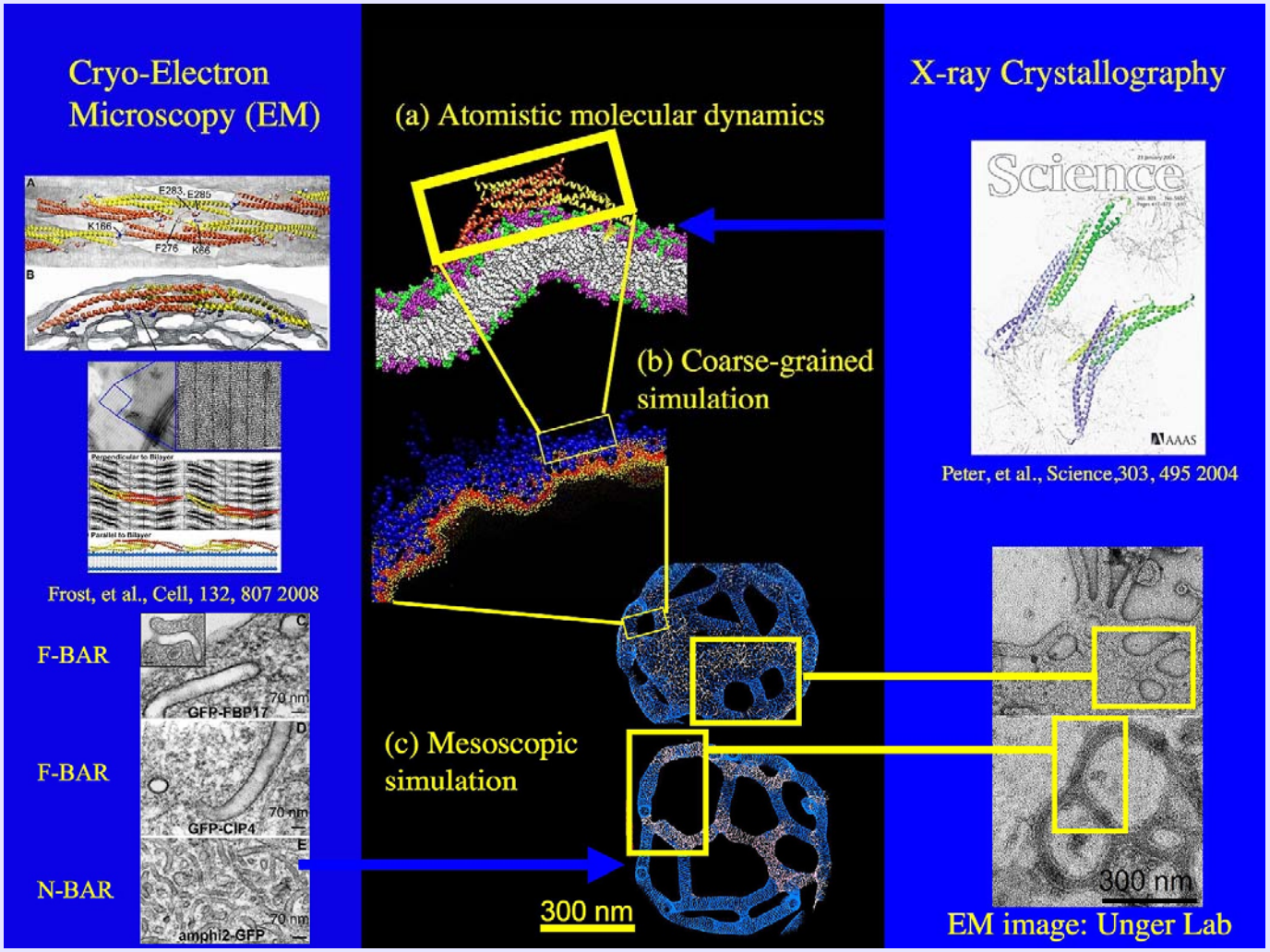
Systematic and Scalable Multiscale Simulation of Multi-Protein Complexes

