Biophysical virology of SARS-CoV-2

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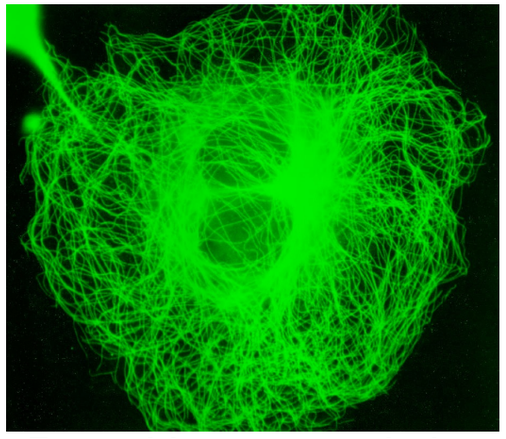
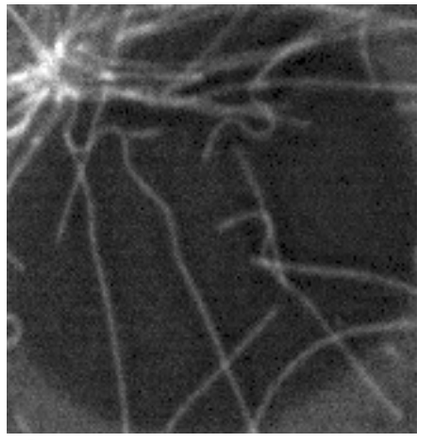
Single-molecule and single-particle biophysics

1. Individuals (spatial and temporal trajectories) can be idenditfied in an ensemble



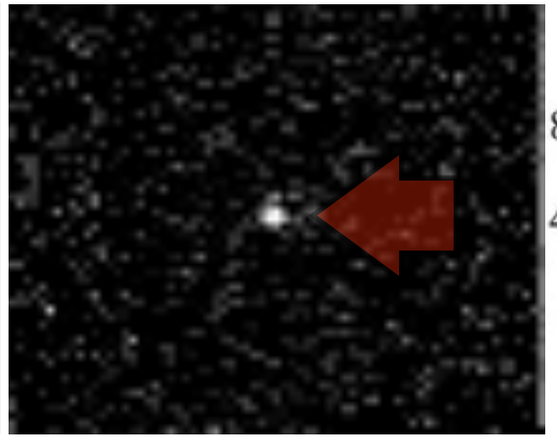
Ensemble - microtubular system

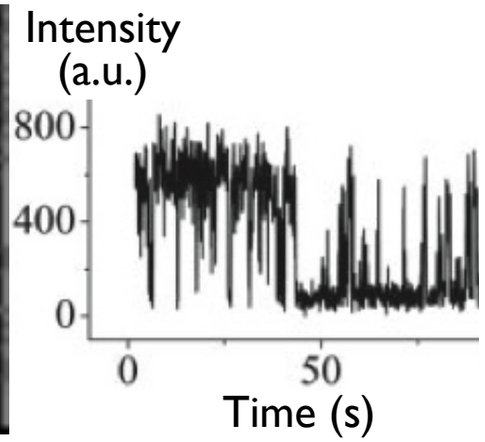


Single microtubules - treadmilling

2. Stochastic events may be discovered

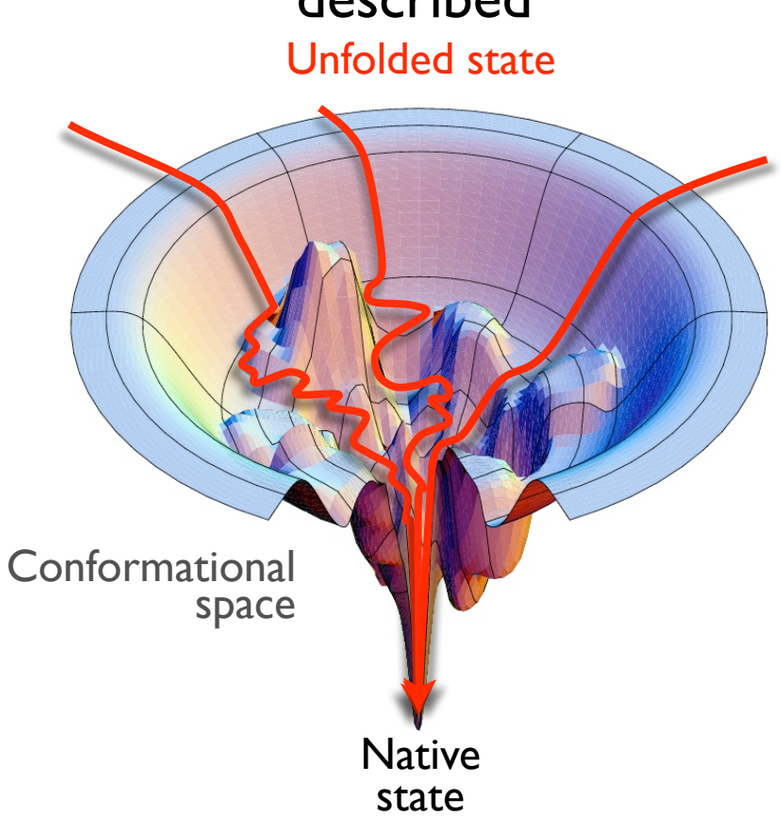
Ensemble - intensity



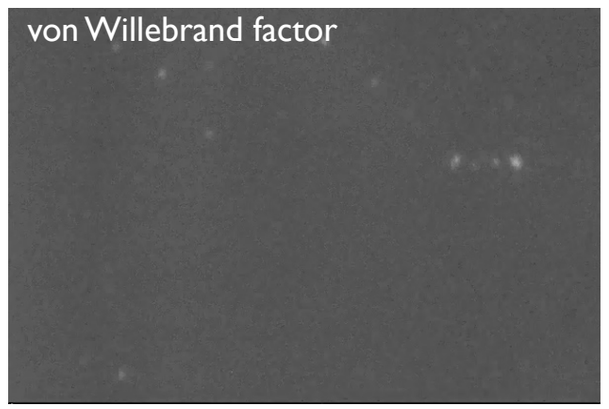


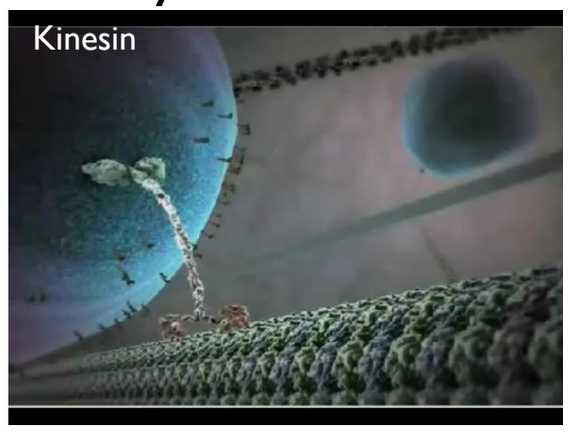
Single quantum dot - blinking

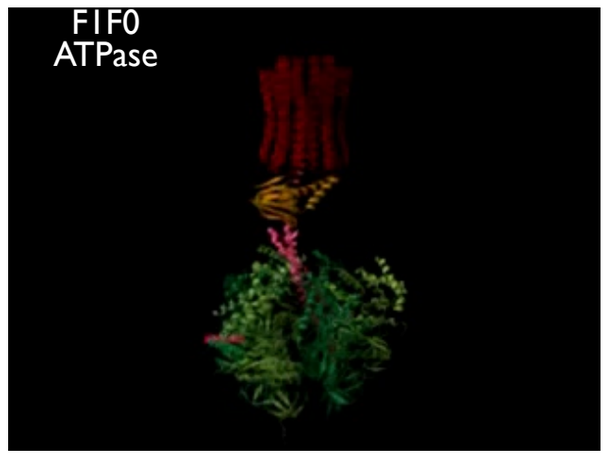
3. Parallel-pathway processes may be described



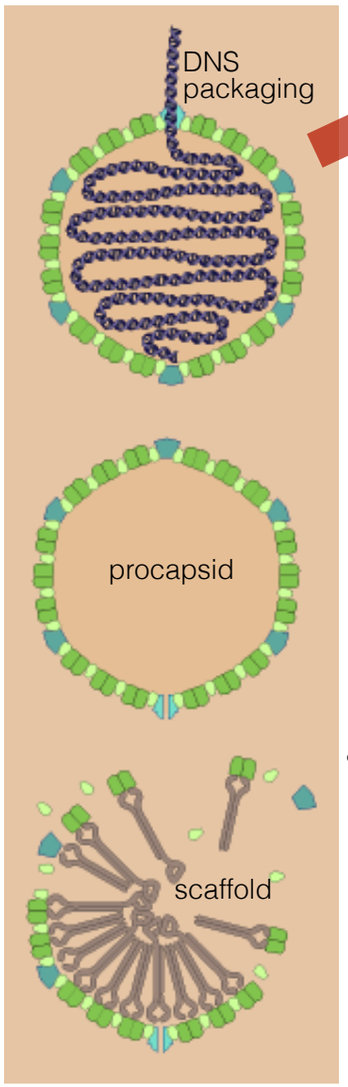
4. Mechanics of biomolecules may be characterized

