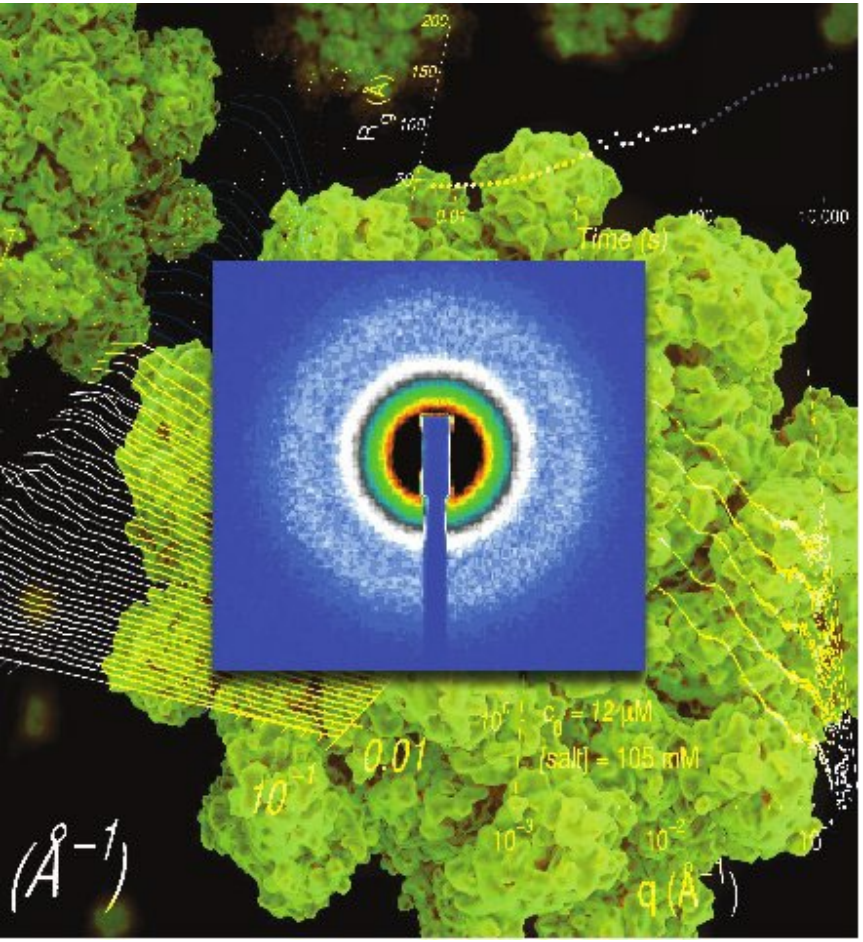

Antivirals alter the kinetic assembly pathway and elastic properties of Hepatitis B virus capsids

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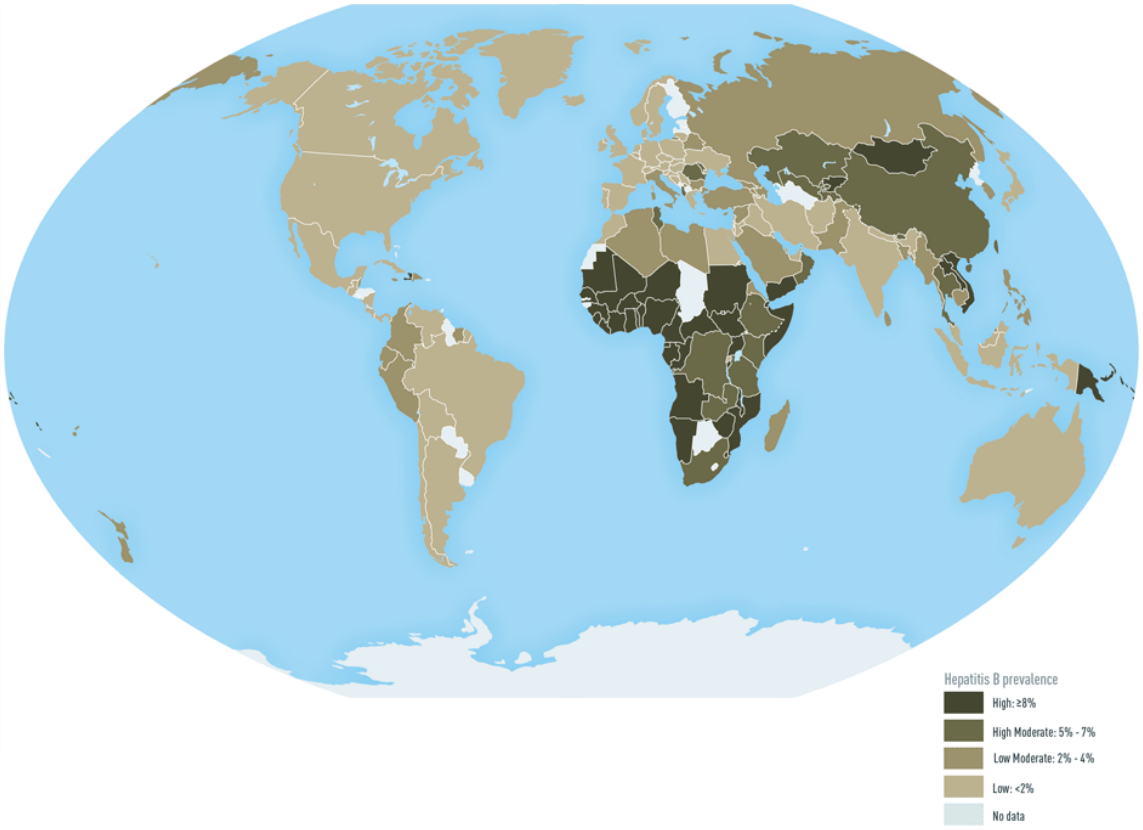
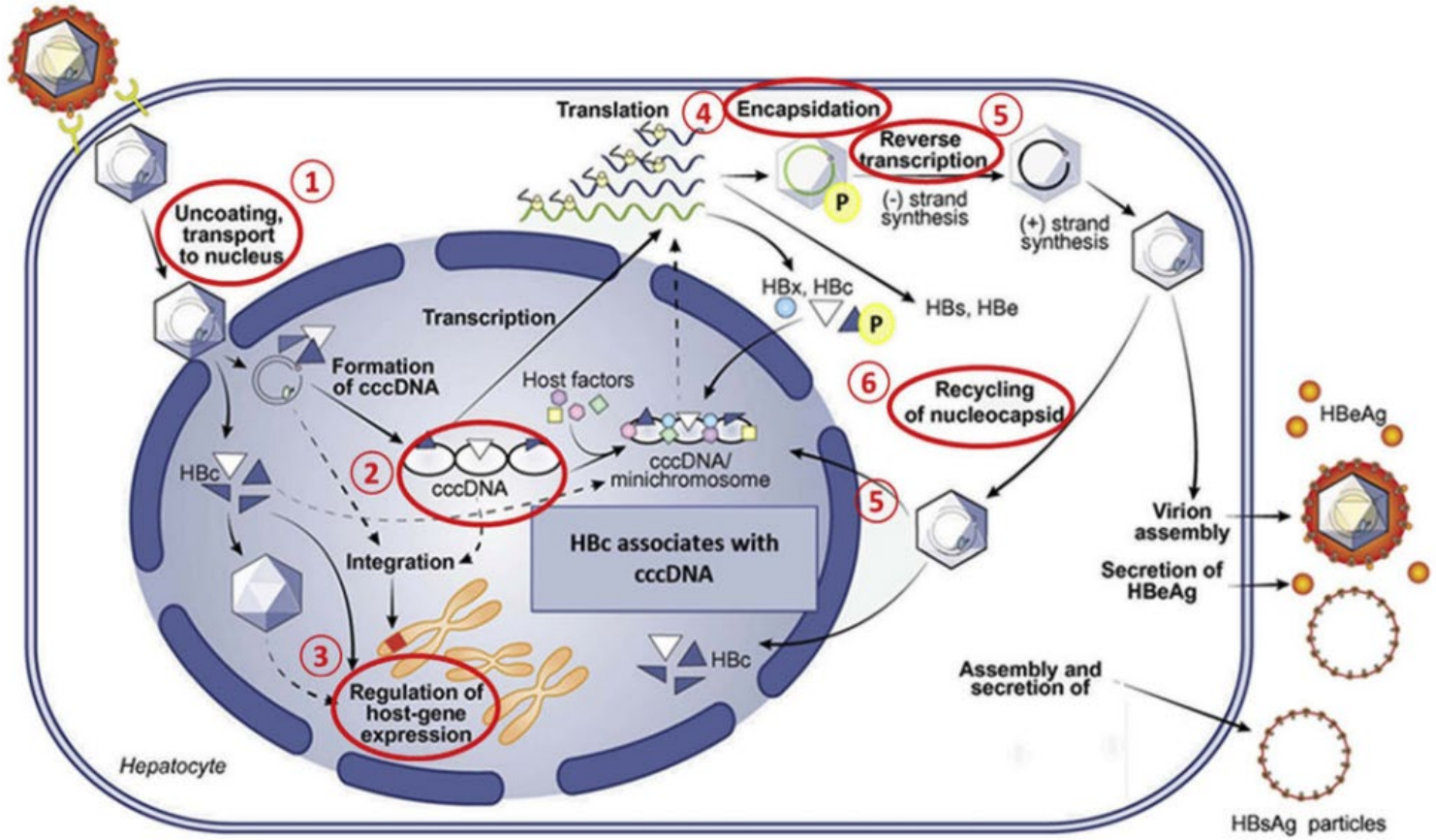
Hepatitis B Disease

