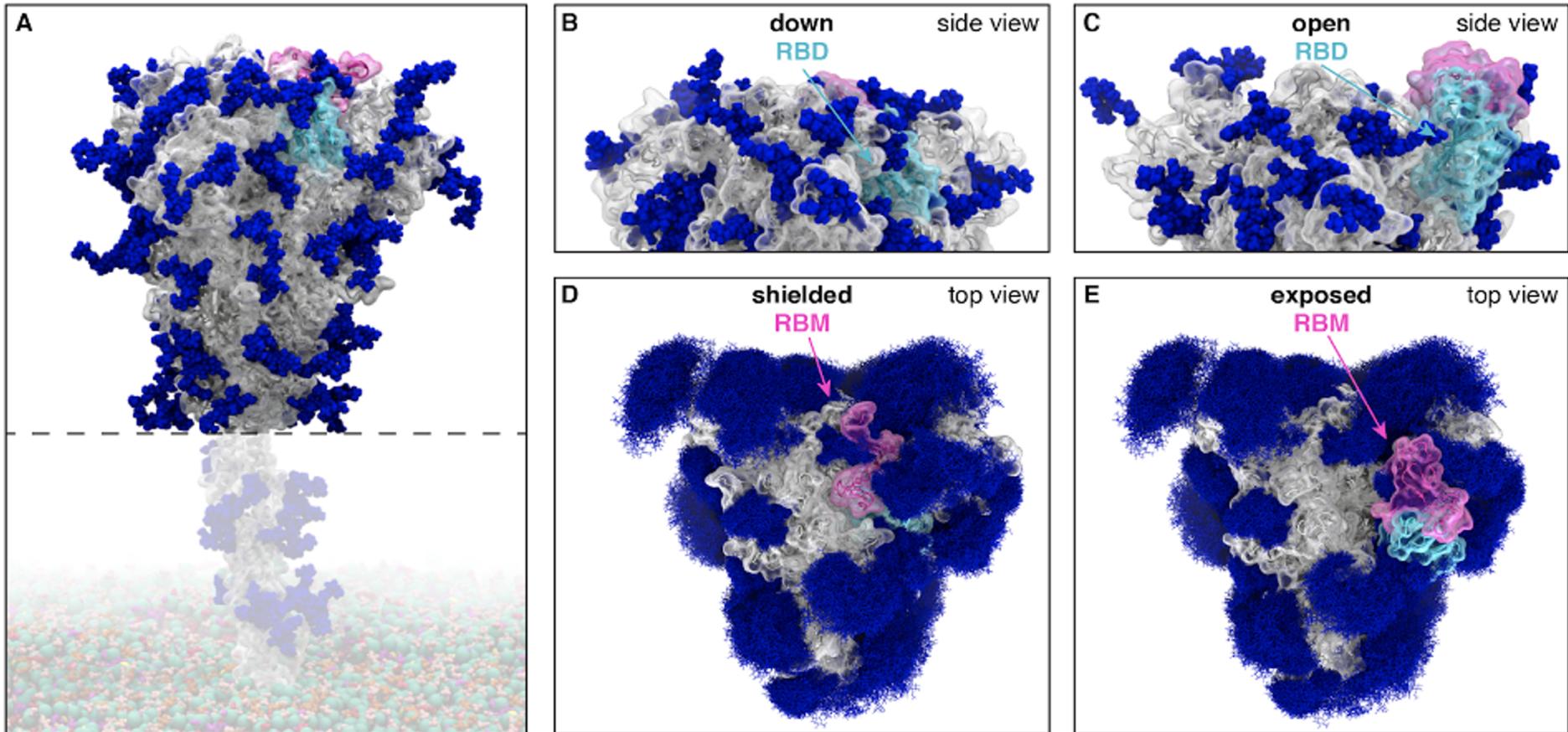




Investigating the opening mechanism of the spike protein of SARS-CoV-2

Surl-Hee (Shirley) Ahn
March 10, 2022
OpenEye CUP XXI

SPIKE RBD NEEDS TO OPEN TO START INFECTION



Casalino, L.†, Dommer, A.C.†, Gaieb, Z.†, Barros, E.P., Sztain, T., Ahn, S.-H., ..., & Amaro, R.E. IJHPCA 2021

Winner of 2020 Association for Computing Machinery Gordon Bell Special Prize for COVID-19

