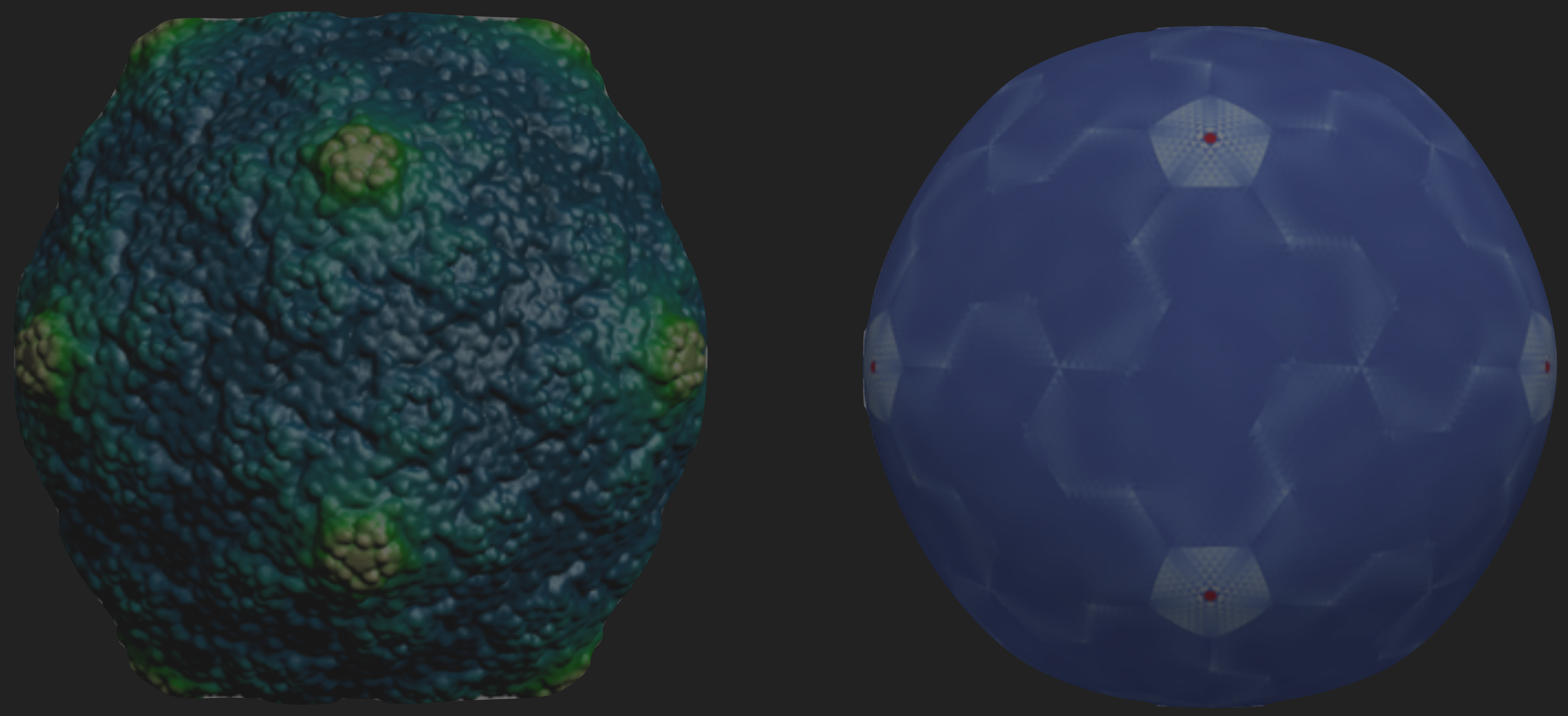


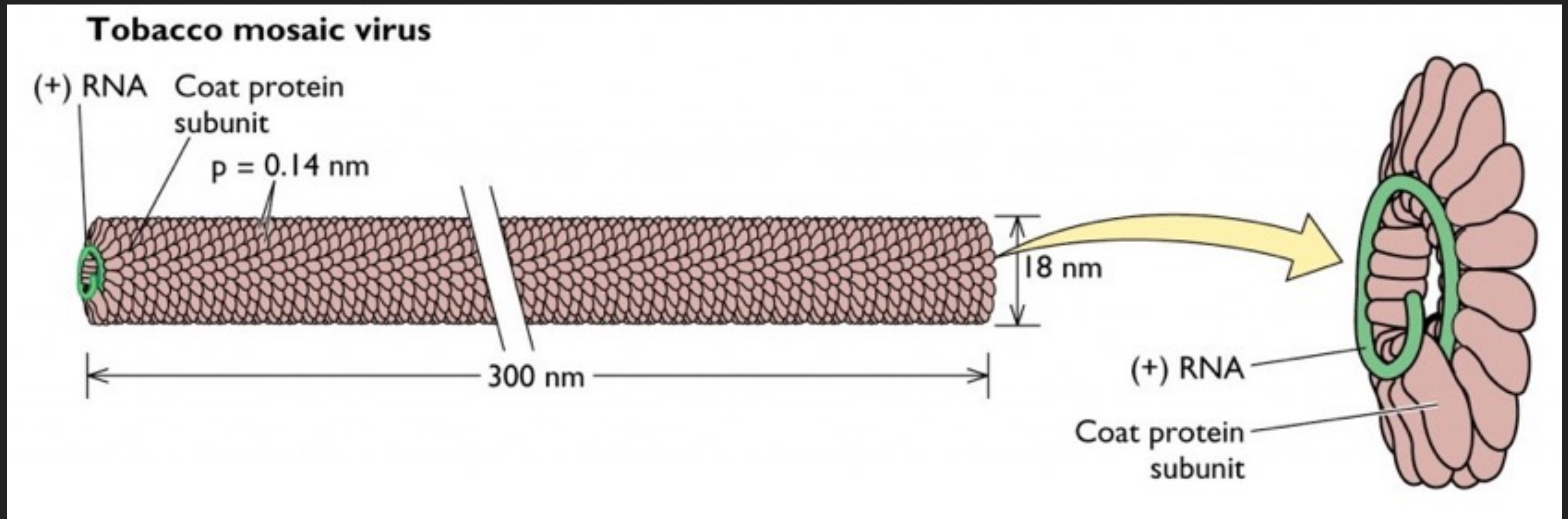
WILLIAM S. KLUG

UCLA

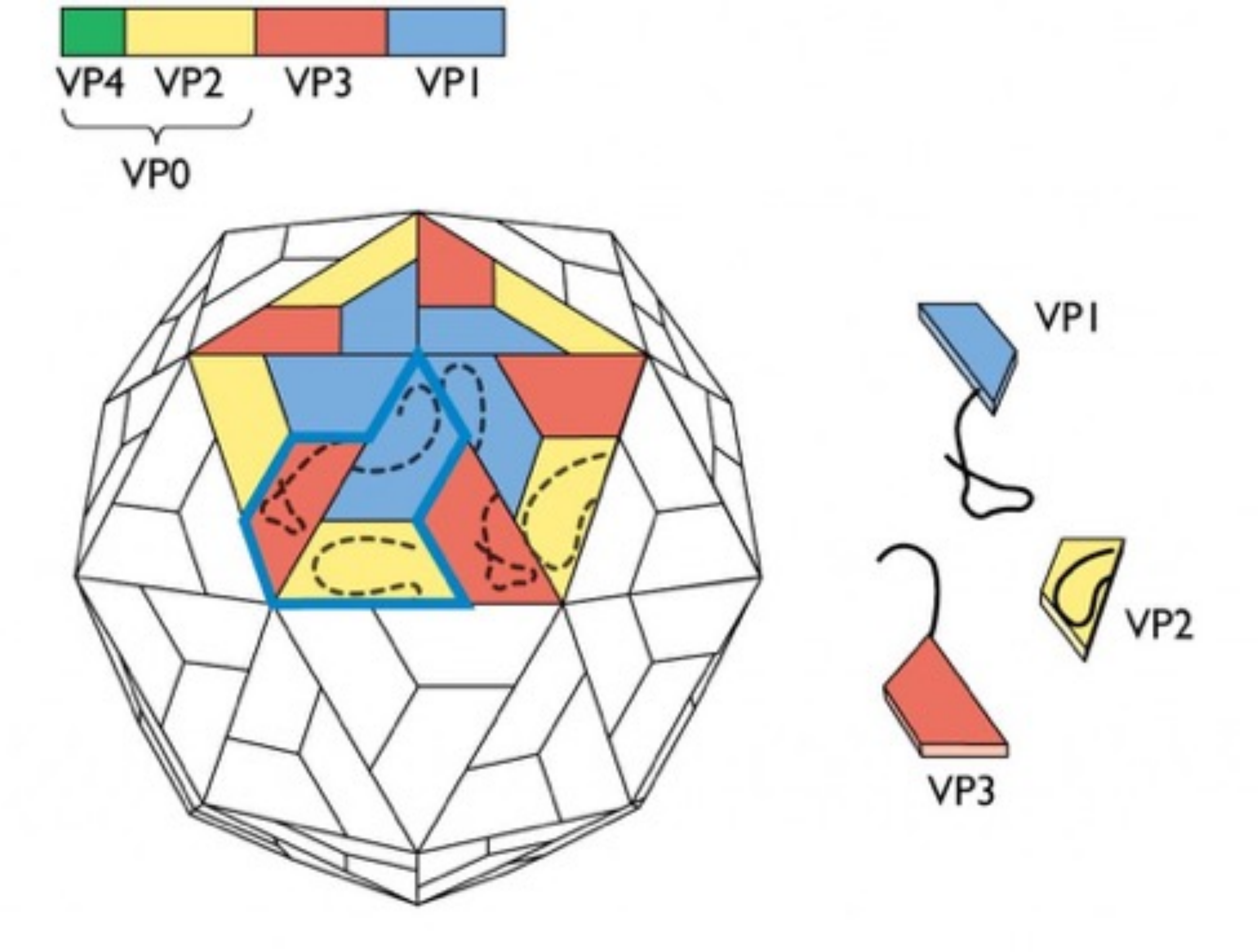
STRUCTURE AND DYNAMICS OF DEFECTS AND SCARS IN THE PROTEIN SHELLS OF VIRUSES

UCLA

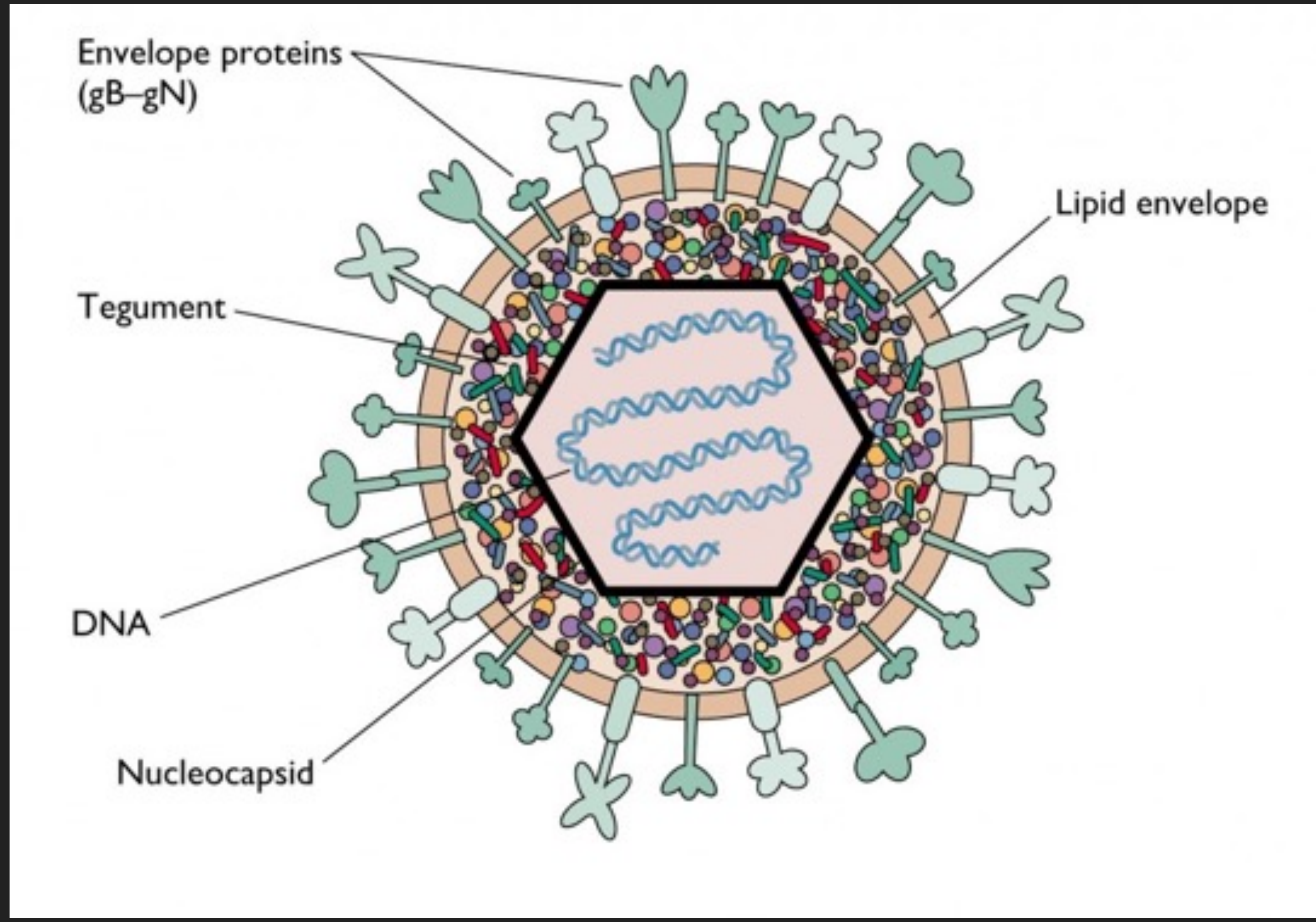
Helical Symmetry



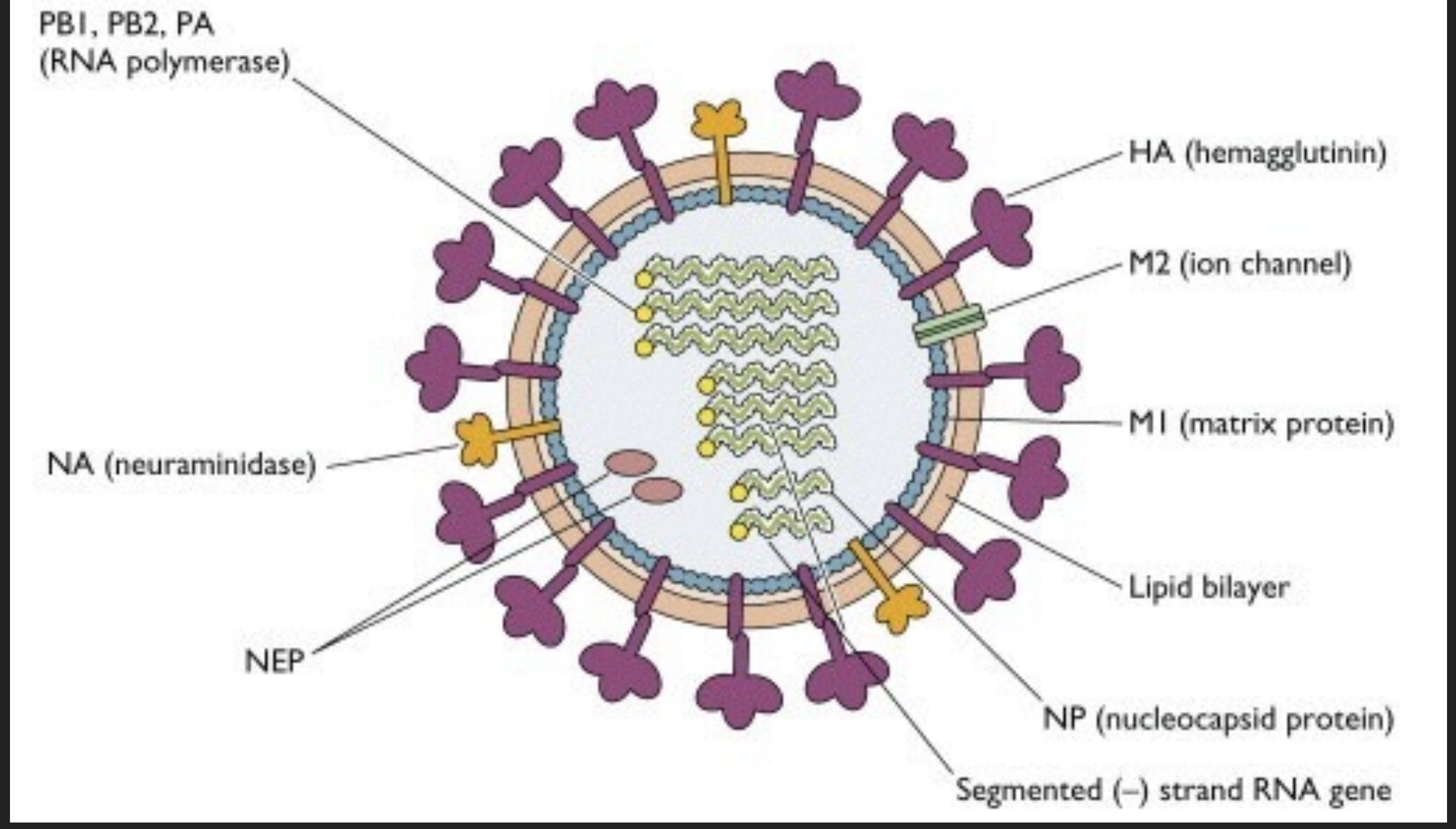
Icosahedral Symmetry



Enveloped with icosahedral nucleocapsid (herpesvirus)

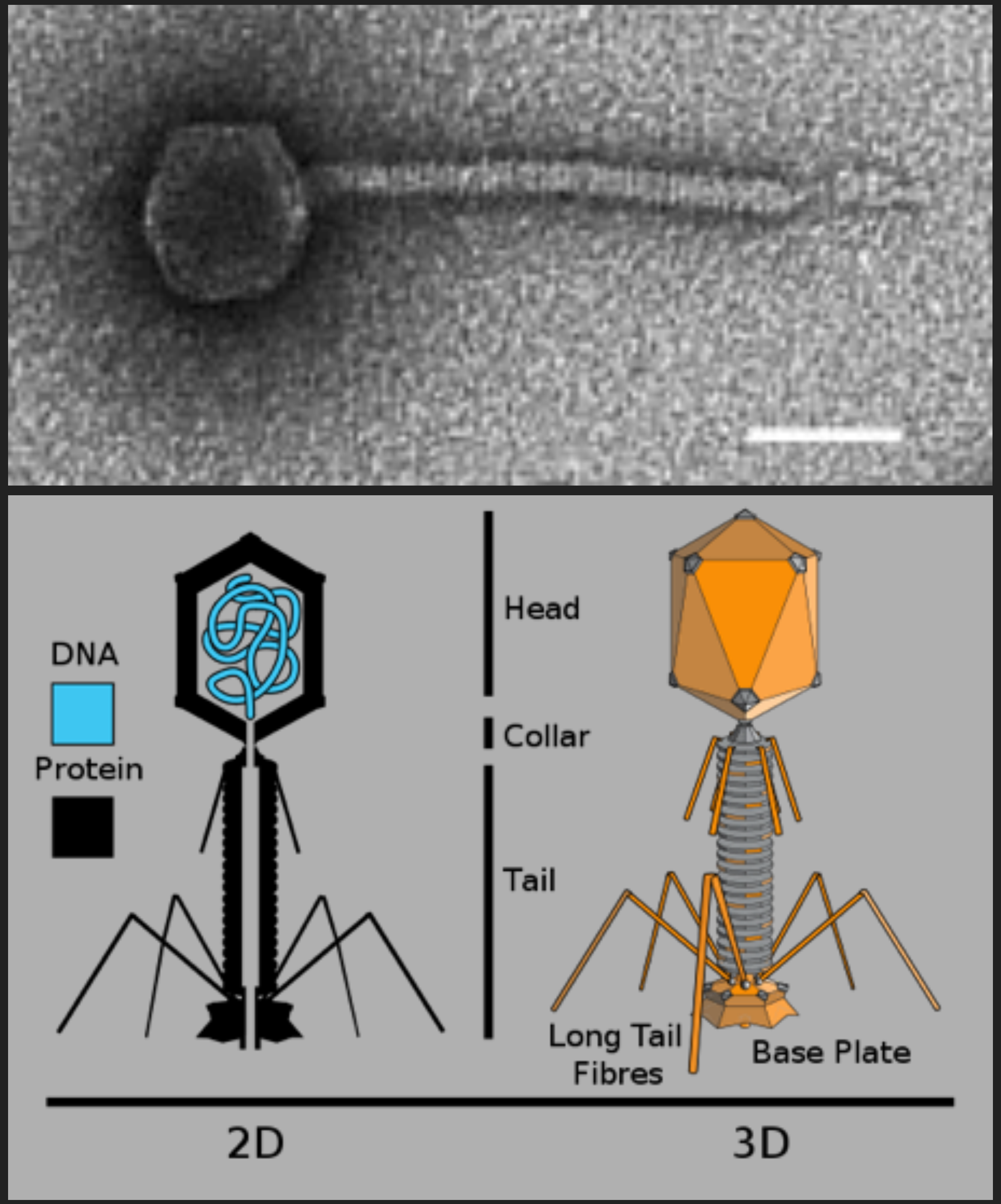


Enveloped with helical nucleocapsid (influenza virus)

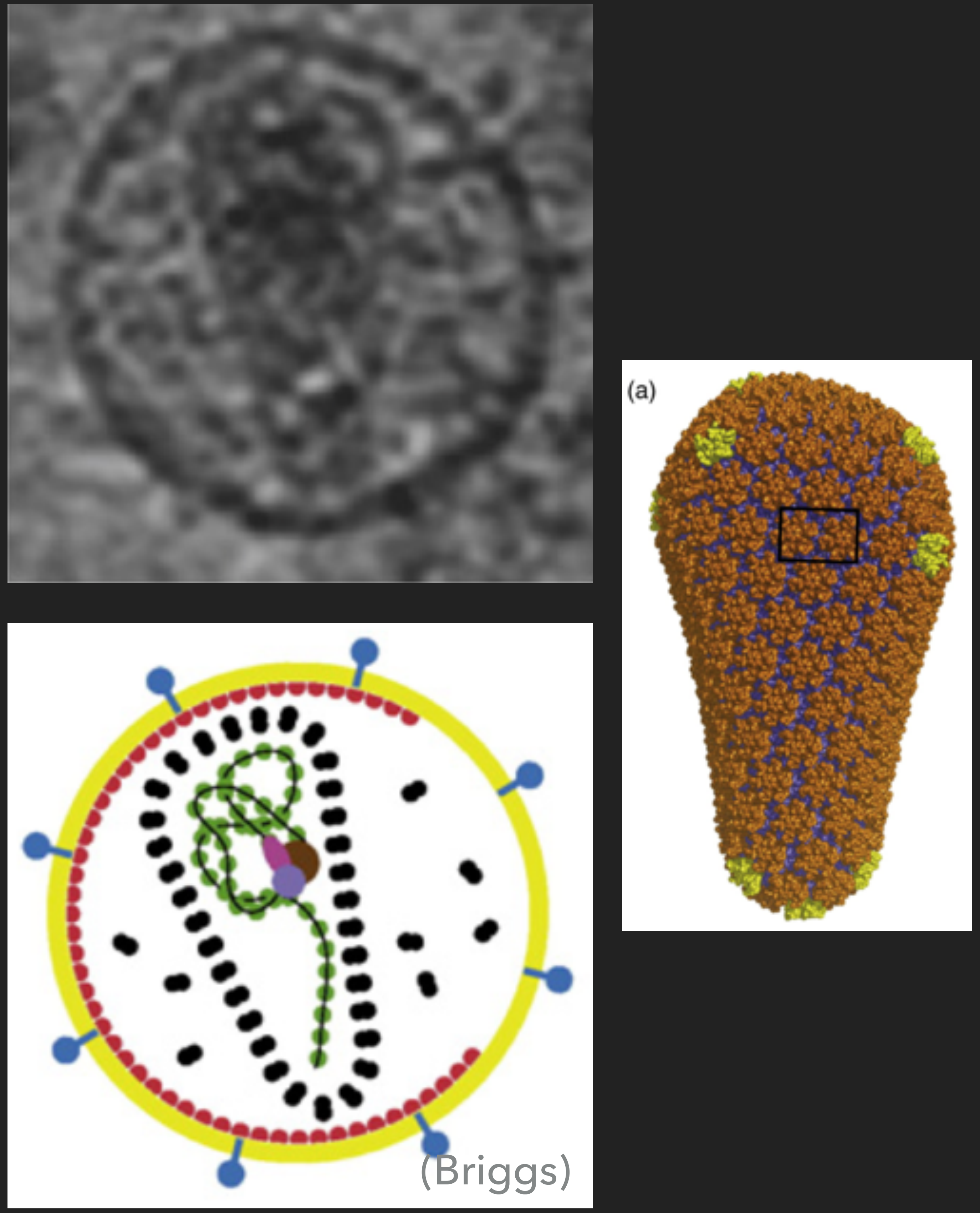


http://www.twiv.tv/

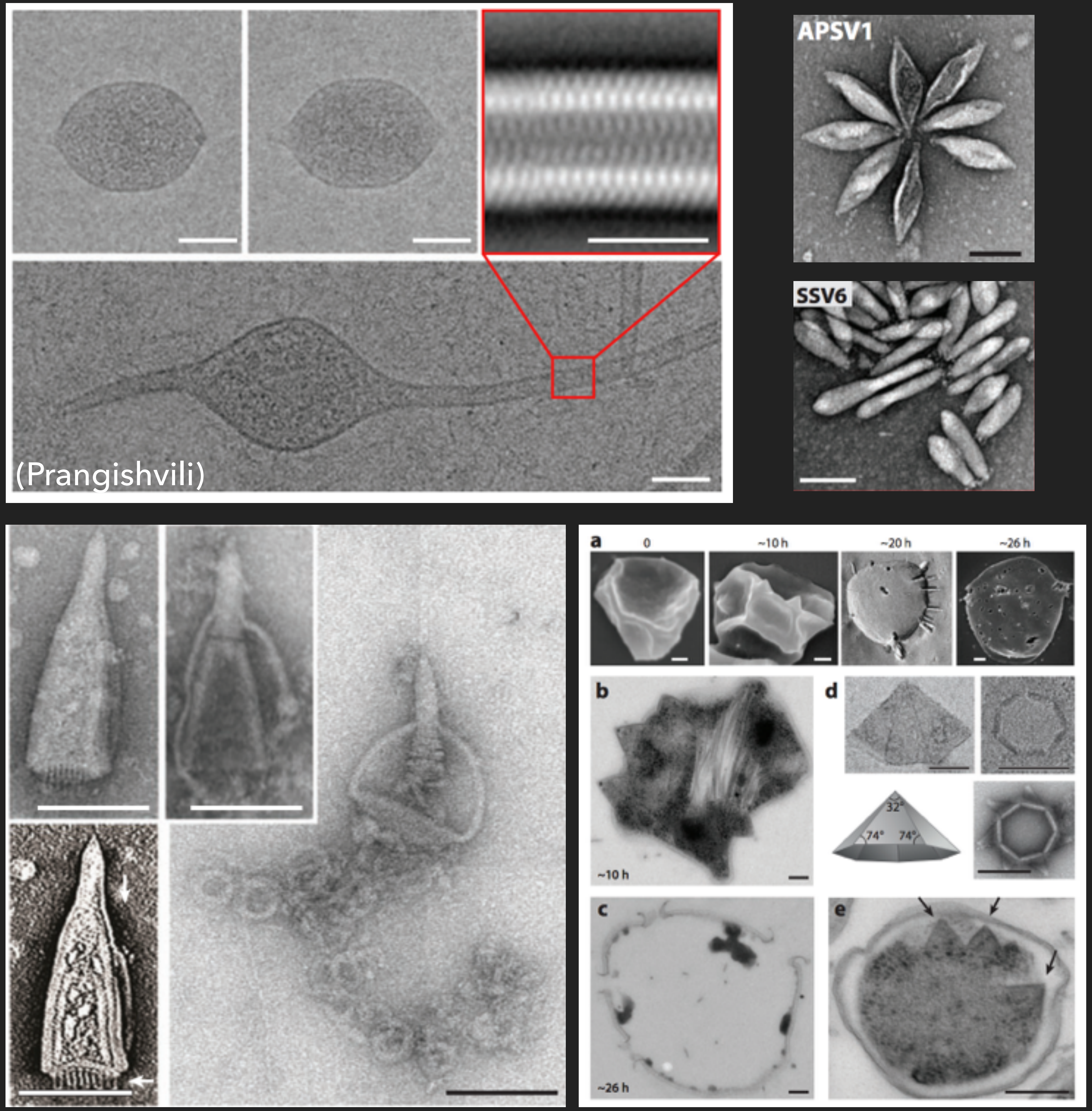
VIRUS STRUCTURE: A QUICK TOUR...



