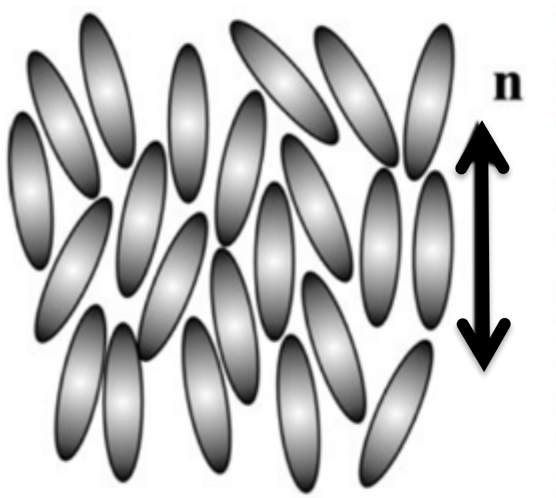
Orientational Phase Transitions and the Assembly of Viral Capsids

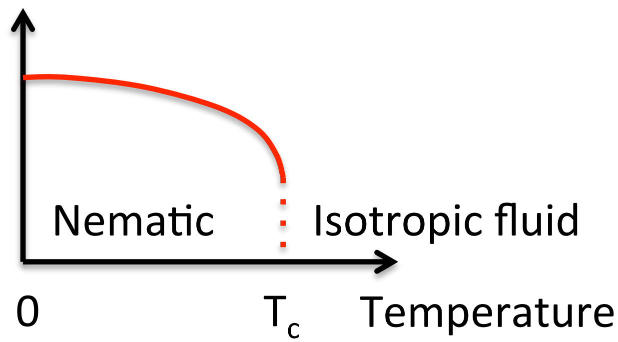
i) Lorman-Rochal theory and the Landau theory of orientational ordering in liquid crystals and glasses.

ii) Extensions of Lorman-Rochal theory.

Orientational ordering in liquid crystals and glasses

- Nematic liquid crystals.

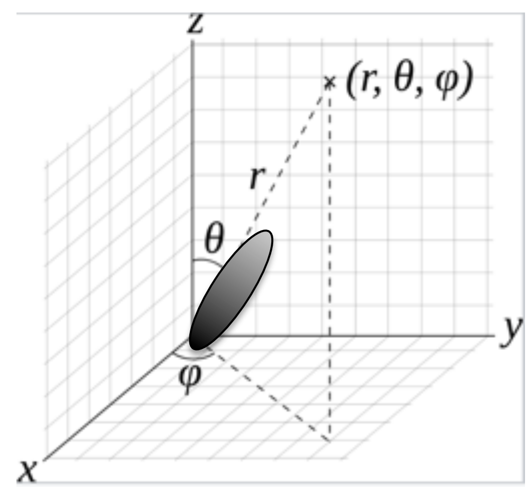




First-order phase transition

Order parameter

$$S = \left\langle P_2^{\,0}(\cos\theta) \right\rangle = \left\langle \frac{3\cos^2\theta - 1}{2} \right\rangle$$



Second Legendre polynomial $P_2^0(x) = (3x^2\text{-}1)/2$?

- Biaxial Nematics (Freiser, 1970)