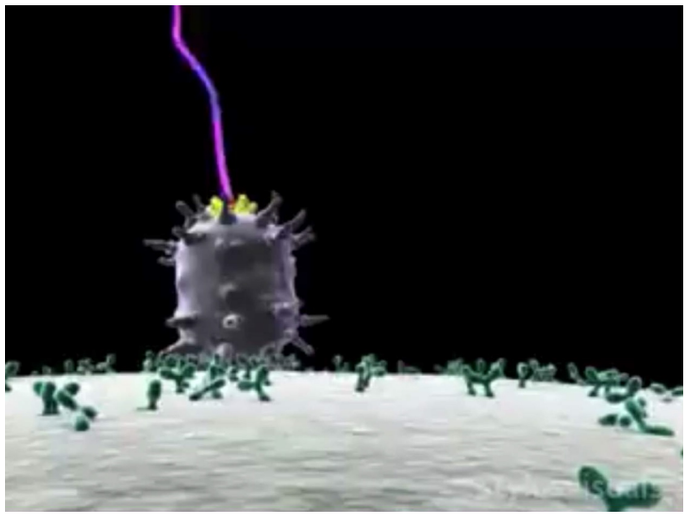




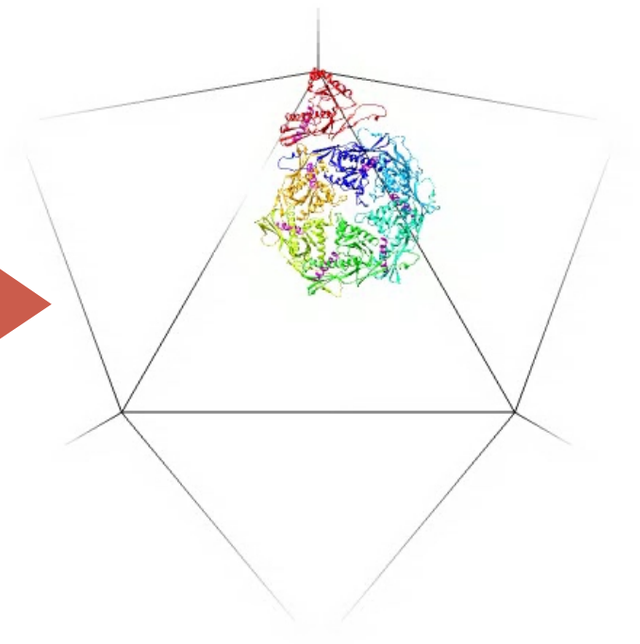


Life-cycle steps of a virus can be best explored with single particle methods

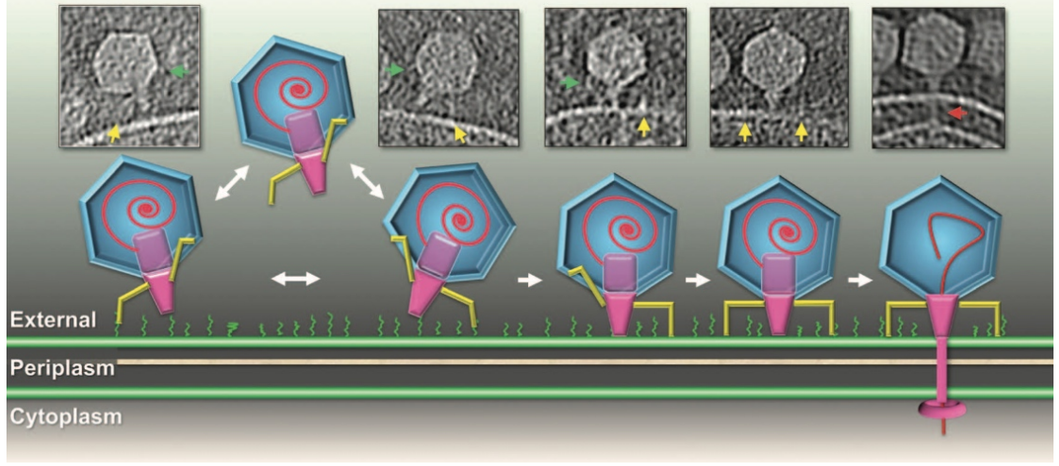




- **DNA packaging** (ATP-dependent, motor-driven process, DNS pressure of ~60 atm is generated!)



Structural maturation:
- Capsid expansion, wall thinning
- *gp10* N-terminal helix unfolds, swings across the wall, then folds.
- Non-covalent, structure-stabilizing bonds are formed.



Infection:
- receptor (e.g., LPS) recognition
- trigger
- injector complex formation
- DNA ejection

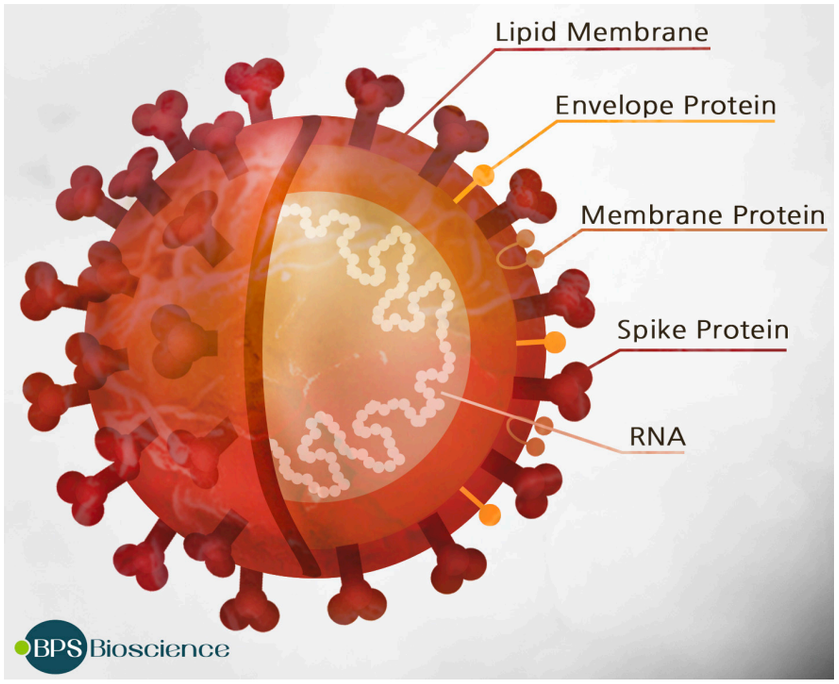
LamB (maltoporin) inducedt λ-phage DNA ejection; repid DNA labeling with SYBR Gold

- **Viral protein synthesis** in host cell

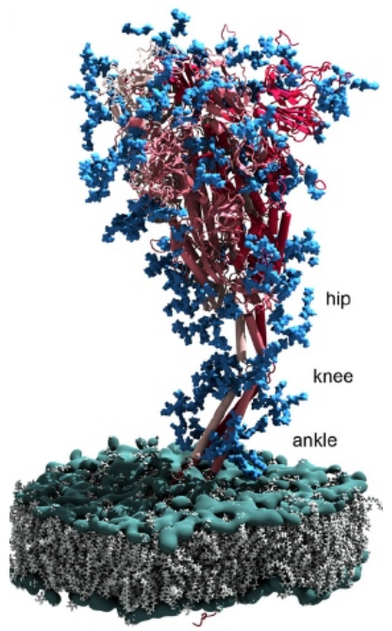
- **DNA-free procapsid formation** (“*scaffold” protein*-dependent process)

