Shape transformation of viral capsids

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Introductory slides 2, 6 and 7 were prepared by Roya Zandi

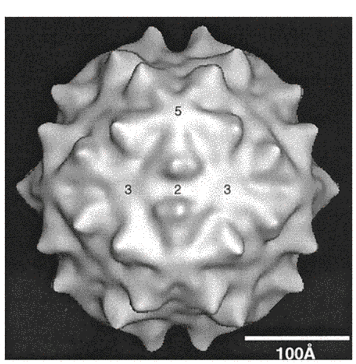
(SIMPLEST) VIRUSES ARE JUST:

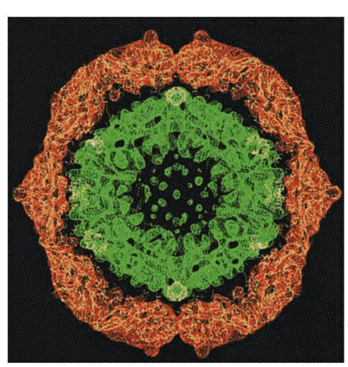
A COMPOSITE OF

a nucleic acid genome:

Ribonucleic acid (RNA) or
Deoxyribonucleic acid (DNA)

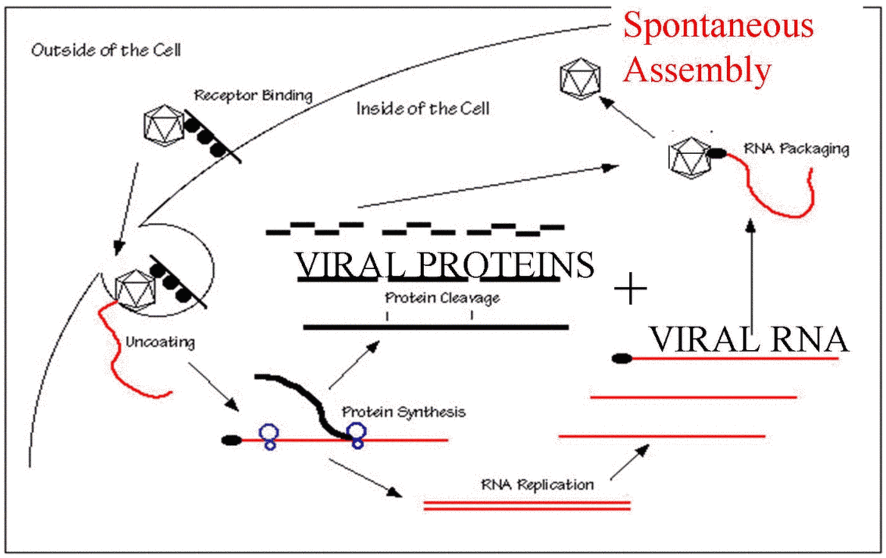
AND a protein shell -- **"capsid"**

Cryo-TEM



X-ray crystallography

Flock-House virus

Virus Life Cycle (Polio)



Viruses: no metabolism → thermal equilibrium
► Thermodynamic and geometric arguments can be applied successfully to describe their physical properties

Icosahedral symmetry of spherical viruses
Caspar, and Klug, *Cold Spring Harbor Symp. Quant. Biol.* **27**, 1 (1962)

Continuum elasticity of spherical protein capsid and buckling transition
Lidmar, Mirny, Nelson, *Phys. Rev.* **E68**, 051910 (2003)

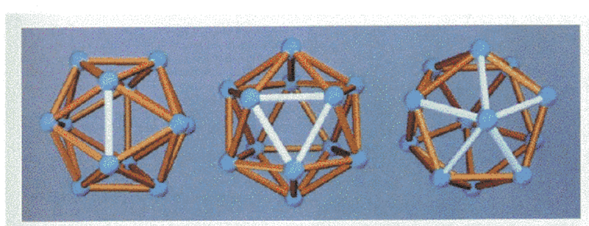
Classification, stability of conical viral capsids
Nguyen, Bruinsma, Gelbart, *Phys. Rev. Lett.*, (2006);
Phys. Rev. **E72**, 051923 (2005).

Capsids properties:

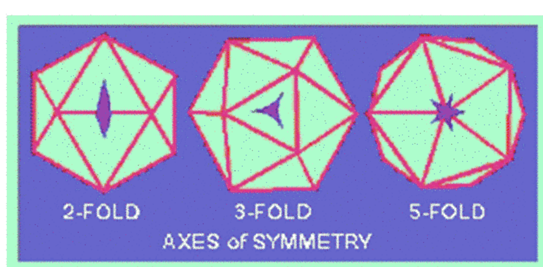
- Geometrical
- Energetic

Icosahedral Symmetry

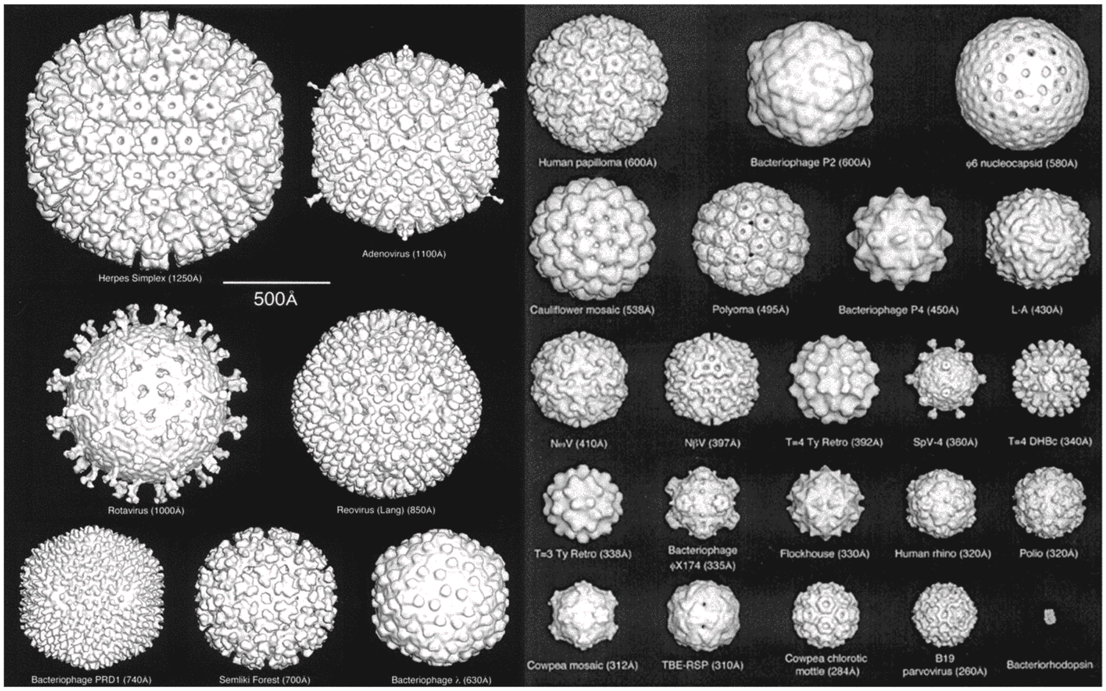
Icosahedron: 20 identical equilateral triangular faces.



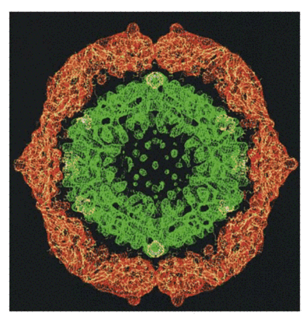
➔ 15 two-fold rotation axes
➔ 10 three-fold rotation axes
➔ 6 five-fold rotation axes



Icosahedral symmetry is ubiquitous among spherical viruses.



Why are viruses icosahedral?

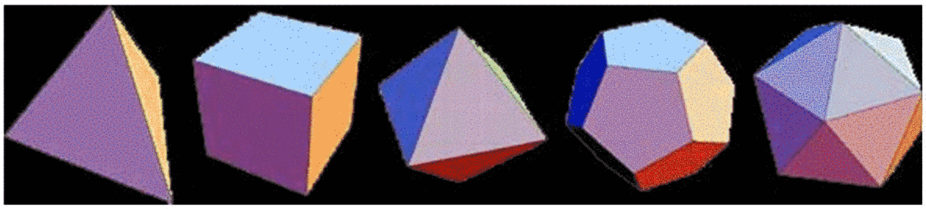


Francis Crick (1956):

1) The small size of the virus genome only allows only a single protein type for the coat. The capsid must be made of *many* identical units of a *single* protein type.
2) The viral shell should be *symmetric*, so these identical proteins can occupy *identical minimum energy environments*. (That's how crystals are organized)
3) The viral shell should have optimal "information storage" capacity (i.e., a low surface to volume ratio).

Mathematical Problem.

Divisions of a *Spherical Surface* into identical unit cells.



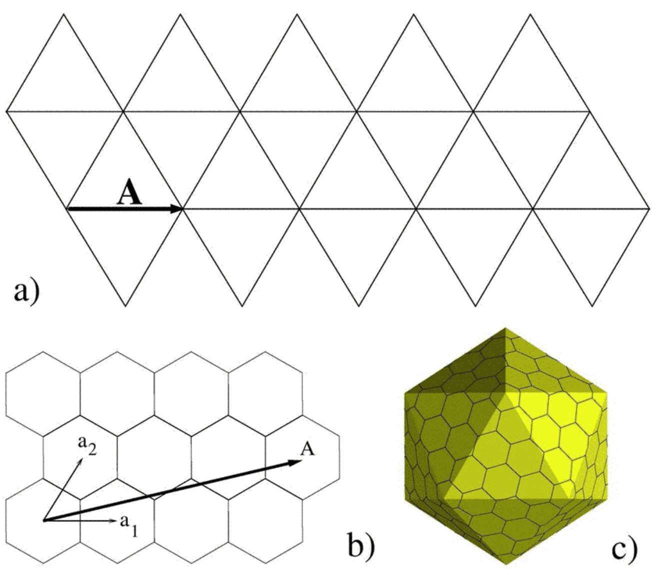
Five “Platonic”Solids

Lowest surface/volume ratio:
Icosahedron **60 proteins**

Actual capsids: # proteins equals 60 times an integer (“T Number”)

Caspar & Klug classification of spherical capsids:

Construct icosahedron from hexagonal sheets

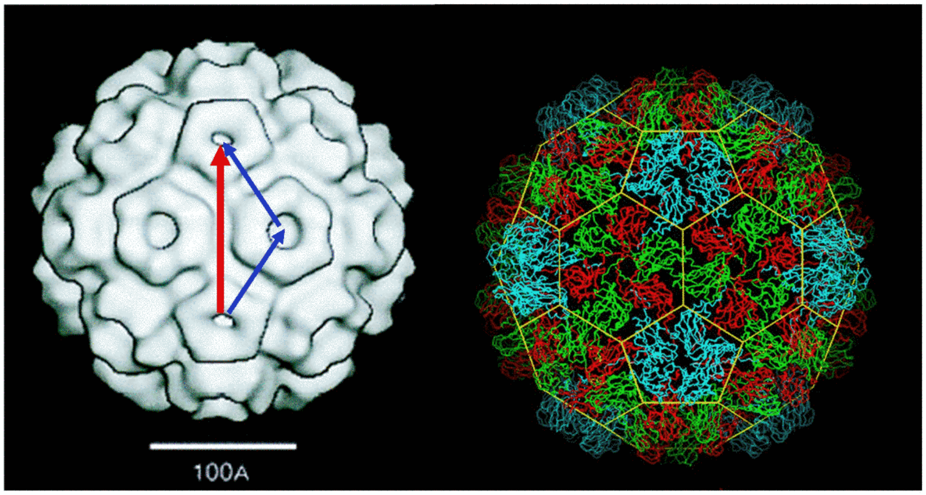


A = h **a** $_1$ + k **a** $_2$

\# of capsomers:
$N = 10\,(h^2+k^2+hk)+2$

T-number
$T(h,k) = h^2+k^2+hk$

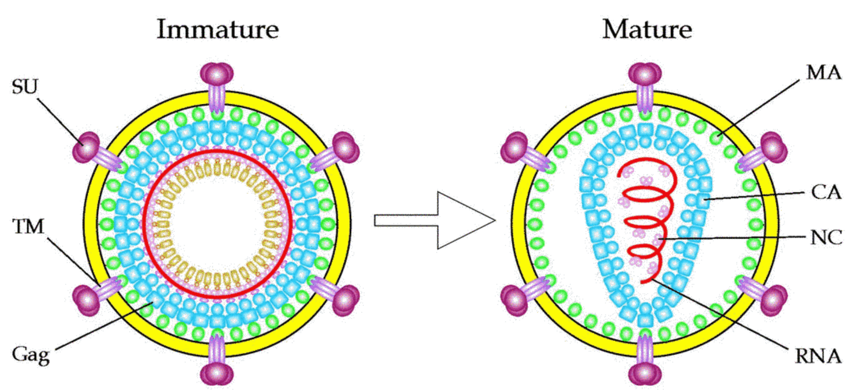
Cowpea Chlorotic Mottle Virus ("CCMV")



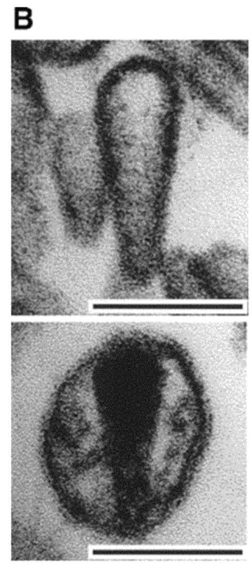
T-number: T(1,1) = 3

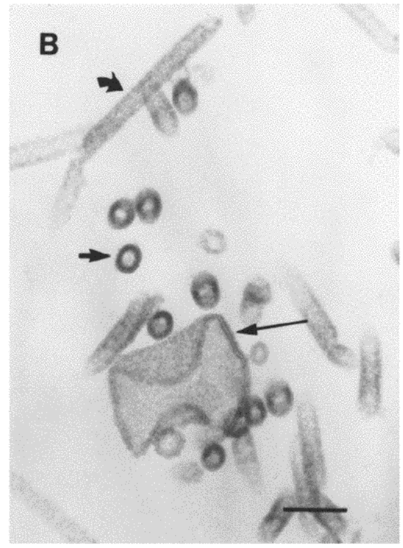
12 pentamers, 20 hexamers, 180 proteins

Human Immunodeficiency Virus (HIV) forms conical capsid upon maturation



HIV capsid assembly *in vitro*



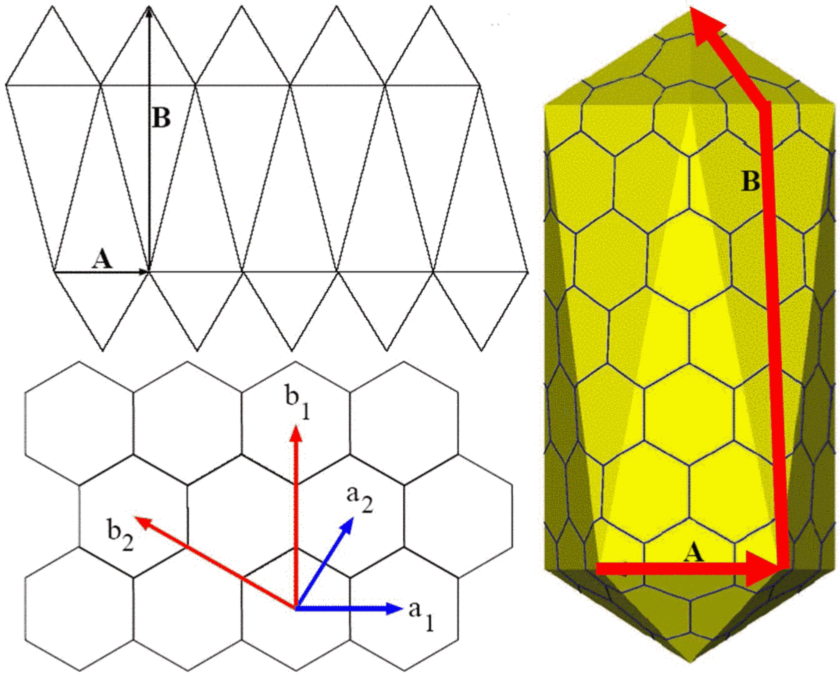


Scale bars: 100nm

Questions

- Can one construct an isometric conical capsid and correspondingly a “Caspar-Klug” classification?
- Is conical shape thermodynamically stable?

