Probing the dynamics of complex molecular assemblies

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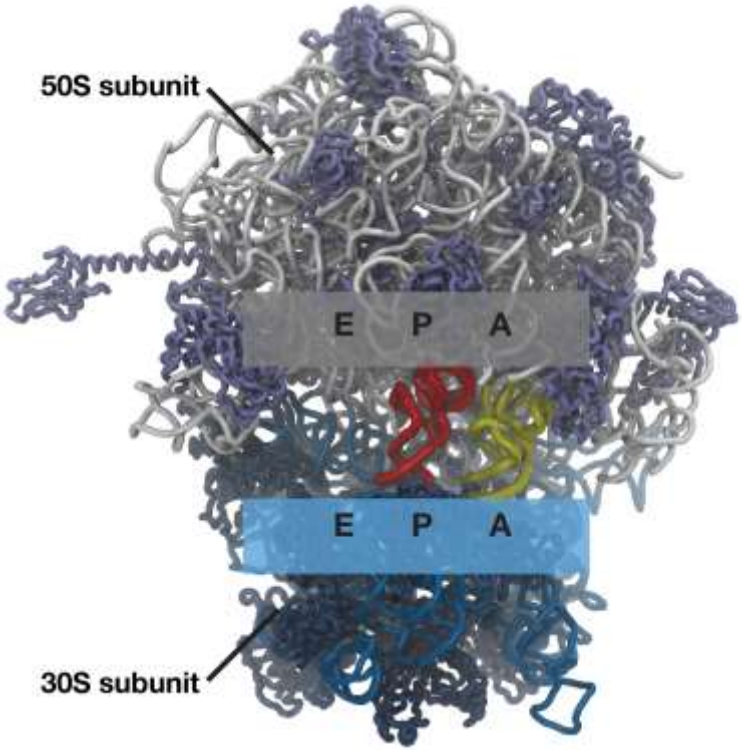
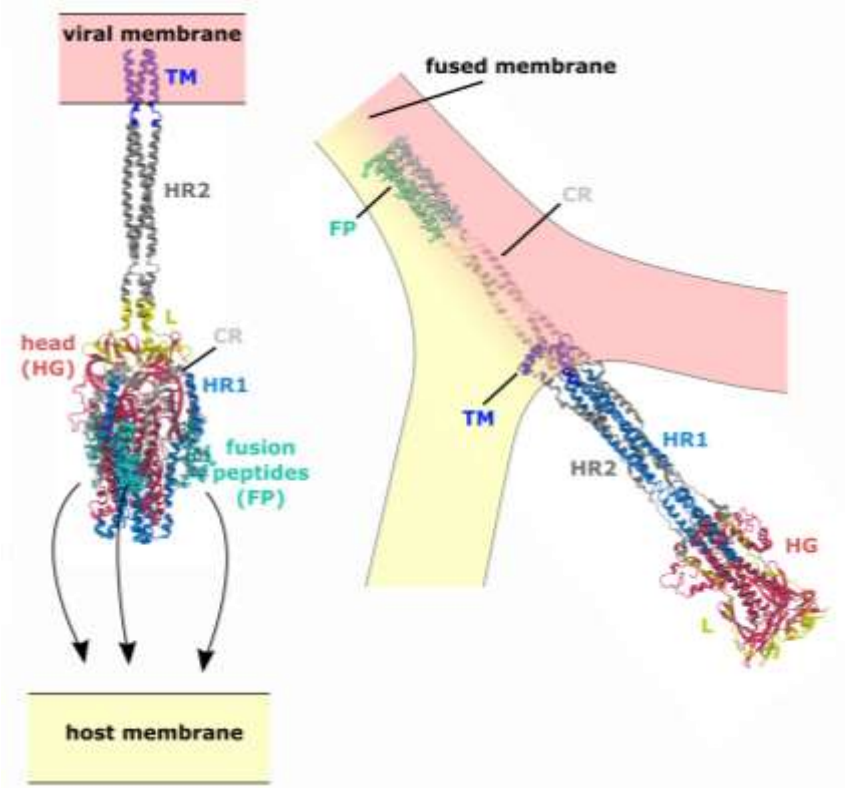
Large-scale conformational rearrangements in biomolecular assemblies



The ribosome: multiple 20-100 Å changes during elongation



SARS-CoV-2 spike protein: global rearrangement during membrane fusion (~200Å)

Why/when are simplified models suitable for complicated systems?

- The challenge: Biomolecular systems have thousands of degrees of freedom and undergo slow dynamics. The complexity of interactions can make direct interpretation of simulations (and experiments) very challenging.

- Our approach: Rather than attempt to get all details, try the simplest model first, and then expand to study the relationships between molecular components and the response to perturbations.

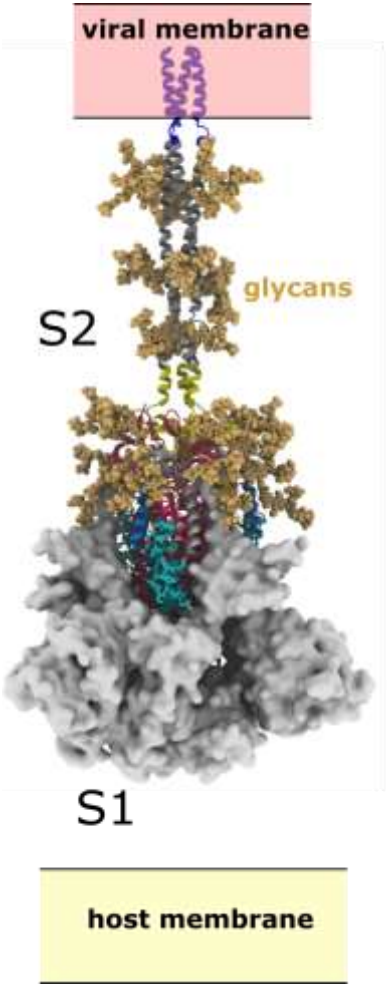
- We aim to bring a physicist's spirit to biomolecular studies
  - Start with a "spherical cow" model for molecular biology ….

