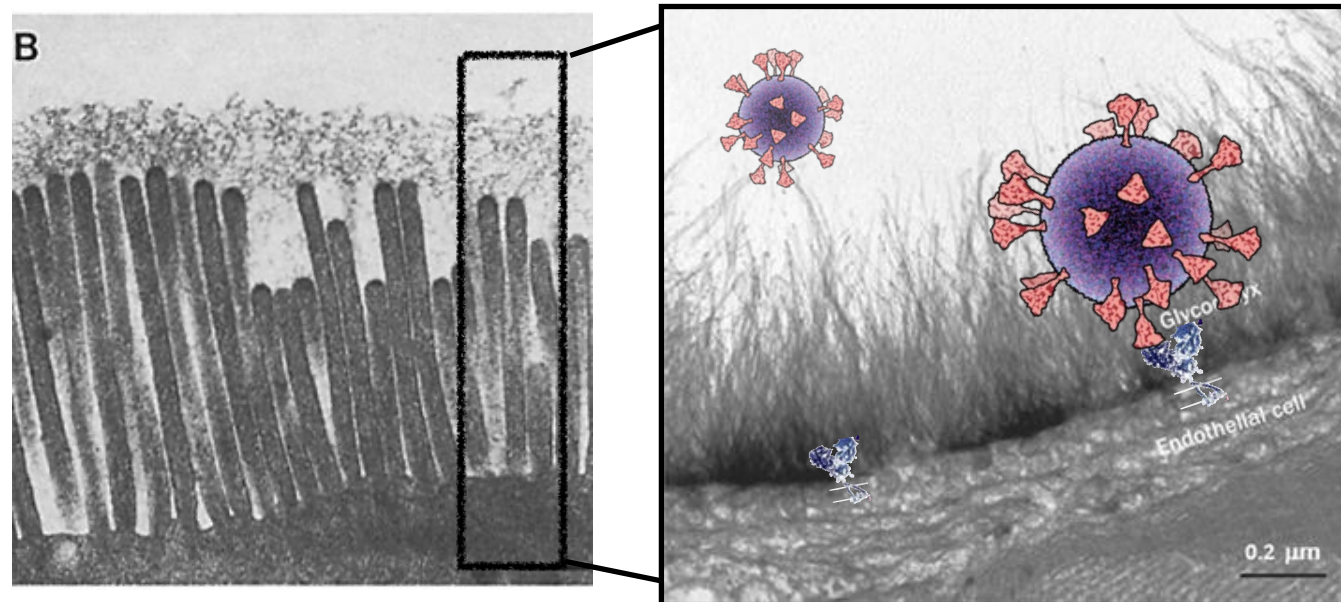
Bubble Bursting through Surfactant



Mucins line our airways and are our first defensive barriers



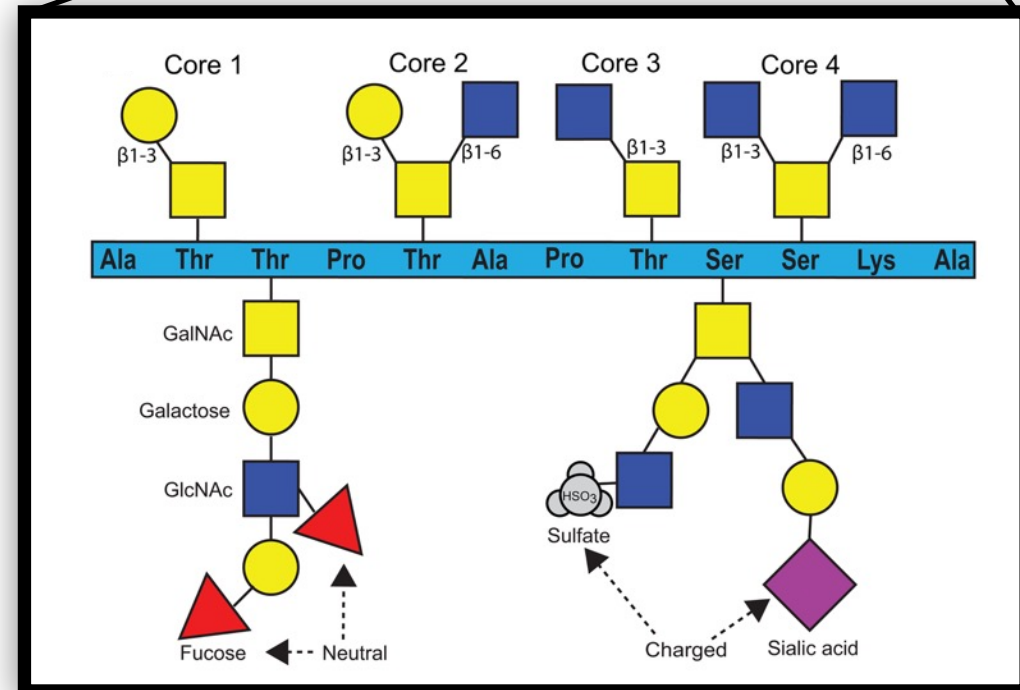
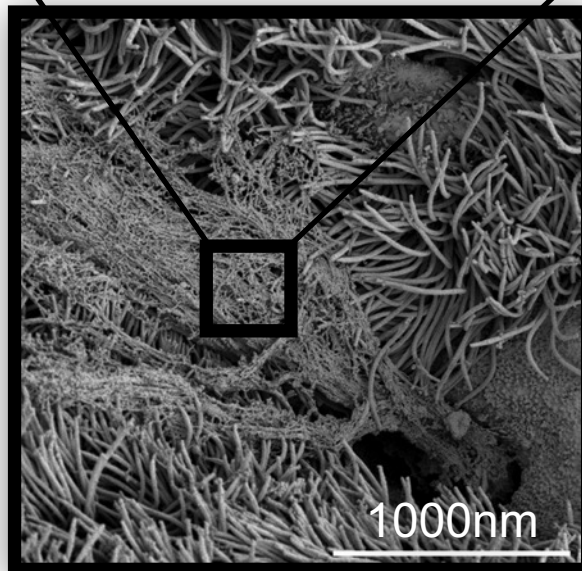
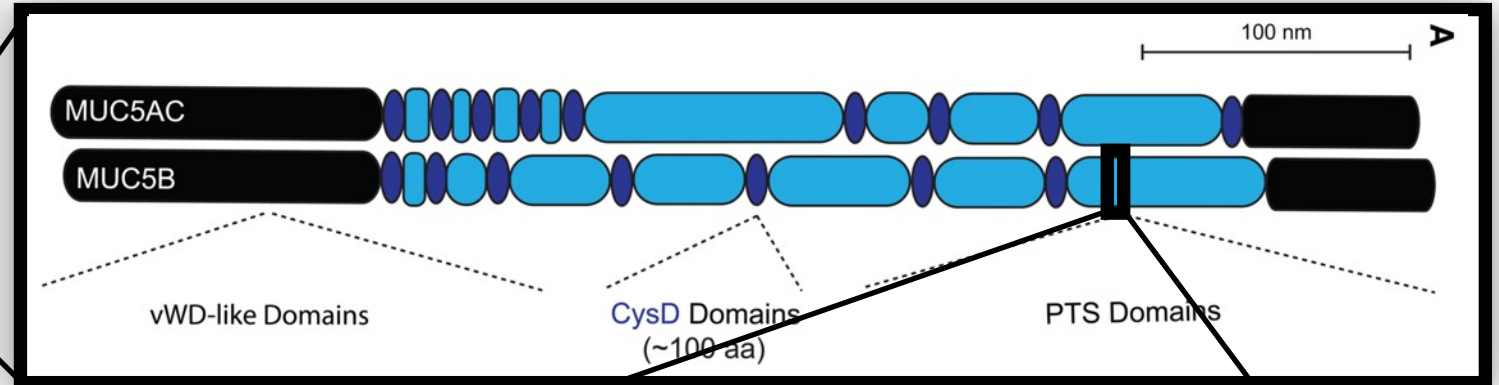