Isometric construction of spherocylindrical capsid

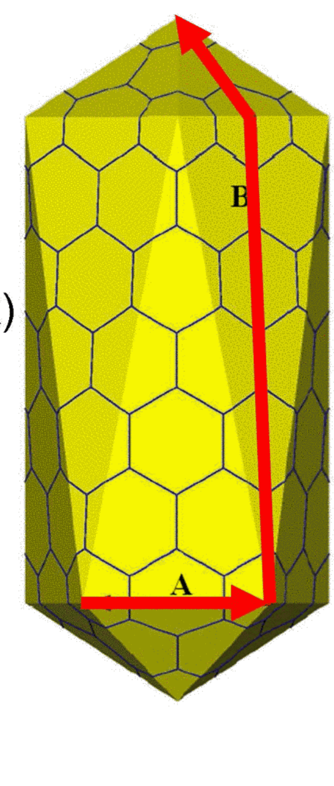


$\mathbf{A} = n(h\,\mathbf{a}_1 + k\,\mathbf{a}_2)$
$\mathbf{B} = m(h\,\mathbf{b}_1 + k\,\mathbf{b}_2)$

# of capsomers:
$N = 10\,mn(h^2+k^2+hk)+2$

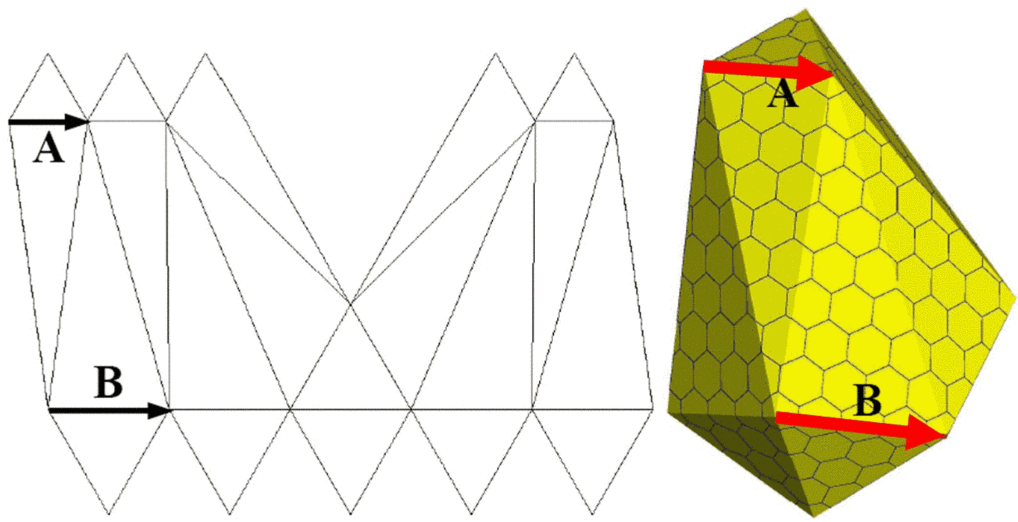
T-number: $T(m,n|h,k) = mn(h^2+k^2+hk)$

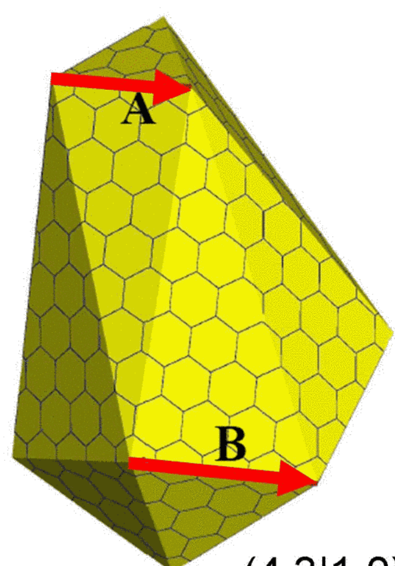
Includes the spherical capsid as a special case with m=n



(4,2|1,0)

Isometric construction of conical capsids





(4,3|1,0)

A = n(h $\mathbf{a}_1$ + k $\mathbf{a}_2$)
B = m(h $\mathbf{a}_1$ + k $\mathbf{a}_2$)

# of capsomers:
N = 10 $(2m^2-n^2)(h^2+k^2+hk)+2$

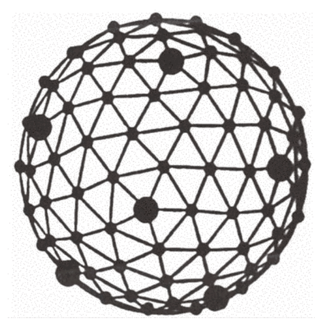
T-number:
$T(m,n|h,k) = (2m^2-n^2)(h^2+k^2+hk)$

Includes the spherical capsid as a special case with m=n

Continuum elastic theory

- Protein capsid = elastic shell with 2D Young modulus Y, bending rigidity K, spontaneous curvature C_0.
- Depends on two dimensionless parameters $\gamma = YA/K$, $\alpha = C_0 A^{-1/2}$ (A is the capsid area).
- Successfully explains "buckling" transition of viral shell.