The new coronavirus: SARS-CoV-2

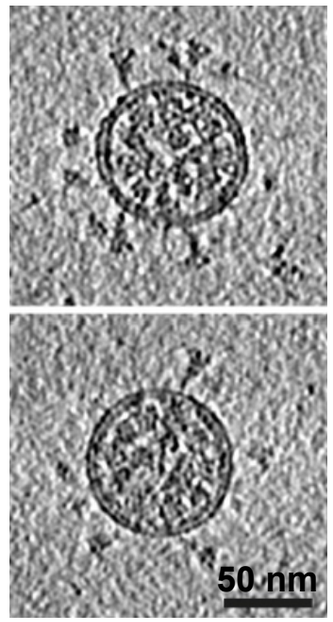
Structure

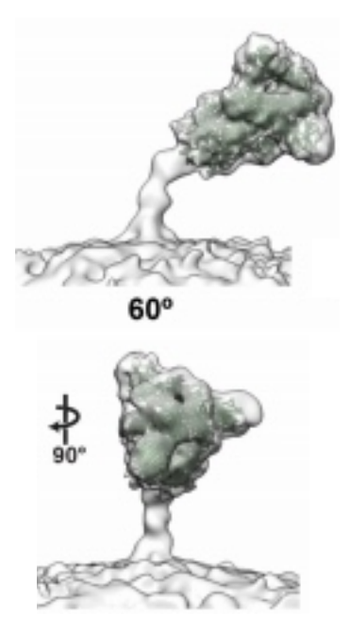


Cryo-electron microscopy on fixed and frozen virions



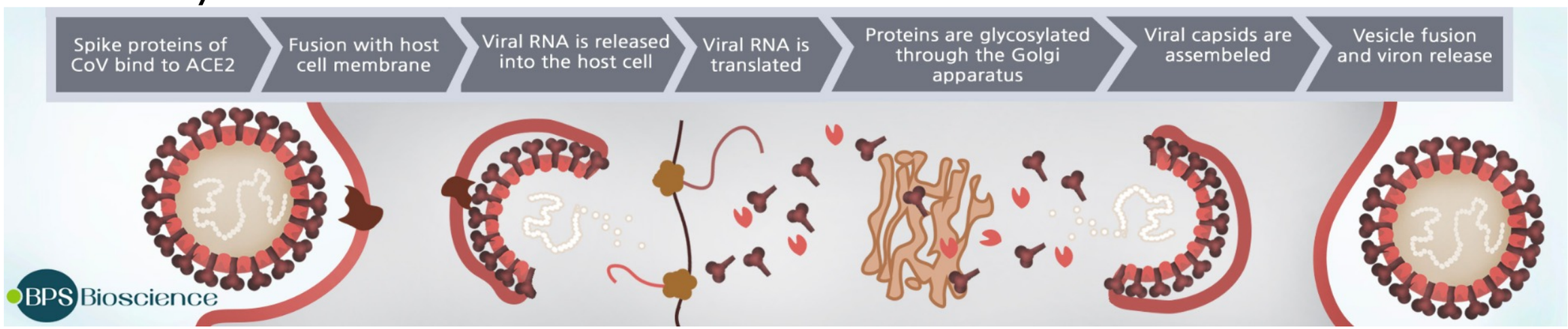
Turoňová, et al. Science 2020





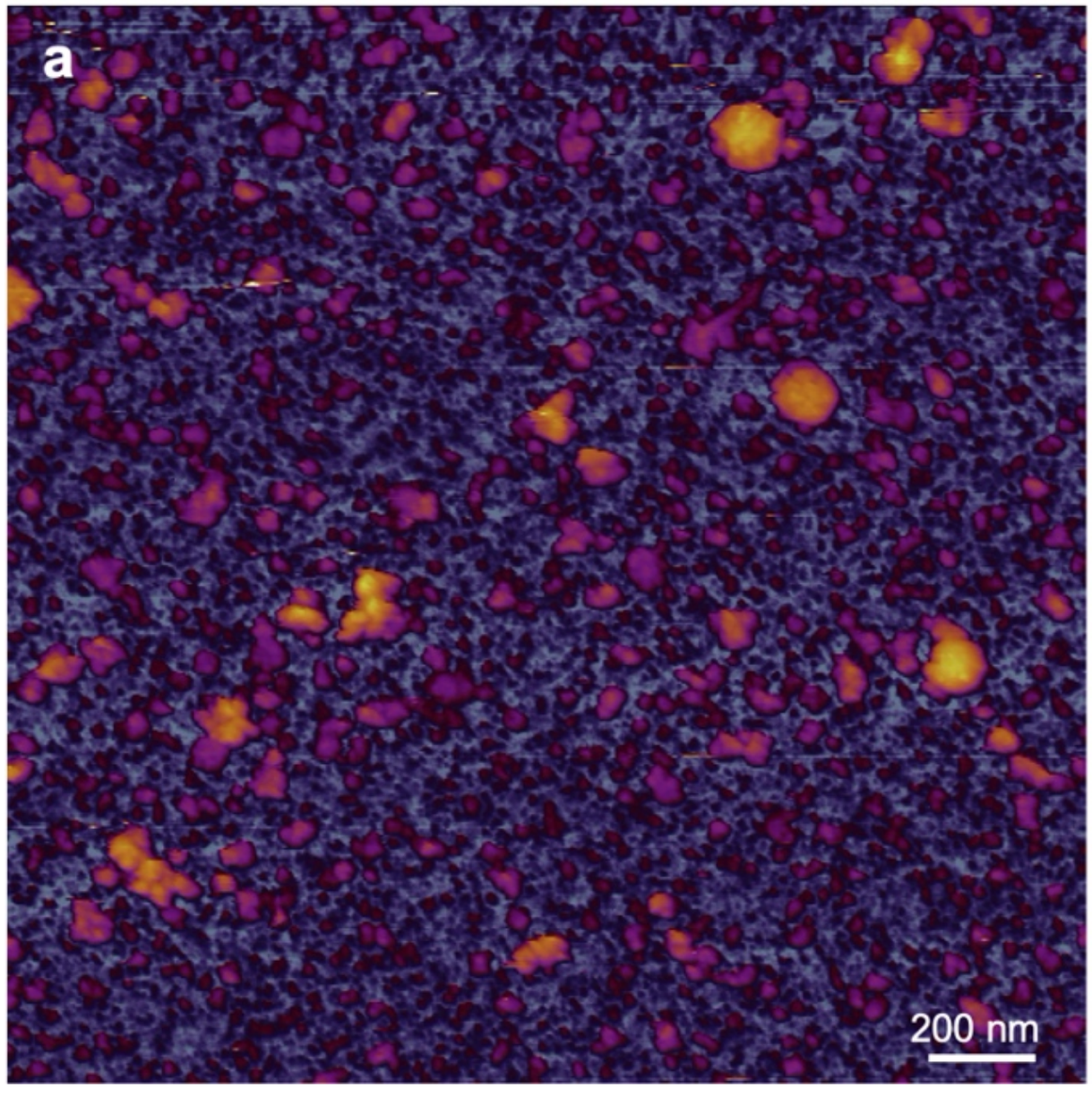
Ke, et al. Nature 2020

Infectious cycle

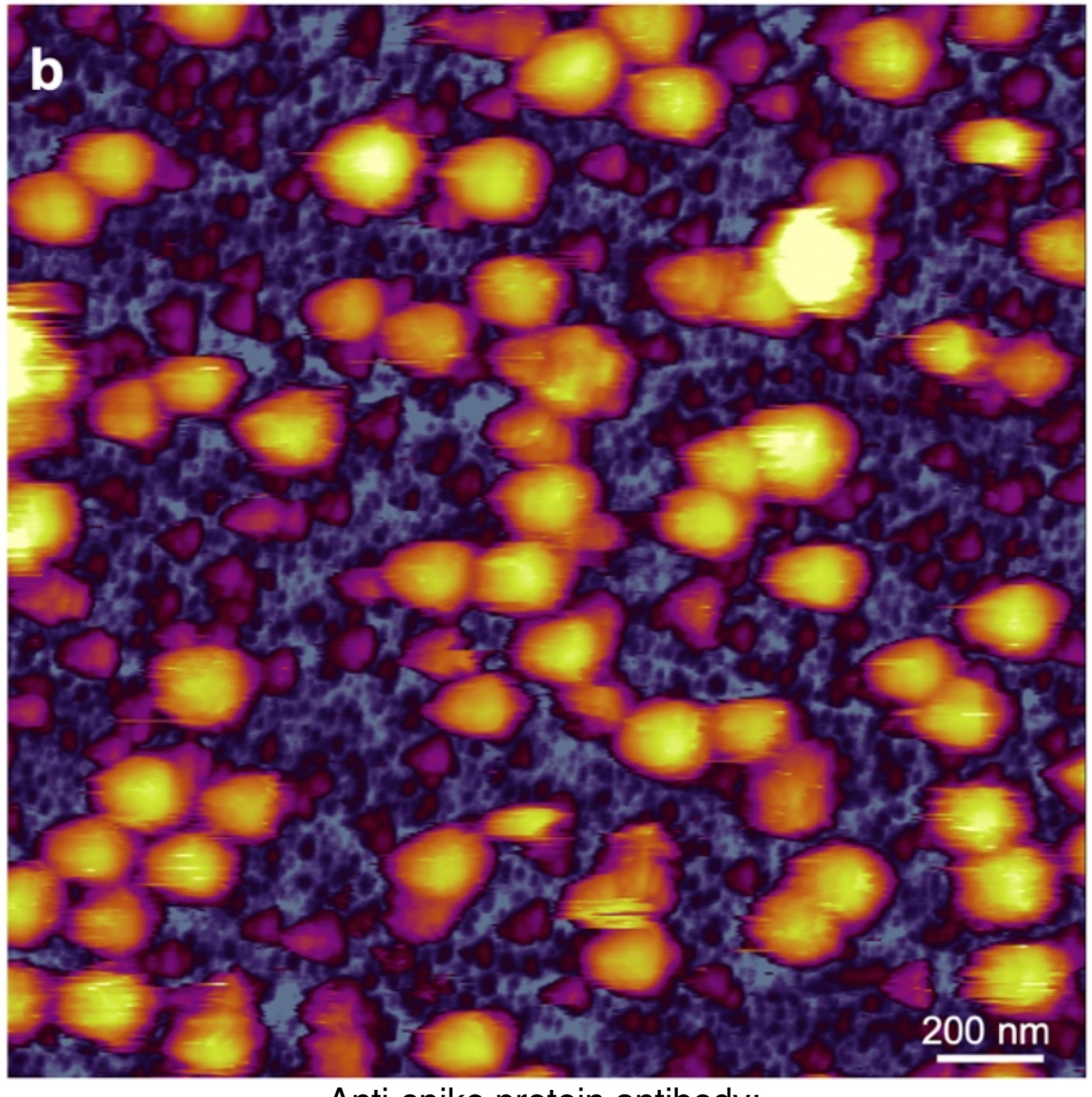


What are the structural, dynamic and mechanical properties of the native, unfixed SARS-CoV-2 virus?