- > 290 million people live with chronic Hepatitis B.
- 820,000 deaths per year, mostly from liver cancer and cirrhosis.
- Need to develop new drugs.

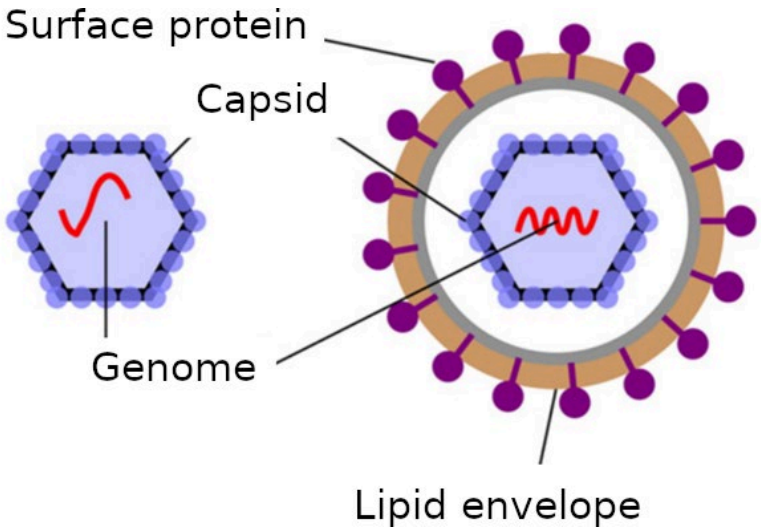


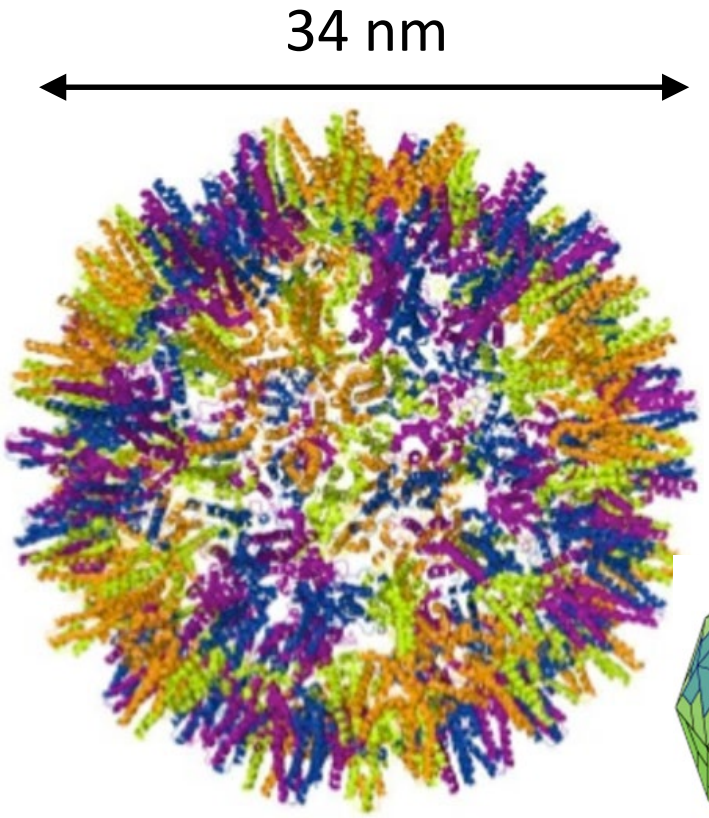
Hepatitis B Virus (HBV) Life Cycle



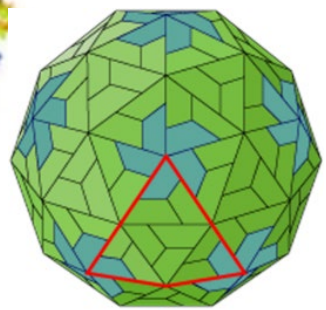
Diab, Antiviral Res. 2018

HBV Structure

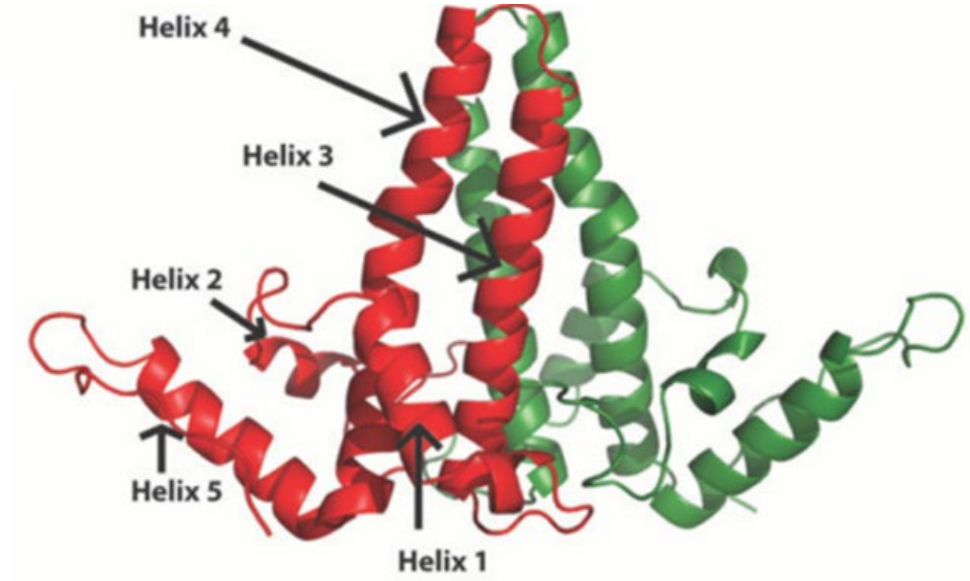