Numerical solution to elastic equations



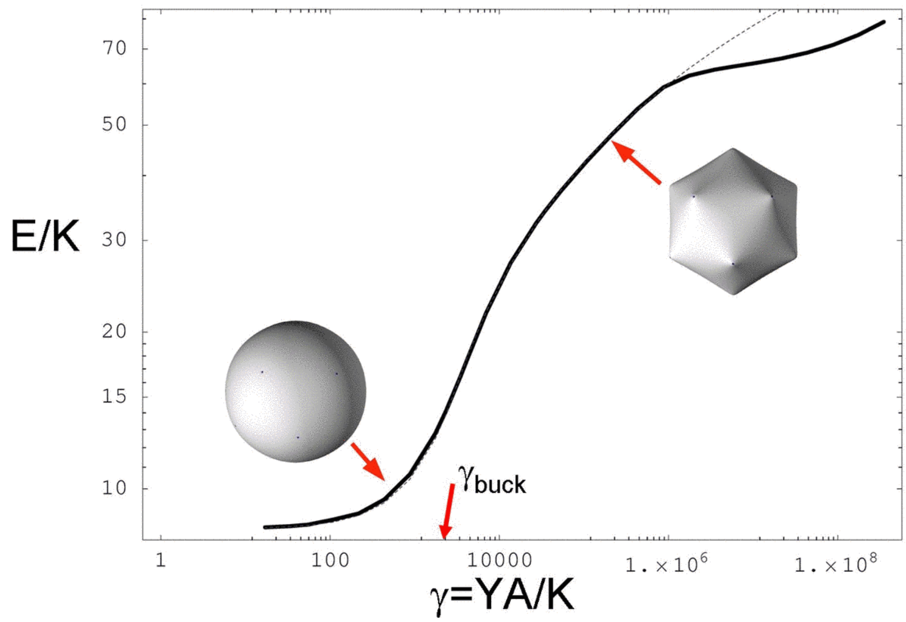
Discretize continuum shell using triangular lattice based on the isometric construction.

$$H = \frac{\varepsilon}{2}\sum_{<ij>}(r_{ij} - a)^2 + \kappa \sum_{<IJ>}[1 - \cos(\theta_{IJ} - \theta_0)]$$

In the continuum limit, $Y = 2\varepsilon/\sqrt{3}$, $K = \sqrt{3}\kappa/2$, $C_0 = 2\theta_0/a$.

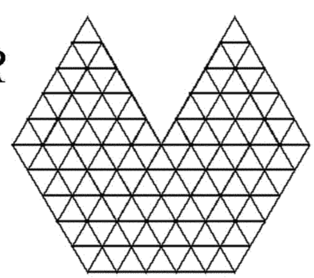
Energy minimization using conjugate gradient method to obtain optimal shape.

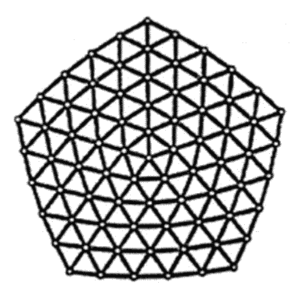
Lidmar, Mirny, Nelson: Spherical capsid energy approximated by sum of 12 isolated five-fold disclinations.