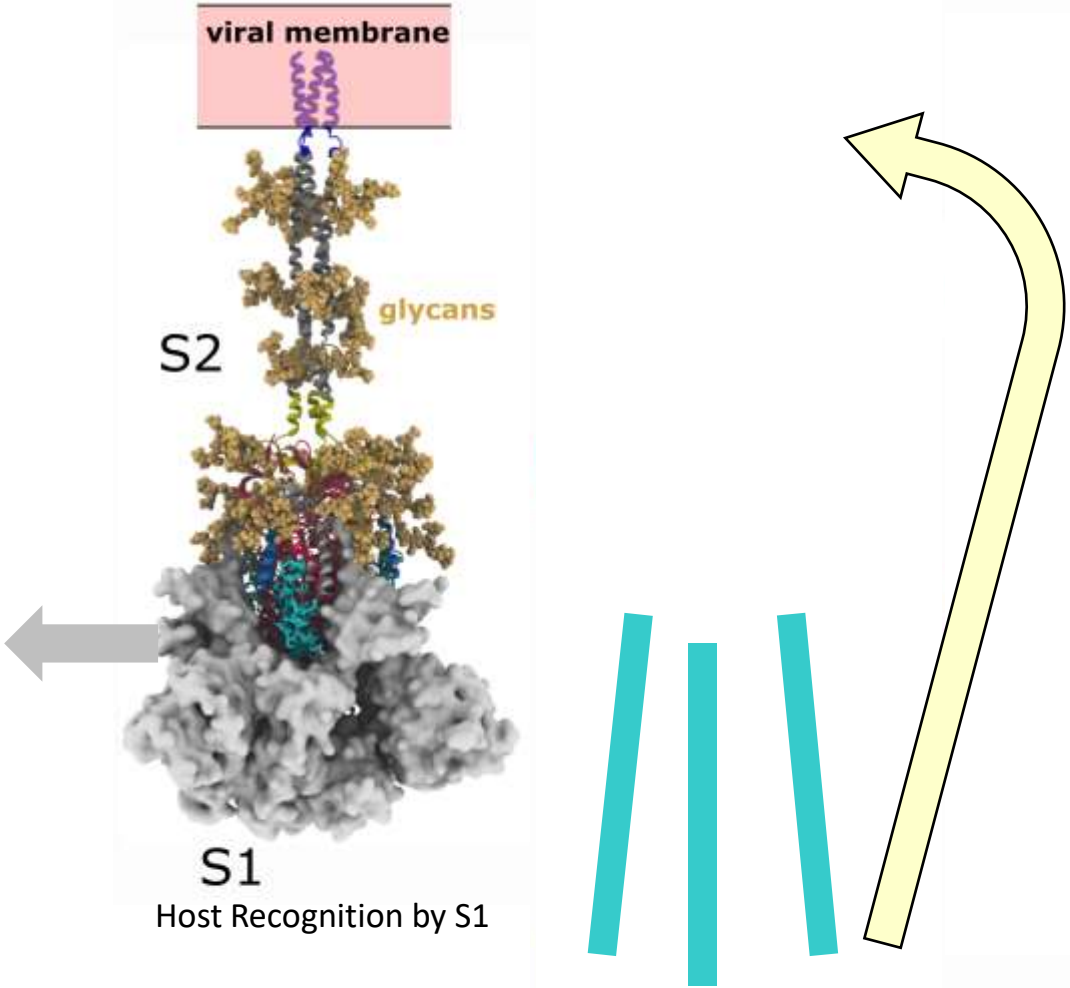
For examples of the philosophy:
Freitas, Byju, Hassan, Oliveira and PCW.
Quantifying biomolecular diffusion with a "spherical cow" model
American Journal of Physics, 2022.

Understanding COVID-19

- SARS-CoV-2 Spike protein (right) recognizes human cells and allows the virus to enter

- Using simulations to tackle Spike from multiple angles
  - **Effort 1: Biophysical characterization may help identify the "Achilles' Heel" of the Spike**
  - Effort 2: Simulation can guide development of new vaccines





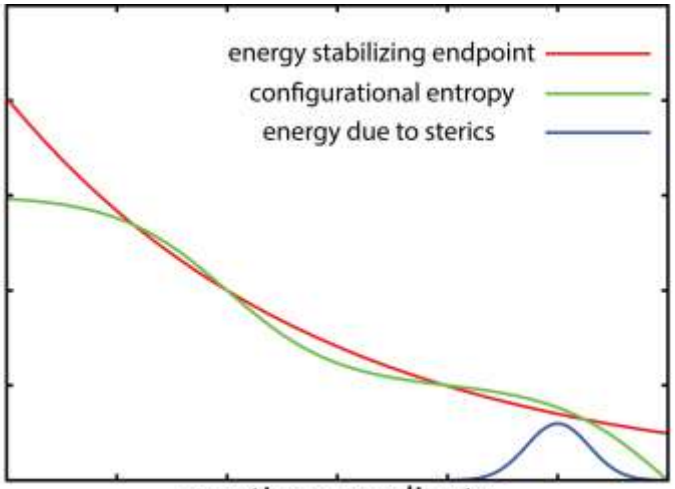
Host Recognition by S1

Membrane fusion

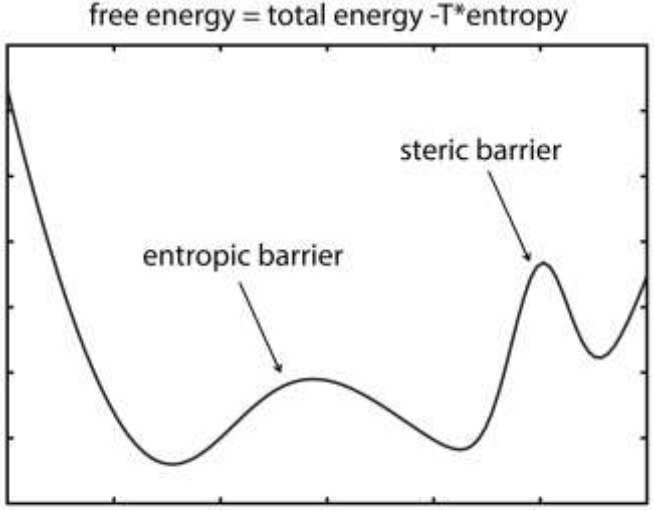
Simulating the Spike during membrane fusion

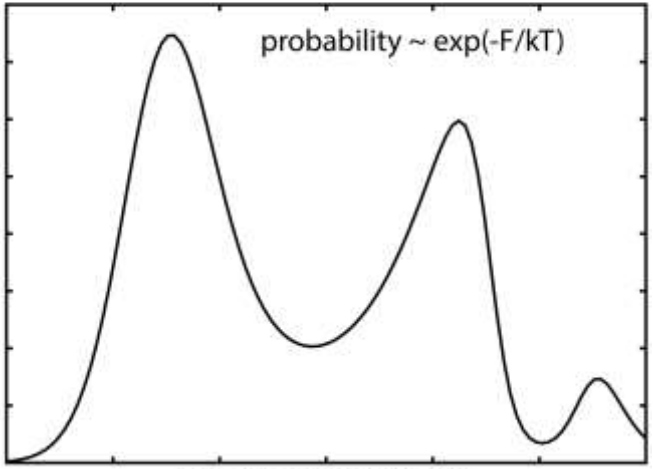
- Experiments have only provided structures before and after membrane fusion
- Membrane fusion involves a ~20 nm rearrangement of the Spike
- By simulating the transitions, we may find which features are more exposed during the rearrangement
- Exposed regions may be targeted with novel vaccines