Two order parameters: S and T

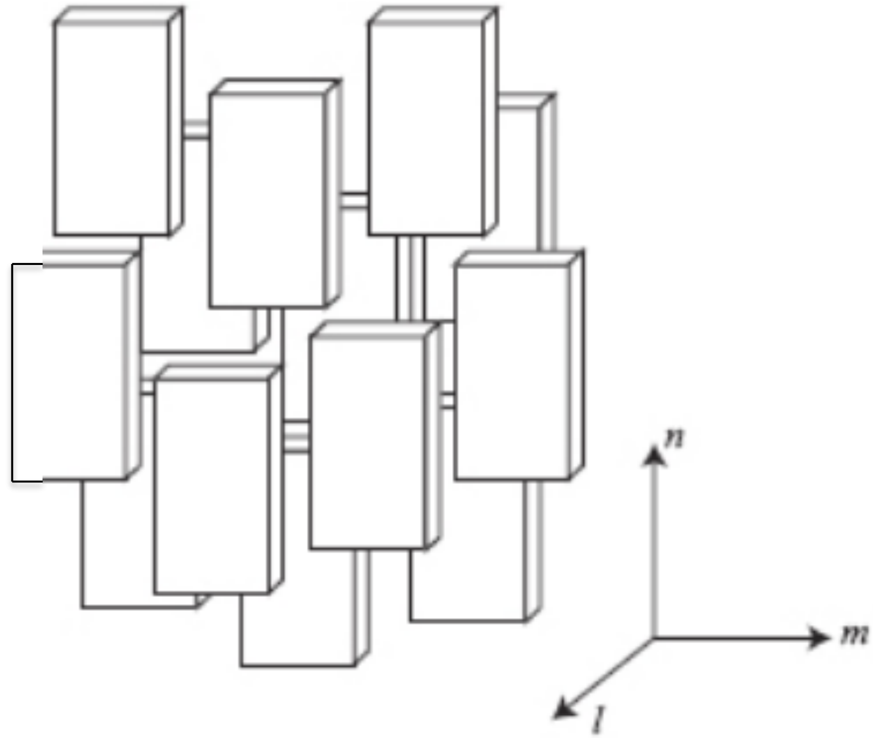
S = T = 0 isotropic

↓

S ≠ 0, T = 0 uniaxial nematic

↓

S ≠ 0, T ≠ 0 biaxial nematic

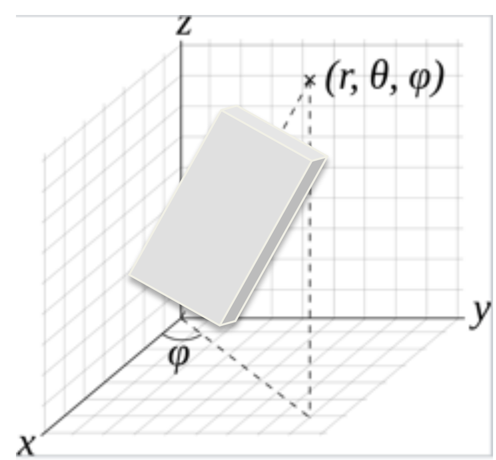


Order parameters

$$S = \left\langle P_2^0(\cos\theta) \right\rangle$$

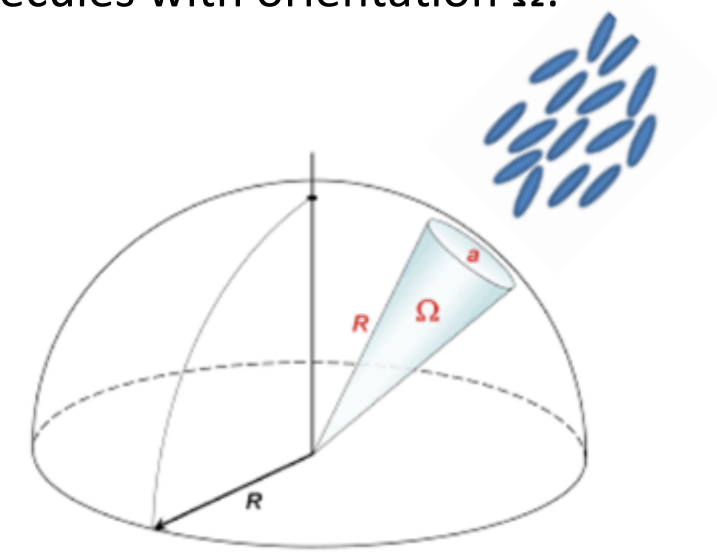
$$T = \left\langle P_2^2(\cos\theta)\exp(i\varphi) \right\rangle = \left\langle P_2^{-2}(\cos\theta)\exp(-i\varphi) \right\rangle$$

$P_2^2(x) = 3\,(1-x^2)$ *Associated* Legendre polynomials ??



- General case: measure the density $\rho(\Omega)$ of molecules with orientation Ω.

- ``Spherical Fourier decomposition”.



$$\rho(\Omega)=\sum_{L=0}^{\infty}\sum_{M=-L}^{+L} Q_{L,M} Y_{L,M}(\Omega)$$

- Spherical Harmonics

$$Y_{L,M}(\theta,\varphi) \propto P_L^M(\cos\theta)\exp(iM\varphi)$$

- Expansion coefficients $Q_{L,M}$ *Orientational order parameter set*

Infinite hierarchy of Orientational Transitions

- Biaxial nematics: L = 2, M = 0, ±2
- Cholesterics, blue phases: L = 2, M = 0, ±1, ±2 Hornreich & Shtrikman (1980, 1981).
- “Cubatic” liquid crystal: L = 4 Nelson & Toner (1981)

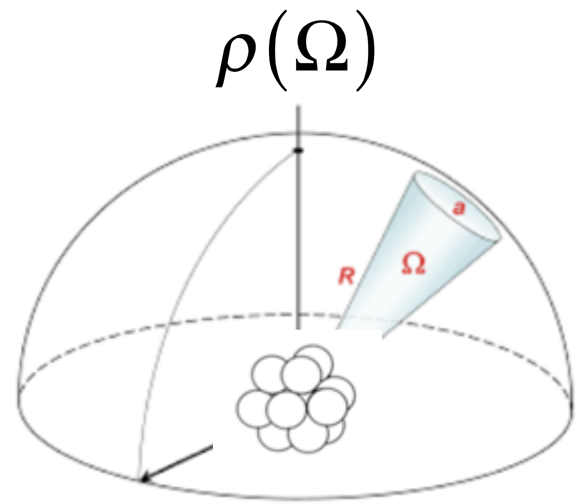
- Icosahedral Glasses/Quasicrystals: L=6 (Steinhardt, Nelson, Ronchetti 1983)

- ρ(Ω): surface density modulation of cluster of atoms in liquids near melting.
  (no positional order)

FCC cluster

HCP cluster

Icosahedral cluster



- What is the best choice for the symmetry of the clusters?
    - Rules of Landau Theory

Lev
Landau

Rule # 1: Free energy = Sum of the scalar invariants of the order parameters $Q_{L,m}$ (under group SO(3) of rotations).

Rule # 2: Use one ``irreducible representation". Pick one single L. (but which L?)

Rule # 3: Minimize free energy with respect to $Q_{L,M}$.

``Wigner 3-j symbol"

$$F = r \sum_{M=-L}^{+L} \left| Q_{LM} \right|^2 + w \sum_{\left\{ \substack{-L \le M_{1,2,3} \le L \\ M_1+M_2+M_3=0} \right\}} \begin{pmatrix} L & L & L \\ M_1 & M_2 & M_3 \end{pmatrix} Q_{L\,M_1} Q_{L\,M_2} Q_{L\,M_3} + u\{Q^4\} + ..$$

quadratic invariant cubic invariant quartic invariant

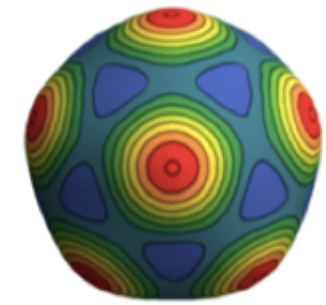
- r, w, u : Phenomenogical parameters.

- Simpler: expand free energy in powers of orientational density ρ (Ω)

$$F\left(\left\{\rho(\vec{r})\right\}\right) = \int_{Surface} dS \left\{ r\rho(\vec{r})^2 + w\rho(\vec{r})^3 + u\rho(\vec{r})^4 + \ldots \right\}$$

Insert $\rho(\Omega) = \sum_{M=-L}^{+L} Q_{L,M} Y_{L,M}(\Omega)$

- Free energy minimum for L=6 has icosahedral symmetry

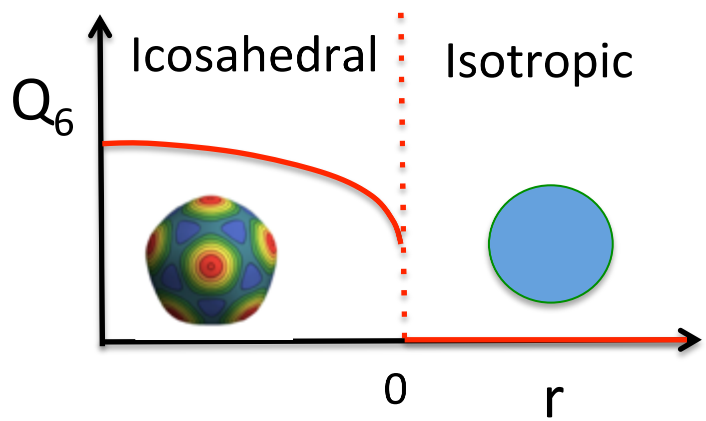


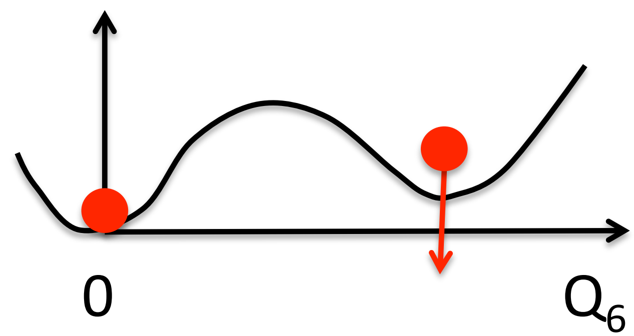
$$\rho(\Omega) = Q_6\left(Y_{0,0} + \sqrt{\frac{7}{11}}Y_{6,5} - \sqrt{\frac{7}{11}}Y_{6,-5}\right)$$

- L = 6 ``icosahedral spherical harmonic”

$$F_6 = rQ_6{}^2 + wQ_6{}^3 + uQ_6{}^4$$

- Q_6 = Order parameter ``amplitude”





First-order transition (cubic term non-zero)

- Icosahedral state is thermodynamically stable against fluctuations.