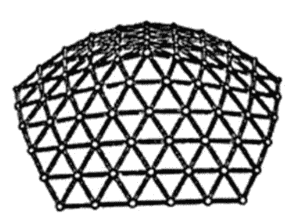
Disclination energy

$$E_{stretch} = \int Y u_{\theta\theta}^2 dS \sim YR$$



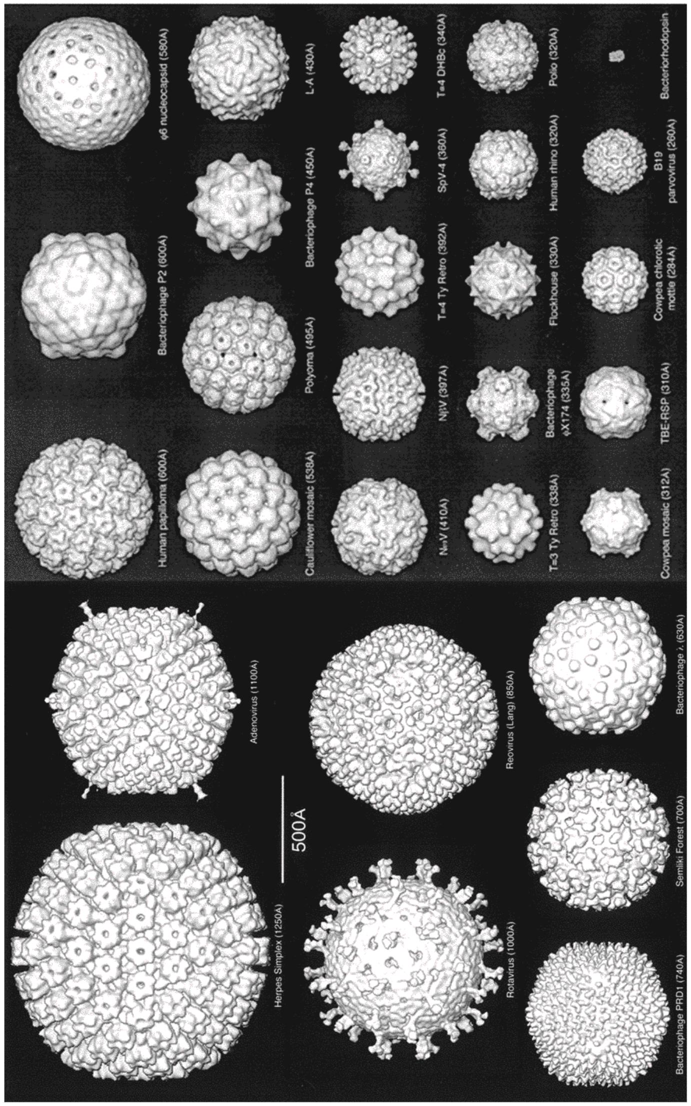


$$E_{bend} = \frac{1}{2}\int \kappa H^2 dS \sim \kappa \int_{R_b}^{R} \left(\frac{1}{R}\right)^2 R dR \sim \kappa \ln \frac{R}{R_b}$$

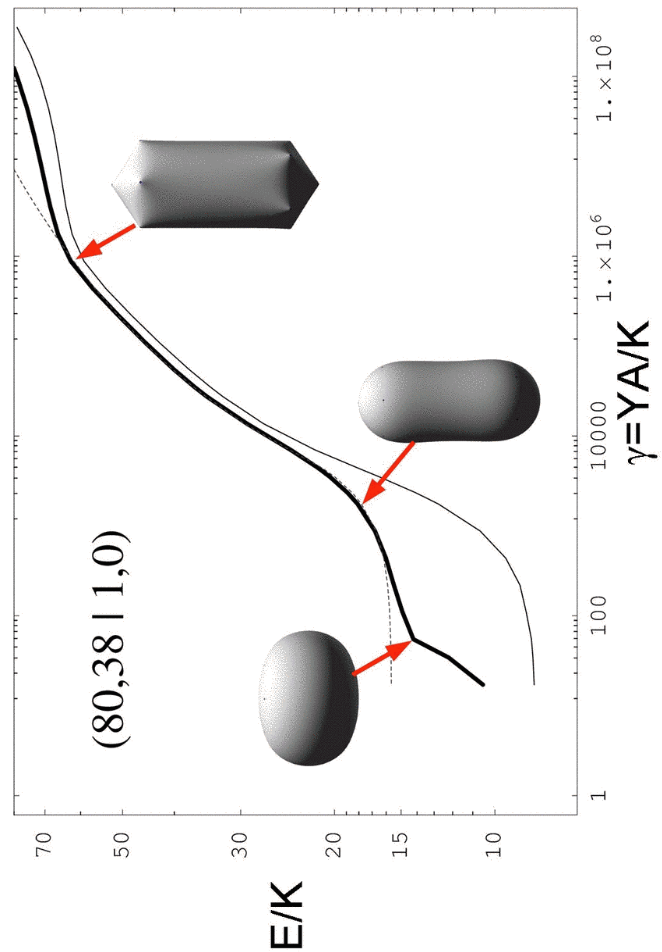


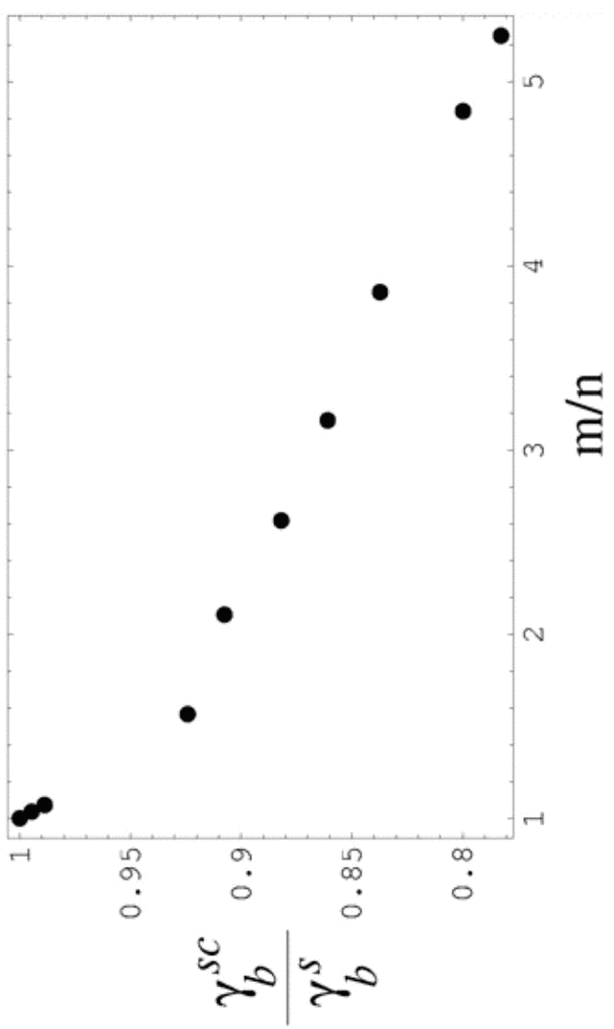
$$\gamma_{buck} = Y\, 2\pi R_b^2 / \kappa \sim 1000$$