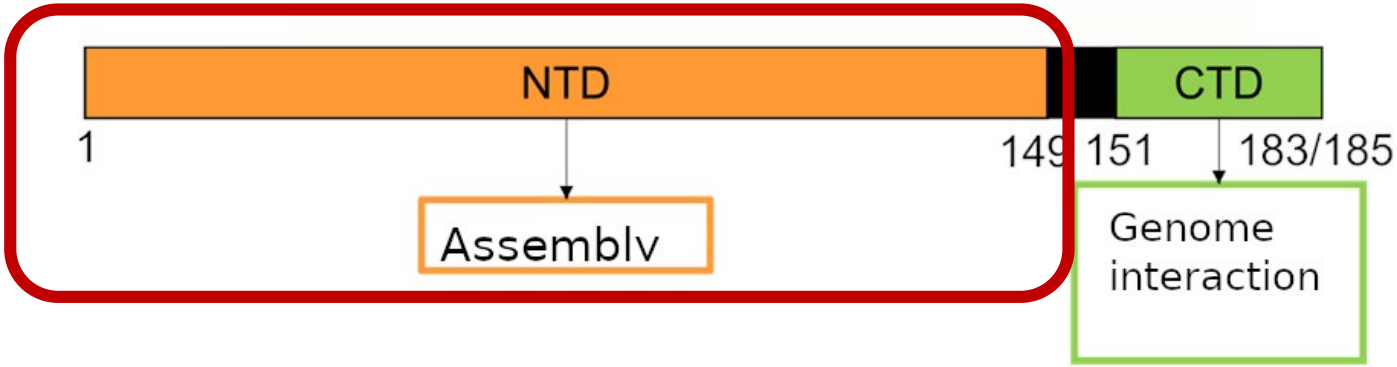
120 protein subunits



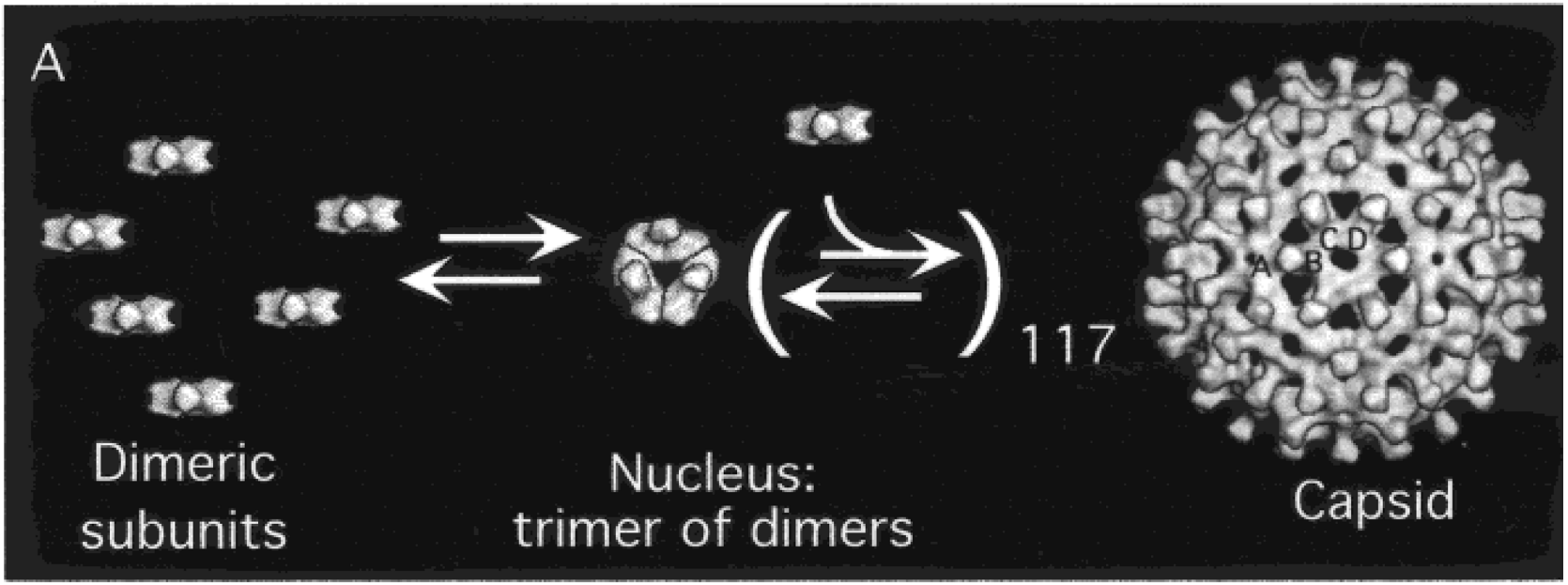
Capsid Protein Structure



Cp149



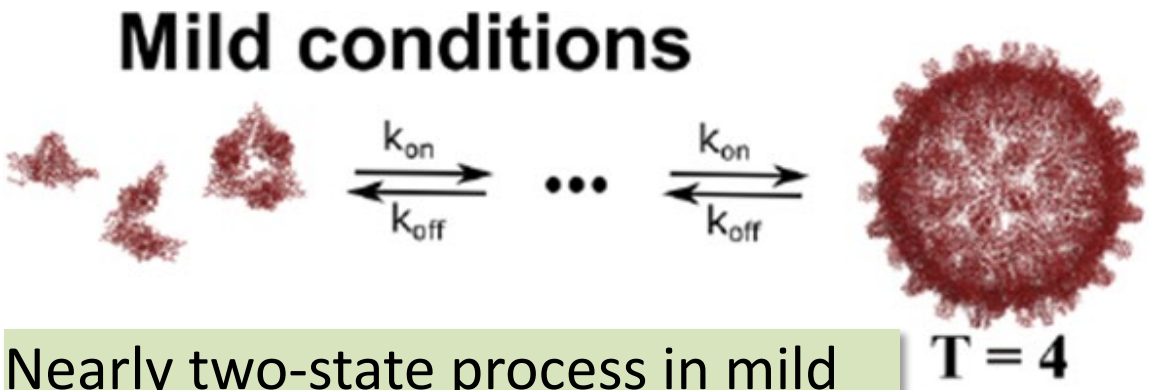
Early Work: Nucleation-Growth Process



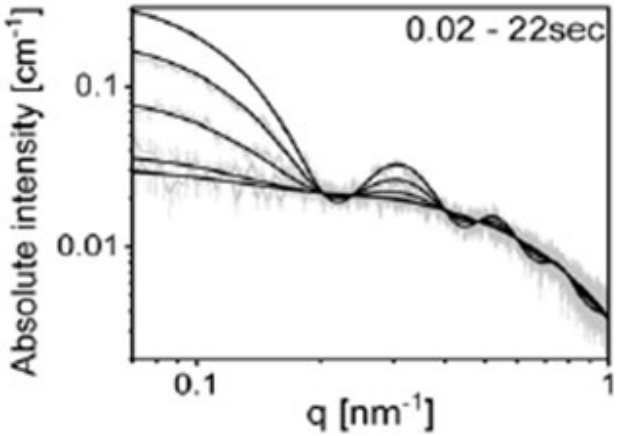
Zlotnick, Biochemistry 1999

- Capsid assembly investigated by static light scattering.
- Nucleation-growth process with a nucleus of trimer of dimers.

