Elucidating the Mechanisms of Genome Release in Picornaviruses using Cryo-EM and Coarse-Grained Simulations

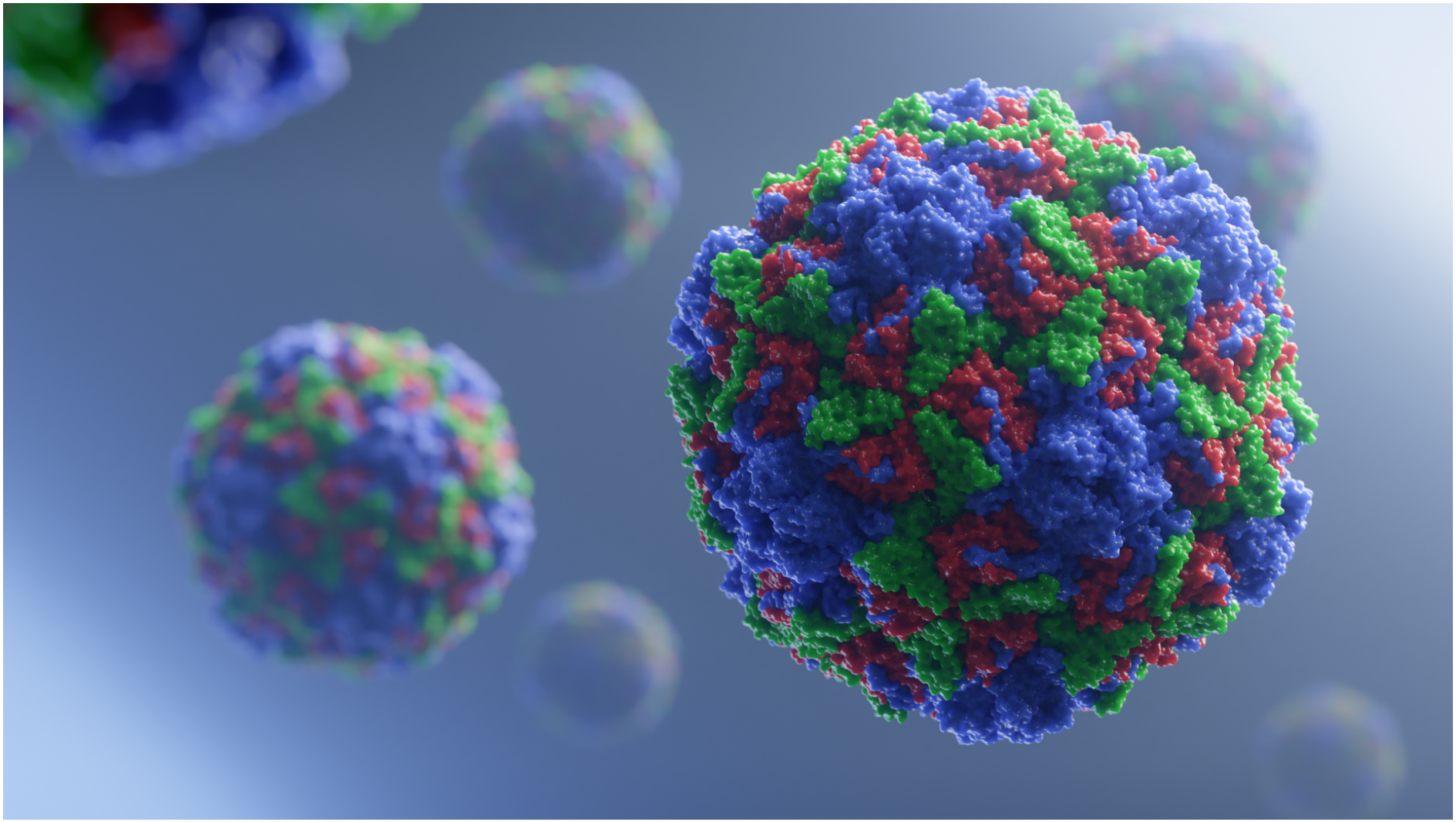
Lukáš Sukeník

Masaryk University, CEITEC

August 2, 2023

National Institute
of Virology and Bacteriology

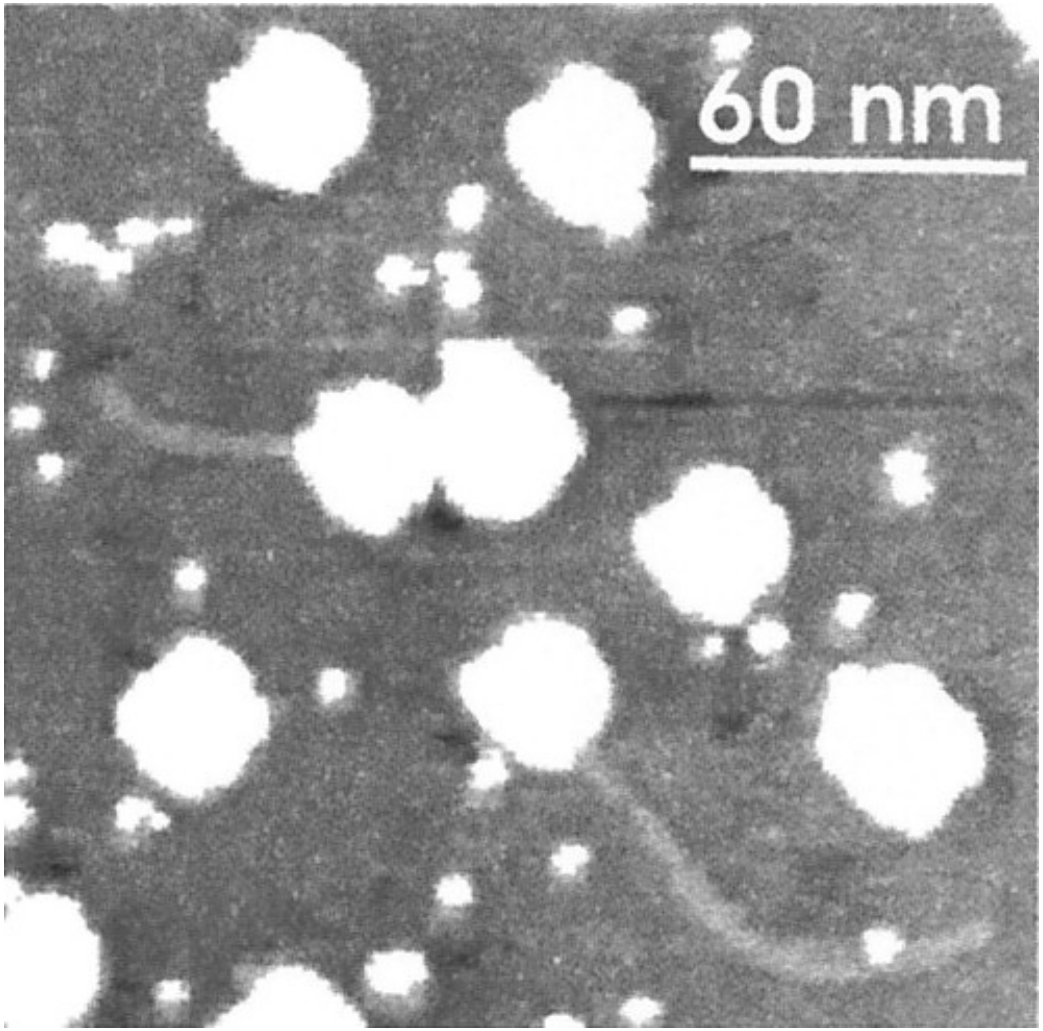
Viruses are an evident threat to global health