Regular



Irregular



Just plain weird

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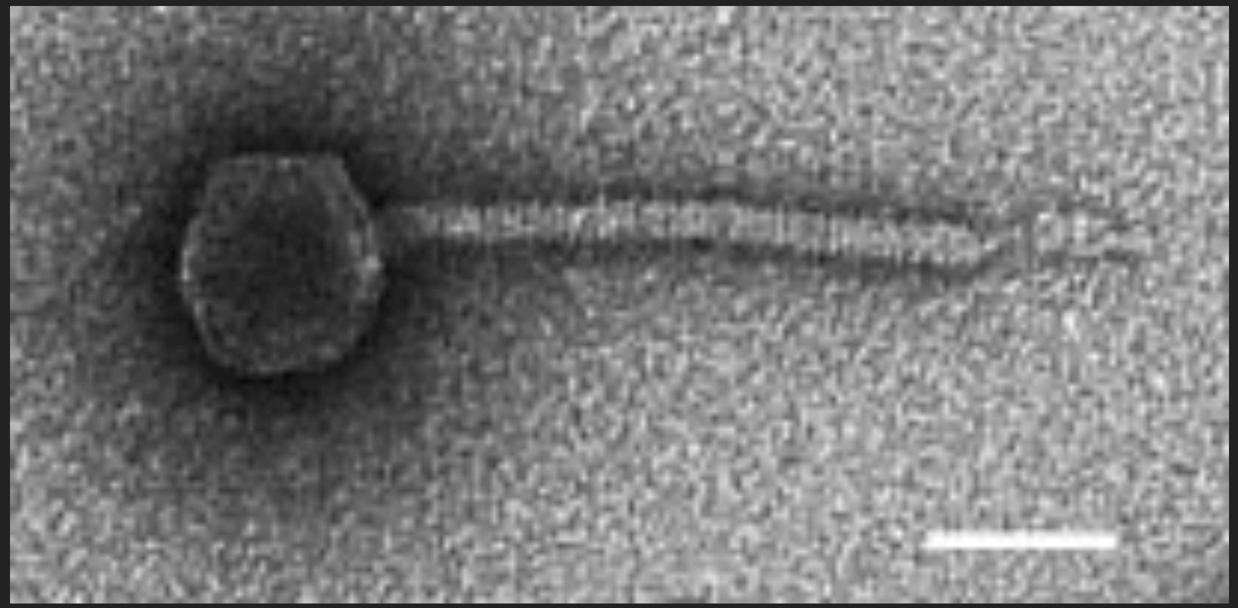
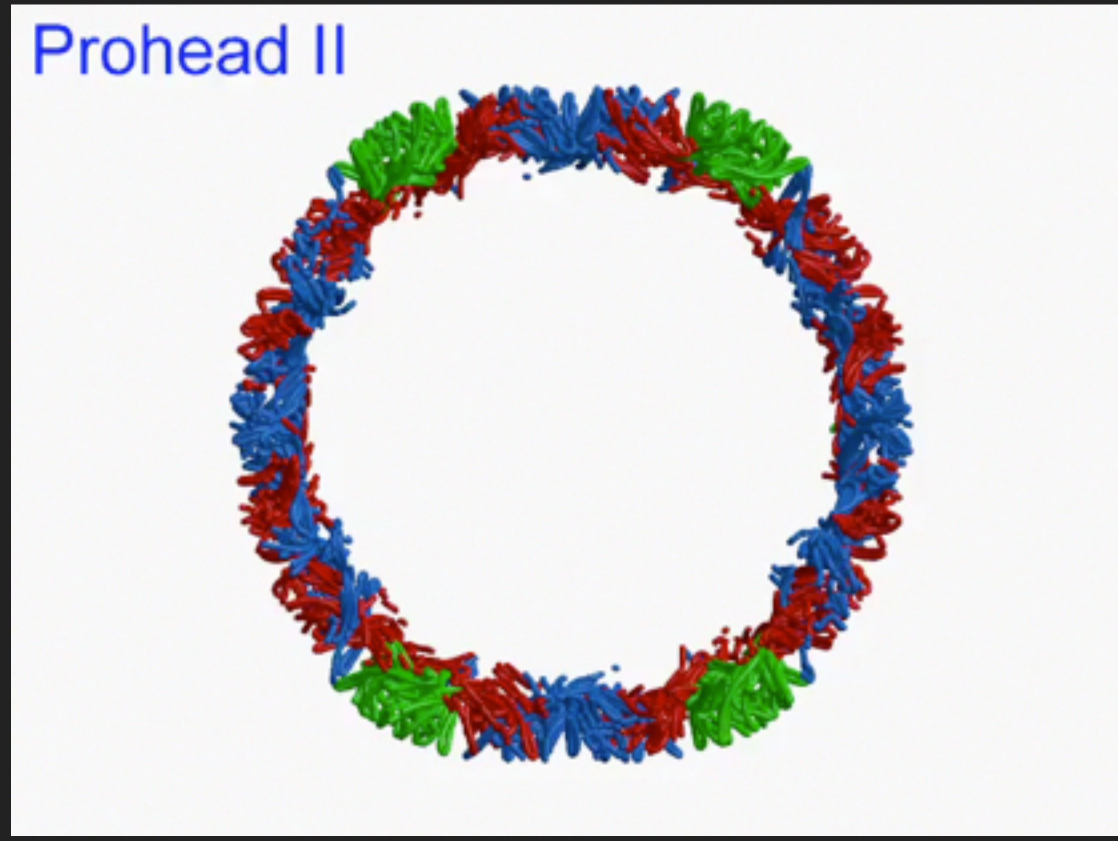
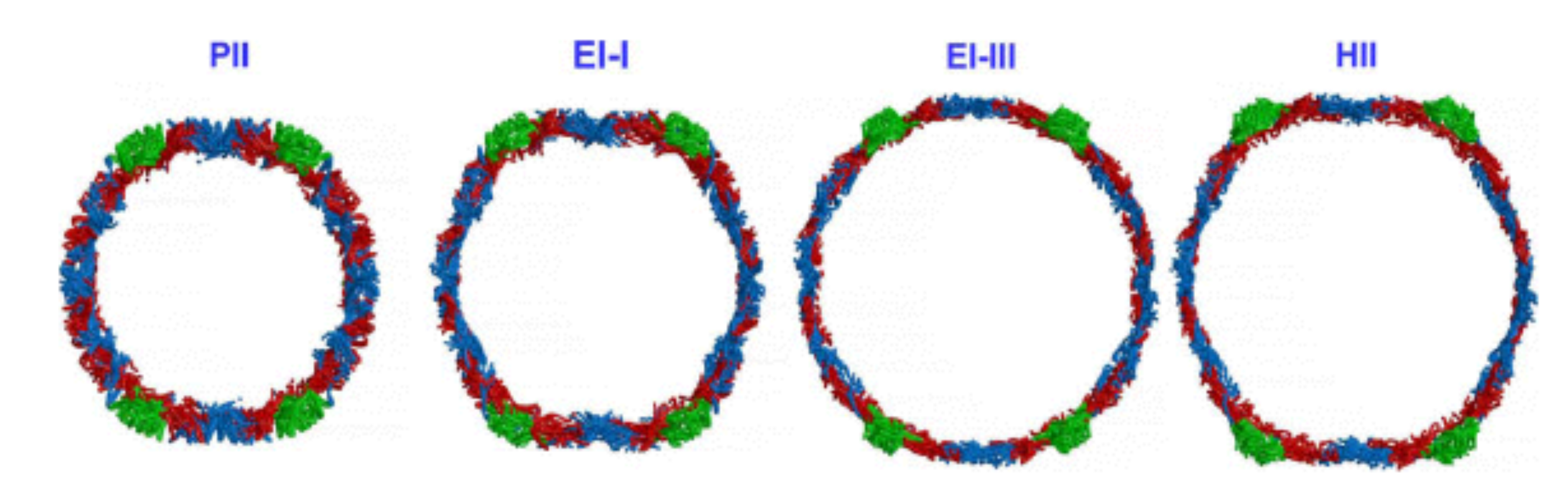
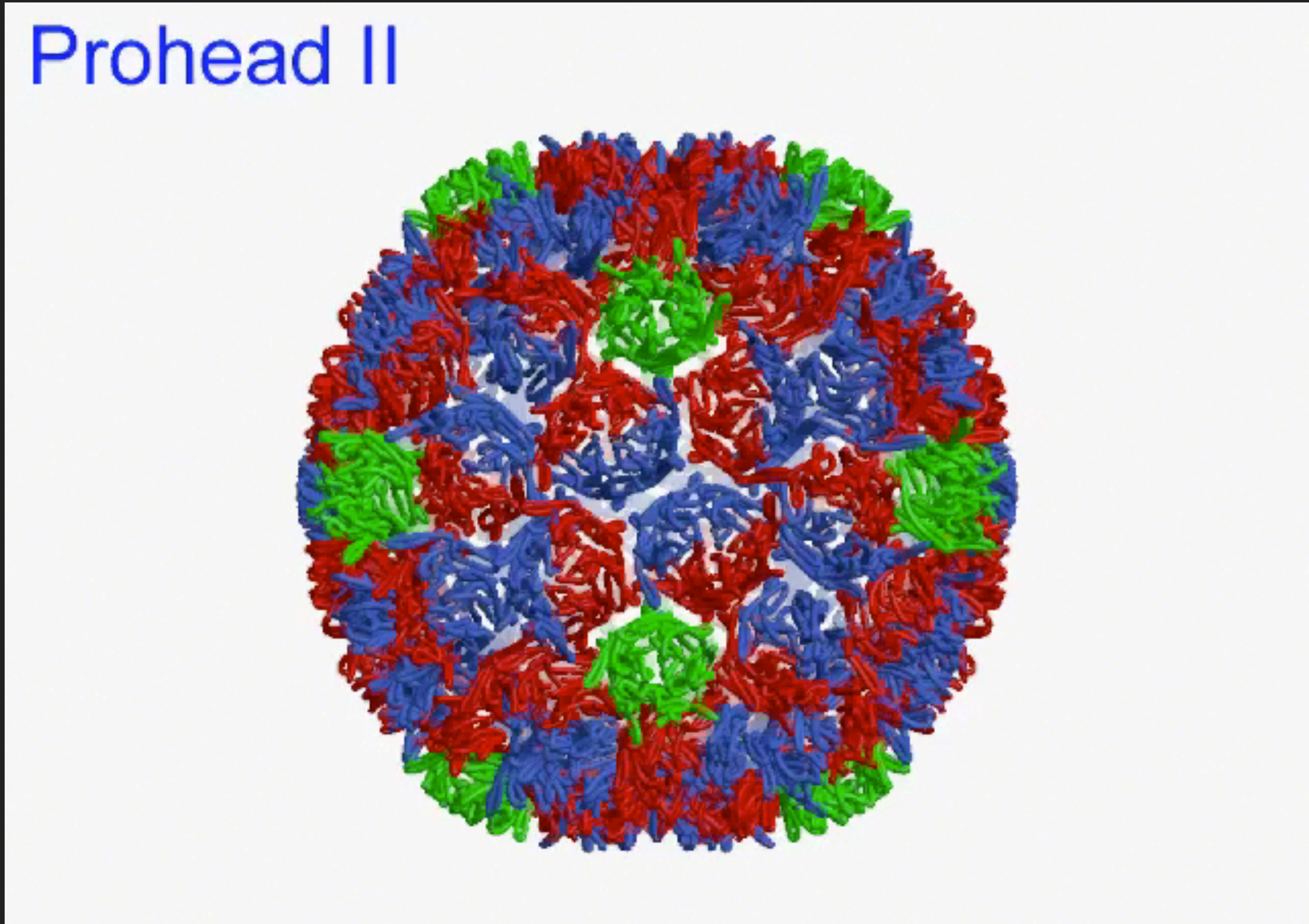
BACTERIOPHAGE HK97









(Wikoff et. al., *J Struc Biol*, 2006)

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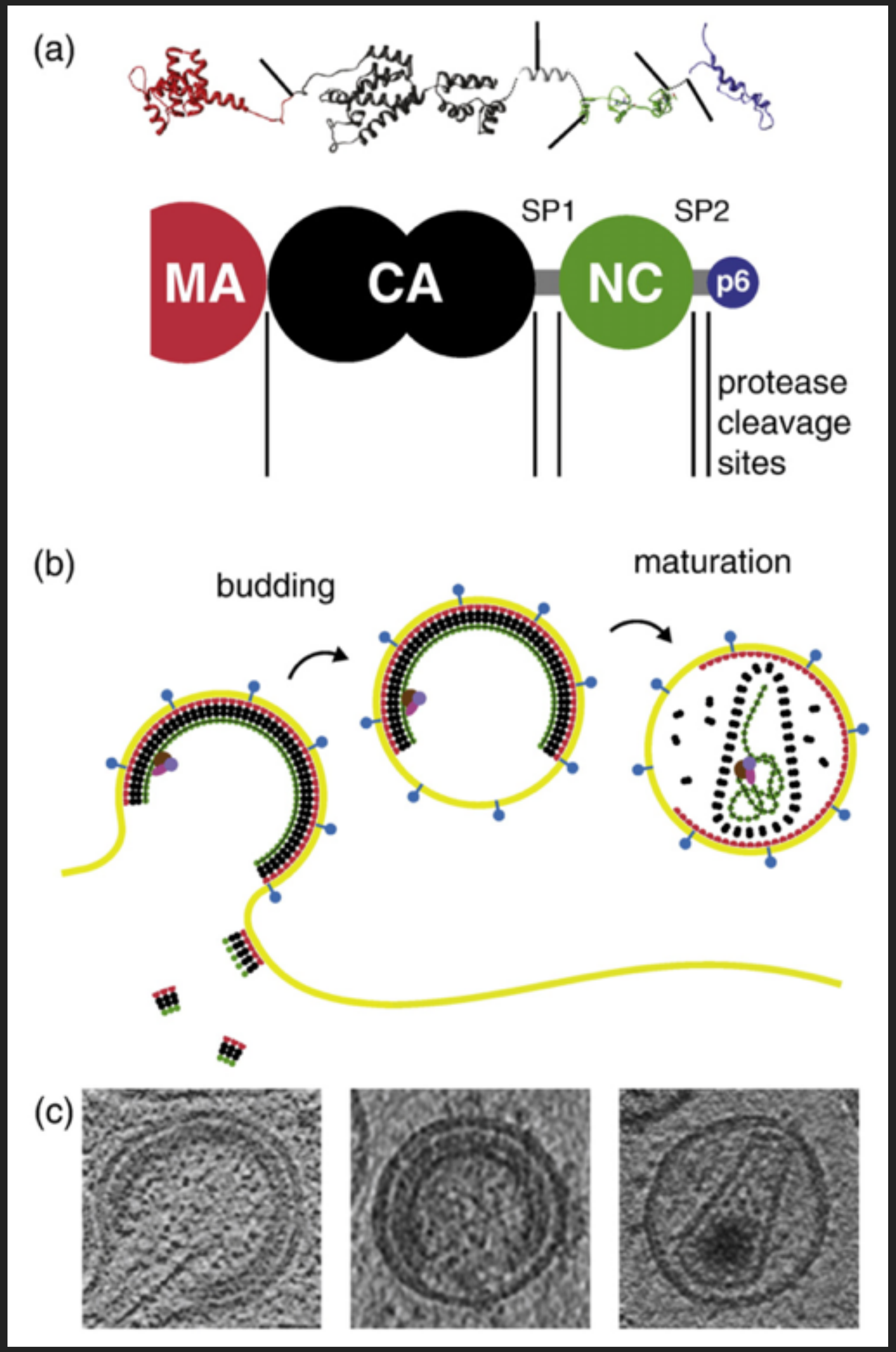
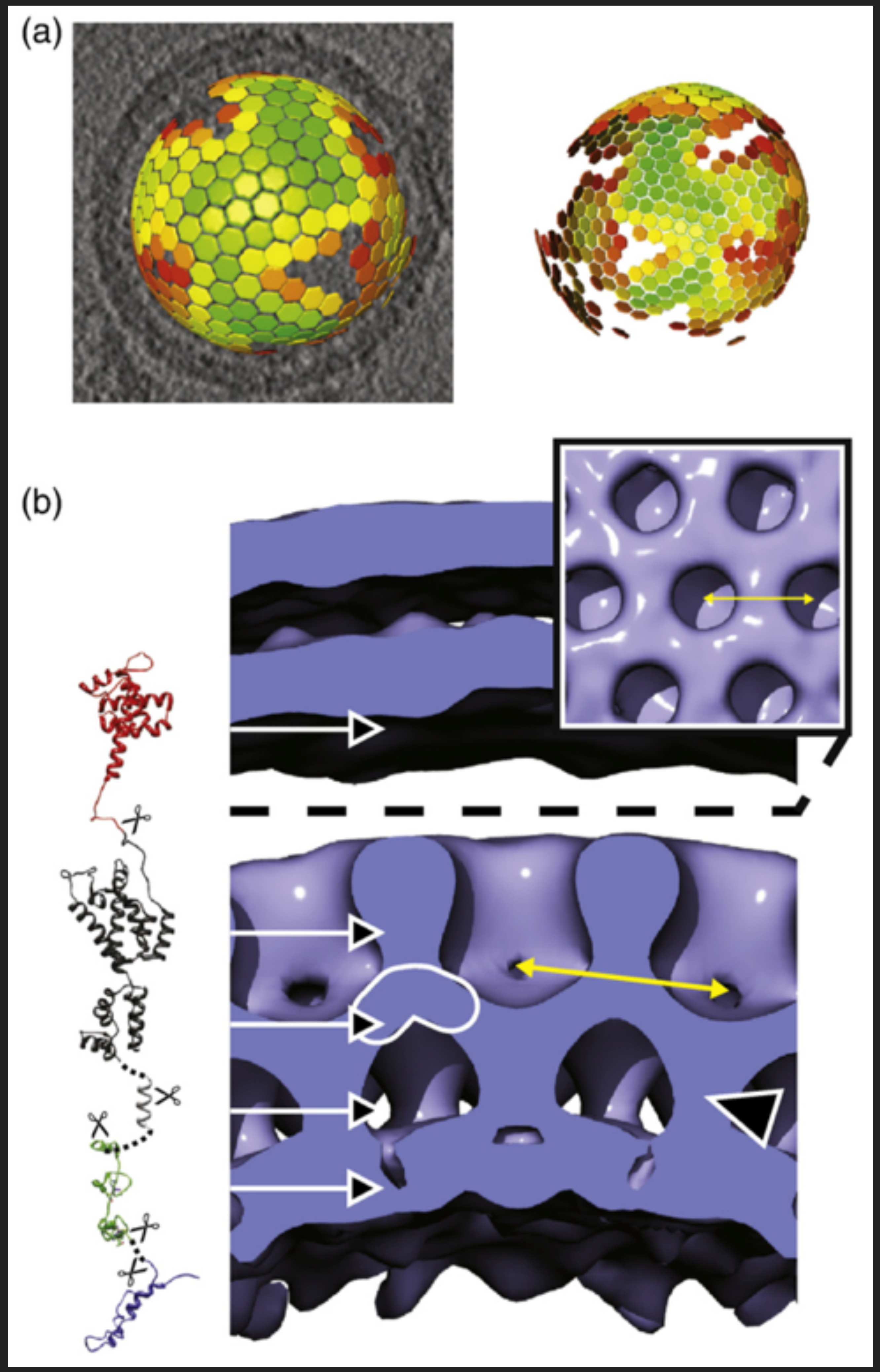
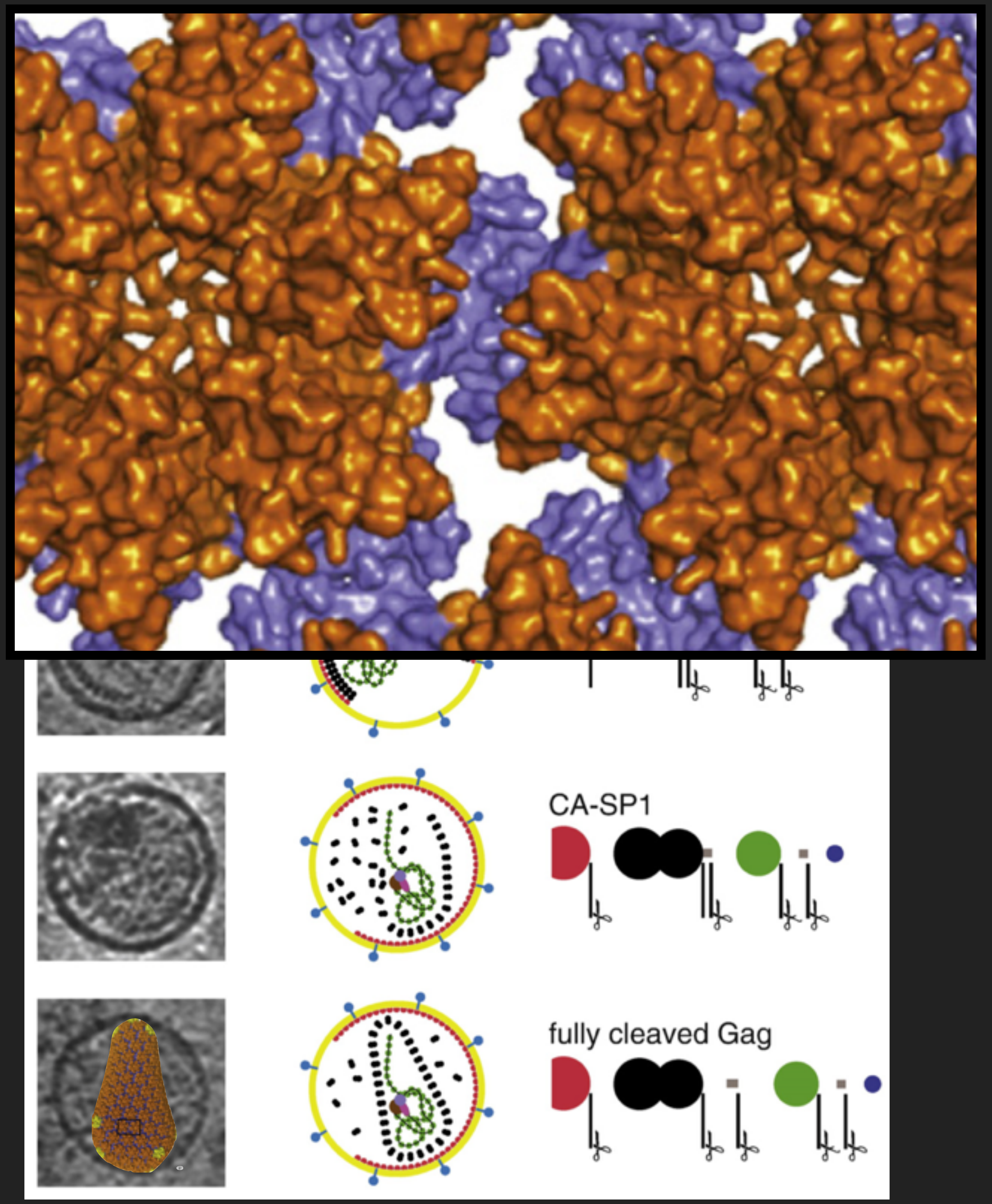
HIV







(Briggs, 2011)

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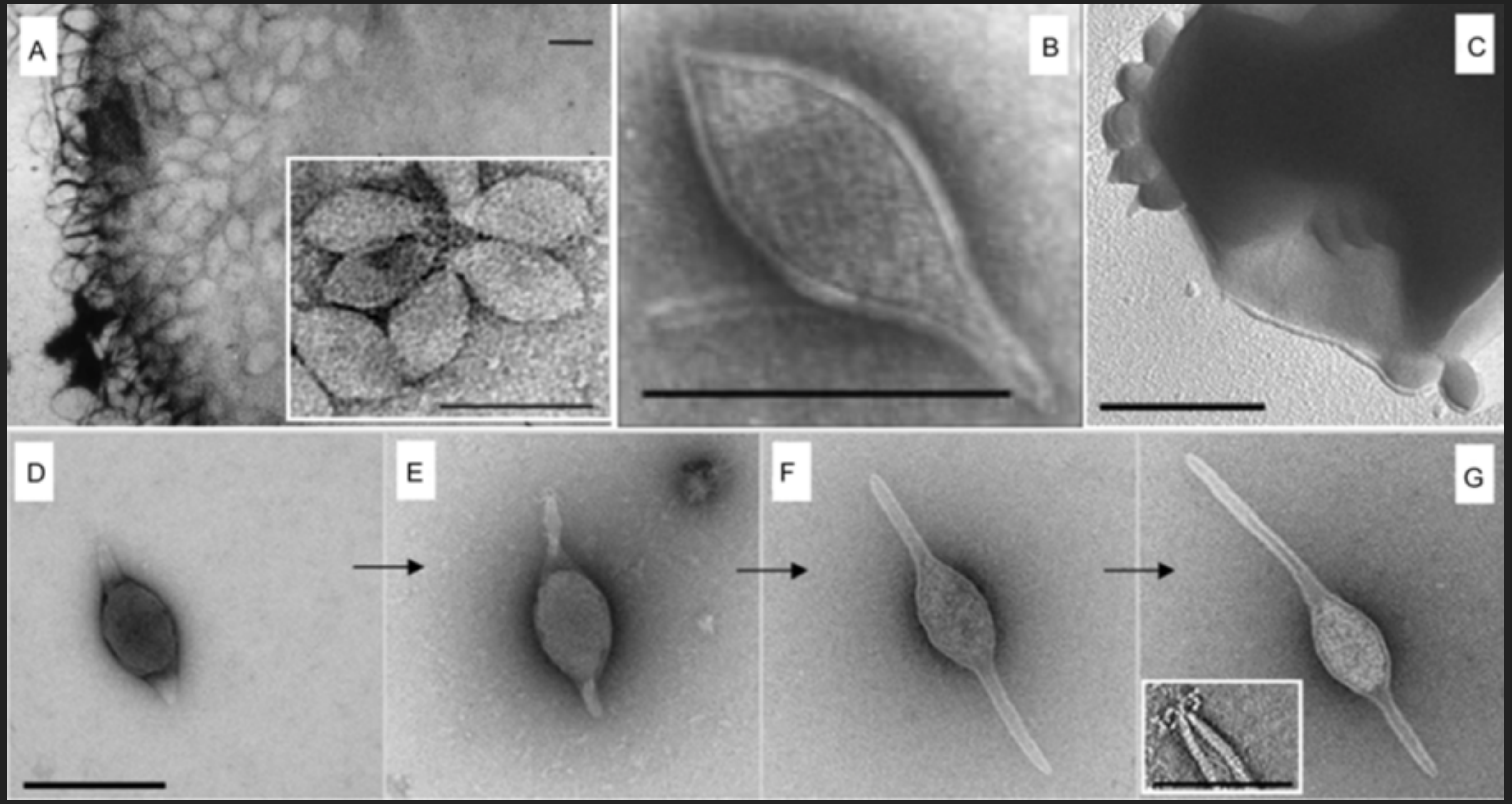
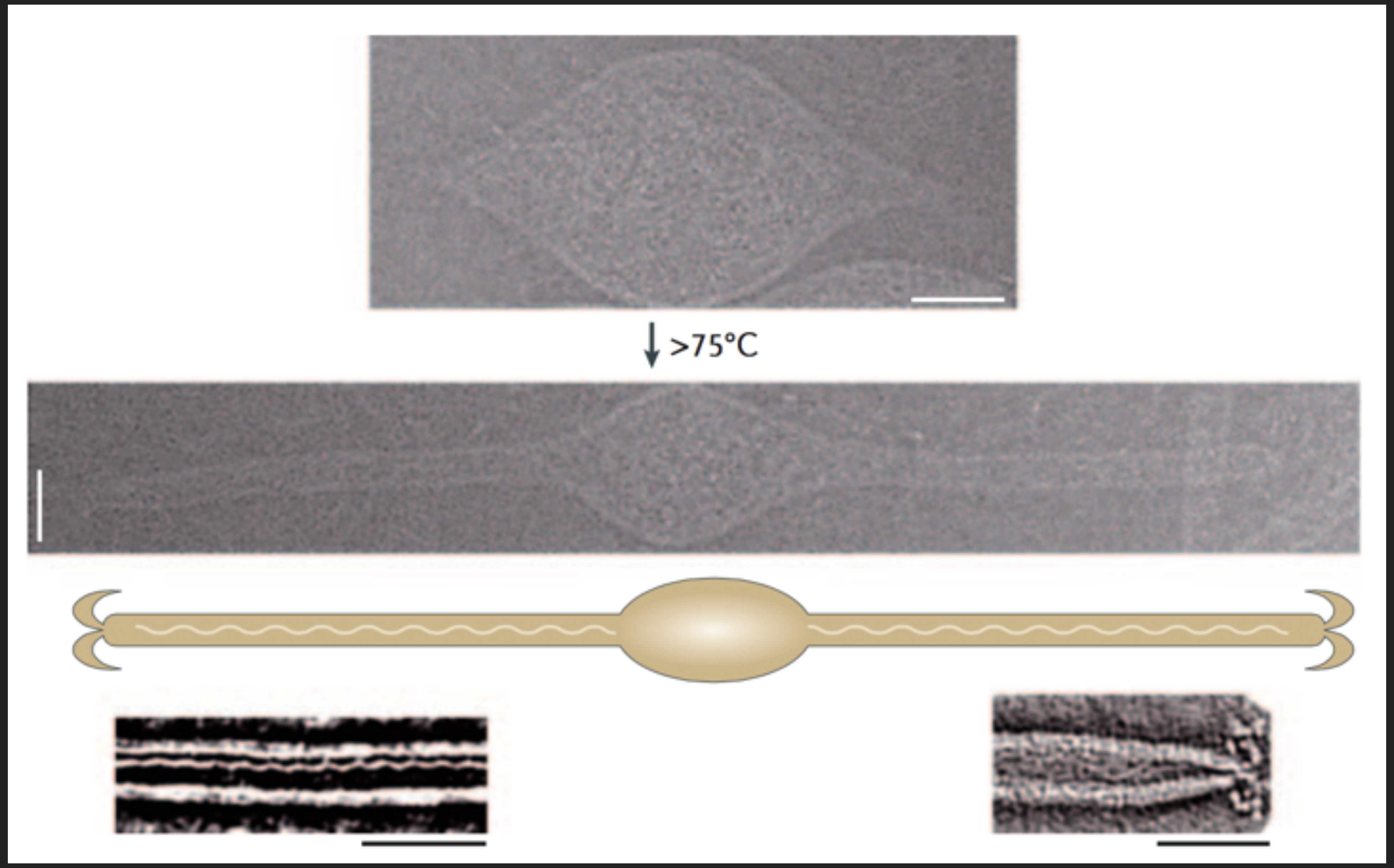
ARCHAEAL VIRUSES



(Xu, 2012)



(Prangishvili, 2006)

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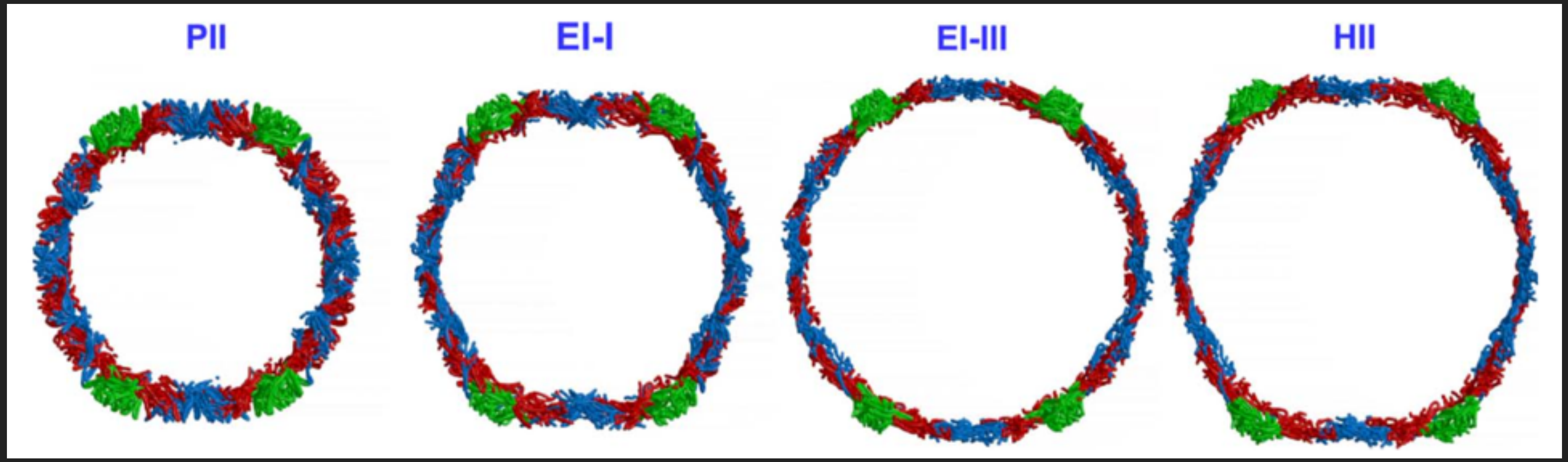
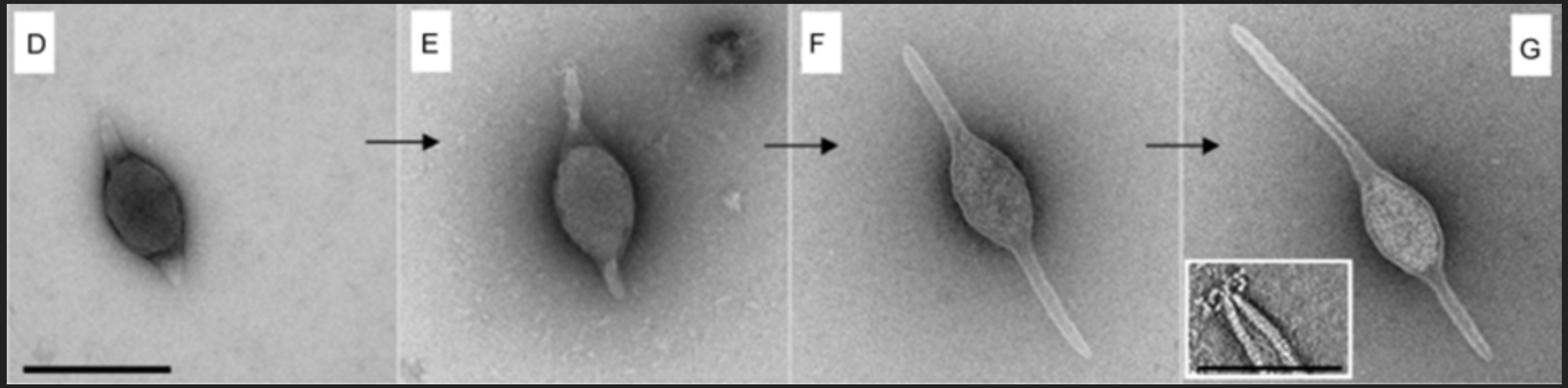
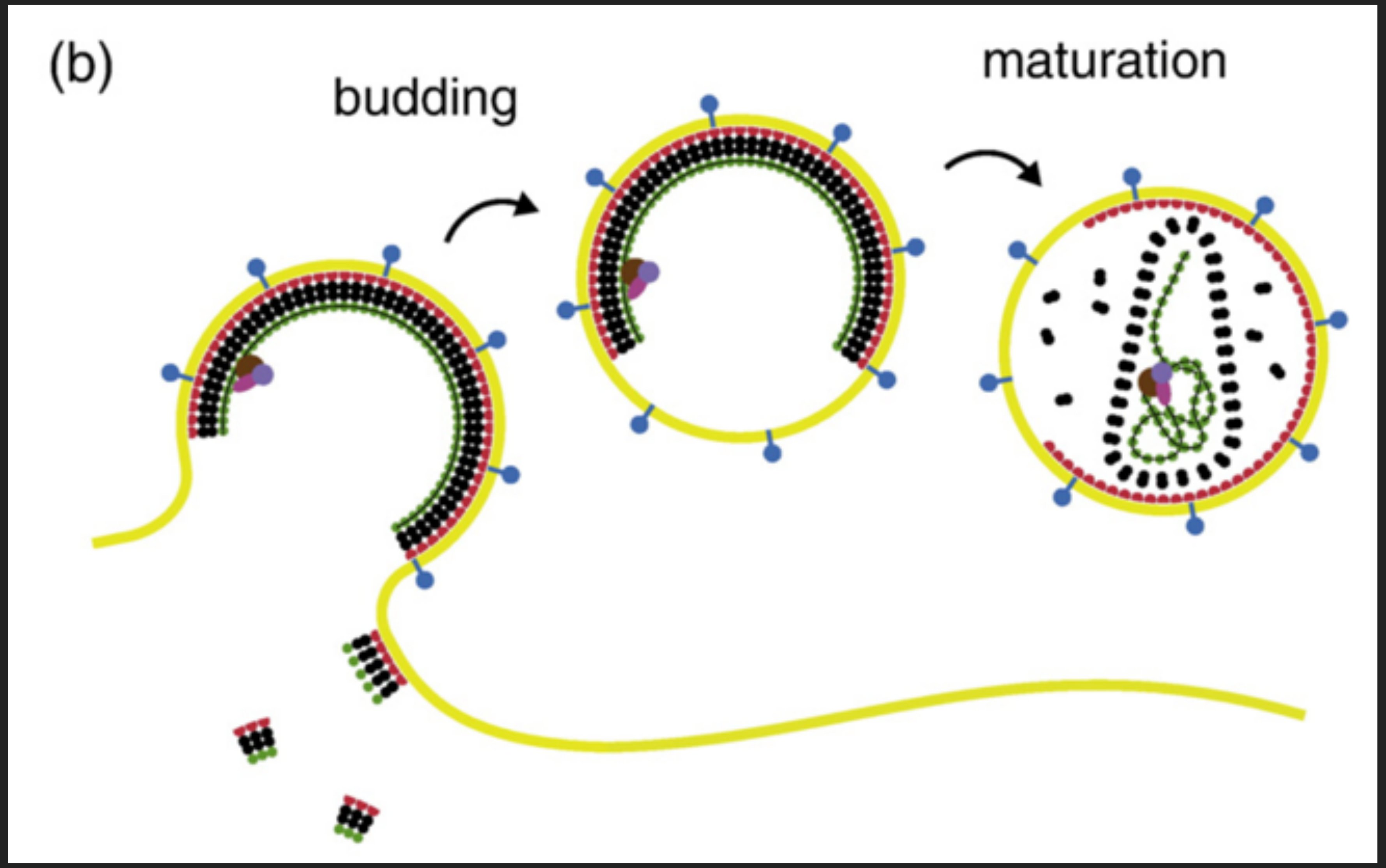
THE PHYSICS OF VIRUS SHAPE

- What drives shape and structure?
  - Symmetric shells?
  - Pleomorphic shells?
- Why and how does shape change?