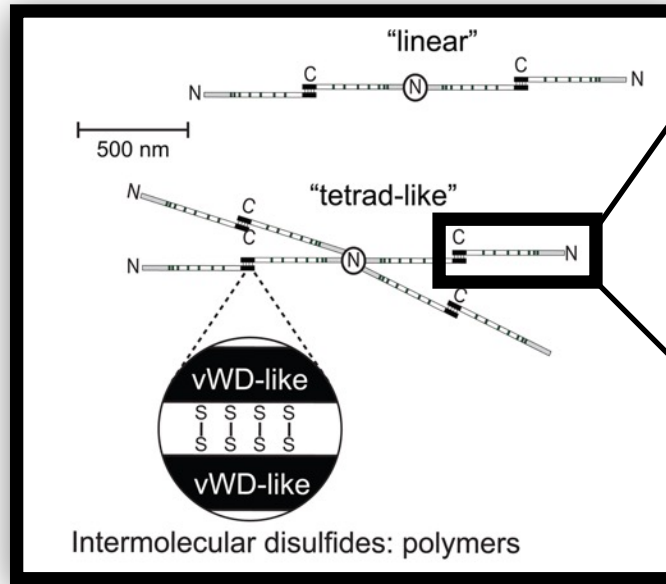
Selo, M. A., Sake, J. A., et al (2021). *Advanced Drug Delivery Reviews*, 177, 113862.



Frey, A., Giannasca, et al. (1996). *Journal of Experimental Medicine*, 184(3), 1045–1059.

Bashandy, G. M. N. (2015). *Journal of Anesthesia*, 29(2), 269–278.