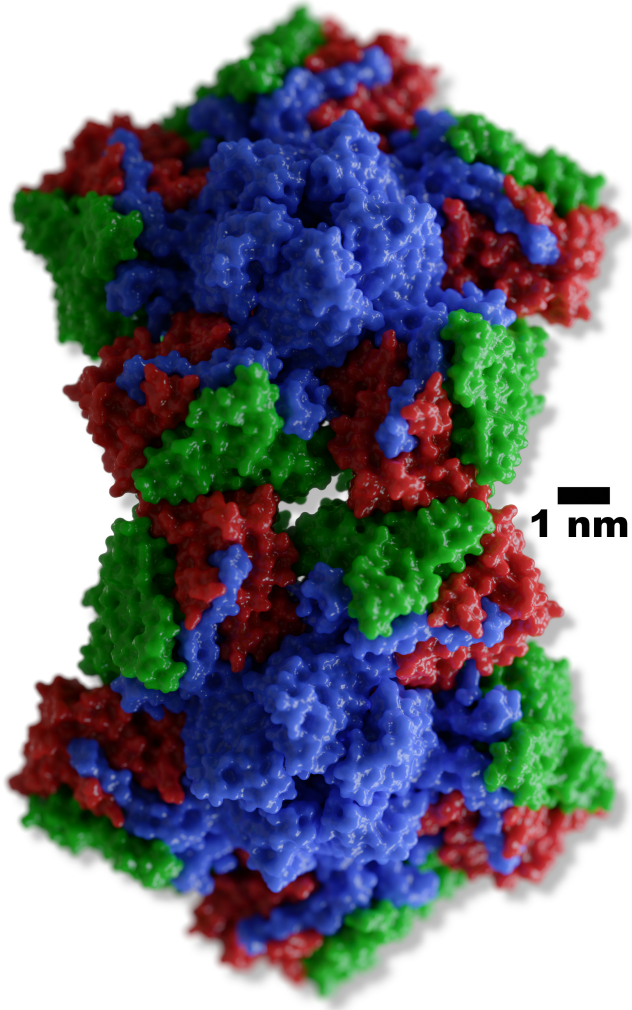
Causative agent of common cold - Human Rhinovirus type 2

- To infect the cell, viruses have to release their genome

Long-standing hypothesis of genome release



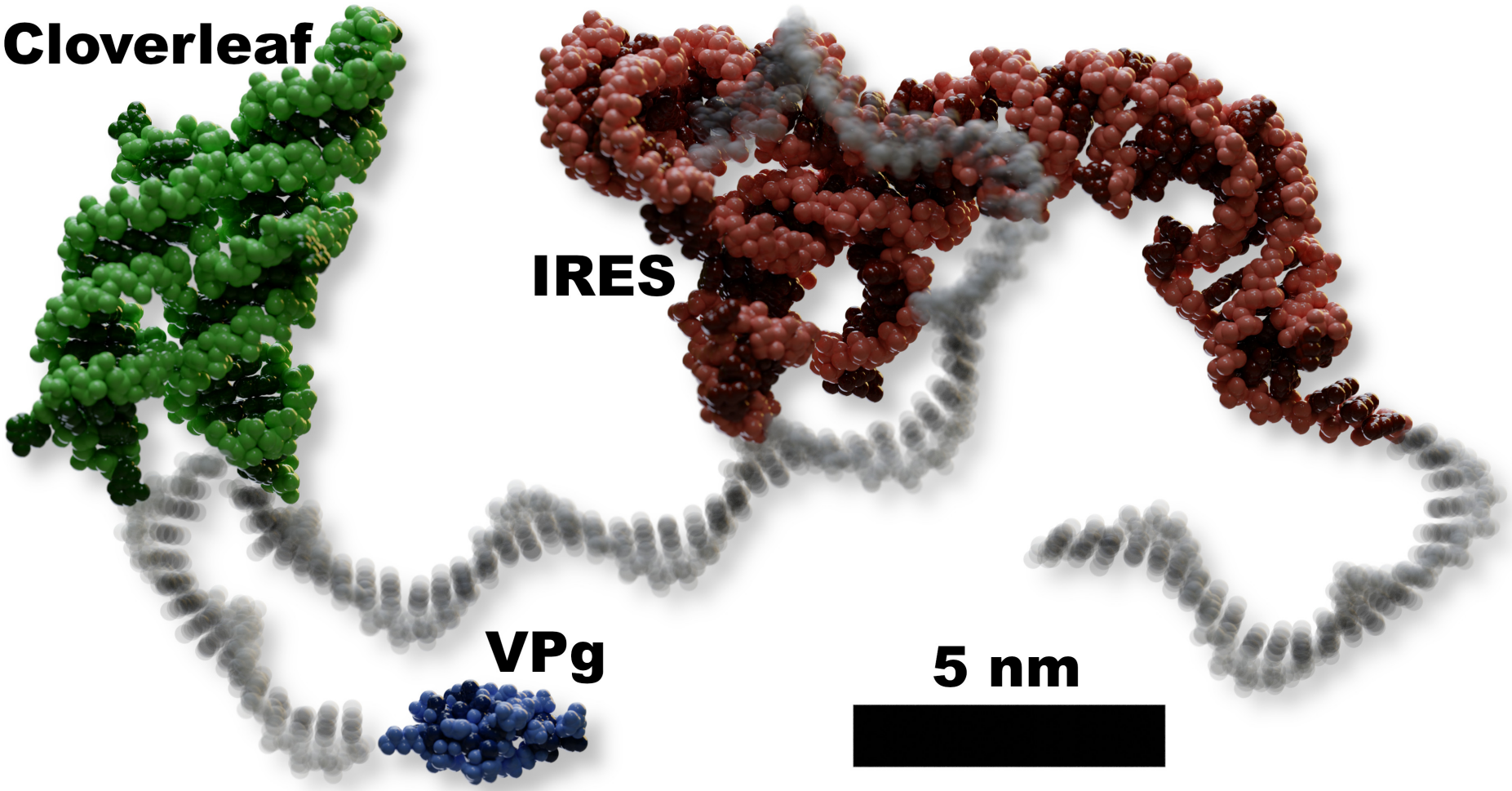
Rhinovirus RNA Release, Kienberger, 2004