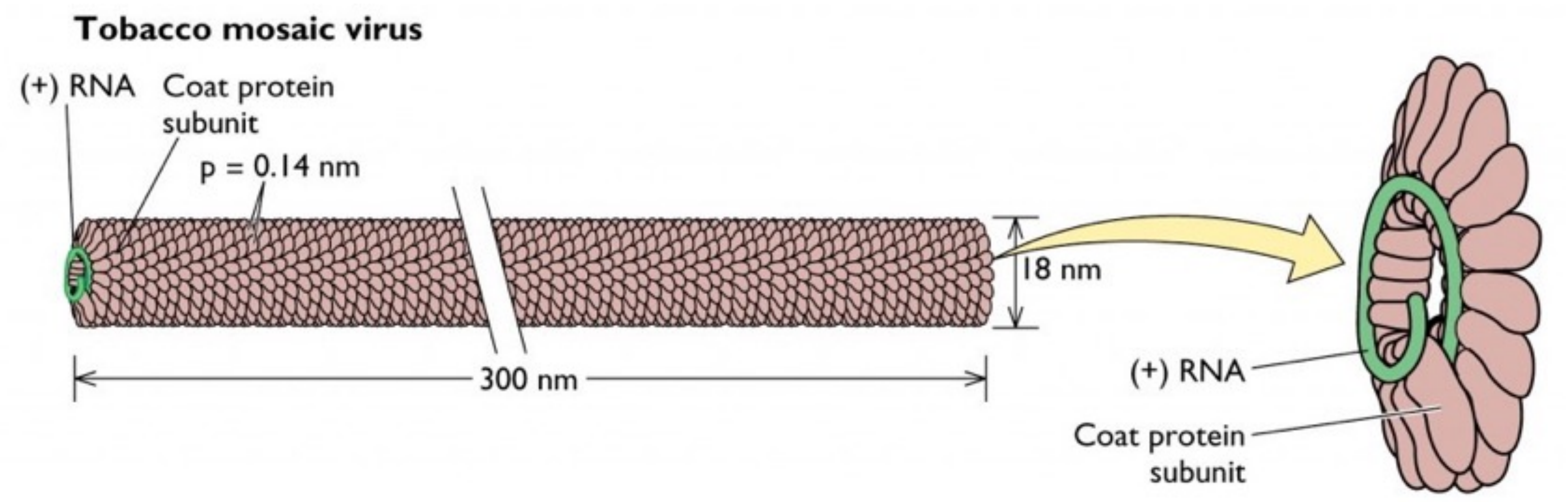






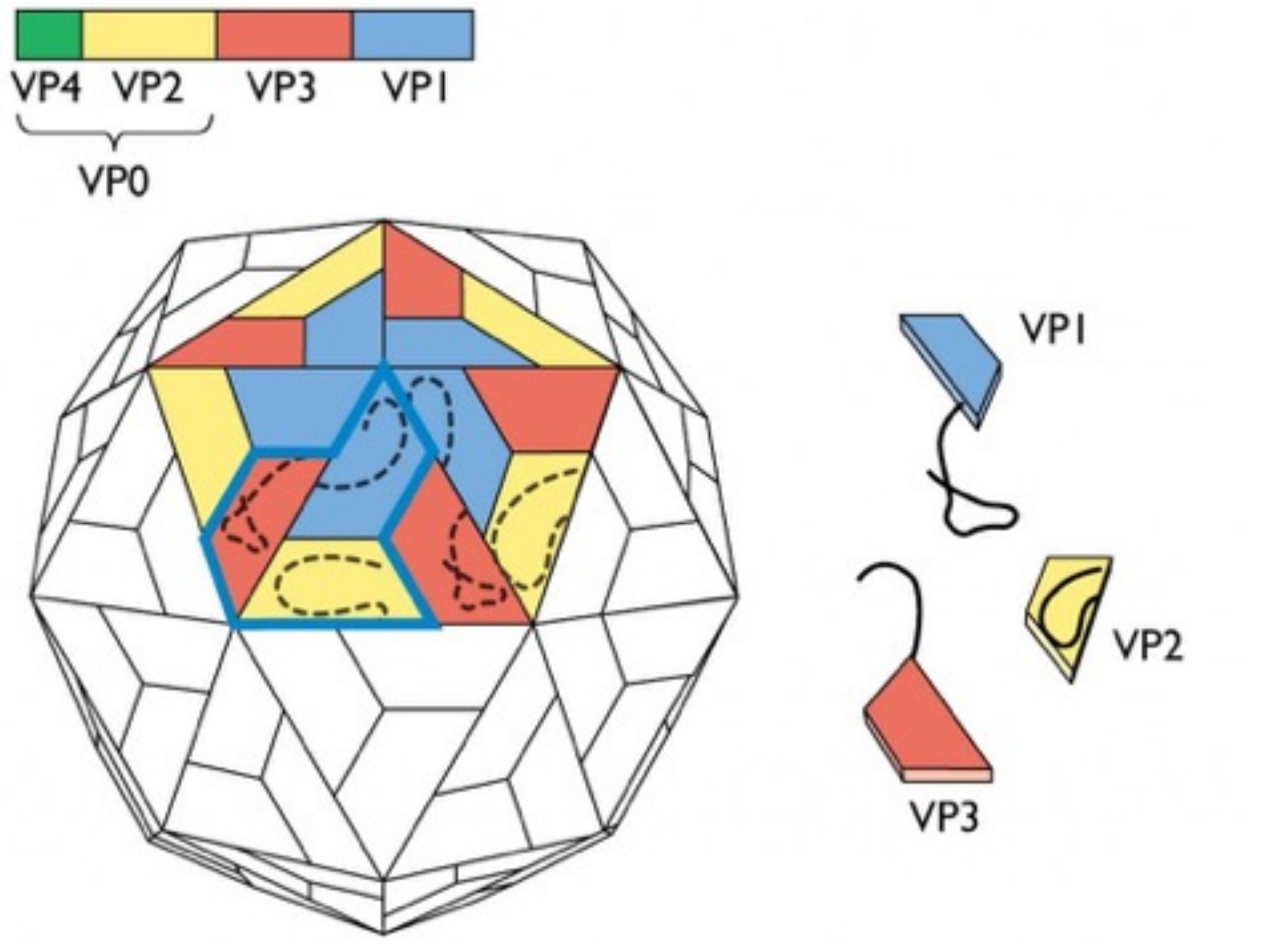
GEOMETRY AND STRUCTURE

Helical Symmetry



Proteins are in EQUIVALENT positions.

Icosahedral Symmetry



Proteins are in QUASI-EQUIVALENT positions.

Physical Principles in the Construction of Regular Viruses

D. L. D. CASPAR AND A. KLUG*

The Children's Cancer Research Foundation, The Children's Hospital Medical Center,
and the
Department of Biophysics, Harvard Medical School, Boston, Massachusetts;
**Medical Research Council Laboratory of Molecular Biology, University Postgraduate Medical School, Cambridge, England.*

Caspar and Klug, Ventura, CA, Feb 2015

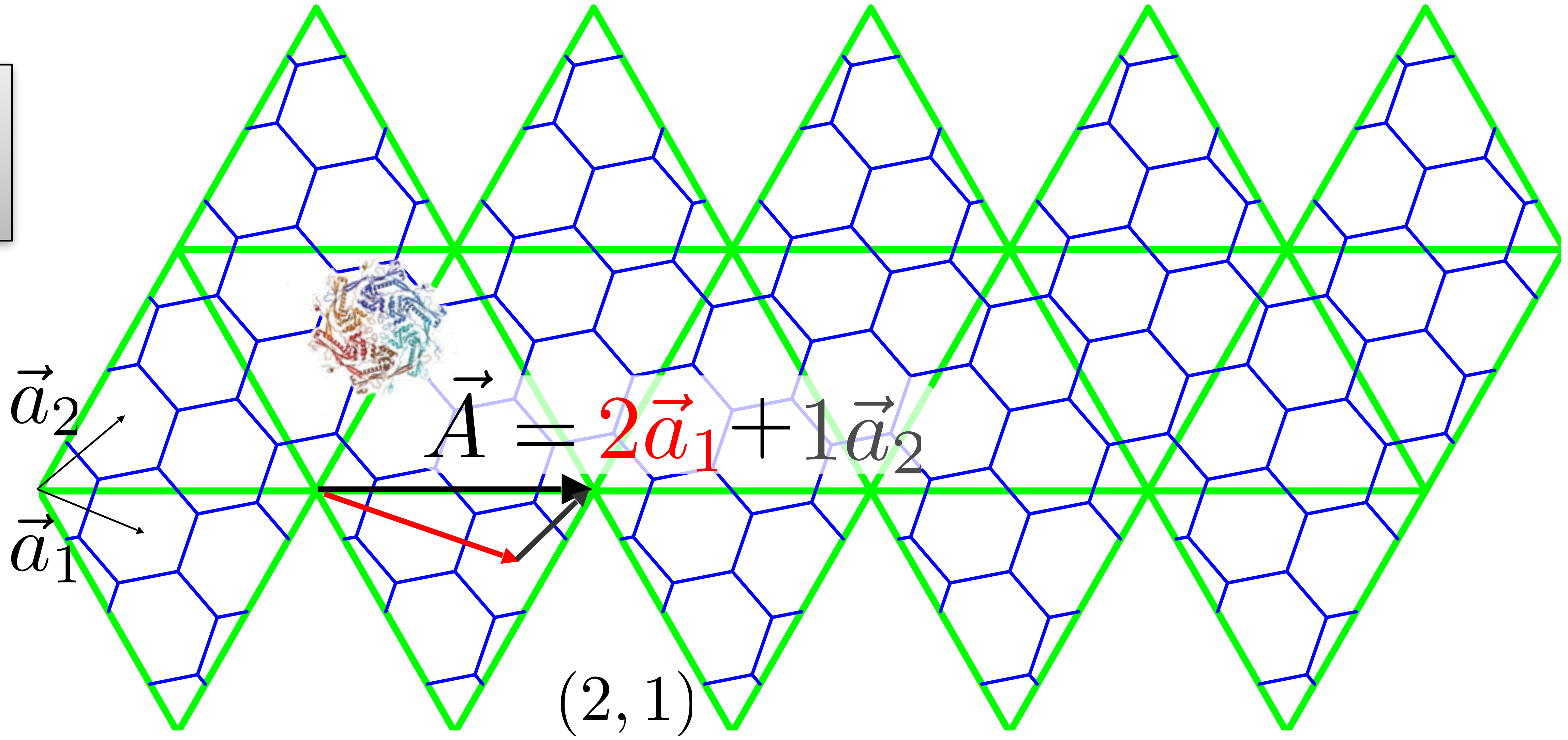
Physical Principles in the Construction of Regular Viruses

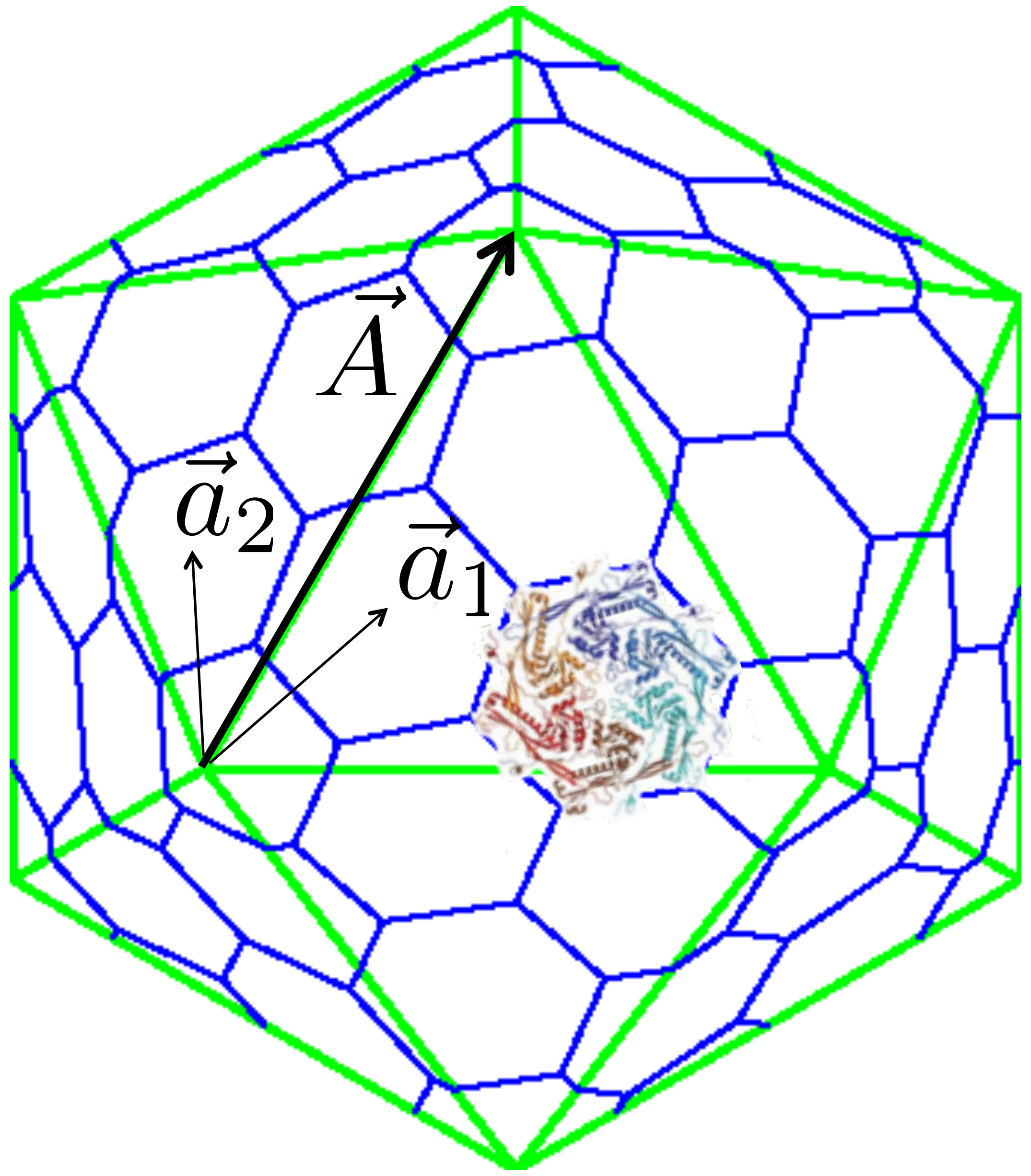
D. L. D. Caspar and A. Klug*
The Children's Cancer Research Foundation, The Children's Hospital Medical Center, and the Department of Biophysics, Harvard Medical School, Boston, Massachusetts;
**Medical Research Council Laboratory of Molecular Biology, University Postgraduate Medical School, Cambridge, England.*

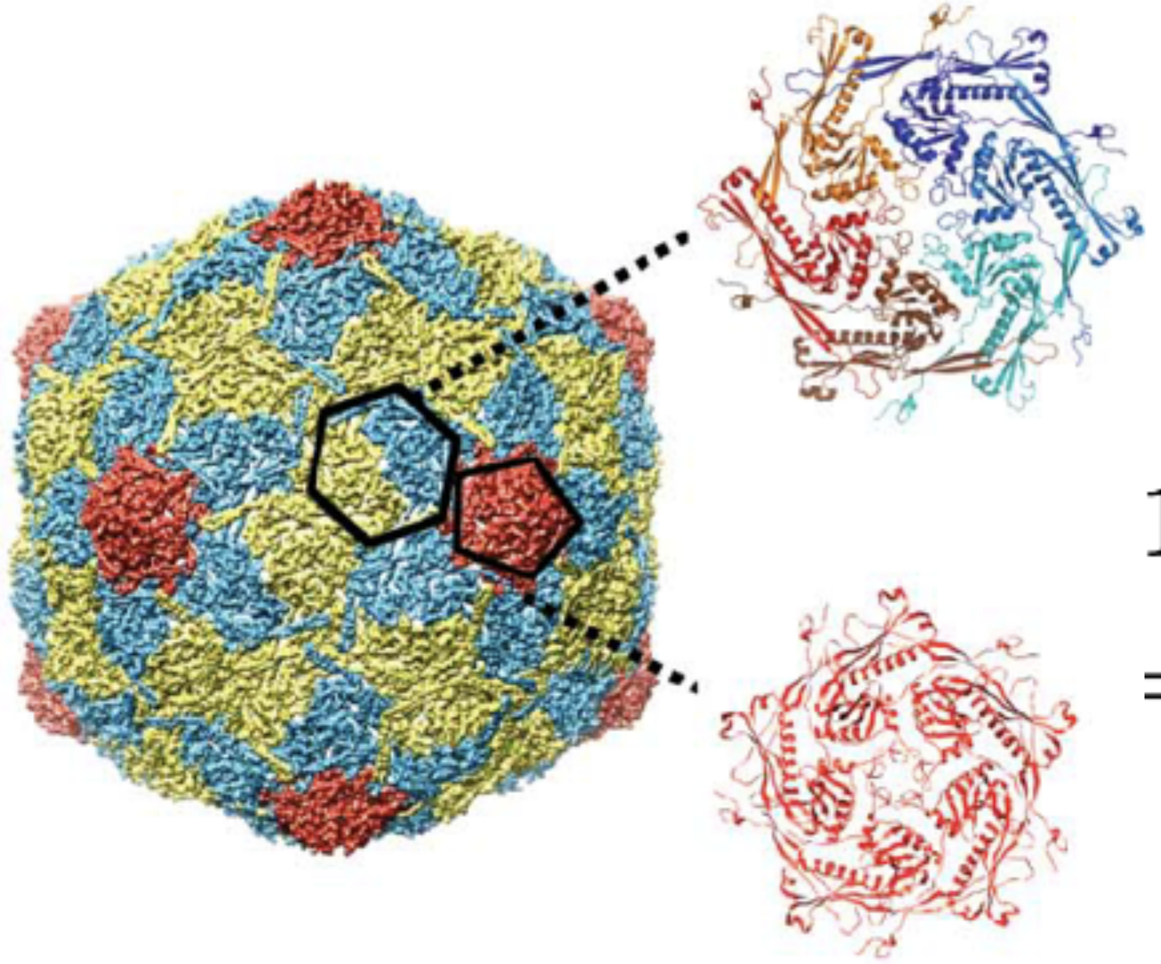
Hexagonal lattice wrapped onto an icosahedron

$$\vec{A} = h\vec{a}_1 + k\vec{a}_2$$

(h, k) integers







$T = 7(l)$

$$T = h^2 + hk + k^2$$

$12 \times 5 + 60(T - 1)$

$= 60T$ protein subunits per shell

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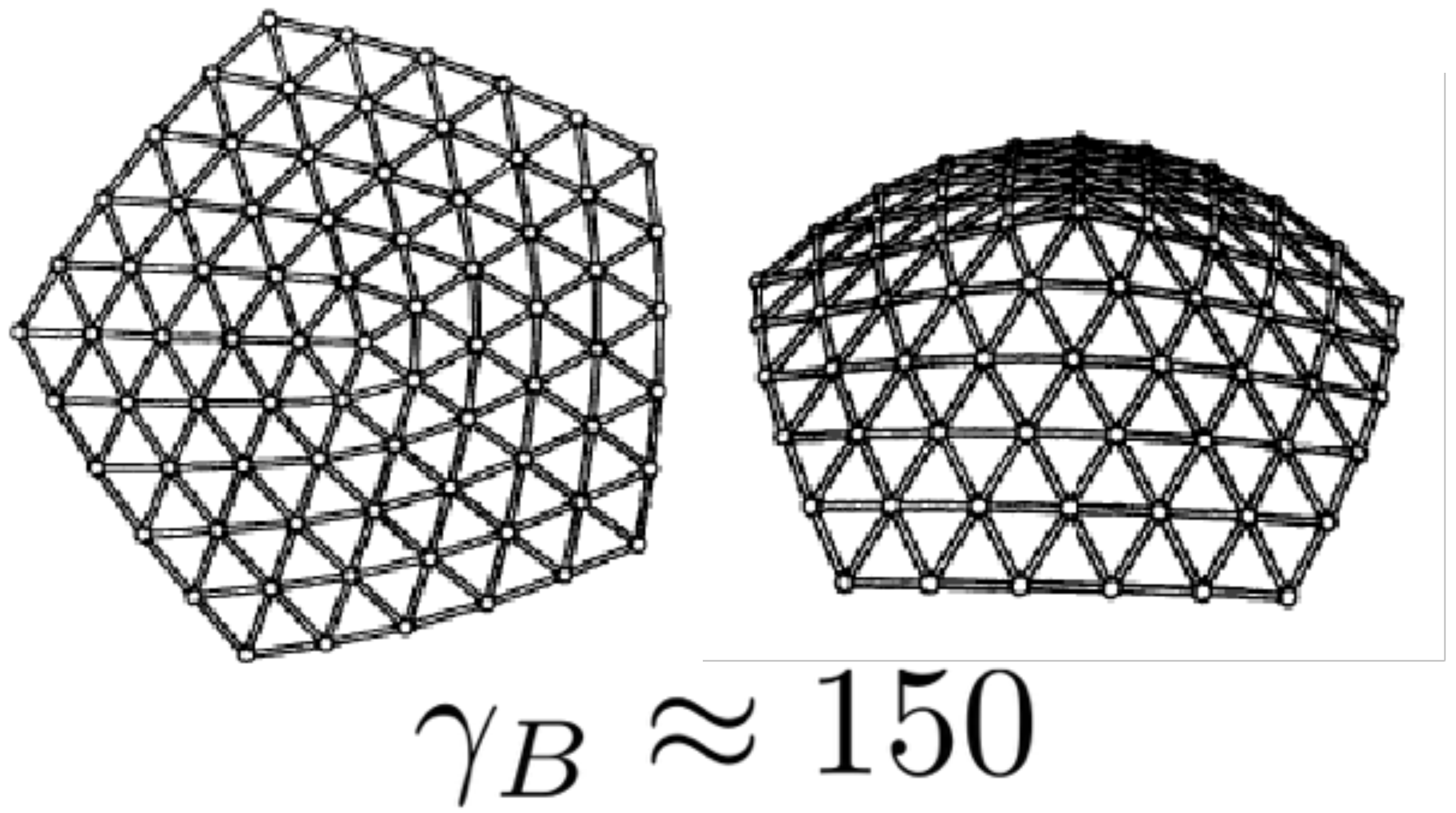
THE FÖPPL-VON KÁRMÁN NUMBER $\gamma = \frac{YR^2}{\kappa}$

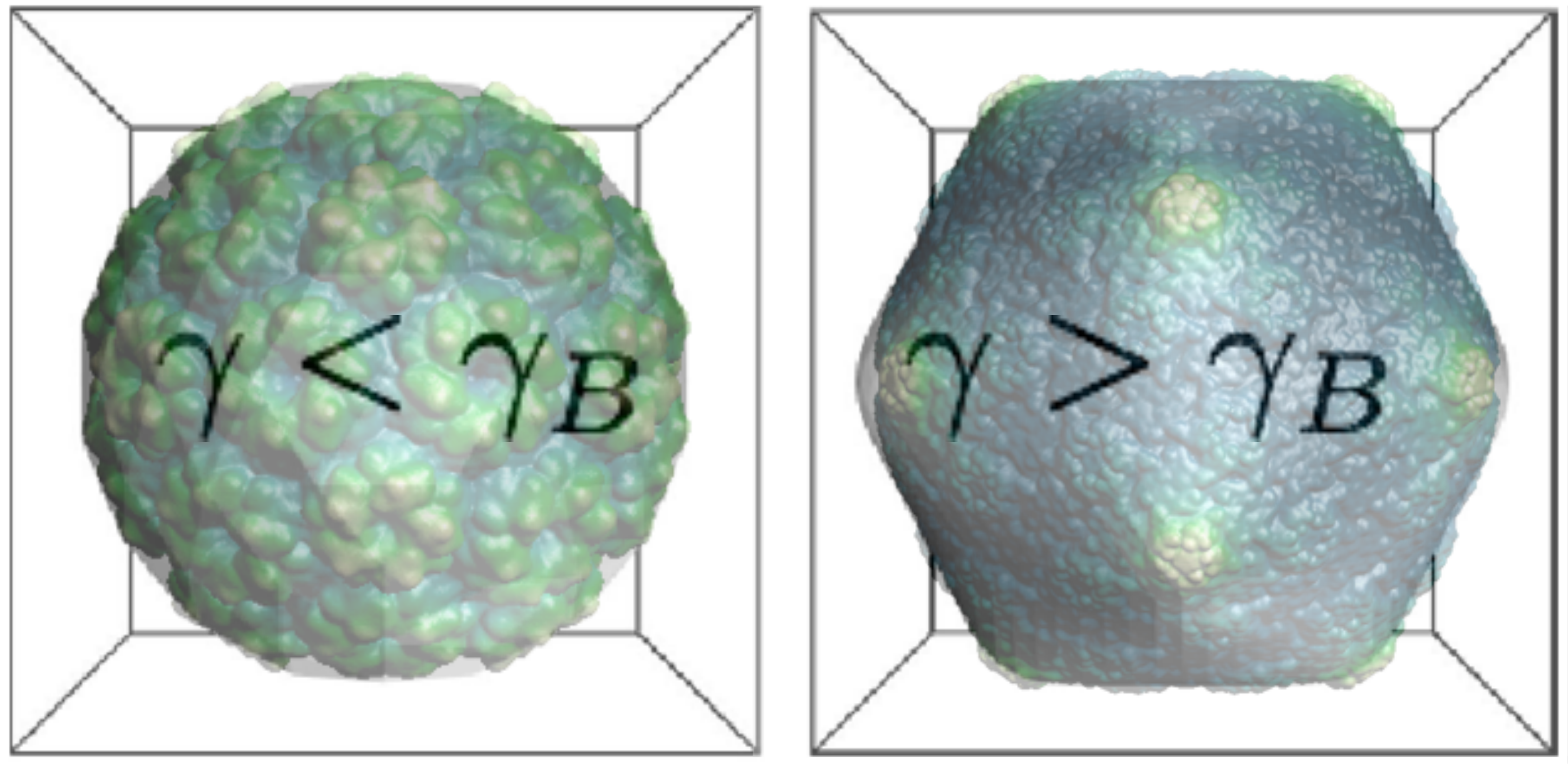
- Elastic energy of a thin shell

$$\mathcal{H} = \int \Big(\underbrace{\frac{\kappa}{2} H^2 + \kappa_G K}_{\text{bending}} + \underbrace{\frac{\lambda}{2} E_{ii}^2 + \mu E_{ij} E_{ij}}_{\text{stretching}} \Big) dA$$

- Pentamers are 5-fold Disclinations
- Capsid facetting (asphericity) results from *buckling*.



Seung & Nelson, Phys. Rev. A (1988)



Lidmar, Mirny, & Nelson, *Phys. Rev. E* (2003)

$$\gamma = \frac{YR^2}{\kappa}$$

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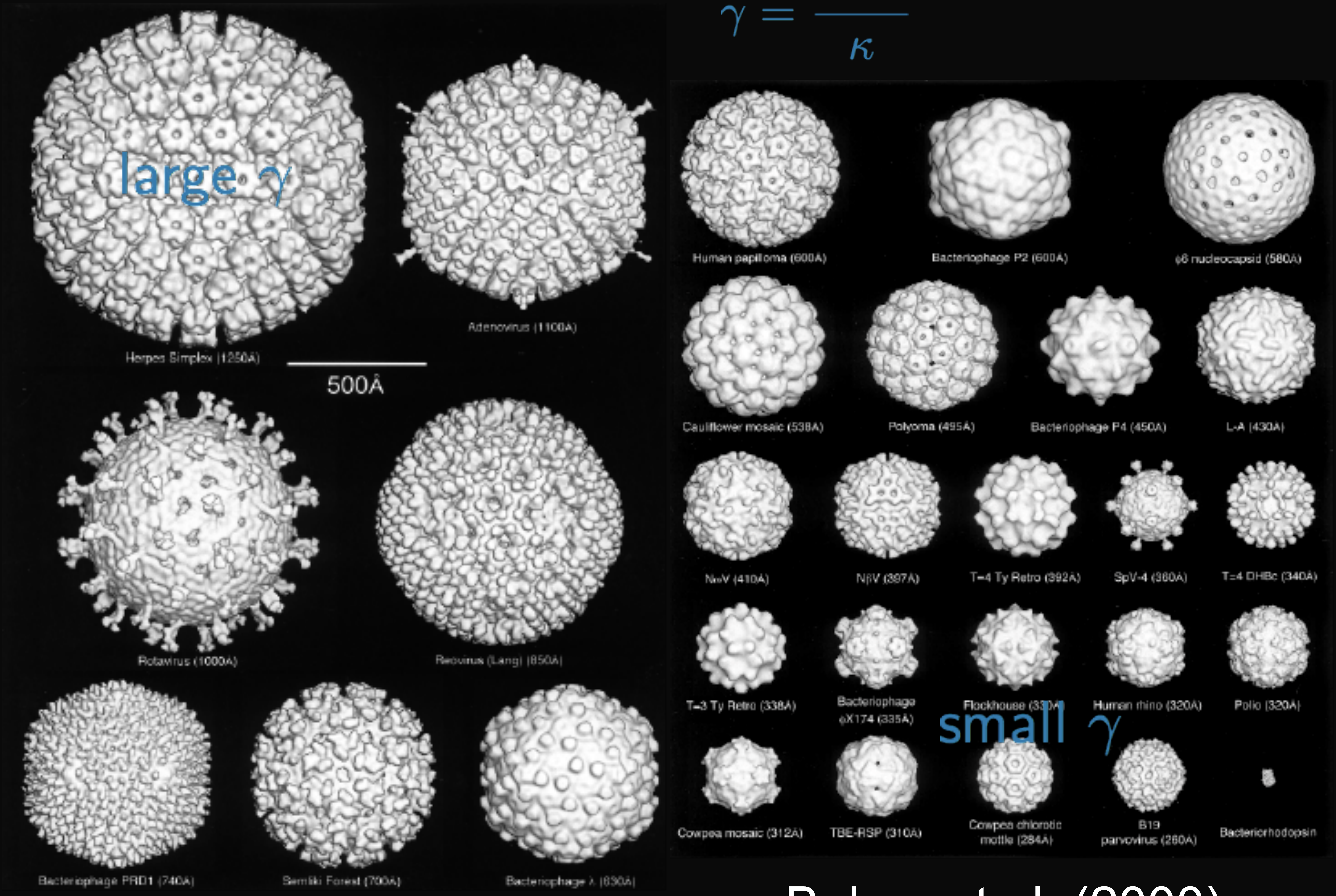
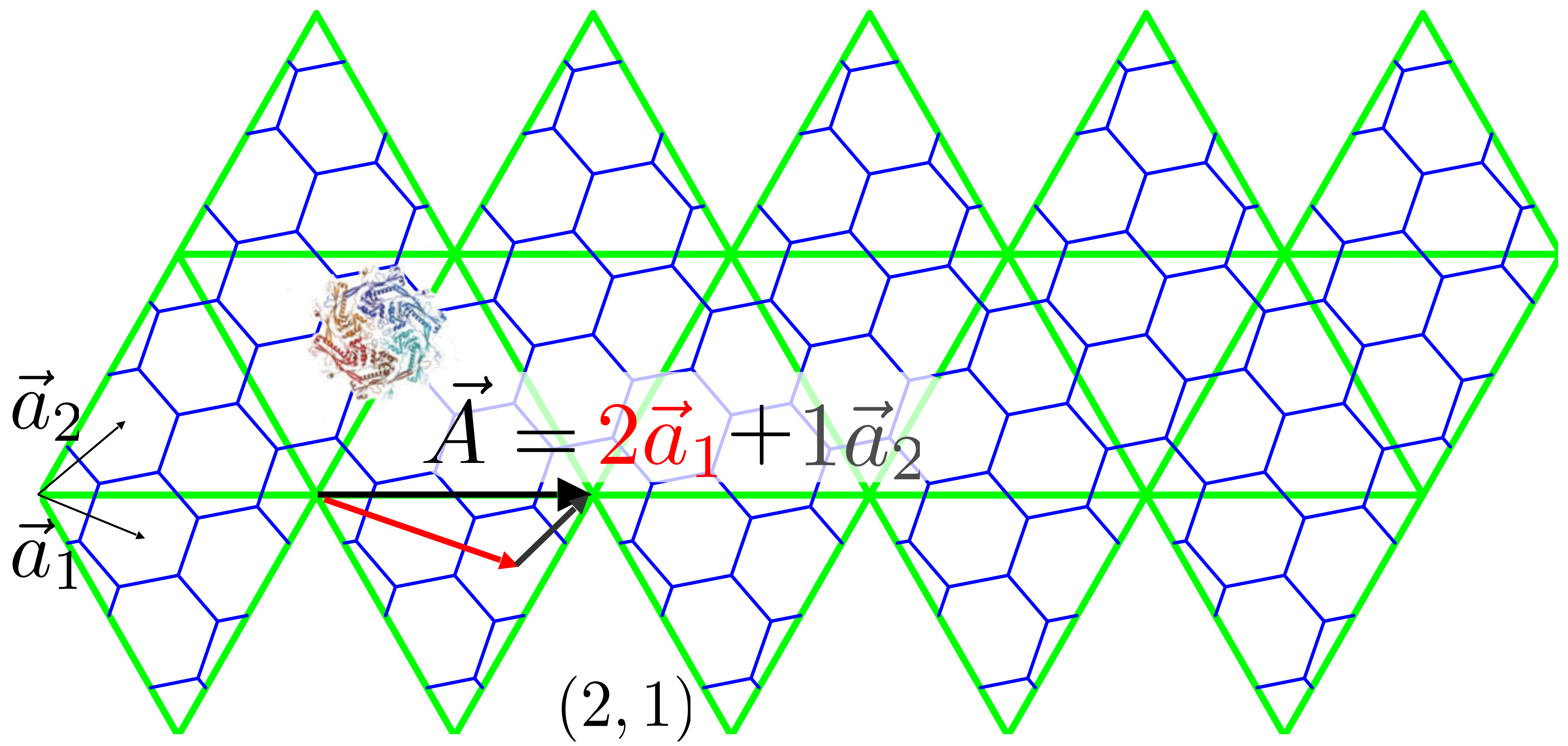
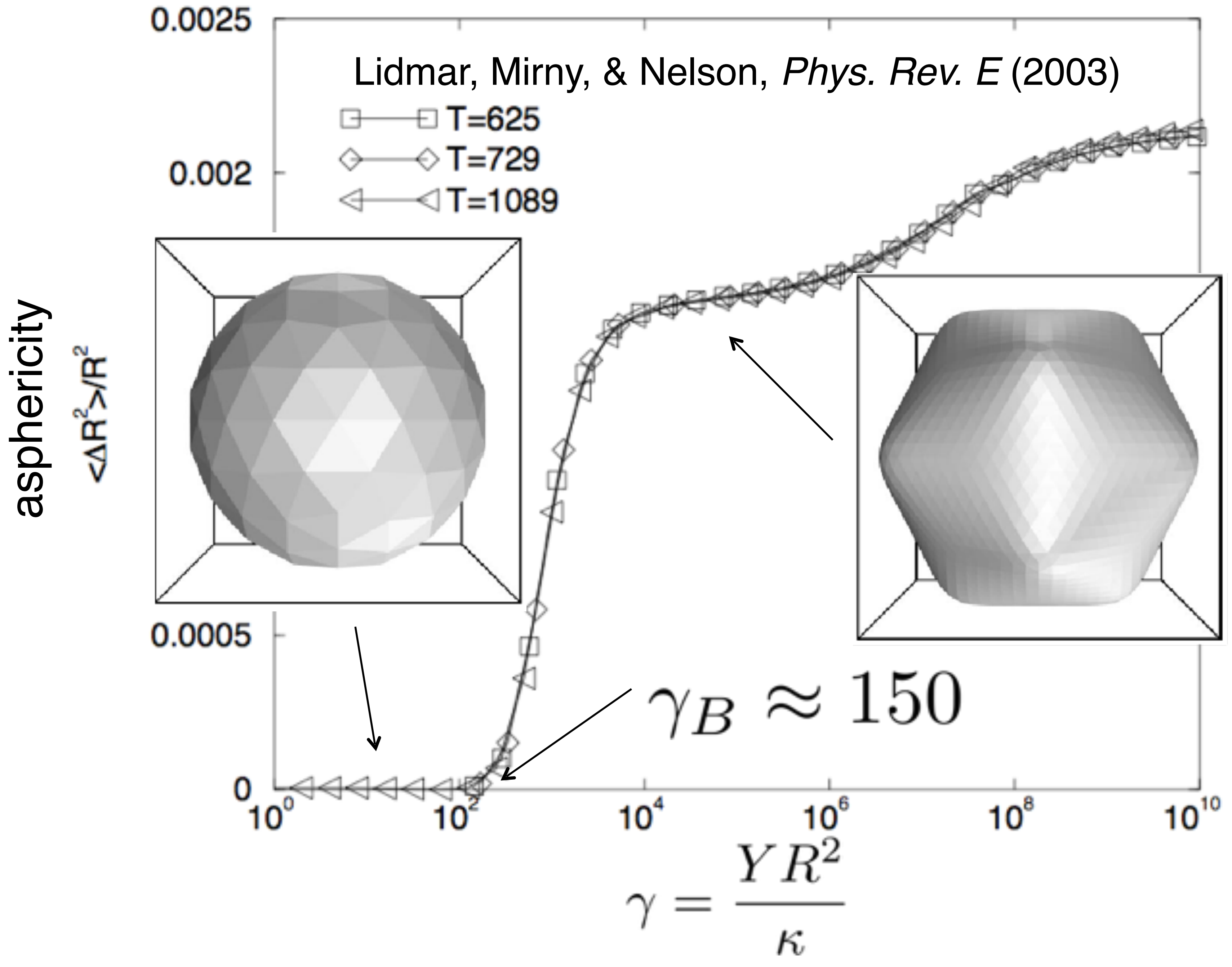