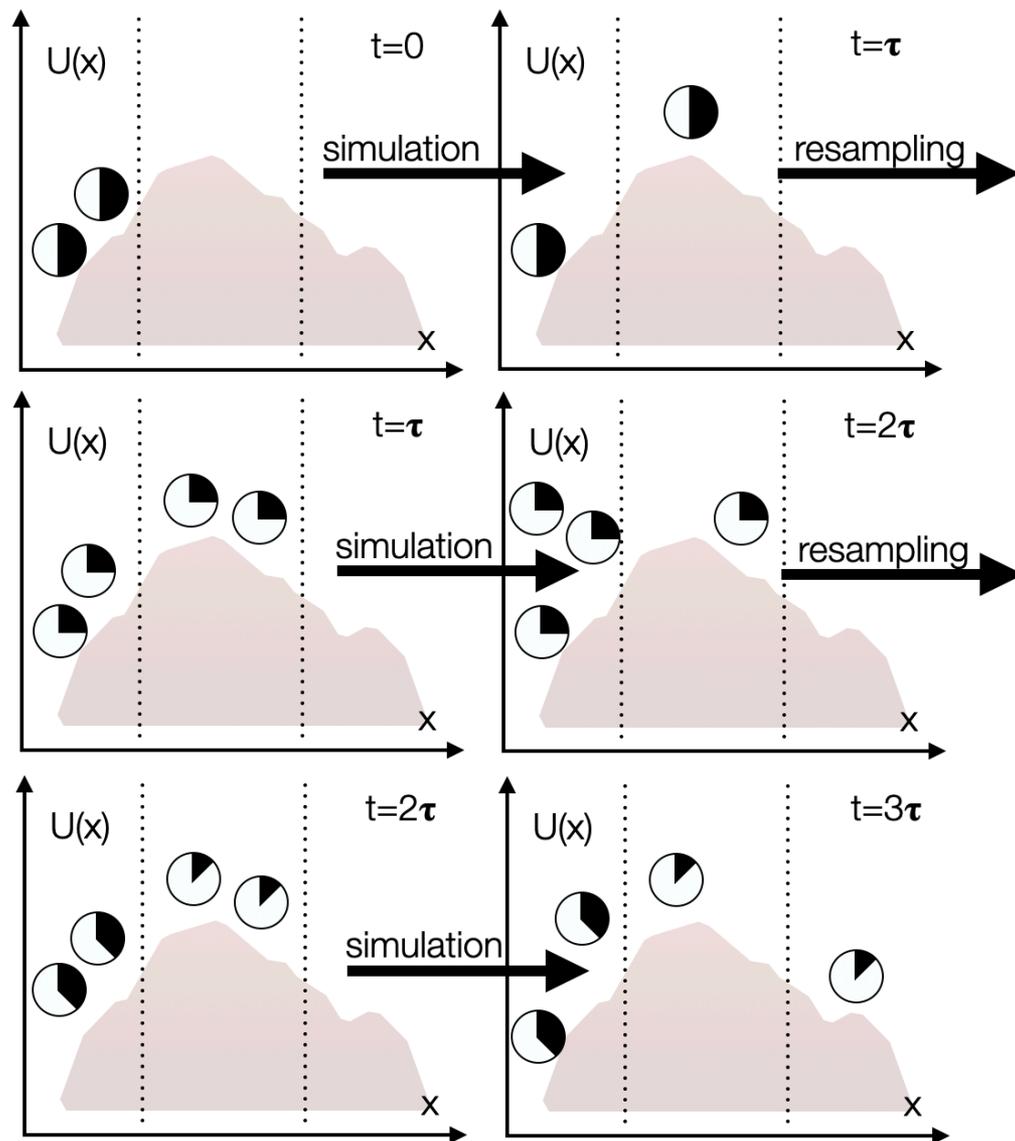
Sztain, T.†, Ahn, S.-H.†, ..., & Amaro, R.E. Nature Chemistry 2021

†These authors contributed equally to this work

WEIGHTED ENSEMBLE (WE) METHOD

Weighted ensemble (WE) method (Huber and Kim. Biophys. J. 1996):

1. Define bins. Set collective variables (CVs), simulation length τ , and target number of short simulations or “walkers” per bin.
2. Let walkers explore.
3. Bin each walker to appropriate bin.
4. “Resample” the walkers in each bin.
5. Repeat steps 2-4 until convergence.

