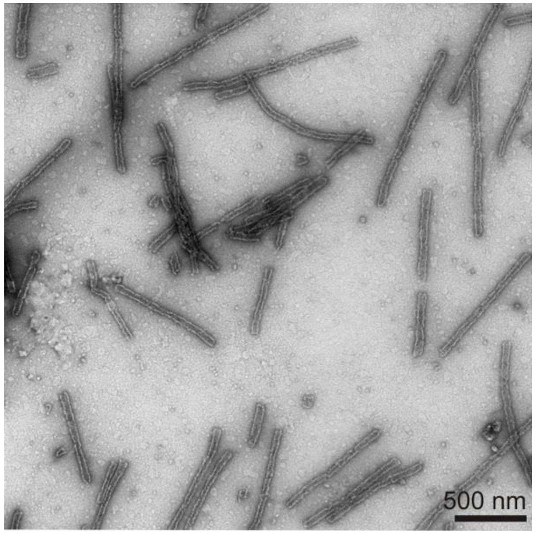
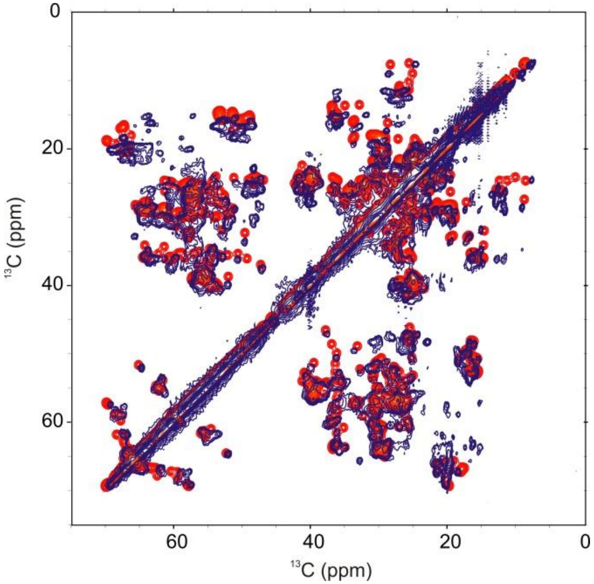
Structure, dynamics and assembly mechanism of the capsid of HIV-1 virus by solid state NMR, Transmission Electron Microscopy and Monte Carlo simulation

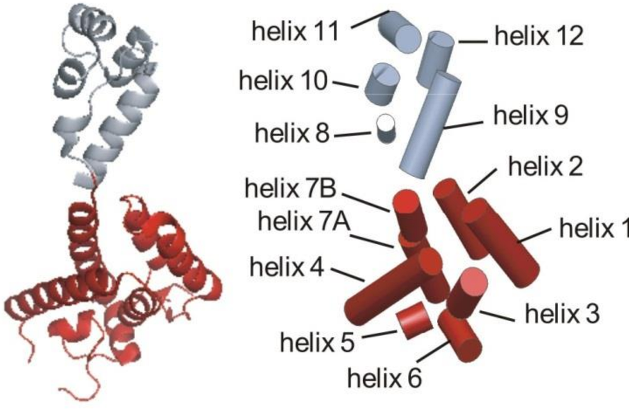
Bo Chen



Bright field TEM image of negatively
Stained capsid protein assembly in vitro



NMR 2D ^{13}C-^{13}C correlation spectrum
of capsid protein assembly in vitro



A novel coarse grain model captures
The backbone structure of protein

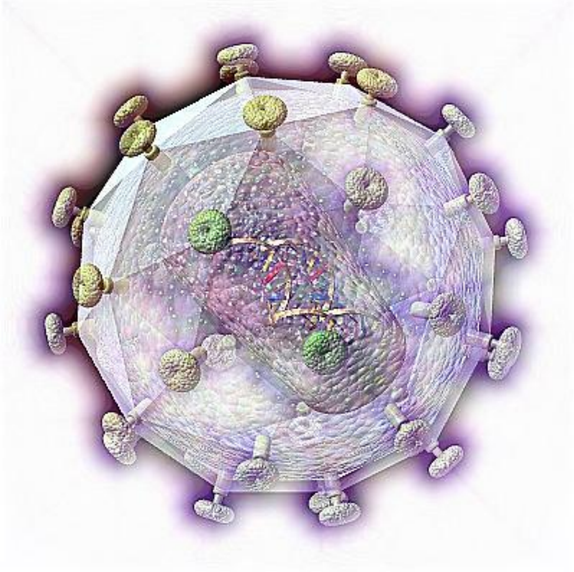
UIUC Beckman Institute

AUG 2013

Outline

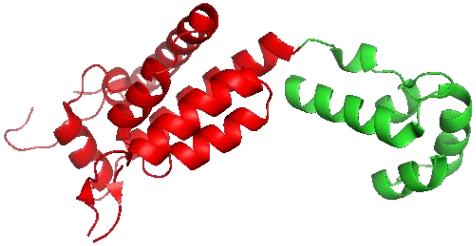
1. Background of the problem
2. Model set up
3. What we did
4. What can we do
5. What we want to achieve

The capsid is essential to HIV virus

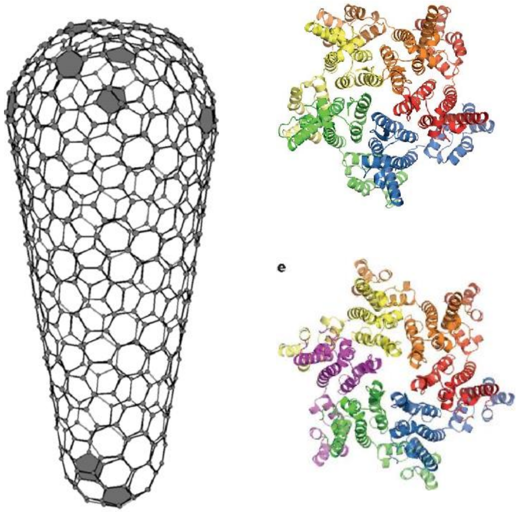


Facts
~120 nm
25 million
33.3 million

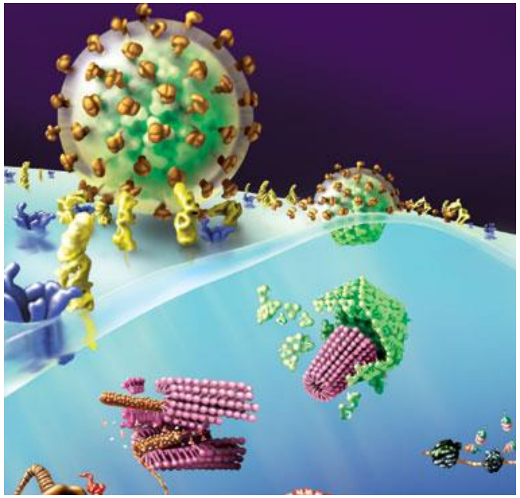
No Cure !!!