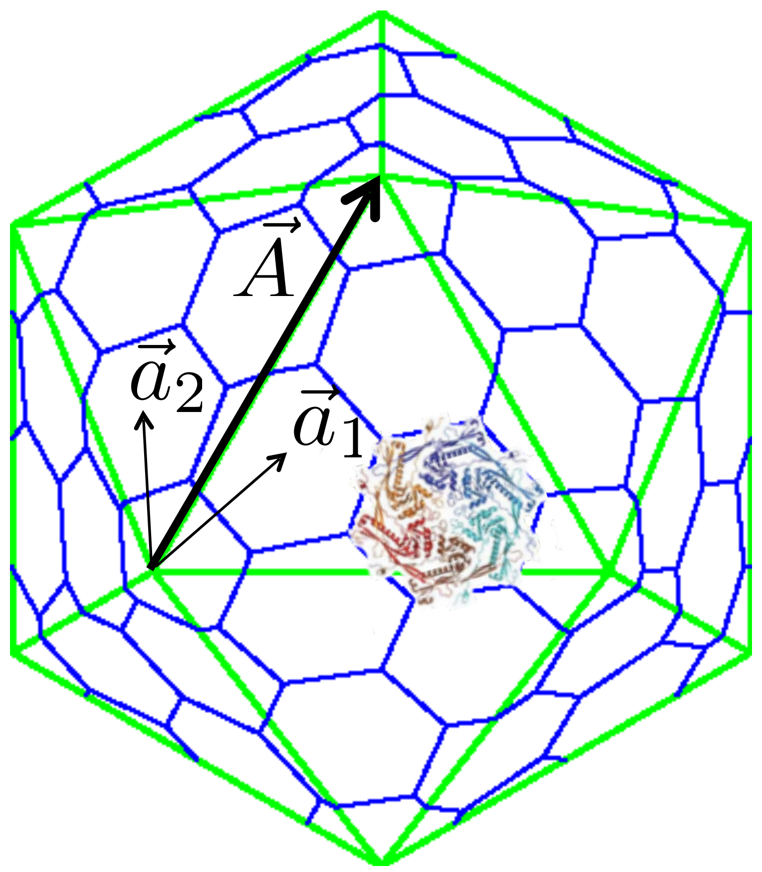
Baker, et al. (2000)

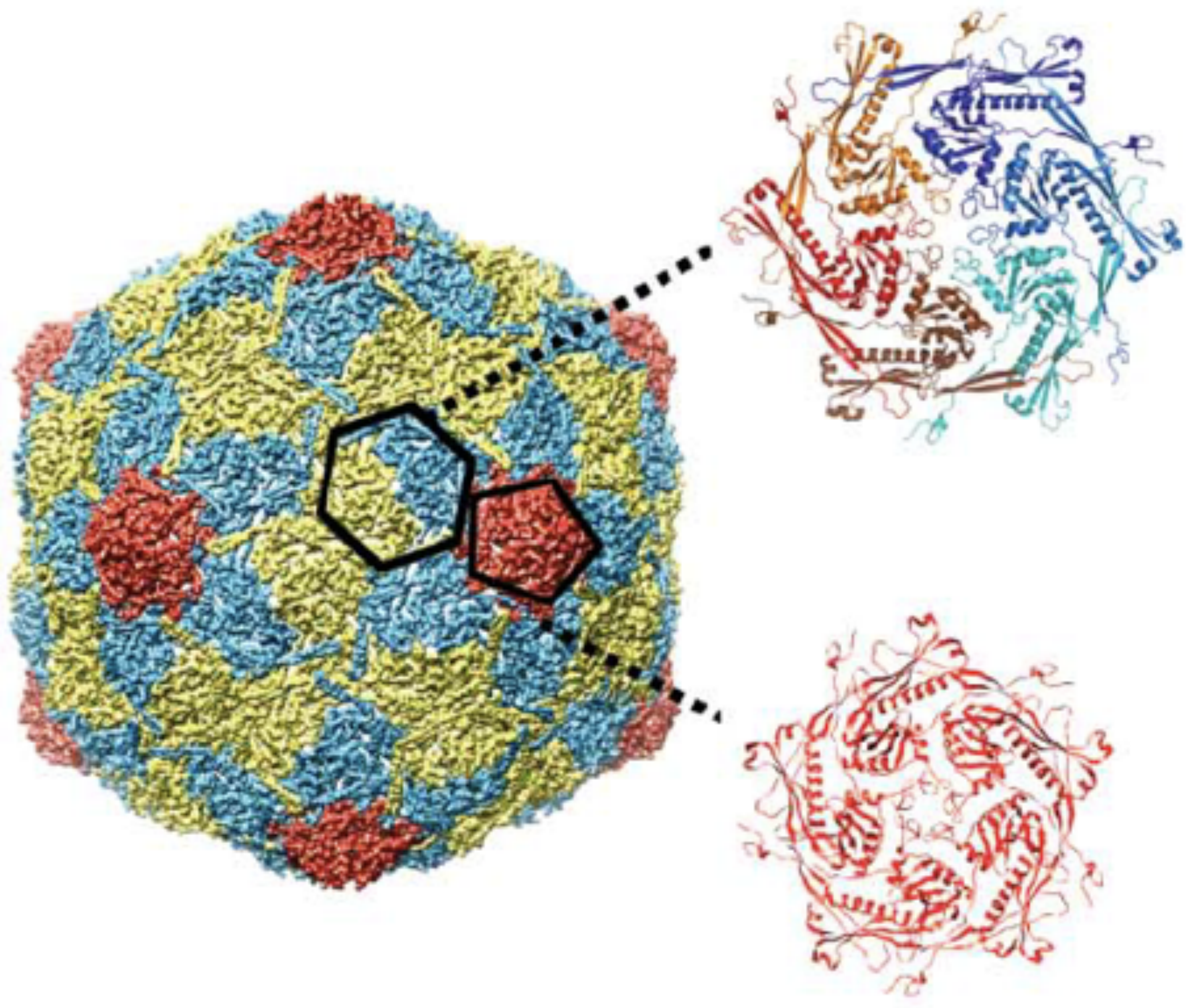
5-FOLD ELASTIC DEFECTS DRIVE A "BUCKLING TRANSITION"

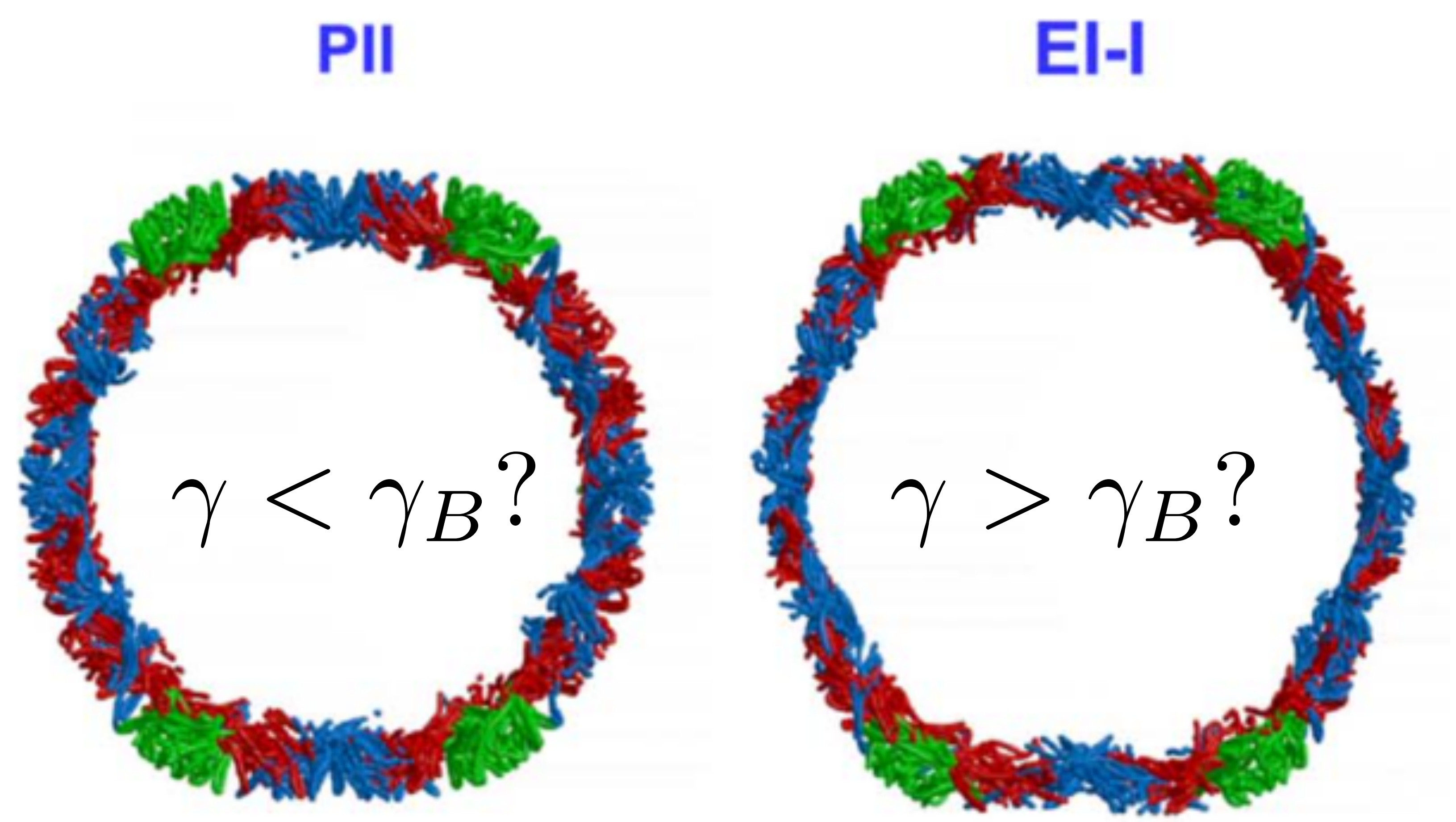


Reference State

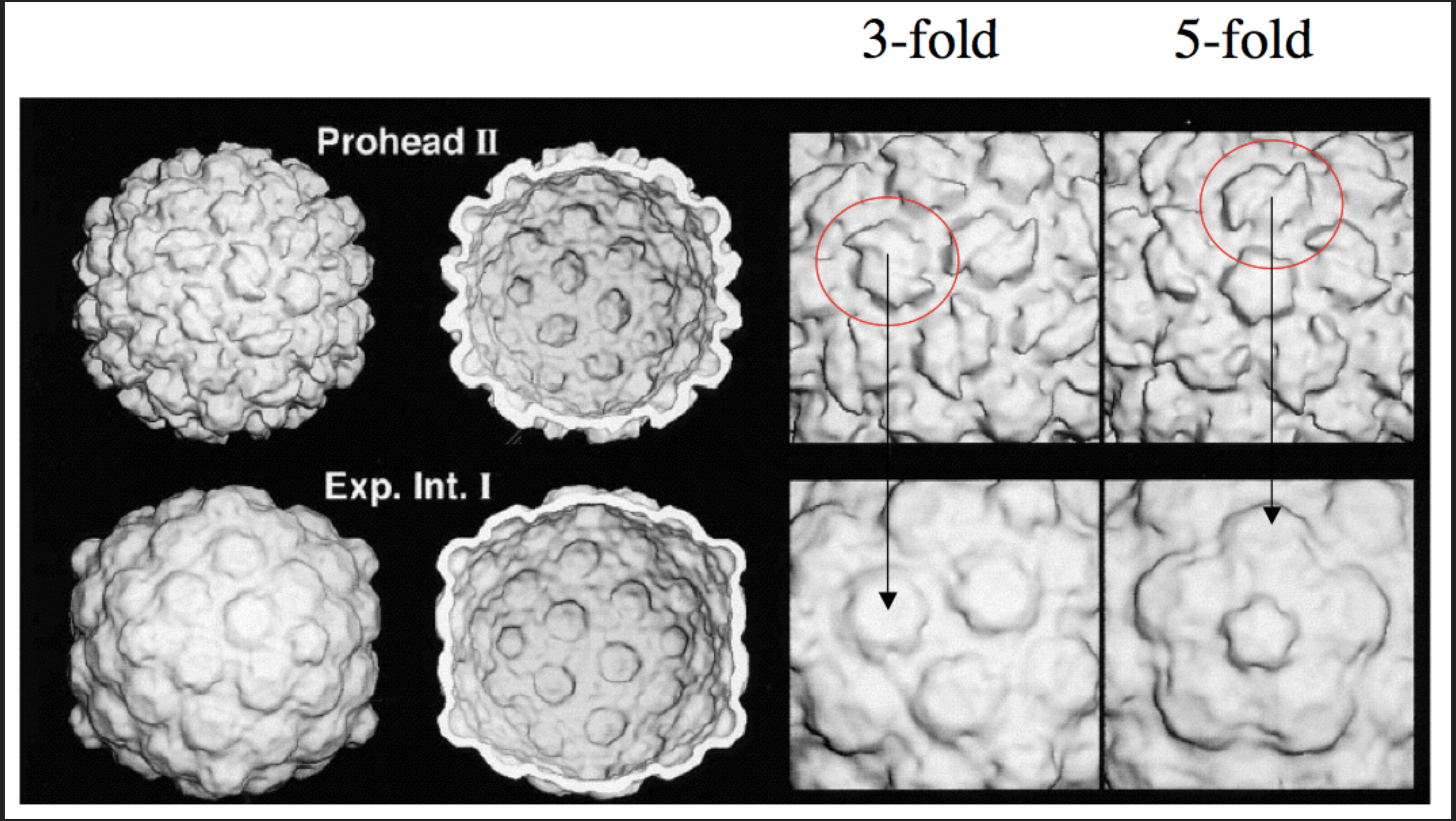








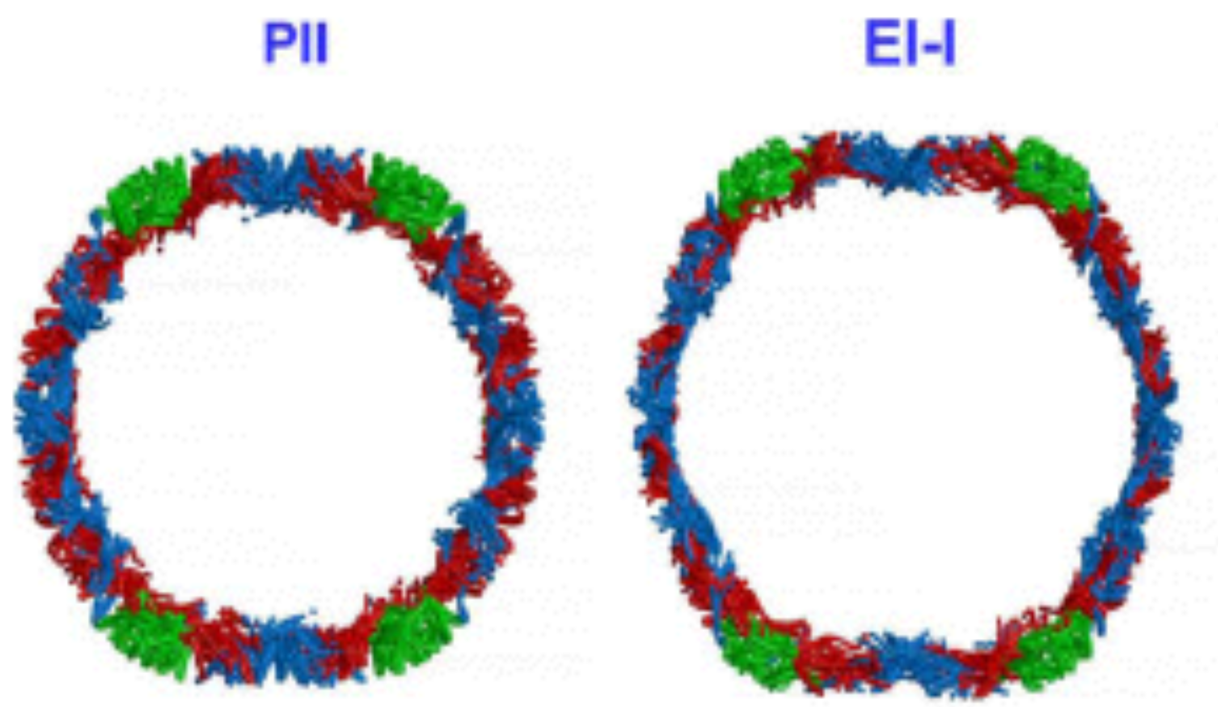
BUT WAIT…



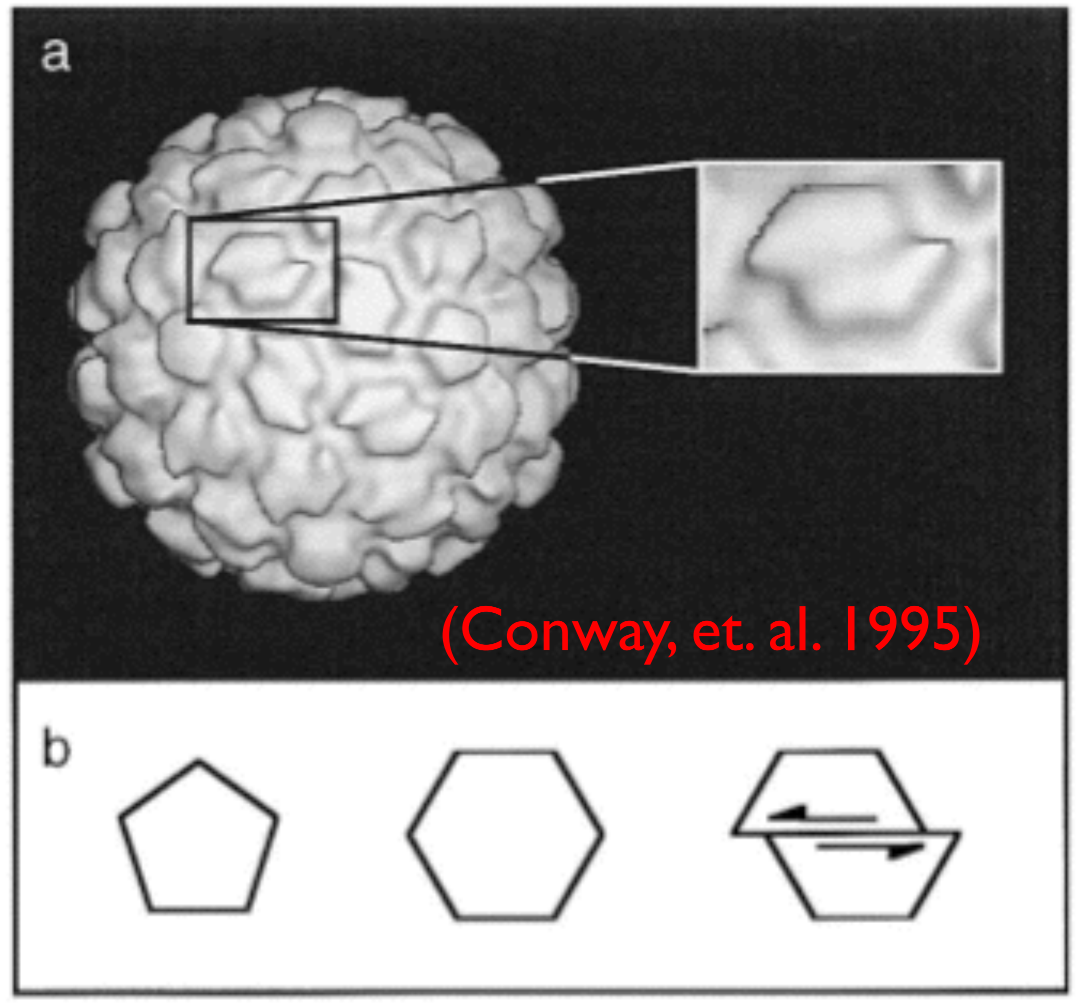
(Lata, et. al. 2000)

- *P-II to EI-I Displacement pattern does not agree with theory.*

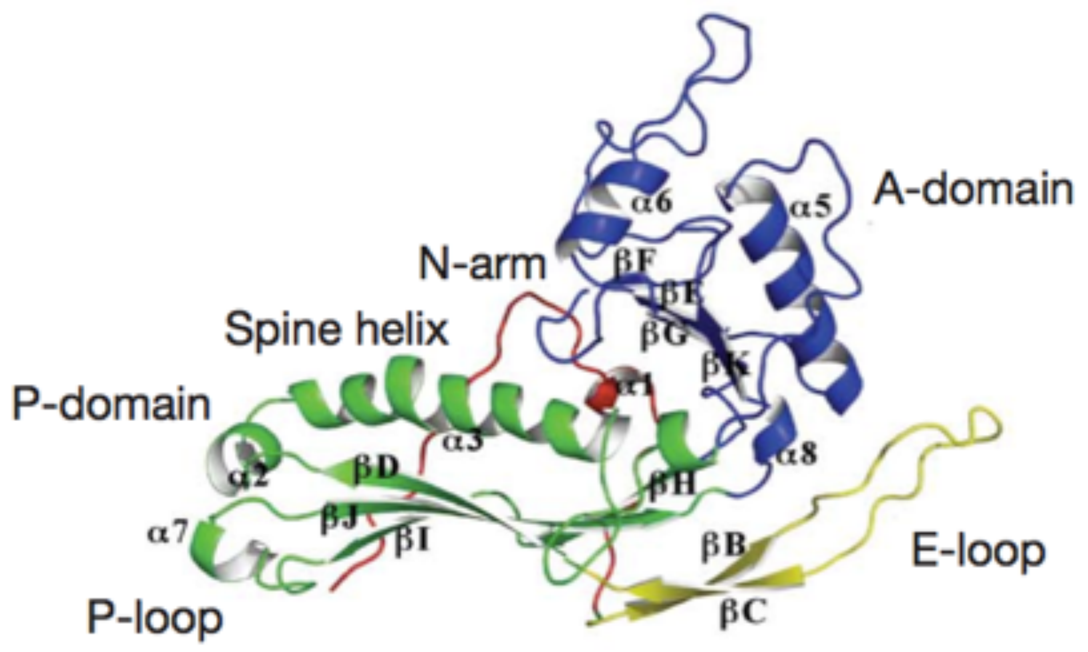
PII TO EI-I TRANSITION DRIVEN BY HEXON SHEAR



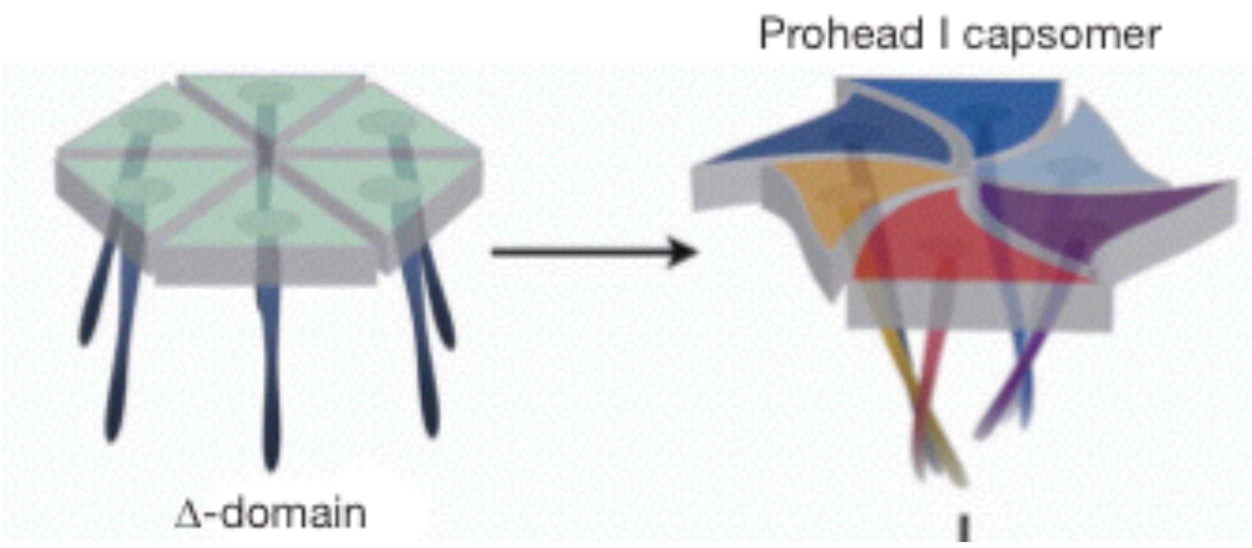
(Wikoff et. al. 2006)



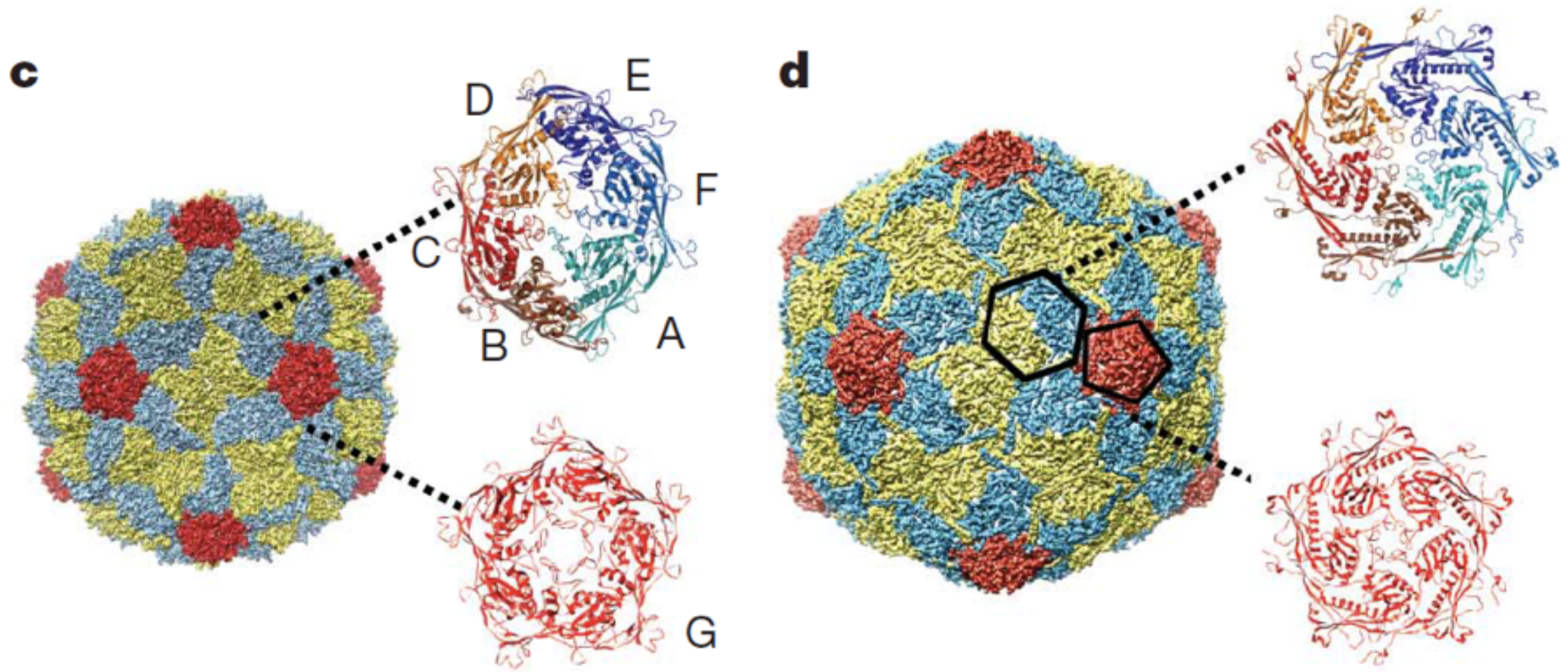
(Conway, et. al. 1995)



- Delta domains cleaved
- Skewed hexons become symmetric
- Energy released “like a coiled spring”

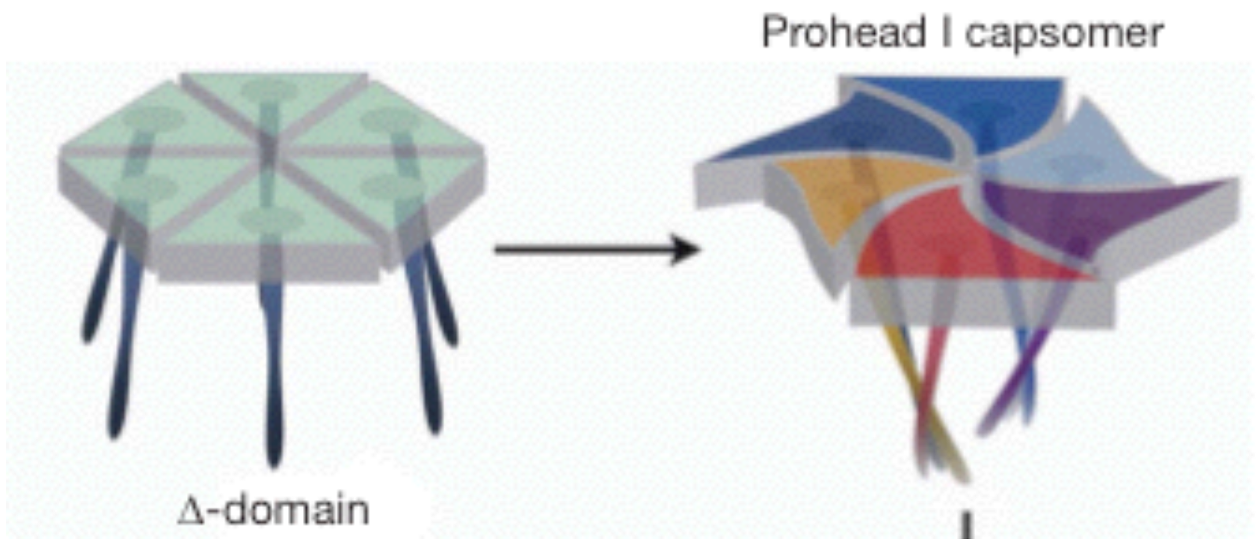


(Gertsman, et. al. 2009)