PHYSICAL REVIEW B **77**, 224109 (2008)

Landau theory of crystallization and the capsid structures of small icosahedral viruses

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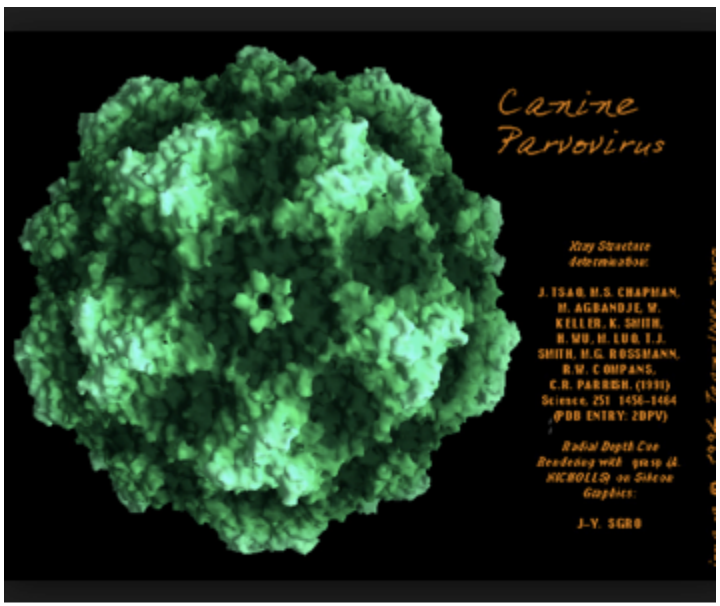
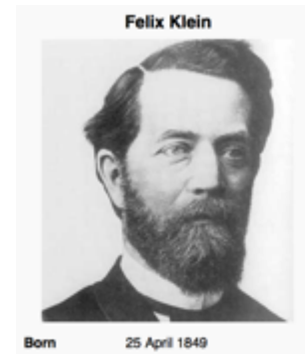
Capsid Canine Parvovirus



$$\rho_{15}(\Omega) \propto \sum_{M=-15}^{+15} Q_{15,M} Y_{15,M}(\Omega)$$

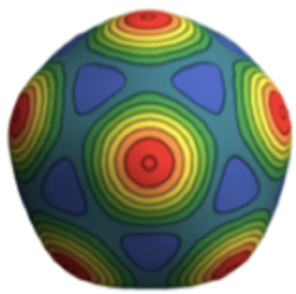
L=15 Icosahedral spherical harmonic

For certain L there is a unique linear combination $Y_h(L)$ of the $Y_{L,M}$ that transforms as a scalar or as a pseudo-scalar under the icosahedral symmetry group.

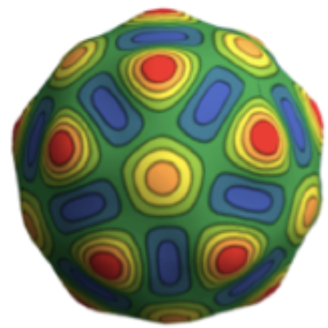


- Even L   L = 6, 10, 12, 16, ...

L=6



L=10



$Y_h(L)$

scalar density

even under inversion r ➔ - r

- Odd L   L = 15, 21, 25, 27, ...

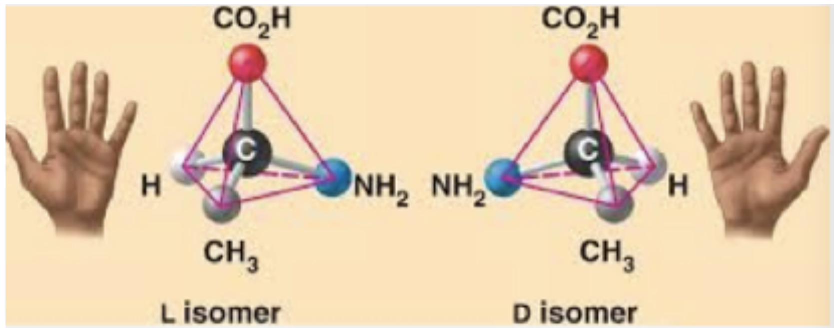
$Y_h(15)$

pseudo-scalar density
odd under inversion

- *Chiral pairs* (isomers)