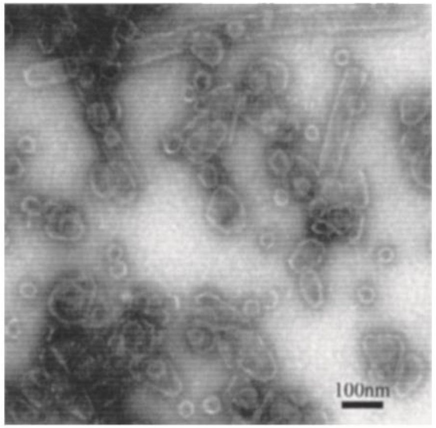
Pornillos *et al*., Cell (2009)



Proposed structure of capsid:
Ganser *et al*., Science (1999)

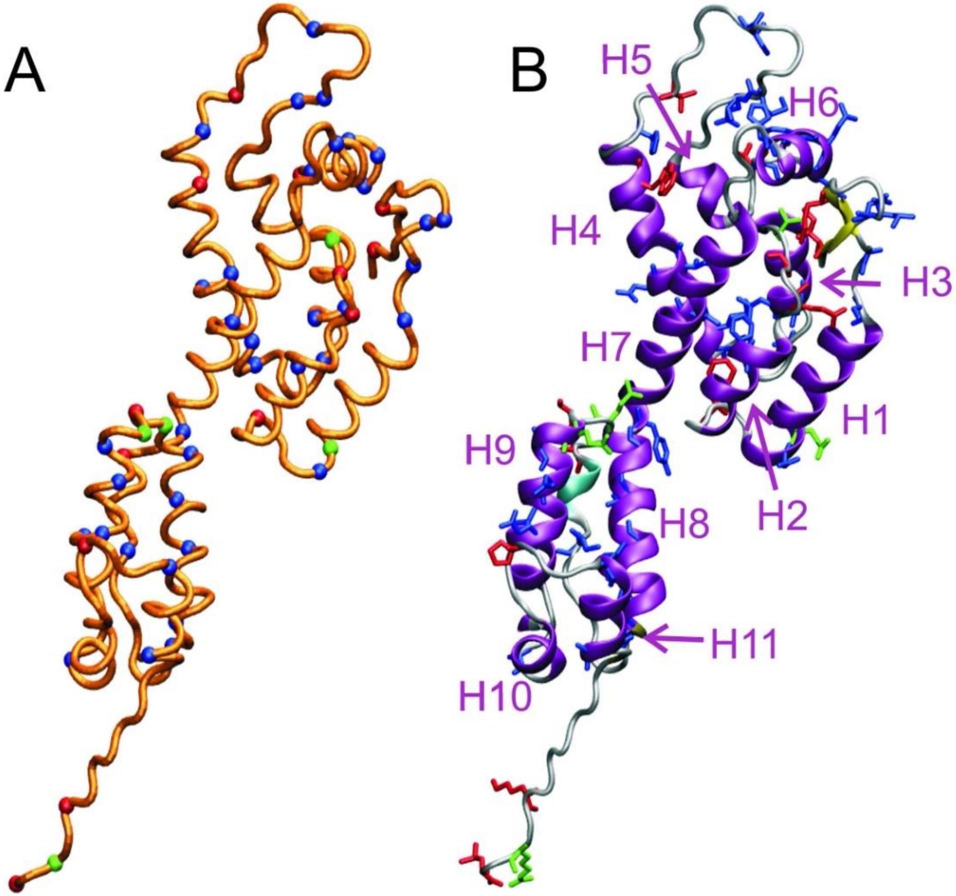


Cameron Slayden



Ganser-Pornillos *et al*.,
J. Virology (2004)

Coexistence of rigid and flexible regions of CA

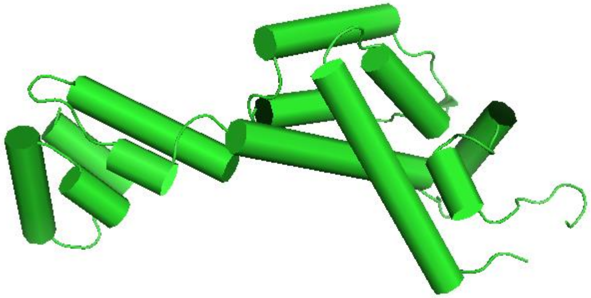


Flexible: 🔴 🟢

Rigid: 🔵

Bo Chen and Robert Tycko, Protein Science (2009)

CA assembly in 2-dimension



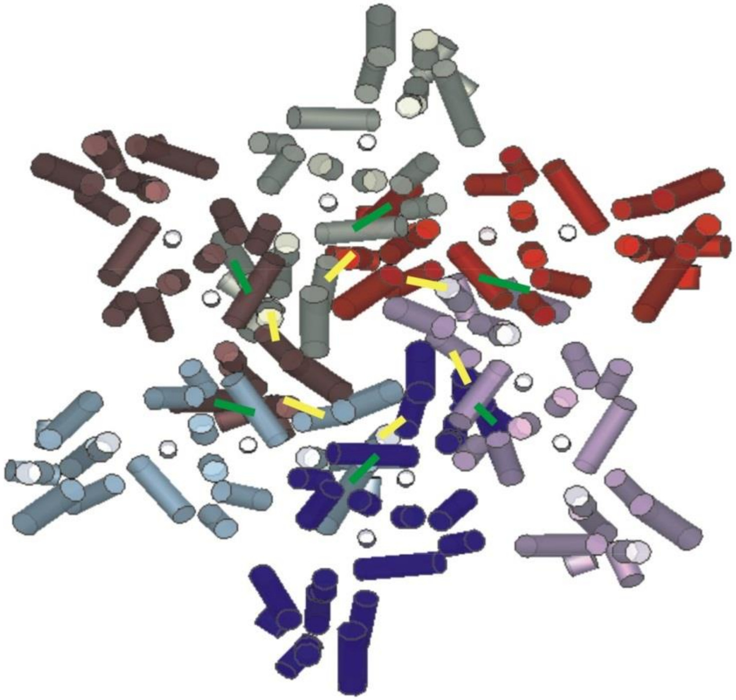
Attractive Interaction

$$f(\theta)=\begin{cases}\dfrac{|\theta-\theta_0|}{\theta_{\max}}-1, & |\theta-\theta_0|\le\theta_{\max}\\ 0, & |\theta-\theta_0|>\theta_{\max}\end{cases}$$