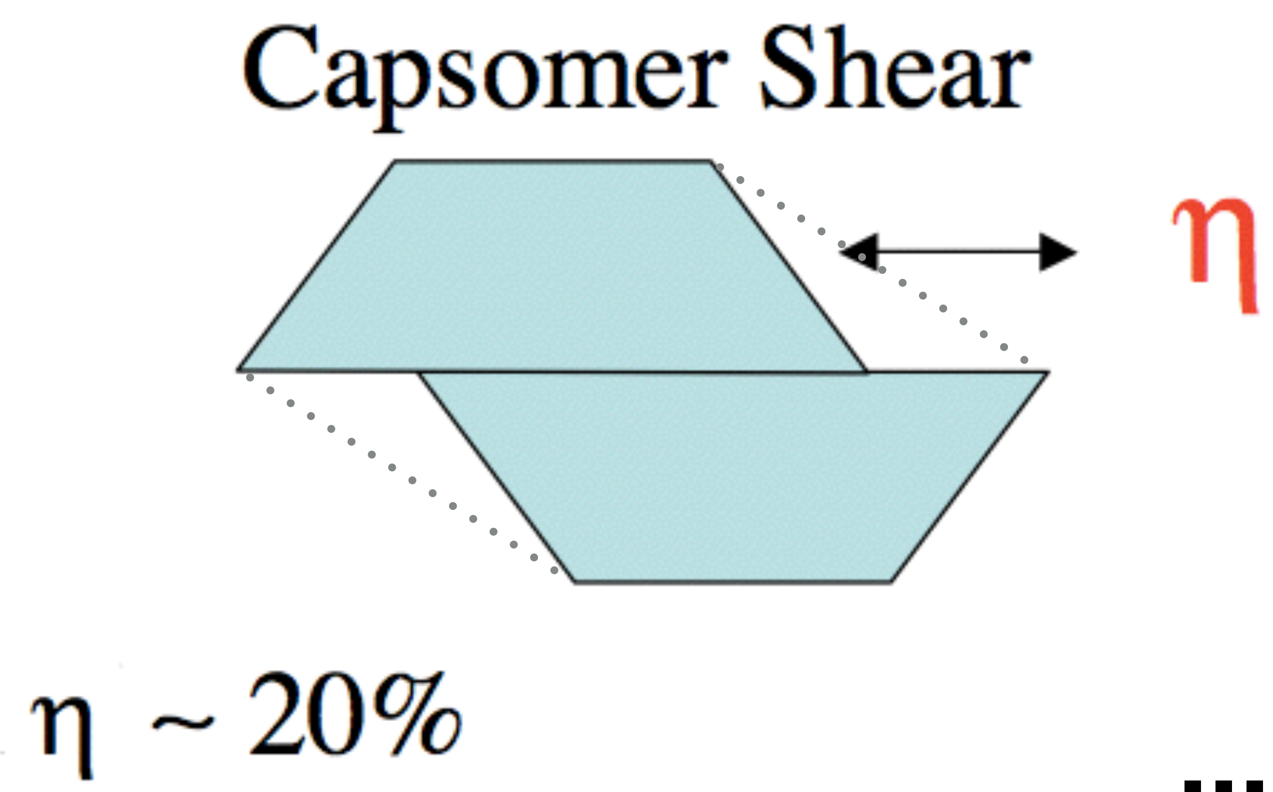
THREE FUNDAMENTAL PROBLEMS

I. **Stored Internal Prestress.**
What is the stress-free reference state?

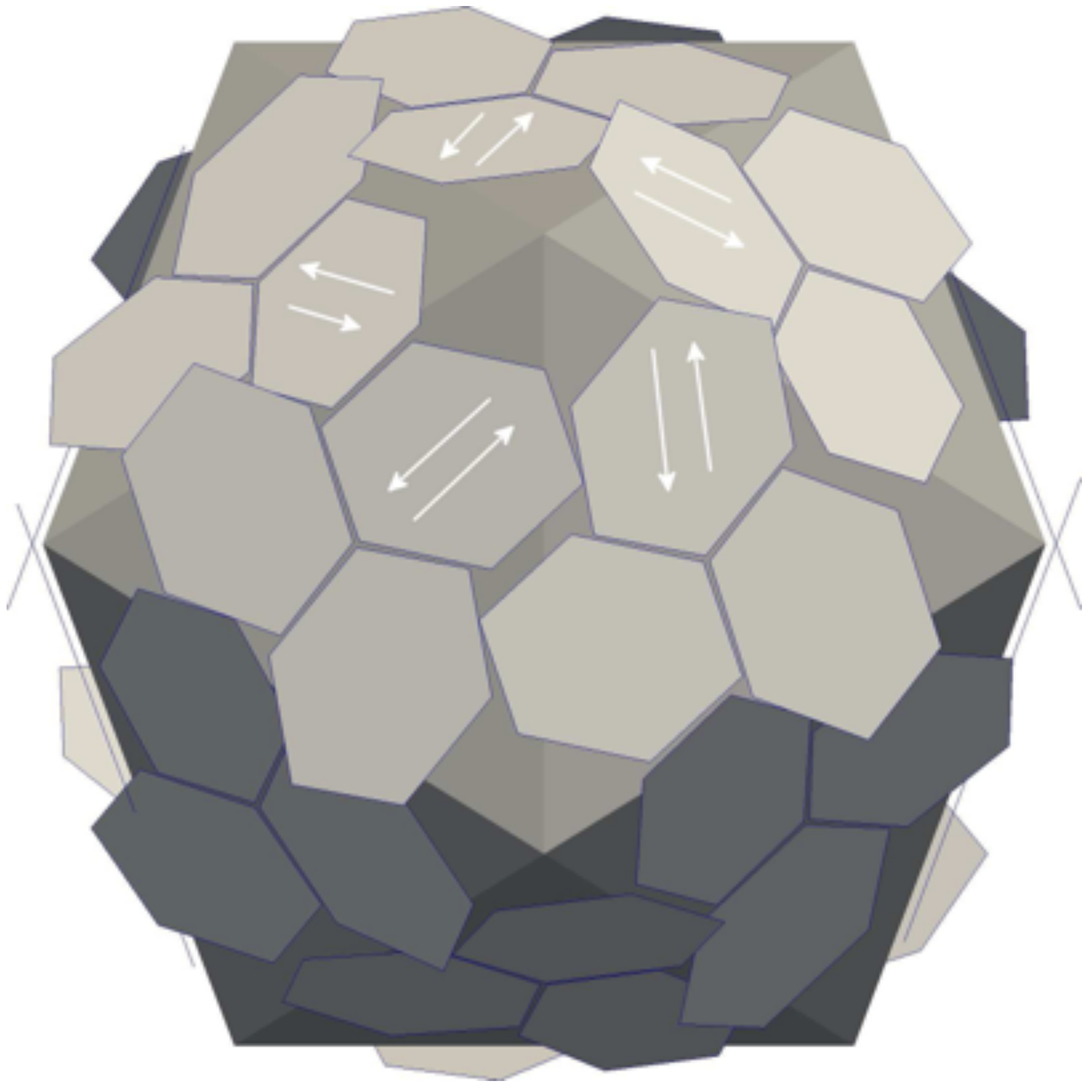


(Gertsman, et. al. 2009)

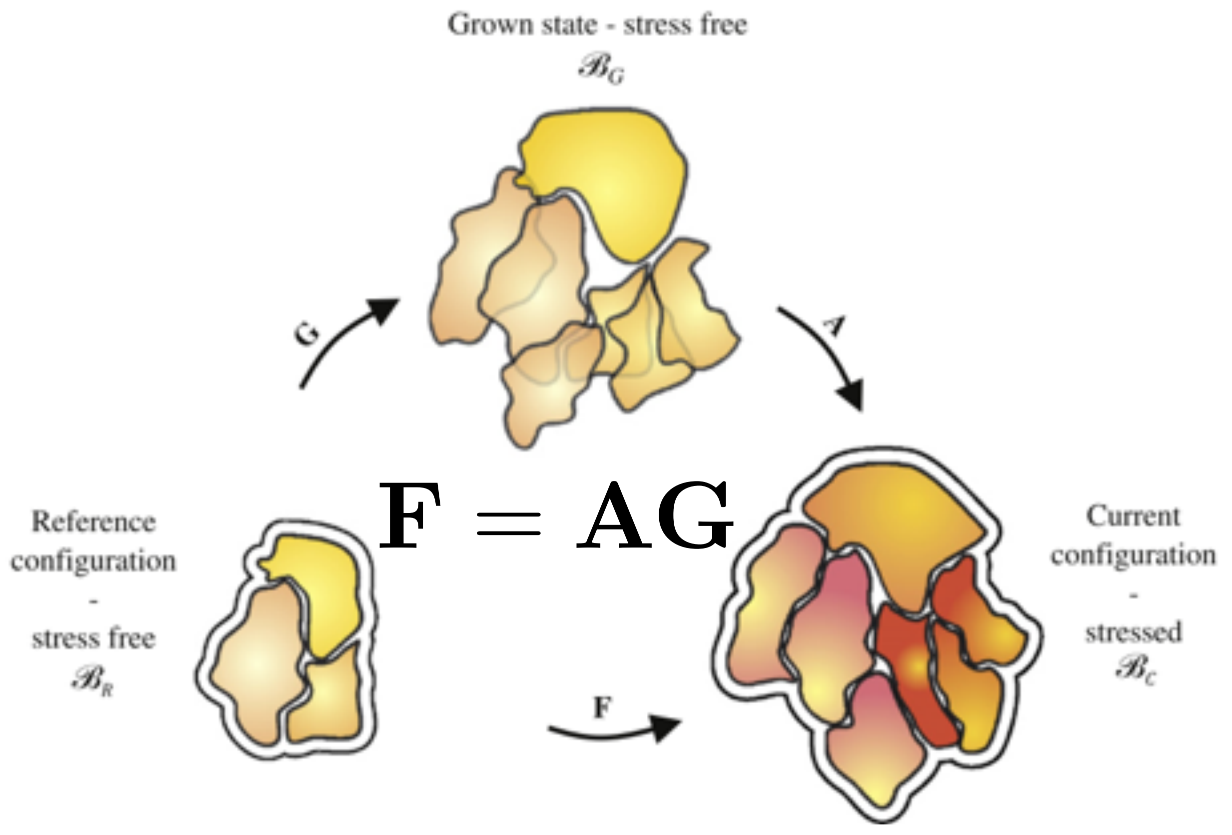
II. **Small Strain Assumption.**
Conformational Shears are large.



III. **Shape Incompatibility**
Sheared capsomers do not fit on a CK shell.



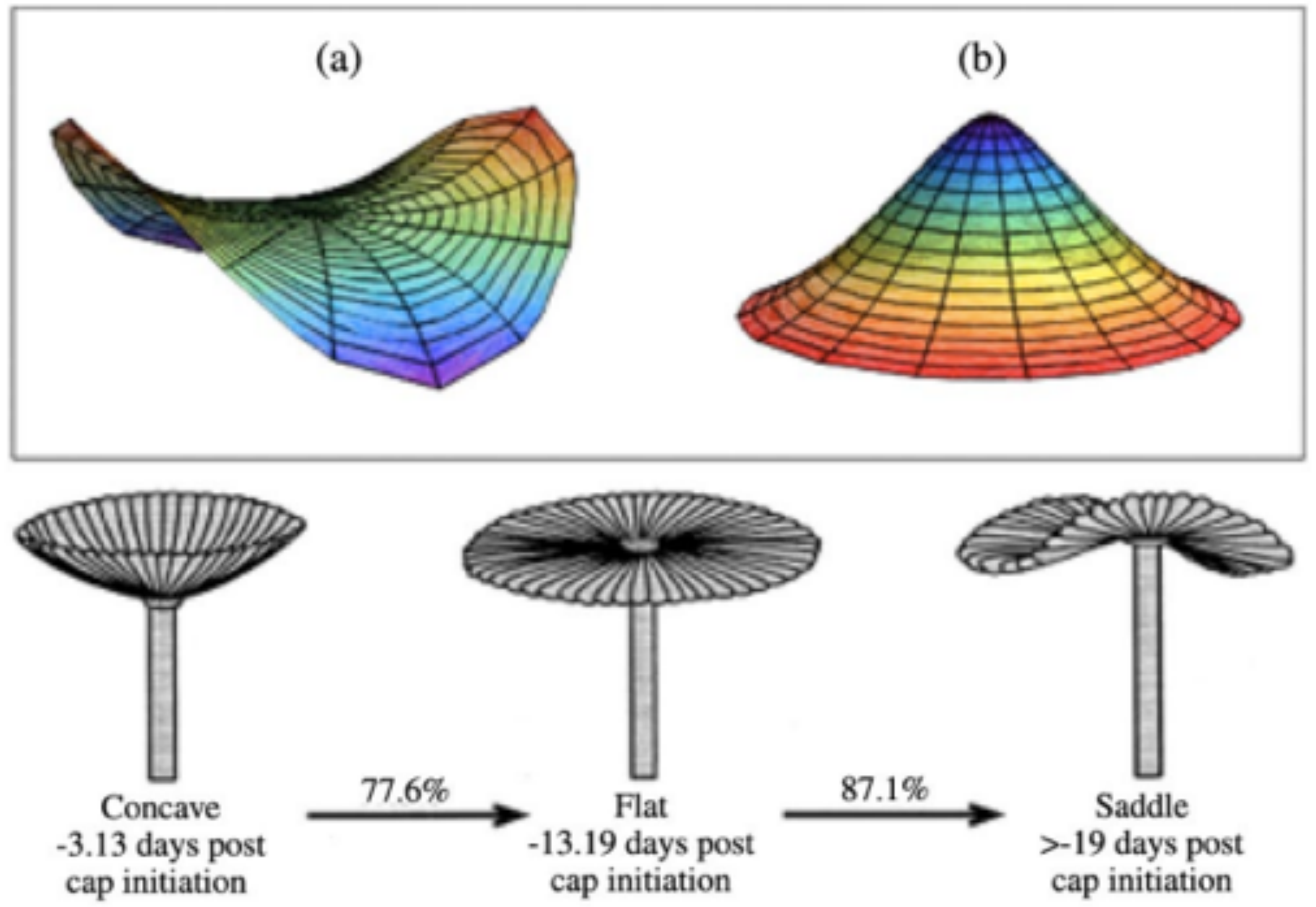
GROWTH/METRIC-INDUCED BUCKLING

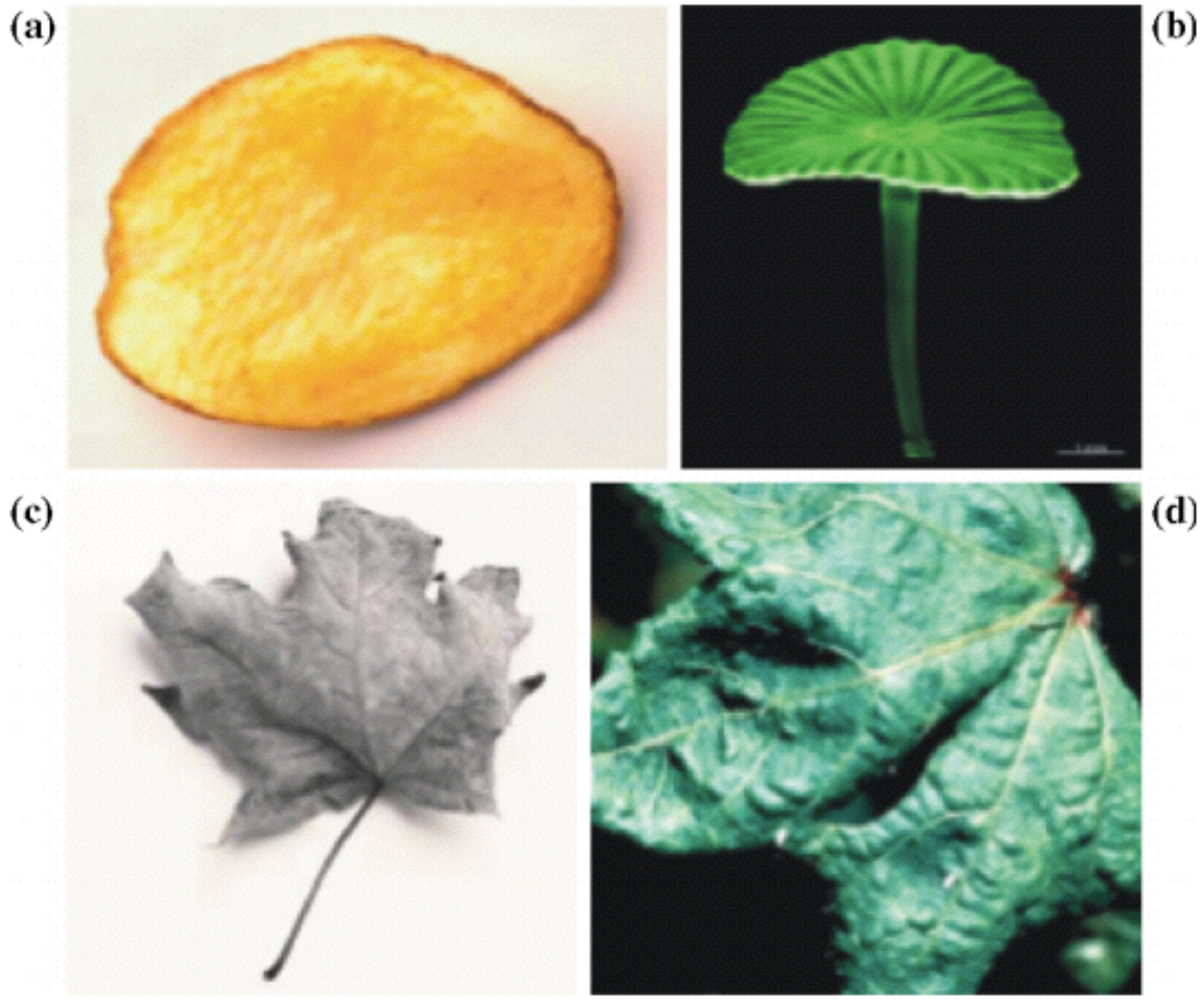


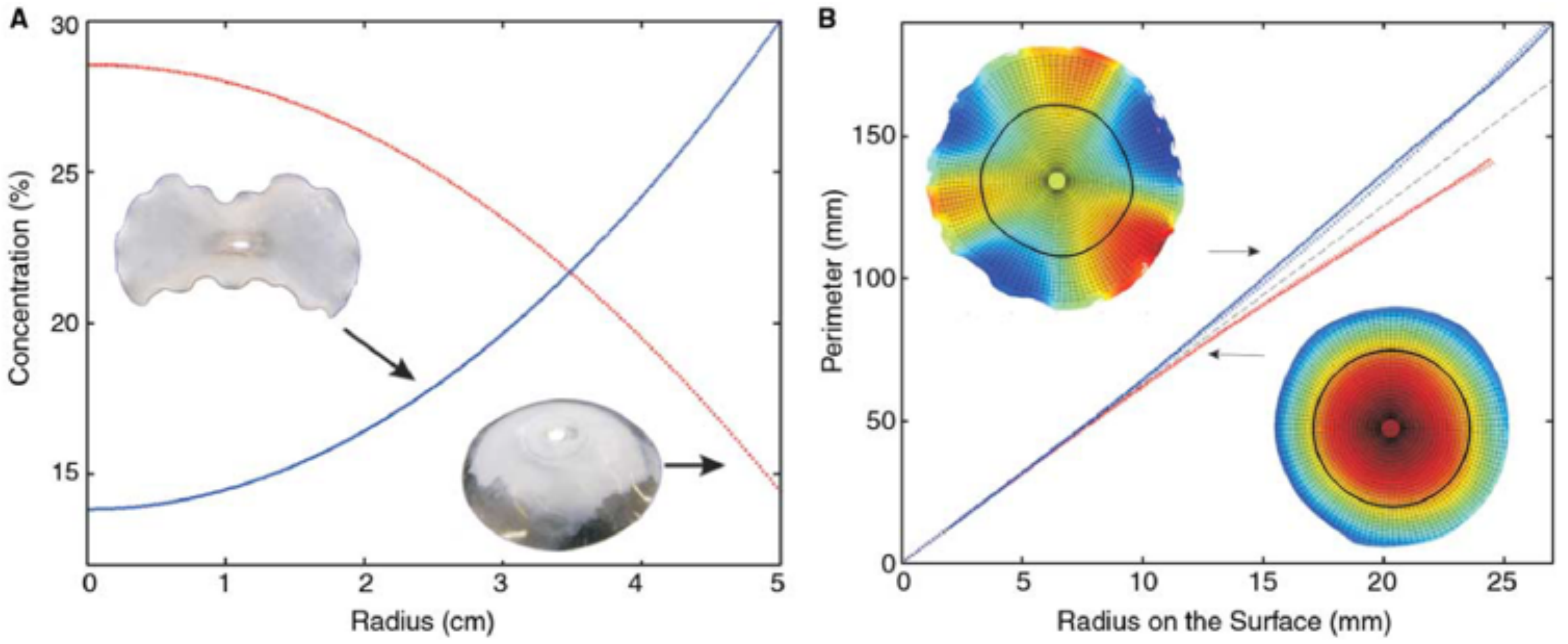
$$\mathbf{F} = \mathbf{A}\mathbf{G}$$

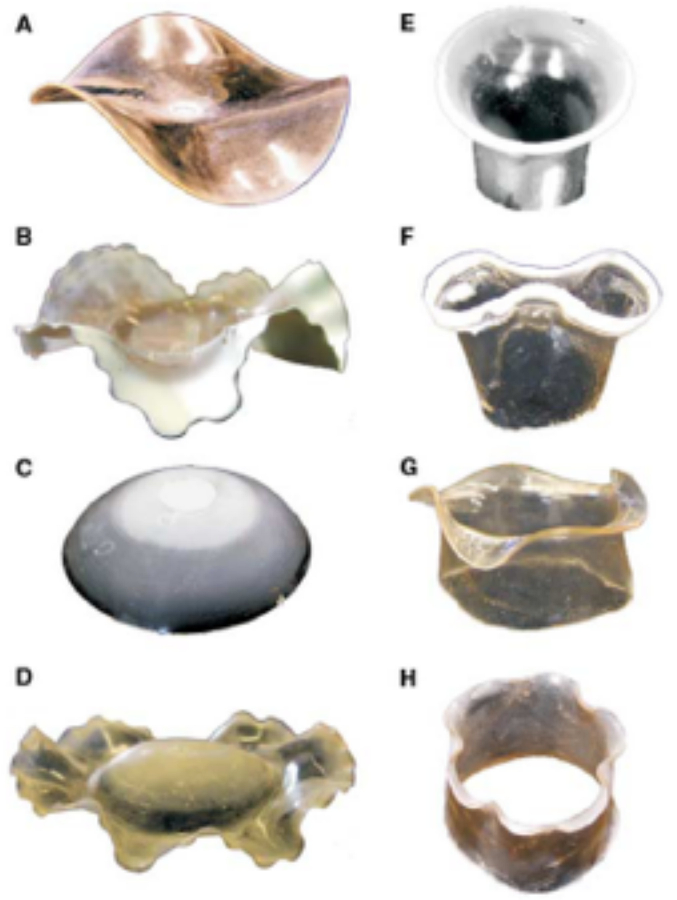
$$\mathcal{E}[\vec{x}] \equiv \int_{\mathcal{B}_G} \mathcal{W}(\mathbf{A})\, dV_G$$

(Dervaux & Ben-Amar, PRL)









(Sharon, et al.)

$$\varepsilon_{ij} = \tfrac{1}{2}(g_{ij} - \bar{g}_{ij}) \qquad w = \frac{1}{2} A^{ijkl} \varepsilon_{ij} \varepsilon_{kl}$$

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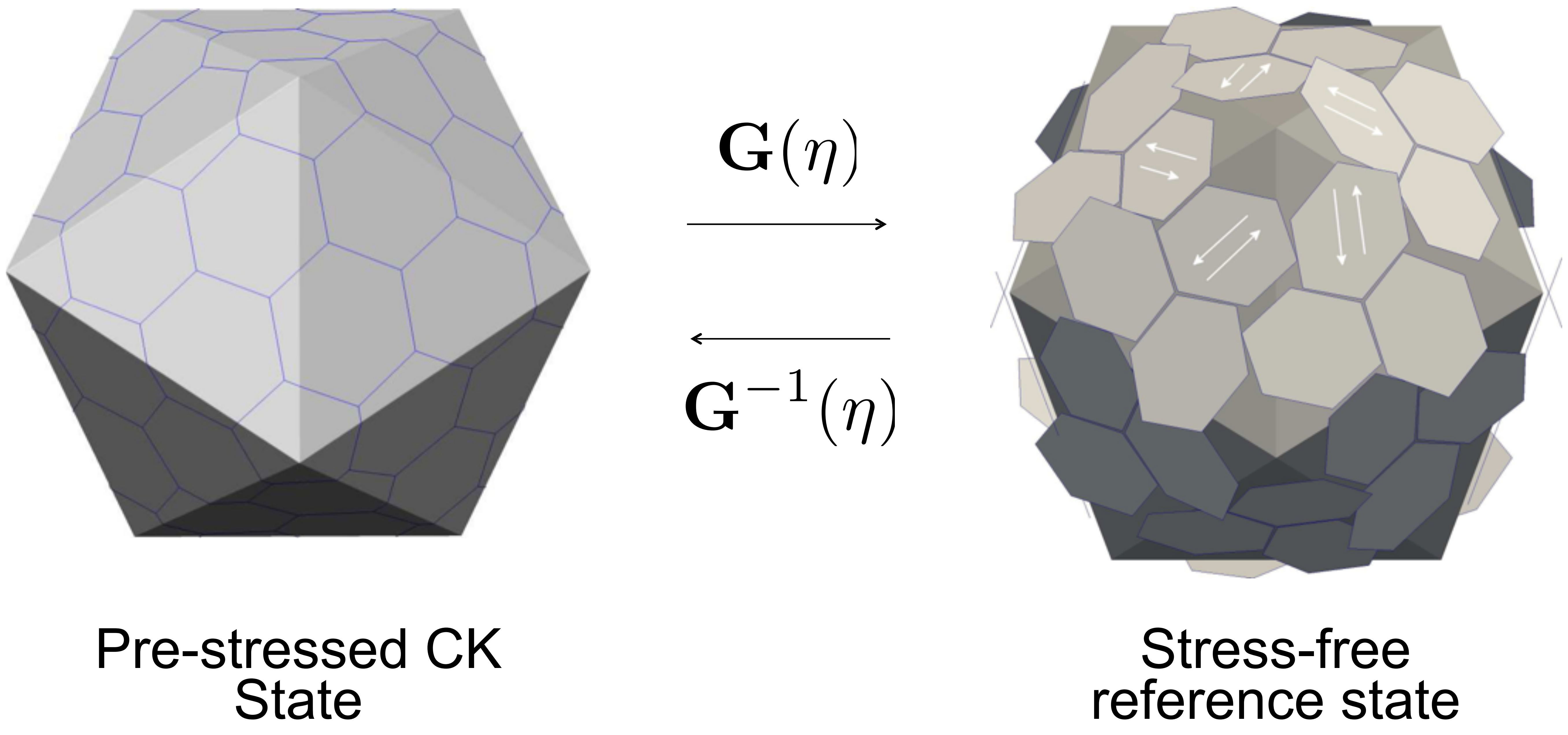
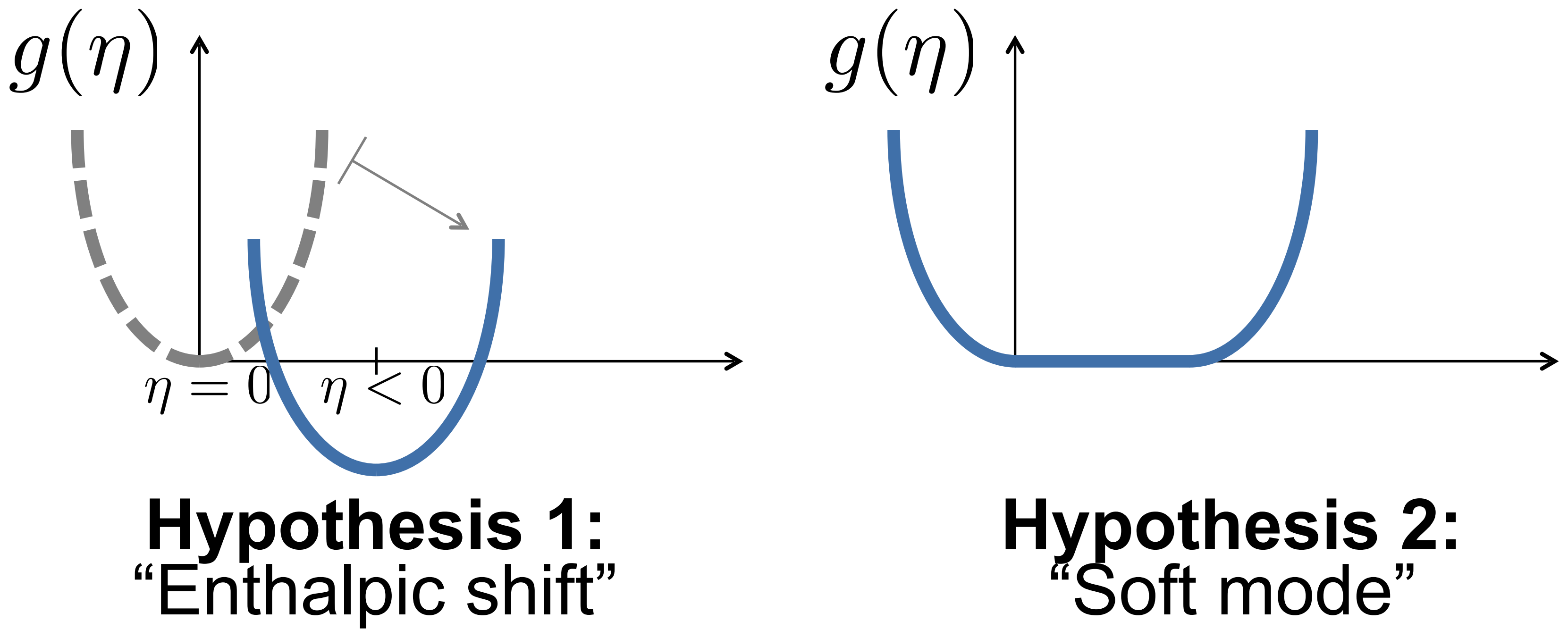
MAP CK CAPSOMERS ONTO NON-INTERACTING CAPSOMERS.