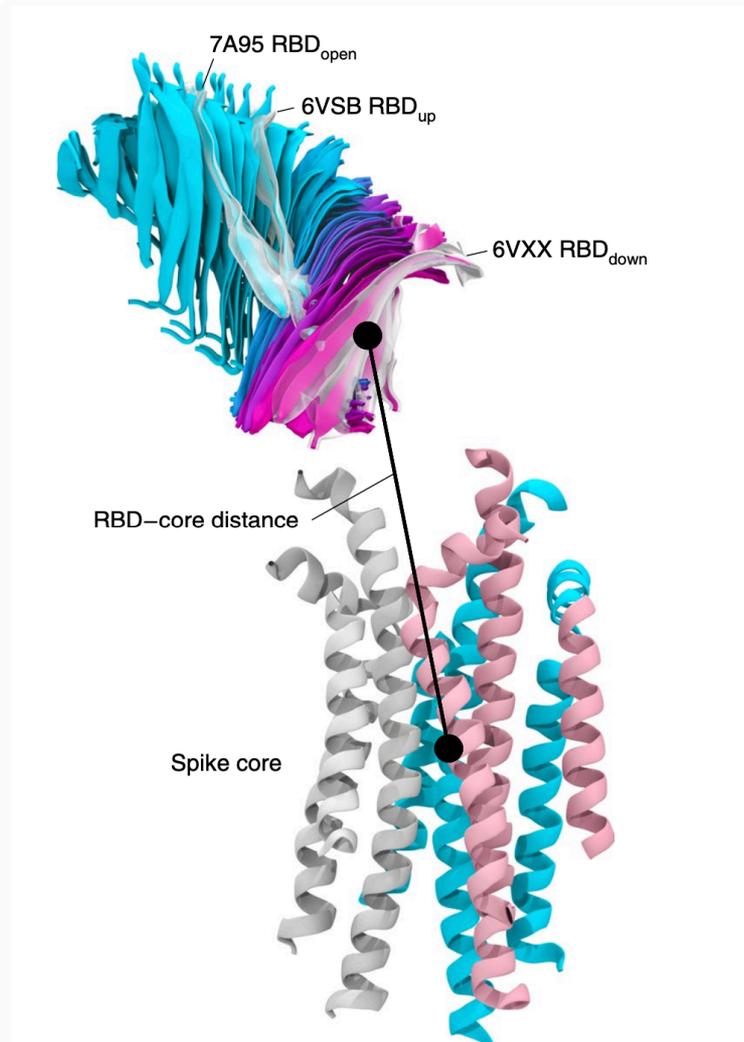
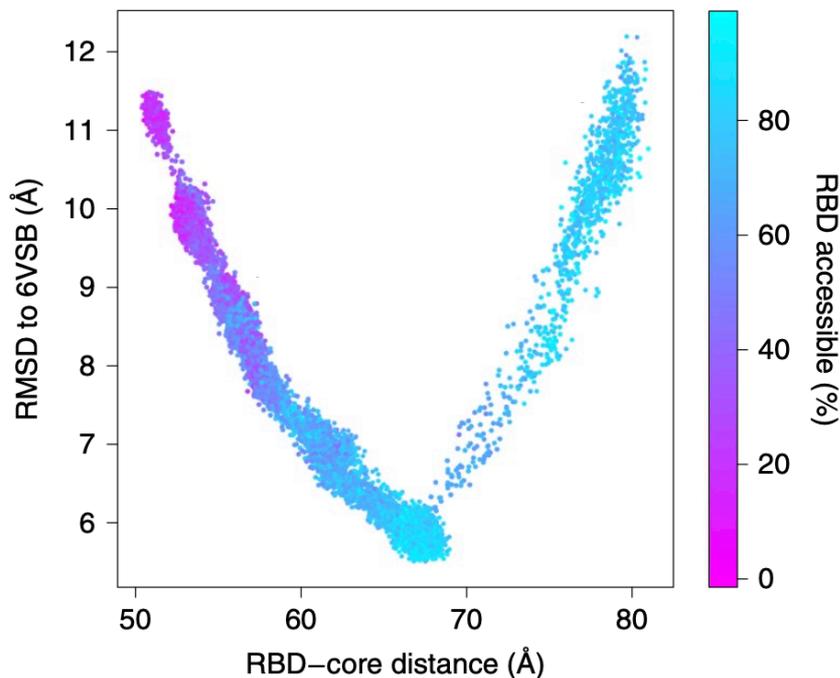


WE METHOD SIMULATION

Collective variables (CVs):
RMSD relative to 6VSB RBD_{up}
and RBD—core distance

Simulation length τ : 100 ps

Target number of walkers/bin: 8



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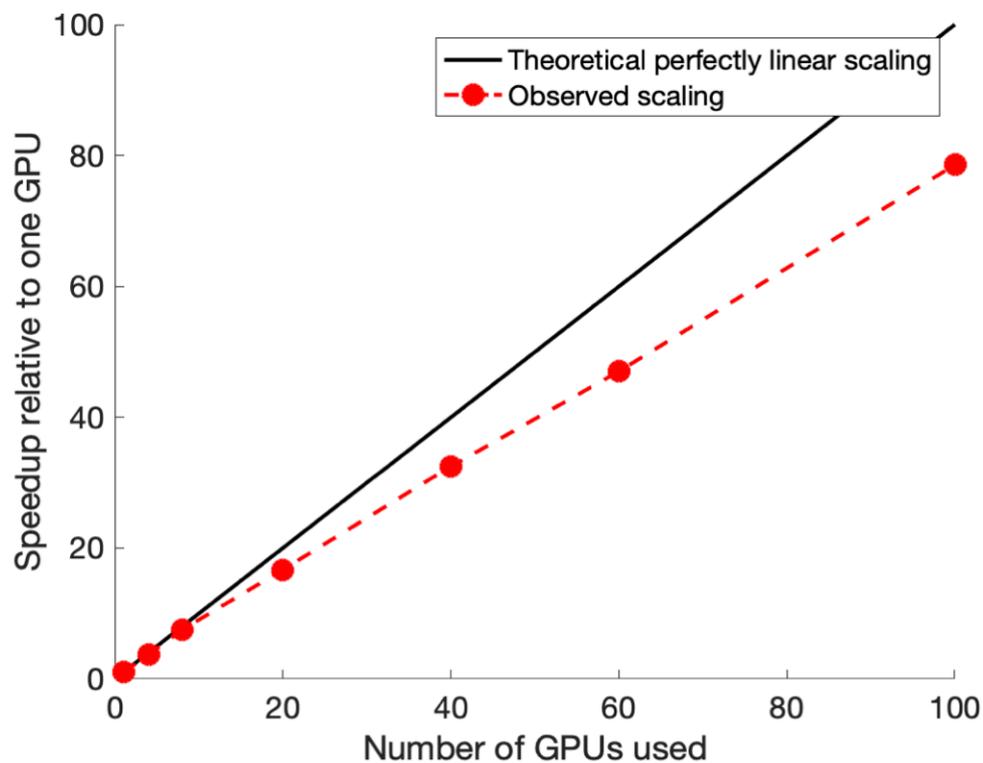
WE METHOD SIMULATION

