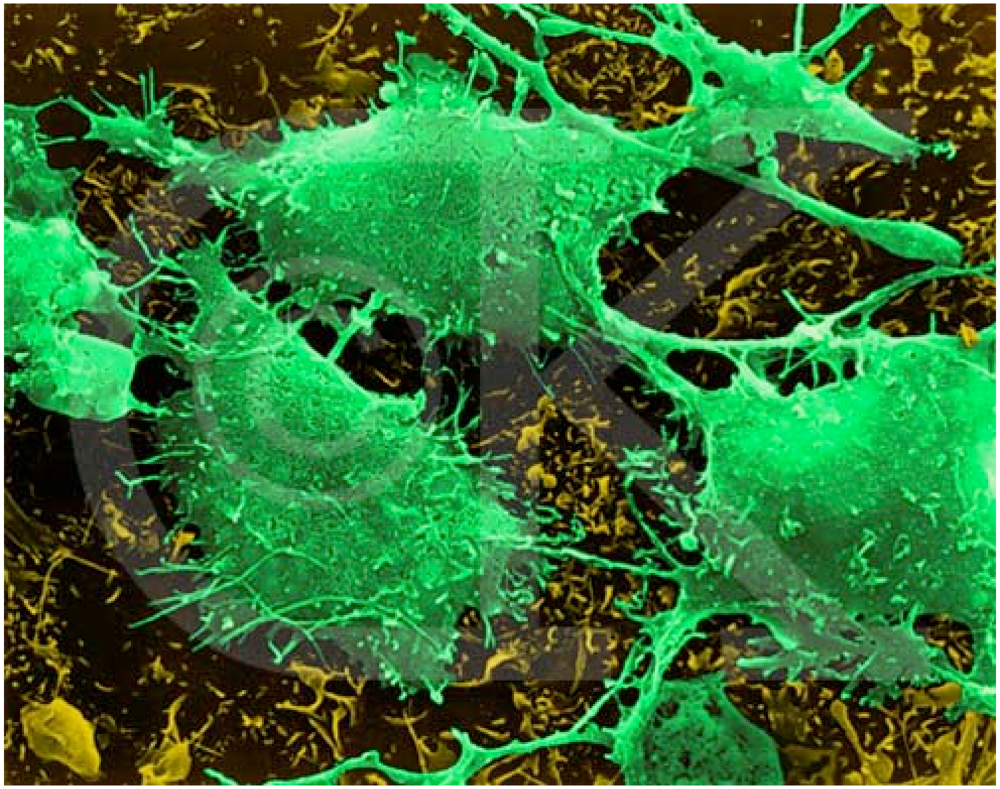
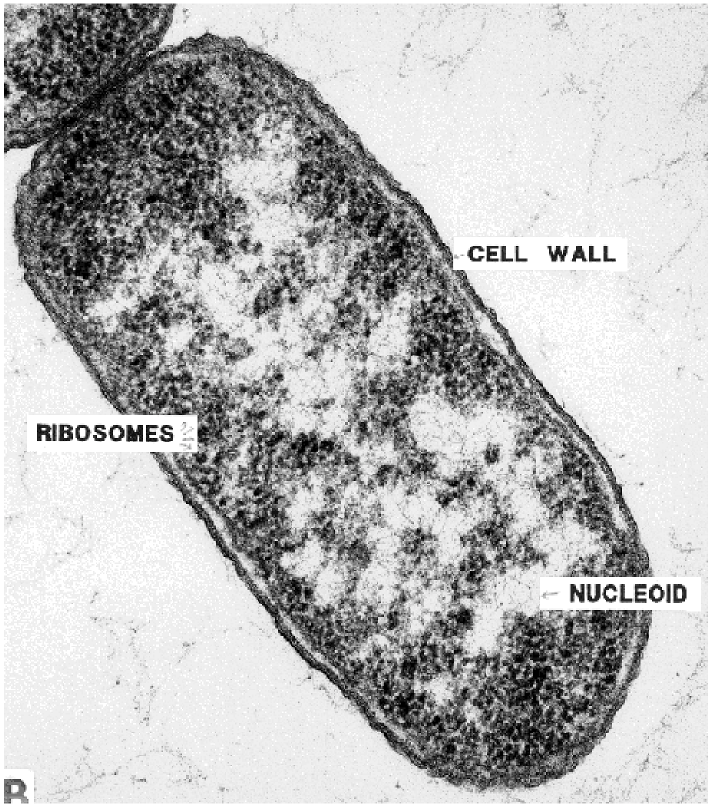
Physical Models of Viruses

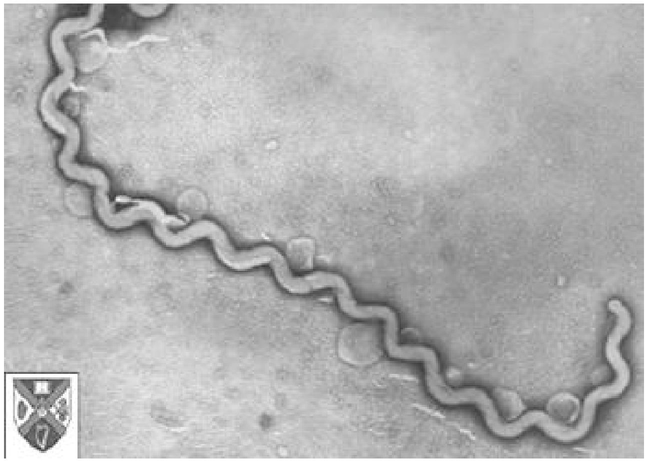
Why?



Brain cancer cells

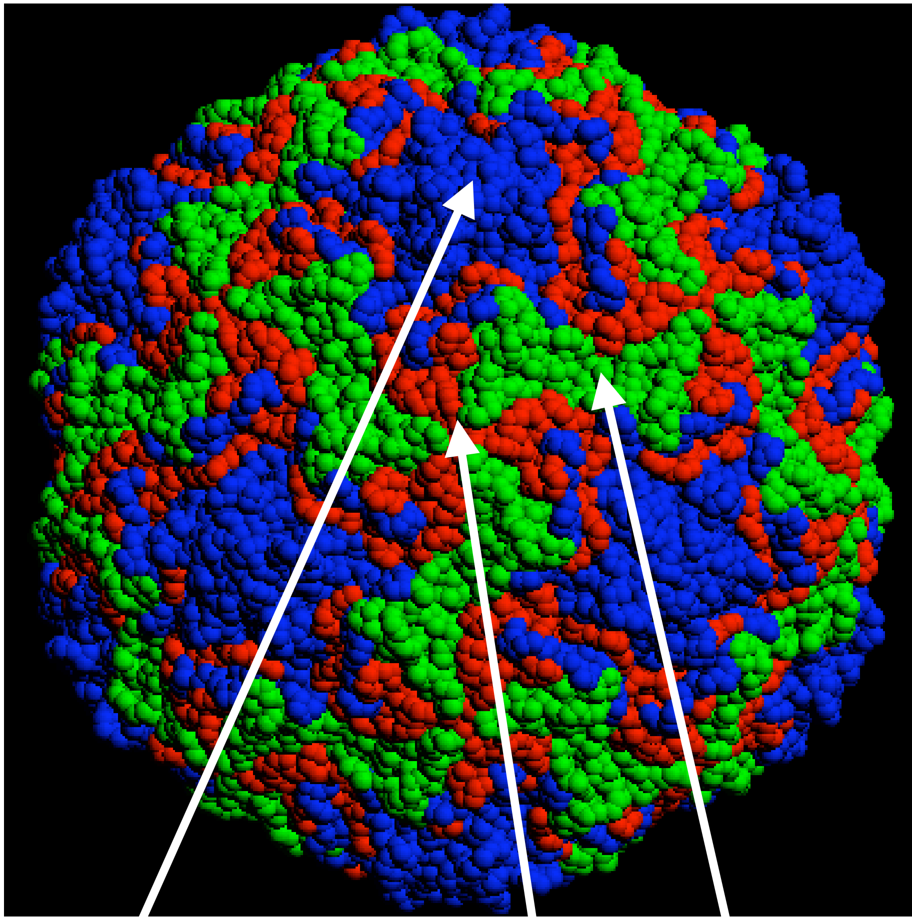


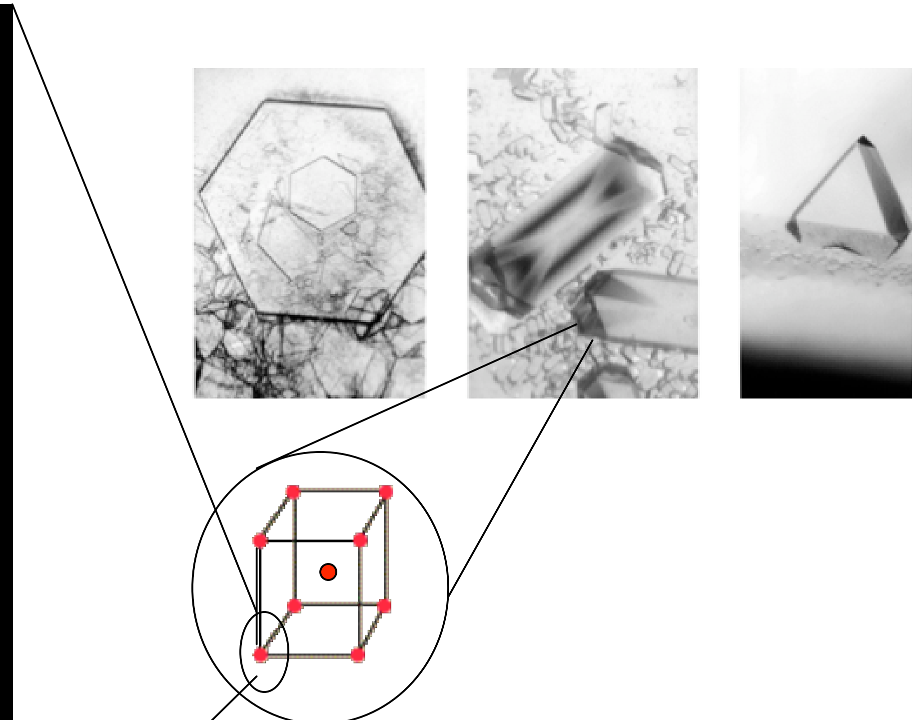
E. coli.



Bacteria & Cells:

- Do not form crystals.
- Have no particular symmetry.





Rhinovirus

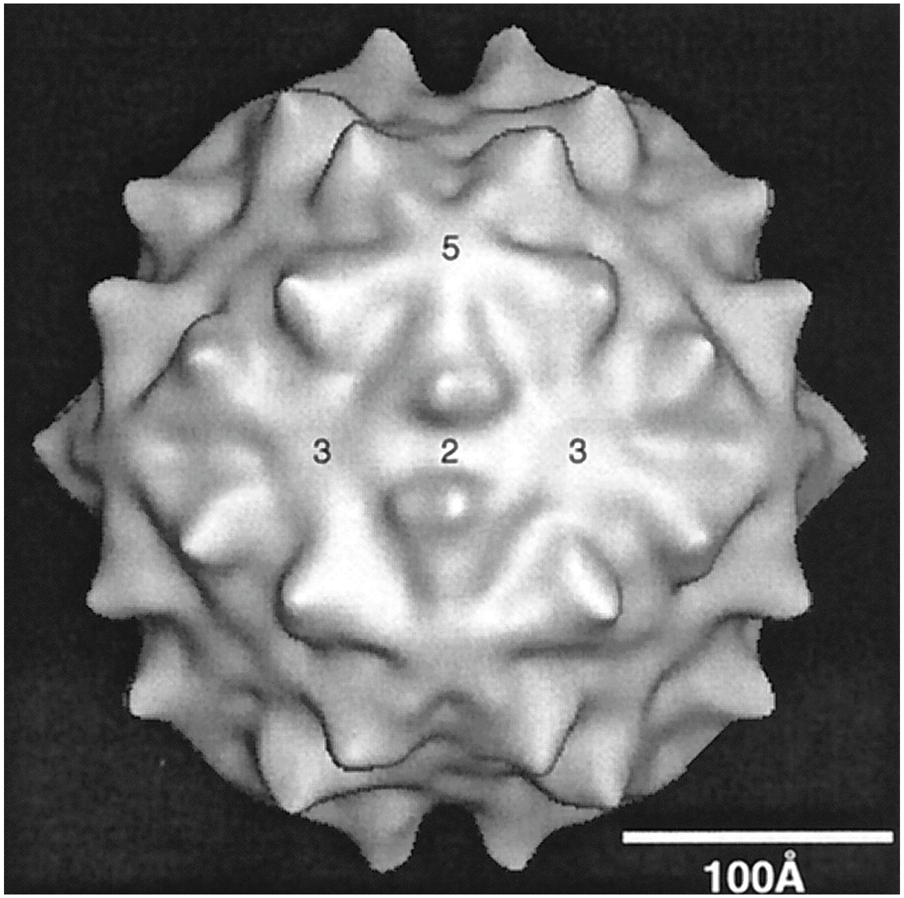
320 Angstroms

Molecular Weight: $> 10^6$

Symmetry Axes: 2 fold, 3 fold, & 5 fold.