- Internal state of each hexon in isolation may be *INCOMPATIBLE* with assembly
- Energy depends on chemistry (pH, temp, …)



$$g(\eta) = \text{“Landau energy”} \qquad \eta = \text{Internal conformational degrees of freedom}$$



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ELASTICITY REPAIRS CONFORMATIONAL INCOMPATIBILITY

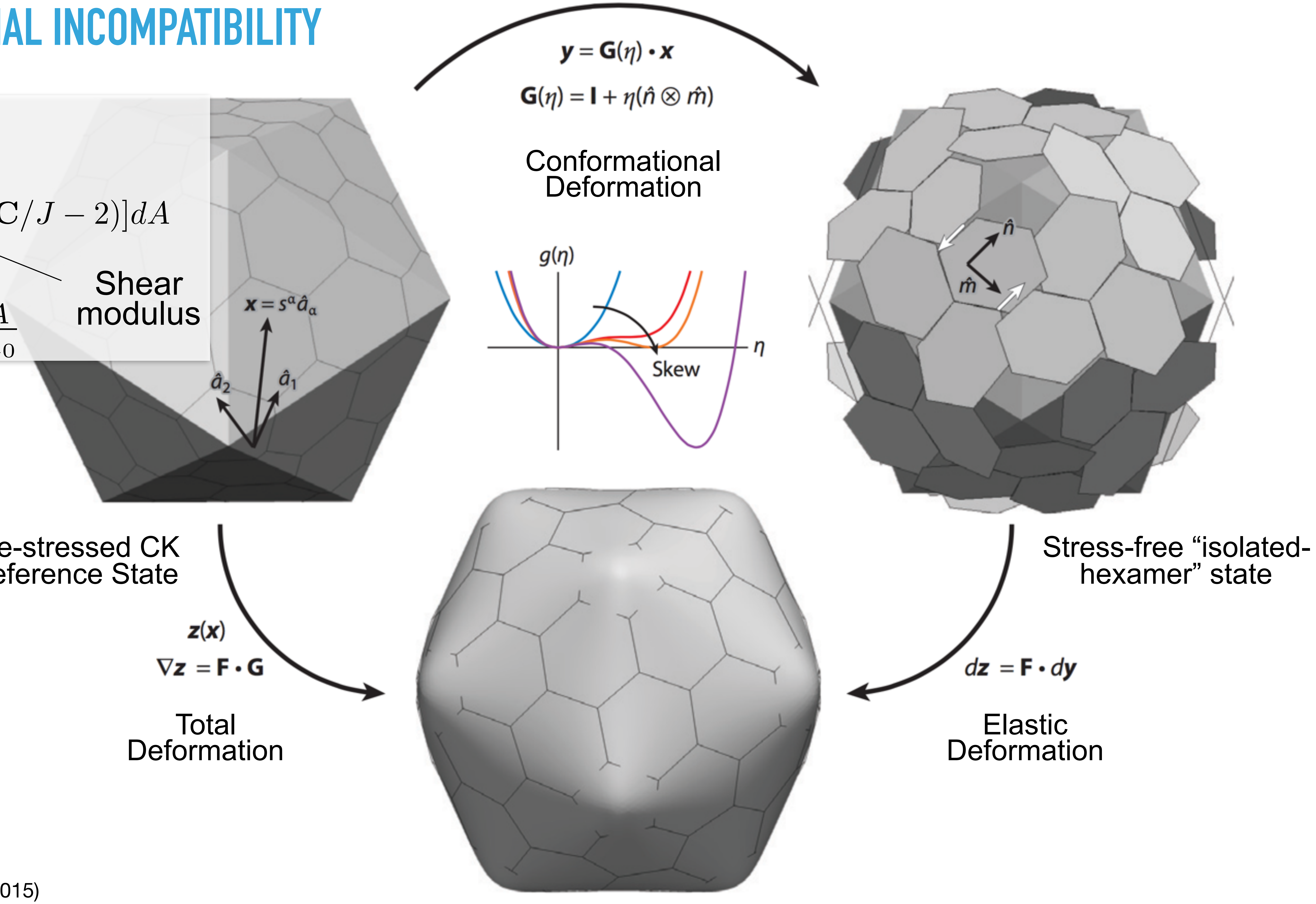
Elastic Energy

$$\mathcal{F} = \int \frac{\kappa}{2} b_{ii}^2 dA + \frac{1}{2} \int [K(J-1)^2 + \mu(\mathrm{tr}\mathbf{C}/J - 2)] dA$$

Compressional modulus

Area ratio $= \det \mathbf{F} = \frac{A}{A_0}$

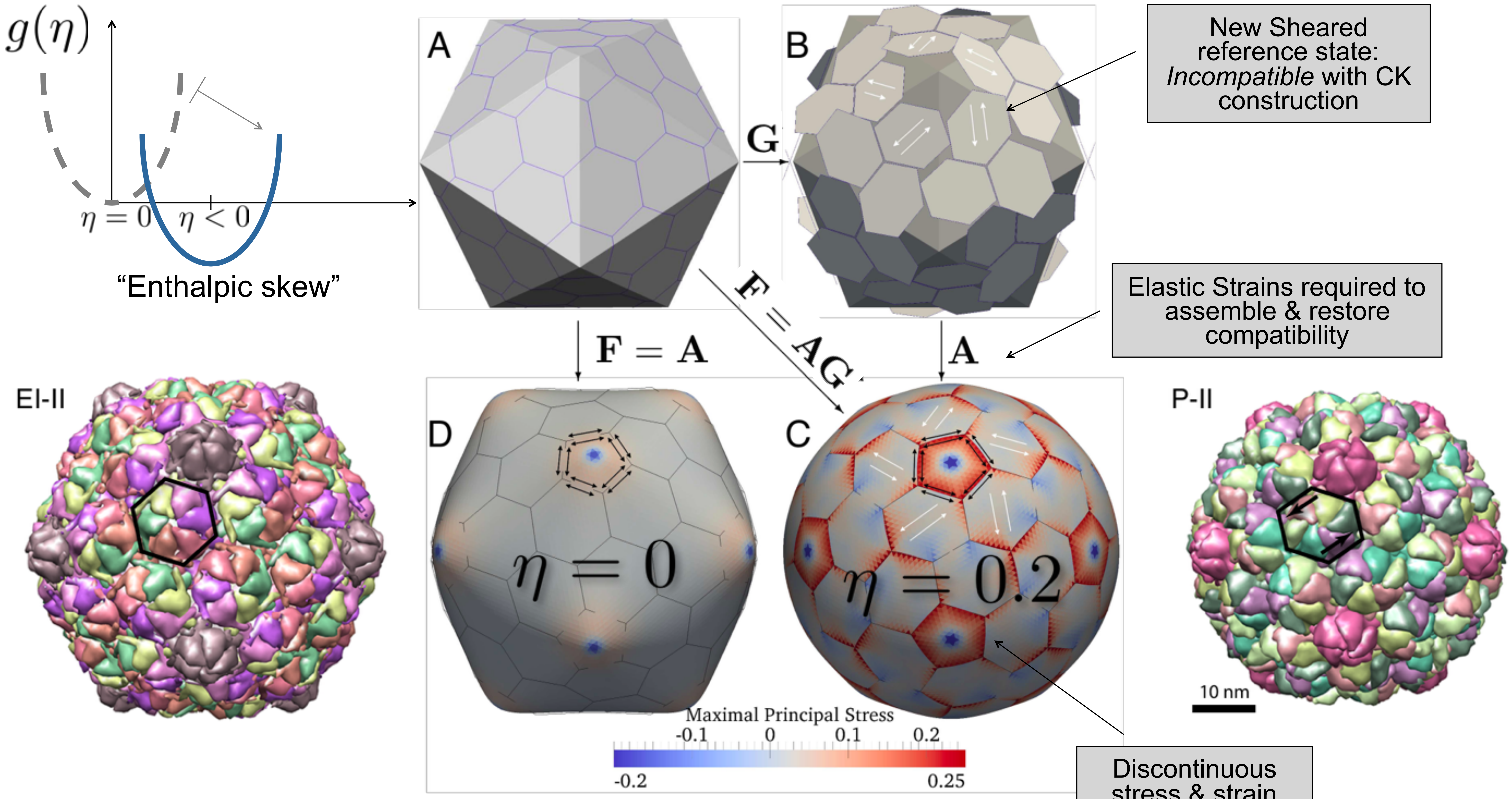
Shear modulus



(Bruinsma and Klug, *Ann Rev Condens Matter Phys*, 2015)

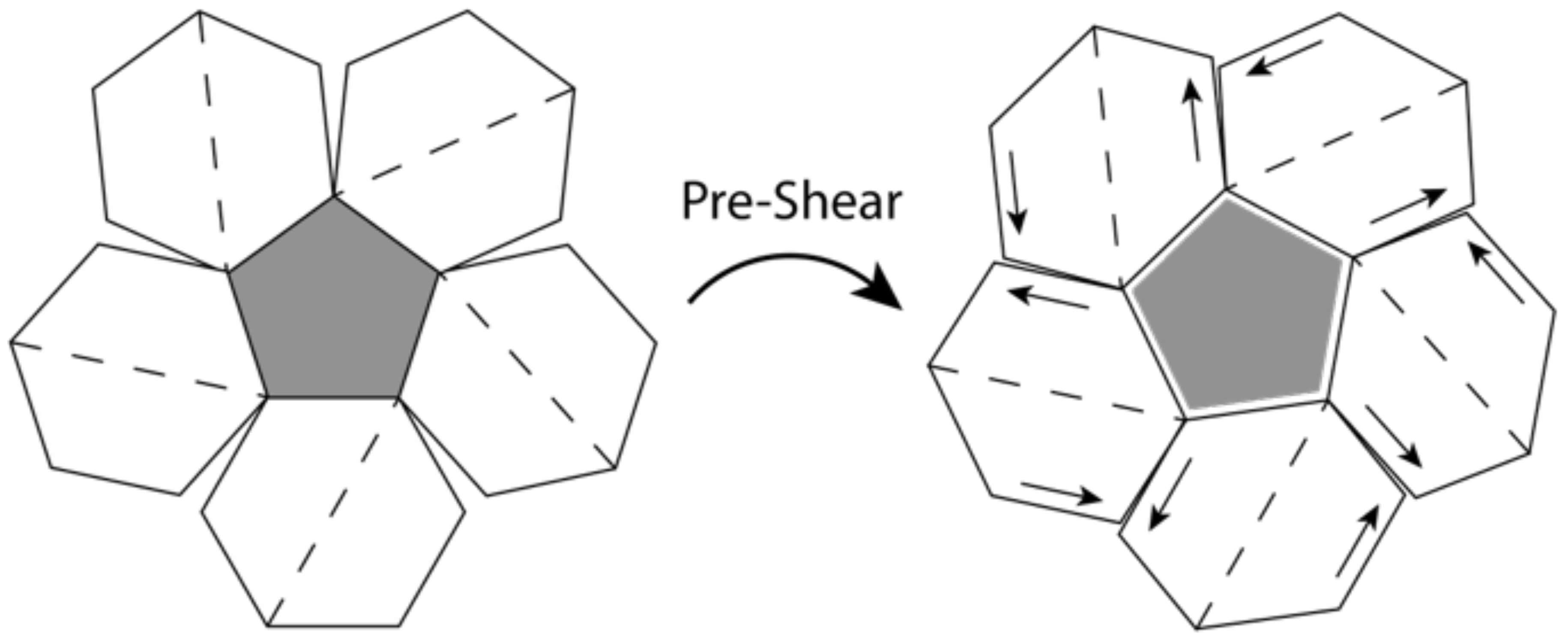
PRE-SHEARED HEXONS DRIVE A "REVERSE BUCKLING TRANSITION"

"Not your mother's thin-shell elasticity theory."
- R. Bruinsma



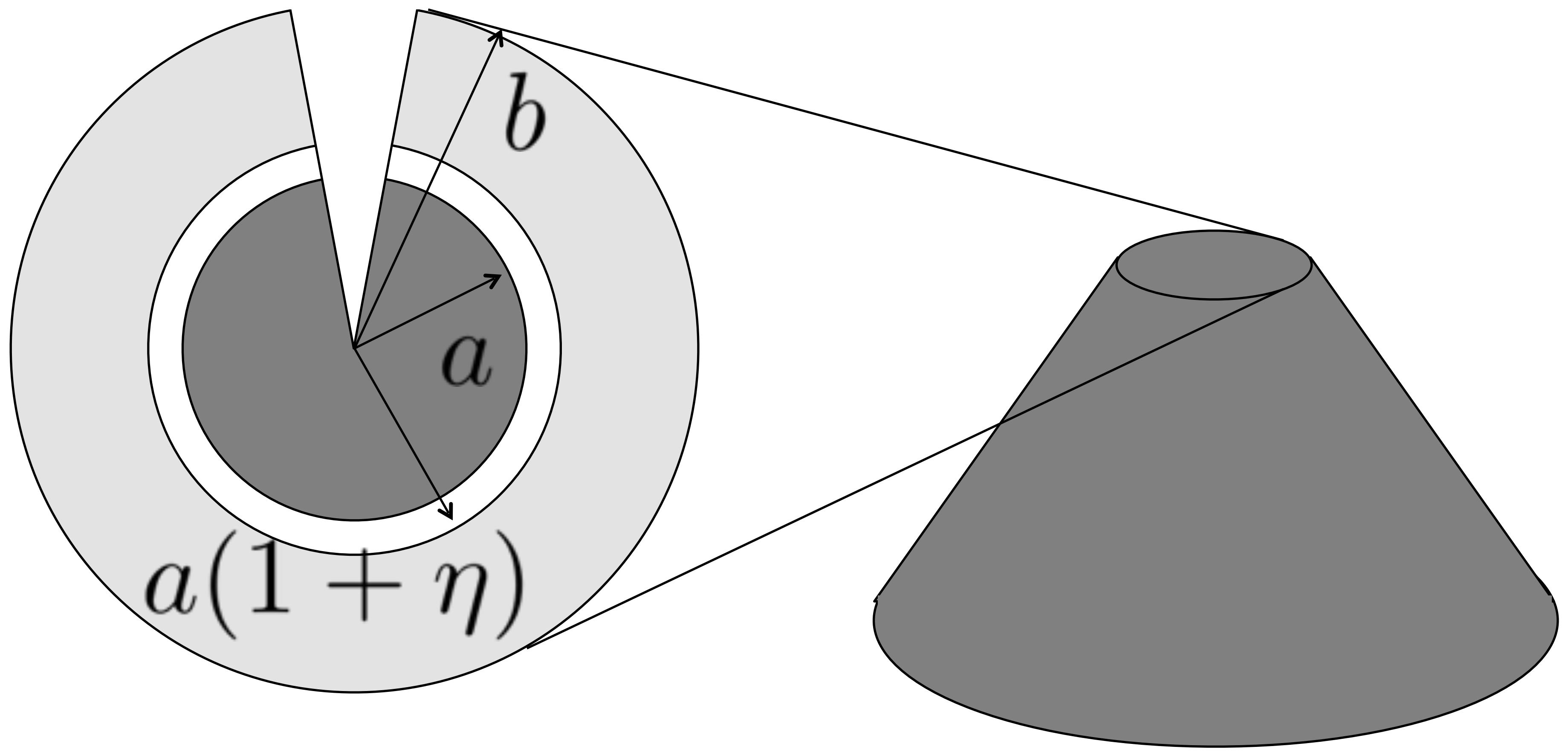
Buckling transition *at fixed FvK number*!

REVERSE BUCKLING TRANSITION – "EFFECTIVE" FVK NUMBER



Pre-shear:

- Changes disclination angle
- Elongates shared pent-hex edges, opens gap between penton and neighboring hexons



- Enforce compatibility to close gaps.

$$\sigma_{rr} = \frac{E\eta}{2}a^2\left(\frac{1}{r^2} - \frac{1}{b^2}\right) + \frac{E\delta}{4\pi}\ln\left(\frac{r}{b}\right)$$

$$\sigma_{\theta\theta} = \frac{E\eta}{2}a^2\left(-\frac{1}{r^2} - \frac{1}{b^2}\right) + \frac{E\delta}{4\pi}\left(\ln\frac{r}{b} + 1\right)$$

- As disc grows, eventually plate can alleviate in-plane strain by buckling into a conical shape.

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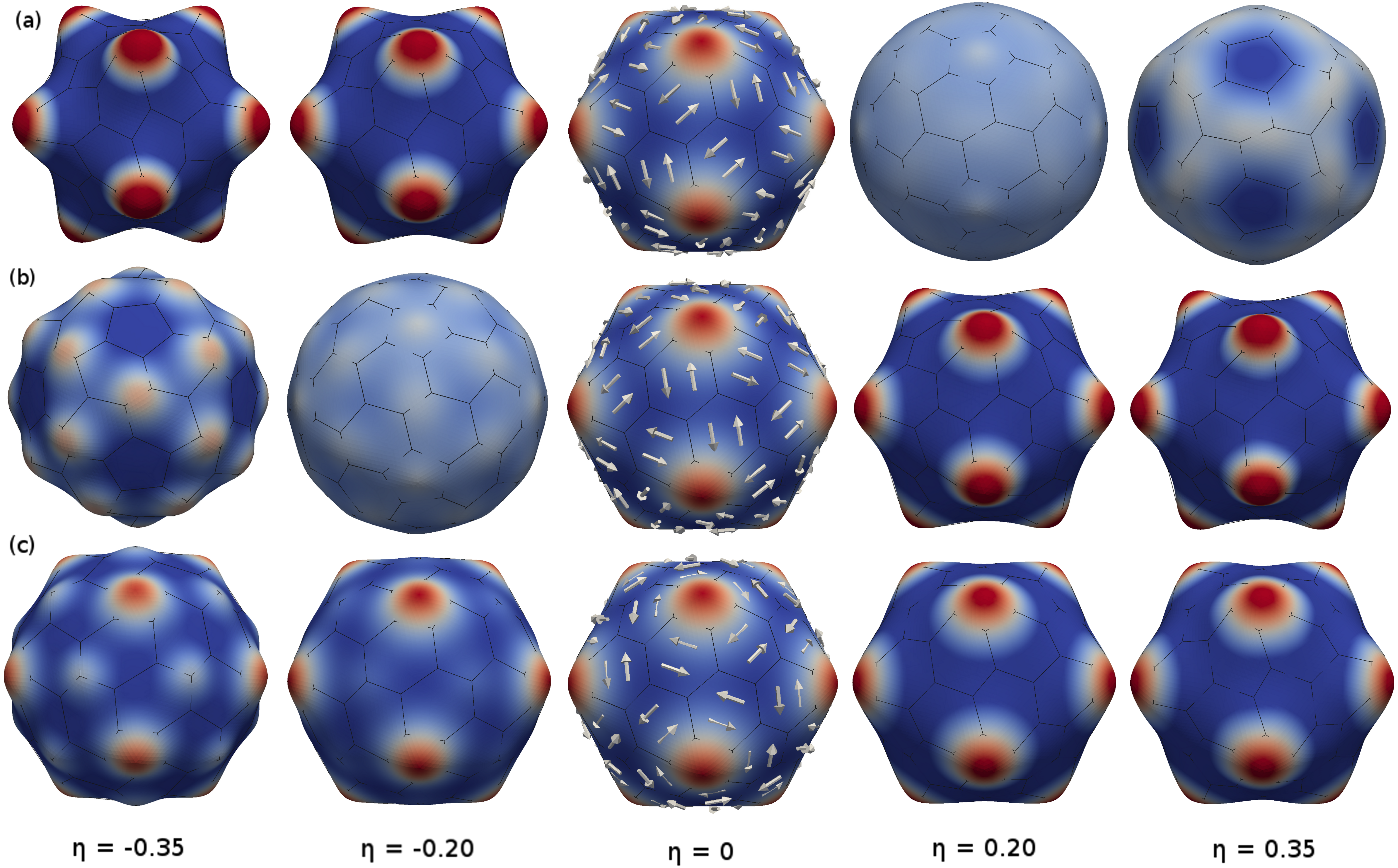
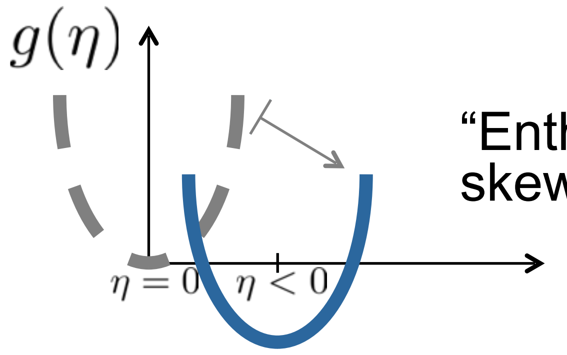
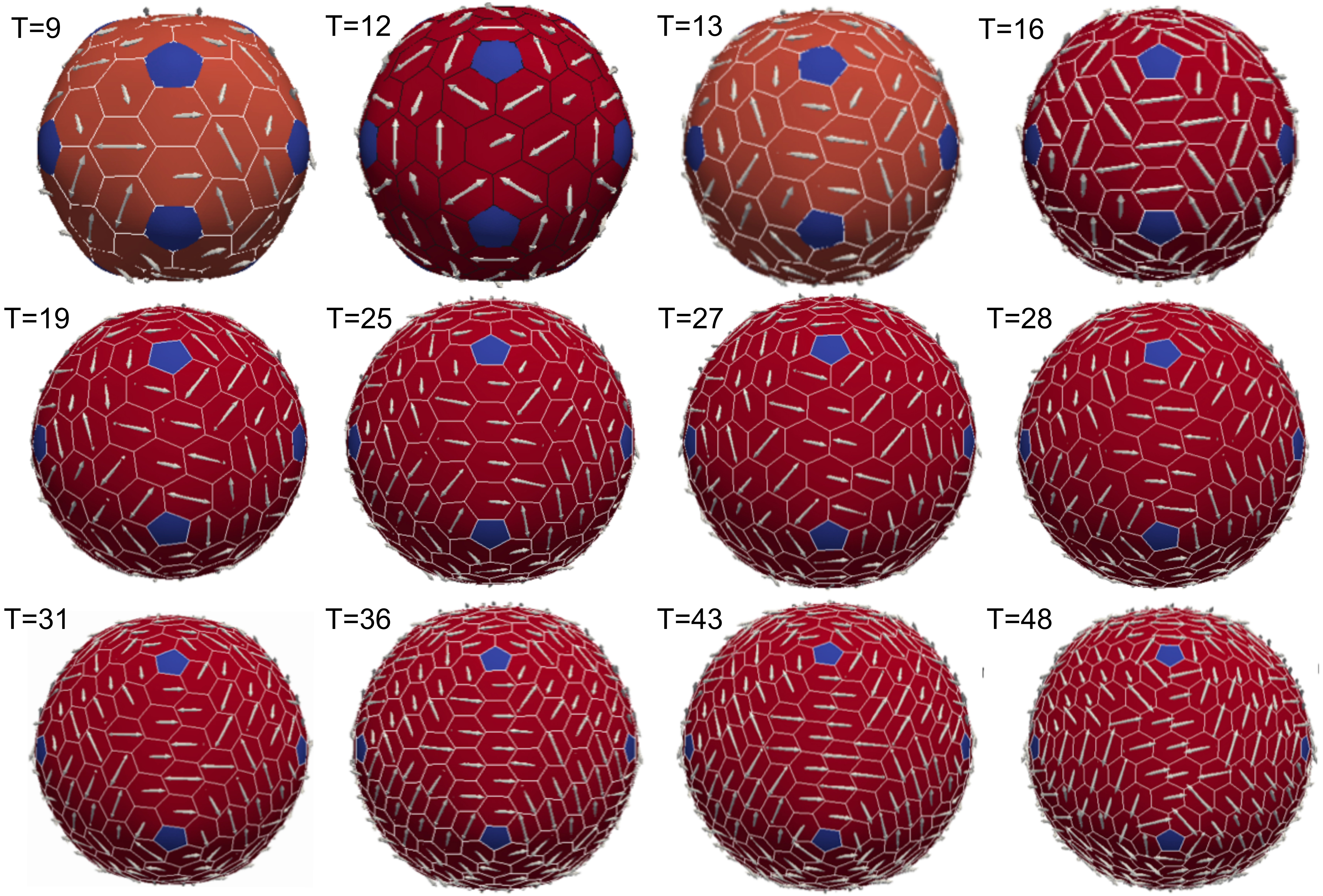
NEW SHAPES



UCLA

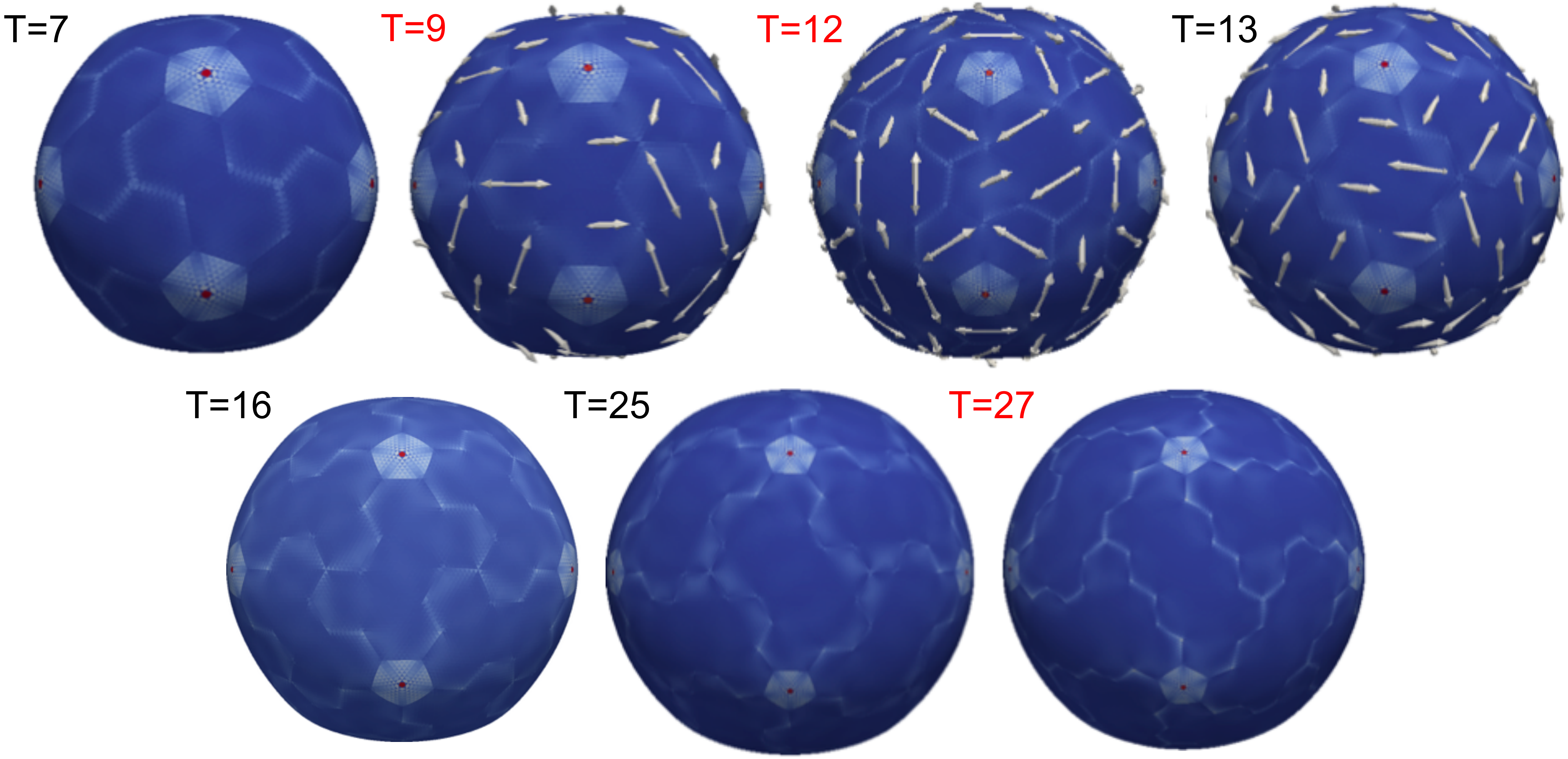
T>7


$g(\eta)$
"Enthalpic skew"
$\eta = 0$
$\eta < 0$


T=9
T=12
T=13
T=16
T=19
T=25
T=27
T=28
T=31
T=36
T=43
T=48

CRYSTALLINE DOMAINS

(STRAIN/STRESS CONTOURS SHOW DISCONTINUITIES AT GRAIN BOUNDARIES)



Hexon @ 3-fold site: icosahedral symmetry broken necessarily

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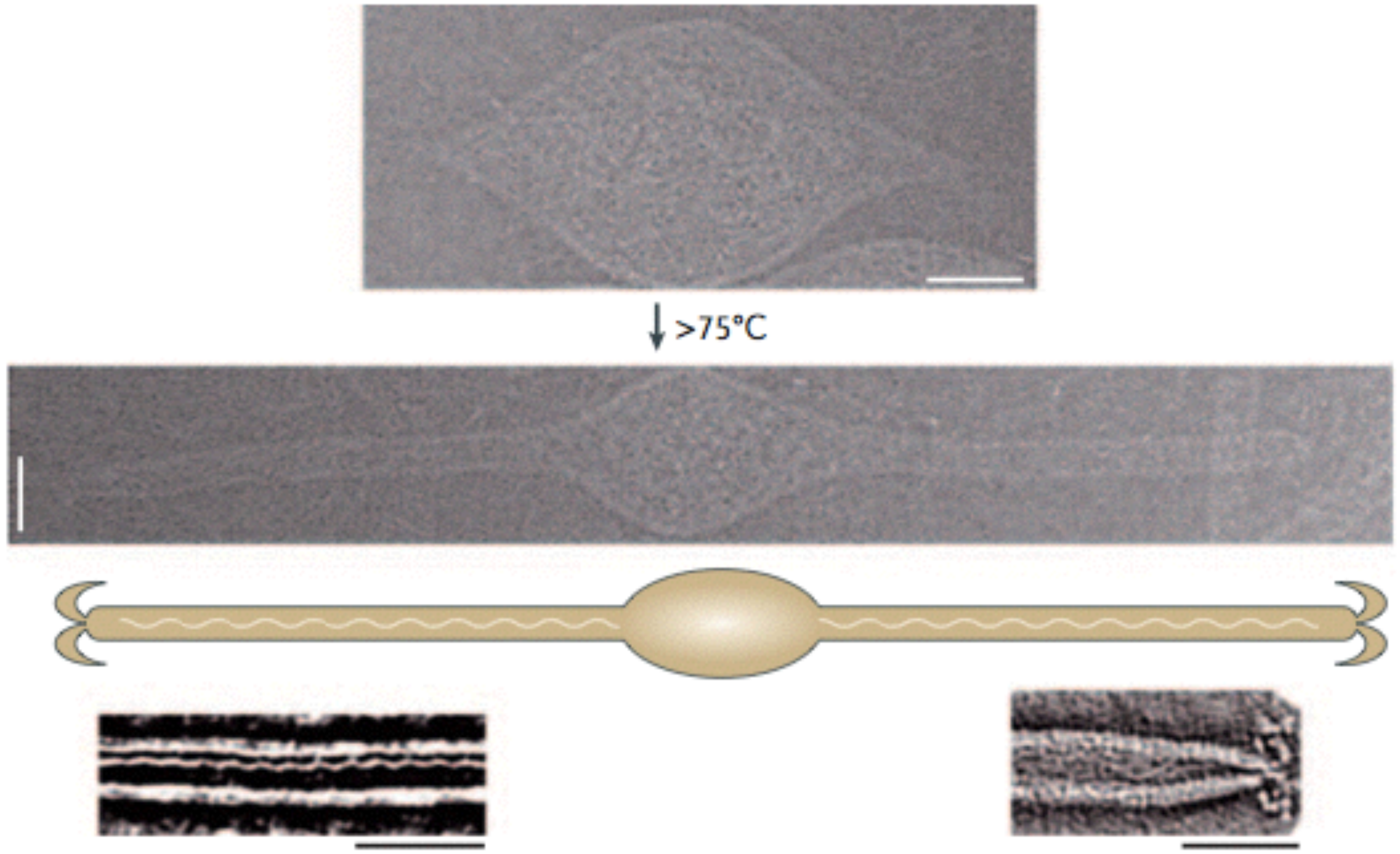
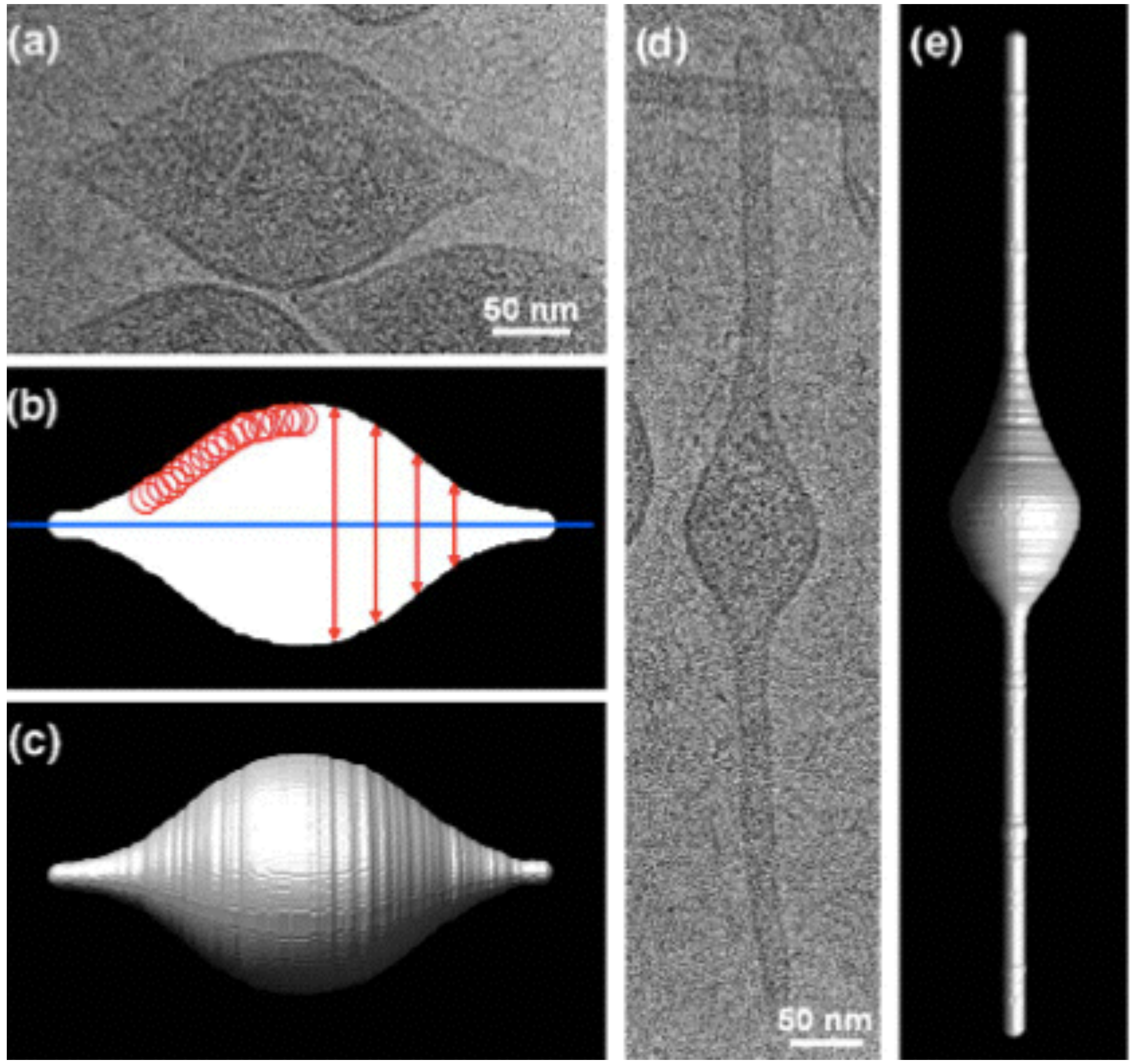
A "SPINDLE-SHAPED" VIRUS ATV





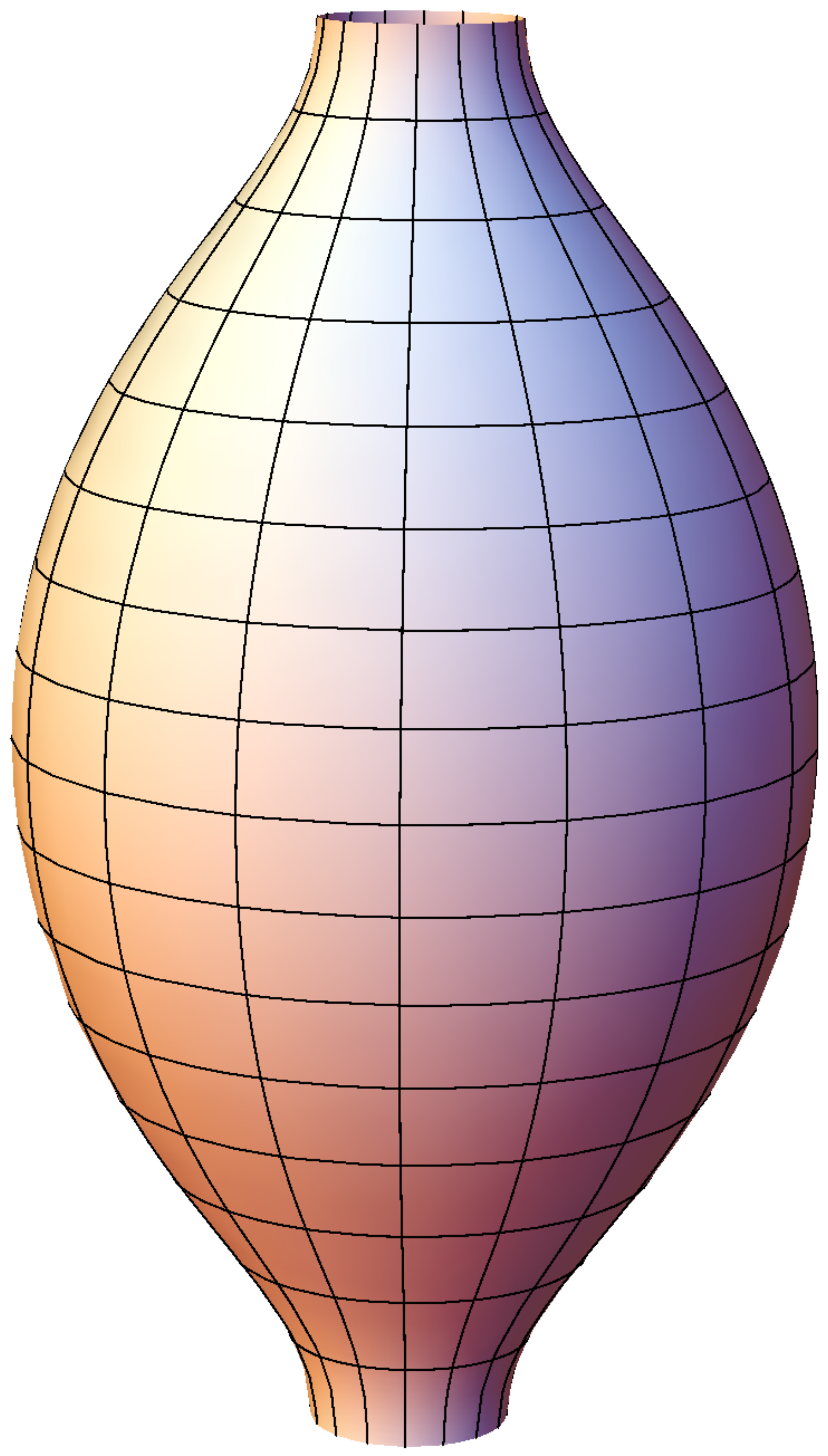
(D. Prangishvili, G. Vestergaard, and M. Häring, J Molec Biol, 2006)

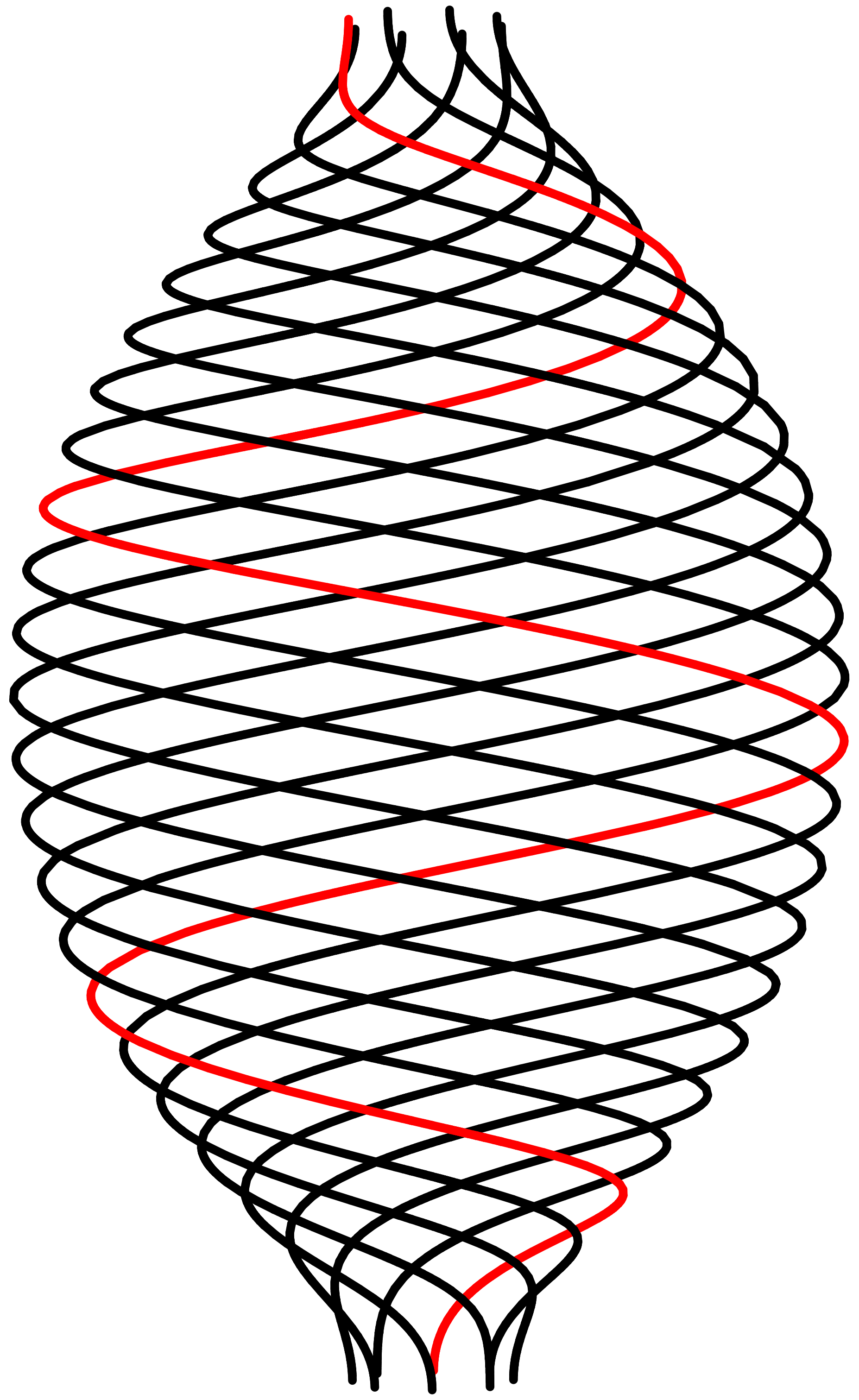
What is the local structure? What is the physics?