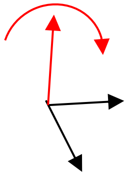
$$V(\theta,r)=f(\theta)\cdot g(r)$$

$$g(r)=4\varepsilon_0[(\frac{\sigma}{r})^{12}-(\frac{\sigma}{r})^{6}]$$

$$bindingstrength=4\frac{\varepsilon_0}{RT}$$



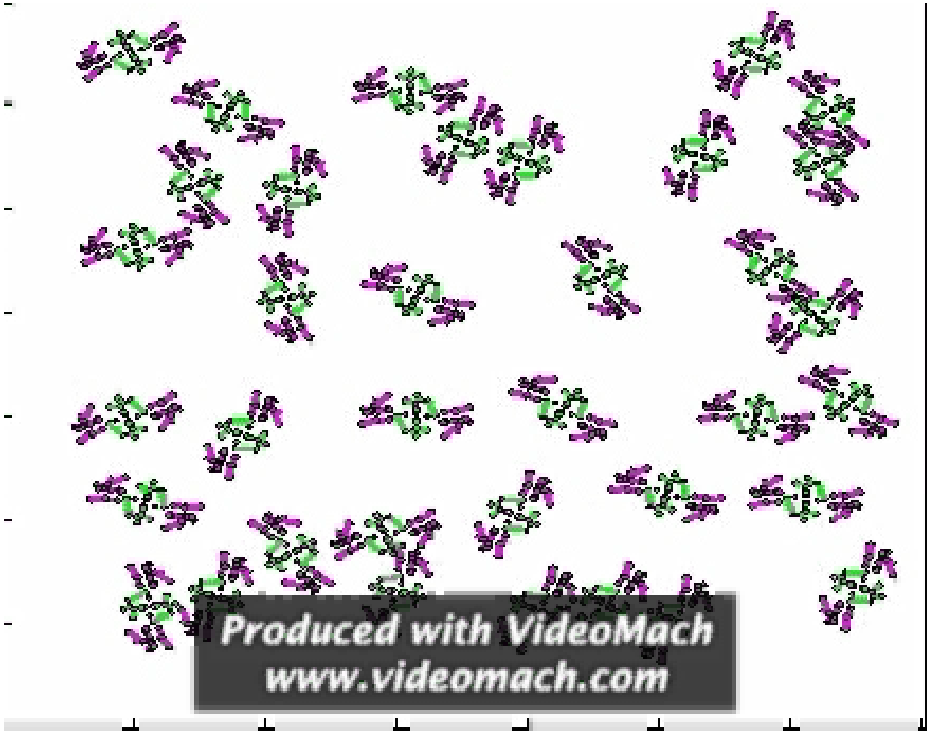
Repulsive Interaction:
No collision & overlap

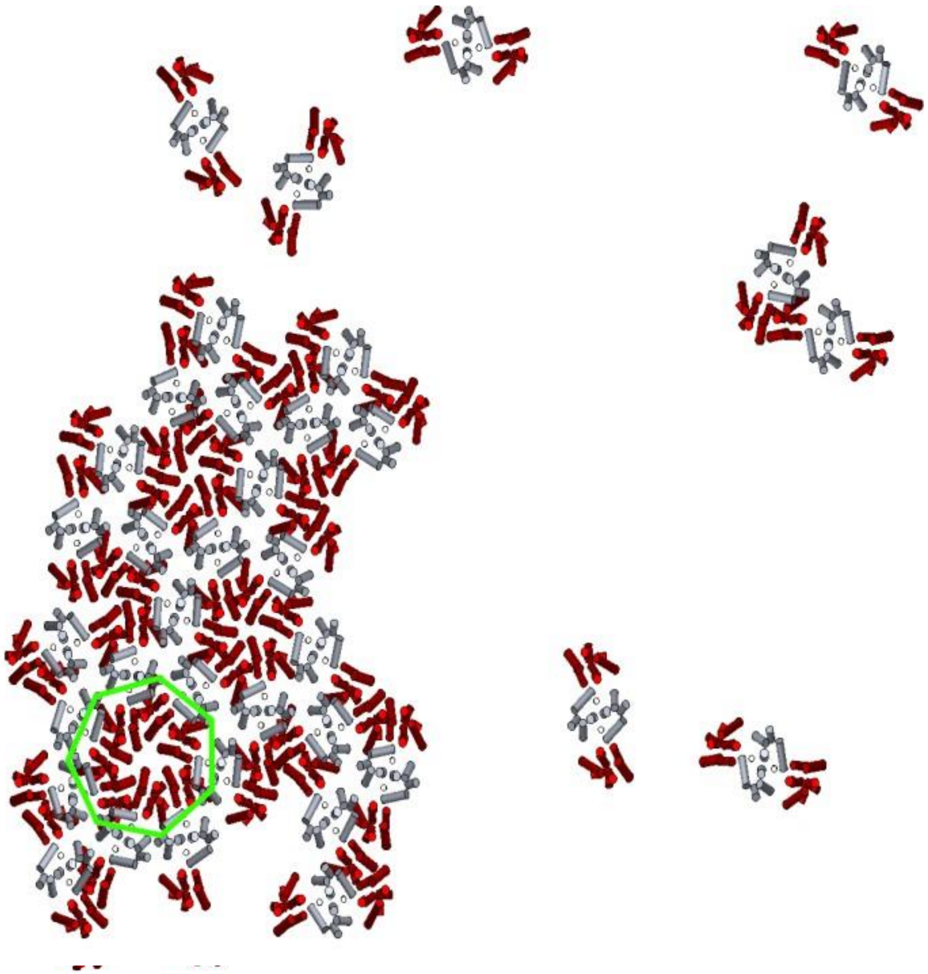


Baillie, C.F. *et al*. Phys. Rev. D. (1989)
Meakin,P. *et al*. JCP (1983)

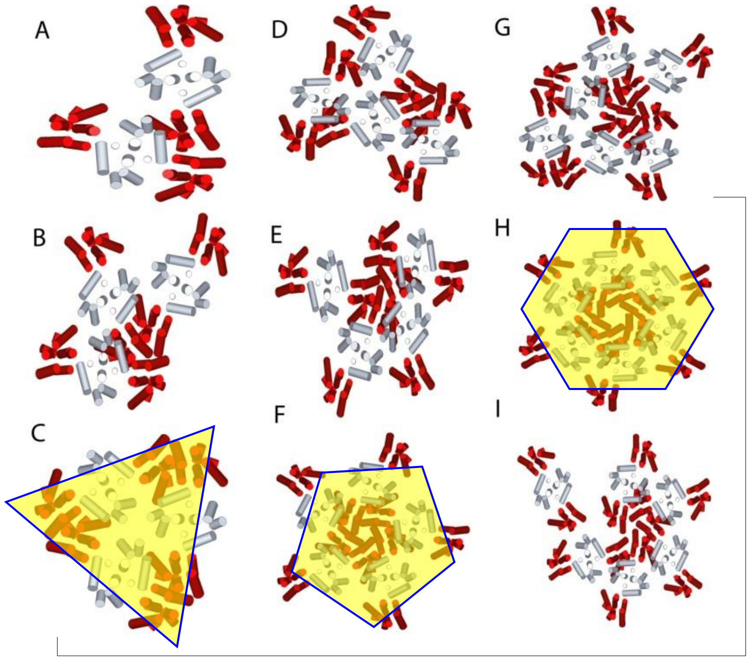
Metropolis Criterion:
rand_num < exp(-ΔE/kT)