Capsid 2-fold axis pore

- Picornaviruses release their genome via a capsid pore

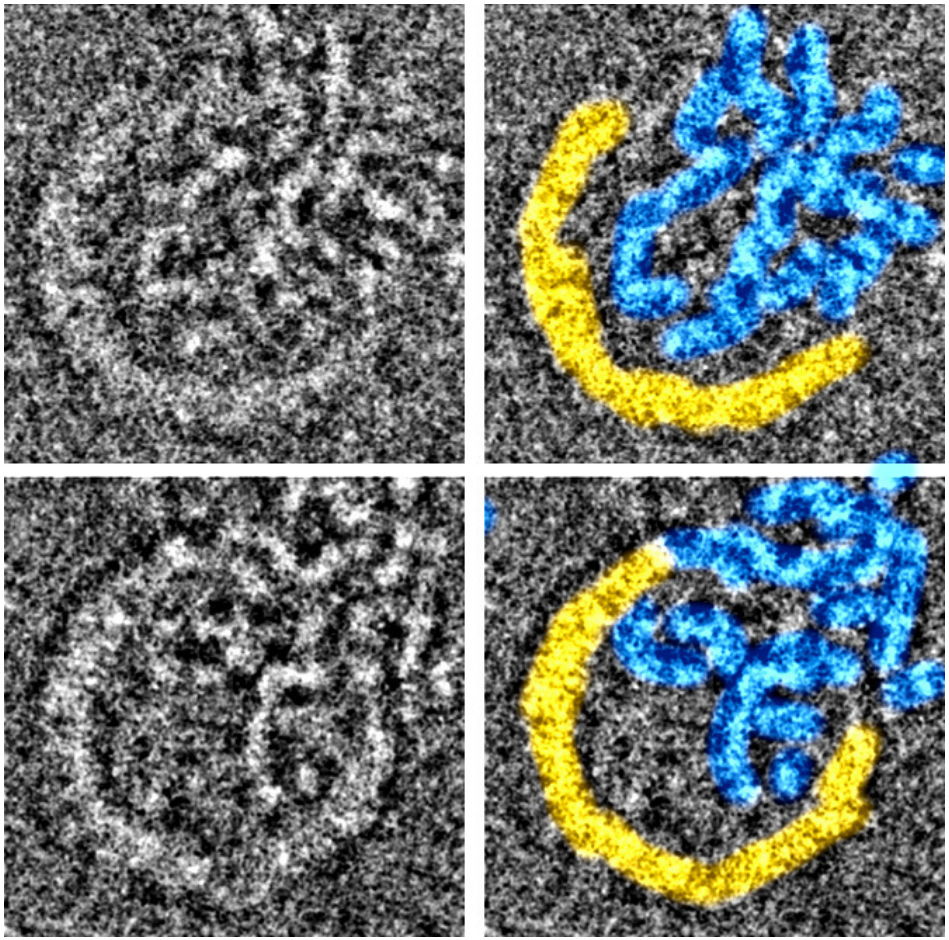
But, genomes contain regions of tertiary structures