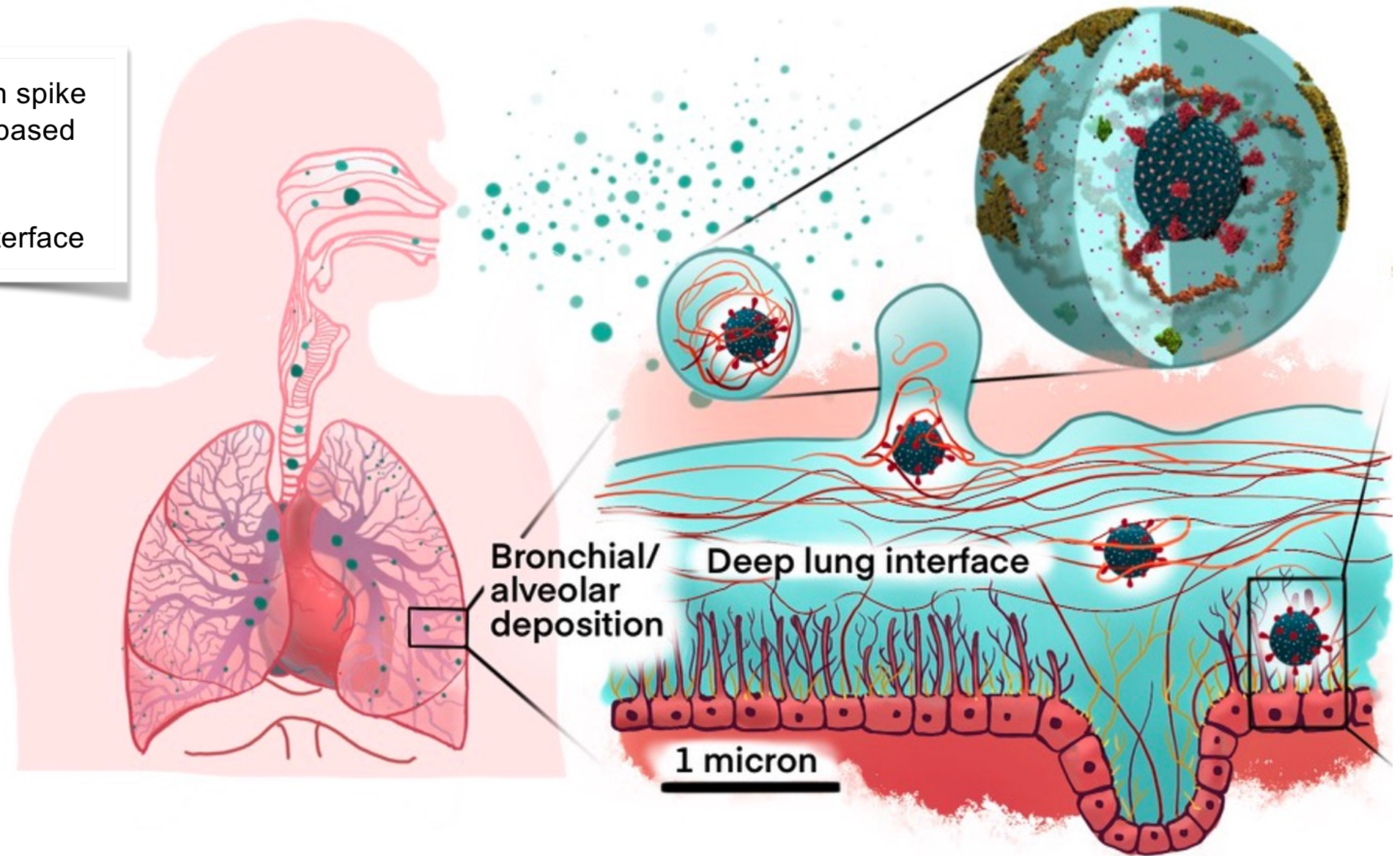
What is a mucin?



SARS-2 in its two environments: aerosolized & air-lung interface

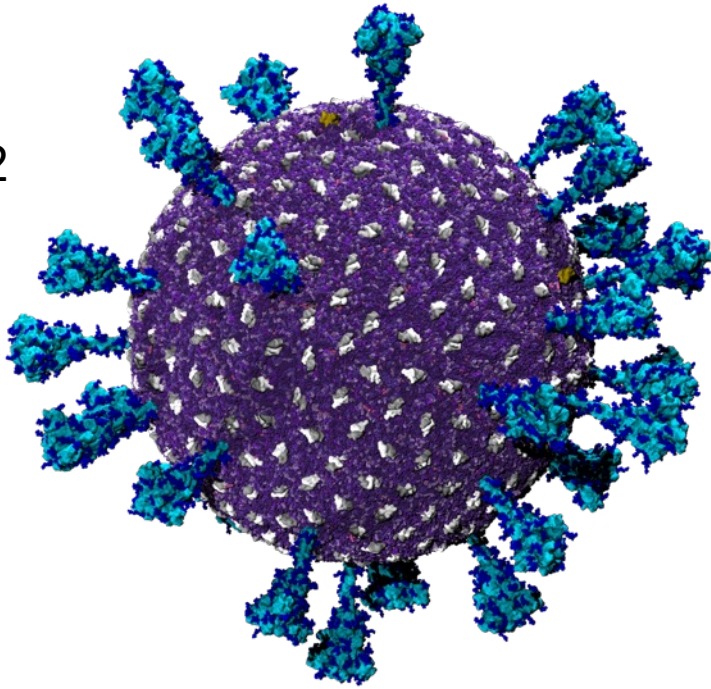
Mucin interactions with spike are expected to differ based on their environment:

Aerosol vs. air-lung interface

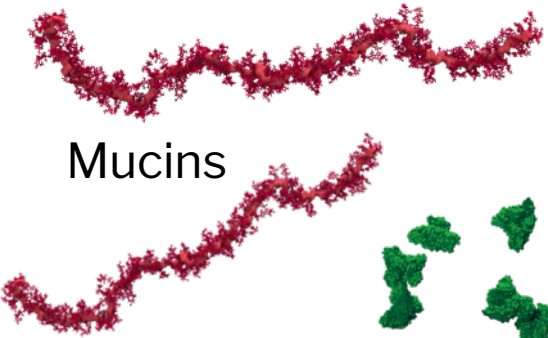


Everything in a Respiratory Aerosol

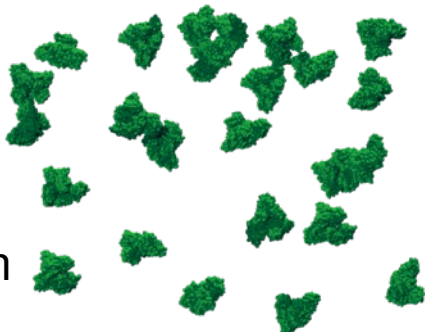
SARS-CoV-2
Delta Virion



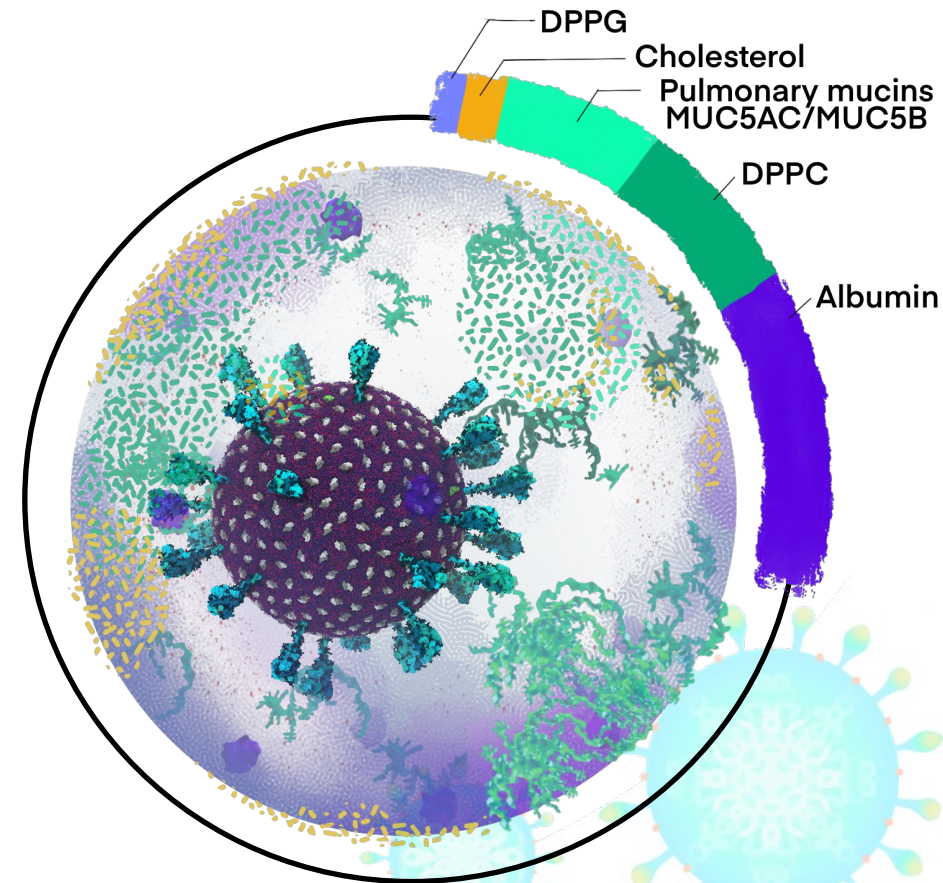
Mucins



Albumin

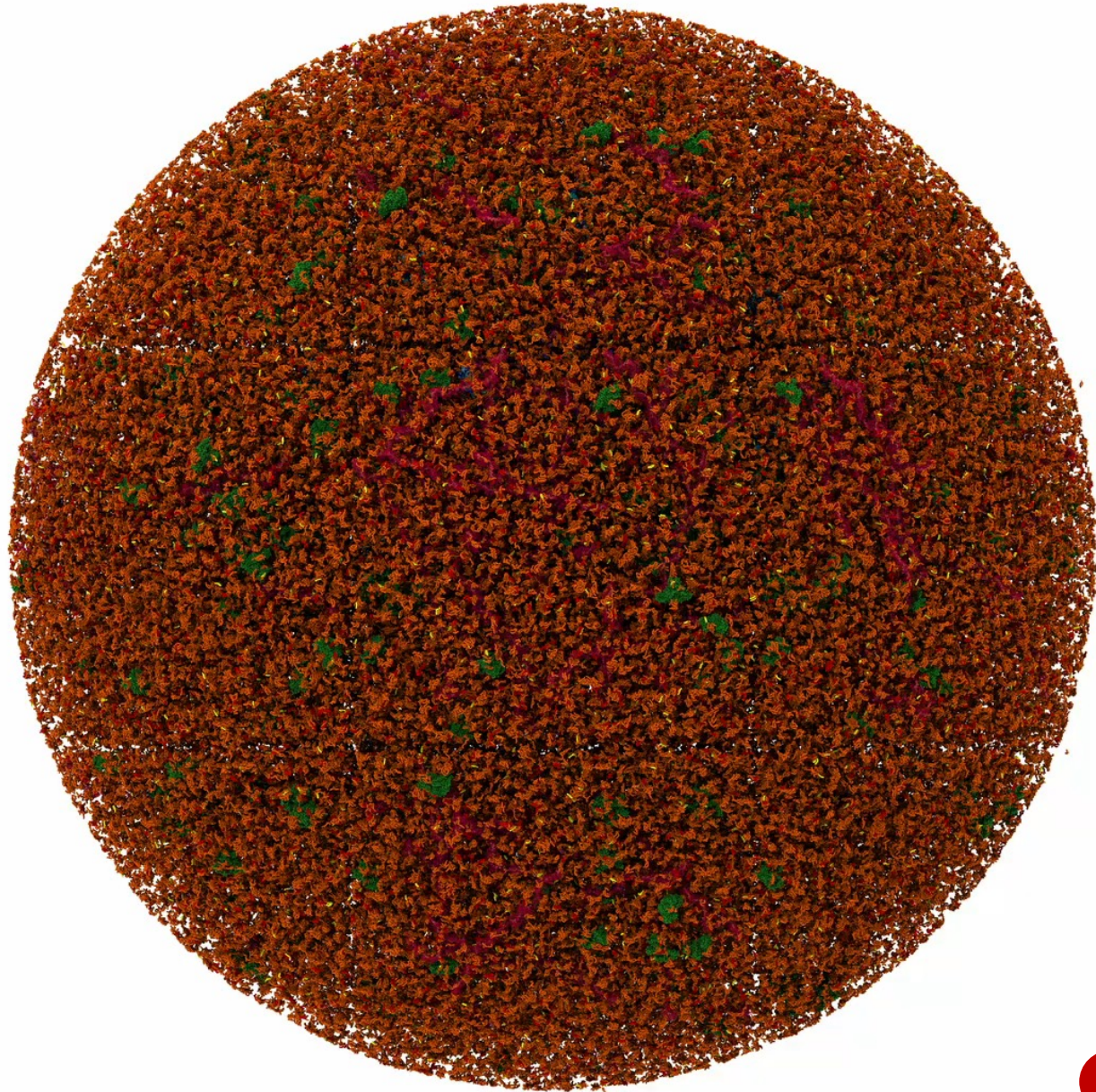


Deep lung
fluid



Surrogate Deep Lung
Respiratory Aerosol

The messy environment of an aerosol



Early observations:

- Lipids organize at the surface and into micelles
- Mucins, albumin, and lipids form a matrix-like structure

Impacts to look further into:

- Local diffusion around the virus?
- Component's impact on viscosity of the full aerosol?
- Spike and membrane changes due to components?
- Lipid and mucin impacts on hygroscopicity?
- Ion gradients throughout the aerosol?