Greg Voth

University of Chicago



C B M S

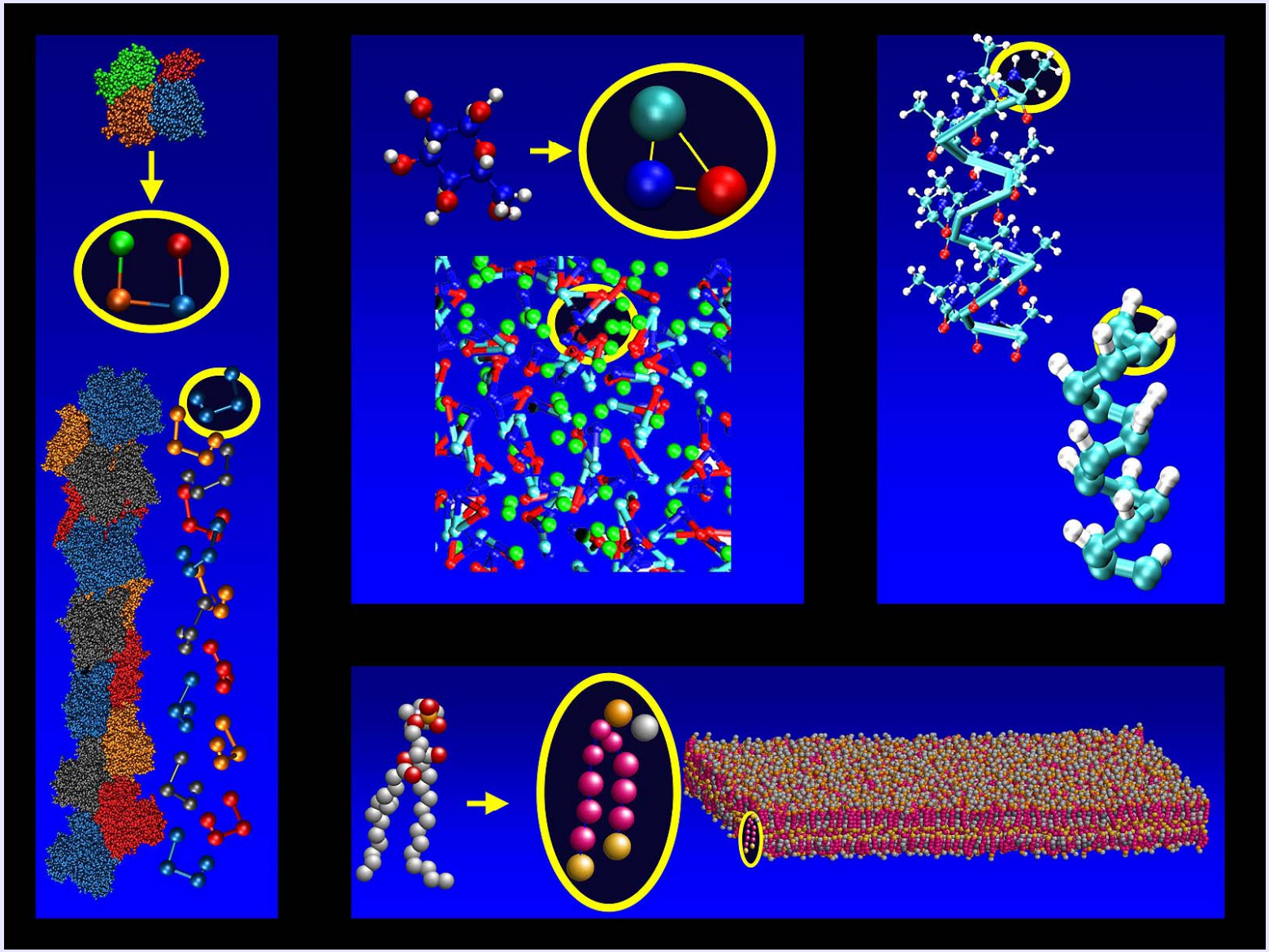
Outline of the Seminar

- **Coarse-graining as a Form of Renormalization**
  (Coarse-graining versus Coarse-grained Modeling?)

- **The Special Challenge of Coarse-graining Large Proteins and Multi-Protein Assemblies**

- **A Key Application**

Coarse-graining = Reduction in “Resolution”



Coarse-graining as a Form of Renormalization

Renormalization concepts have a long history:

- **Quantum Electrodynamics and Field Theory**
- **Lattice Spin Models and Phase Transitions**
- **Polymers**

The key concept is that part of the problem is formally "integrated out", resulting in effective interactions for what's left behind.

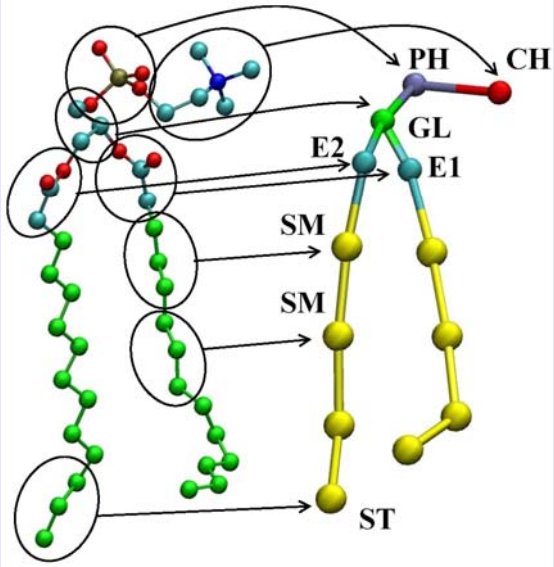
Coarse-Graining with Thermodynamic Consistency (Renormalization)

$$\exp(-\beta F) \propto \int d\mathbf{r} \exp[-\beta V(\mathbf{r})] \qquad (\beta = 1/k_B T)$$

$$\int d\mathbf{r} \exp[-\beta V(\mathbf{r})] \equiv \int d\mathbf{R}_{CG} \exp[-\beta V_{CG}(\mathbf{R}_{CG})] \qquad \left(N_{\mathbf{R}_{CG}} << N_{\mathbf{r}}\right)$$