Rochal & Lorman: *capsid density cannot be presented by the even L scalars*

amino-acids

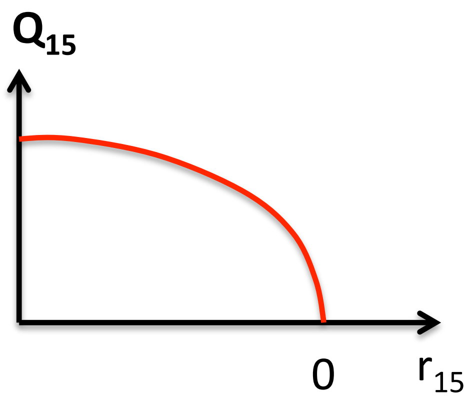


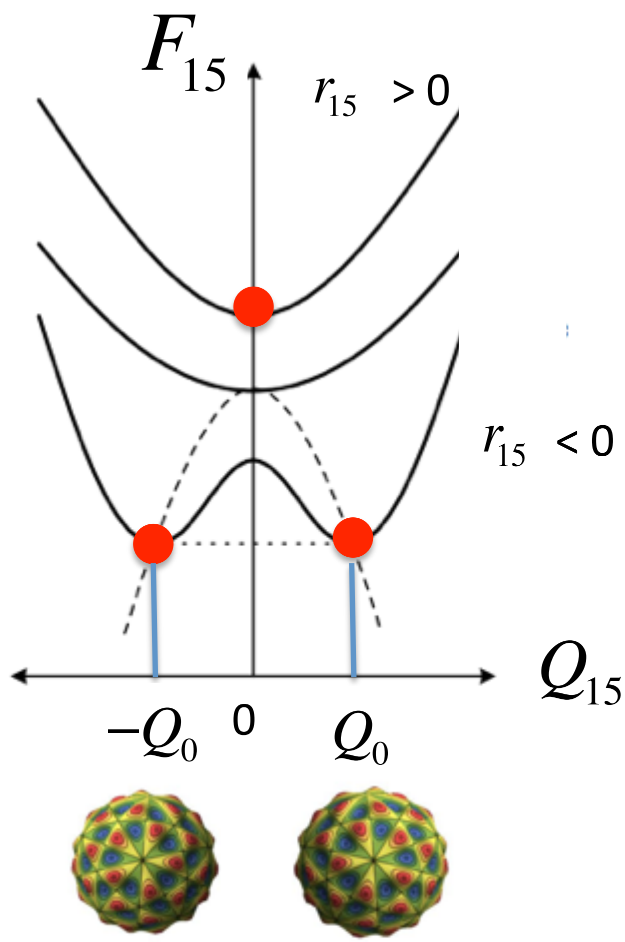
- Capsid densities are not even under inversion: *only odd L spherical harmonics*.

- Smallest viral capsids should correspond to Y_h (L=15): T=1 viruses.

Parvovirus (T=1) *:* $\rho(\Omega) = Q_{15} Y_h(15)$

Landau free energy (L=15): $F_{15} = r_{15} Q_{15}^2 + u Q_{15}^4$





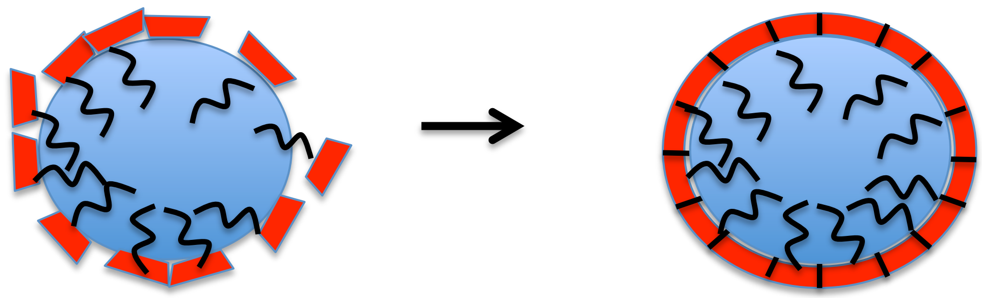
Cubic term zero for any odd L !

"Spontaneous chiral symmetry breaking transition".

$$Q_0 = \sqrt{\frac{-r_{15}}{2u}}$$

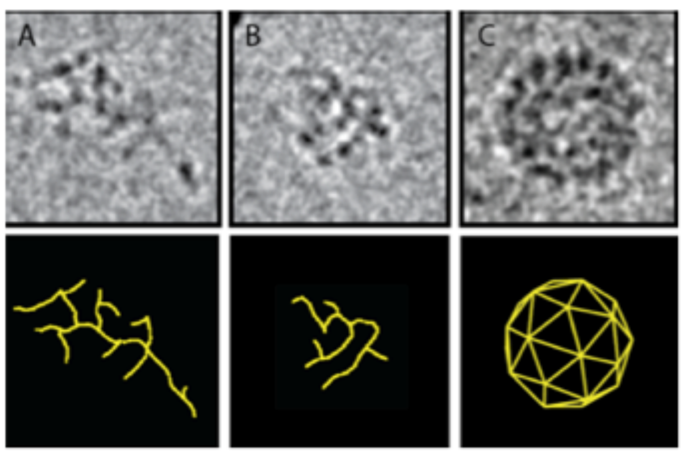
Questions

1) Second-order transition?



Collective assembly pathway

Cowpea Chlorotic Mottle Virus (CCMV)



R. Cadena-Nava, M. Comas-Garcia, R. Garmann, A. Rao C. M. Knobler, and W. M. Gelbart J. Virol. 86, 3318 (2012).

R. Garmann, M. Comas-Garcia, A. Gopal, C. M. Knobler, and W. M. Gelbart J. Mol. Biol. 426, 1050 (2013)

- Fluorescence thermal shift assay CCMV: first-order transition

Guillaume Tresset, Jingzhi Chen, Maelenn Chevreuil, Naïma Nhiri, Eric Jacquet, and Yves Lansac Phys. Rev. Applied 7, 014005, 2017

2) Spontaneous chiral symmetry breaking transition at $r_{15} = 0$.
Uniform state is already chiral.

3) Thermodynamic stability against fluctuations: expand free energy around $Y_h(15)$ solution

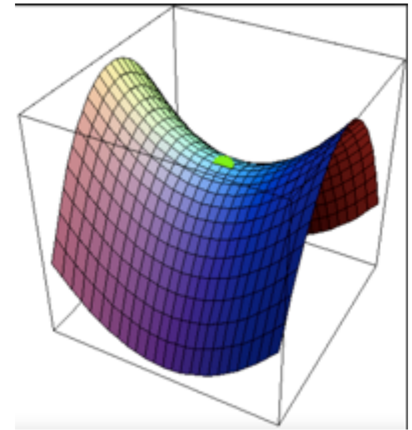
$$\rho(\Omega) = const. + \rho_{15} Y_h(15) + \sum_{M=-15}^{+15} \delta Q_{15,M} Y_{15,M}(\Omega)$$

fluctuation

Fluctuation free energy: $$\delta F_{15} = \frac{1}{2} \sum_{M=-15}^{15} \sum_{M'=-15}^{15} C_{M,M'} \delta Q_{15,M} \delta Q_{15,M'}$$

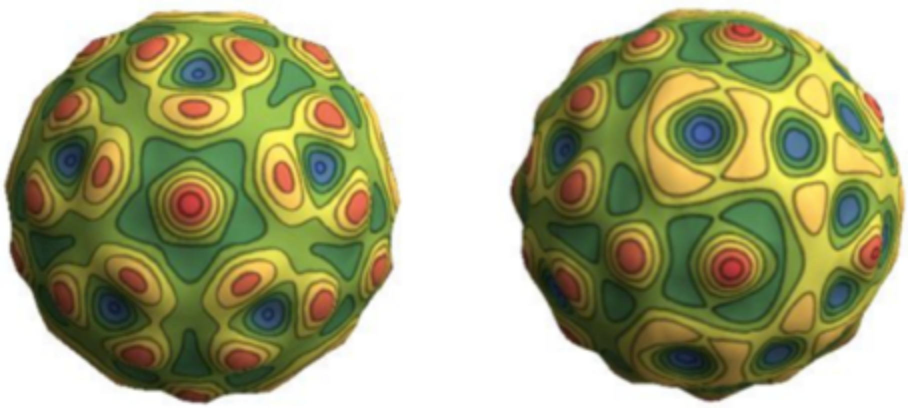
- $C_{M,M'}$: 31 x 31 stability matrix should have positive eigenvalues.
  :