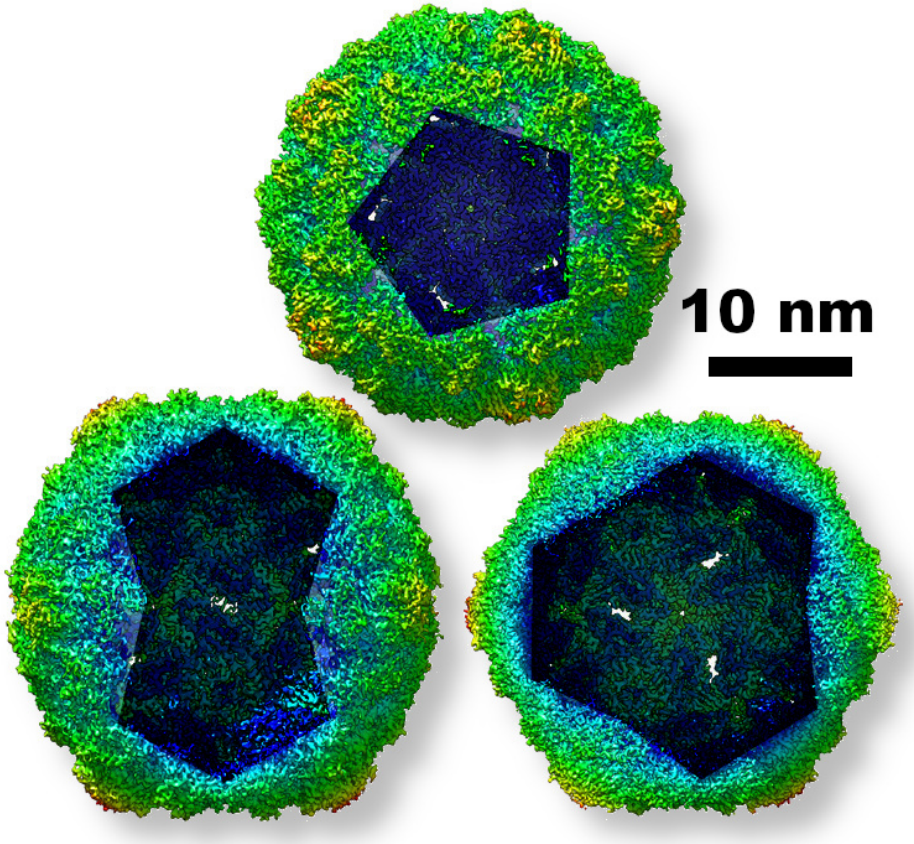
Cloverleaf and IRES tertiary structures

- The release of such structures requires a pore over 4 nm in diameter

We observed genome release by capsids cracking open



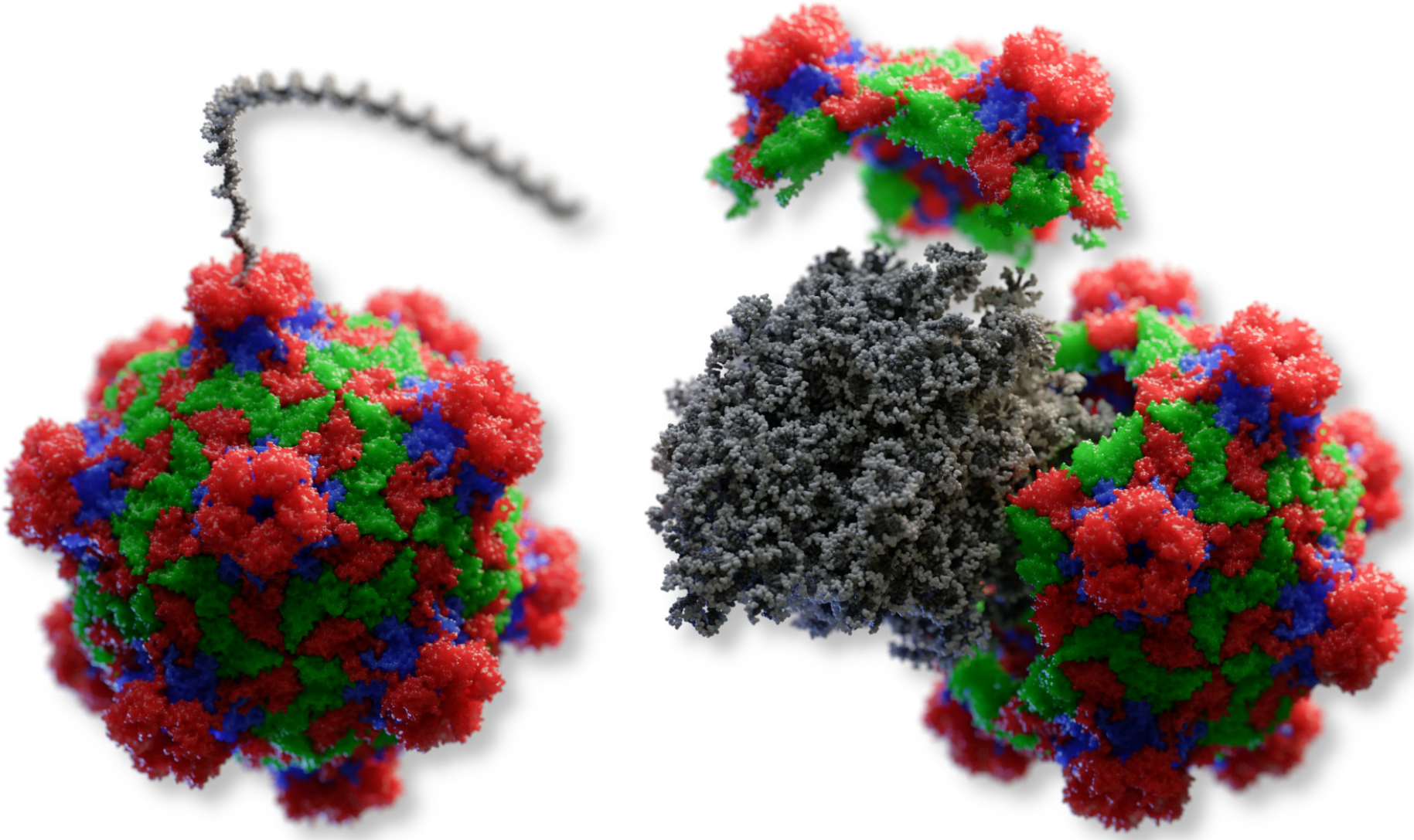
Cryo-EM micrographs of Echovirus 18



Asymmetric 3D reconstructions of empty particles

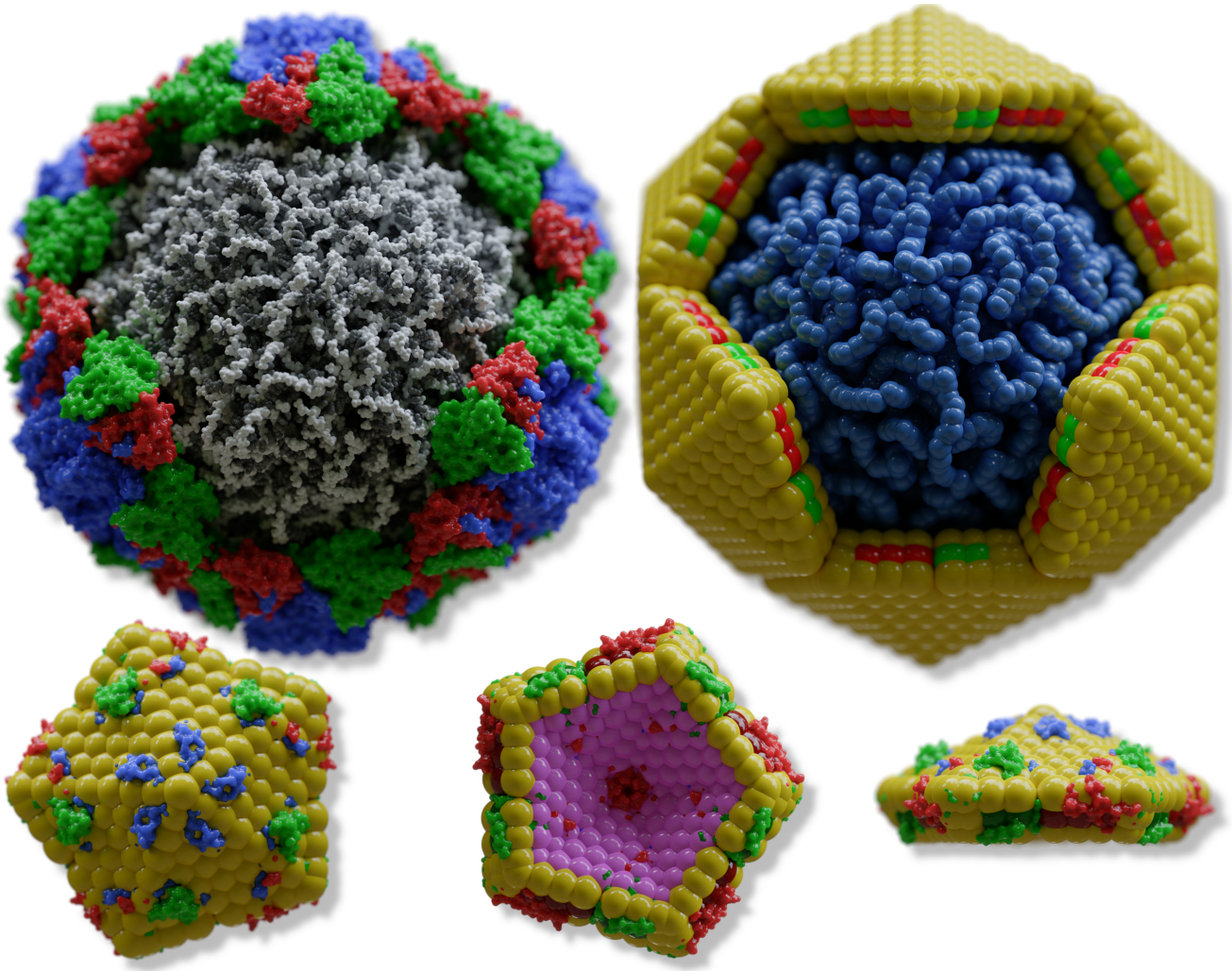