Mucins



Lipids



Albumin



Albumin binds to spike

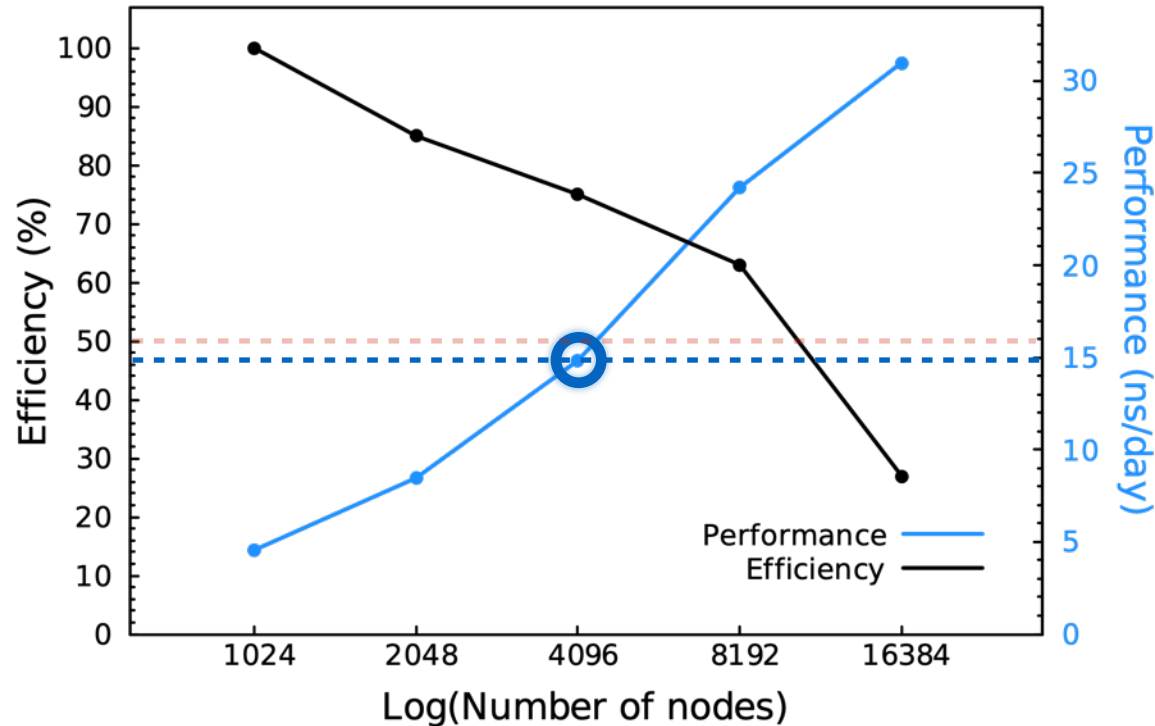
Lipids bind to spike

Mucin binds to spike

Legend: Oranges: Lipids Green: Albumin Red: LPS Blue: Spike

Benchmarks in 2018