How best to define $\mathbf{R}_{CG}$?

How to determine $V_{CG}(\mathbf{R}_{CG})$?



Coarse-Graining with Thermodynamic Consistency: Mathematical Details

For a given $\mathbf{R}_{CG}$: $\left(N_{\mathbf{R}_{\mathbf{CG}}} << N_{\mathbf{r}}\right)$

How to determine $V_{CG}(\mathbf{R}_{CG})$?

$$\exp(-\beta F) \propto \int d\mathbf{r} \exp[-\beta V(\mathbf{r})] \qquad (\beta = 1/k_B T)$$

$$\int d\mathbf{r} \exp[-\beta V(\mathbf{r})] = \int d\mathbf{r} \underbrace{\int d\mathbf{R}_{CG} \delta(M_{\mathbf{R}}(\mathbf{r}) - \mathbf{R}_{CG})}_{=1} \exp[-\beta V(\mathbf{r})]$$

Switch Integration Order

$$\int d\mathbf{r} \exp[-\beta V(\mathbf{r})] = \int d\mathbf{R}_{CG} \exp[-\beta V_{CG}(\mathbf{R}_{CG})]$$

(Thermodynamic Consistency)

It Follows That...

$$\exp[-\beta V_{CG}(\mathbf{R}_{CG})] \equiv \int d\mathbf{r}\, \delta(M_{\mathbf{R}}(\mathbf{r}) - \mathbf{R}_{CG}) \exp[-\beta V(\mathbf{r})]$$

The Multiscale Coarse-Graining (MS-CG) Approach* ("Force Renormalization")

$\vec{r}$: **Atomic coordinates**

$\vec{R}$: **CG site coordinates**

$\vec{F}_\alpha^{CG}$: **Exact CG force**

V_{CG} : **Exact CG potential**

$\vec{F}_\alpha$: **Instantaneous sum of atomic forces acting on the CG site**

M : **Total number of CG sites**

χ^2 : **The residual**

$\langle K \rangle$ **average over configurations**

$$\chi^2\left[\vec{F}^{CG}\right] = \frac{1}{3M}\left\langle \sum_{\alpha=1}^{M} \left| \vec{F}_\alpha^{CG}(\vec{R}) - \vec{F}_\alpha(\vec{r}) \right|^2 \right\rangle$$

Find $\vec{F}_\alpha^{CG}(\vec{R})$ **from** $\dfrac{\delta\chi^2\left[\vec{F}^{CG}\right]}{\delta \vec{F}_\alpha^{CG}} = 0$

Have Now Proven That: $\vec{F}_\alpha^{CG}(\vec{R}) = -\dfrac{\partial V_{CG}(\vec{R})}{\partial \vec{R}_\alpha}$

*S. Izvekov and GAV, J. Phys. Chem. B 109, 2469 (2005); J. Chem. Phys. 123, 134105 (2005); W. G. Noid, et al., J. Chem. Phys. 128, 244114 (1-11) (2008); 128, 244115 (1-20) (2008).

The MS-CG Algorithm

(1) Assume pairwise decomposable radial non-bonded forces:

$$\vec{F}_{\alpha}^{CG} \xrightarrow[\text{with}]{\text{approximate}} \vec{F}_{\alpha}^{MS} \qquad \vec{F}_{\alpha}^{MS} = \sum_{\beta \neq \alpha}^{M} F_{\alpha\beta}^{MS}\left(R_{\alpha\beta};\phi\right)\vec{u}_{\alpha\beta}$$

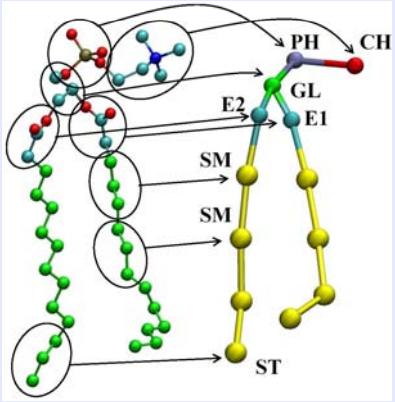
(2) Expand all types of interactions as a *linear expansion of basis functions*:

$$F_{ab}^{MS}\left(R_{ab};f\right) = \sum_{d=1}^{N_d} f_d f\left(R_{ab}, \left\{R_1, \ldots R_{N_d}\right\}\right)$$