Spontaneous assembly in 2D

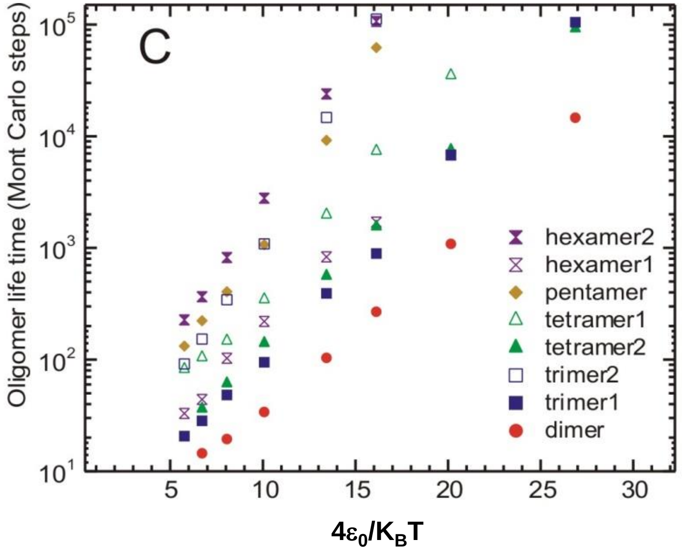


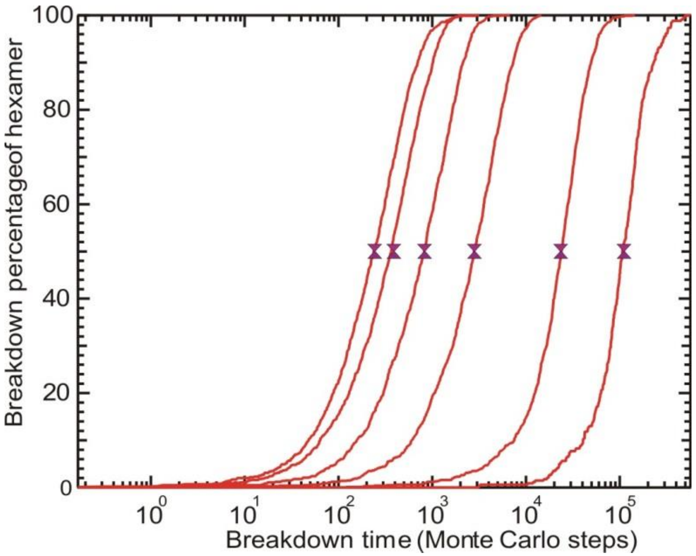


Stability of various oligomeric intermediates

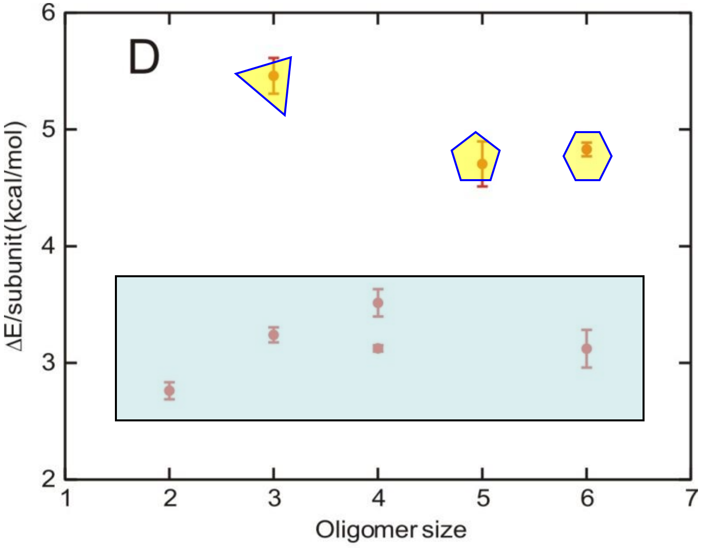