21 positive eigenvalues
3 zero eigenvalues (rotations)
7 negative eigenvalues !



saddle-point

- Lowest free energy state in the L = 15 sector:

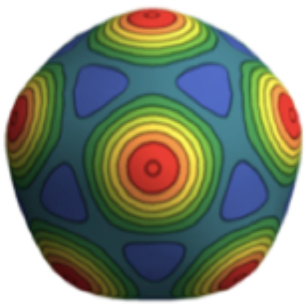


- Symmetry group D_5 :
  One five-fold symmetry axis.
  Five "odd" two-fold axes.

- *All* odd icosahedral spherical harmonic states are unstable.

- *Only* L = 6, 10, 12, and 18 icosahedral states are stable. (L=16 is unstable, Matthews).

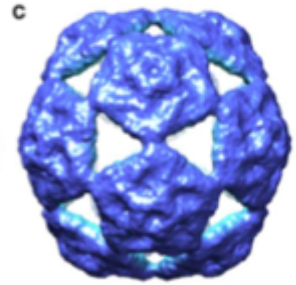
Should we perhaps take another look at the even L states?



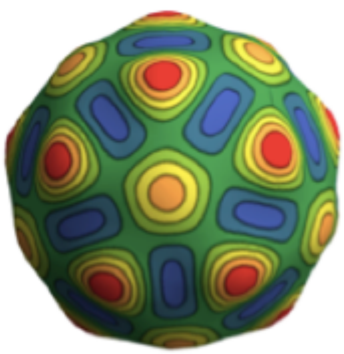
L=6

Picornavirus:
assembles from 12 identical chiral pentagons composed of 15 proteins: capsomers

c

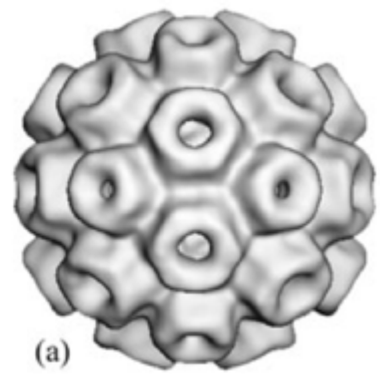


- Interpret ρ (Ω) as the density of capsomer centers. Add chiral capsomers.



L=10

CCMV:
assembles from 32 chiral capsomers 12 pentamers + 20 hexamers.



(a)

- But .... no signature of chirality in the density of capsomer centers??

Extensions of Lorman-Rochal

- **Step 1**: Landau-*Brazovskii* theory
  - smectic-nematic transition
  - chiral liquid crystals (cholesterics)
  - weak solidification (block co-polymers).

$$F_{LB} = \int dS \left\{ \left| \left(\nabla^2 + k_0^2 \right) \rho(\vec{r}) \right|^2 + r\rho(\vec{r})^2 + w\rho(\vec{r})^3 + u\rho(\vec{r})^4 \right\}$$

- Wavenumber $k_0=2\pi/a$. Dominant molecular length-scale: a = protein size.

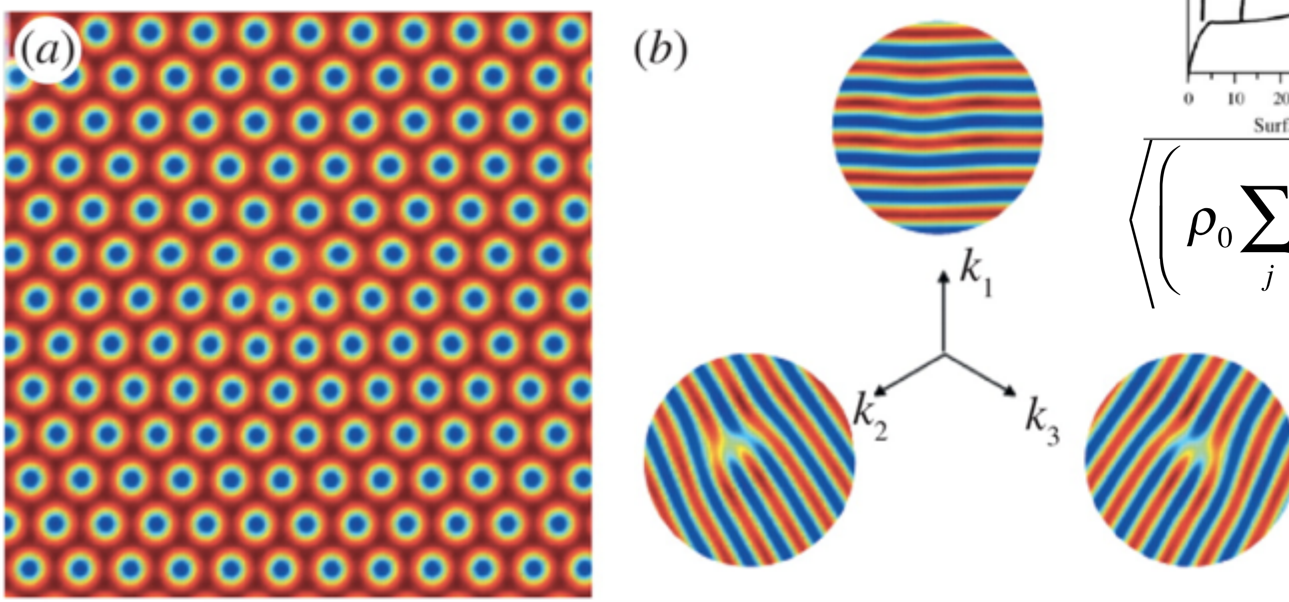
- First term minimized by density waves $\rho(\vec{r}) \propto \exp i\left(k_0 \hat{n} \cdot \vec{r}\right)$

$$\left(\nabla^2 + k_0^2\right) \exp i\left(k_0 \hat{n} \cdot \vec{r}\right) = 0$$