Amber 18 with pmemd.cuda

100 NVIDIA V100 GPUs on
TACC Longhorn

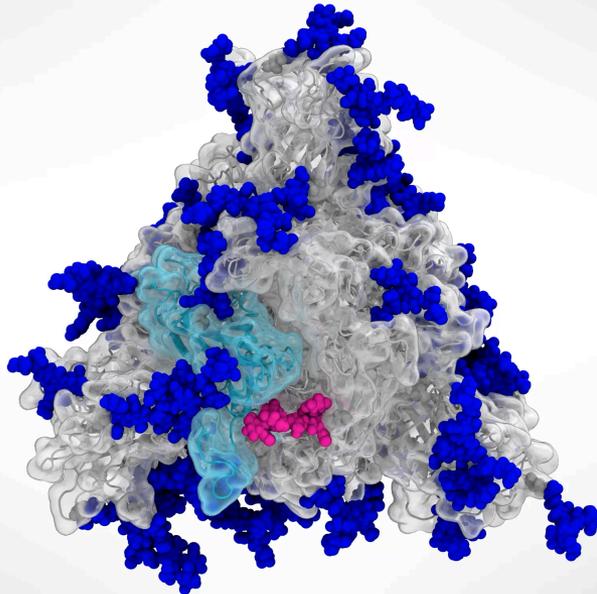
>130 μ s simulation time

300+ continuous pathways



SPIKE RBD OPENING

Closed Spike *Top view*



MOVIE BY L. CASALINO

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

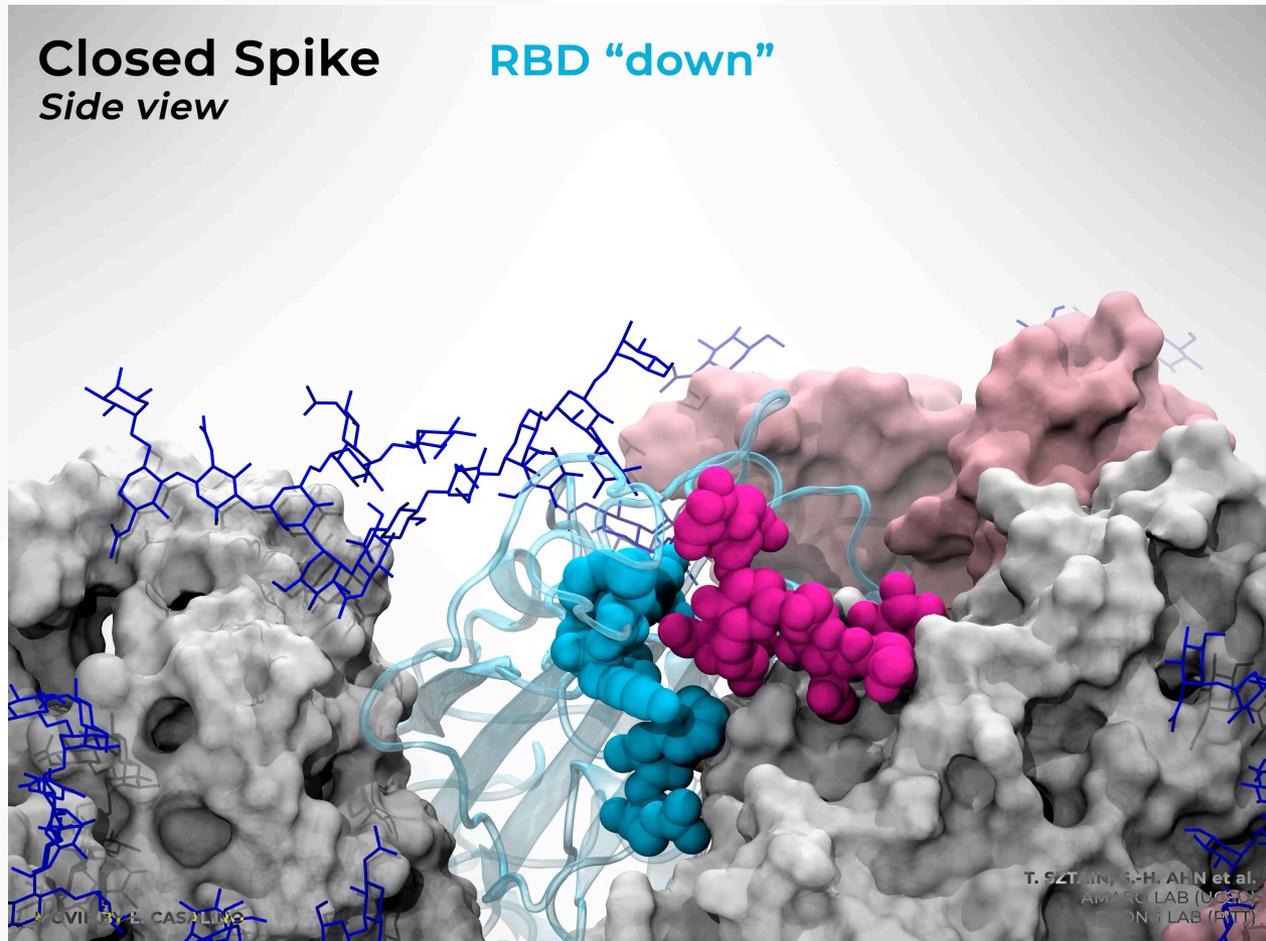
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†These authors contributed equally to this work