Capsid Assembly and Antivirals

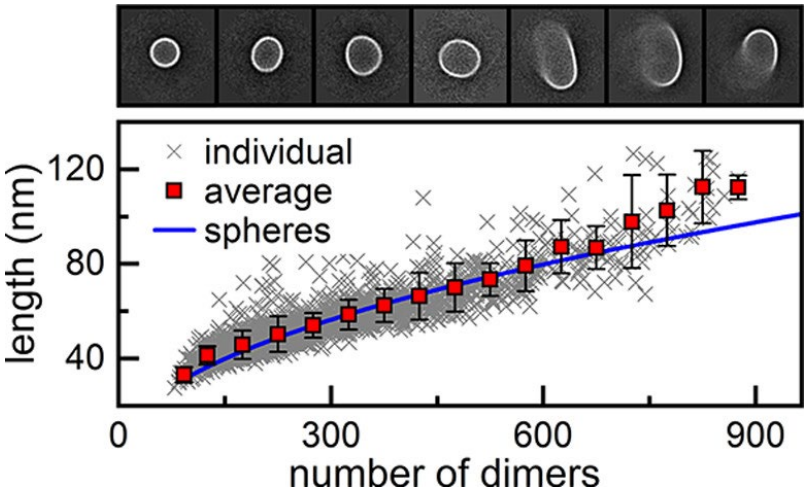


Nearly two-state process in mild salt (physiological) concentration.



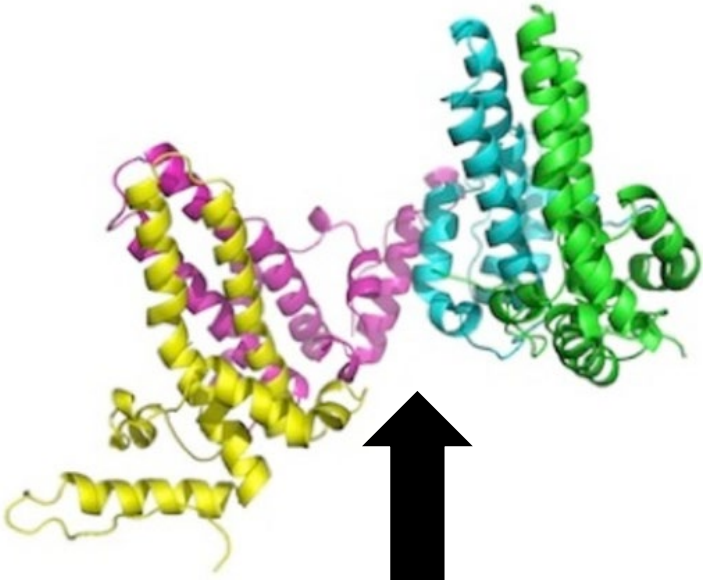
Asor, J. Am. Chem. Soc. 2020

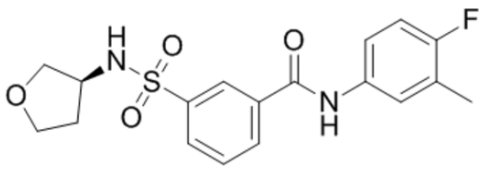
Capsid deformation induced by capsid assembly modulator (CAM).



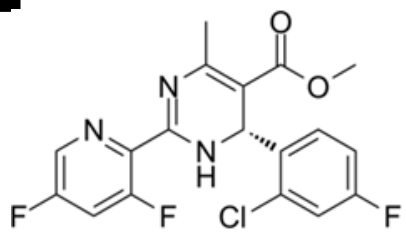
Kondylis, J. Am. Chem. Soc. 2019

Objective:
Investigating Capsid Assembly Kinetics with Antivirals

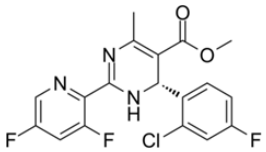




JNJ (CAM-E)

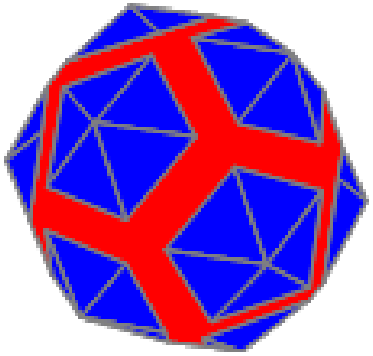


Bay (CAM-A)



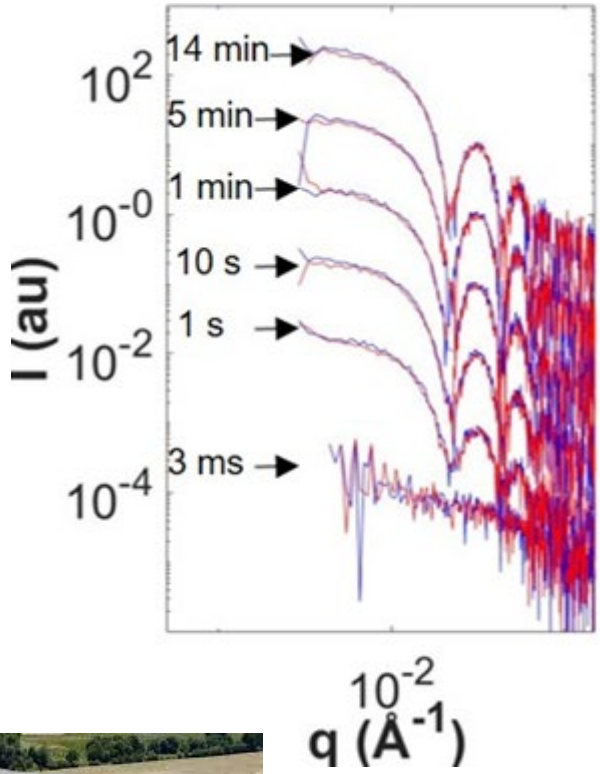
Ionic strength ↗

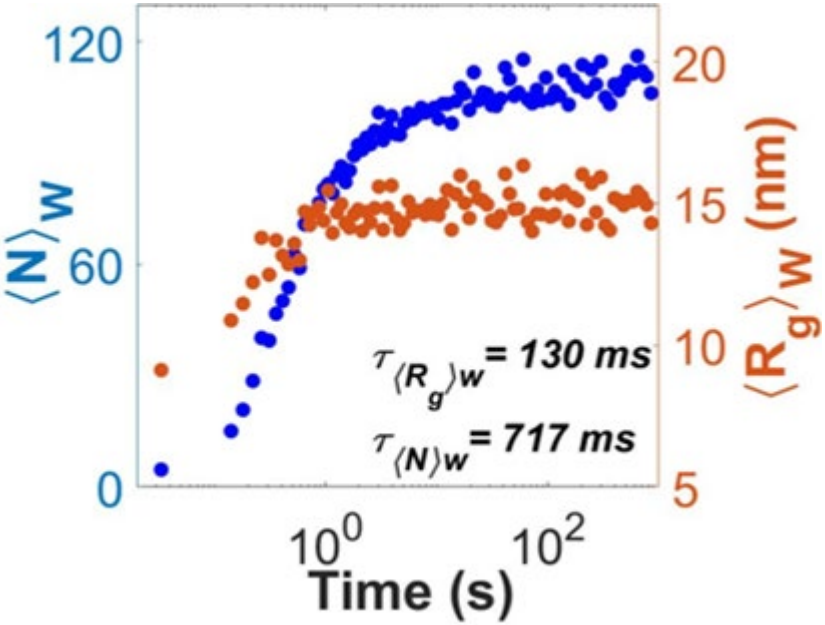
?