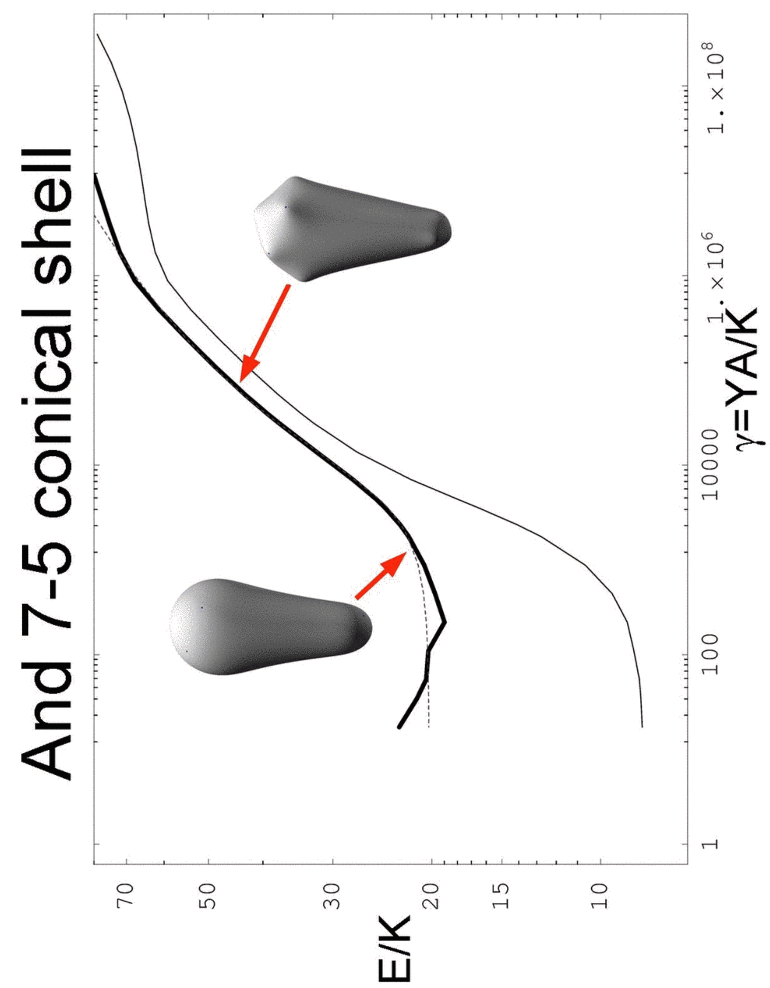
Icosahedral symmetry is ubiquitous among spherical viruses.