Stochastic ~ $\exp(-\Delta E/RT)$

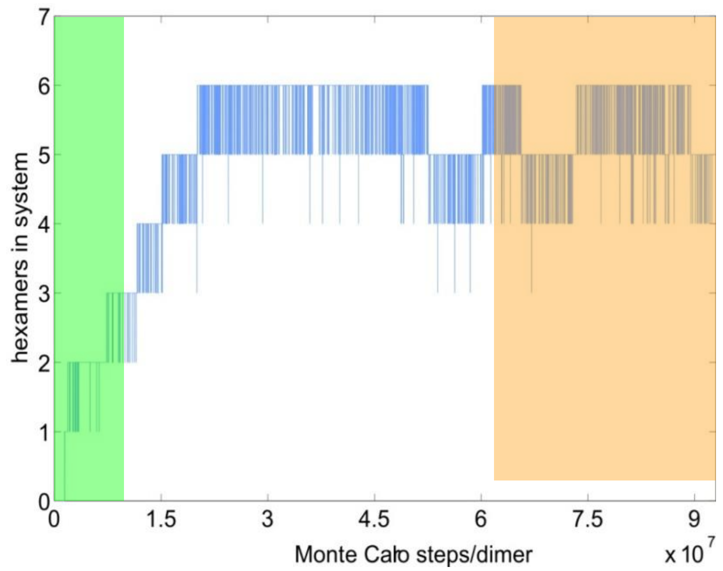


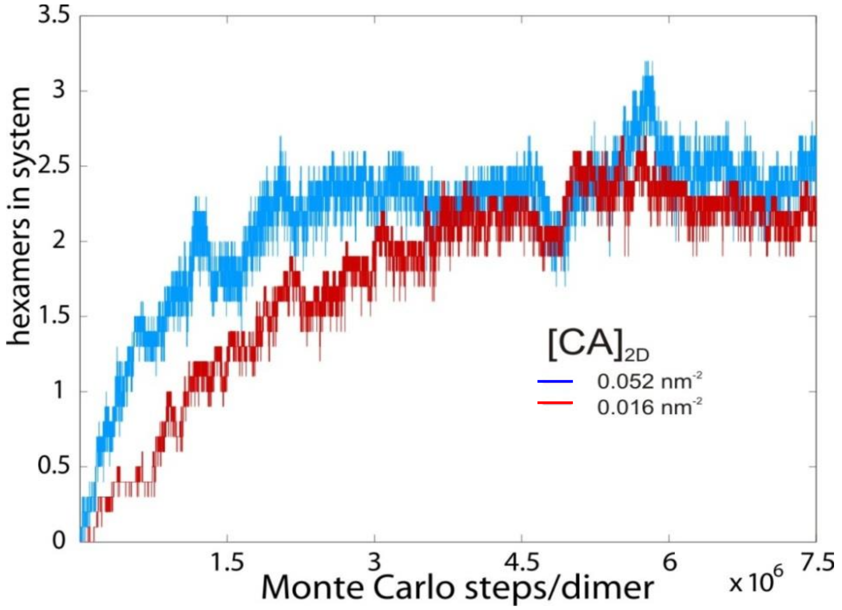


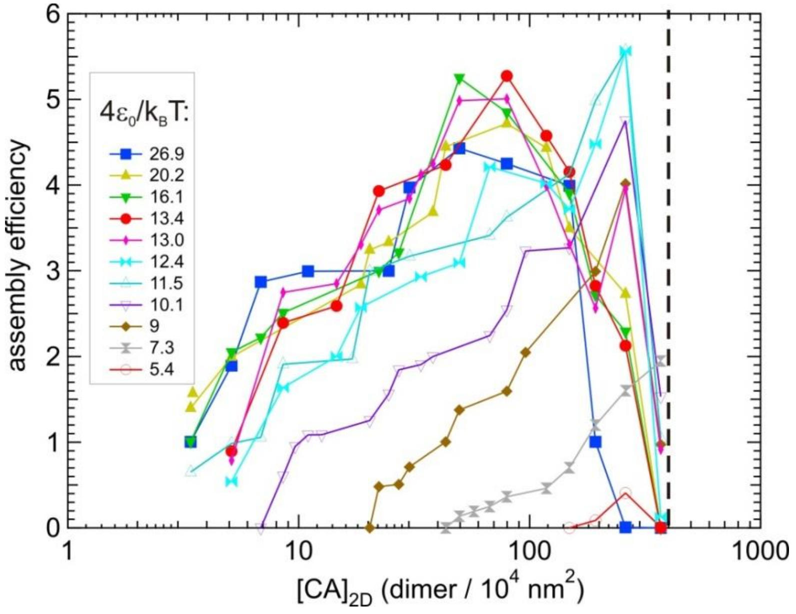
Exp Val ~ 2- 4 kcal/mol

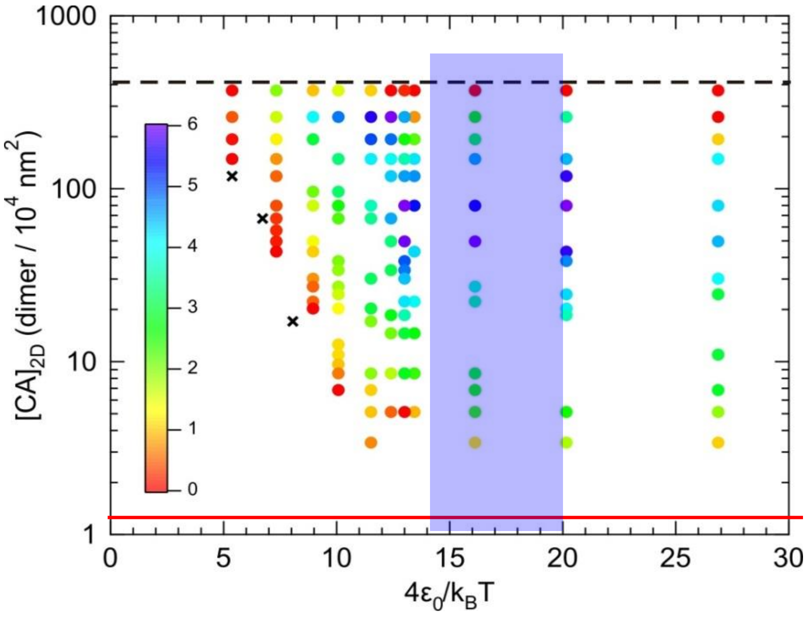