Capsid Assembly without CAM

Javier PEREZ





$$I_0 = I(q \to 0) \propto \langle N \rangle_w$$

$$I(q) \approx I_0(1 - \langle R_g^2 \rangle_w q^2/3)$$

~99% T = 4 capsids.

A Kinetic Model for Capsid Assembly (Model A)

$$\frac{\partial \phi}{\partial t} = \Gamma \frac{\partial F}{\partial \phi}$$

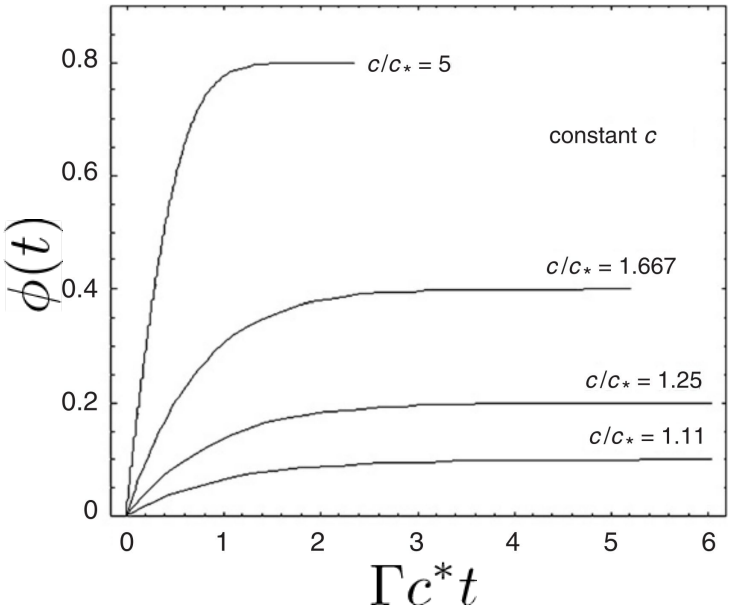
Relaxation rate

Free energy

$$\frac{d\phi}{dt} = -\Gamma c \left(-\ln \frac{1-\phi}{1-\phi_\infty} + \frac{1}{N} \ln \frac{\phi}{\phi_\infty} \right)$$

Total subunit concentration

Number of subunits in capsids



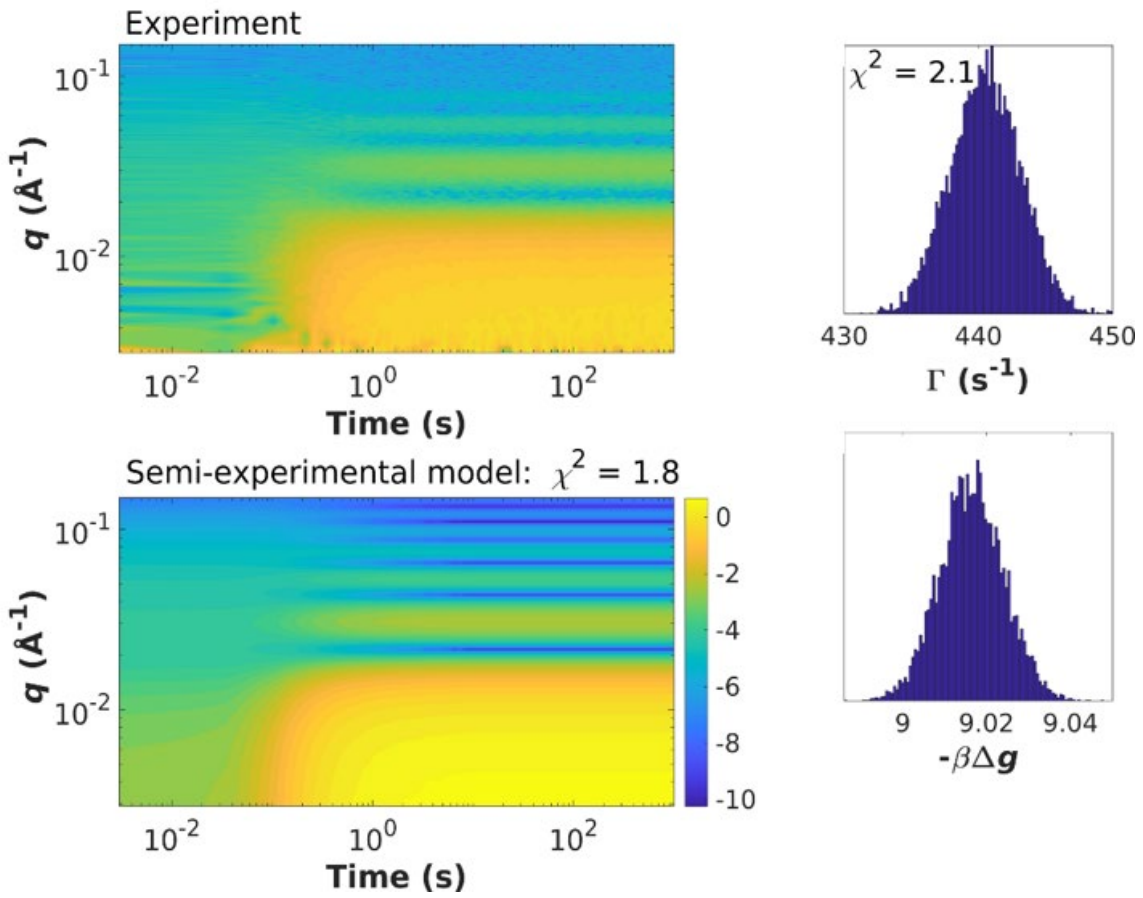
van der Schoot, Phys. Biol. 2007

Subunit binding energy:

$$\beta \Delta g = \ln \left[(1-\phi_\infty) c \right] - \frac{1}{N} \ln \left(\frac{\phi_\infty}{N} c \right)$$