- Empty particles were lacking parts of their capsids.

What is the release mechanism?



- Why some capsids pore release, while others expel parts of their capsid?

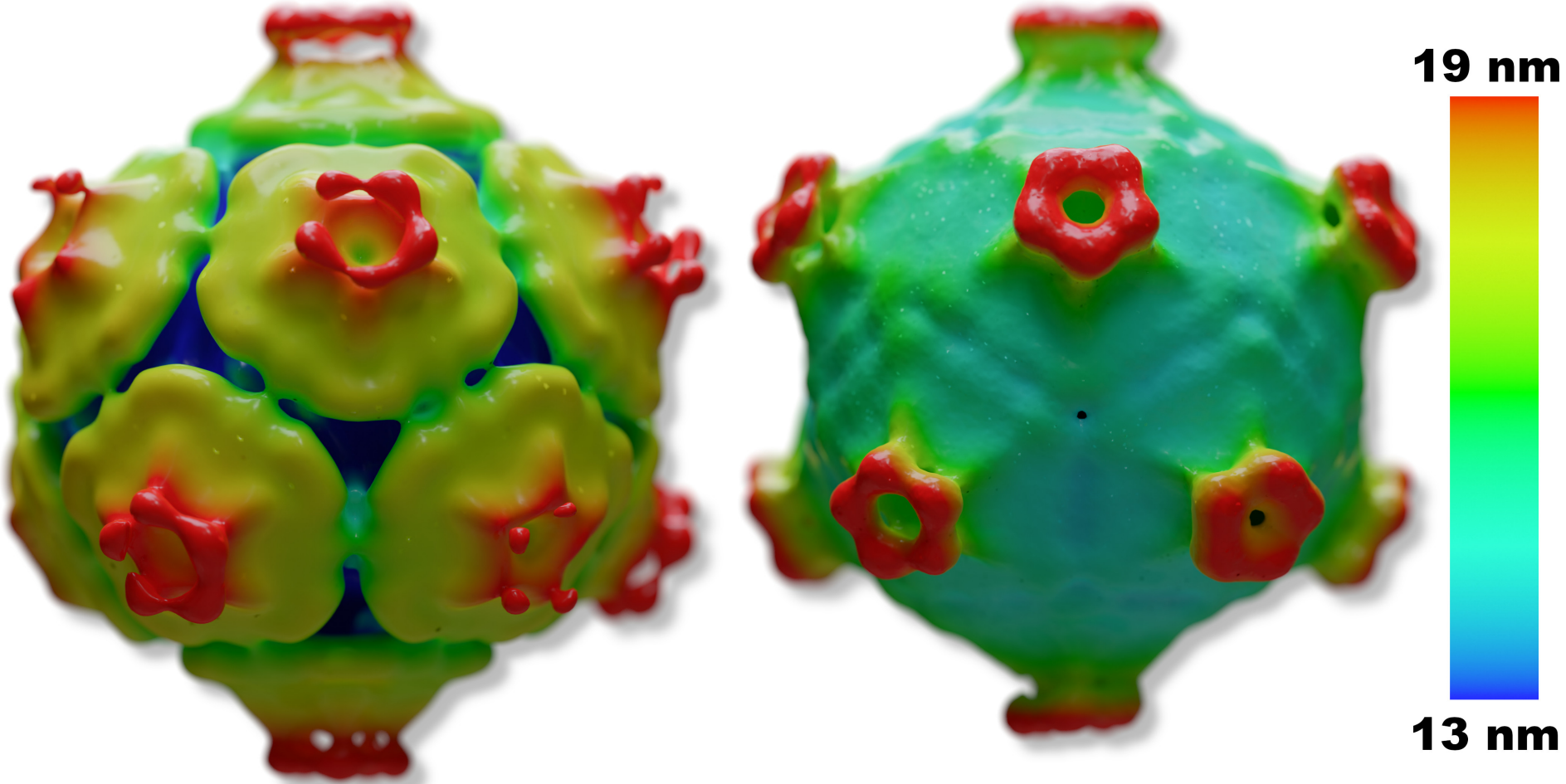
Mesoscopic virion model based on Echovirus 18



Comparison of all-atom echovirus 18 to its mesoscopic model

- The model replicates pentamer geometry and mimics its interactions.