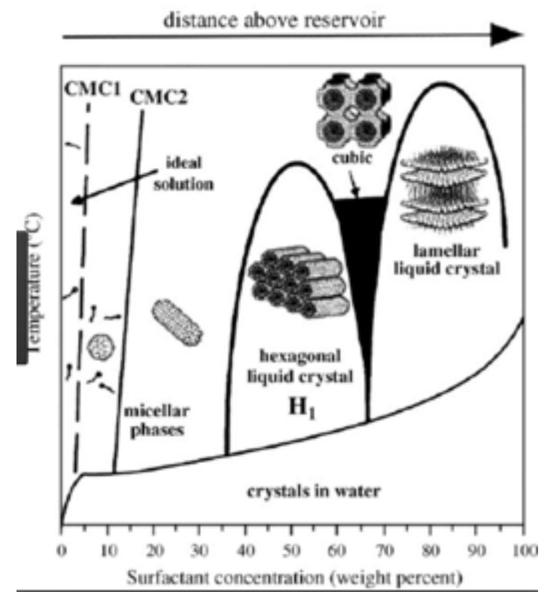
n = unit vector

- Look for *combinations* of density waves

$$\rho(\vec{r}) = \rho_0 \sum_{j=1}^{3} \cos\left(k_0 \hat{n}_j . \vec{r}\right)$$



Pezzutti et al.



$$\left\langle \left(\rho_0 \sum_j \cos\left(\vec{k}_j . \vec{r}\right) \right)^3 \right\rangle \neq 0$$

$$\vec{k}_j = k_0 \hat{n}_j$$

- First-order transition: cubic term in Landau energy non-zero
- Block co-polymers (L. Leibler): competition between hexagonal phases, lamellar phases and other symmetries.

Landau-Brazovskii on a spherical surface.

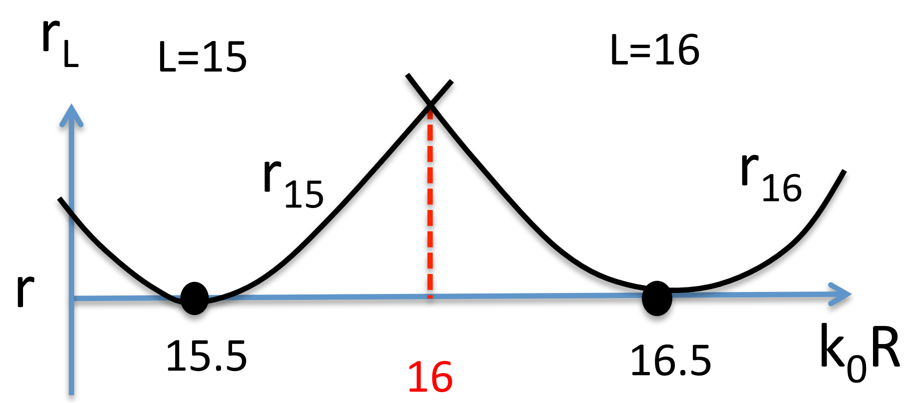
- Insert $\rho(\Omega) = \sum_{L=1}^{\infty} \sum_{M=-L}^{+L} Q_{L,M} Y_{L,M}(\Omega)$ in Landau-Brazovskii free energy.

$$F_{LB} = \sum_{L} r_L \sum_{M=-L}^{+L} \left| Q_{L,M} \right|^2 + w \sum_{\left\{ \substack{L_1 L_2 L_3 M_1 M_2 M_3 \\ M_1+M_2+M_3=0} \right\}} \begin{pmatrix} L_1 & L_2 & L_3 \\ M_1 & M_2 & M_3 \end{pmatrix} Q_{L_1,M_1} Q_{L_2,M_2} Q_{L_3,M_3} + u\{Q^4\}$$

- Sum over all L.

- $$r_L = r + \left[L(L+1) - (k_0 R)^2 \right]^2$$

Predict the L value of a capsid !



r_L has minimum when $k_0R \approx L$

Step 2: Include chirality directly in free energy

P-G De Gennes

Chiral liquid crystals: add lowest-order chiral pseudoscalar to the Landau free energy of the achiral liquid crystal.

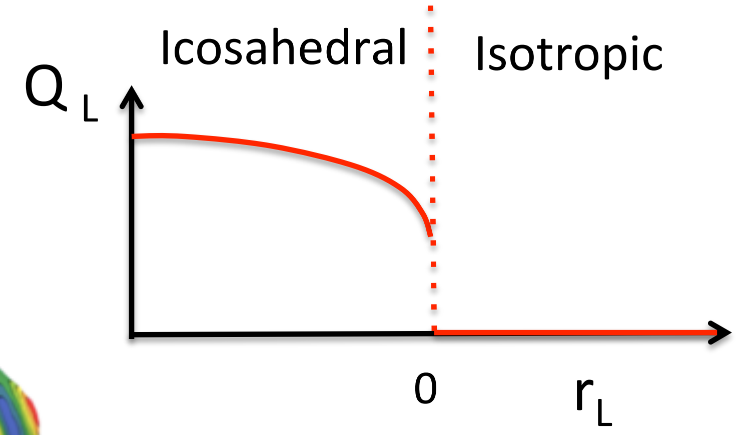
scalars

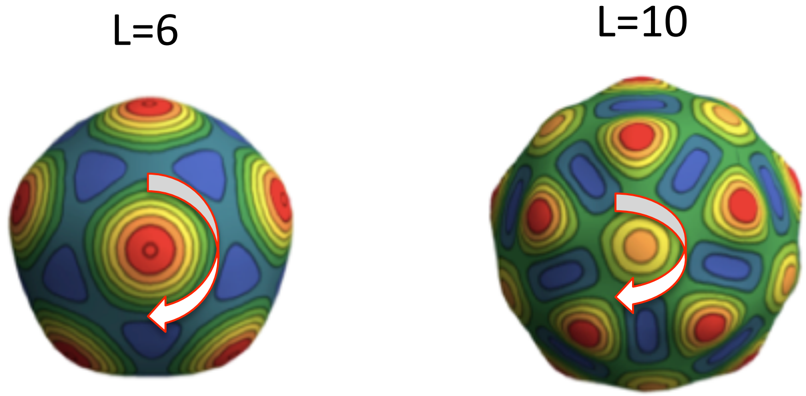
$$F = \int_{S^2} \left[\left(\frac{1}{2}\left((\Delta + k_o^2)\rho\right)^2 + \frac{r}{2}\rho^2 + \frac{u}{3}\rho^3 + \frac{v}{4}\rho^4 + ... \right) + \chi\left(\nabla\rho \cdot (\nabla\nabla\rho)^2 \cdot (\mathbf{n} \times \nabla\rho)\right) \right] dS.$$

- lowest non-zero pseudo-scalar
- variant of ``Helfrich-Prost''
- Sanjay Dharmavaram

- Now let's try again

- Stable minima for L=6, 10, 12, and 16.