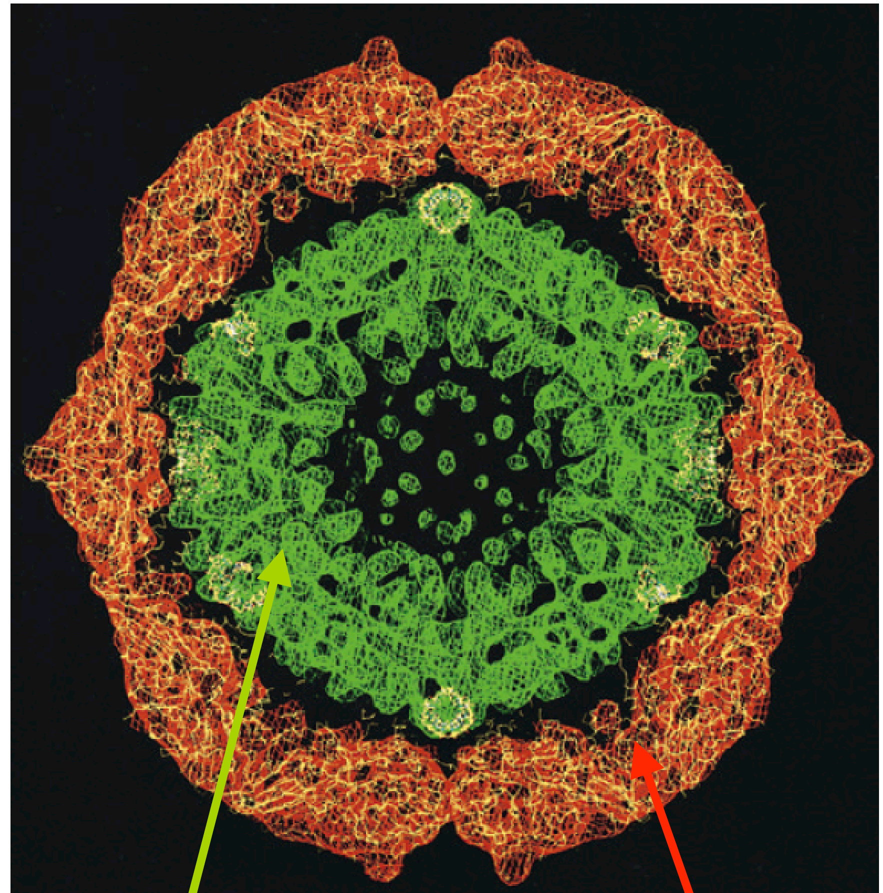
- No metabolism.
- No reproduction.
- "Pincus Principle."

Cryo-TEM



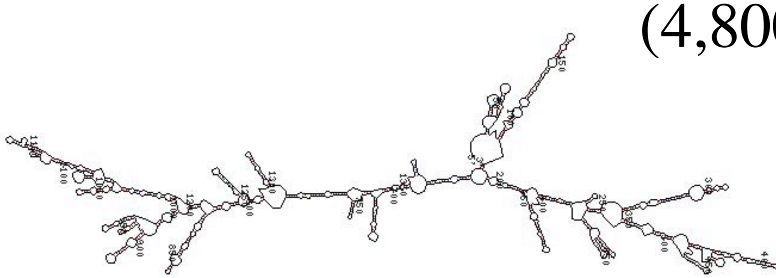
Flock-House Virus

X-ray Crystallography



Genome: two RNA molecules
(4,800 bases: 4 genes)

"Capsid":
180 identical proteins

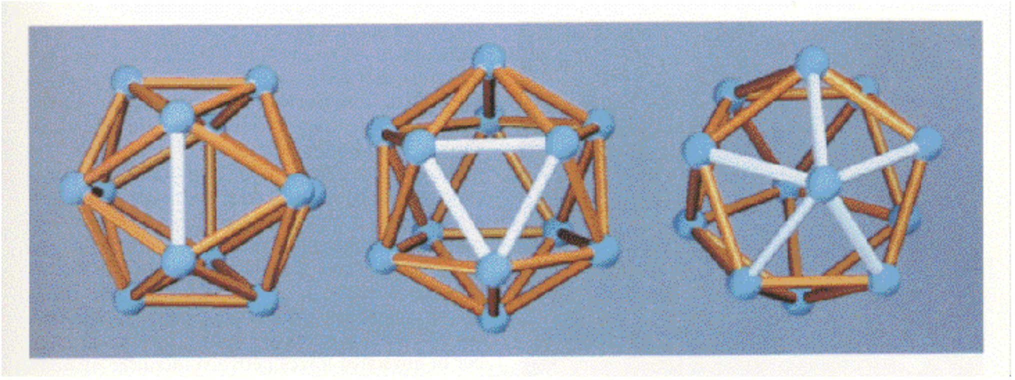


RNA1

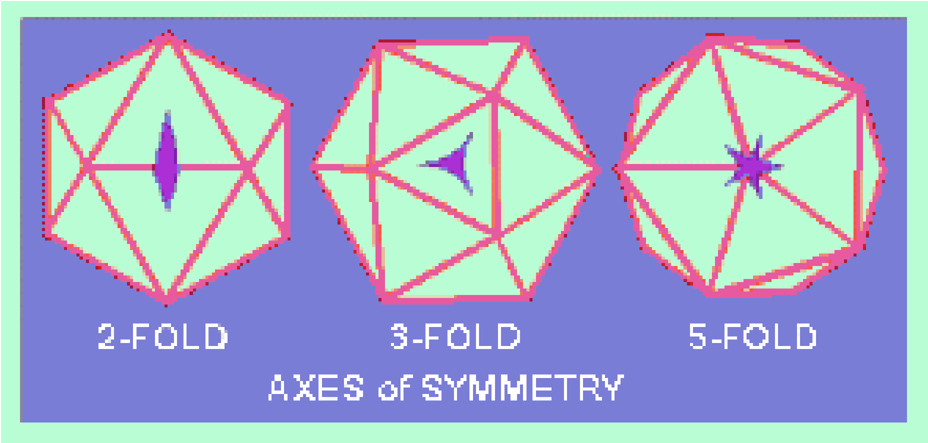
Icosahedral Symmetry

Aaron Klug, 1965

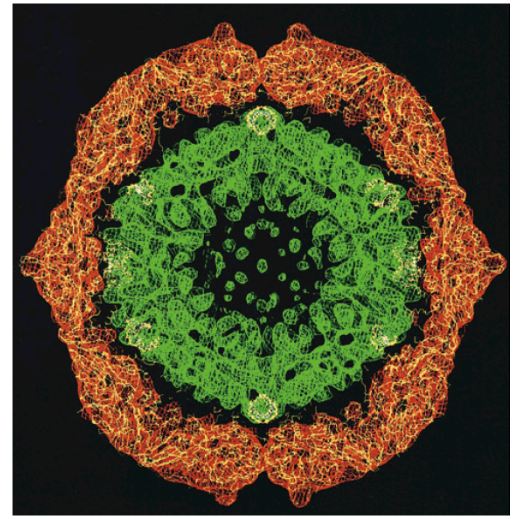
*Nearly all spherical viruses.
*Does not depend on details protein-protein interactions.



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



1) Why are viruses icosahedral?

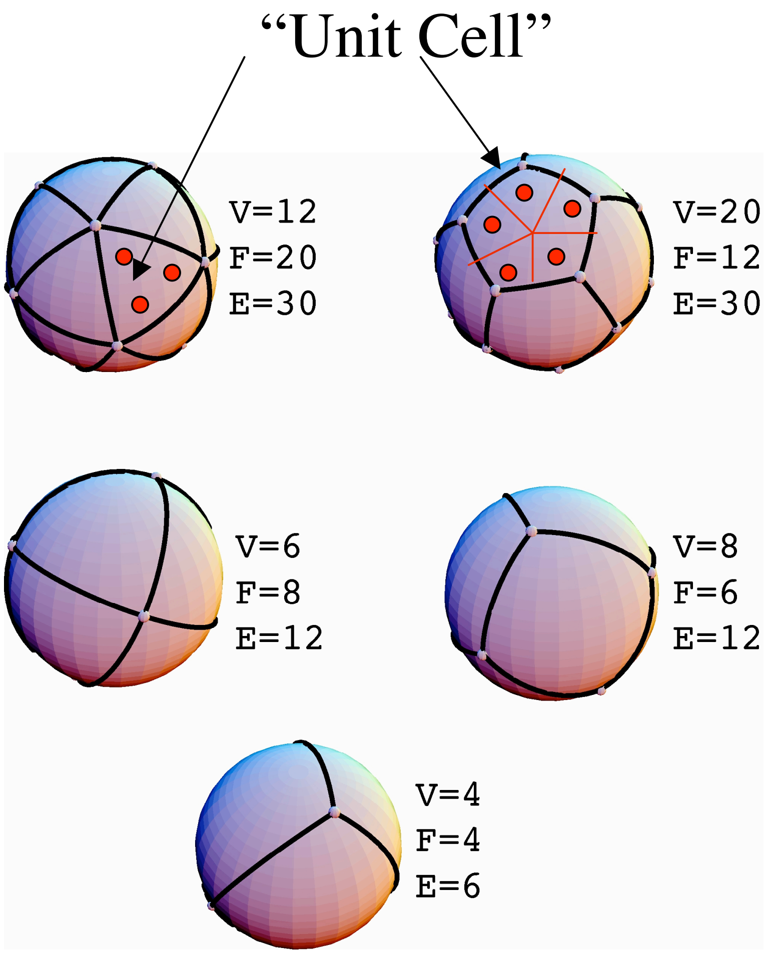


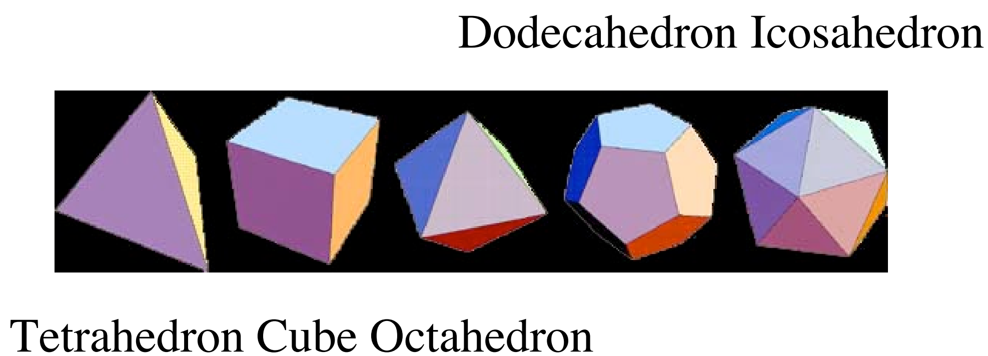
Francis Crick:
(crystallographer)

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

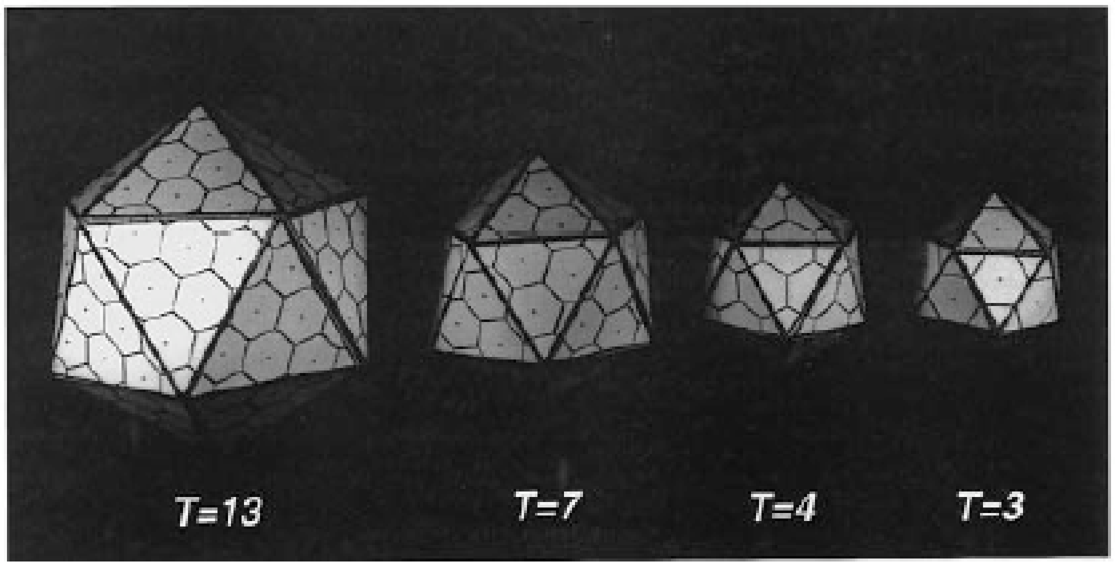
Lowest surface/volume ratio:

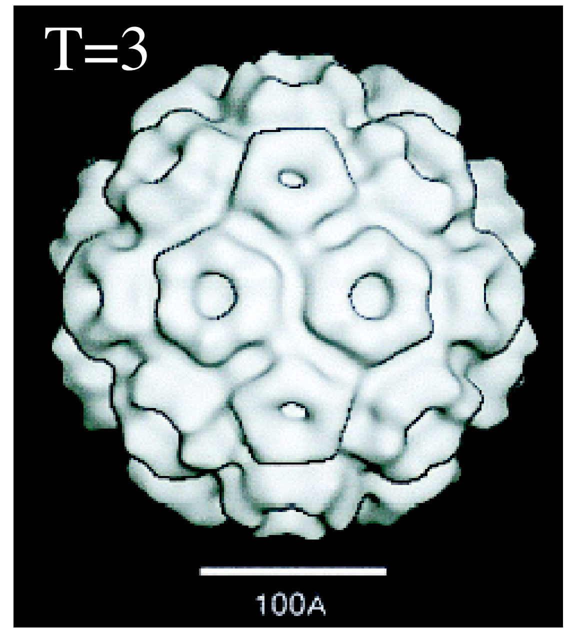
Icosahedron **60 proteins**

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

T-Number Classification: (Caspar & Klug, 1968)

-> Construct closed icosahedral shells from hexagonal sheets
-> 12 Pentamers





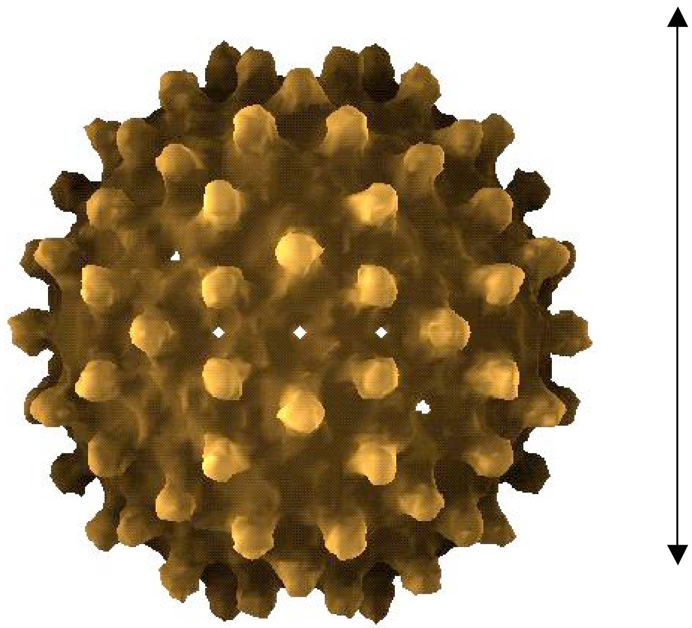
Capsomers: 10 T + 2 with T=1, 3, 4, 7,… (12 pentamers)
Proteins: 60 T

Nearly all spherical viral shells follow T-Number classification!

Buckminster Fuller

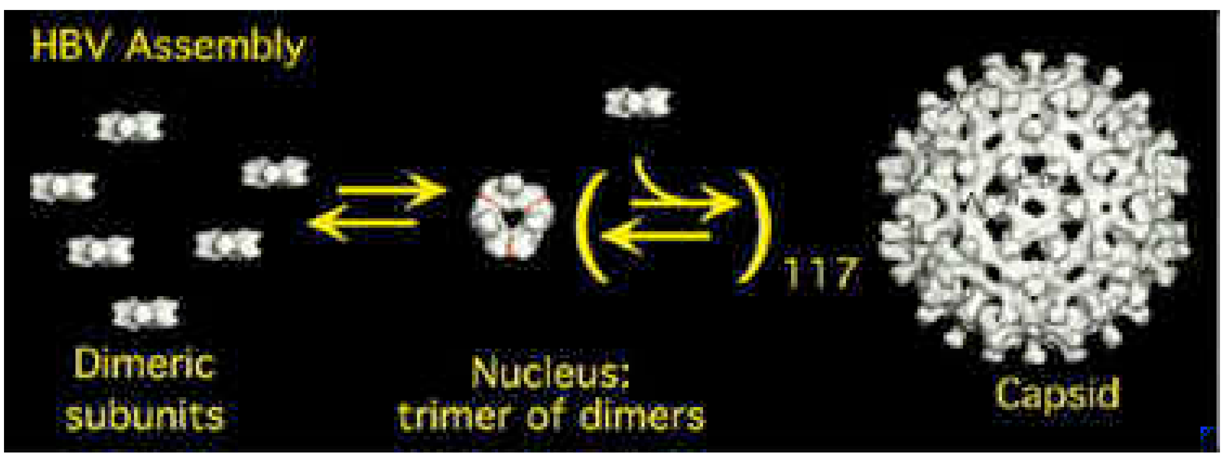
2) How is a virus assembled?

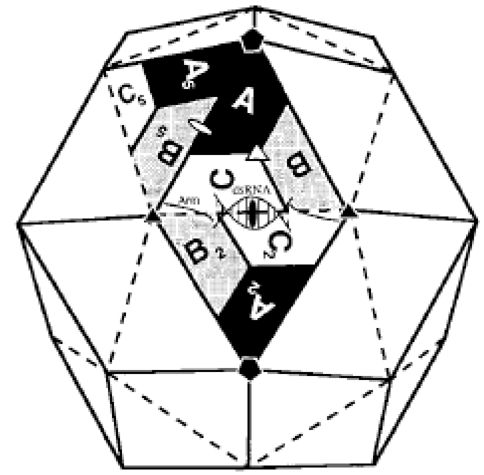
Ceres & Zlotnick (2002): Hepatitis B Virus



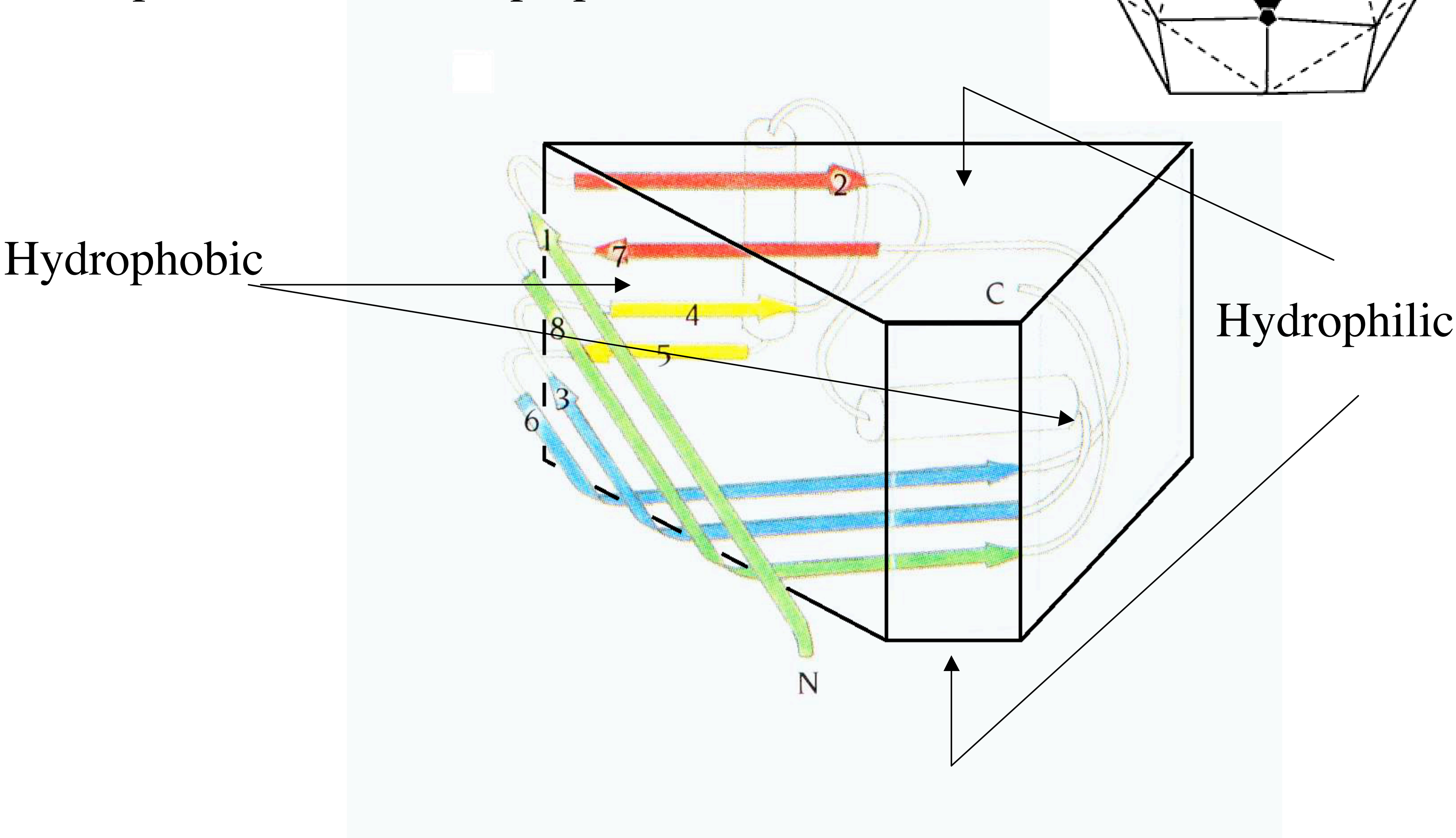
30 nm

240 protein capsid





Capsid Proteins: “Amphiphilic” molecules



Law of Mass Action: minimize free energy F

formation energy

free energy

$$\frac{\beta F}{\phi} = \underbrace{(1-f)\ln\phi(1-f)}_{\text{dimers}} + \underbrace{\frac{f}{N}\ln\phi\frac{f}{N} + \frac{f}{N}\beta\Delta f_c^{\,0}(N)}_{\text{capsids}}$$

dimers

capsids: N = 120 (T = 4)
N = 90 (T = 3)