N343 GLYCAN PUSHES THE RBD FROM DOWN TO UP



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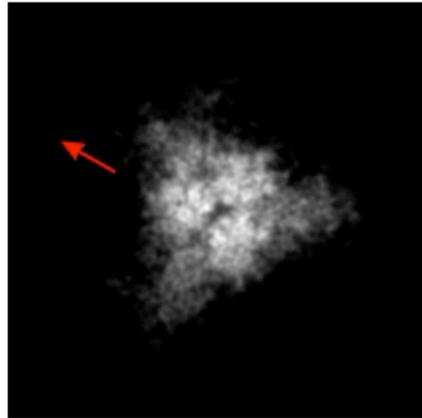
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†These authors contributed equally to this work

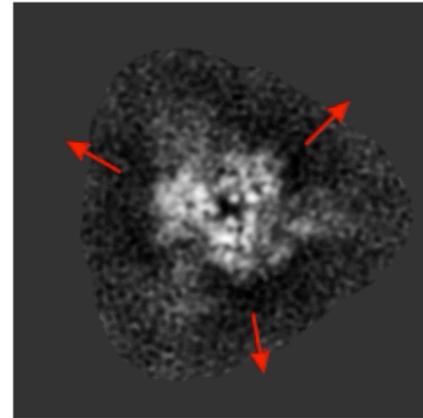
MANIFOLD EM CONFORMATIONAL COORDINATES

Top-down view (PD 112)

WE Trajectory



MEM CC2



Playback: 0

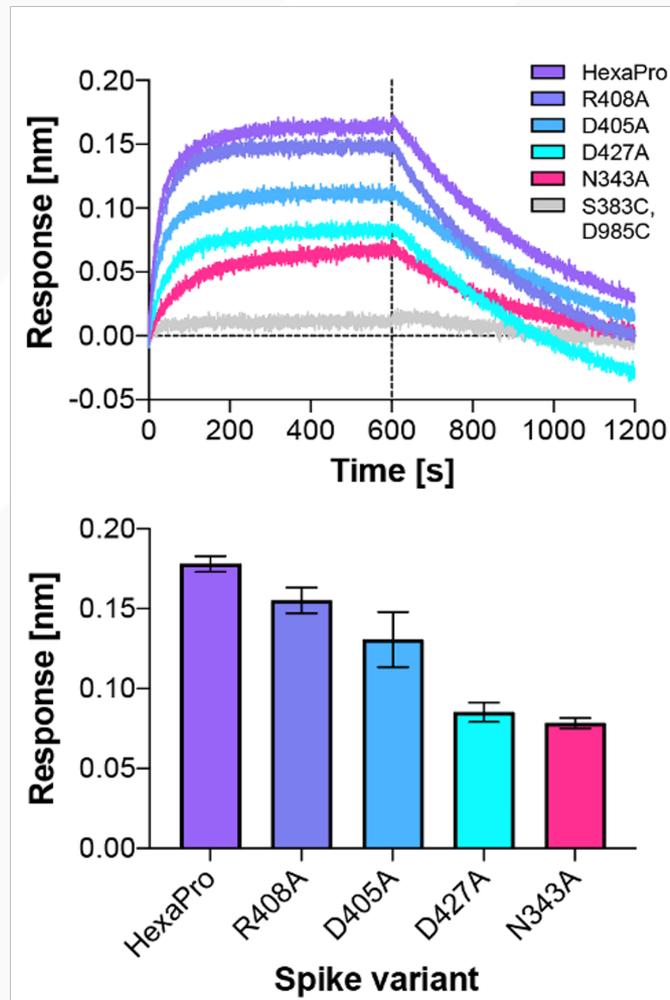
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BLI SHOW MUTANTS' REDUCED SPIKE LEVEL BINDING