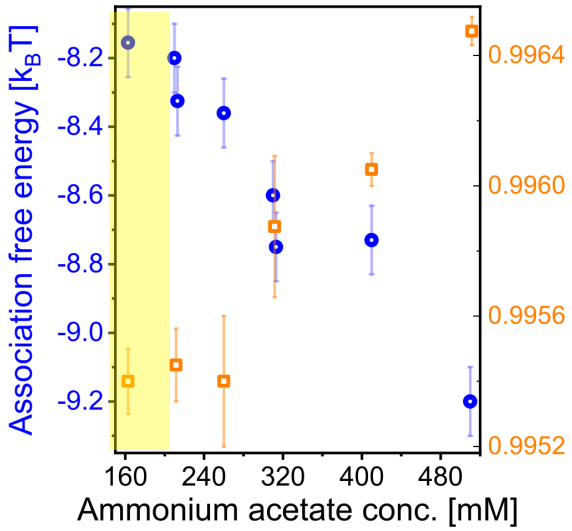
Model A Applied to Capsid Assembly without CAM

$$I(t,q) \propto [1-\phi(t)]\, P_1(q) + \phi(t) P_N(q)$$



$\Gamma \simeq 440\ \mathrm{s}^{-1}$ (later fixed)

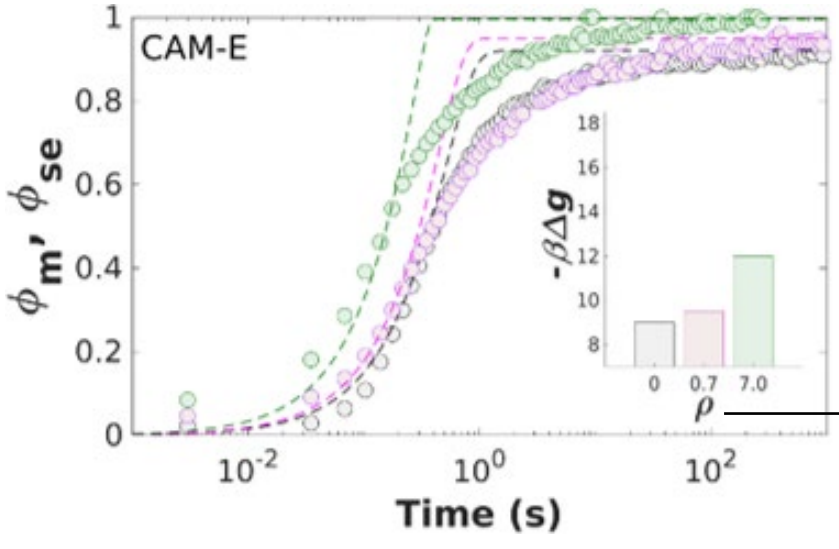
$-\beta\Delta g \simeq 9.0$

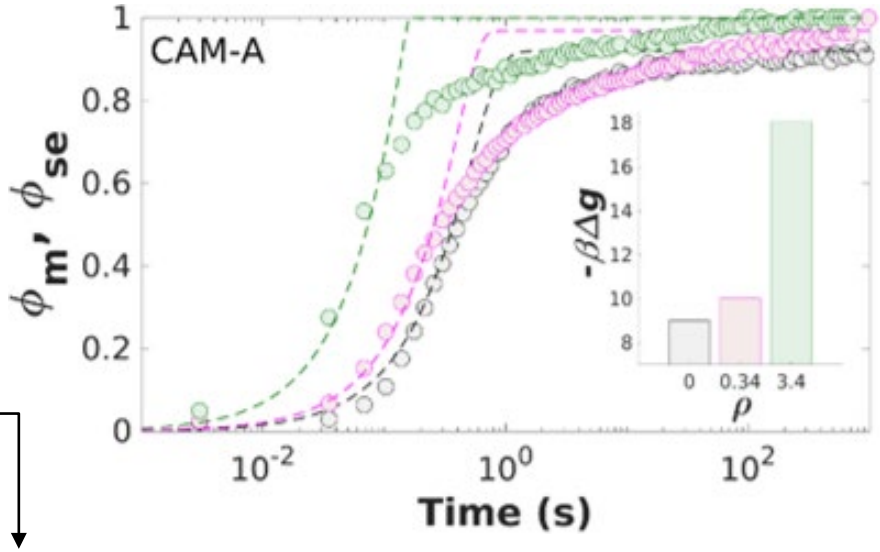


Asor, J. Am. Chem. Soc. 2020

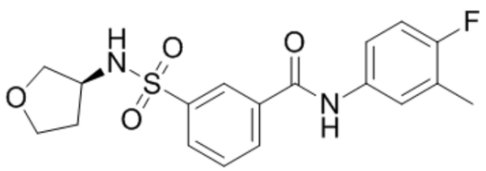
CAMs Increase Subunit Binding Energy

Only one fitting parameter.

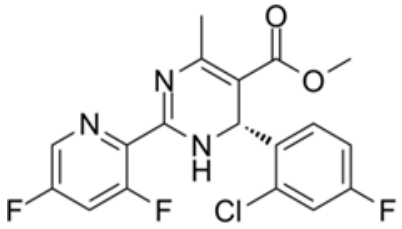




CAM-to-subunit molar ratio

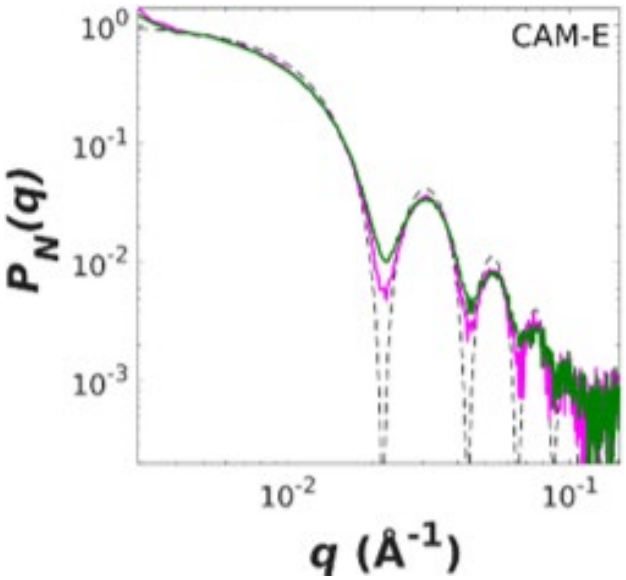


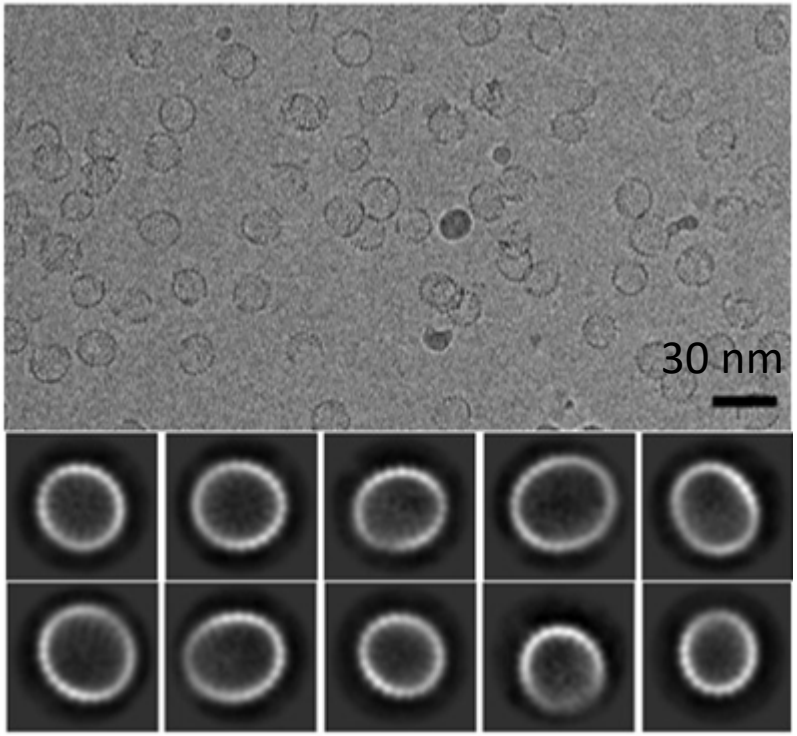
JNJ (CAM-E)