Using simplified models



prefusion reaction coordinate postfusion





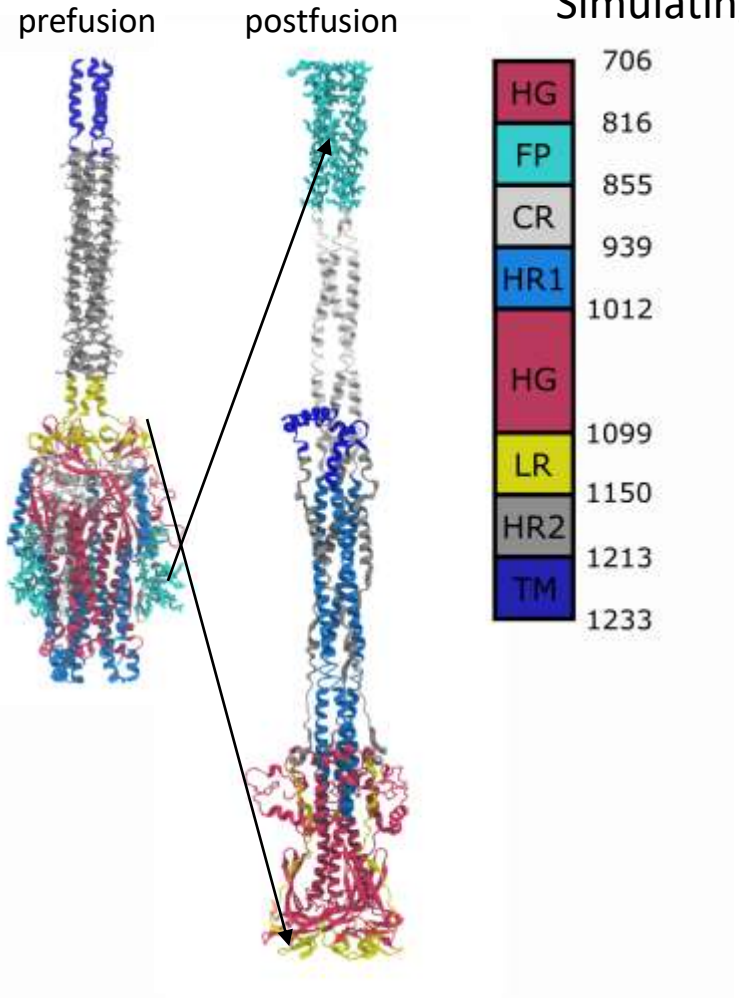
The Structure-based (SMOG) Model:

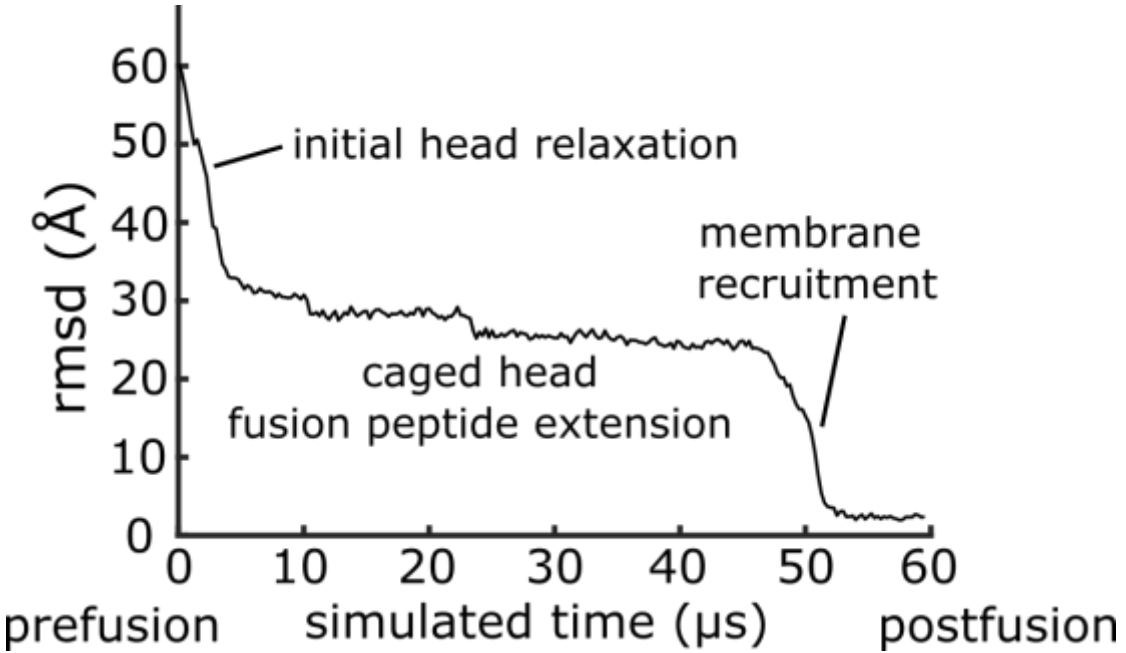
- **Includes all heavy (non-hydrogen atoms) atoms**
- postfusion state is the lowest effective-enthalpy state
- Consistent with the notion of the Spike acting as a 'molecular spring' that uses stored energy to capture a host cell

- All-atom SMOG models (PCW et al. *Proteins* 2009)

Reviewed in Levi, Noel, PCW *Methods* (2019).