equilibrium

$$\frac{\partial F}{\partial f} = 0 \Rightarrow f = NK\phi^{N-1}(1-f)^N$$

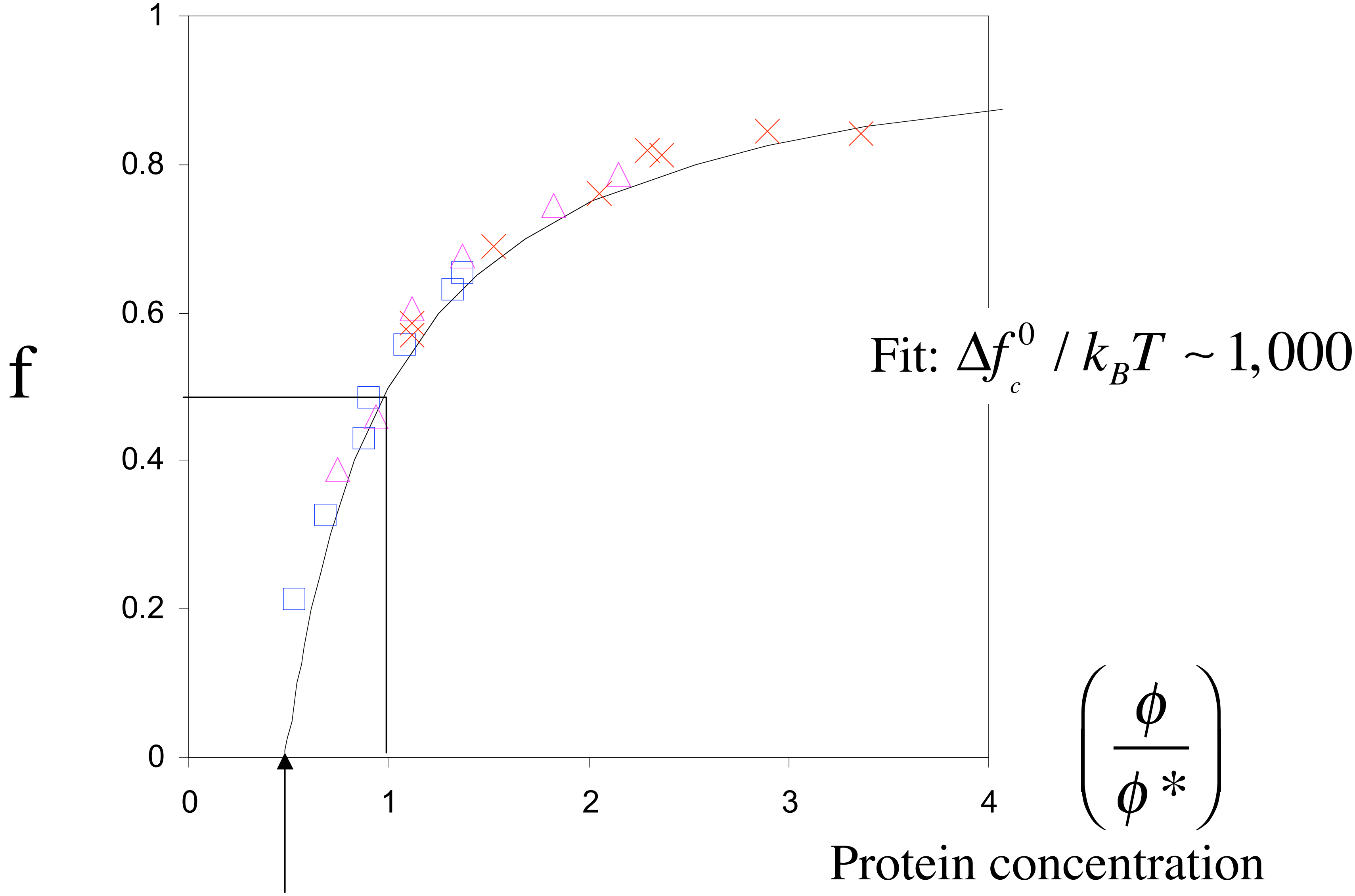
$$K = \exp - \beta\Delta f_c^0$$

f: fraction of protein in capsid form.

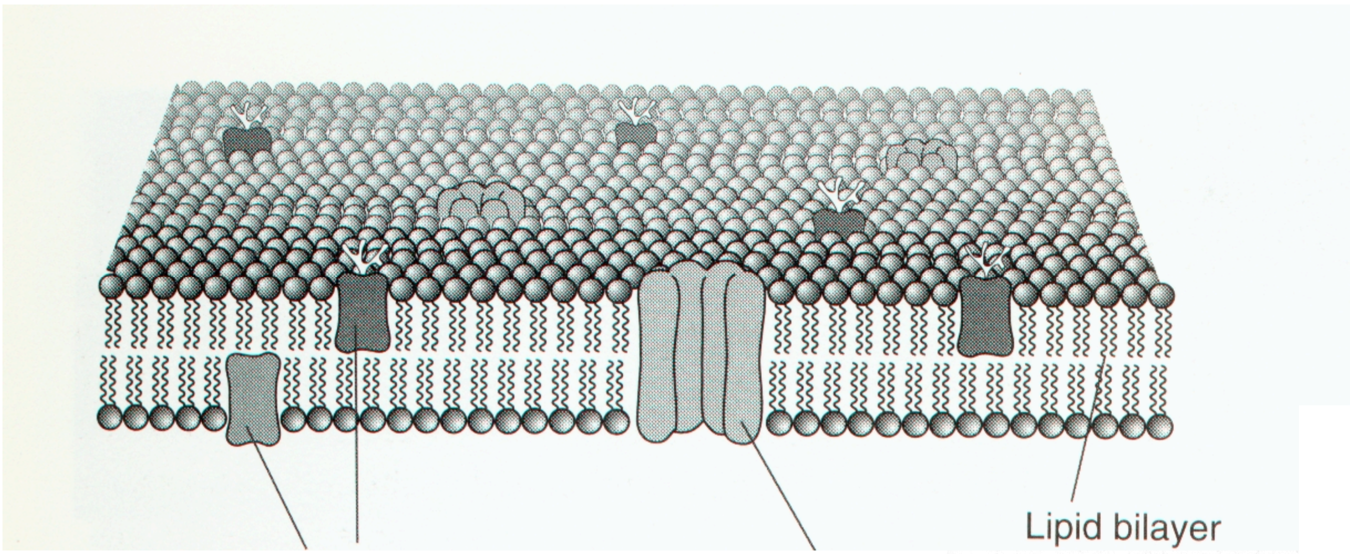
ϕ: concentration of proteins.

(van der Schoot & Kegel)

Capsid Protein Fraction (HBV)



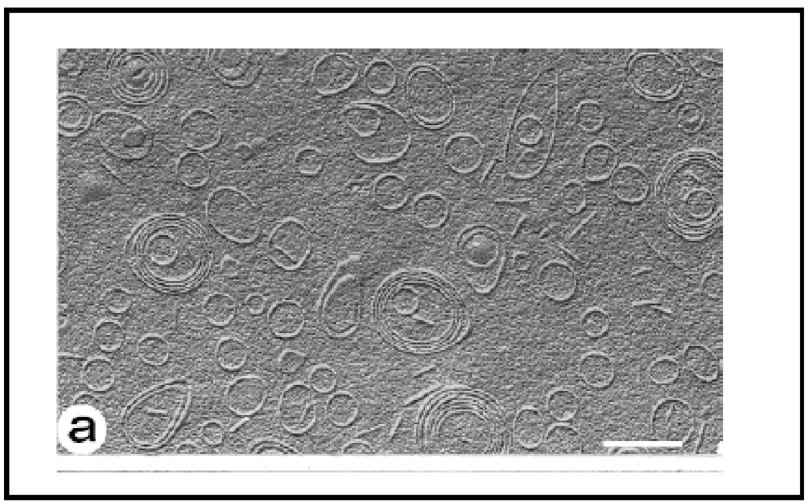
Self-Assembly by “Amphiphiles”

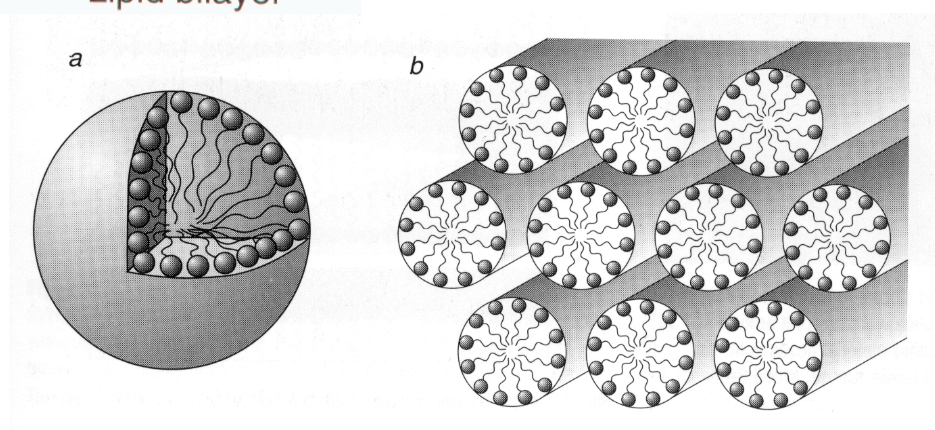


Hydrophilic

Hydrophobic

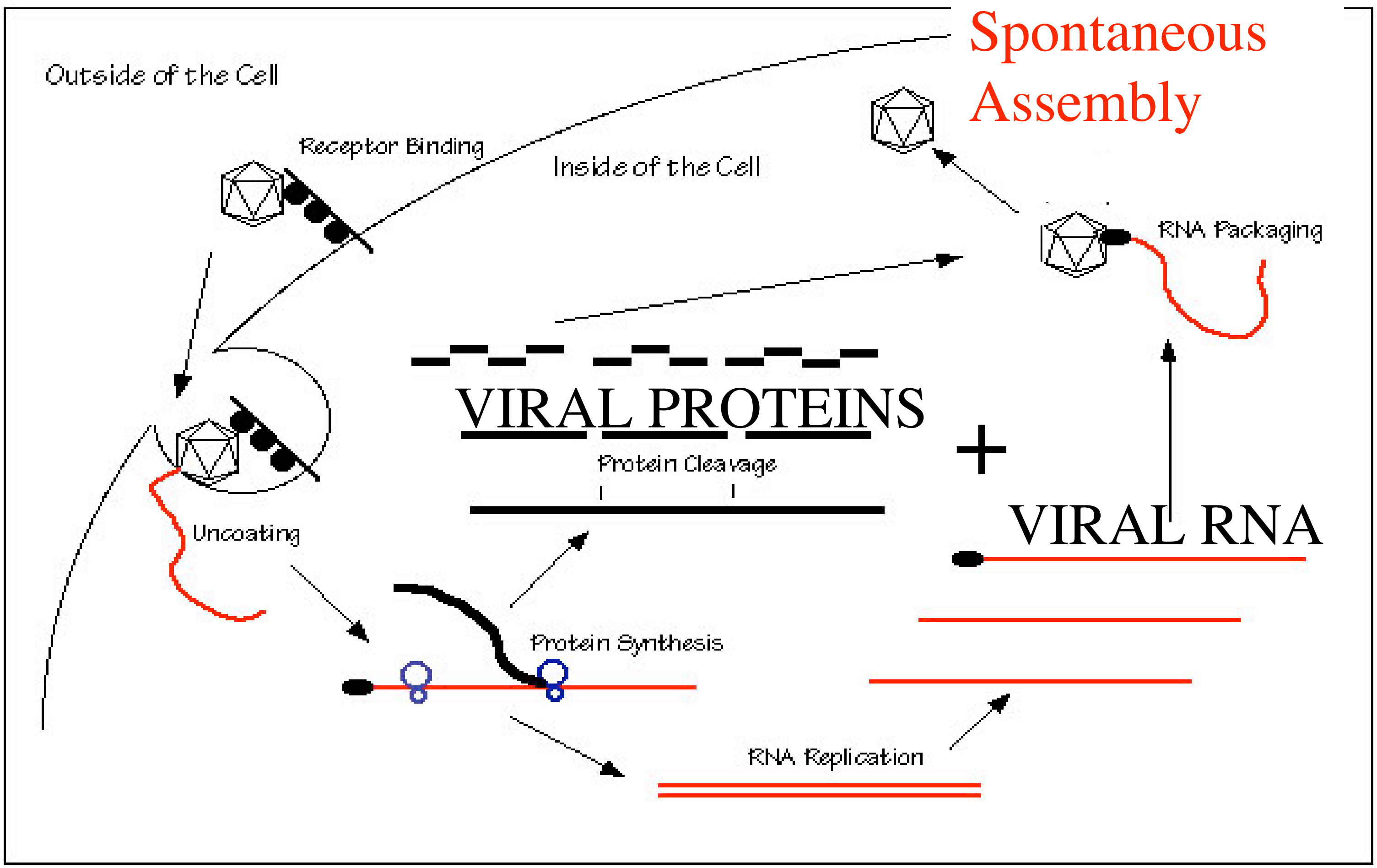
Vesicles





“Free Energy Minimization”

Virus Life Cycle (Polio)



3) <u>Formation Energy?</u>

Icosahedral symmetry: energy minima?

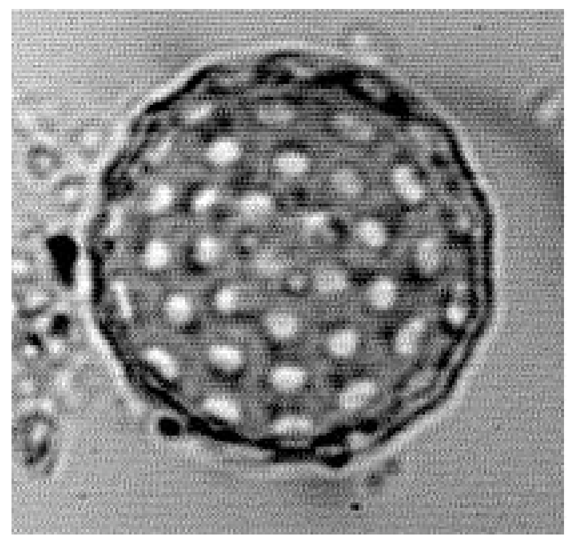
Capsomer

*Treat capsomers as *attractive disks*. (hydrophobic edge)

*Pack *maximum number* of disks on the sphere: "Tammes Problem".