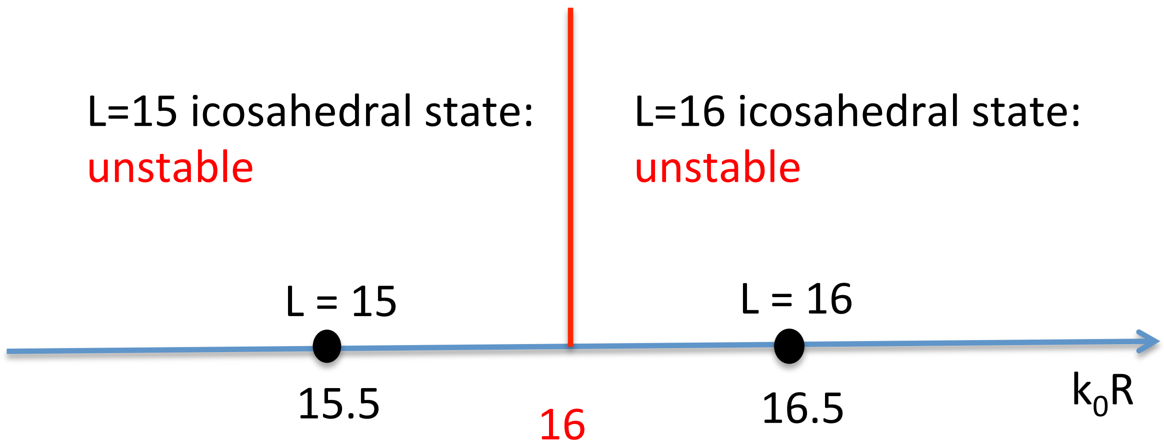


- *Thermal fluctuations* around the isotropic and $Y_h(L)$ states are chiral.

- *No spontanous chiral symmetry breaking at r_L = 0.*

➔ Conclusion: L = 6, 10, 12, and 16 icosahedral spherical harmonics are possible representations for collective capsid assembly.🡐

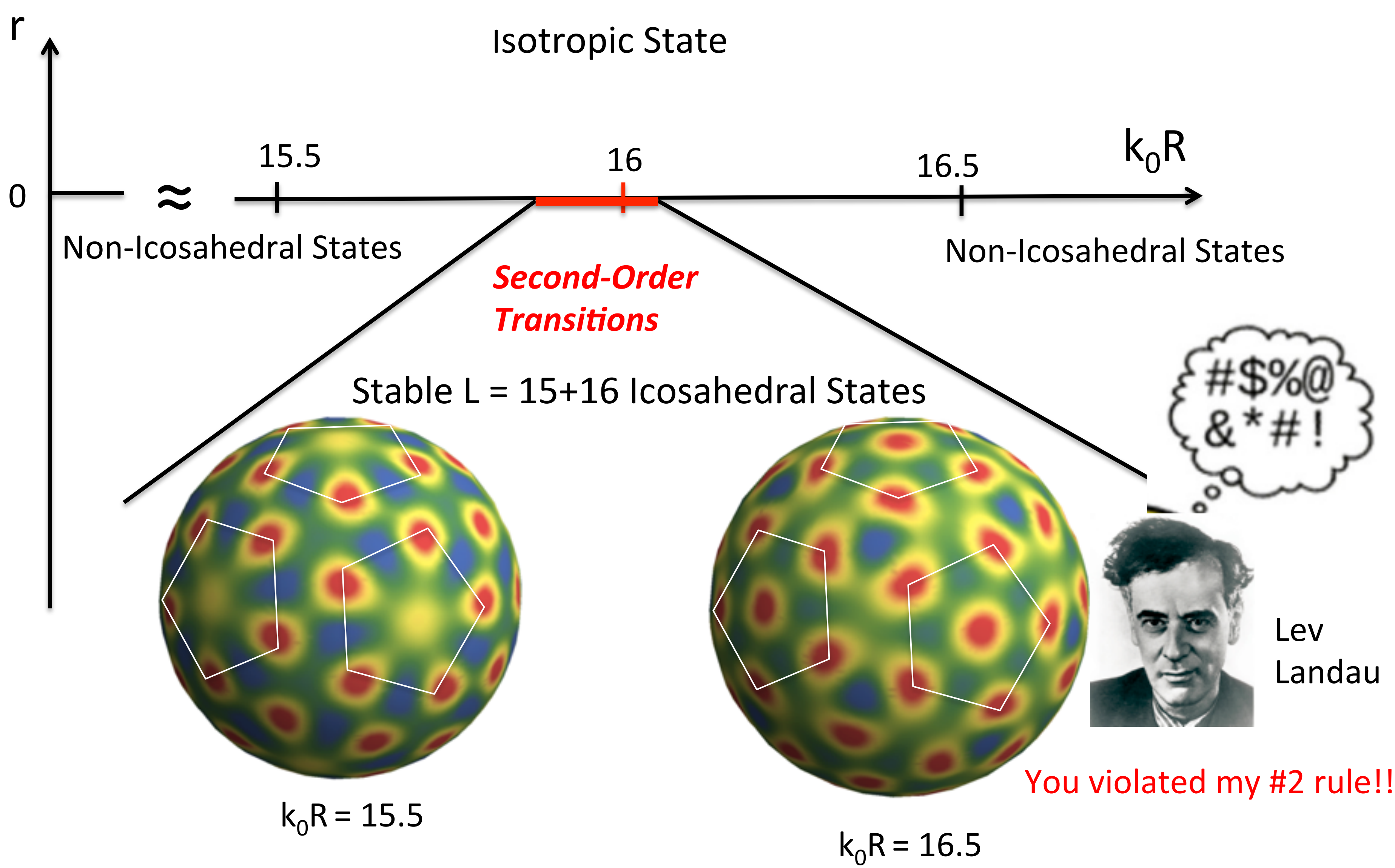
- But .... odd L icosahedral spherical harmonics states remain unstable!



- $r_{15} = r_{16}$ when $k_0 R = 16$

- Could there be a stable icosahedral order parameter composed of two one-dimensional ``irreducible representations" of SO(3) near $k_0R = 16$?