Affinity binding enhances surface adsorption of SARS-CoV-2

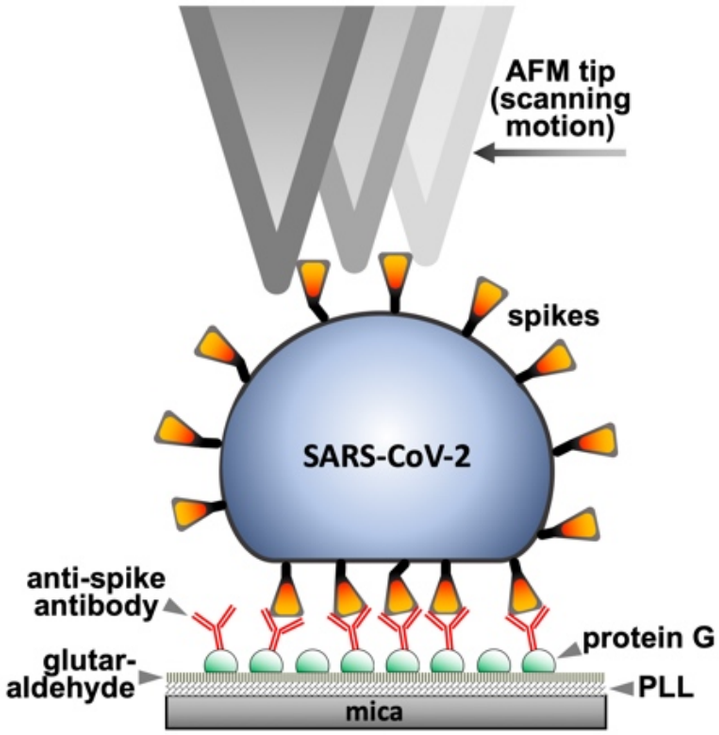


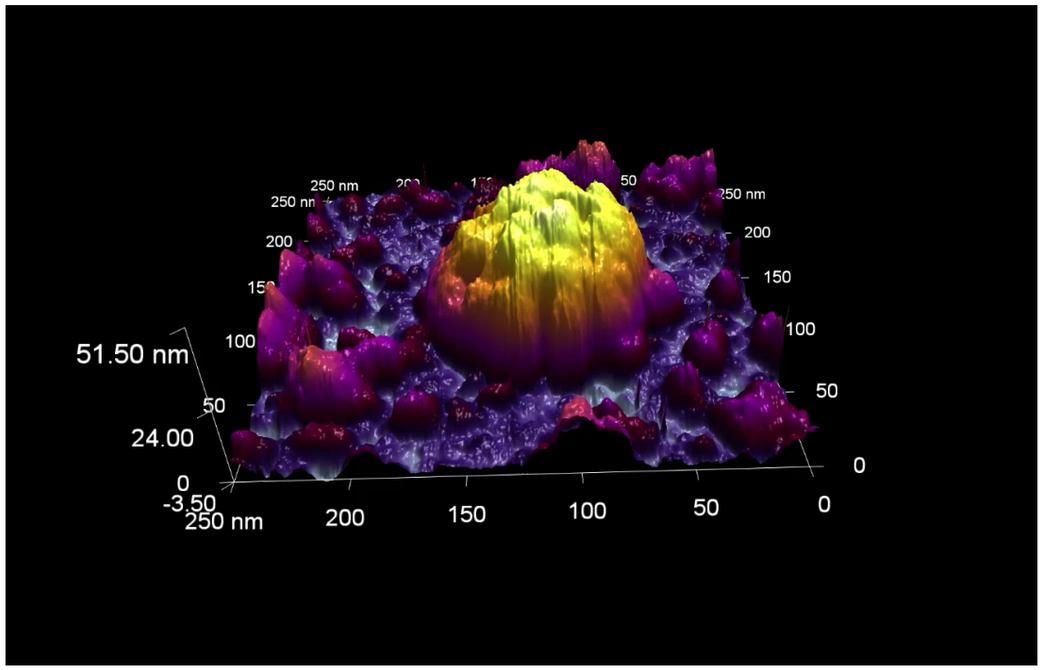
Direct binding to mica surface

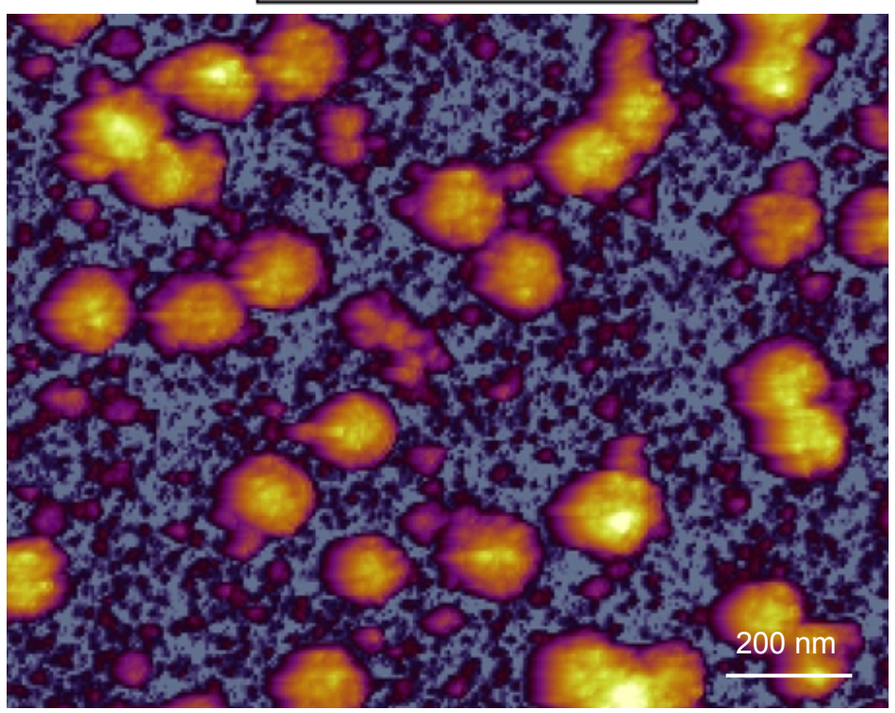


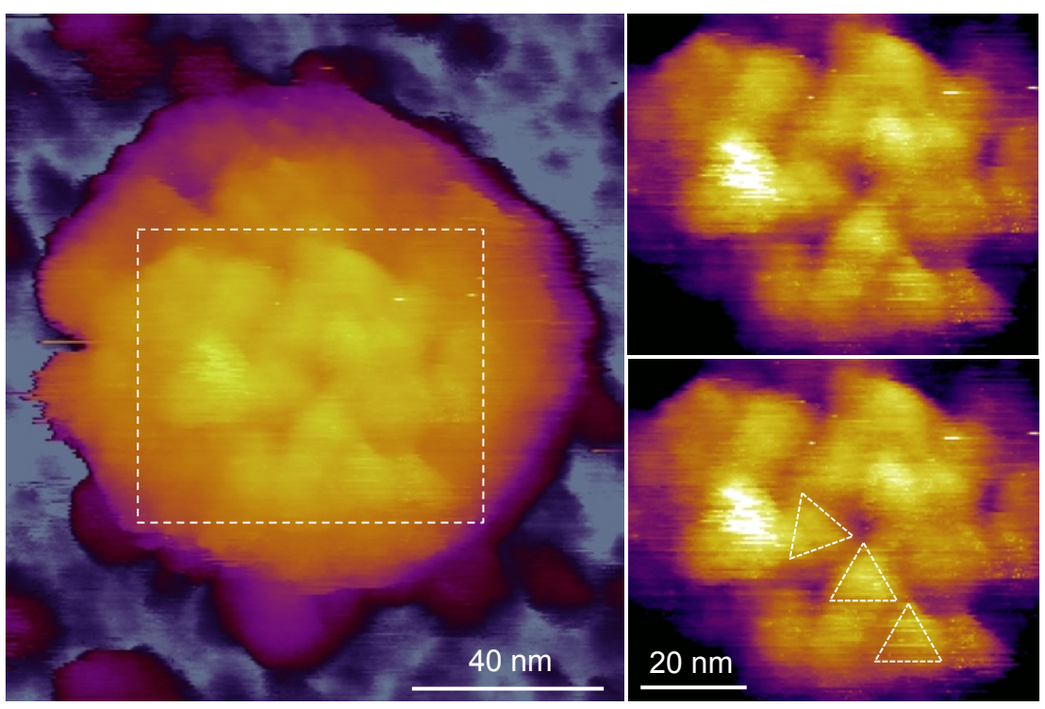
Anti-spike protein antibody:
~100x enhancement in particle number