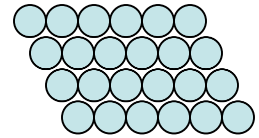
$$\rho(N) = \frac{Surface\ Area\ N\ disks}{Surface\ Area\ Sphere}$$

Measure of attractive energy.

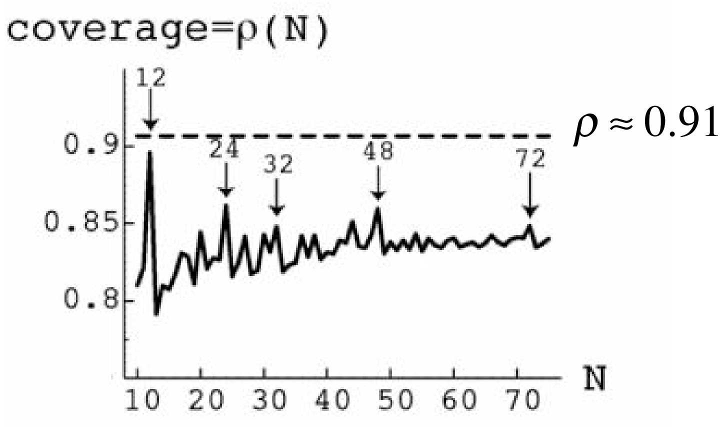


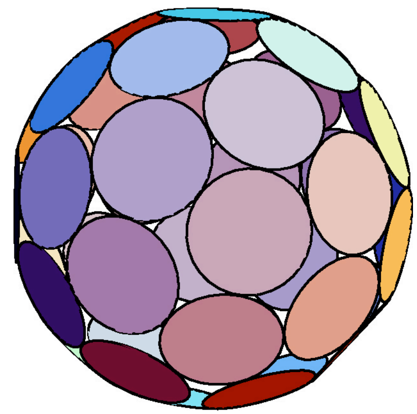
*Maximum coverage of a *flat* surface: Hexagonal close-packing.

$\rho \approx 0.91$

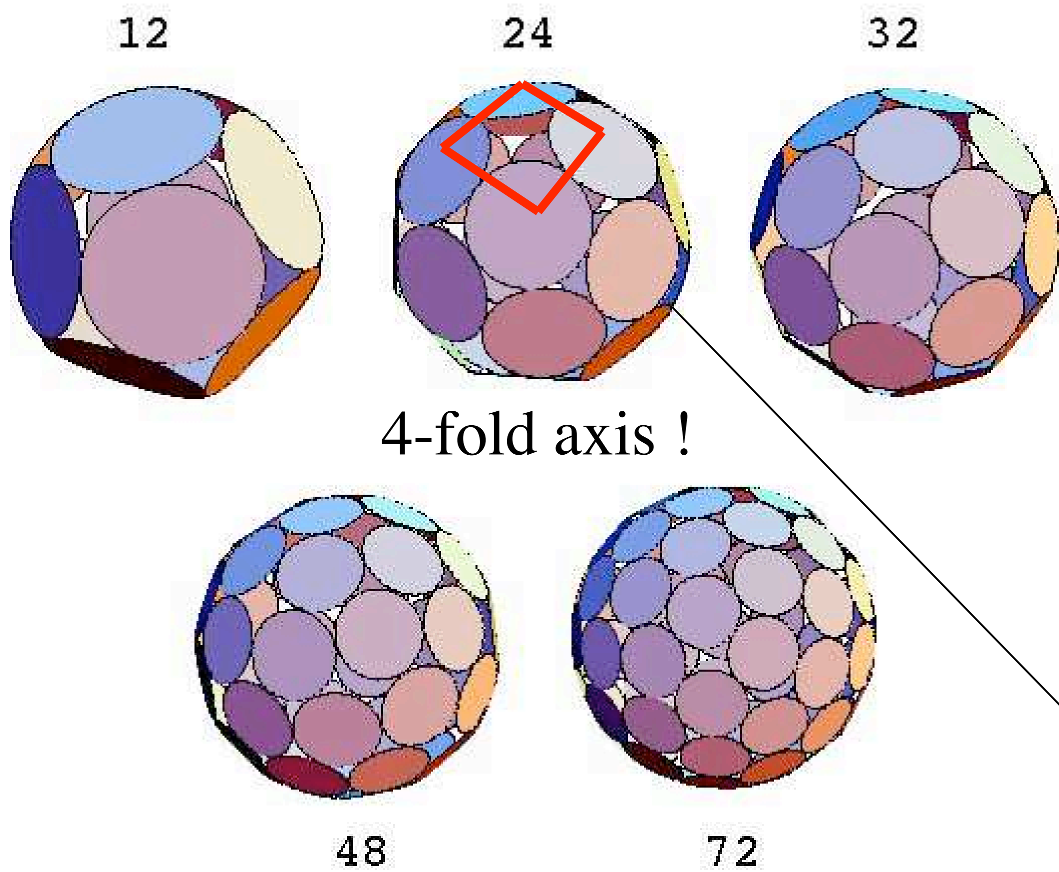


*Maximum coverage of a sphere:

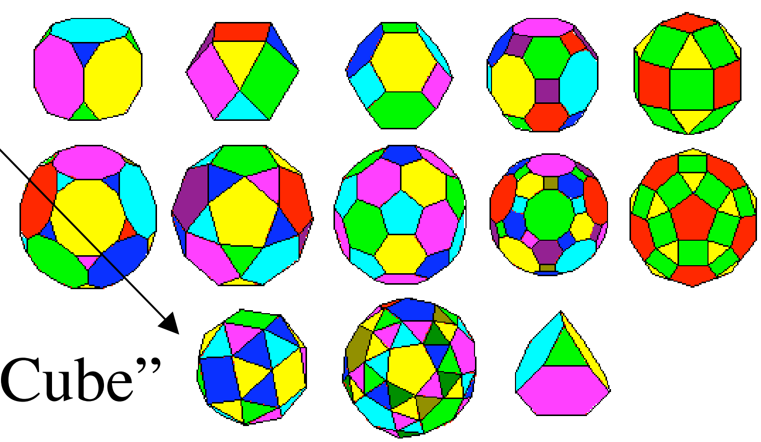




Tammes shells with high coverage: N= 12, 24, 32, 48, or 72.



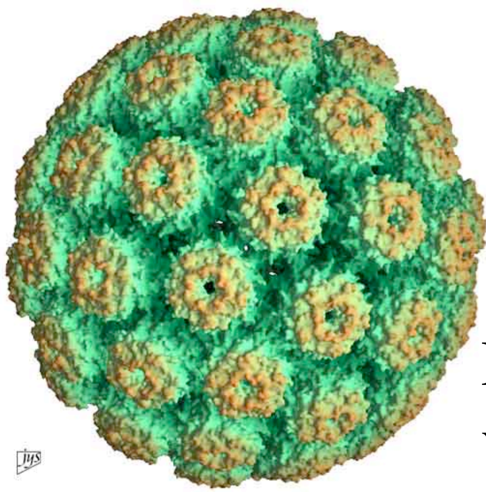
13 “Archimedean” Solids.



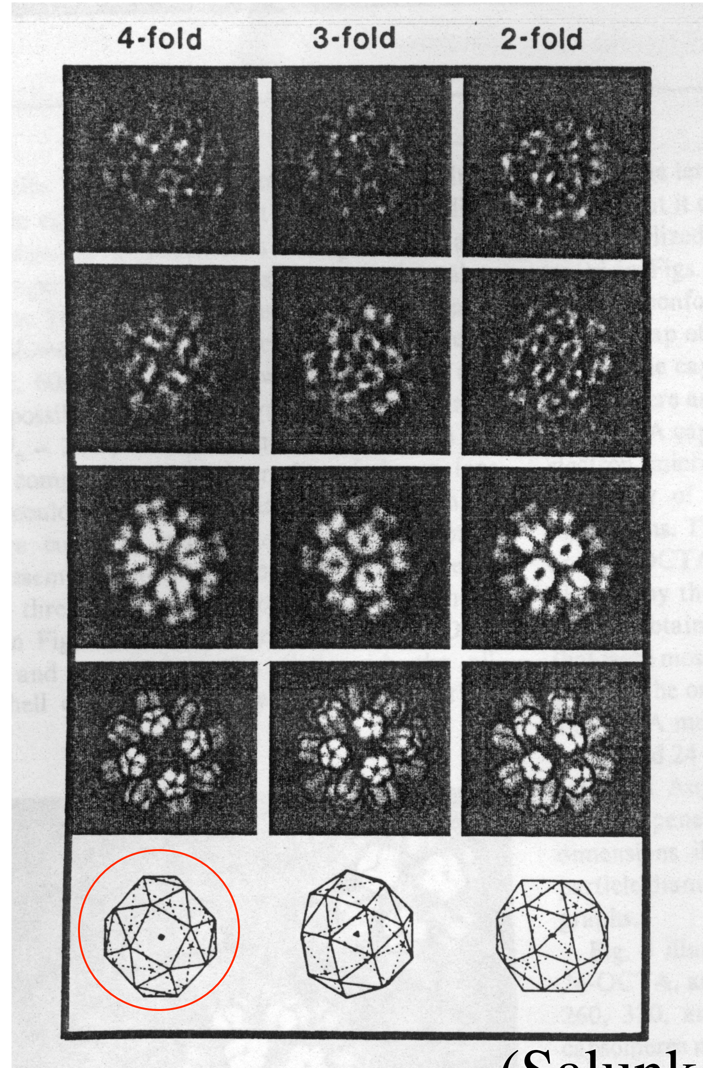
“Snub Cube”

Only Tammes shell with icosahedral symmetry is N=12!?

*Model Unrealistic?



Polyoma virus



(Salunke)

Aggregates of capsid proteins:
Spherical with N=12, N=24, & N=72.

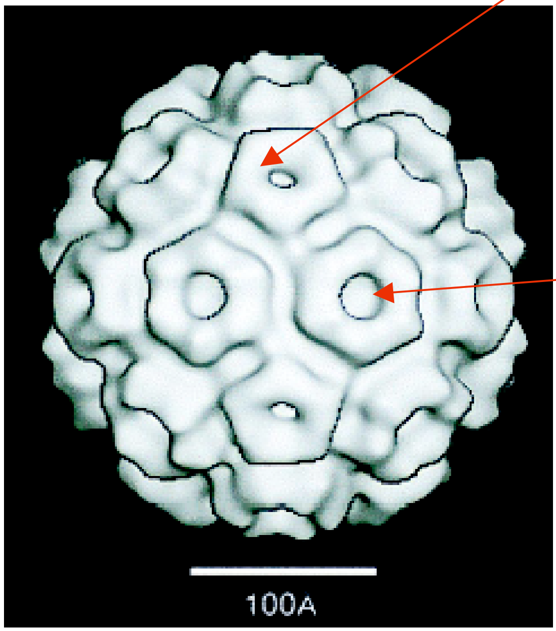
N=24: Snub-Cube!

*Non-icosahedral structures: thermodynamically stable!
*What's special about Polyoma ? *All capsomers same*.