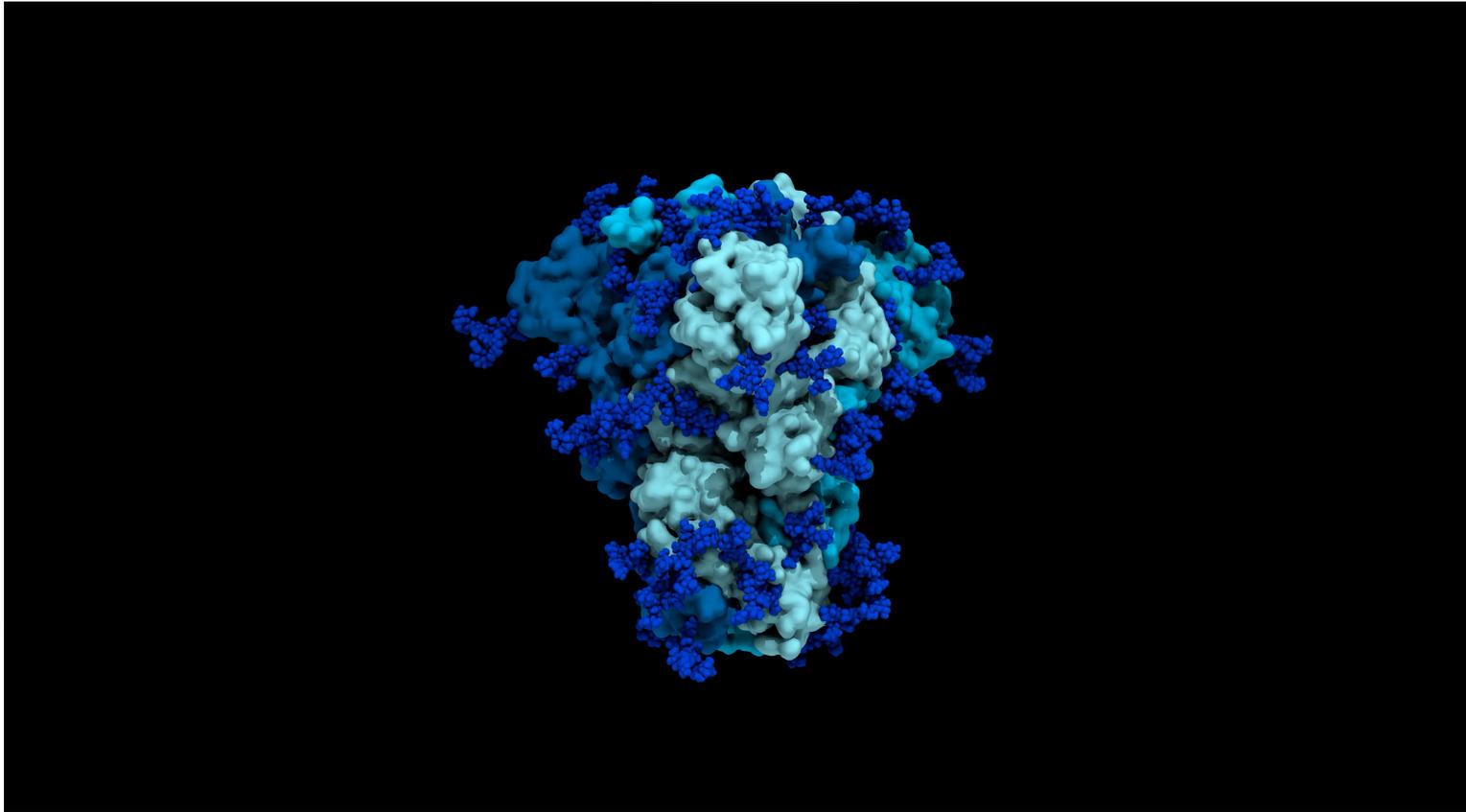
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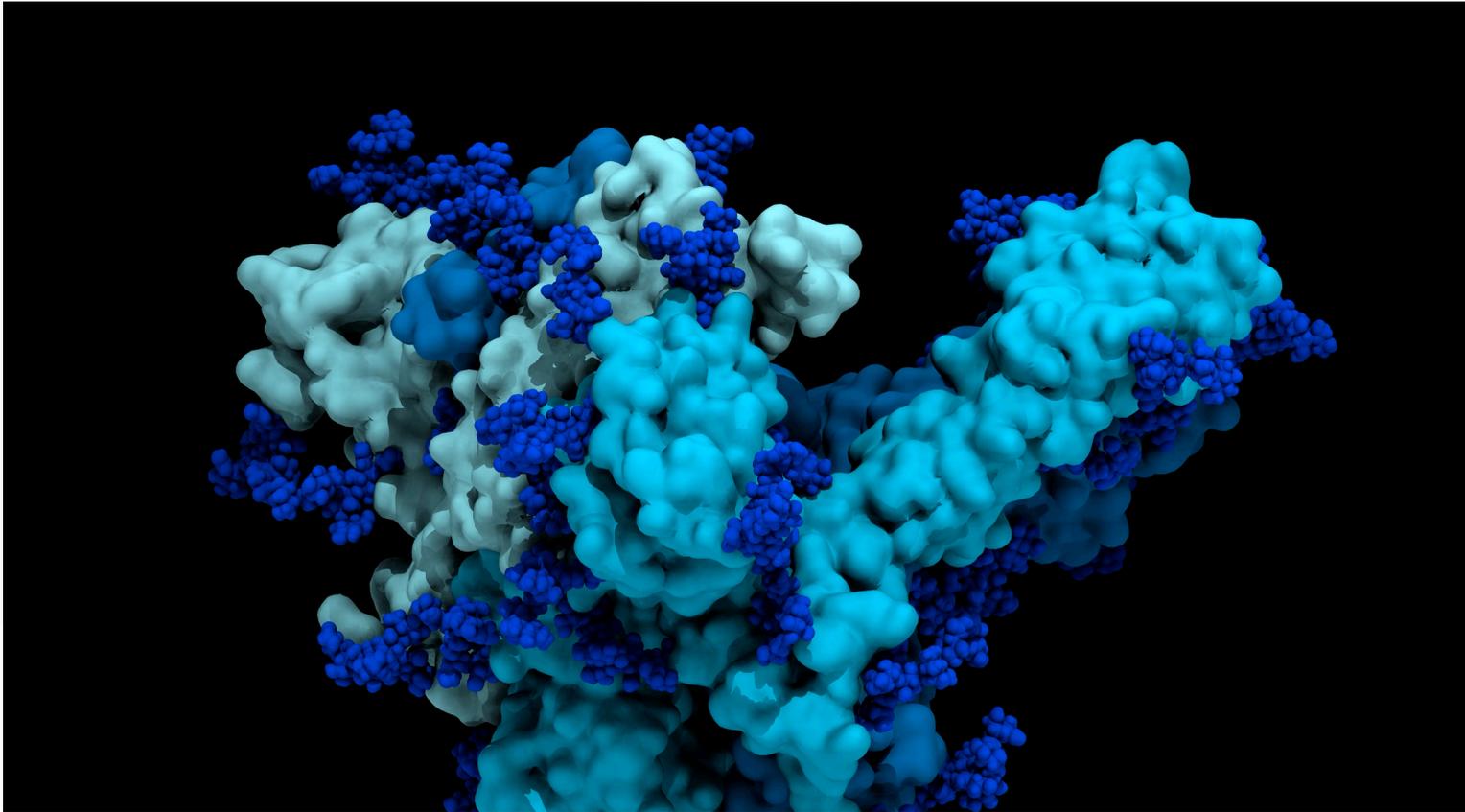
DELTA VARIANT SPIKE PROTEIN