Spikes can be resolved on the surface of fixed SARS-CoV-2 virions

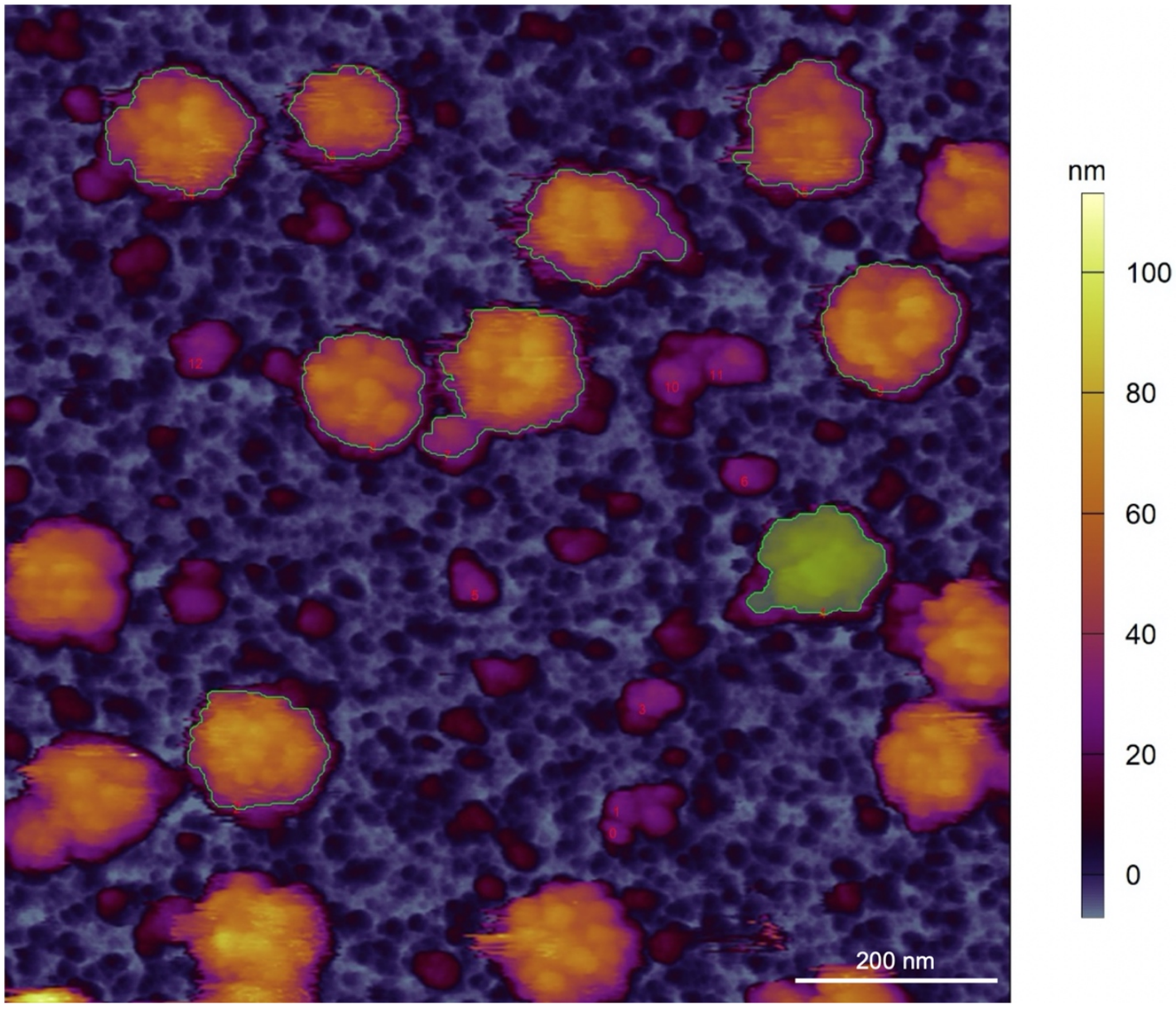






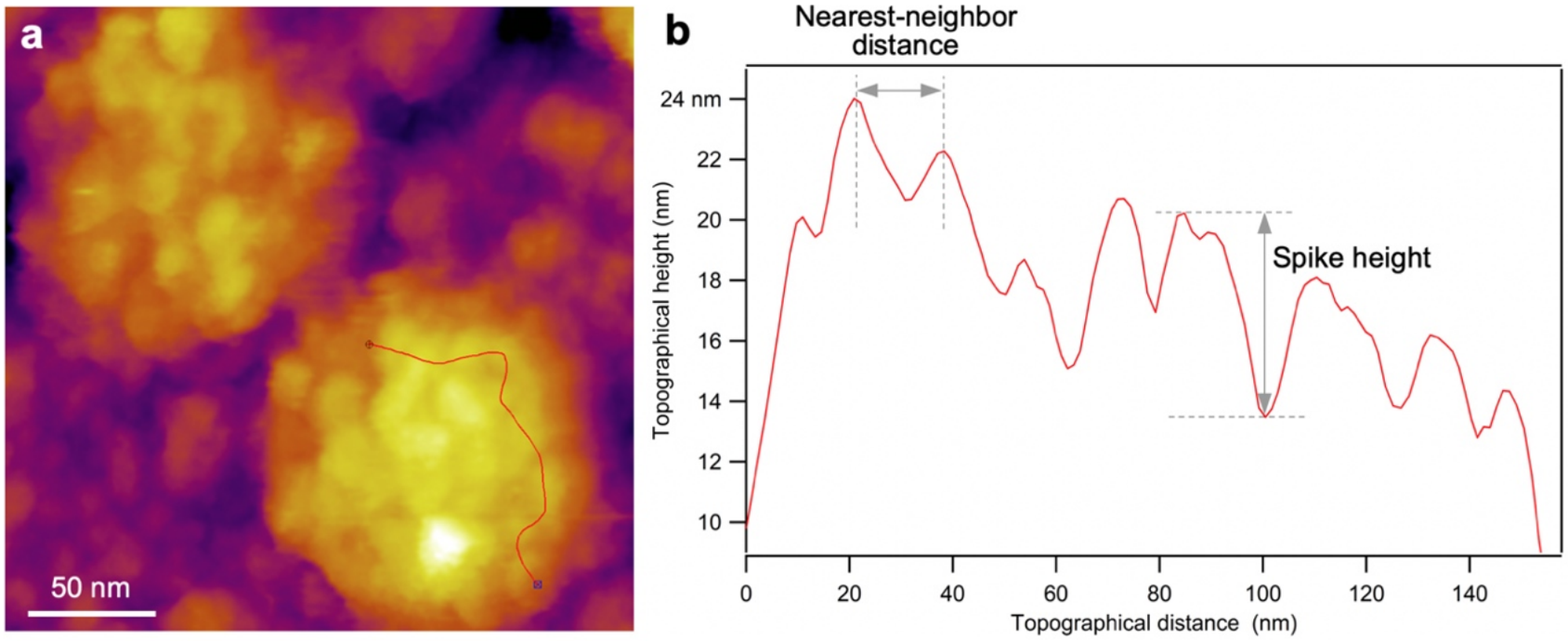


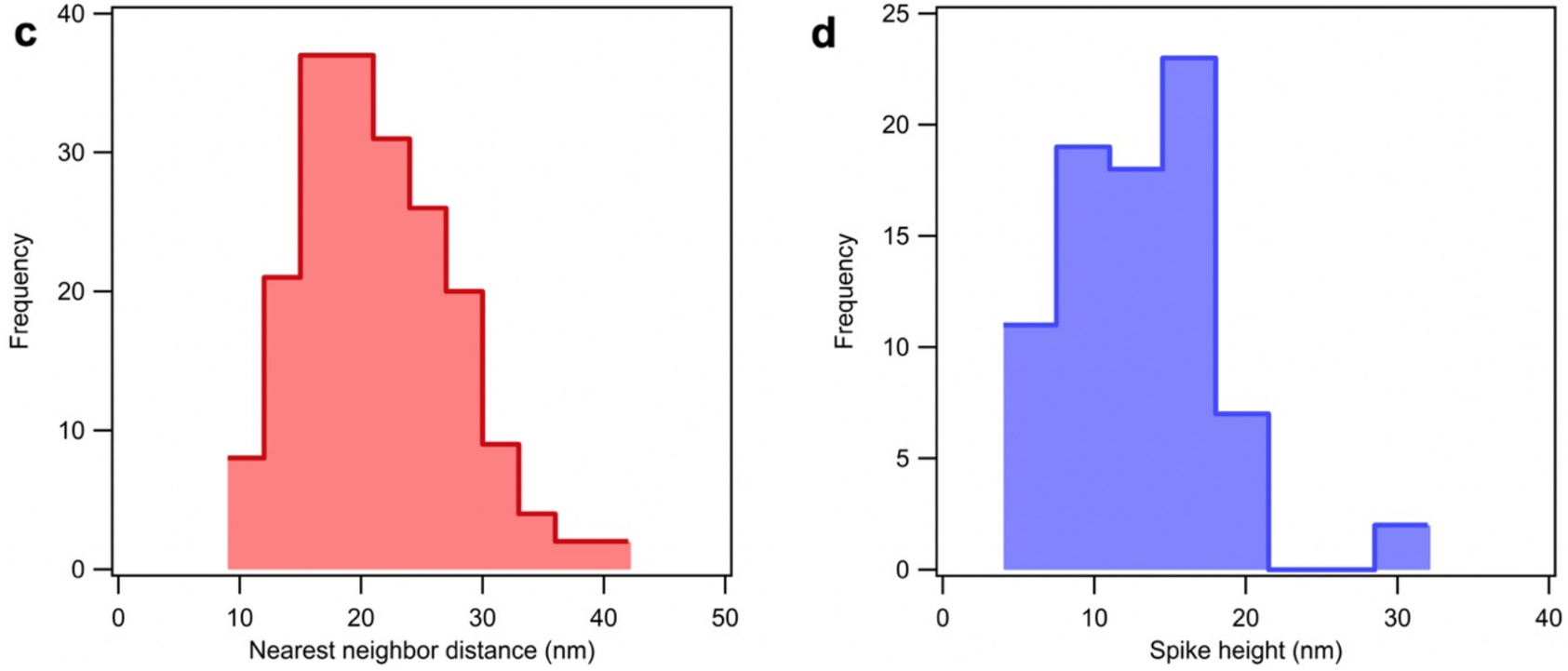
SARS-CoV-2 particle analysis



	Height (nm)	Volume (nm^3)	Diameter (nm)	n
Fixed	62 ± 8	574 000 ± 212 000	120 ± 16	51
Native	83 ± 7	490 000 ± 107 000	99 ± 11	47
Heated (90 ˚C)	82 ± 10	600 000 ± 152 000	108 ± 12	37

SARS-CoV-2 spike analysis

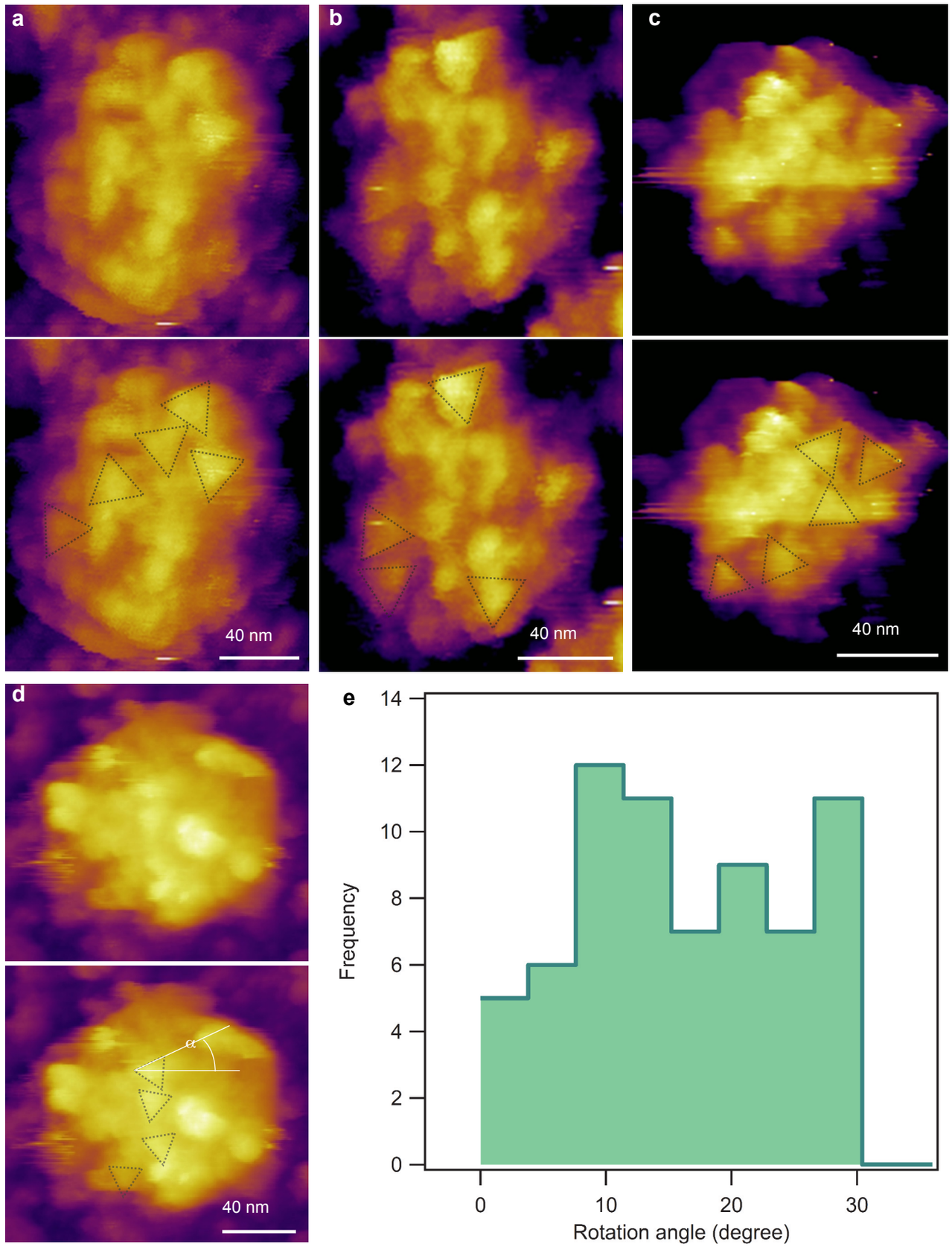




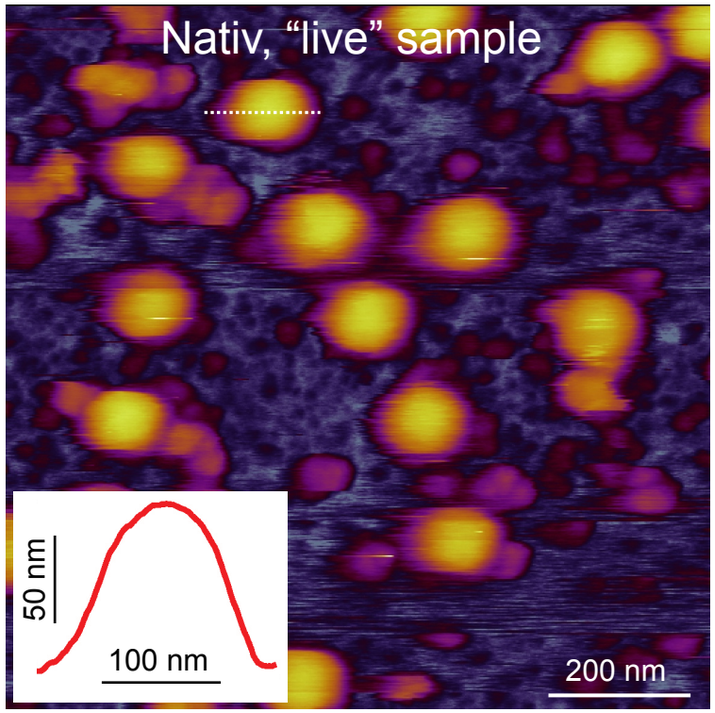
	Mean ± S.D. (nm)	n
Nearest-neighbour distance	21 ± 6	197
Spike height	13 ± 5	80