Cowpea Chlorotic Mottle Virus ("CCMV")

TWO capsomer types:

Pentamers (12)

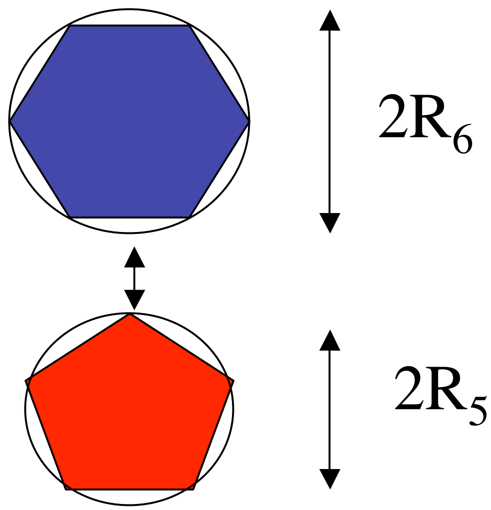


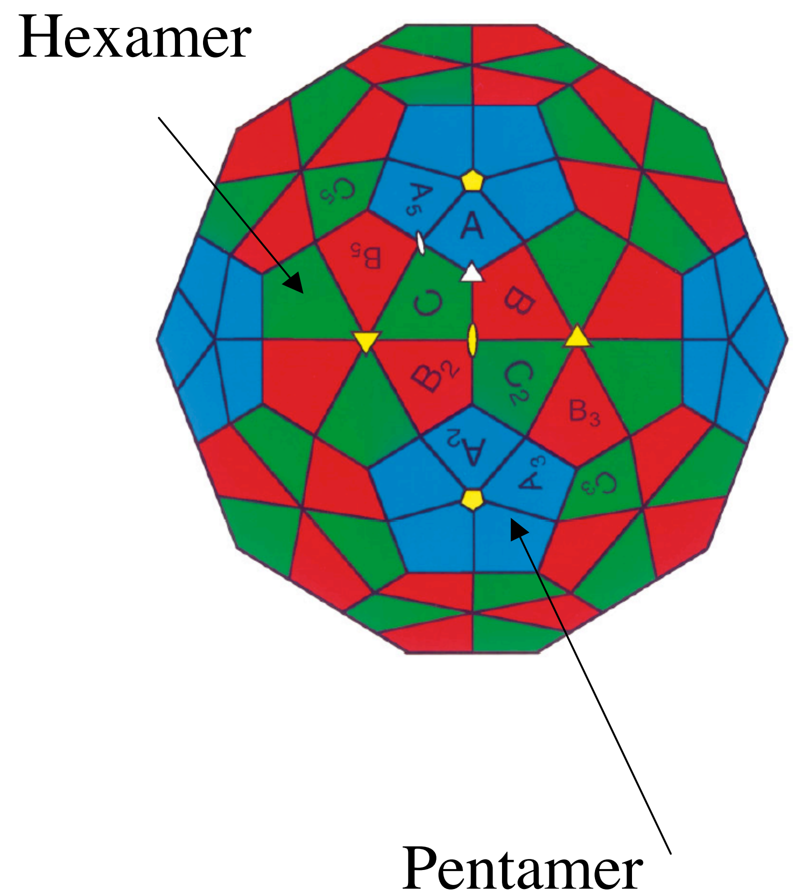
Hexamers (20)

Icosahedral Symmetry: Pentamers at 12 five-fold sites

Two-State Capsomer Model

Capsomer: Hexamer or Pentamer





*Size Difference $R_5 / R_6 = 0.93$

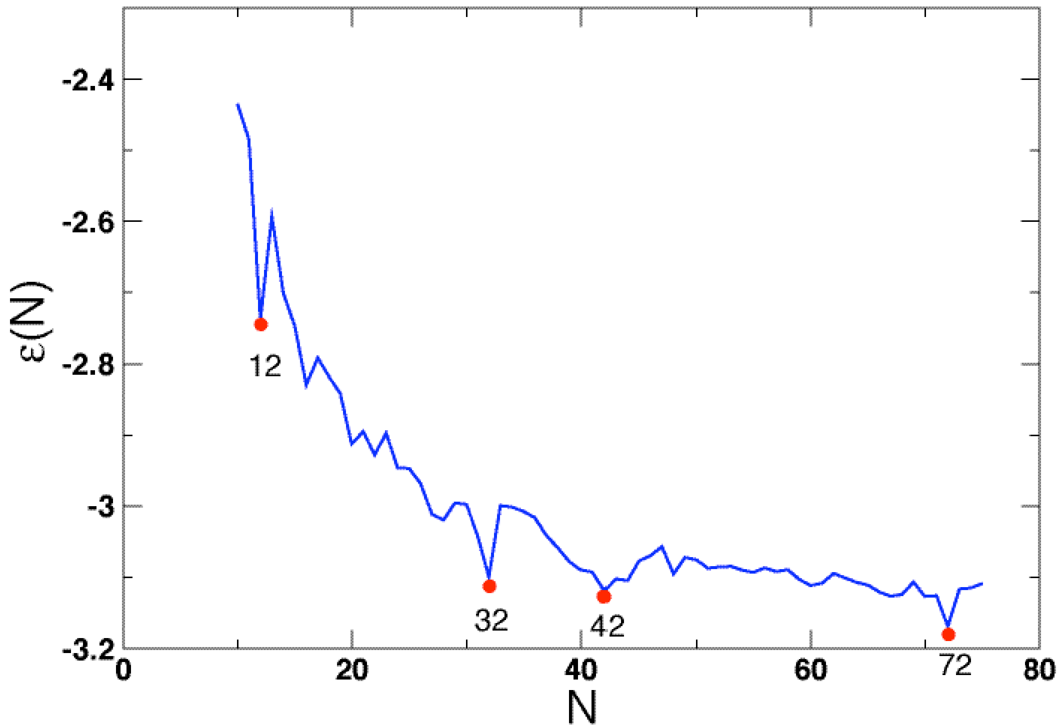
*Adjustable Energy Difference: ΔE

*$N_5 + N_6 = N$ fixed

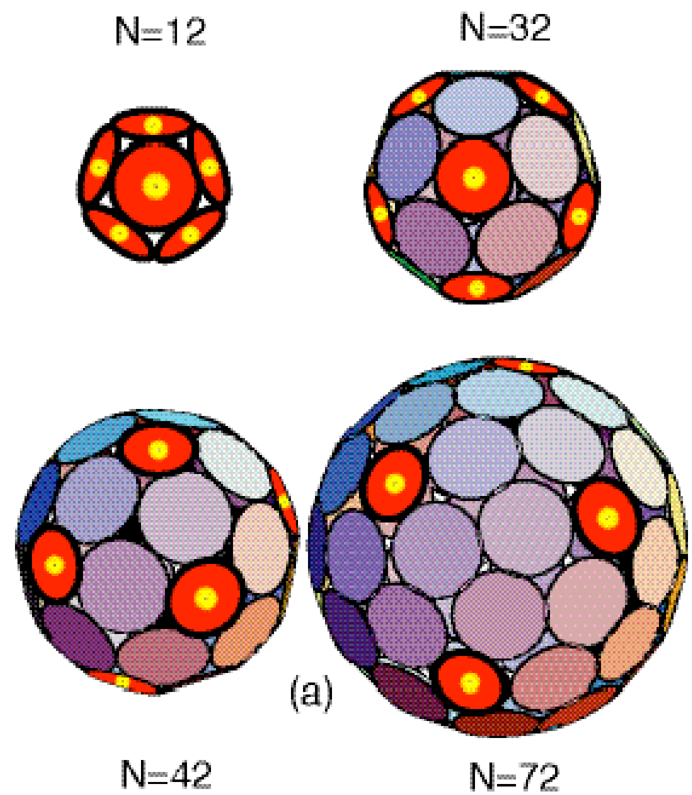
Variable

*Numerical simulation (Roya Zandi & David Reguera)

***Energy per capsomer versus the Number N of capsomers ($\Delta E=0$)**

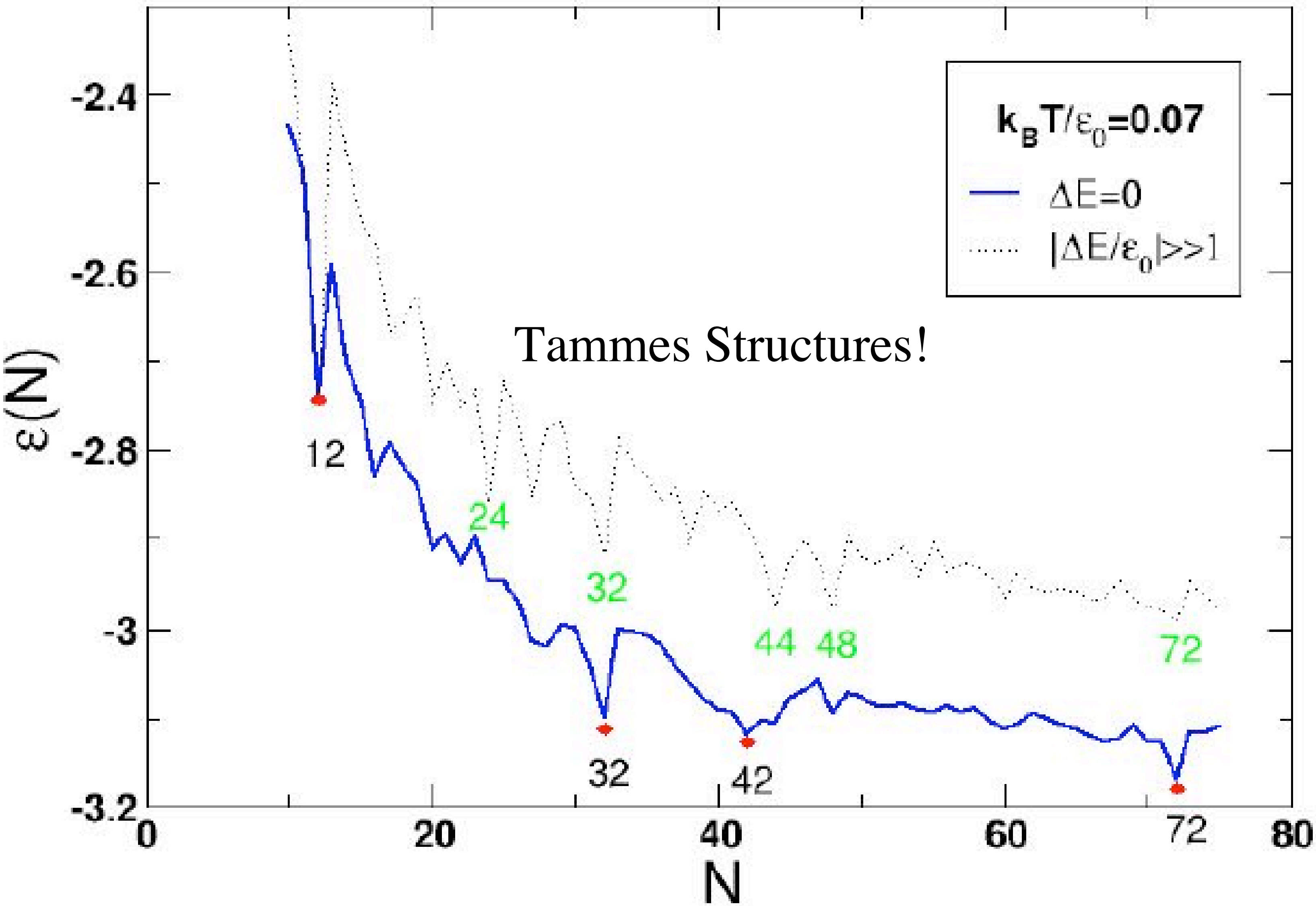


Capsid structure associated with the minima of energy



Energy Minima: T-Number Icosahedra

Increase ΔE ?



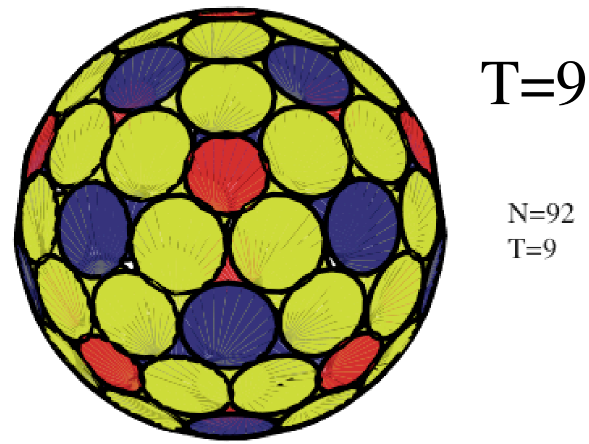
k_BT/ε_0=0.07
ΔE=0
$|\Delta E/\varepsilon_0|$>>1
Tammes Structures!
12
24
32
32
44
48
42
72
72
ε(N)
N
-2.4
-2.6
-2.8
-3
-3.2
0
20
40
60
80

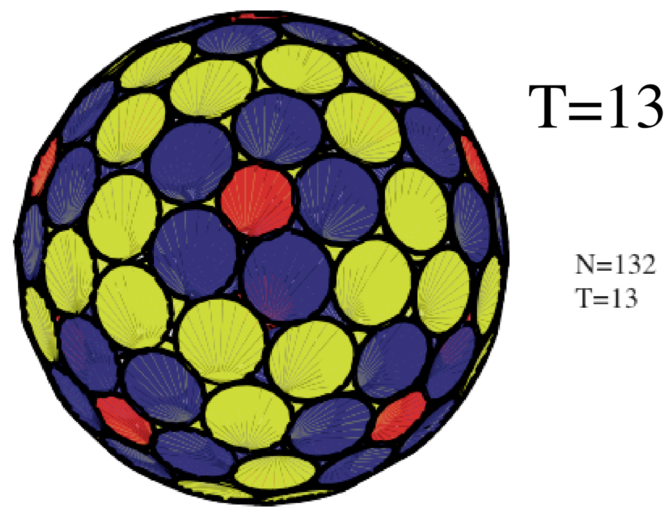
Icosahedral symmetry is not obligatory!
Advantage ?