Simulating Rearrangements in Spike

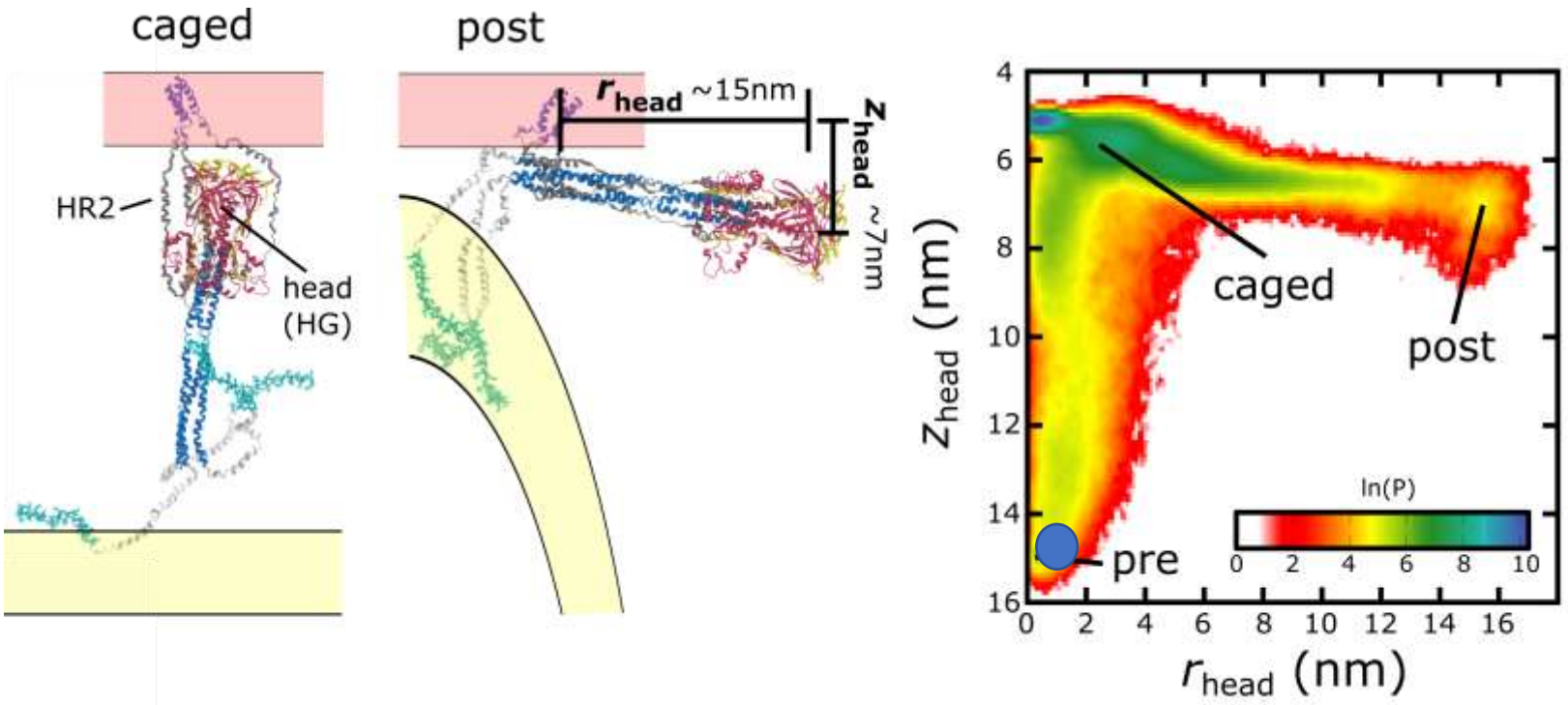




Simulations capture the full rearrangement process
Each atom moves (on average) ~6 nm (up to ~30 nm)

Dodero-Rojas, Onuchic and Whitford *eLife* 2021

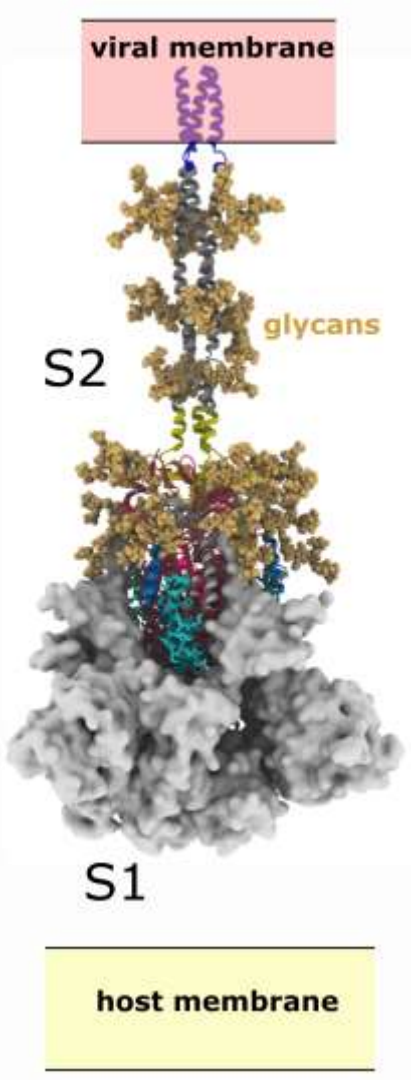
Statistical Properties from 1000 events



Dodero-Rojas, Onuchic and Whitford *eLife* 2021

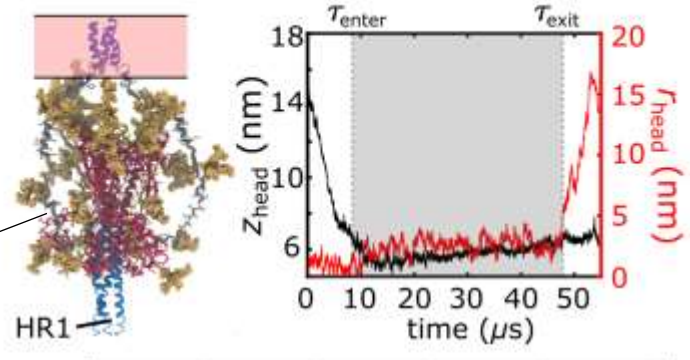
What about the glycans?

- Glycans are simple sugars (gold) that coat the Spike protein
- Others have suggested that glycans can protect the spike from recognition by the immune system
- Our simulations suggest the system can become caged for an extended period of time
  - *Perhaps glycans also influence this process*



Dodero-Rojas, Onuchic and Whitford *eLife* 2021

Glycans slow down the rearrangement



The caged state appears to engage the glycans

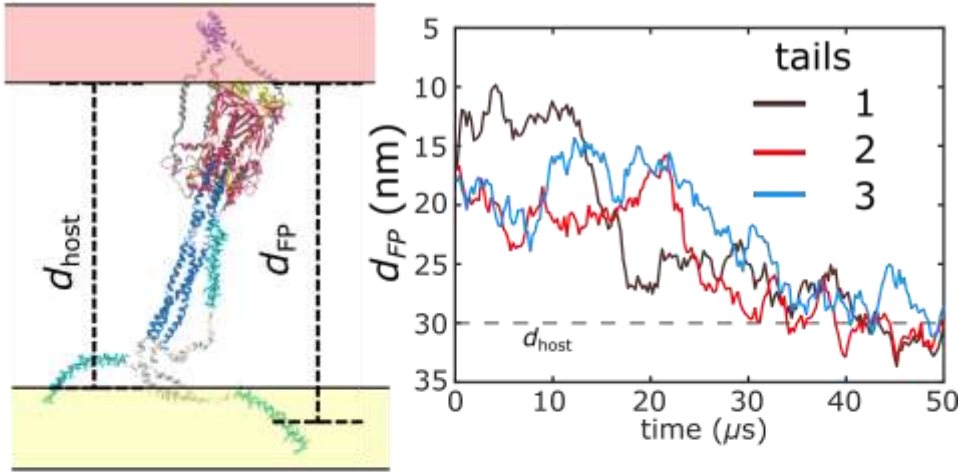
Spike can remain caged for long times when glycans are present

In absence of glycans, caged state is bypassed!