A FLUID MEMBRANE MODEL

Unduloid Construction Surface of revolution of an elliptic catenary (constant nonzero mean curvature)

$$\Delta p = \gamma \left(\frac{1}{R_1} + \frac{1}{R_2} \right)$$





(Perotti, et al., submitted)

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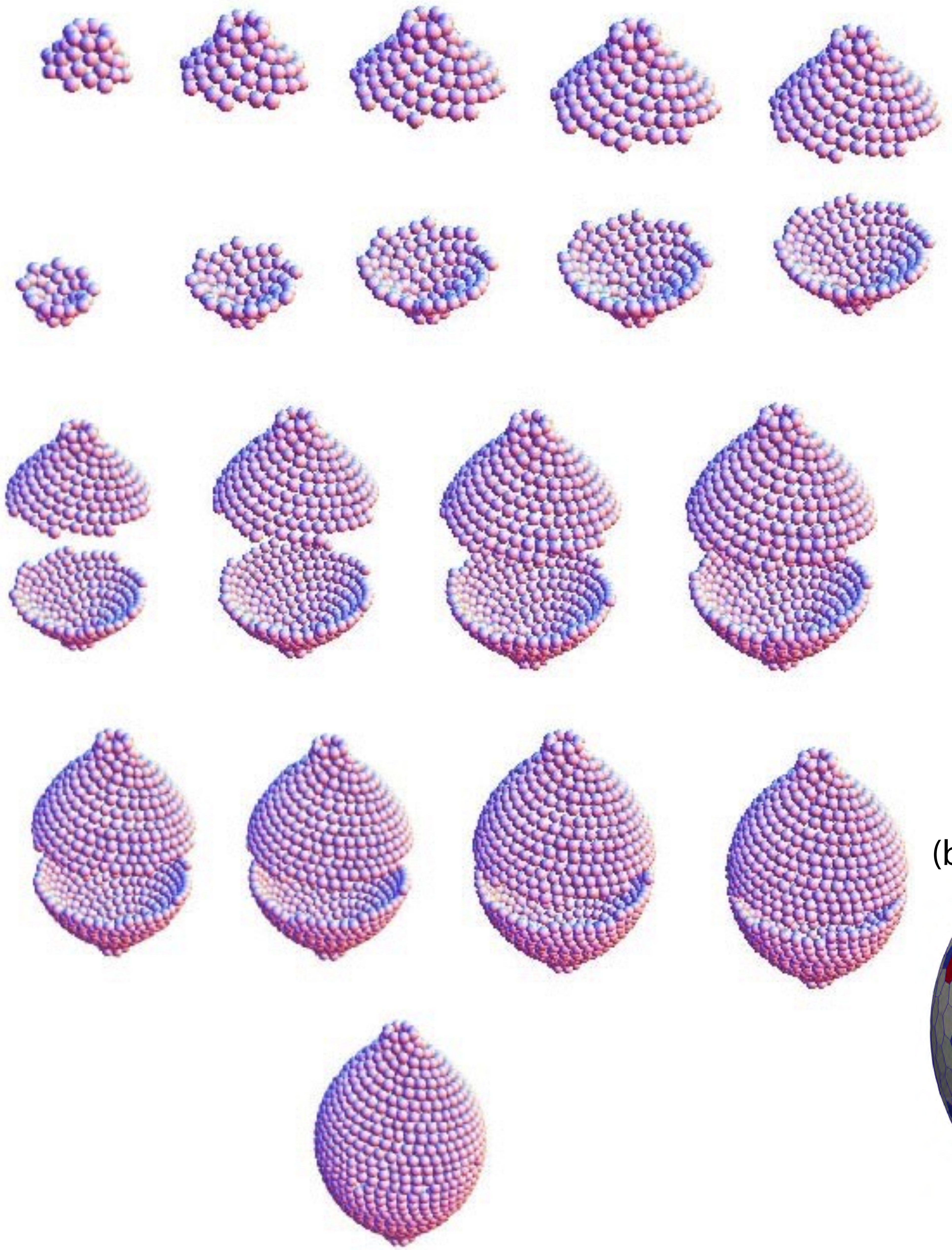

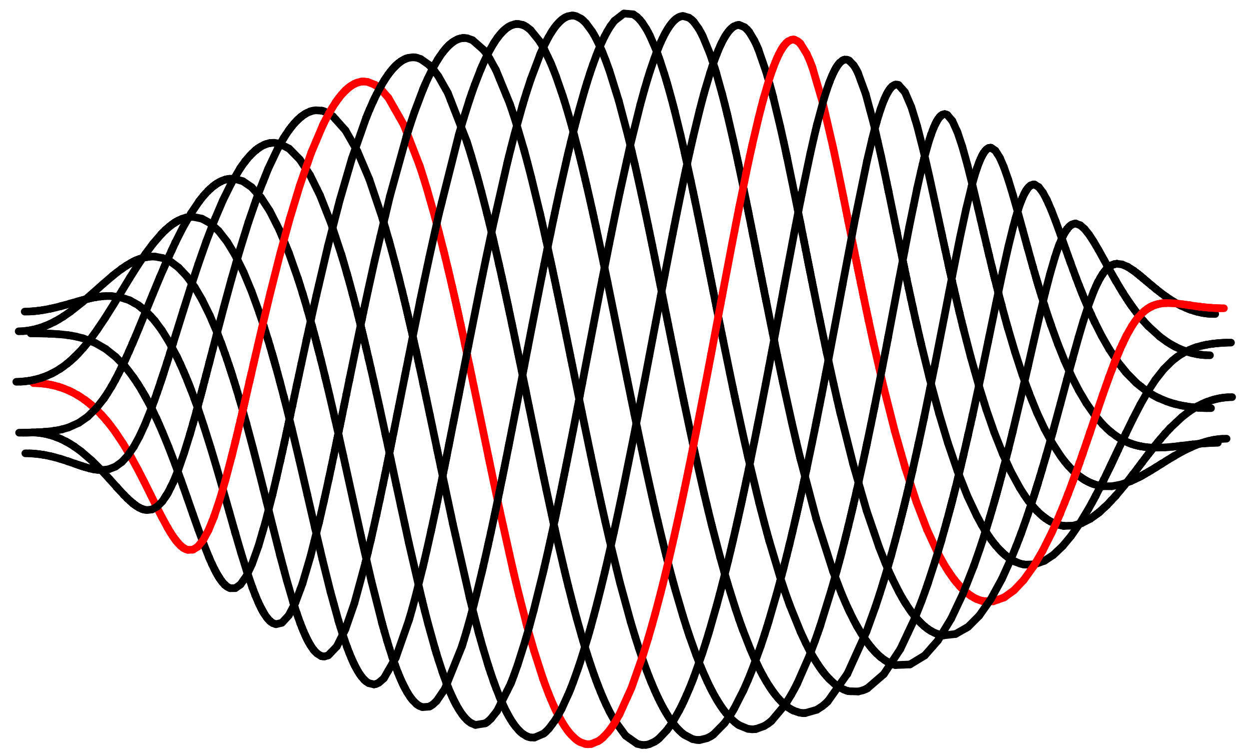

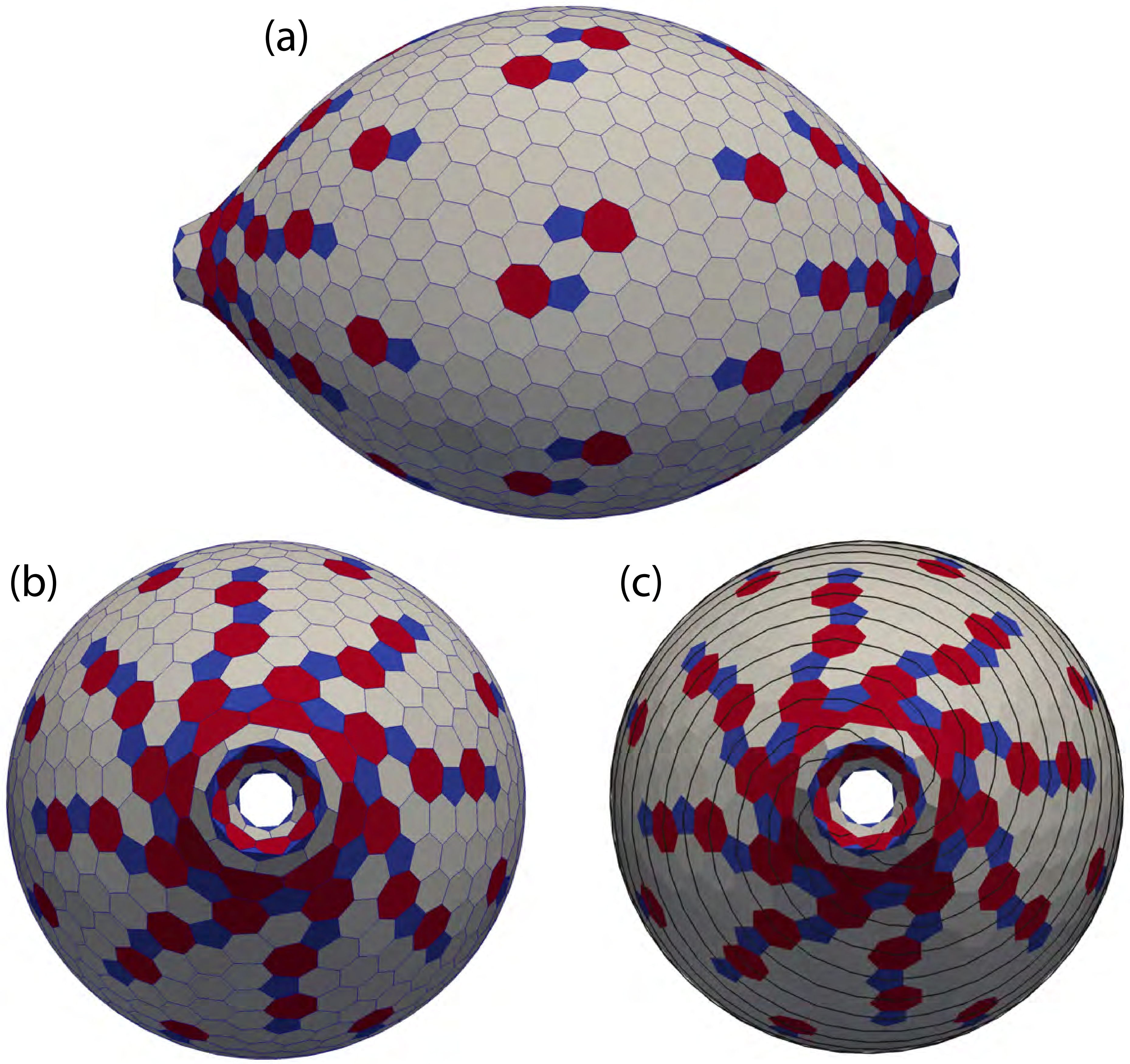

(Perotti, et al., submitted)

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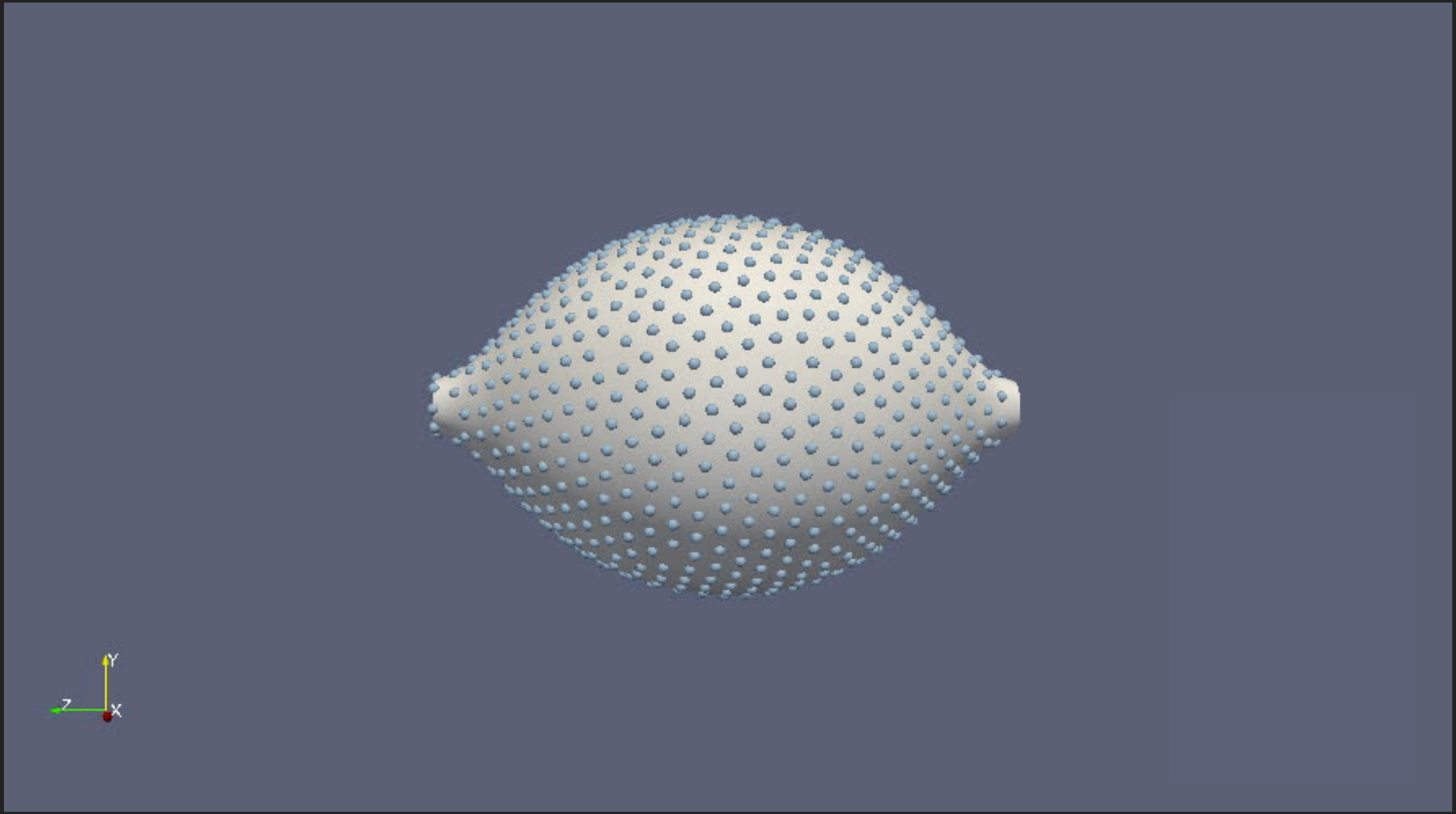
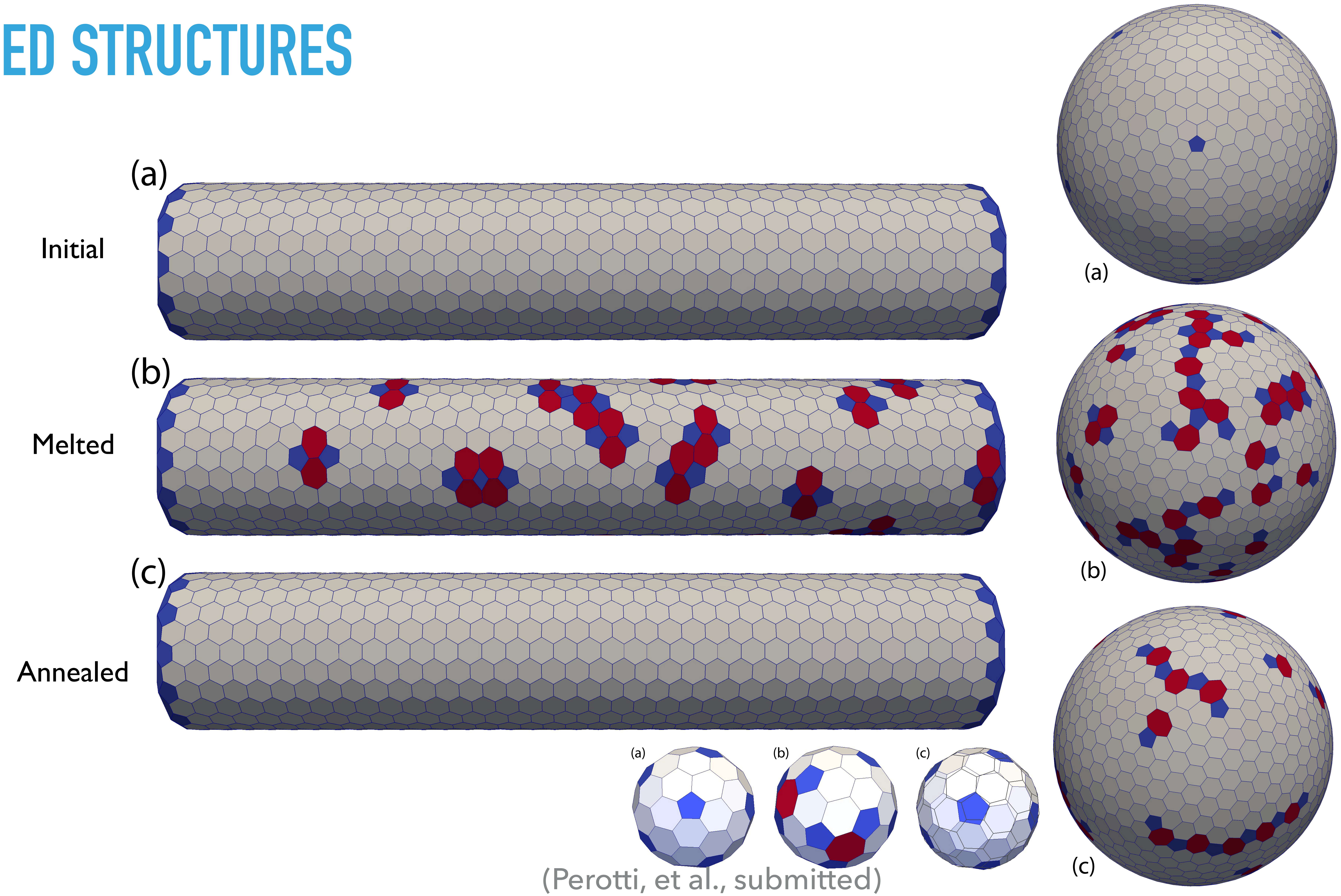
ANNEALING



ANNEALED STRUCTURES

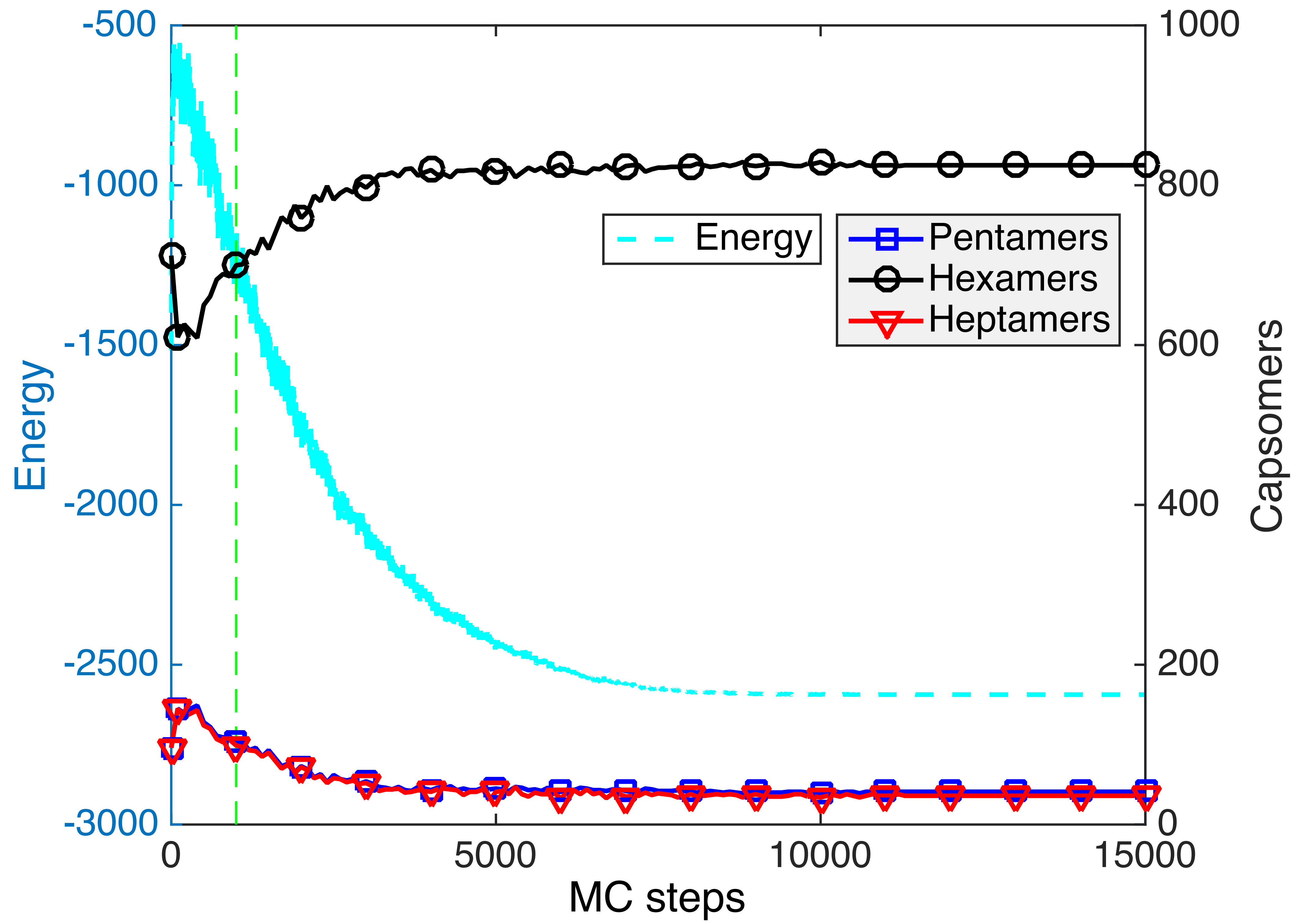


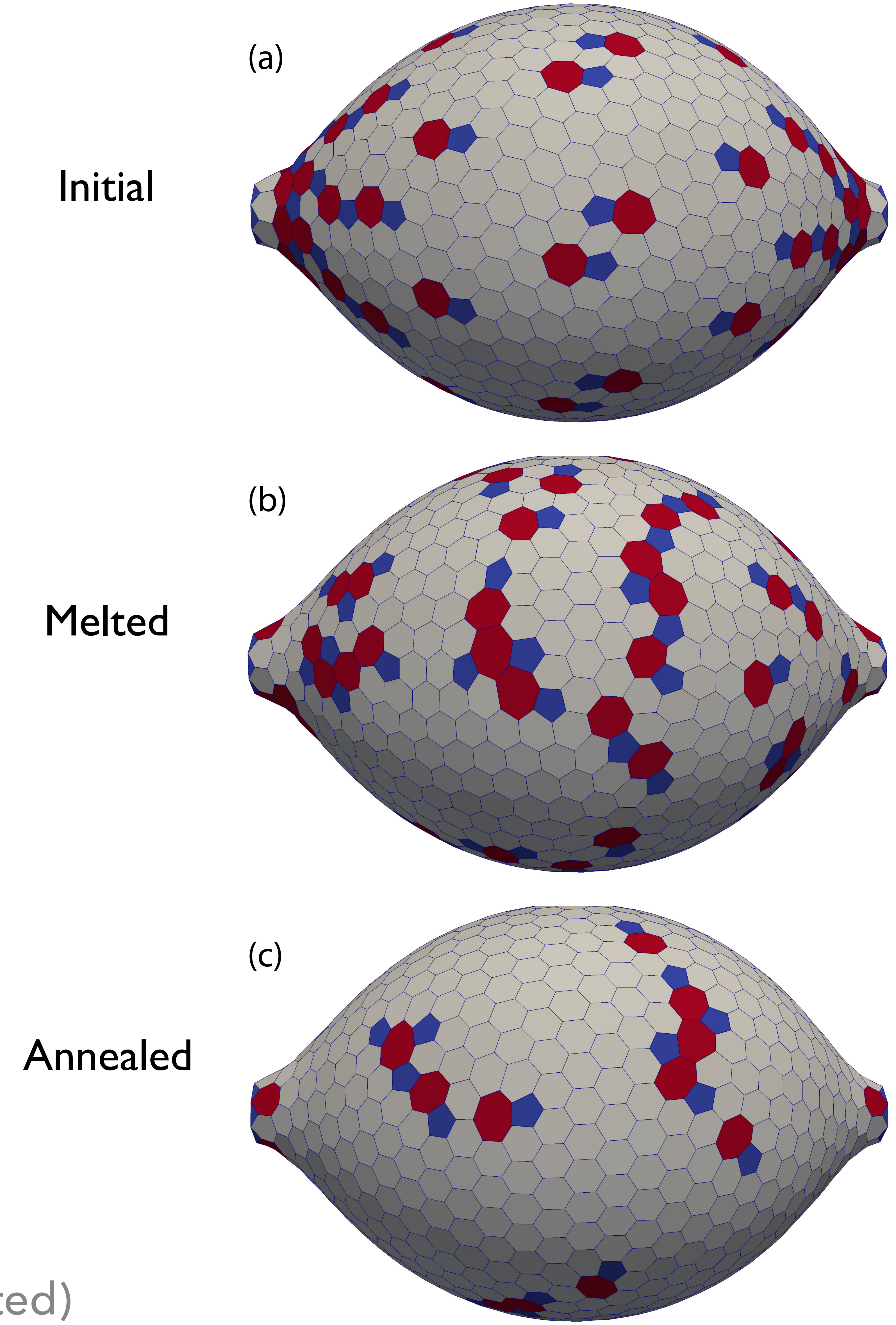
(Perotti, et al., submitted)

ANNEALED STRUCTURES

Monte Carlo simulation of Lennard-Jones Particles on unduloid surface

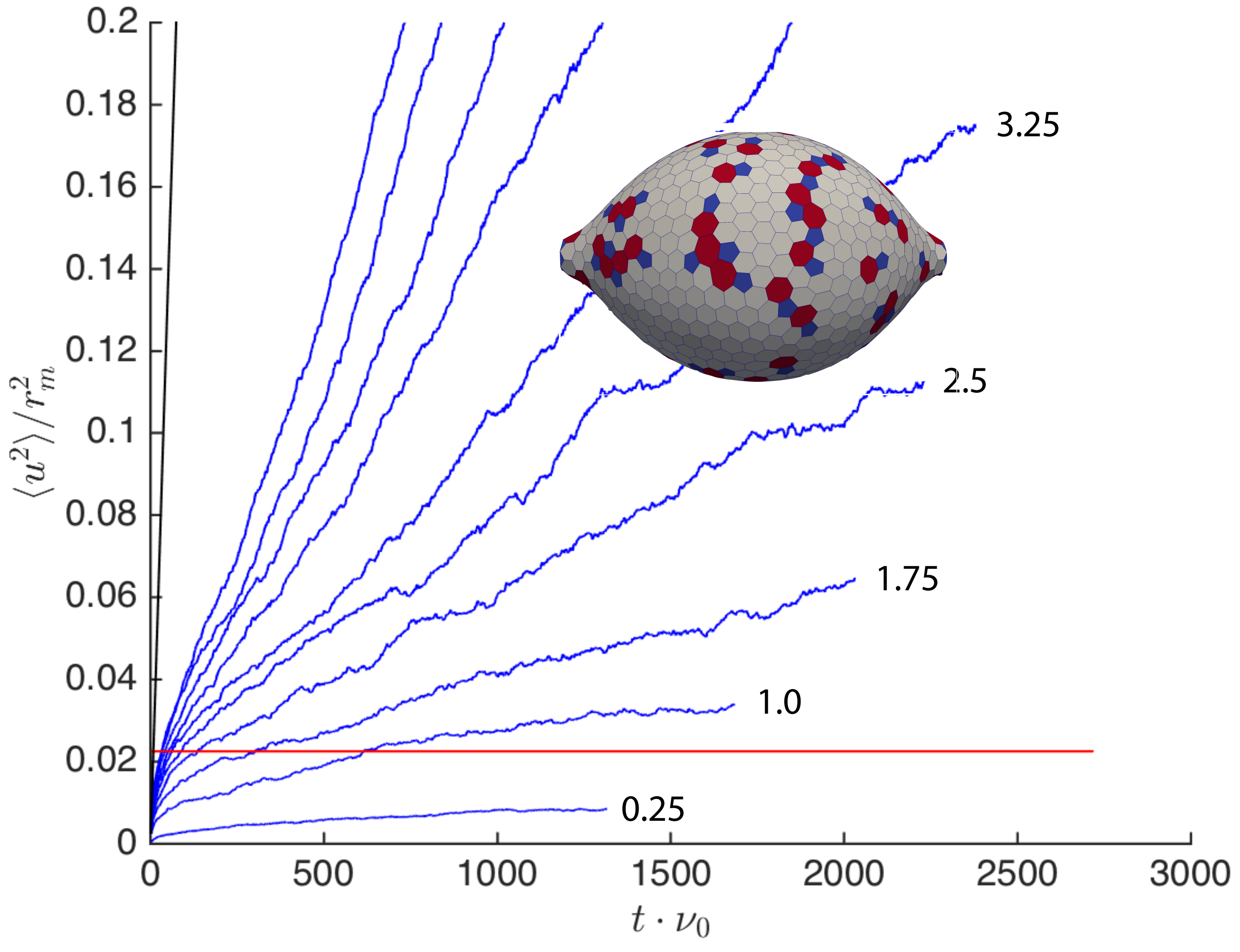
$$V(r) = \epsilon\left[(r_m/r)^{12} - 2(r_m/r)^6\right]$$