- L = 15 + 16 space has 31+33 = 64 dimensions

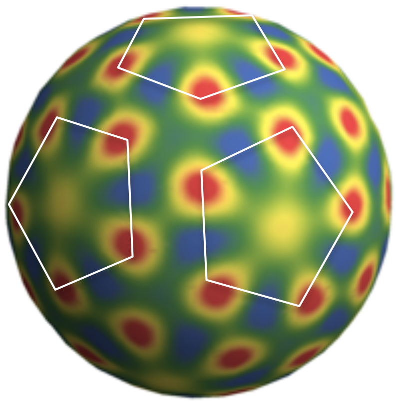


15 + 16 stable mixture, *mostly* L = 15, chiral, 60 maxima

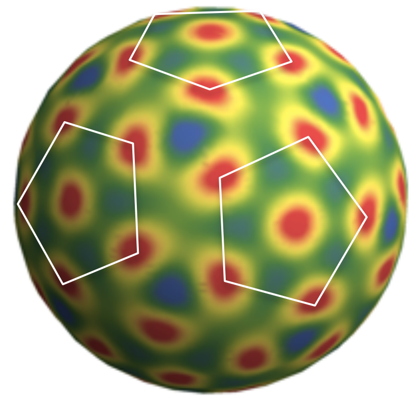
15 + 16 stable mixture, *mostly* L = 16 chiral, 72 maxima

Dharmavaram, S., Xie, F., Klug, W., Rudnick, J., & Bruinsma, R. (2017). *Orientational phase transitions and the assembly of viral capsids*. Physical Review E, 95(6), 062402.

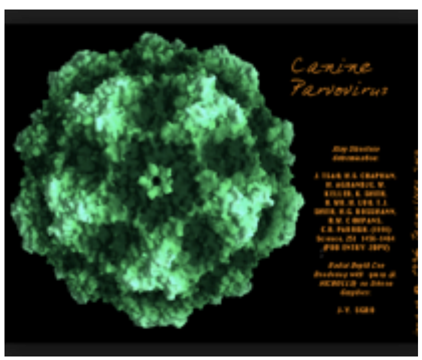
Examples



$k_0R = 15.5$

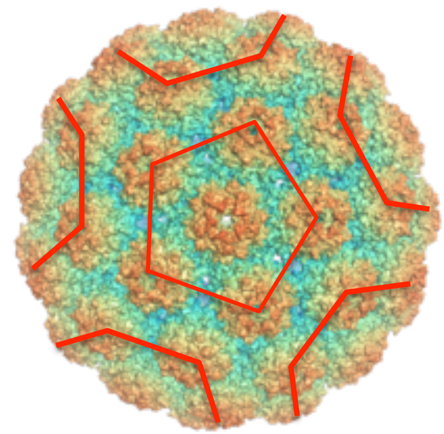


$k_0R = 16.5$



Parvovirus

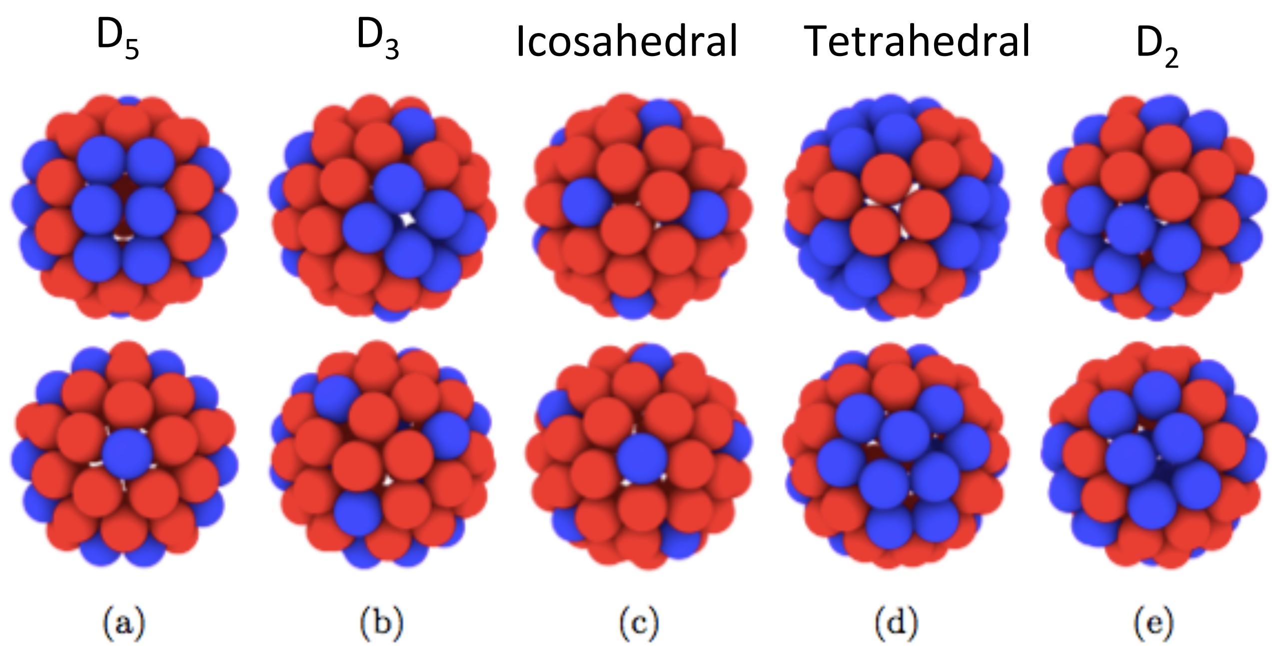
Maxima: *single capsid proteins*



Polyomavirus

72 maxima: *capsid protein pentamers*

Numerical simulations: 72 particles on a spherical surface



- Icosahedral state: *very fragile*. Competes with other states that have D_3, D_5, T symmetry.

S. Paquay, H. Kusumaatmaja, D. Wales, R. Zandi, and P. van der Schoot, Energetically favoured defects in dense packings of particles on spherical surfaces http://arxiv.org/abs/1602.07945

WHY WAS ICOSAHEDRAL SYMMETRY SELECTED FOR VIRUSES?

Conclusion

Lorman-Rochal theory (+ some extensions) is a powerful mathematical tool for the study of capsid assembly.

- Two modes of viral assembly :

  Assembly of mixed L, *intrinsically chiral* shells via (quasi) continuous transitions.

  Assembly of pure L, *effectively achiral* shells via strongly first-order transitions.

- Viral assembly: laboratory for testing and (maybe) violating Landau theory!

- Substantial experimental problems!


Kevin Zhang
Luigi Perotti
Joseph
Rudnick
Emmy
Amit
Singh
Sanjay
Dharmavaram
Josh
Kelly
William
Klug
BRUINS

with thanks to:

Bill Gelbart | Rees Garmann | Chuck Knobler