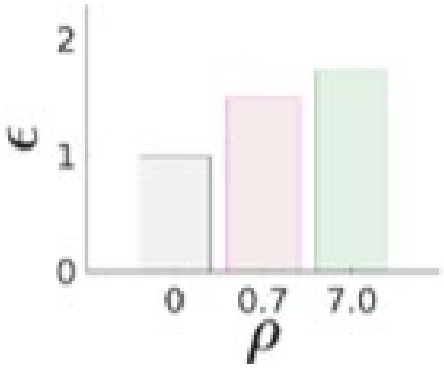


Bay (CAM-A)

CAM-E Yields Slightly Elongated Capsids



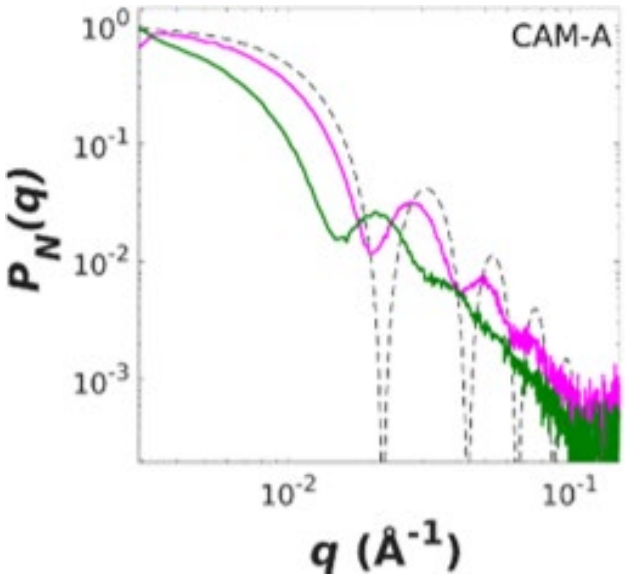


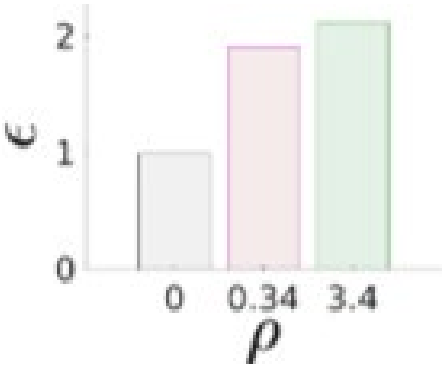


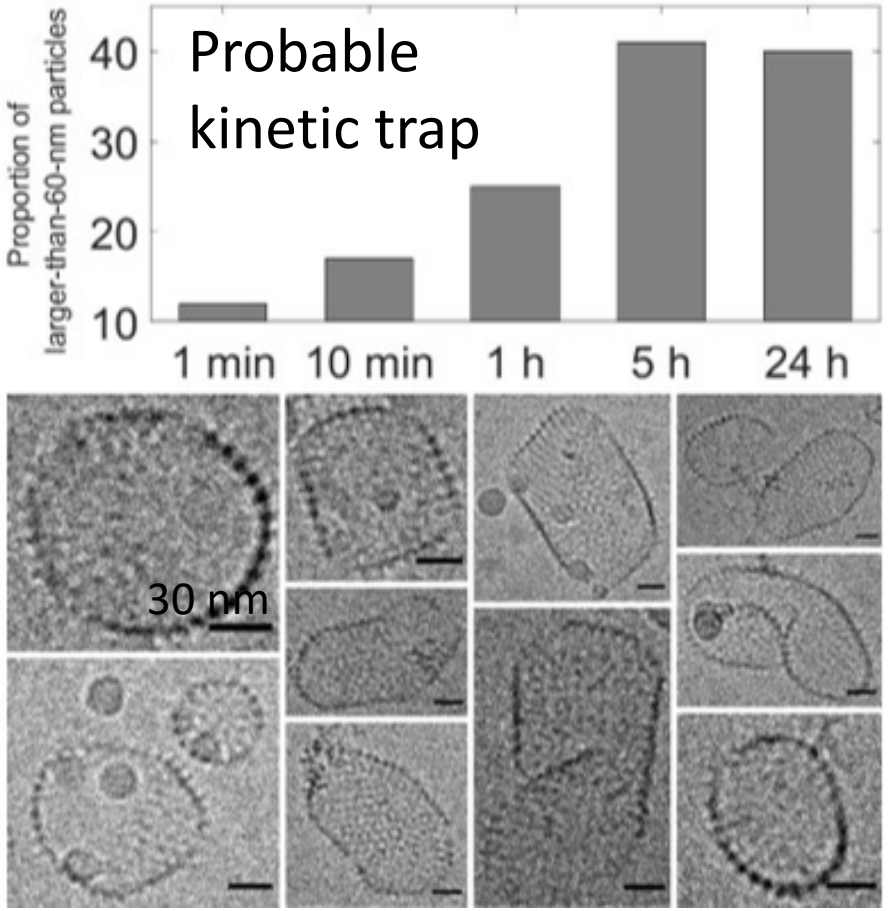
$$\frac{I(q)}{I_0} = 1 - \frac{R_g^2}{3}q^2 + f(\epsilon^2)q^4 + \dots$$