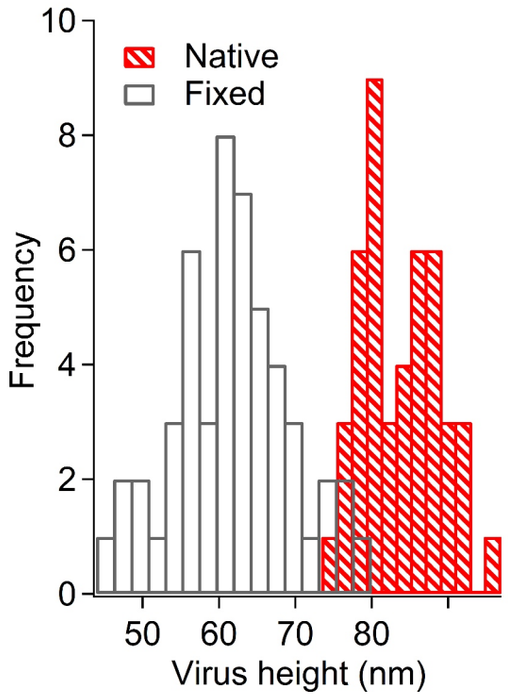
→ ~61 spikes/virion

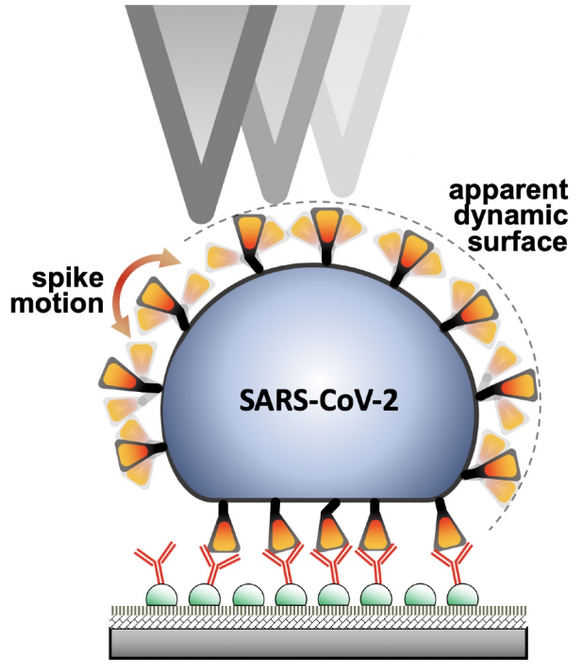
Spikes display rotational freedom

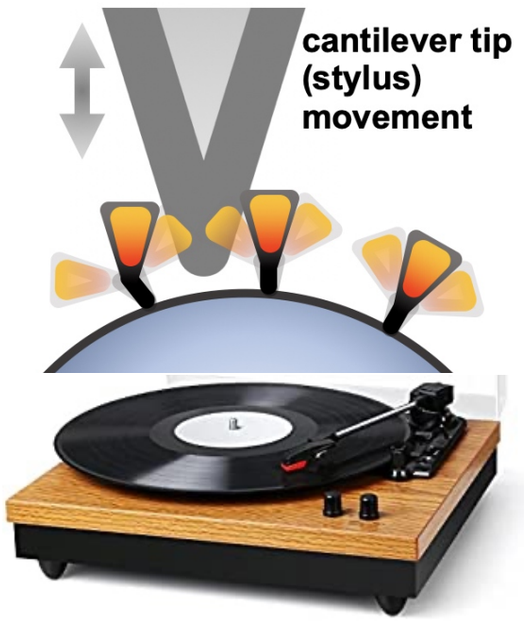


Spike dynamics increase apparent virion diameter

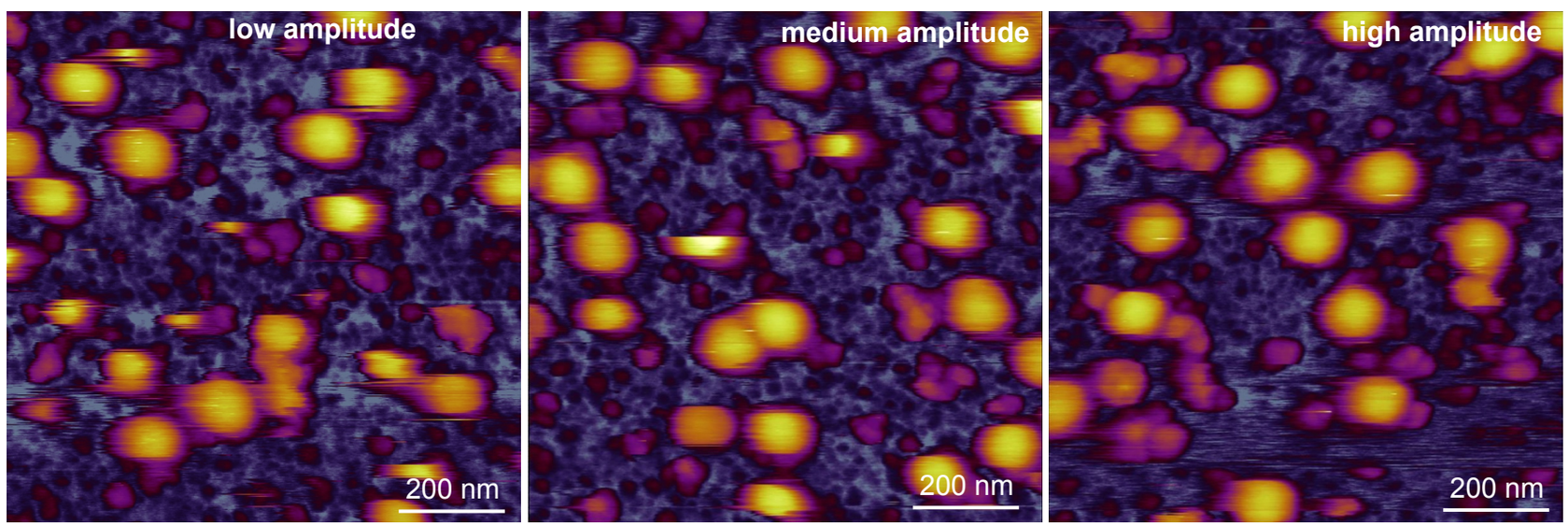




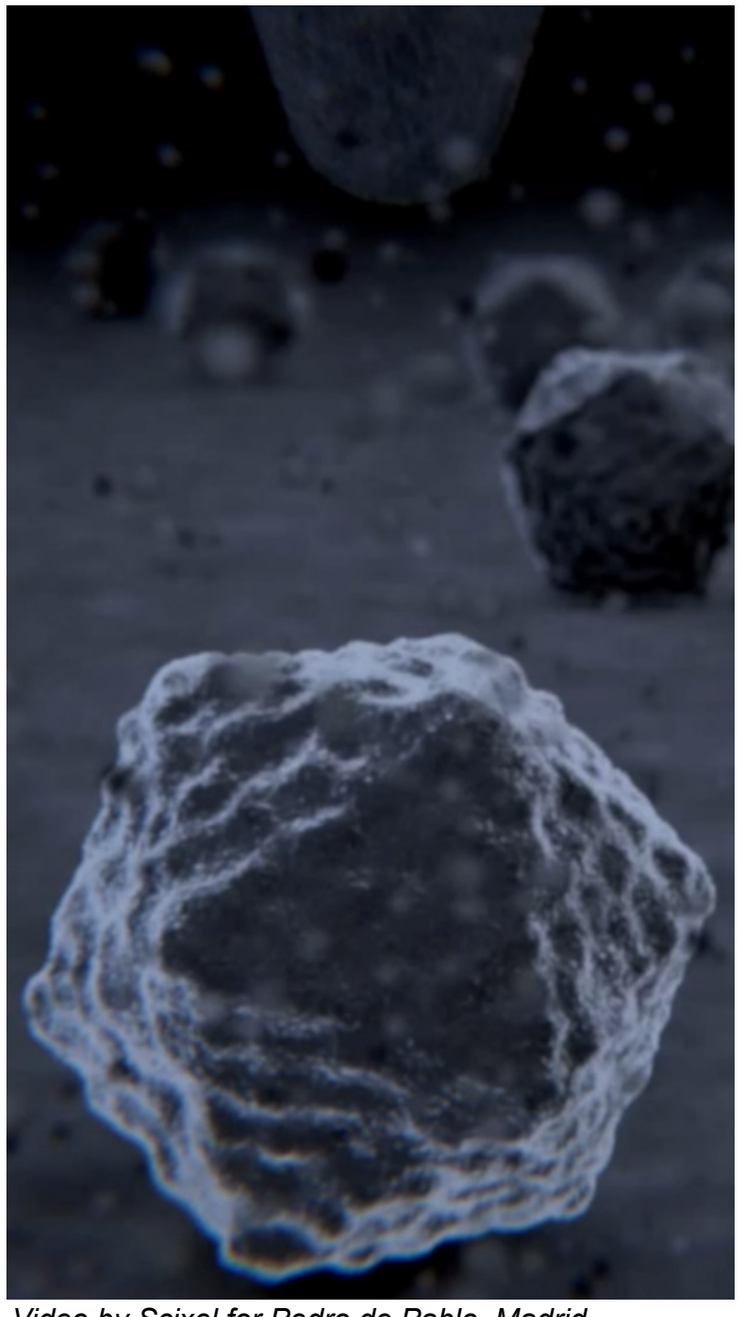




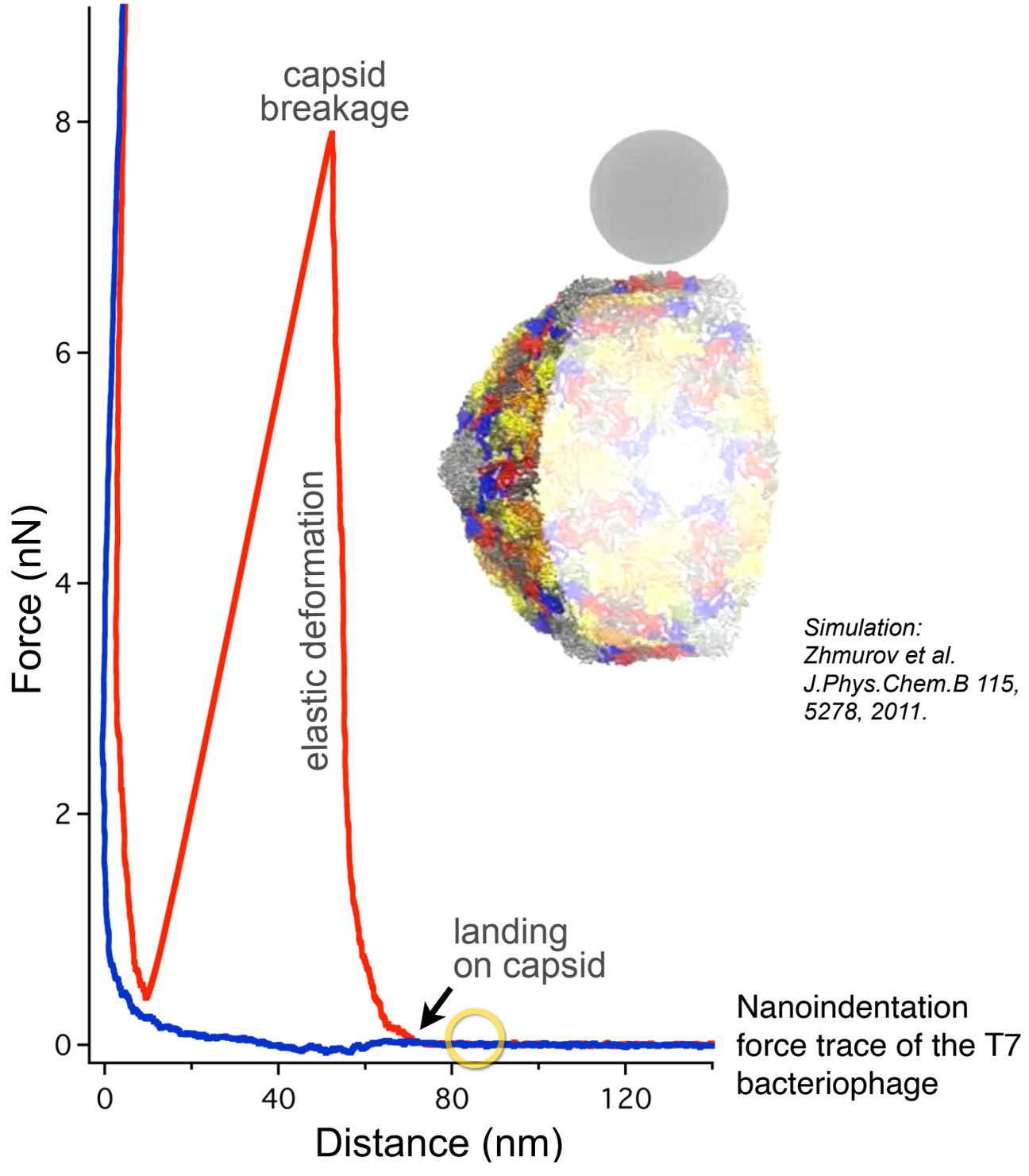
Effect of scanning force on SARS-CoV-2 topography