Driving forces and phase diagram of self-assembly

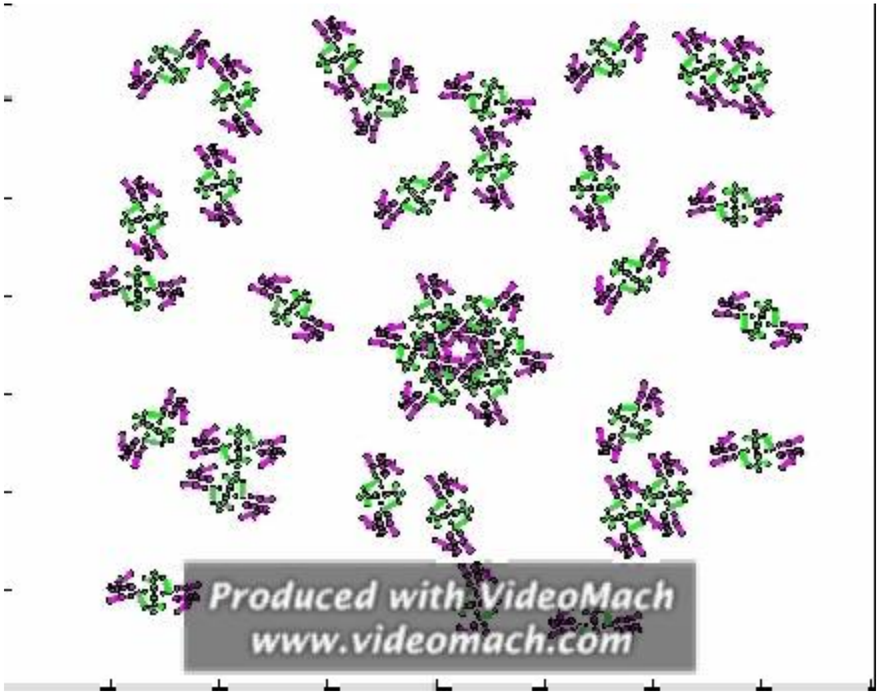


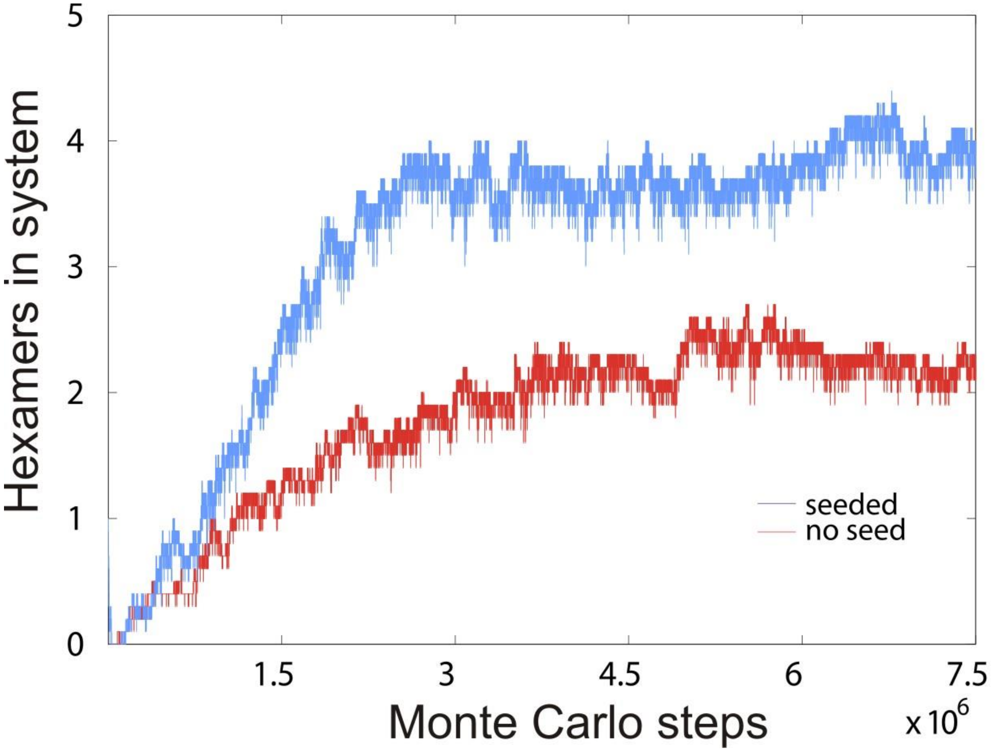






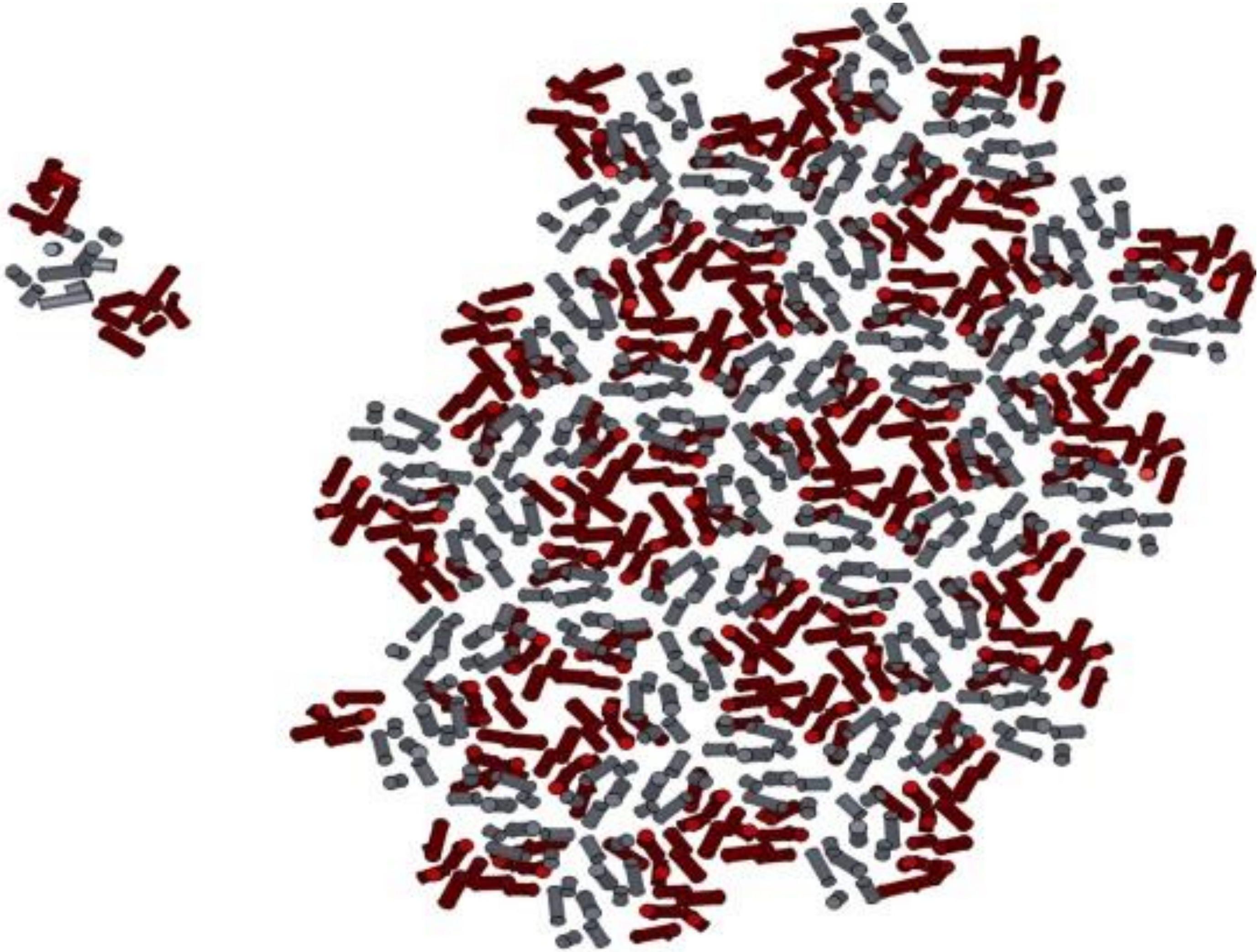
Self-assembly is not nucleated by template