(In Press) Dommer, A.†, Casalino, L.†, Kearns, F.†, Rosenfeld, M., Wauer, N., **Ahn, S.-H.**, ..., & Amaro, R.E. IJHPCA 2022
Finalist for 2021 Association for Computing Machinery Gordon Bell Special Prize for COVID-19
Featured in the New York Times article “The Coronavirus in a Tiny Drop”

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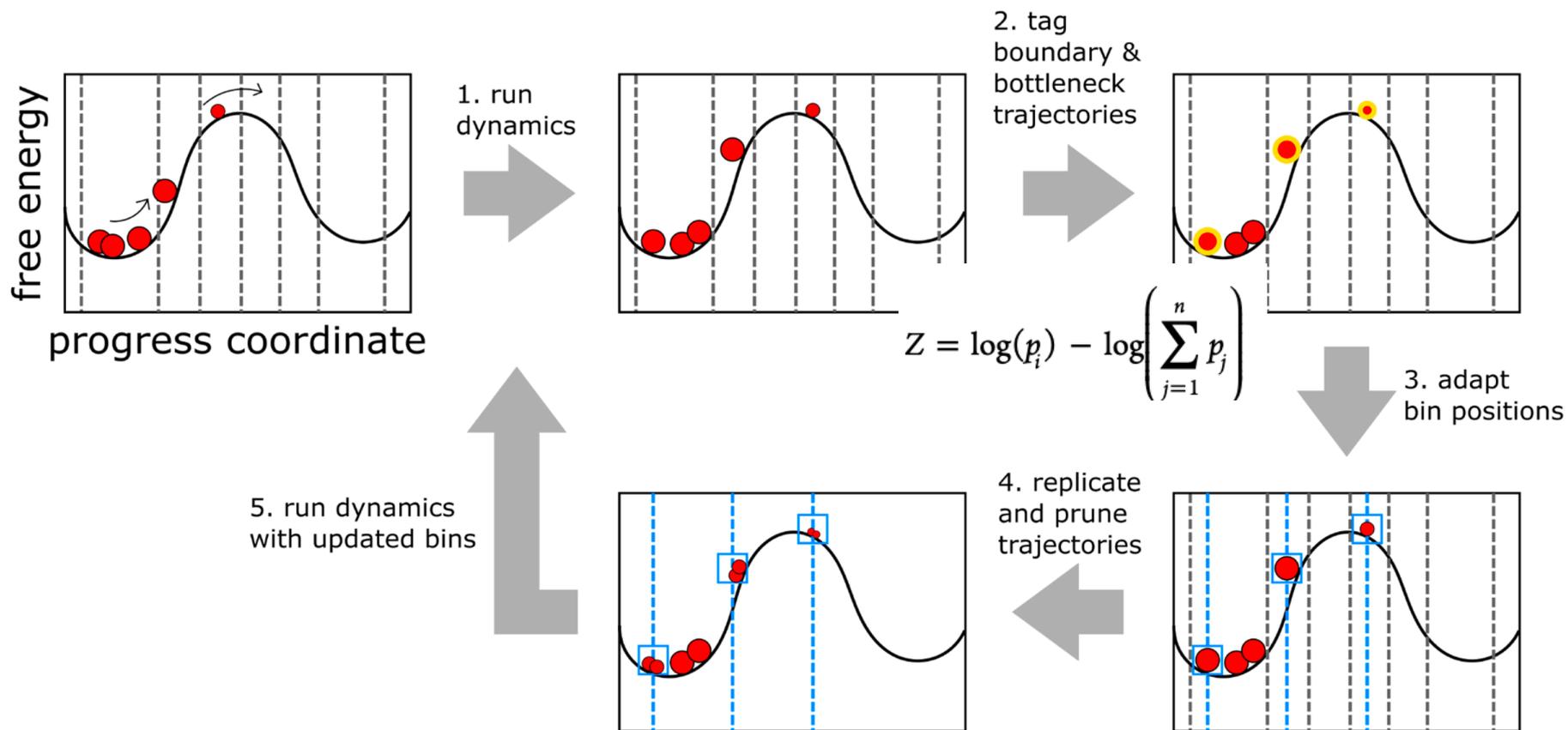
DRAMATIC OPENING OF DELTA VARIANT SPIKE PROTEIN