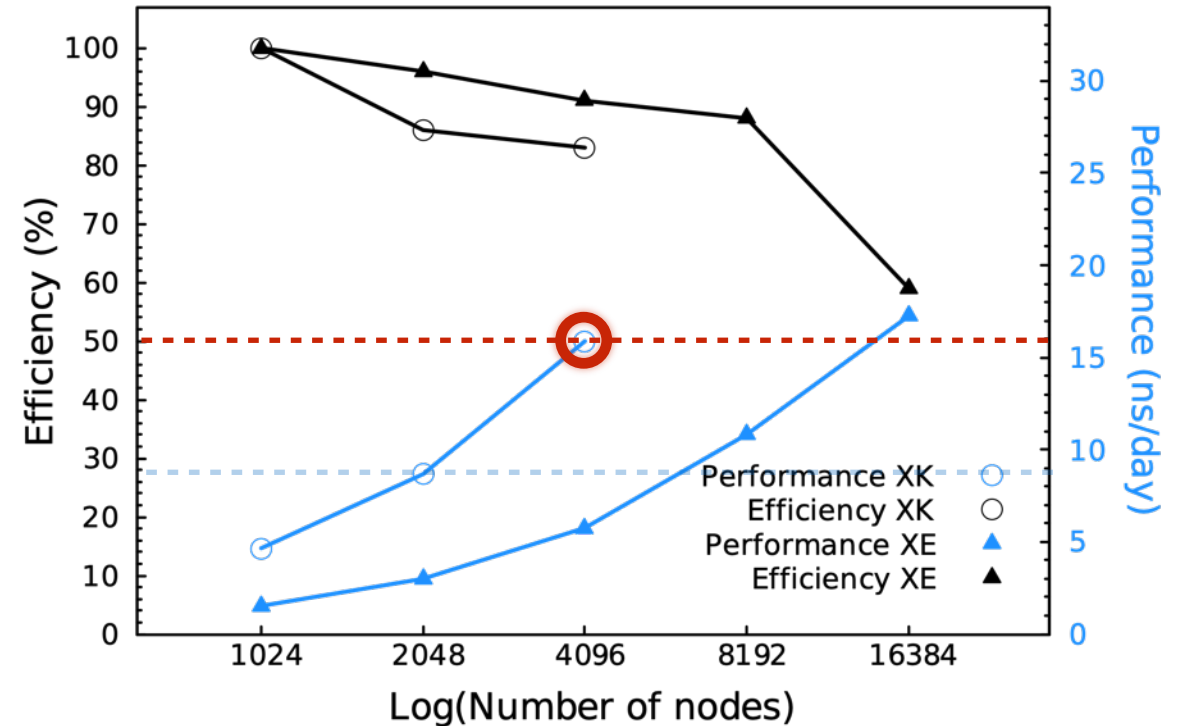
TITAN (OAK RIDGE)



14.83 ns/day on 4096 nodes

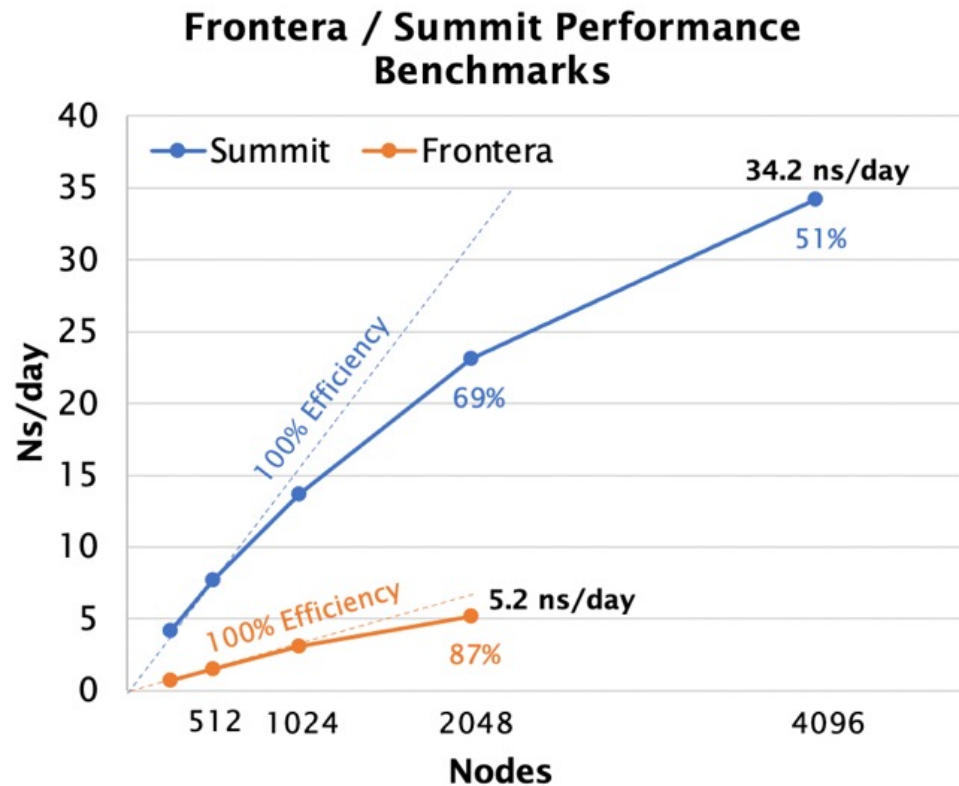
- NAMD2.13 (CUDA memory optimized) + CHARMM36 ff; 2 fs timestep
- 161 million atoms
- Box size: 115 x 120 x 116 nm