Dodero-Rojas, Onuchic and Whitford *eLife* 2021

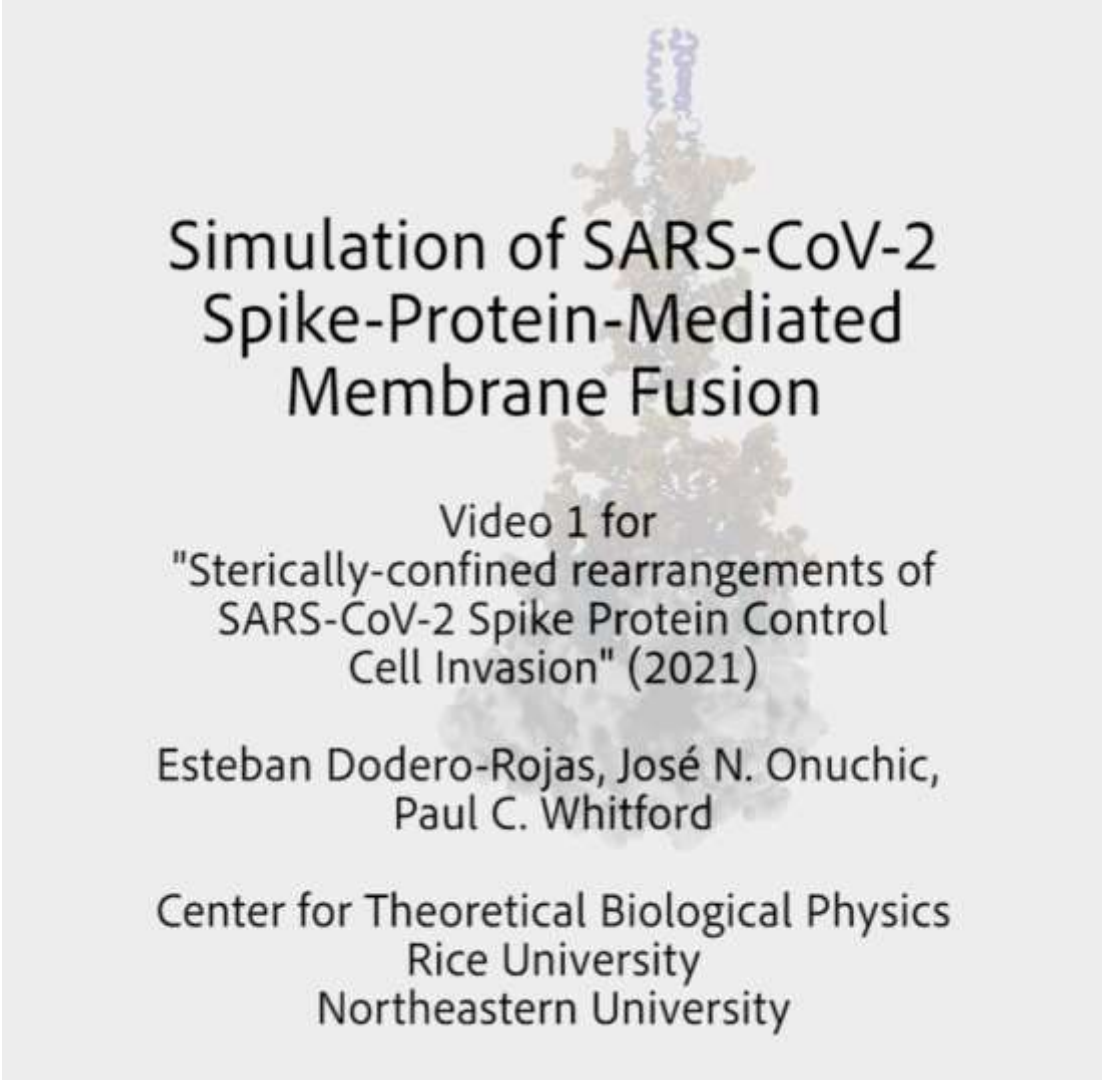
Glycans extend reach of fusion peptides

In order to infect a cell, the fusion peptides (tails) must reach the host (yellow)



The chance of reaching the host ($P_{capture}$) is much larger when glycans are present

Dodero-Rojas, Onuchic and Whitford *eLife* 2021



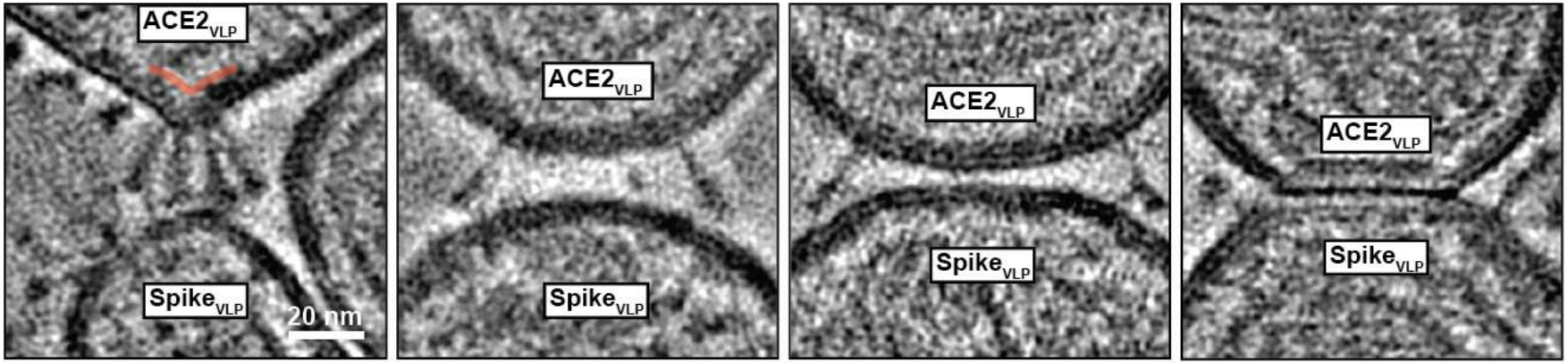
Simulation of SARS-CoV-2 Spike-Protein-Mediated Membrane Fusion

Video 1 for
"Sterically-confined rearrangements of SARS-CoV-2 Spike Protein Control Cell Invasion" (2021)

Esteban Dodero-Rojas, José N. Onuchic, Paul C. Whitford

Center for Theoretical Biological Physics
Rice University
Northeastern University