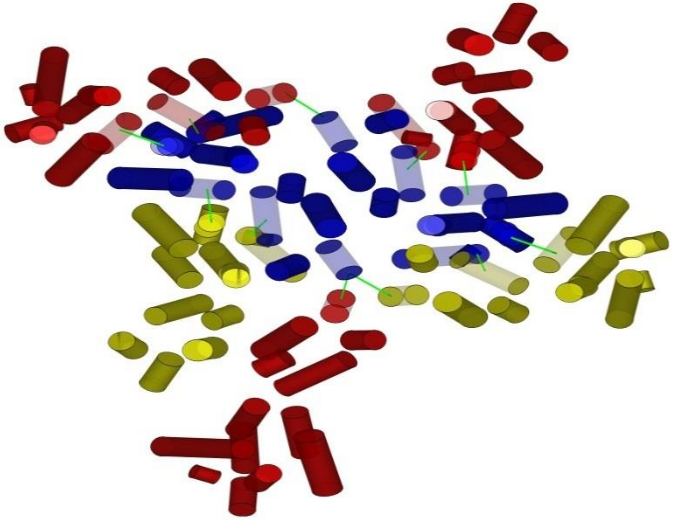


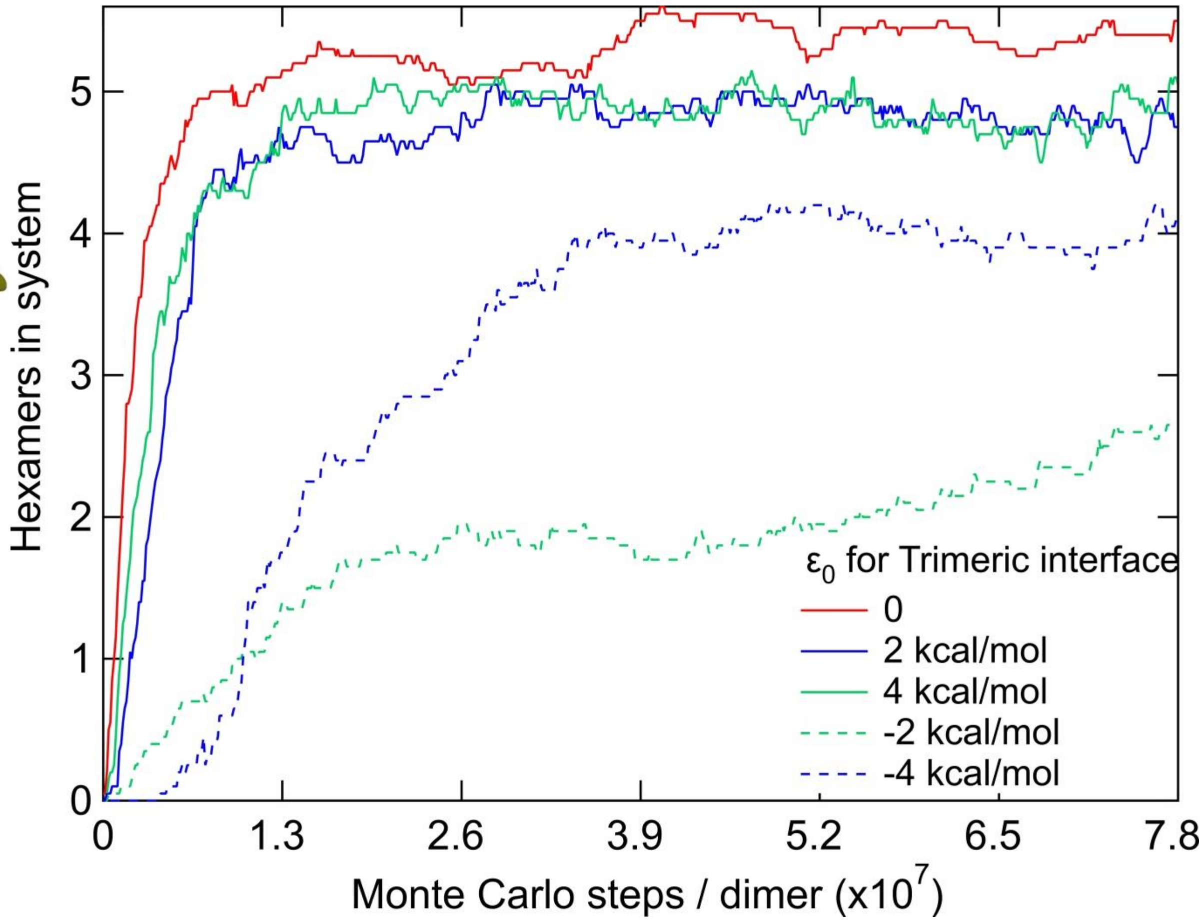
Bo Chen et al. Biophysical Journal 2011

Semi 3D simulation of self-assembly



Correlate assembly mechanism with protein structure





Zhao, Gongpu and Perila, Juan et al. Nature 2013

Current Status

Better collision detection algorithm improves the efficiency 10-fold

Sorted Verlet list(pair list) improves the efficiency 170-180%.

Openmp helps the best. Multi-threading with dynamic workload schedule.

200 subunits assembly in 4 days on one Xeon E5 1620 (4 core 3.5 GHz).

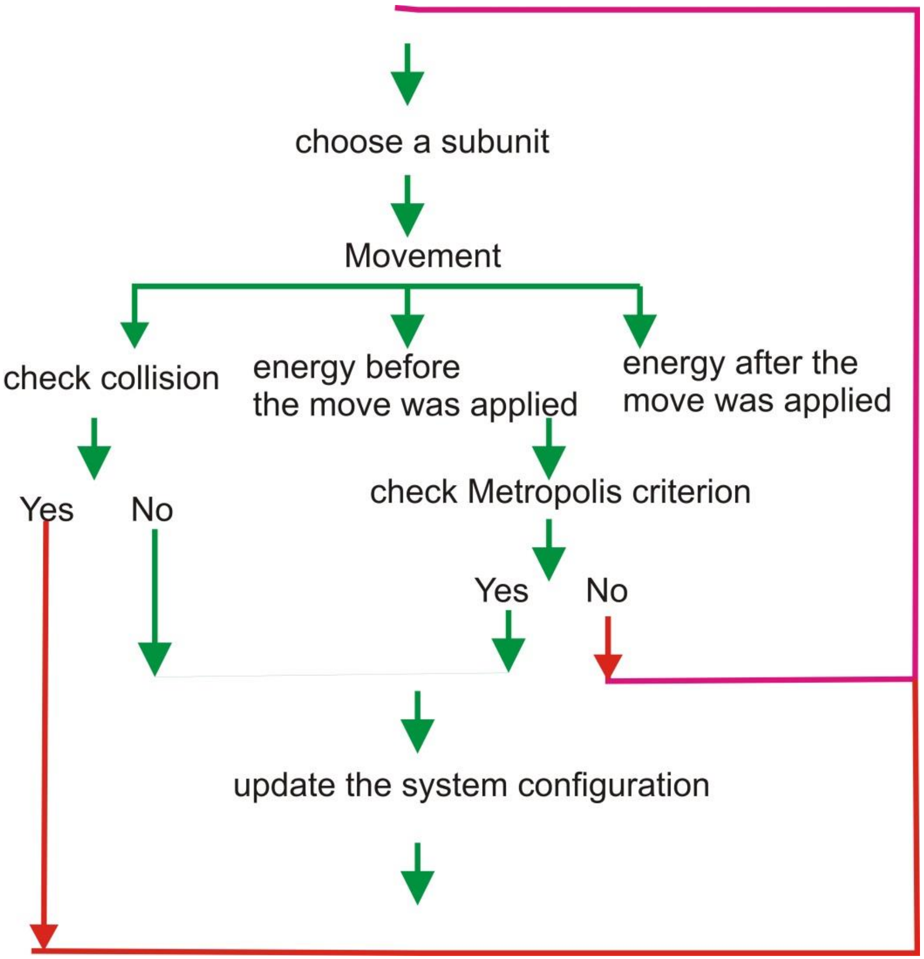
Goal => the need for speed

10x speed to boost the system size ~ 2000 or more

Simulate assembly of different curvatures based on experimental constraints.

Simulate gag polyprotein assembly, the immature capsid lattice.