High Elastic Stress

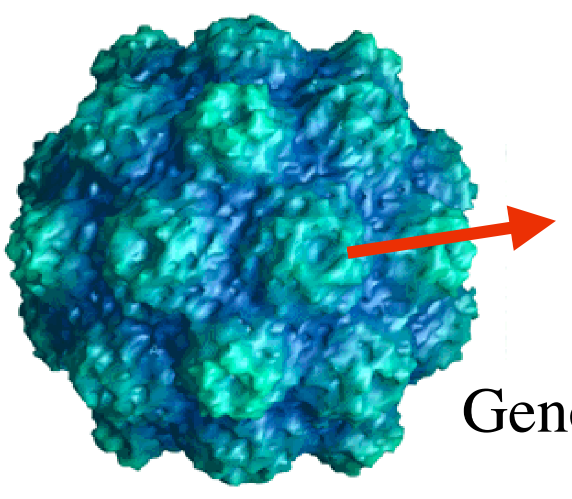
Intermediate Stress

Low Stress



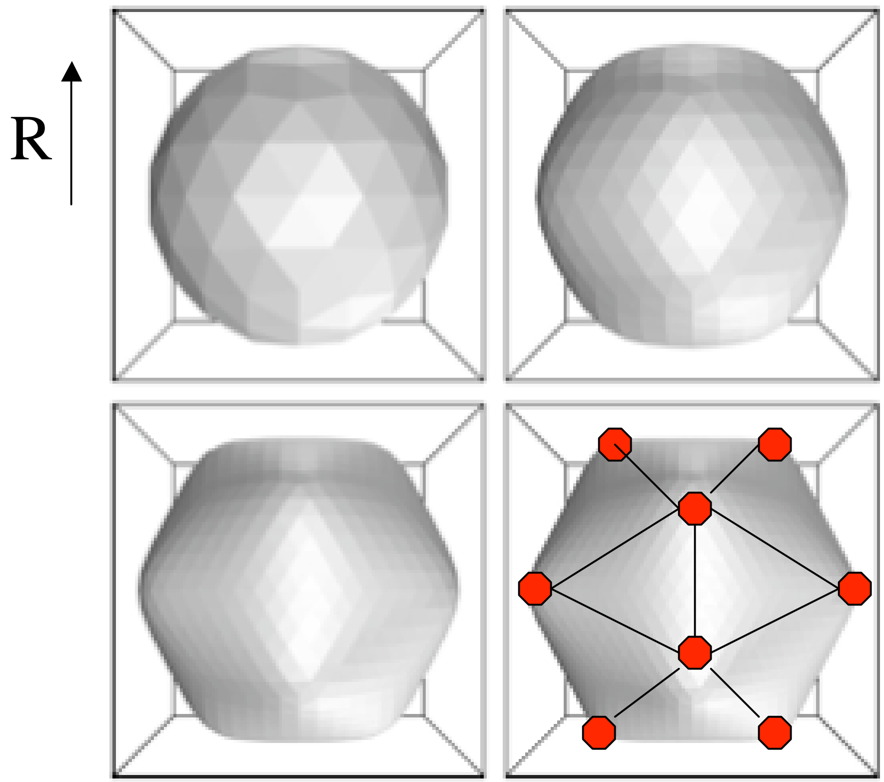


Five-fold sites: *Focus of strong radially outward force.*



Genome release: Pentamer ejection (Tymovirus)

Elasticity Theory (D.Nelson)



"Young's Modulus"

Thickness

$$"FK\#" = \frac{YhR^2}{\kappa}$$

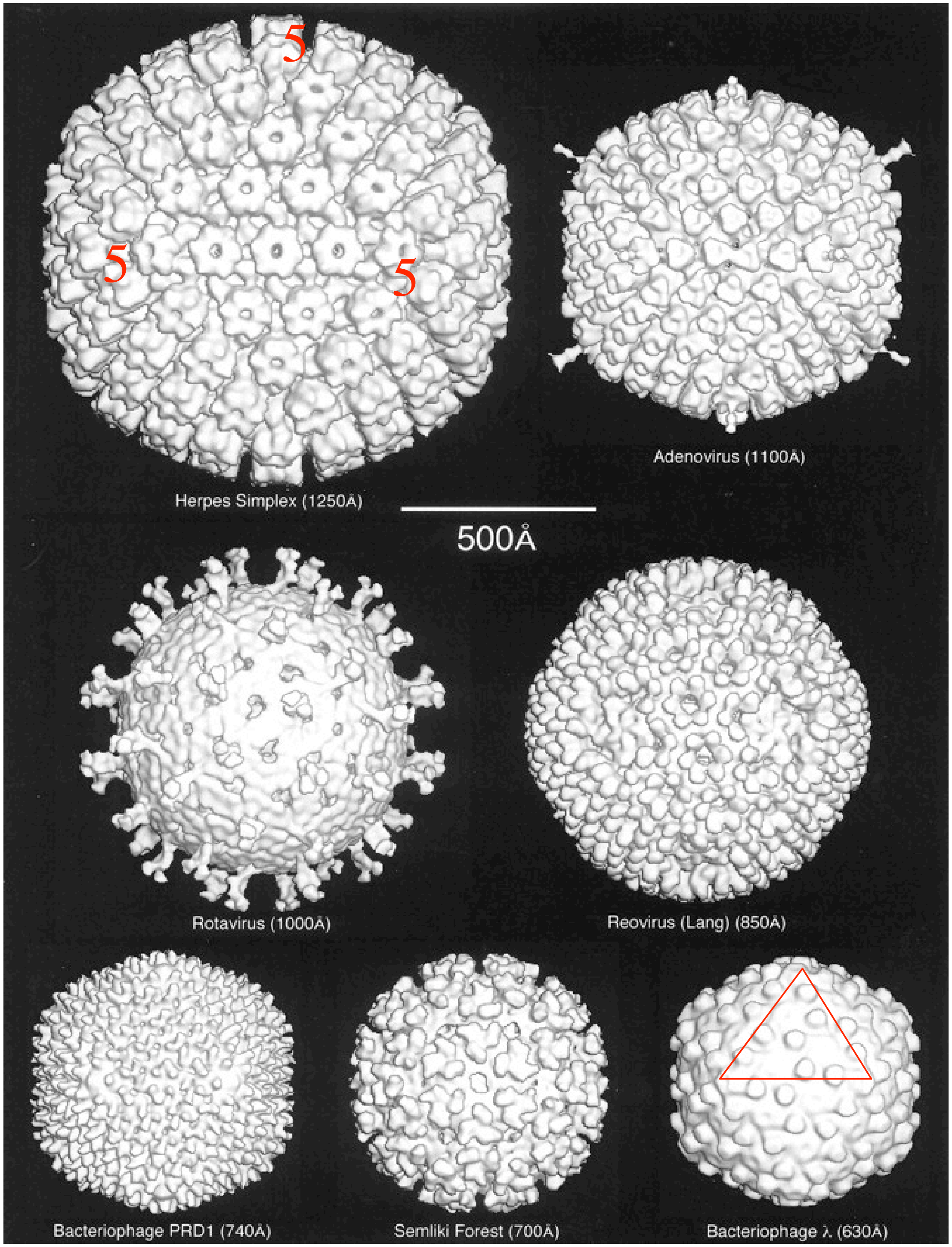
"Bending Modulus"

Buckling Transition:

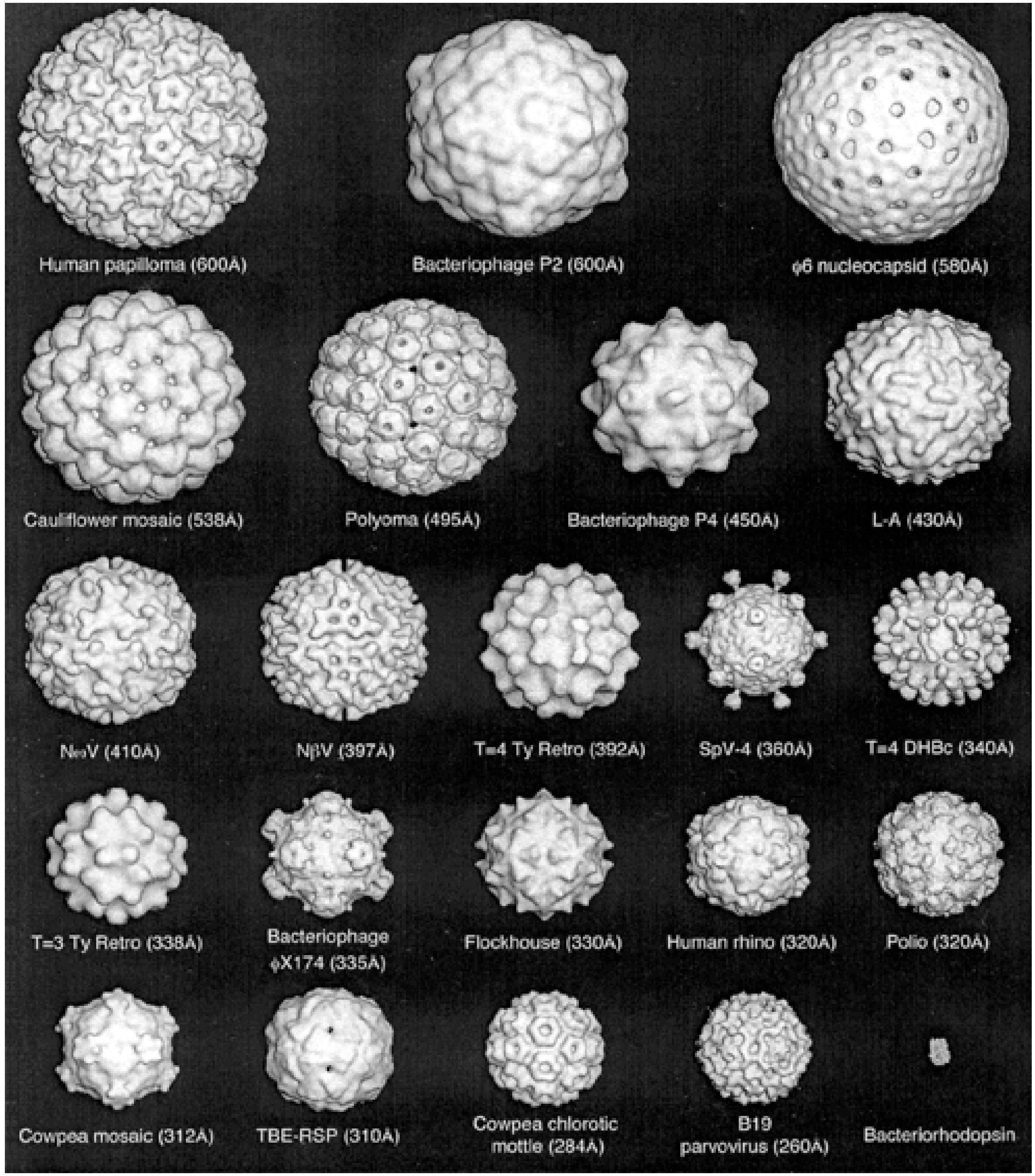
FK < 10^3: Spherical Shell.

FK > 10^3 : Icosahedral Shell.