Uncovering virus capsid mechanics with nanoindentation



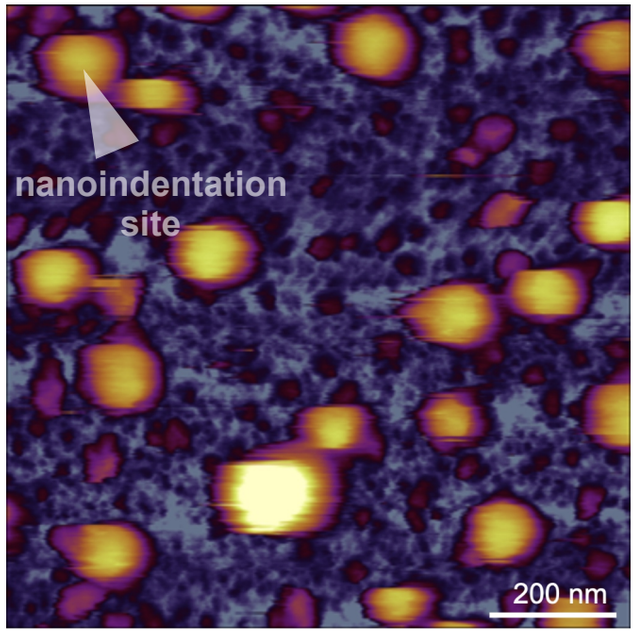
Video by Scixel for Pedro de Pablo, Madrid

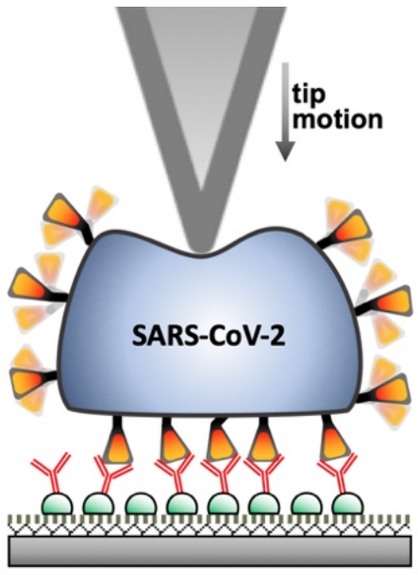


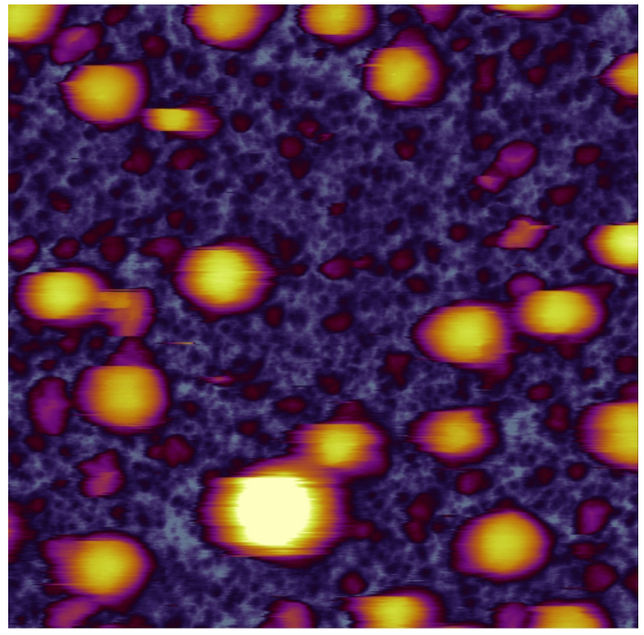
Simulation: Zhmurov et al. J.Phys.Chem.B 115, 5278, 2011.

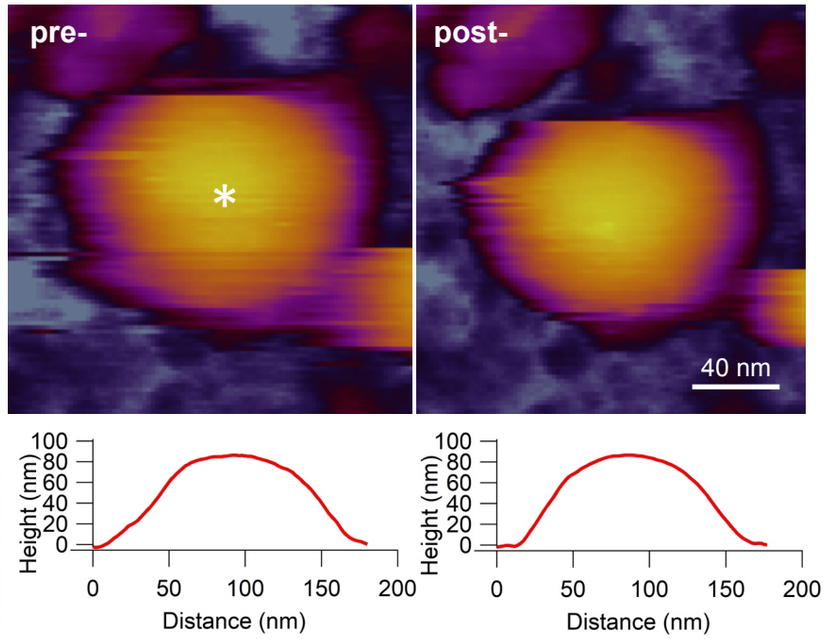
Nanoindentation force trace of the T7 bacteriophage