Internal pressure arises from tight confinement of genome



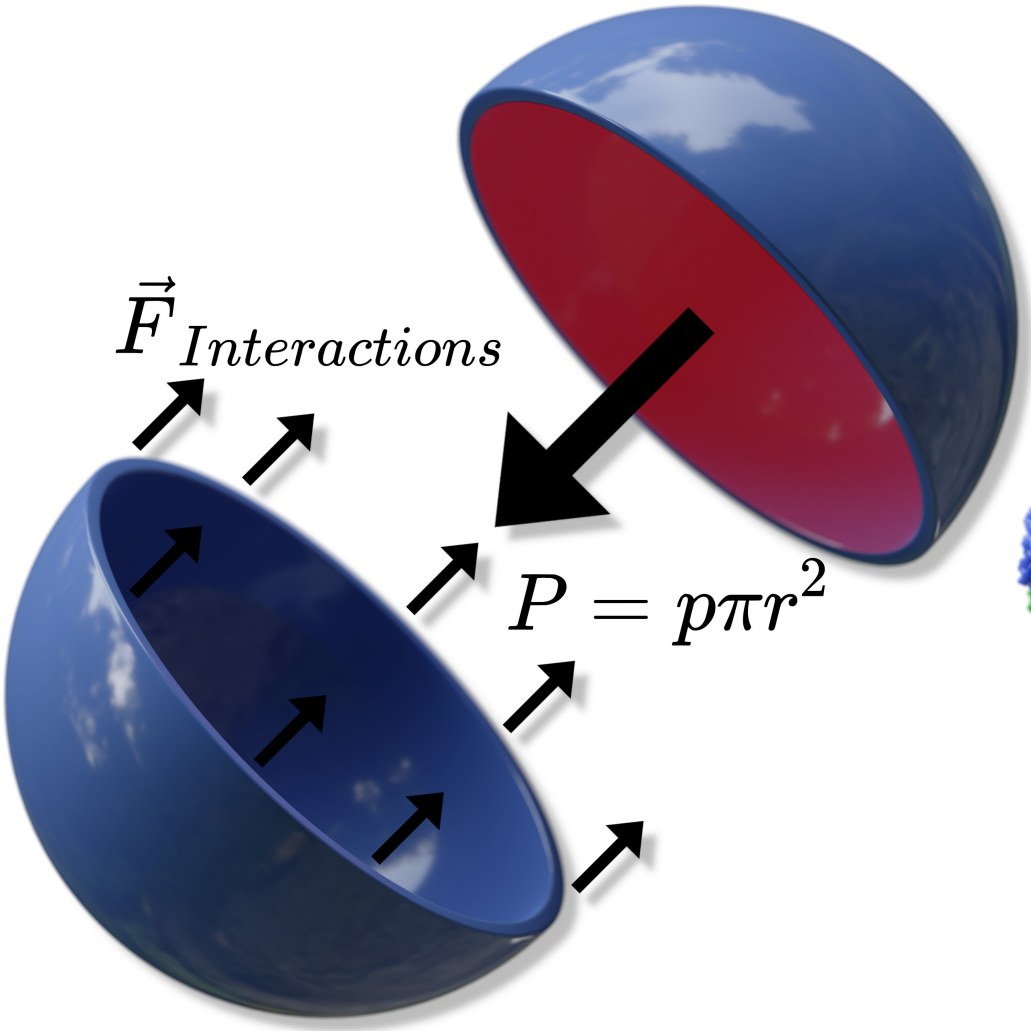
Activated virion

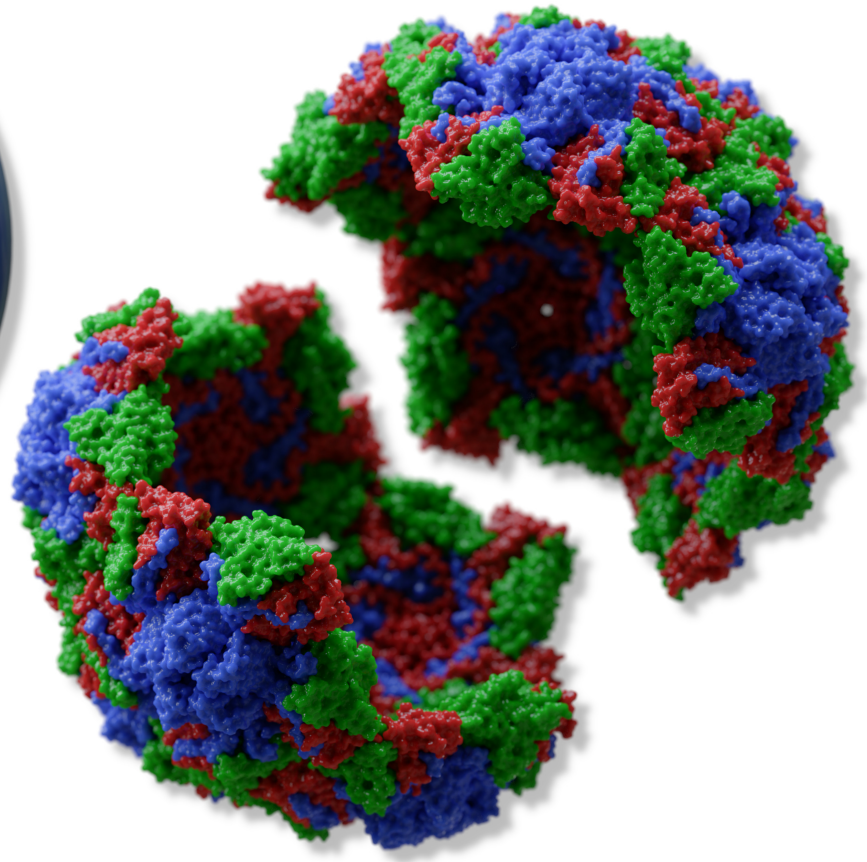
Empty particle

Activated particles and empty capsids of Deformed wing virus exposed to low pH