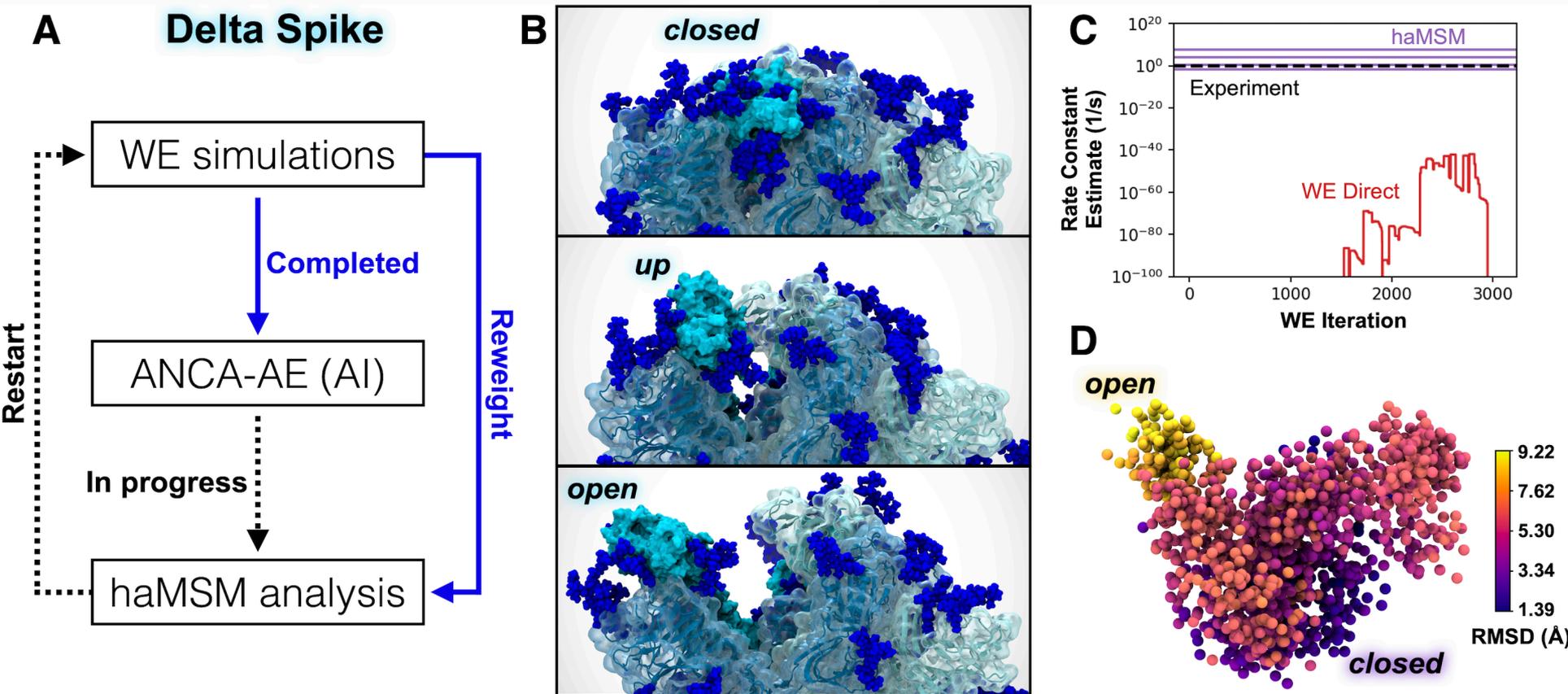
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MINIMAL ADAPTIVE BINNING (MAB) SCHEME



DELTA SPIKE OPENING MECHANISM AND RATE



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NEXT STEPS

- Re-run original, delta, etc. spike systems on Oracle Cloud for direct comparison
- haMSM analysis for rates
- Analyze interactions of glycans with the mutated residues on the RBD
- Map residue contacts to RBD throughout opening pathways
- Extract nonbonded (electrostatic and vdW) energies for RBD and core to see if there are correlations between the energies and RBD opening



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McCammon/Amaro lab
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Lorenzo Casalino, Dr. Fiona
Kearns, Mia Rosenfeld



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COVID-19 HPC
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