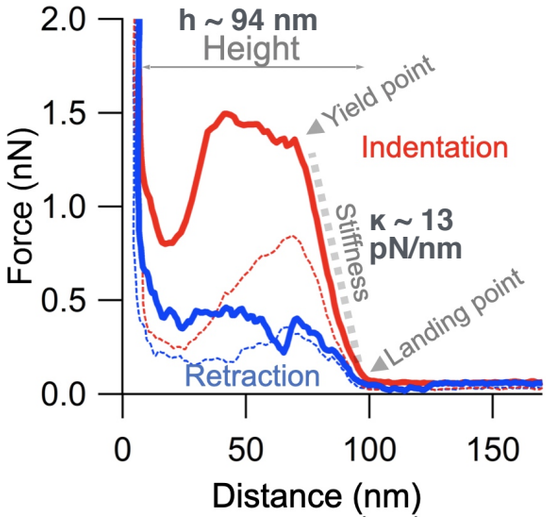
SARS-CoV-2 is highly resilient

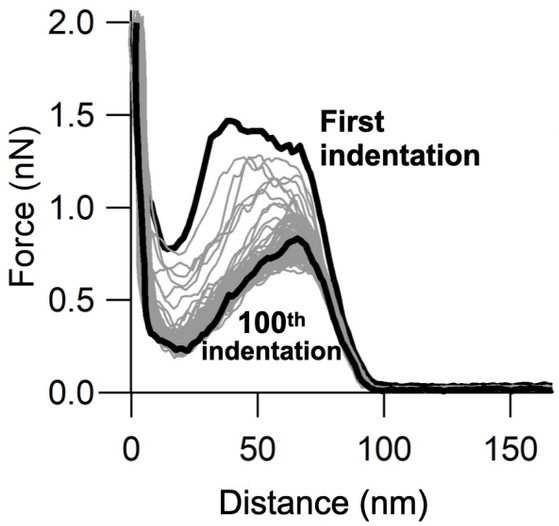


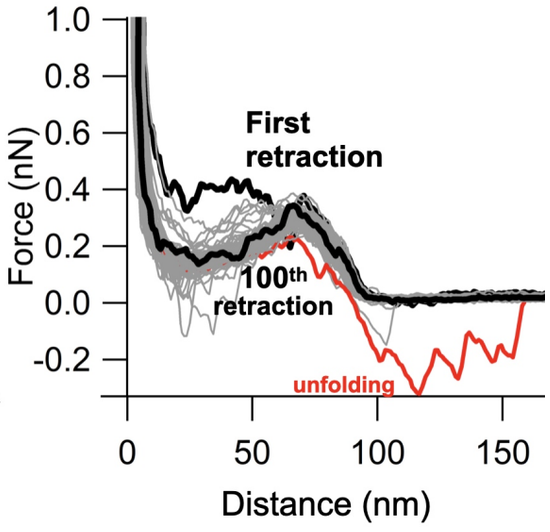


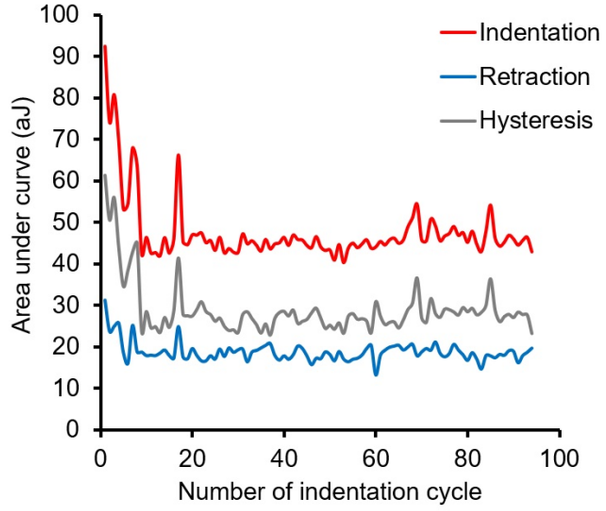


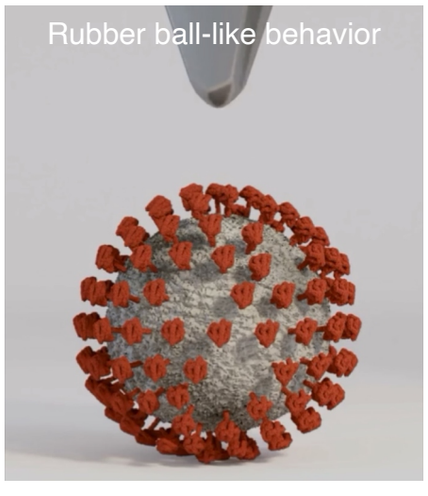




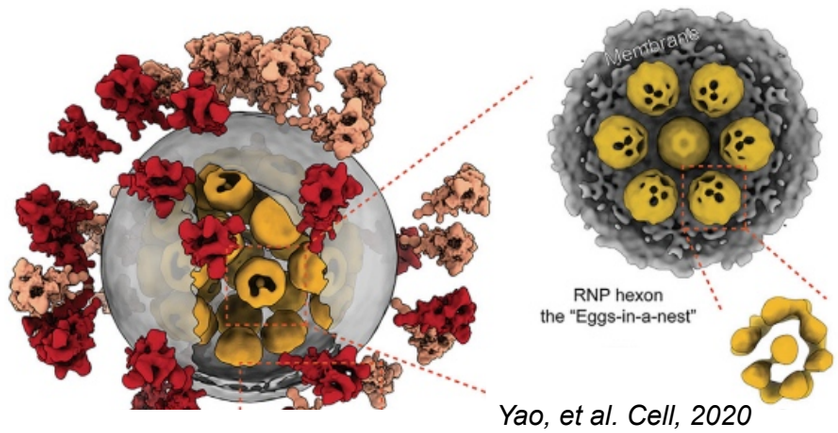








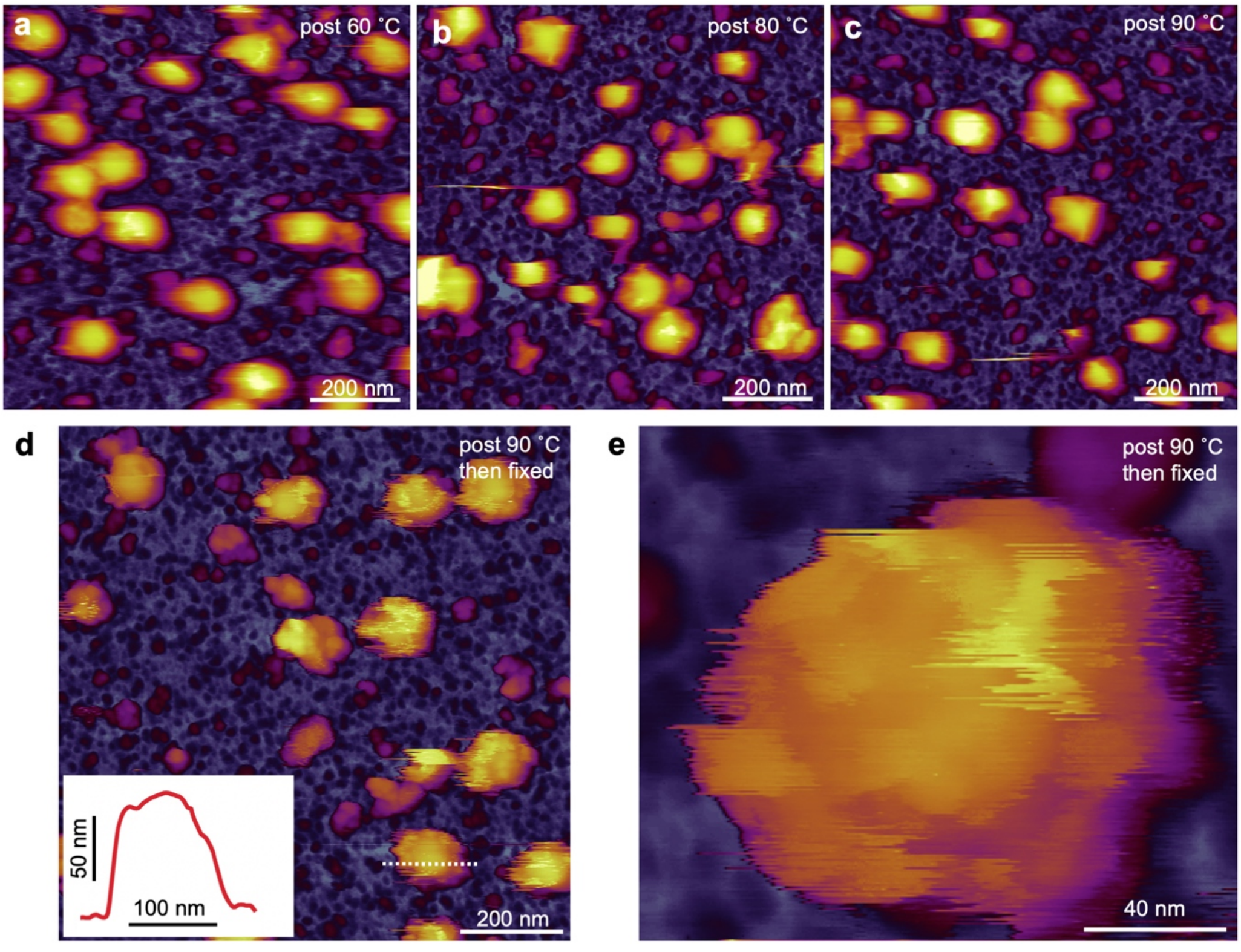
Video by Scixel



Yao, et al. Cell, 2020

Nest-like organization of RNP in SARS-CoV-2 may yield to nanoindentation

Global structure of SARS-CoV-2 is heat tolerant



Summary

- The spikes on the SARS-CoV-2 virion are highly dynamic - potential role in infectiousness.
- SARS-CoV-2 is the most compliant virion known to date.
- The SARS-CoV-2 virion is mechanically resilient and its structure recovers after multiple mechanical interventions ("self-healing" ability).
- The global structure of SARS-CoV-2 is rather resistant to thermal exposure; its thermal sensitivity is likely caused by the dissociation of its spikes.

Acknowledgements

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- Zoltán Kis, Bernadett Pályi (National Public Health Center)

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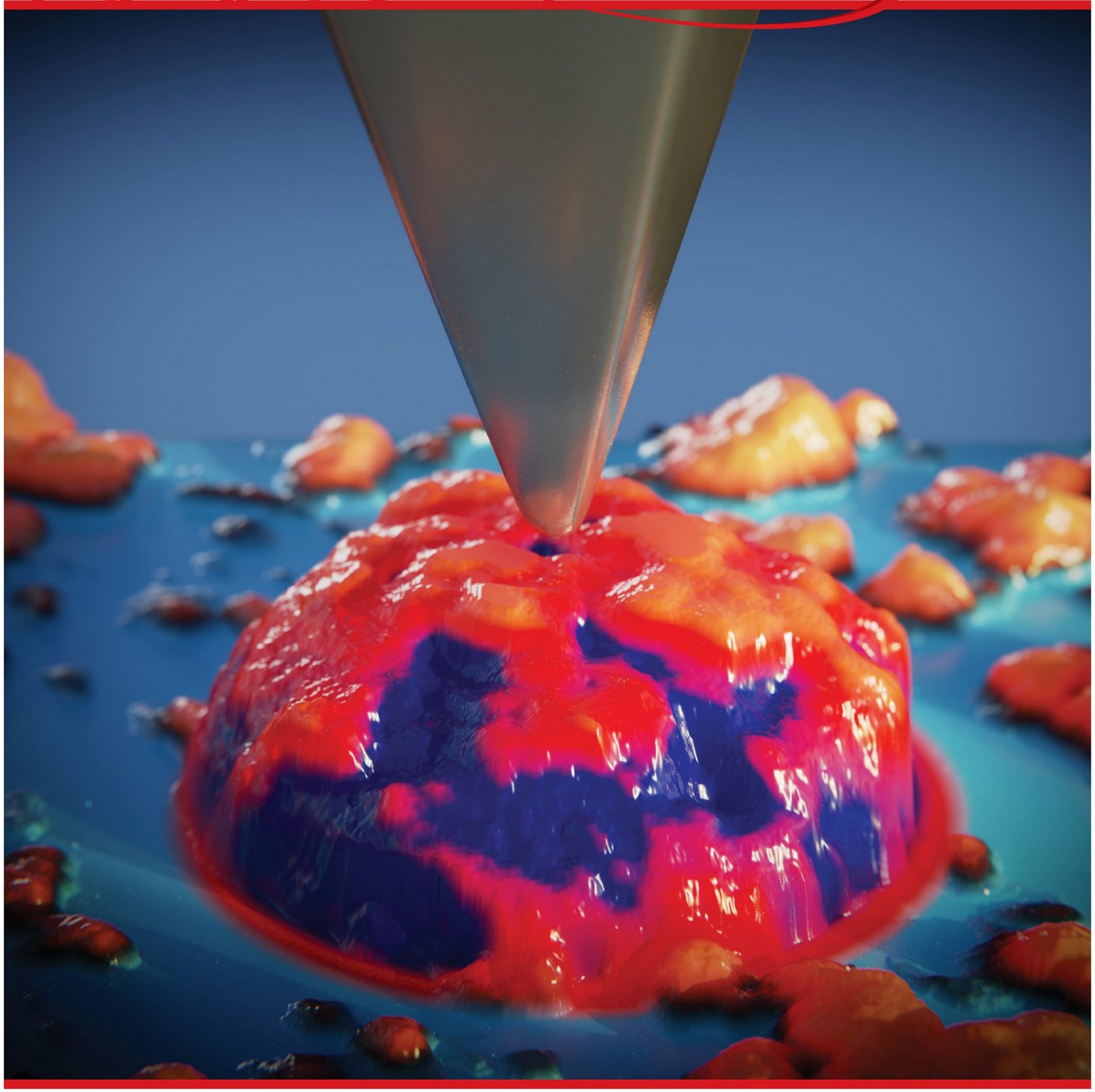

Kiss B, Kis Z, Pályi B, Kellermayer MSZ. Nano Lett. 2021 Mar 24;21(6):2675-2680.