OPENMP Parallelization



choose a subunit

Movement

check collision

energy before the move was applied

energy after the move was applied

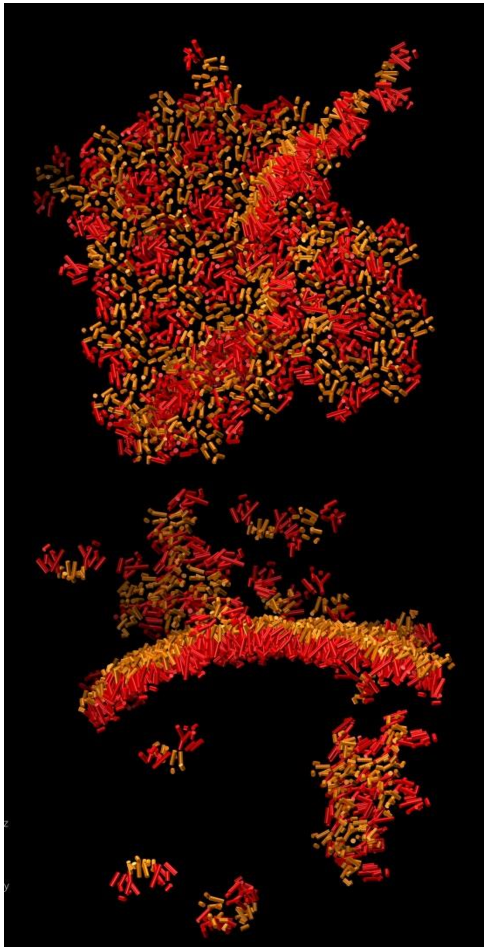
Yes No

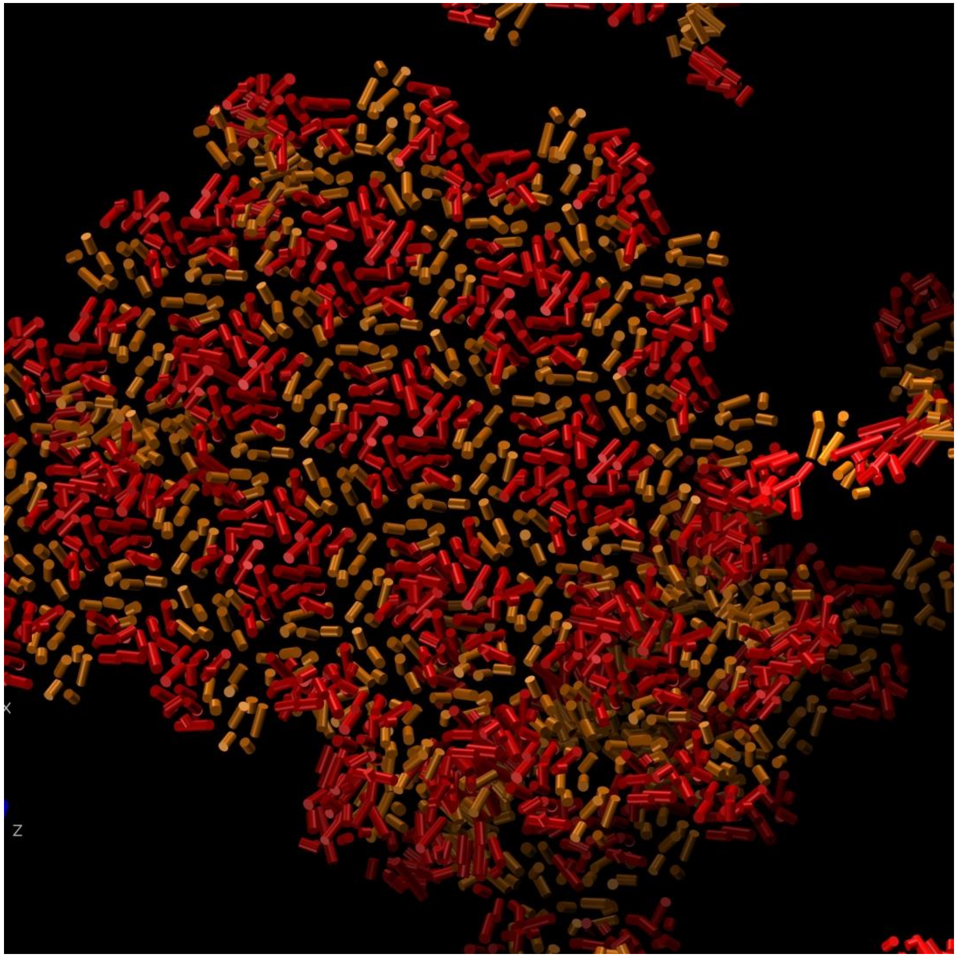
check Metropolis criterion

Yes No

update the system configuration

New Hope

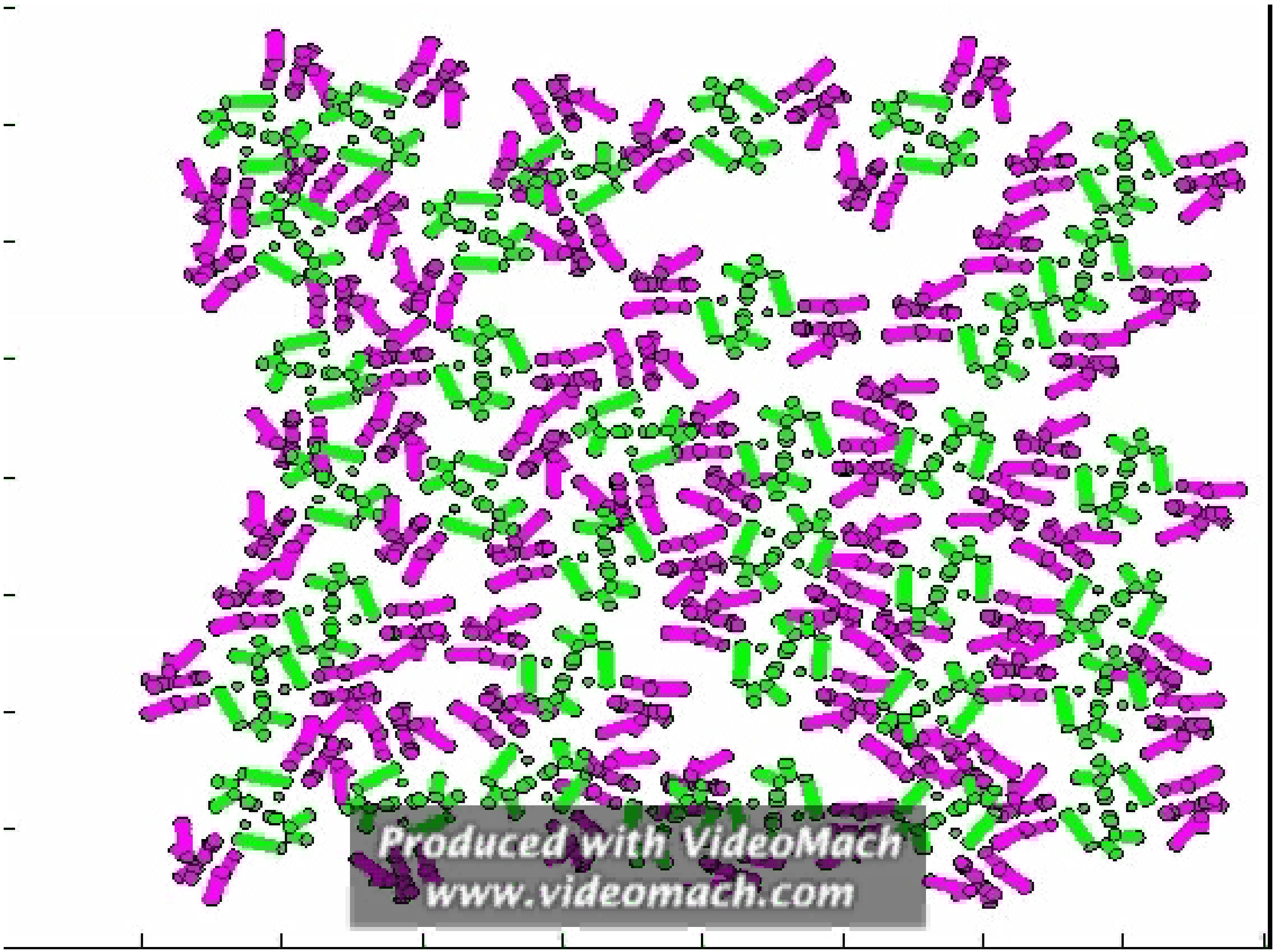




Movie

Acknowledgement

- Robert Tycko
- Jeff Webber
- UCF In-house grant
- AFOSR Young Investigator Award



Seeded growth