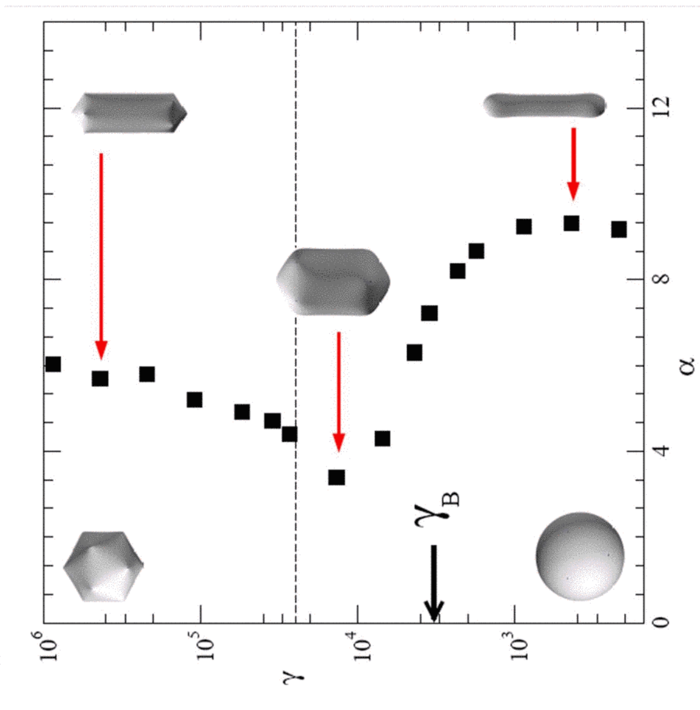
Extension to cylindrical shell



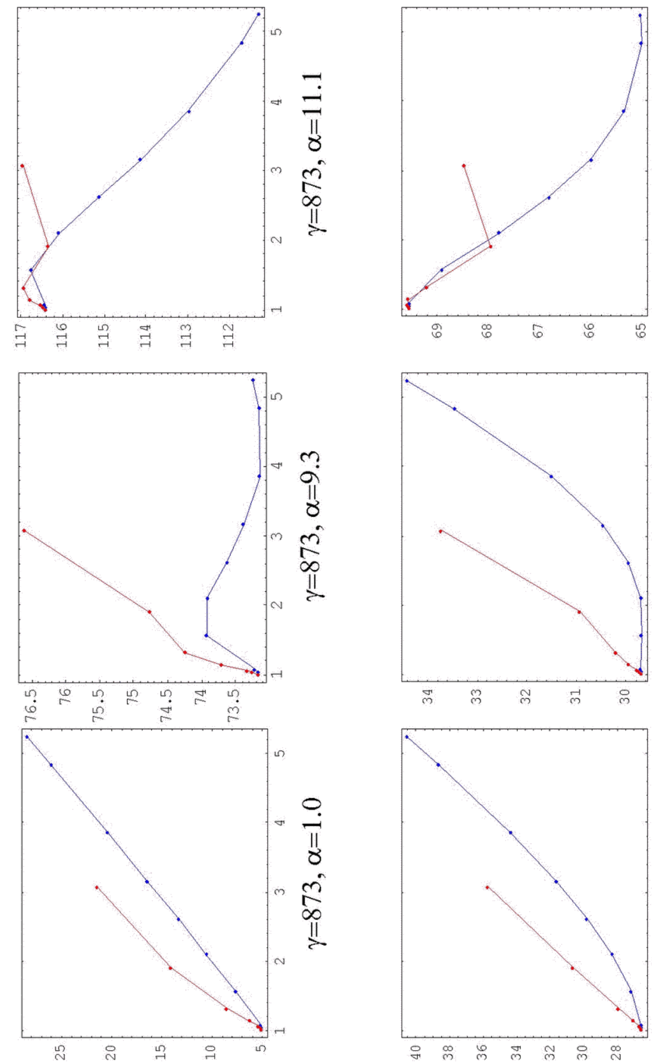

m/n
$\frac{\gamma_b^{sc}}{\gamma_b^{s}}$


And 7-5 conical shell
E/K
γ=YA/K

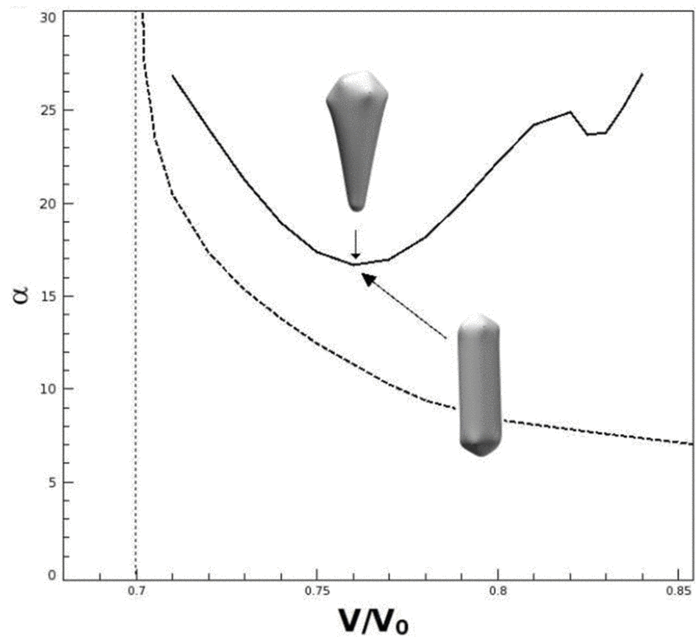
Phase diagram of empty capsids at constant area



E(γ,α) *vs.* m/n aspect ratio

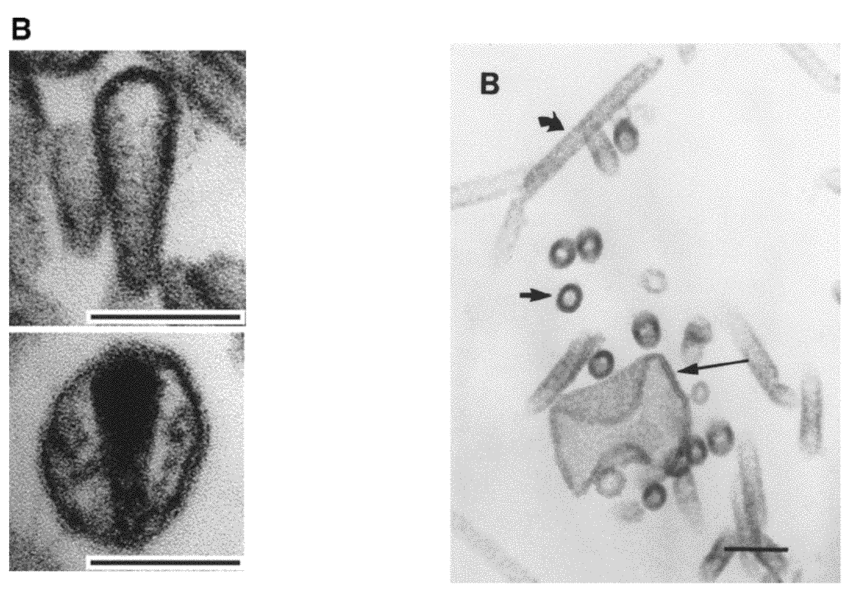


Cylindrical-Conical shape transition under volume constrain



$\gamma = 25000$

HIV capsid assembly *in vitro*



Scale bars: 100nm

Conclusions

- Generalized "Caspar – Klug" classification suggested to describe cylindrical and conical virus capsid.
- Continuum elastic theory used to model the protein capsid shell. Among empty capsid shell with the same area, conical shells is not the shape with lowest energy.
- Conical capsids is the thermodynamically lowest energy state only if constrains on capsid assembly is imposed: assembly inside lipid vesicles or with RNA template.