BLUE WATERS



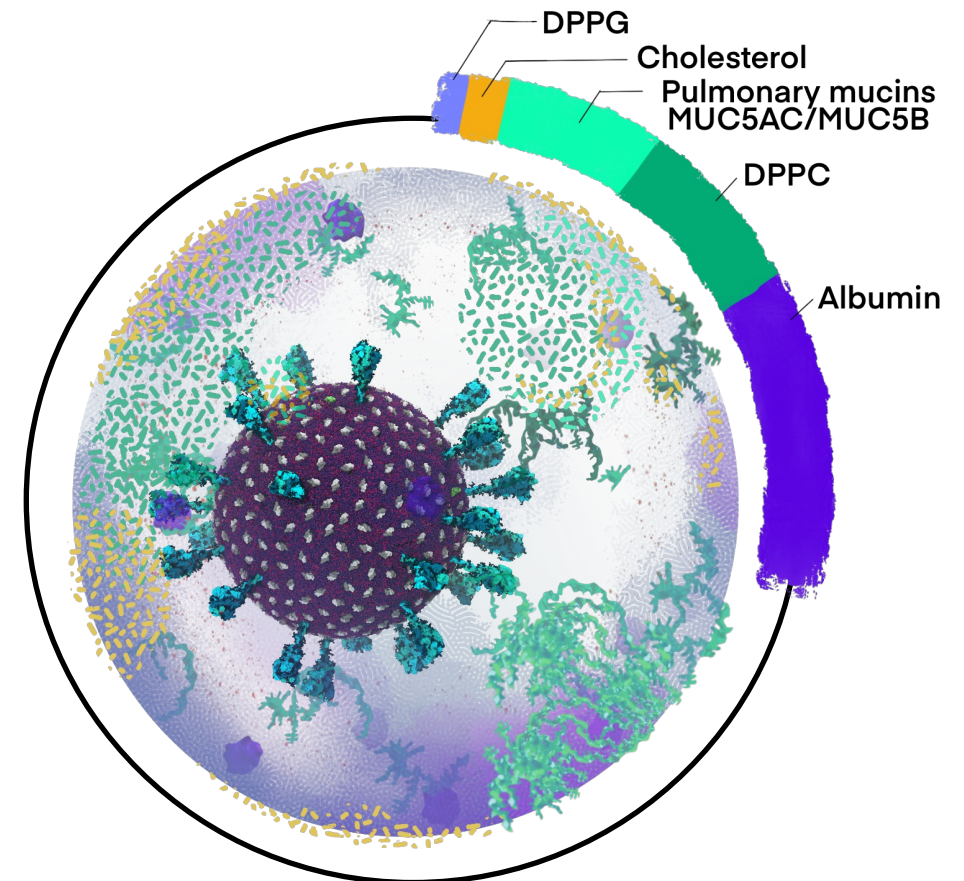
15.83 ns/day on 4096 nodes

Benchmarks on Current Machines



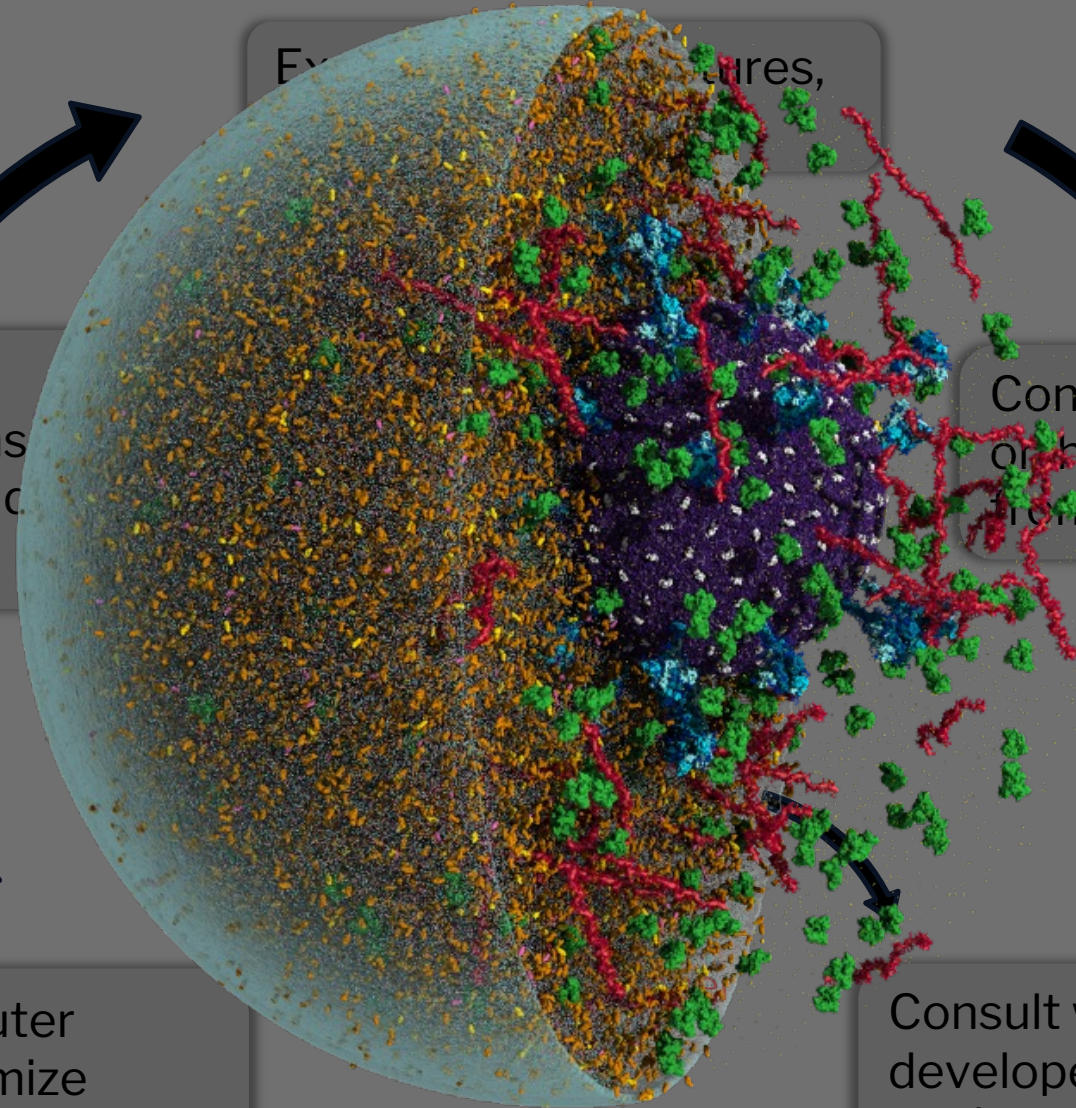
34.2 ns/day on 4096 nodes

- 1.04 billion atoms
- Box size: 284 x 284 x 284 nm
- Great Scaling up to 1024 nodes on Summit
- NAMD2.15 (CUDA memory optimized) + CHARMM36 ff; 4 fs timestep



**Surrogate Deep Lung
Respiratory Aerosol**

It takes a village to raise an aerosol



Experimental data, hypotheses, and questions

Develop workflows for generating non-standard system set ups

Construct aerosol model based on hypotheses and questions from experimental results

Consult with NAMD and VMD developers to optimize the MD engine

Work with supercomputer centers to further optimize simulation parameters (Summit & Frontera)

Provide test systems to aid the construction and development of future leadership class facilities (TACC CSA)

Generate data and develop hypotheses and mechanisms experimentalists to test/validate

Summary and Conclusions

Innovations

- First physically relevant all-atom MD simulation of this scale (1+ Billion Atoms)
- First molecular model of mucins (applications to other computational glycobiology systems)
- Pioneering the use of MD in airborne pathogen research

Dynamics on the Respiratory Aerosol

- 374ns of simulation time done so far
- 29 spikes for 10.8 μ s of sampling
- 360 M dimers for 134 μ s sampling
- ~100 μ s sampling for mucins and albumin

Key Areas of Interest

- Spike-Mucin interactions (Ion mediated?)
- Aerosol surface properties (gas transport, lipid arrangements)
- SARS-CoV-2 Delta simulation data (Spike, membrane protein interactions, protein lipid interactions)

Acknowledgments



The Airborne
Institute