- Activated particles of DWV are 5% expanded relative to empty capsids

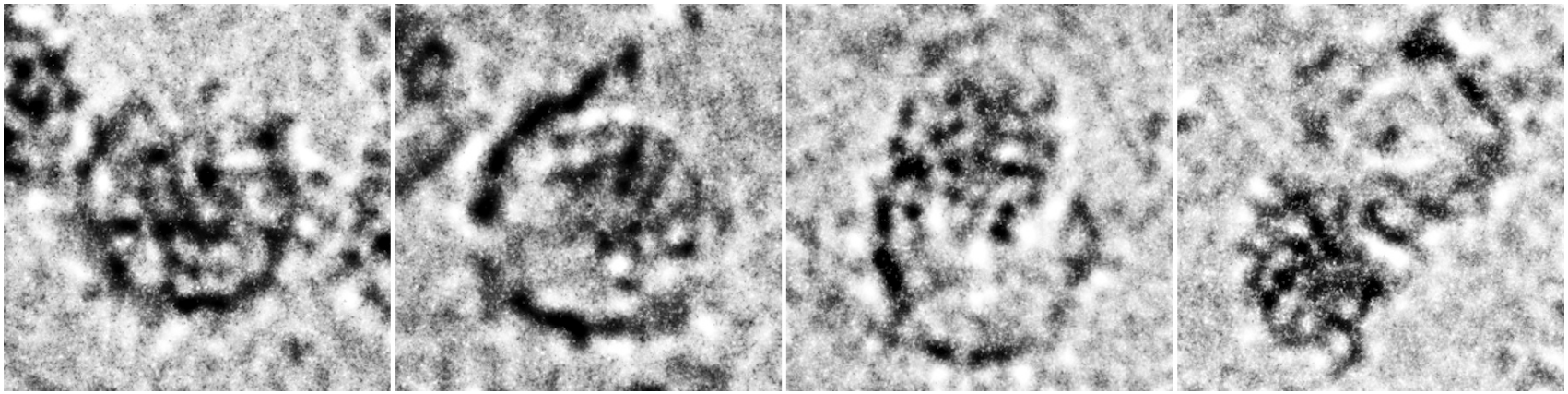
Virions are microscopic spherical pressure vessels



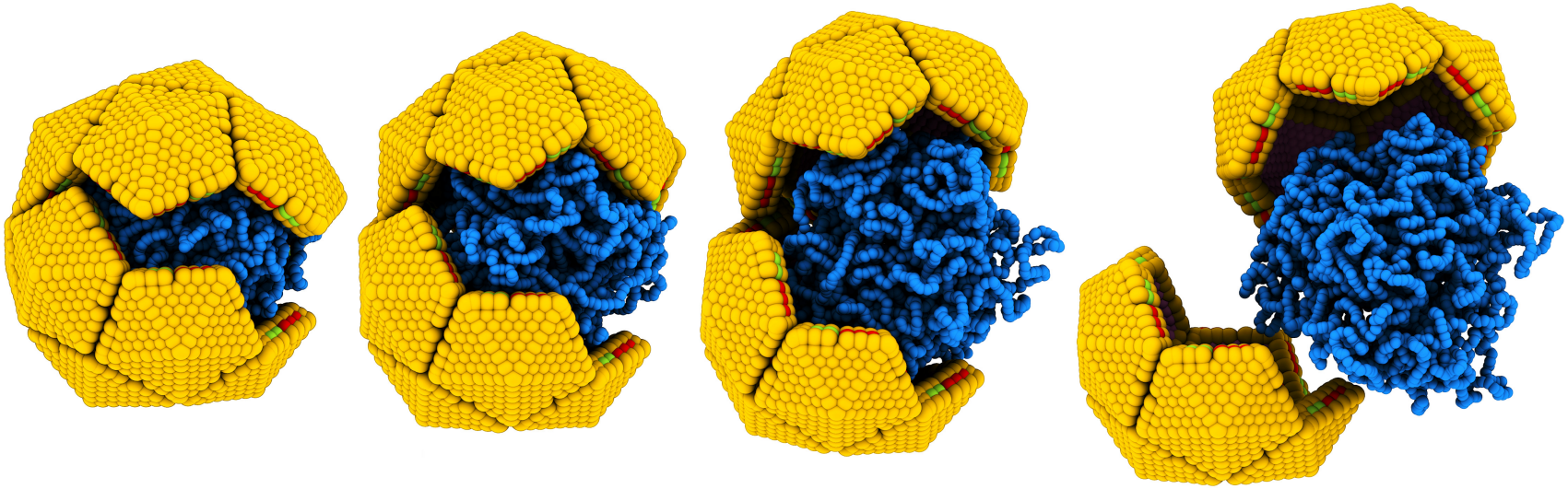


- However, thermal motion leads to the spontaneous emergence of a capsid weak point