Large R


5
5
5
Herpes Simplex (1250Å)
Adenovirus (1100Å)
500Å
Rotavirus (1000Å)
Reovirus (Lang) (850Å)
Bacteriophage PRD1 (740Å)
Semliki Forest (700Å)
Bacteriophage λ (630Å)

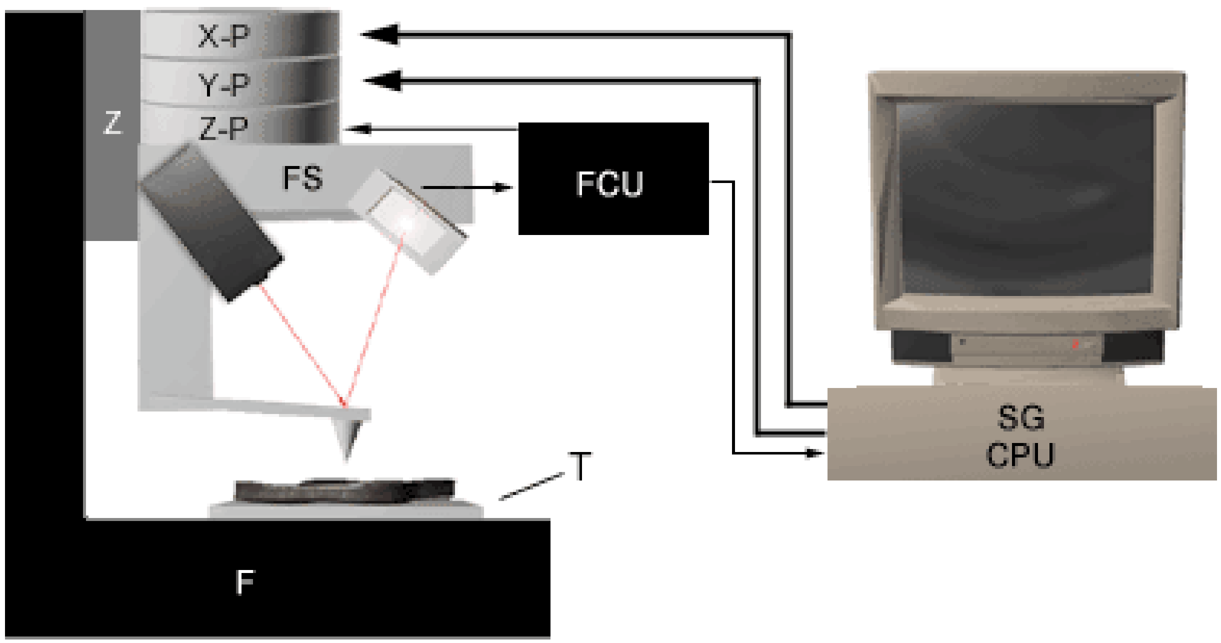
Small R



Human papilloma (600Å)
Bacteriophage P2 (600Å)
φ6 nucleocapsid (580Å)
Cauliflower mosaic (538Å)
Polyoma (495Å)
Bacteriophage P4 (450Å)
L-A (430Å)
NωV (410Å)
NβV (397Å)
T=4 Ty Retro (392Å)
SpV-4 (360Å)
T=4 DHBc (340Å)
T=3 Ty Retro (338Å)
Bacteriophage φX174 (335Å)
Flockhouse (330Å)
Human rhino (320Å)
Polio (320Å)
Cowpea mosaic (312Å)
TBE-RSP (310Å)
Cowpea chlorotic mottle (284Å)
B19 parvovirus (260Å)
Bacteriorhodopsin

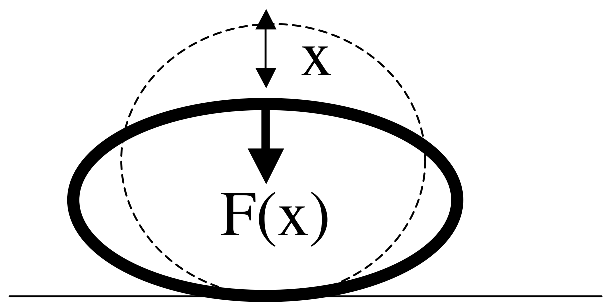
Are viral capsids *really* miniature elastic shells ?

•Capsid proteins have a complex internal structure.



"Atomic Force Microscope" (AFM)

Force (F) versus Compression (x).



Hollow Elastic Shell:

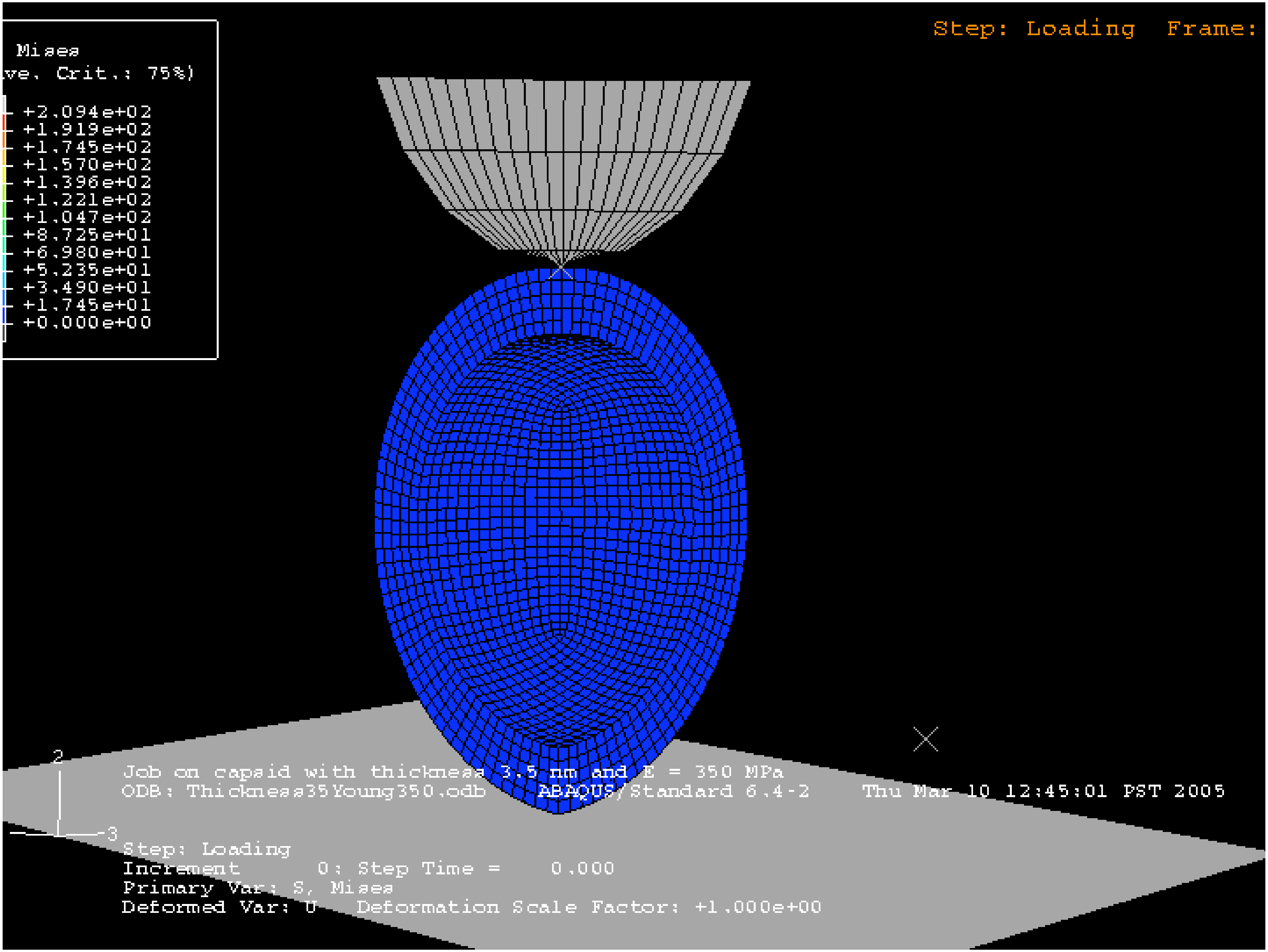
F(x) = kx

k: spring constant

$$k = 2.25 \frac{Yh^2}{R}$$

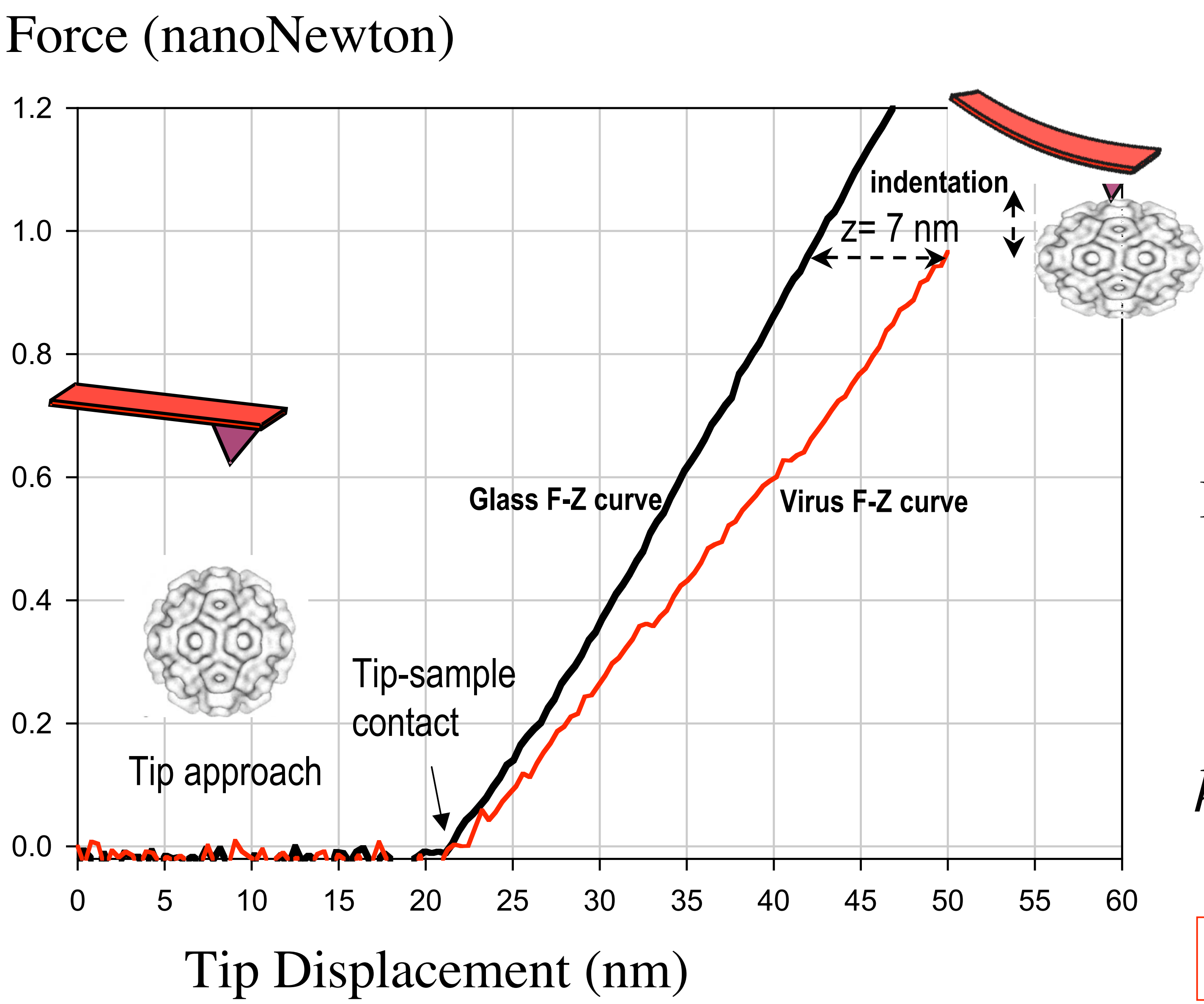
Y: Young's Modulus
h: Thickness
R. Radius

M.Gibbons & W.Klug


Mises
ve. Crit.: 75%)
+2.094e+02
+1.919e+02
+1.745e+02
+1.570e+02
+1.396e+02
+1.221e+02
+1.047e+02
+8.725e+01
+6.980e+01
+5.235e+01
+3.490e+01
+1.745e+01
+0.000e+00
Step: Loading Frame:
2
3
Job on capsid with thickness 3.5 nm and E = 350 MPa
ODB: Thickness35Young350.odb ABAQUS/Standard 6.4-2 Thu Mar 10 12:45:01 PST 2005
Step: Loading
Increment 0: Step Time = 0.000
Primary Var: S, Mises
Deformed Var: U Deformation Scale Factor: +1.000e+00

CCMV – empty capsid

J-P. Michel&
C. Knobler



$$F(z) = kz$$

↓

k=0.13 N/m

↓

$$k = 2.25\,\frac{Yh^2}{R}$$

↓

Y≈ 0.1-1.0 GPa

(Microtubules)

Roya Zandi

David Reguera

Jean-Philippe Michel

Joe Rudnick

Bill Gelbart

Chuck Knobler