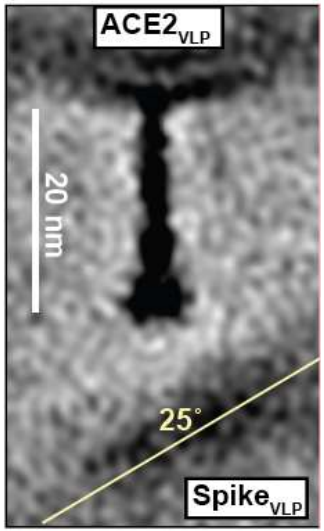
Imaging study of membrane fusion



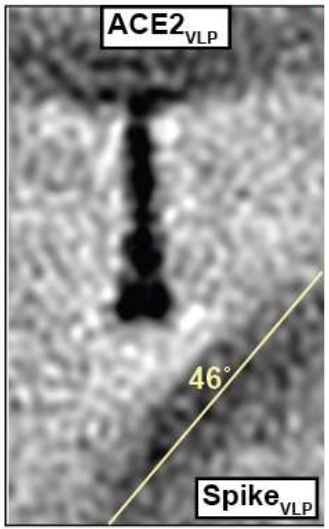
Prepared virus-like particles (VLPs) that are decorated with Spike or ACE2 receptor
Cryo-ET imaging identified Spike-ACE interactions at the VLP-VLP interface
Experiments performed independently by Mothes Lab (Yale Univ)

Grunst et. *Science* 2024

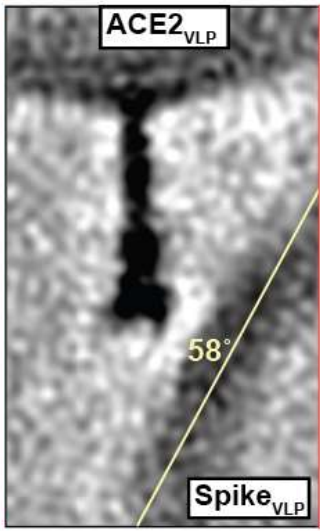
Comparison of simulated conformations with cryo-ET reconstructions



Low membrane tilt



Mid tilt



High tilt

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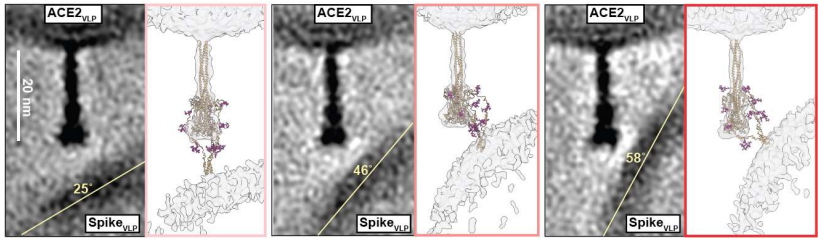
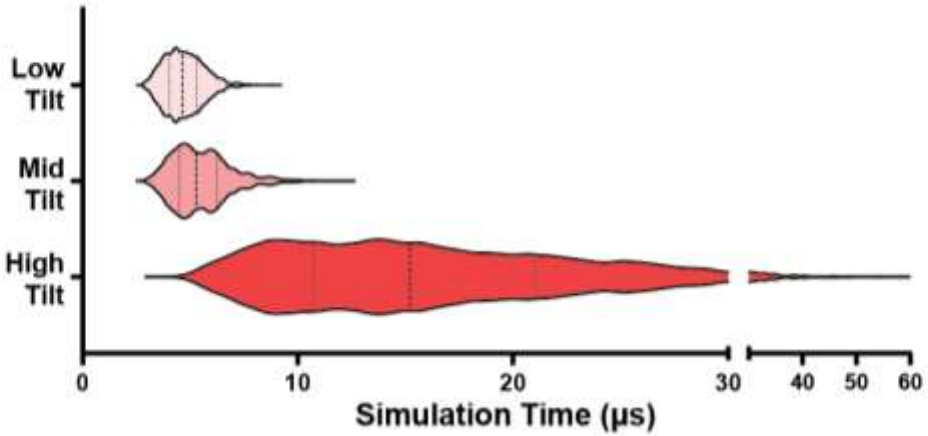
Comparison of simulated conformations with cryo-ET reconstructions



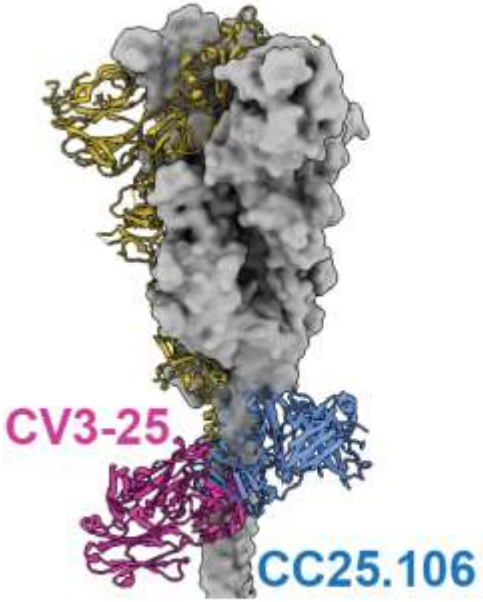


Simulations spontaneously sampled conformations that are consistent with experimental images

Simulations provide distributions of times for each state

Grunst et. *Science* 2024

Antibody binding epitopes are transiently exposed



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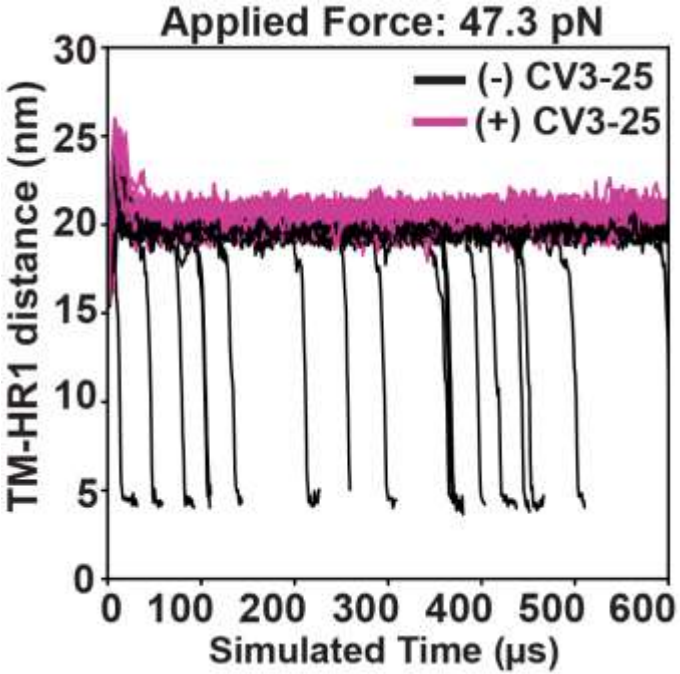
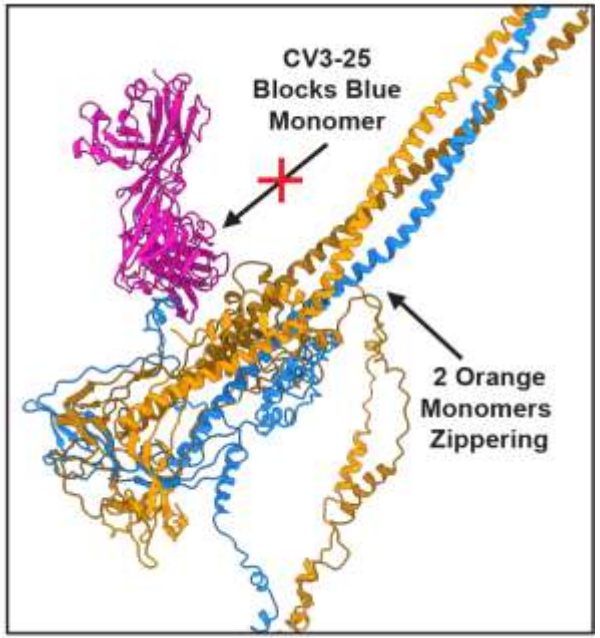
CV3-25 Fab impedes conformational change