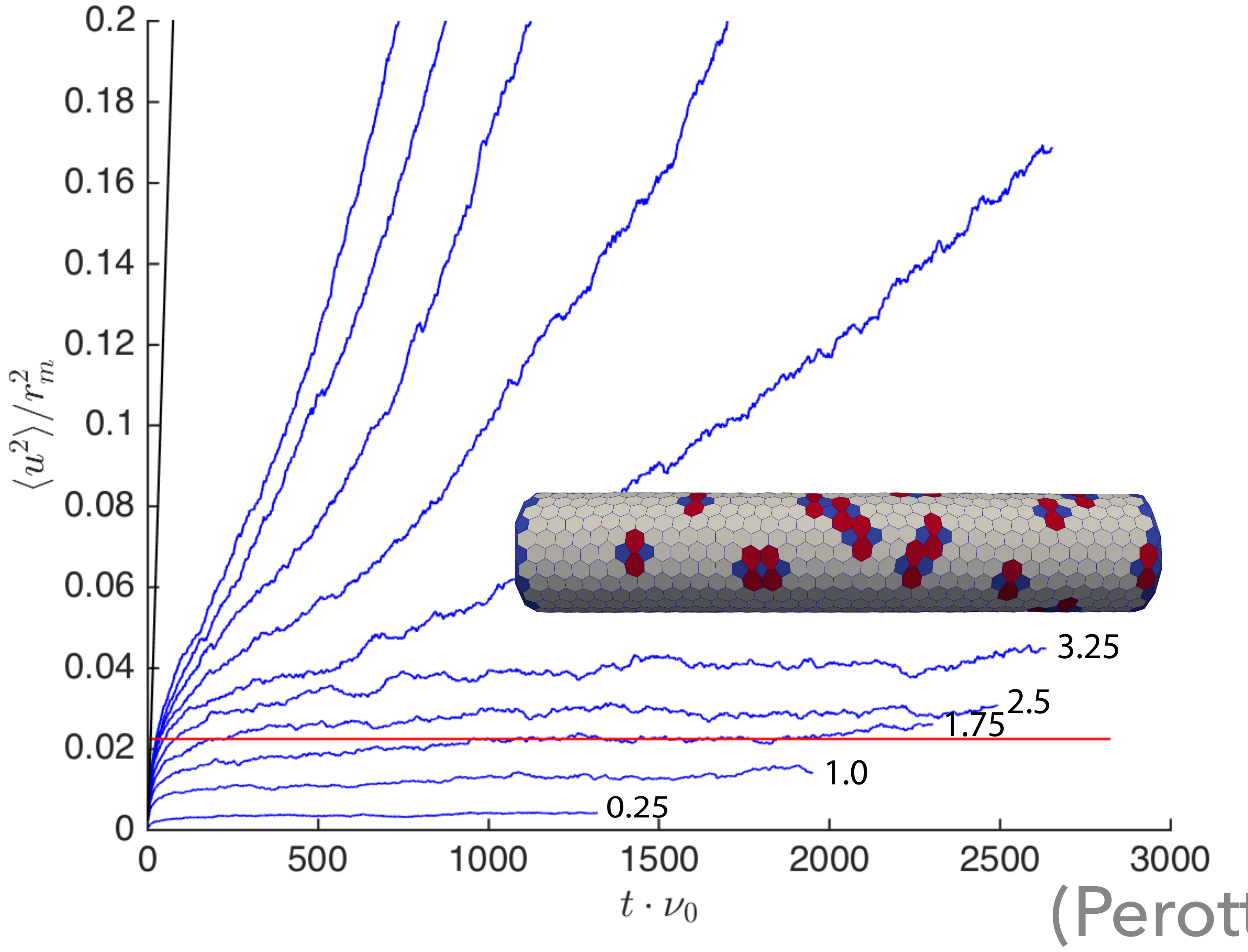




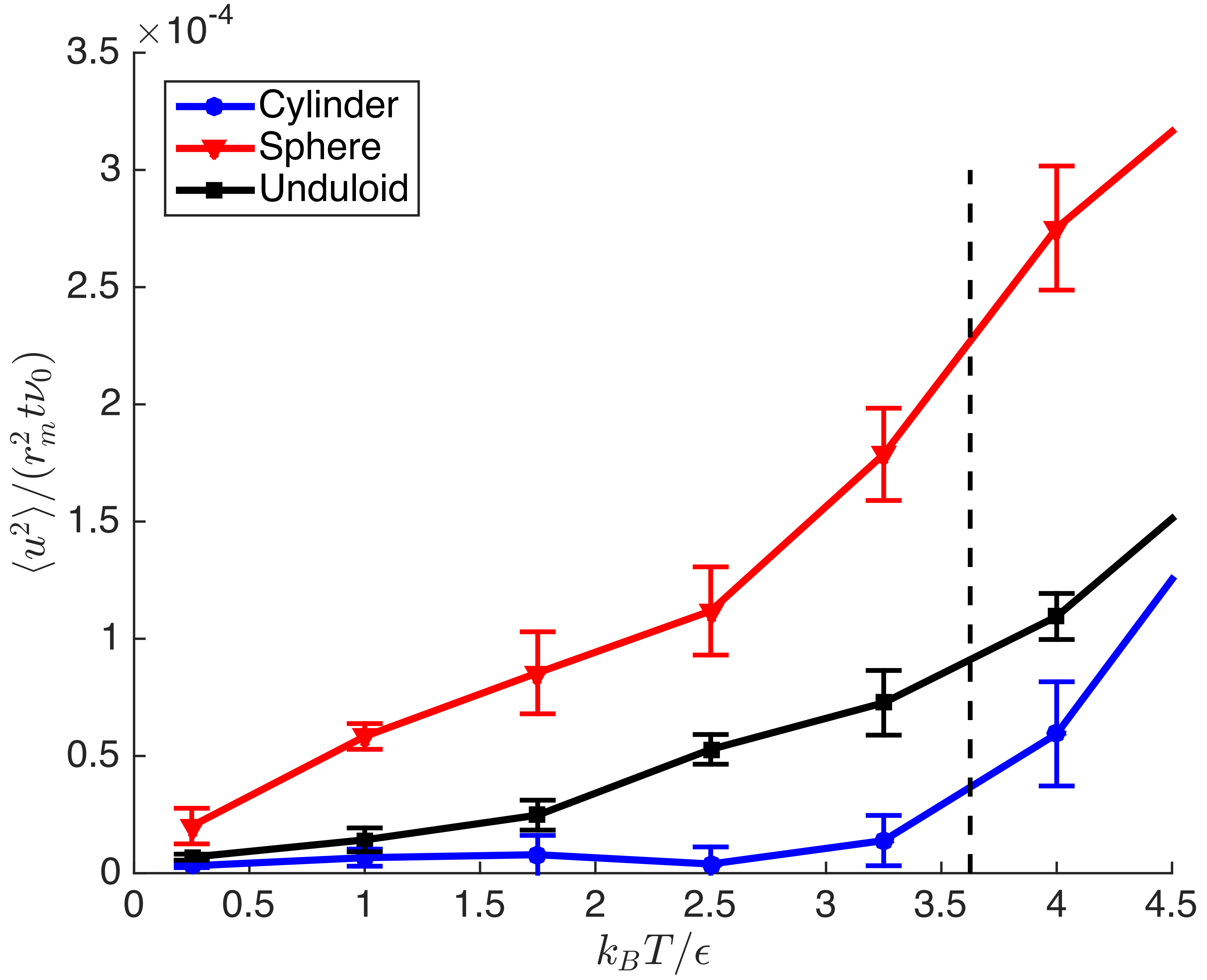
(Perotti, et al., submitted)

TRANSPORT

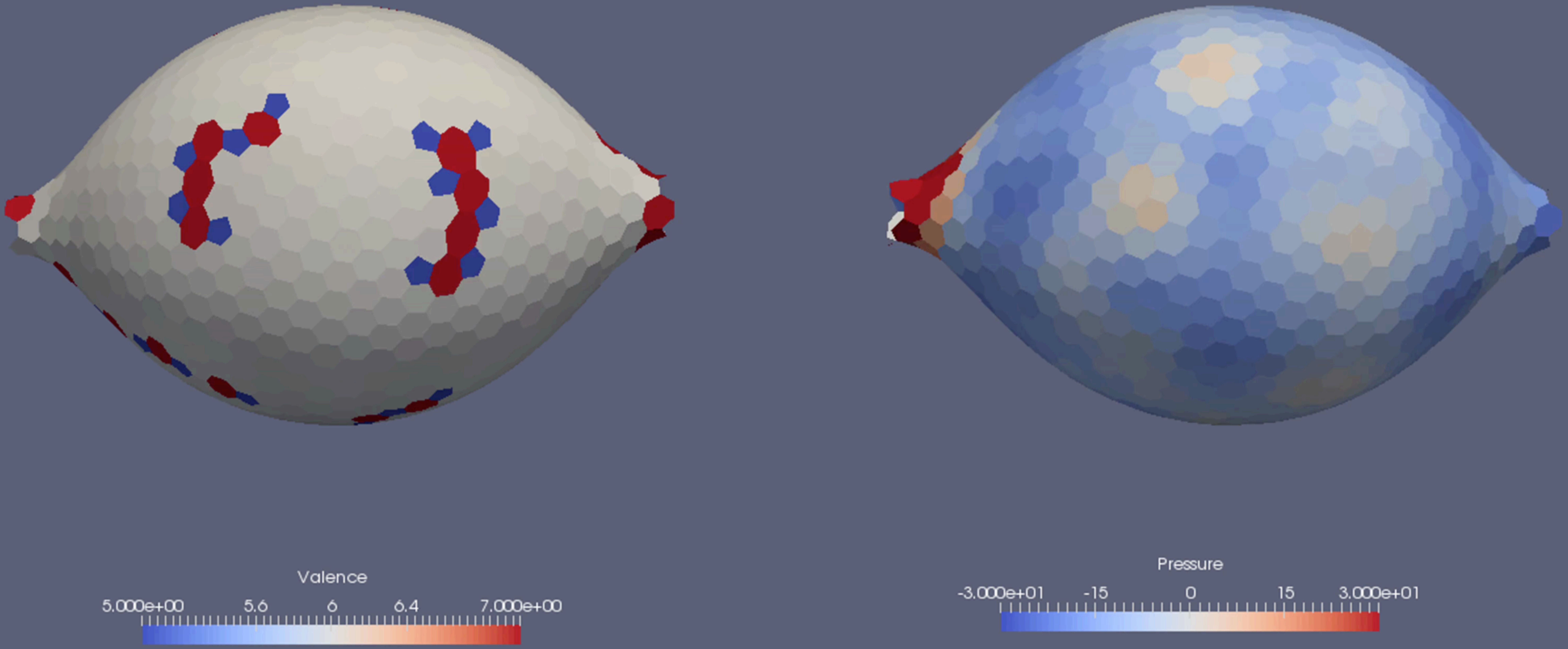




Diffusion of Defects enhances fluidity



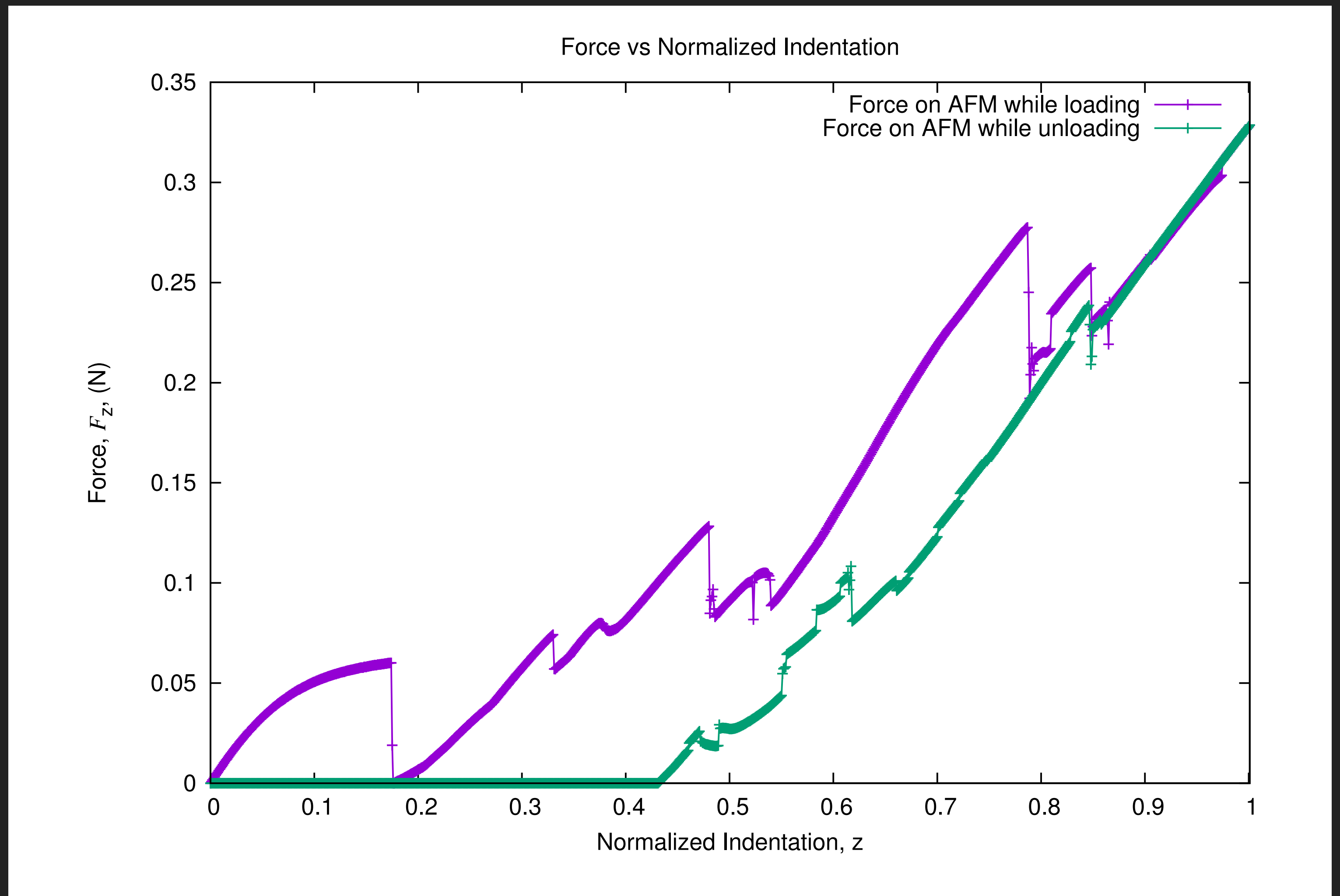
(Perotti, et al., submitted)

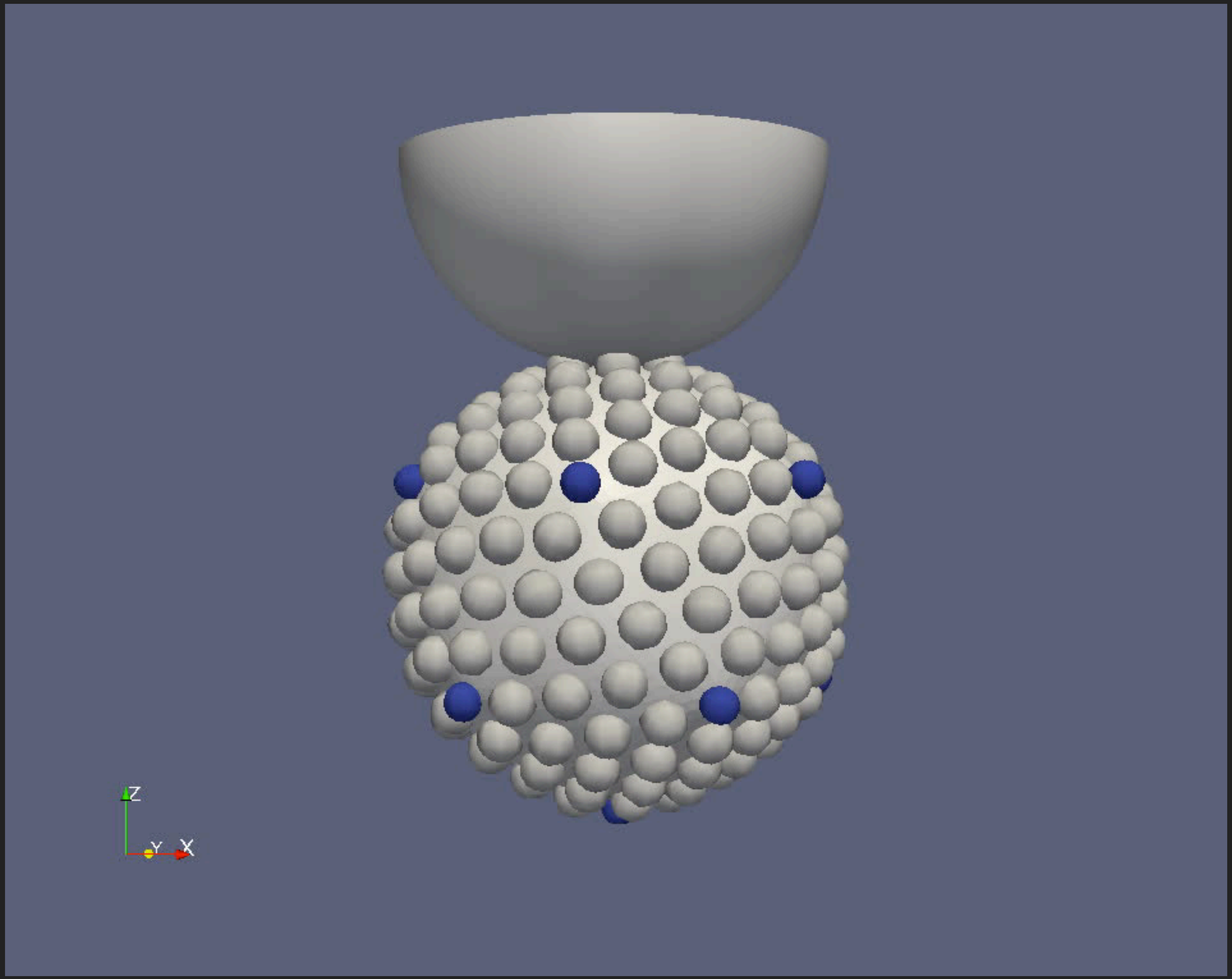


Valence
5.000e+00
5.6
6
6.4
7.000e+00
Pressure
-3.000e+01
-15
0
15
3.000e+01

AFM INDENTATION

- Hybrid particle-continuum model:
  - Curvature bending energy
  - L-J particle interactions





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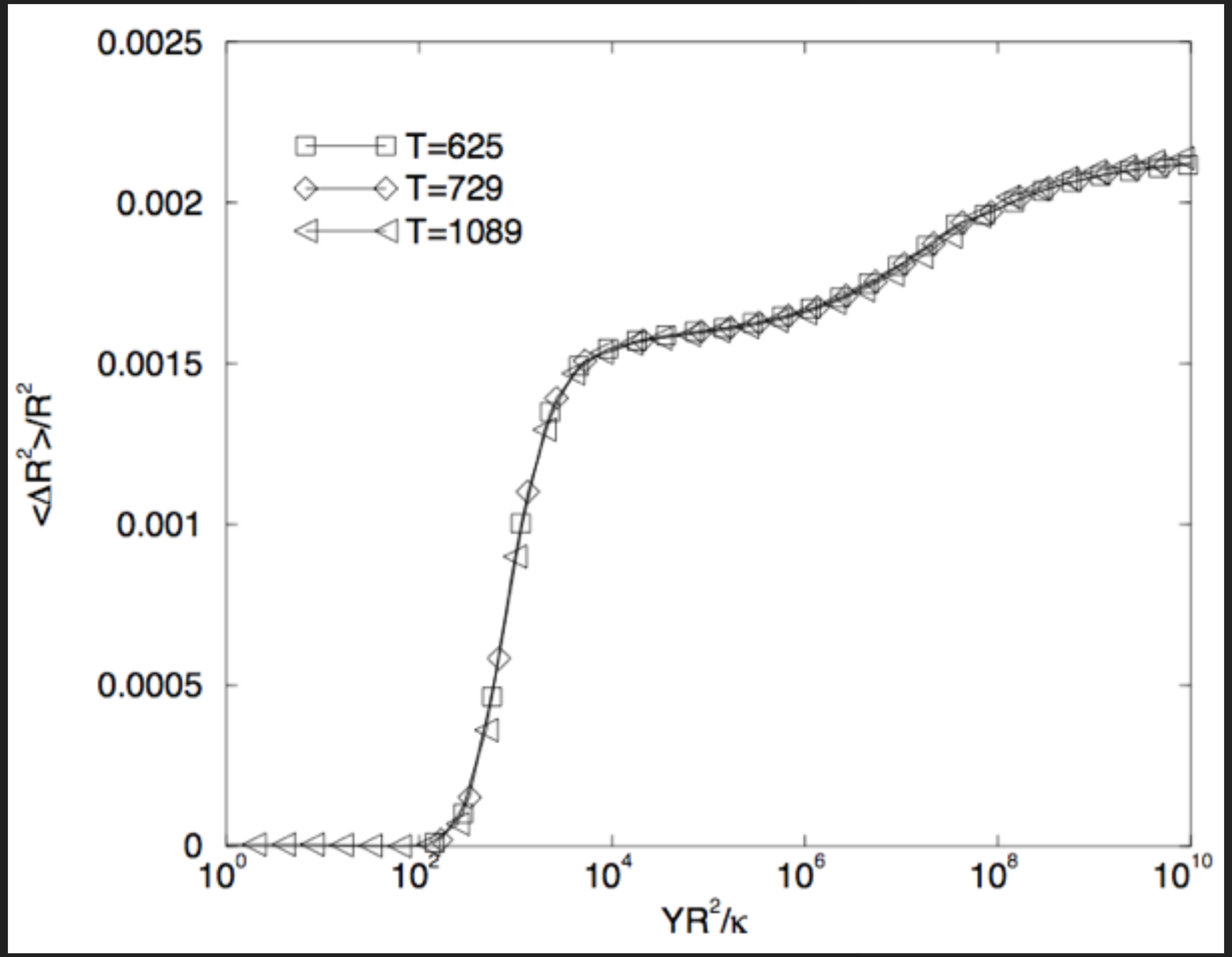
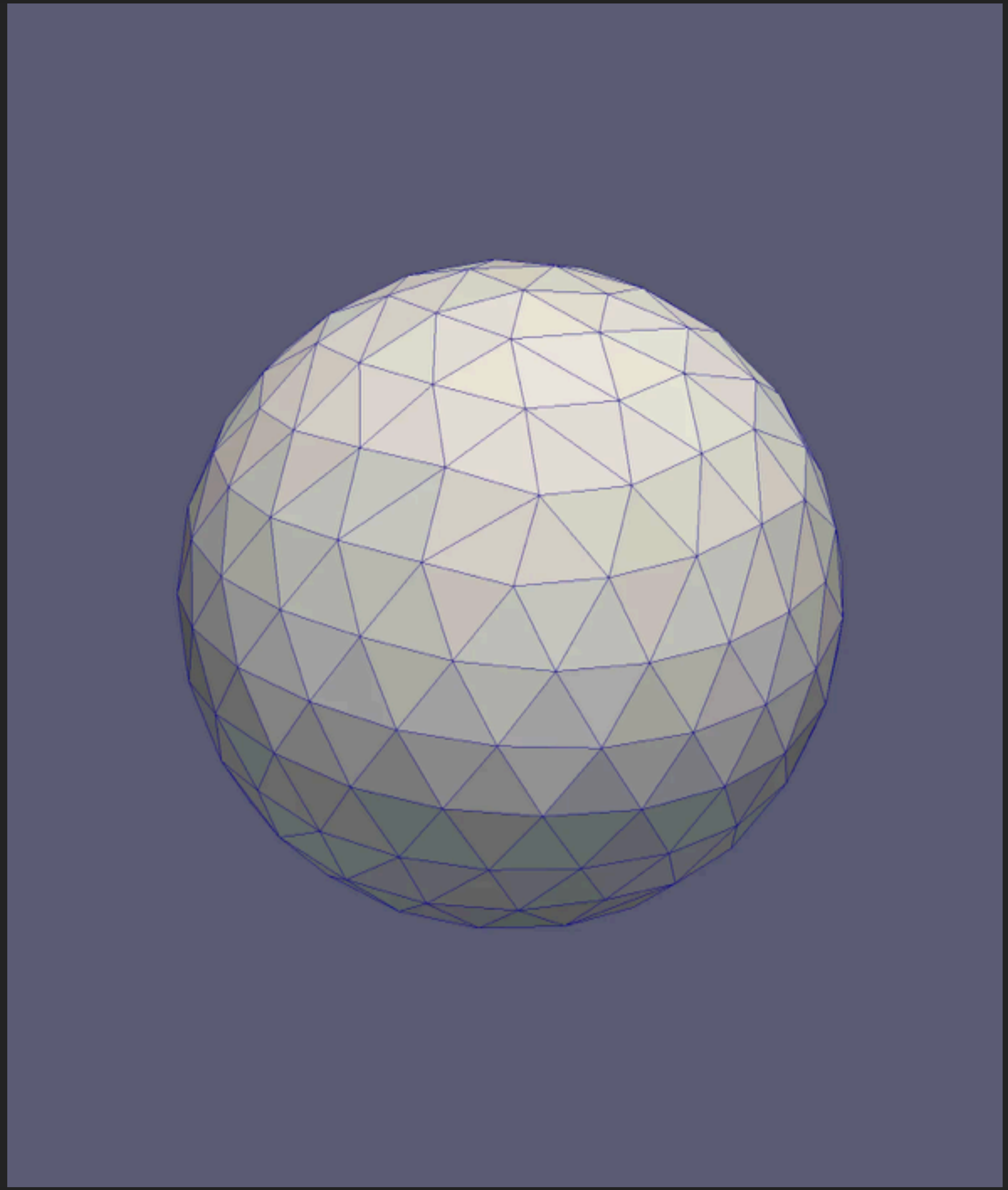
EFFECTIVE FVK NUMBER?





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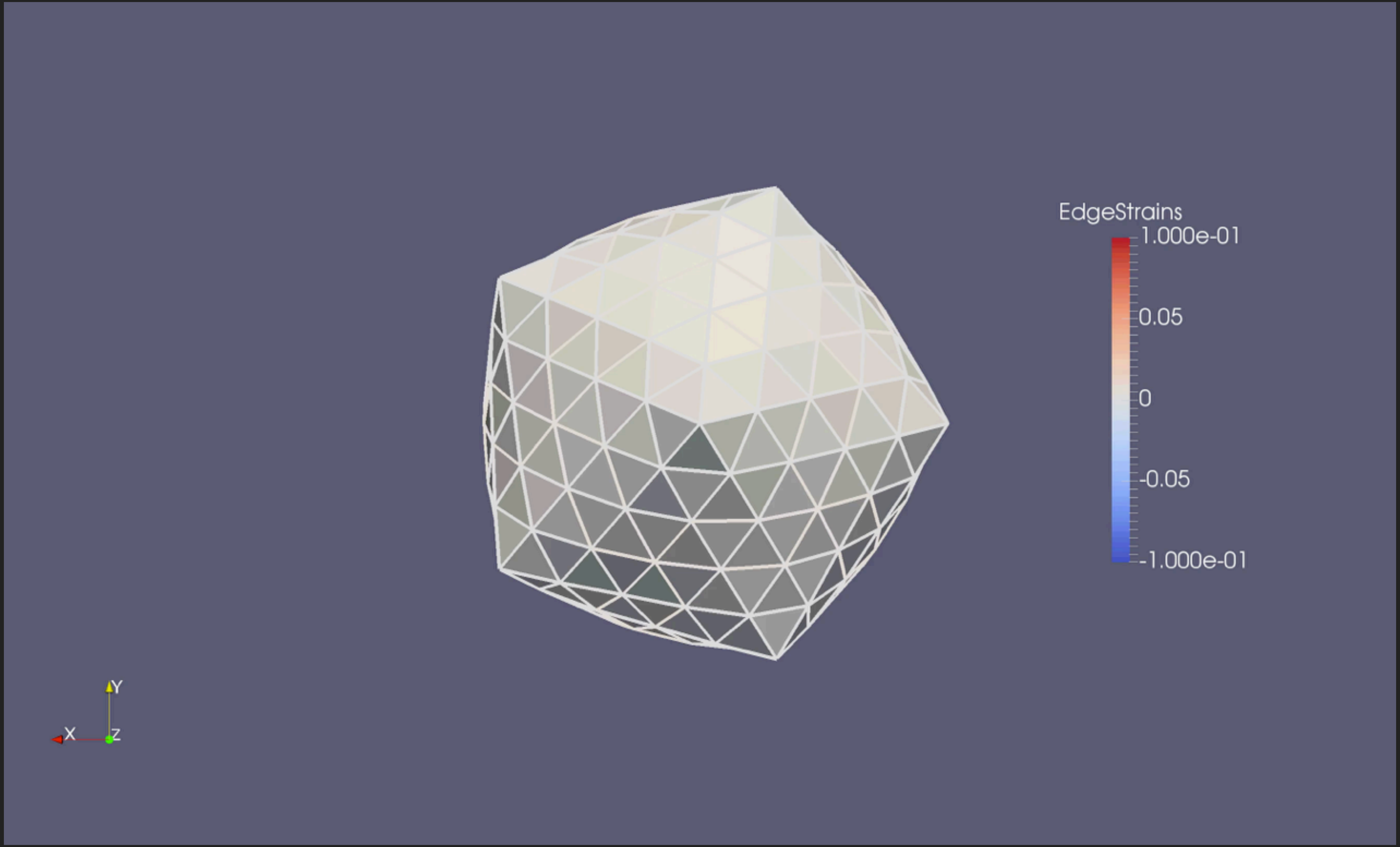
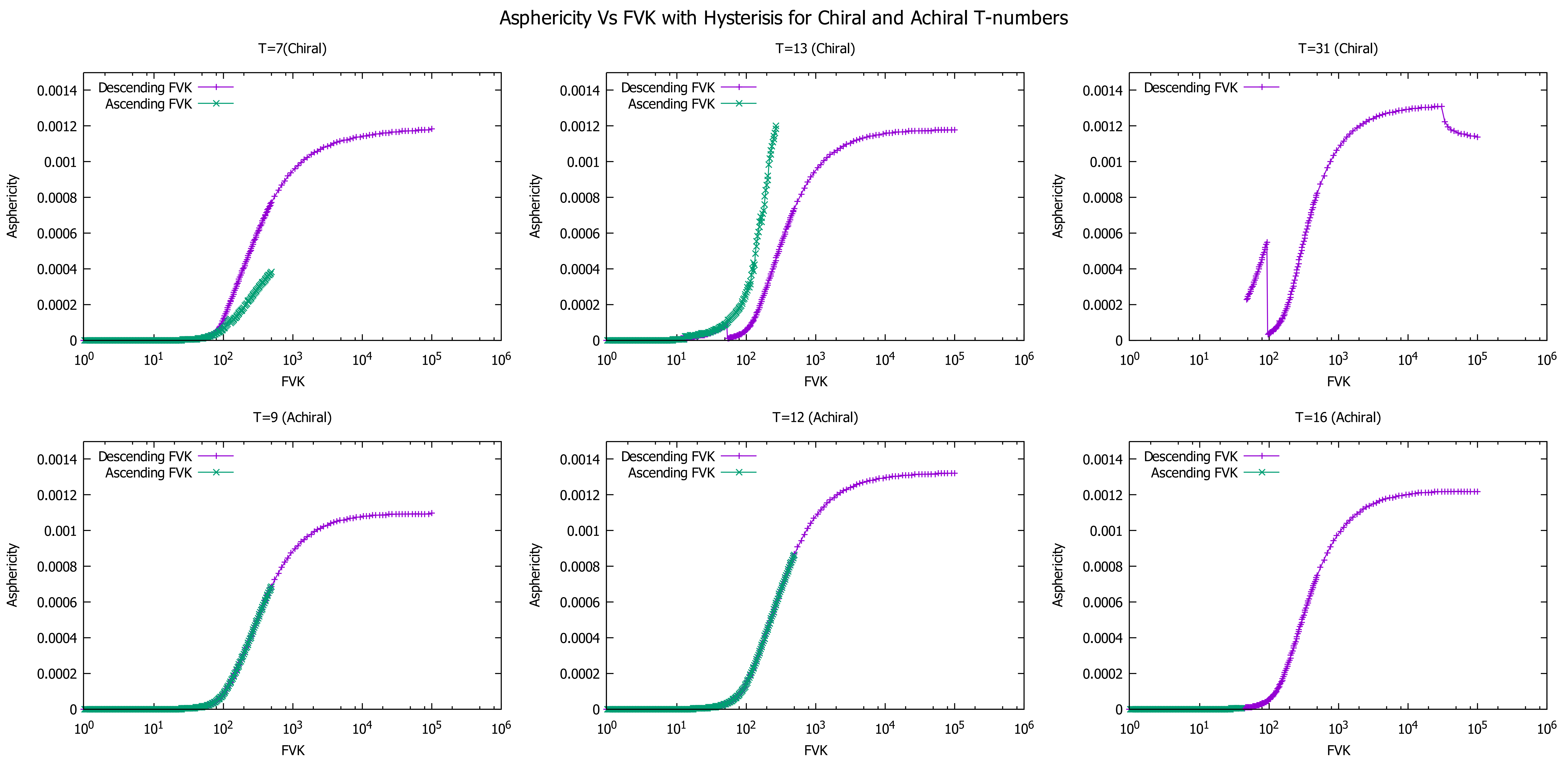
ADD PRESSURE TO STABILIZE CRUMPLING



HYSTERESIS IN CHIRAL SHELLS



QUESTIONS TO THINK ABOUT

- What is the reference configuration for a protein shell?
  - Can we know?
  - Treat it as a degree of freedom?
- How do we classify/understand pleomorphic capsids?
  - Solid? Fluid? Something else?
  - Anisotropy?
- Better ways to model defect motion in disordered solids?

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Thanks for your attention!