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Dr. Lorenzo Casalino
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Dr. Mia Rosenfeld
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Dave Hardy

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The NAMD and VMD team
Oak Ridge National Laboratory
Texas Advanced Computing Center
Pittsburgh Supercomputing Center





#COVIDisAirborne: AI-Enabled Multiscale Computational Microscopy of Delta SARS-CoV-2 in a Respiratory Aerosol

Abigail Dommer^{1†}, Lorenzo Casalino^{1†}, Fiona Kearns^{1†}, Mia Rosenfeld¹, Nicholas Wauer¹, Surl-Hee Ahn¹, John Russo,² Sofia Oliveira³, Clare Morris¹, Anthony Bogetti⁴, Anda Trifan^{5,6}, Alexander Brace^{5,7}, Terra Sztain^{1,8}, Austin Clyde^{5,7}, Heng Ma⁵, Chakra Chennubhotla⁴, Hyungro Lee⁹, Matteo Turilli⁹, Syma Khalid¹⁰, Teresa Tamayo-Mendoza¹¹, Matthew Welborn¹¹, Anders Christensen¹¹, Daniel G. A. Smith¹¹, Zhuoran Qiao¹², Sai Krishna Sirumalla¹¹, Michael O'Connor¹¹, Frederick Manby¹¹, Anima Anandkumar¹², David Hardy⁶, James Phillips⁶, Abraham Stern¹³, Josh Romero¹³, David Clark¹³, Mitchell Dorrell¹⁴, Tom Maiden¹⁴, Lei Huang¹⁵, John McCalpin¹⁵, Christopher Woods³, Matt Williams³, Bryan Barker¹⁶, Harinda Rajapaksha¹⁶, Richard Pitts¹⁶, Tom Gibbs¹³, John Stone⁶, Daniel Zuckerman^{2*}, Adrian Mulholland^{3*}, Thomas Miller III^{11,12*}, Shantenu Jha^{9*}, Arvind Ramanathan^{5*}, Lillian Chong^{4*}, Rommie Amaro^{1*}

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⁹Brookhaven National Lab & Rutgers University ¹⁰University of Oxford, ¹¹Entos, Inc., ¹²California Institute of Technology, ¹³NVIDIA Corporation, ¹⁴Pittsburgh Supercomputing Center, ¹⁵Texas Advanced Computing Center,

¹⁶Oracle for Research [†]Joint first authors, ^{*}Contact authors.