CV3-25 Fab was included in the model

Applied force introduced to mimic interaction between host and virus

Fab interferes with zippering, thereby reducing the the force between host and virus

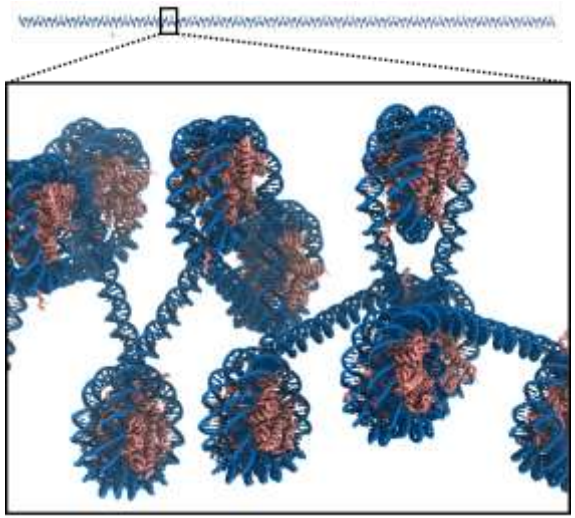
Grunst et. *Science* 2024

How the SARS-CoV-2 virus uses its “spike” protein to infect a cell

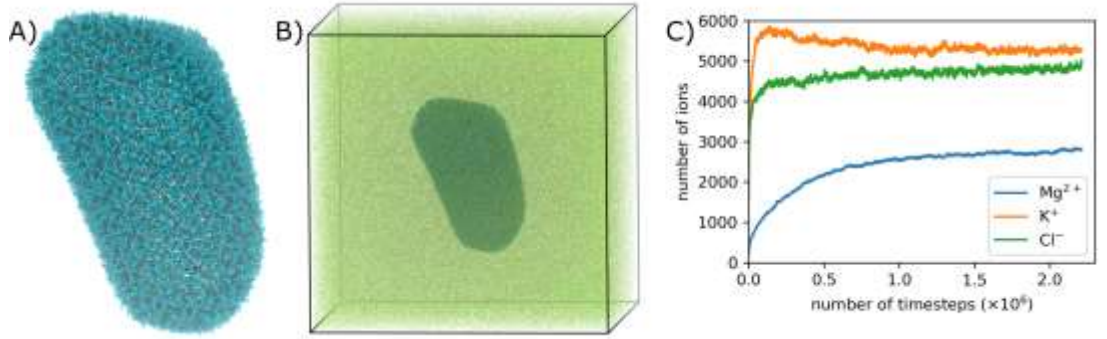
Experimental structures and simulations described in
“Structure and inhibition of SARS-CoV-2
spike refolding in membranes”
Grunst et al. *Science*, 2024

Expanding SMOG capabilities to other complex assemblies

Long chains, e.g. chromosomes
(coarse-grained and all-atom sims)

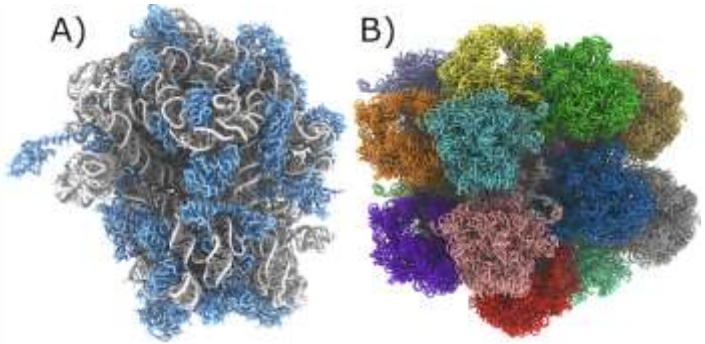


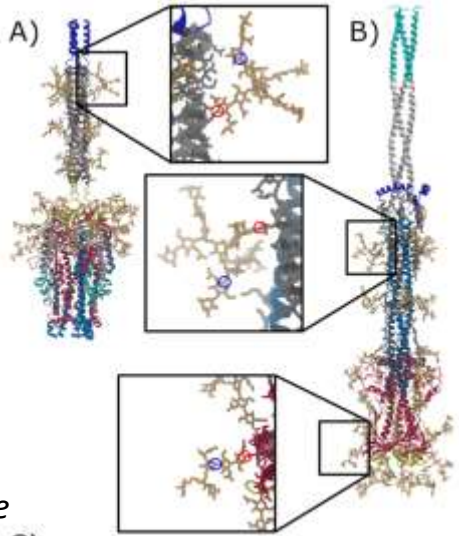
HIV-1 Capsid – explicit ions and electrostatics



COVID Spike Protein

Ribosomes





Our models are supported by

- Gromacs for large systems (millions of atoms on thousands of cores)
- OpenMM (<100k atoms on single GPUs)
- NAMD and LAMMPS

Oliveira, **Contessoto** et al. 2022 *Protein Science*

Thanks

- tRNA-mRNA translocation and hybrid motion
  - Sandra Byju (NU)
  - **Kien Nguyen (NU)**
  - Mariana Levi (NU)
  - Kelsey Walak (NU)
  - Ellen Wang (BC/NU)
  - Udayan Mohanty (BC)
- Subunit Rotation
  - **Asem Hassan (NU)**
  - Mariana Levi (NU)
  - Liah Dukaye (NU)
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  - Ronaldo Oliveira (UFTM)
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  - Mariana Levi (Northeastern)
  - José Onuchic (Rice U)
  - Antonio Oliviera (Rice U)
  - Vinicius Contessoto (Rice U)

RICE

SMOG
A RESOURCE FOR BIOMOLECULAR SIMULATION

Northeastern

All models available with SMOG 2 and OpenSMOG: **https://smog-server.org**

Ribosome Analysis Database powered by RADtool

Searchable database of all known ribosome structures at **http://radtool.org**

Center for Theoretical Biological Physics (CTBP) supports training activities and visitors for those interested in simulating complex assemblies!