Roig-Solvas, J. Appl. Cryst. 2019

CAM-A Leads to Aberrant Capsids

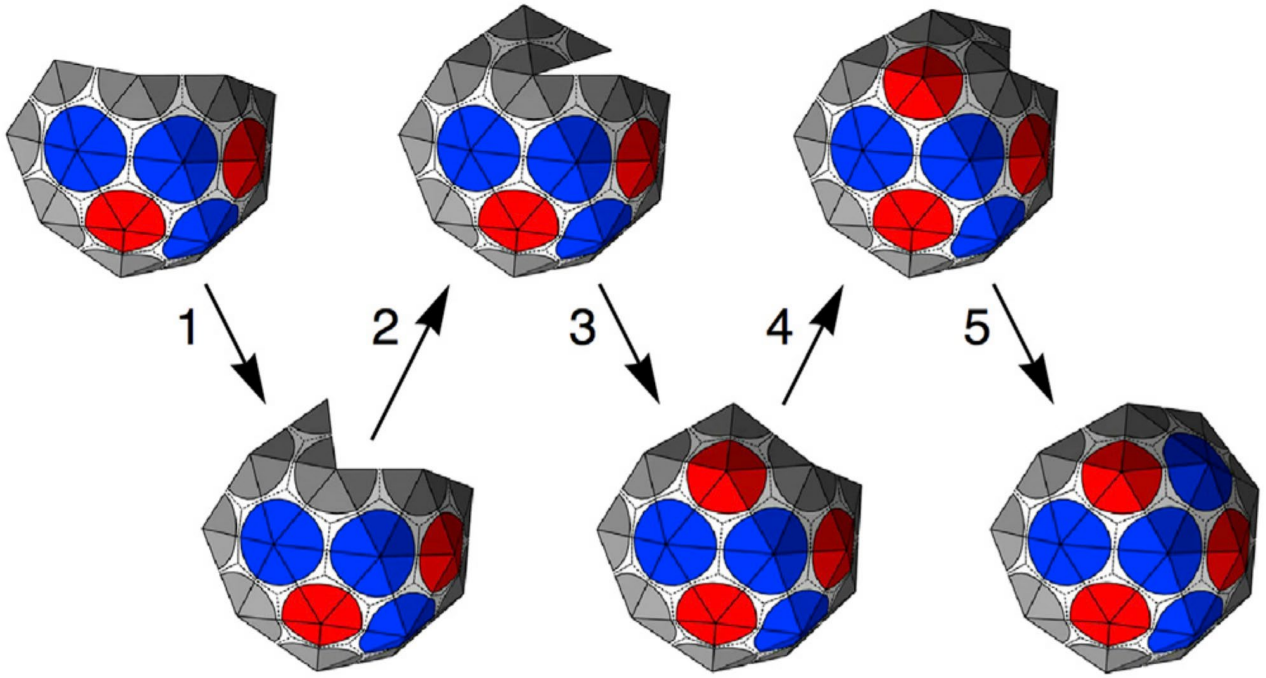






Coarse-Grained Model of Capsid Assembly

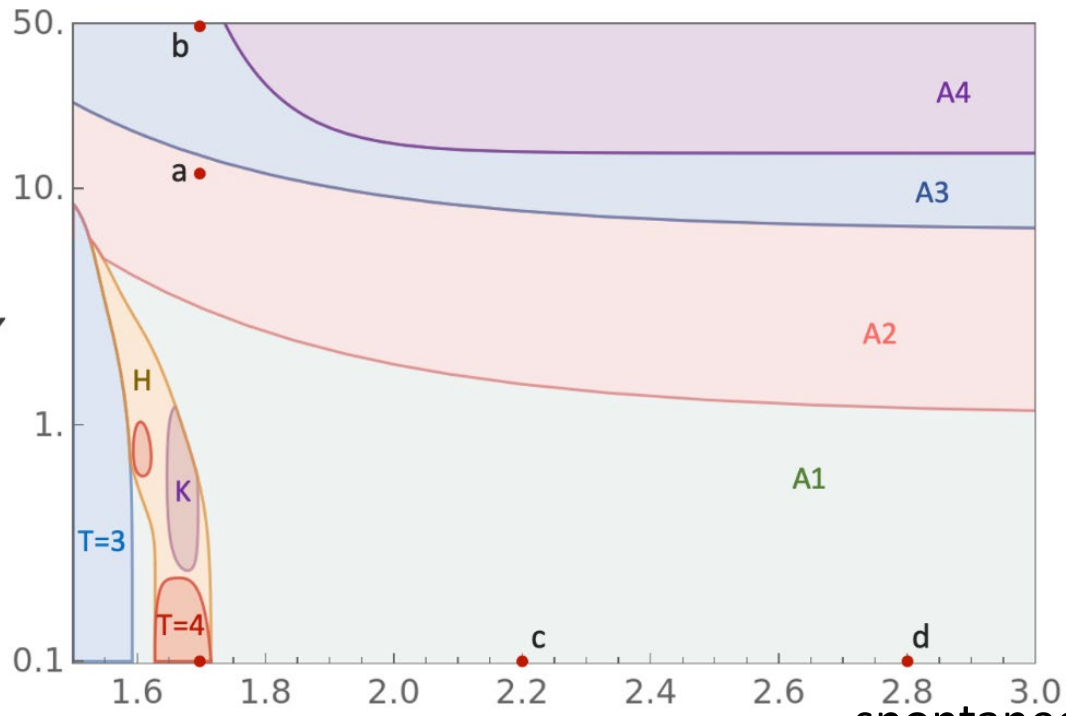
Roya ZANDI & Siyu LI



Wagner, Biophys. J. 2015

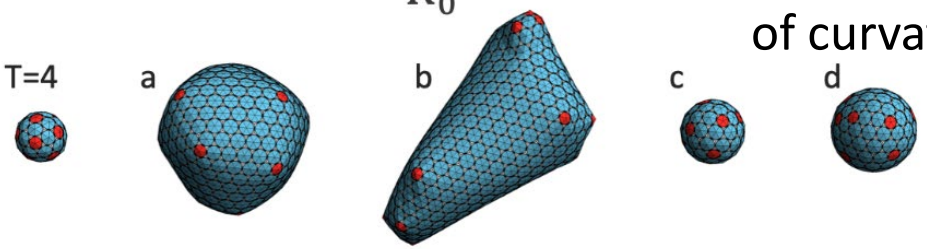
$$E_{\text{shell}} = E_{\text{s}} + E_{\text{b}} = \frac{1}{2} k_{\text{s}} \sum_i (l_i - l_0)^2 + k_{\text{b}} \sum_i [1 - \cos(\theta_i - \theta_0)]$$

Morphologies Are Reproduced by Tuning Elastic Properties



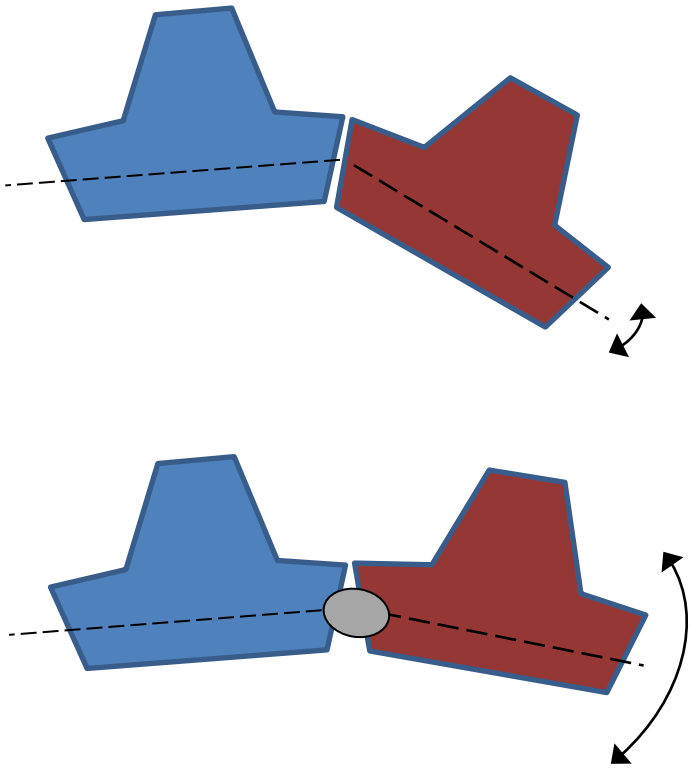
∝ FvK number

spontaneous radius of curvature



Conclusions

- CAMs increase subunit binding energy and
  - CAM-E makes slightly ellipsoidal capsids;
  - CAM-A leads to large, aberrant capsids via kinetic trap.
- The morphologies are reproduced by increasing the FvK number.



Kra, ACS Nano 2023

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