Weak point expands into a fissure, fragmenting the capsid

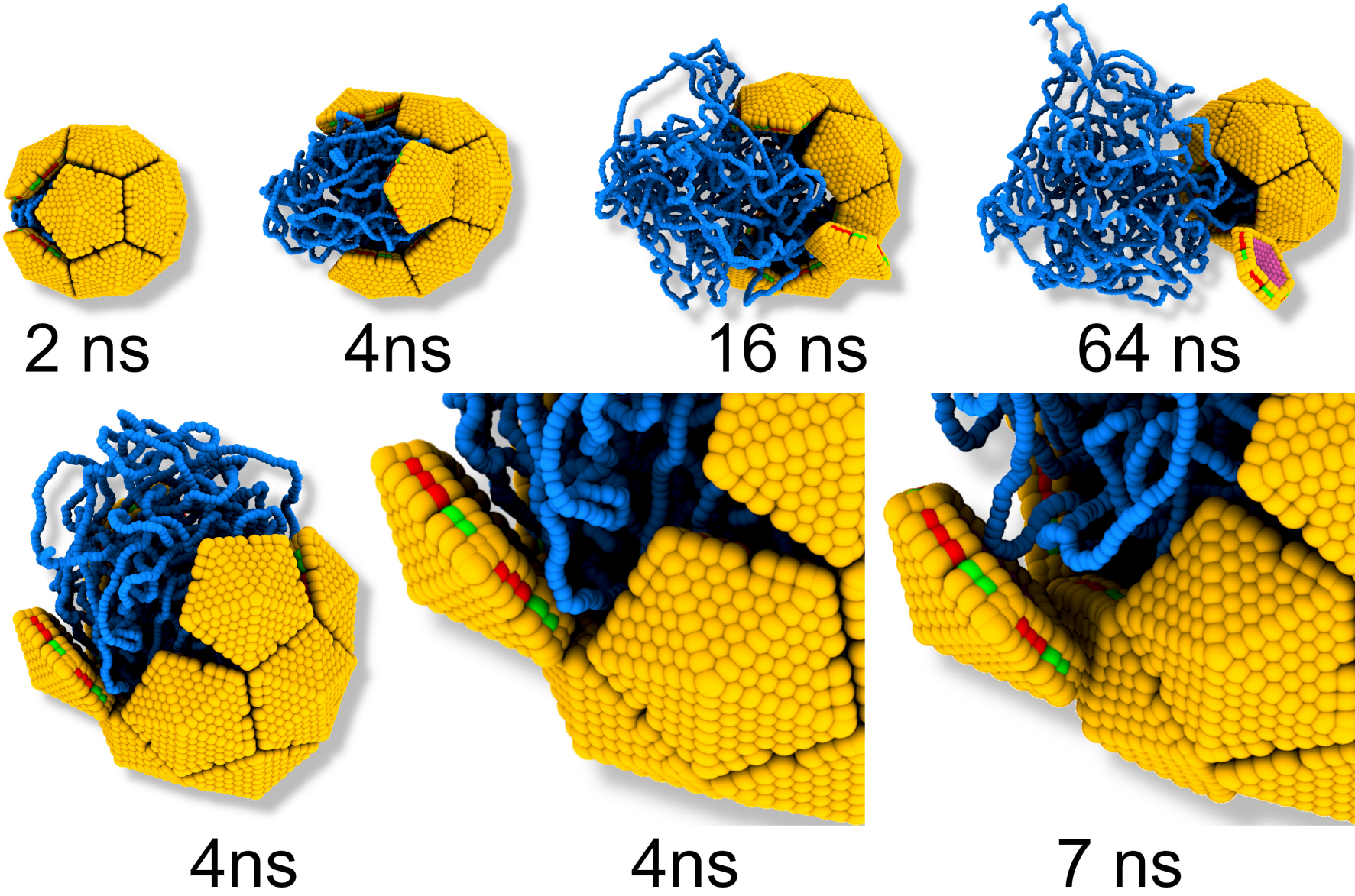


Cryo-EM micrographs of Deformed wing virus



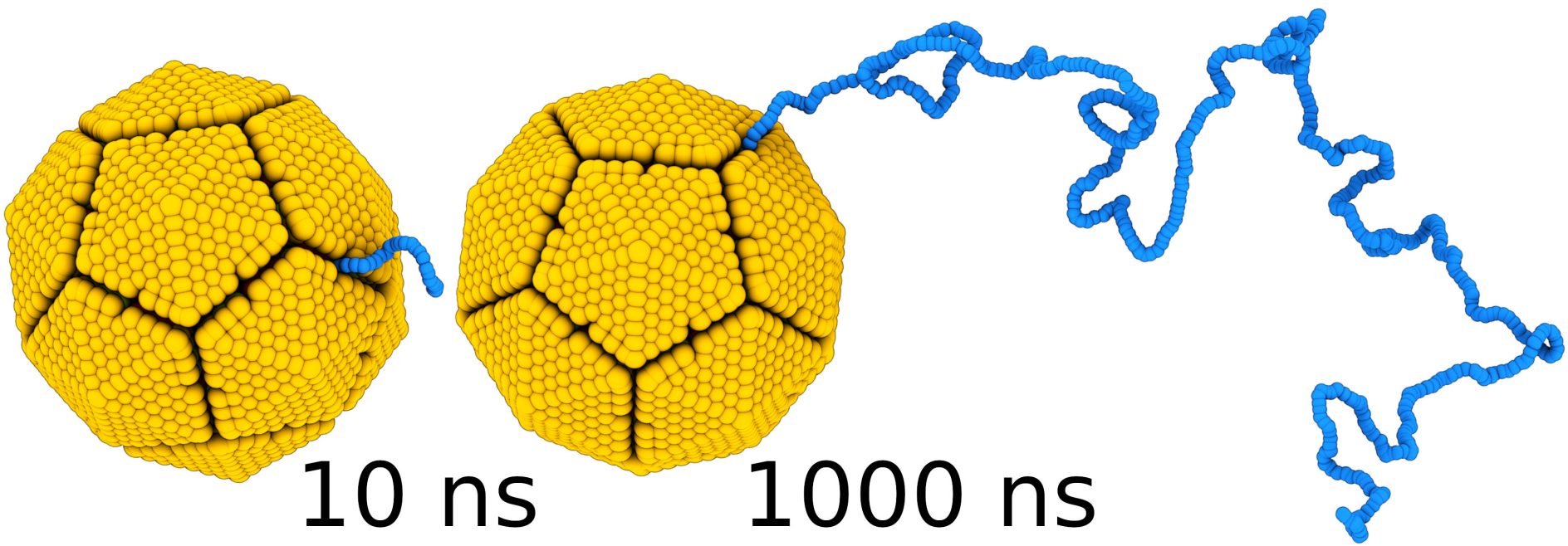
- Capsids crack open when inter-pentamer interactions are short-range (0.5 nm), or the genome is compact

Cracking open disrupts the inter-pentamer interactions



- The escaping genome may dislodge and expel disrupted pentamers

Weak point becomes a transient capsid pore



Genome release via a transient 2-fold axis pore.

- Capsids pore release when inter-pentamer interactions are long-range (1.5 nm), and the genome is not compact

In summary

- Viral capsid is not a static cage; it is a dynamic arrangement of building blocks in constant thermal motion.
- The dynamics of the virion give rise to two mechanisms of genome release
- Understanding the genome release mechanisms informs strategies to effectively combat viral infections
- Our findings suggest a design strategy for virus-like nanoparticles for drug delivery

ACS Nano cover Dec 2021, Volume 15, Issue 12

Buchta, *Nat. Commun* **2019**, 10.1: 1138.
Škubník, *Sci. Adv.* **2021**, 7.1: eabd7130.
Sukeník, *ACS Nano* **2021**, 15.12: 19233–19243.

Acknowledgments

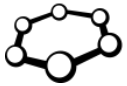
D. Buchta, T. Füzik, D. Hrebík, Y. Levdansky, L. Mukhamedova, J. Moravcová, K. Škubník, M. Procházková, L. Šmerdová, A. Přidal, P. Plevka and R. Vácha

Funding by the project National Institute of Virology and Bacteriology, Program EXCELES, ID Project No. LX22NPO5103 - Funded by the European Union Next Generation EU

Thank you for your attention!

Financováno Evropskou unií
NextGenerationEU

Národní plán obnovy



MUNI CEITEC

National Institute of Virology and Bacteriology