NSF CAREER
MCB/POLS
Physics Frontier Centers

NIH National Institutes of Health
Turning Discovery Into Health

NIGMS R35 program

AMD

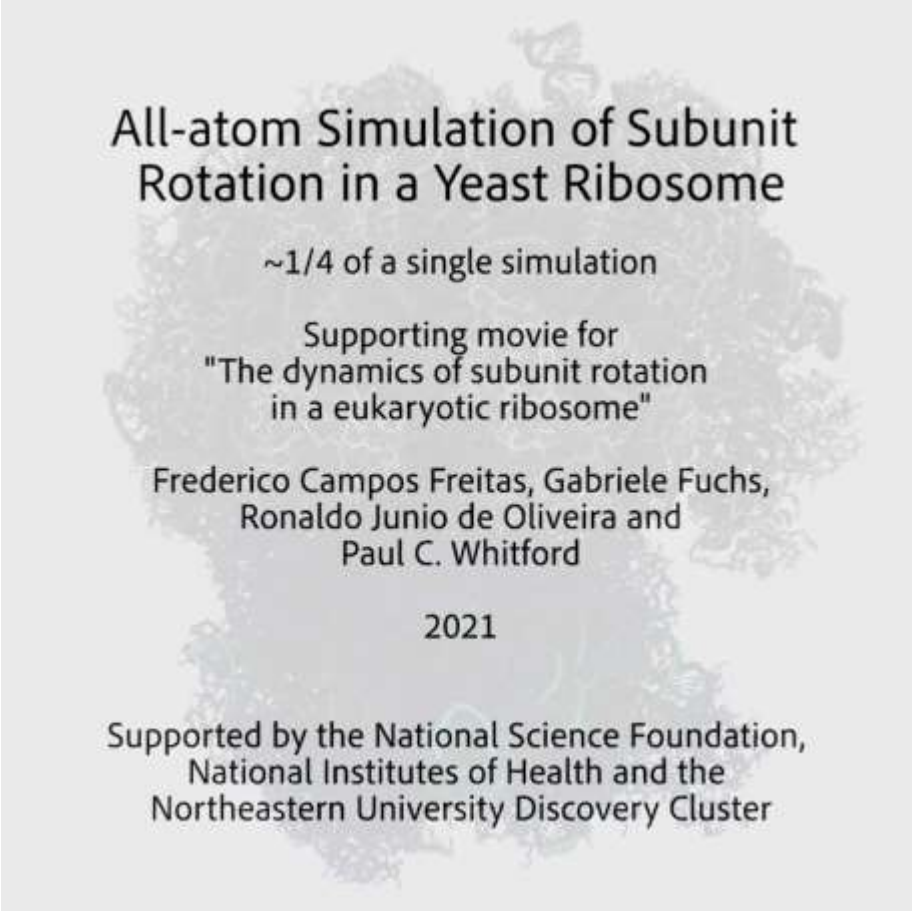
HPC | High Performance Compute Fund

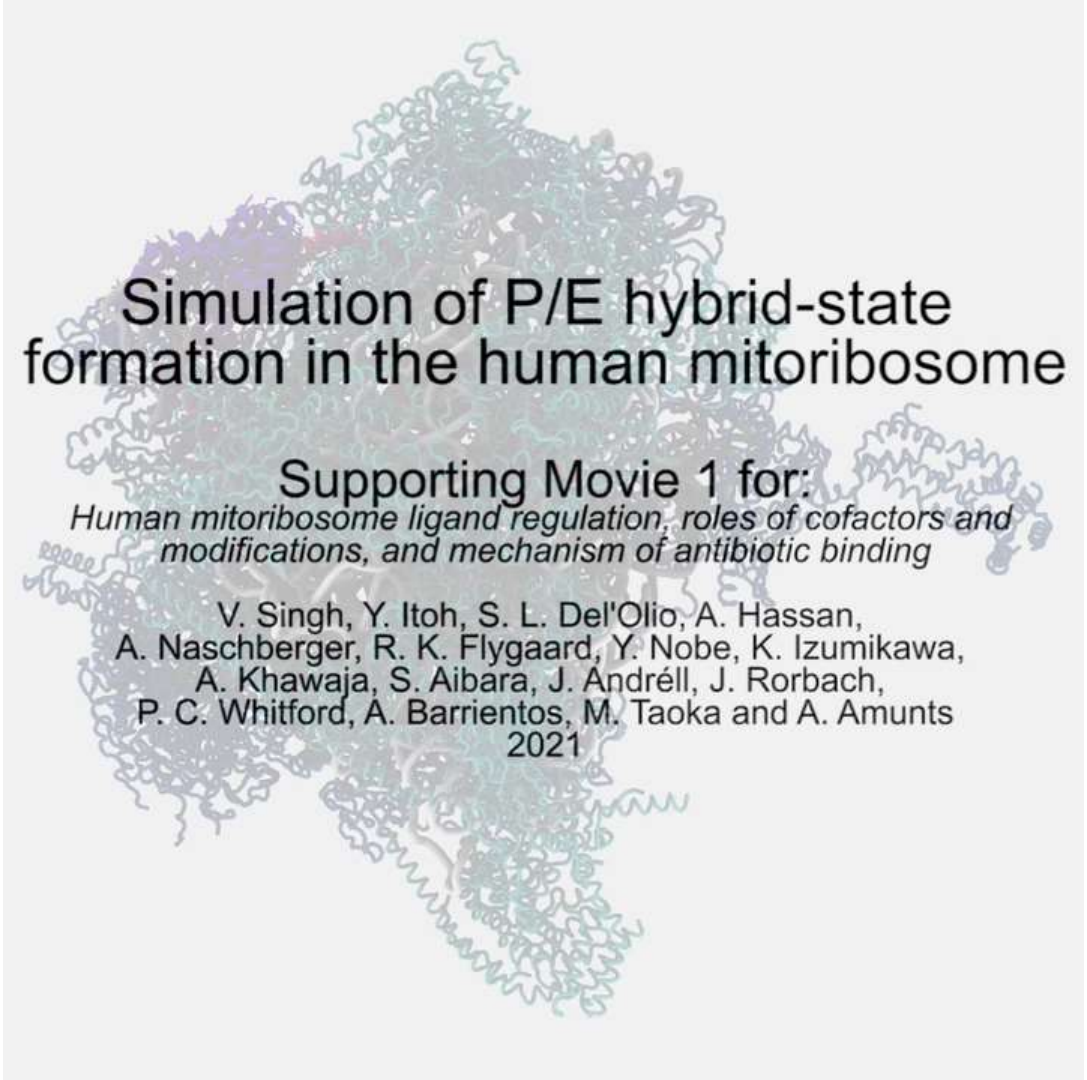
Other applications of SMOG models

Bridging steric descriptions and global rearrangements in the ribosome

We can now simulate global rearrangements using all-atom (>200,000 atoms) variants of the model

Provided a strong temperature-dependence of the free-energy landscape of rotation (entropy rules! See Freitas et al. *Biophysica* 2021)





Singh et al.
Nature Comm (2024)