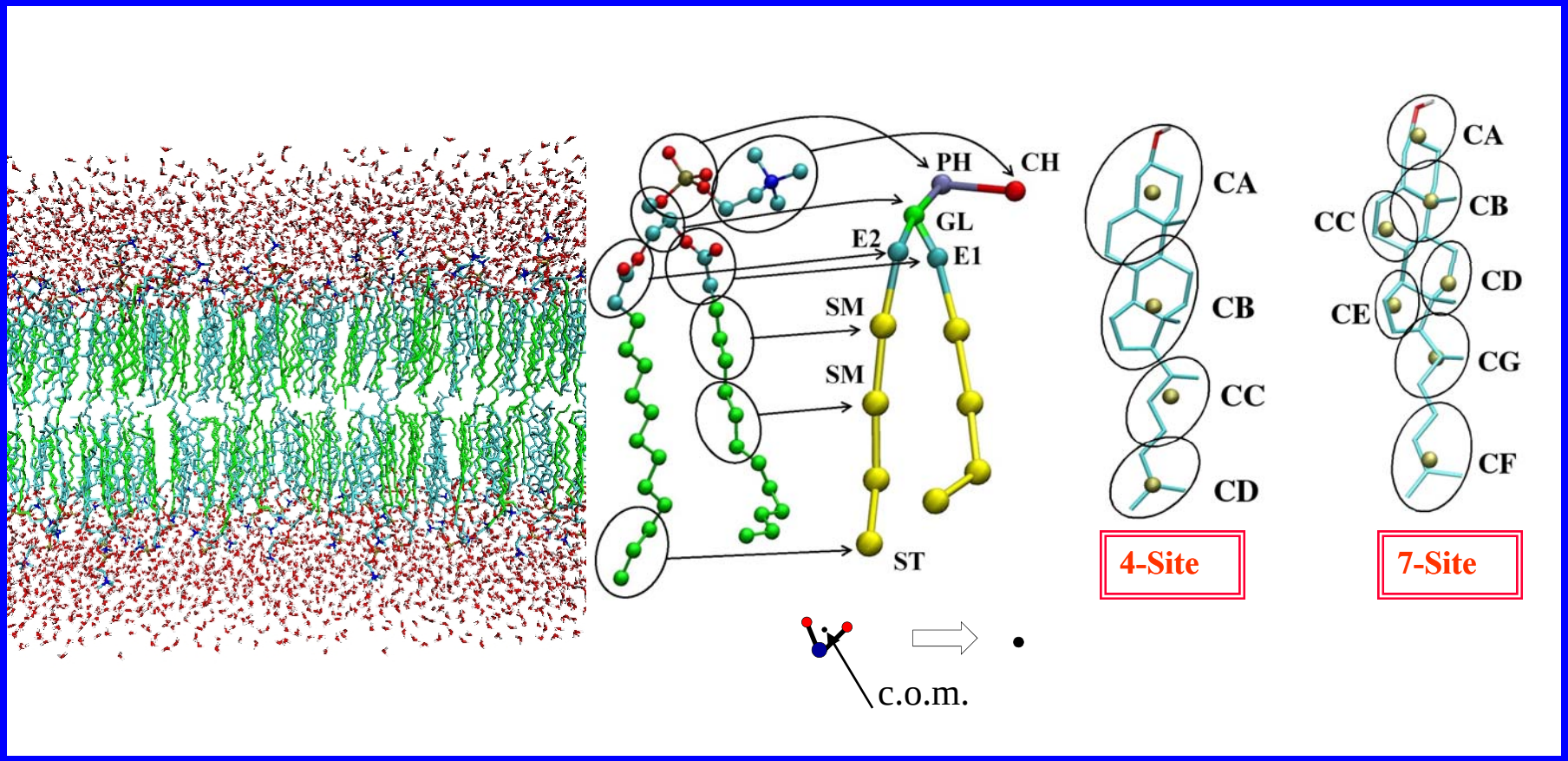
(3) Force matching becomes a linear least squares problem:

$$\chi^2\left[\phi\right] = \frac{1}{3M}\left\langle \sum_{\alpha=1}^{M}\left|\vec{F}_{\alpha}^{MS}\left(\vec{\boldsymbol{R}};\phi\right) - \vec{F}_{\alpha}\left(\vec{\boldsymbol{r}}\right)\right|^2 \right\rangle$$

$$\frac{\delta\chi^2\left[\phi\right]}{\delta\phi_{d'}} = 0$$



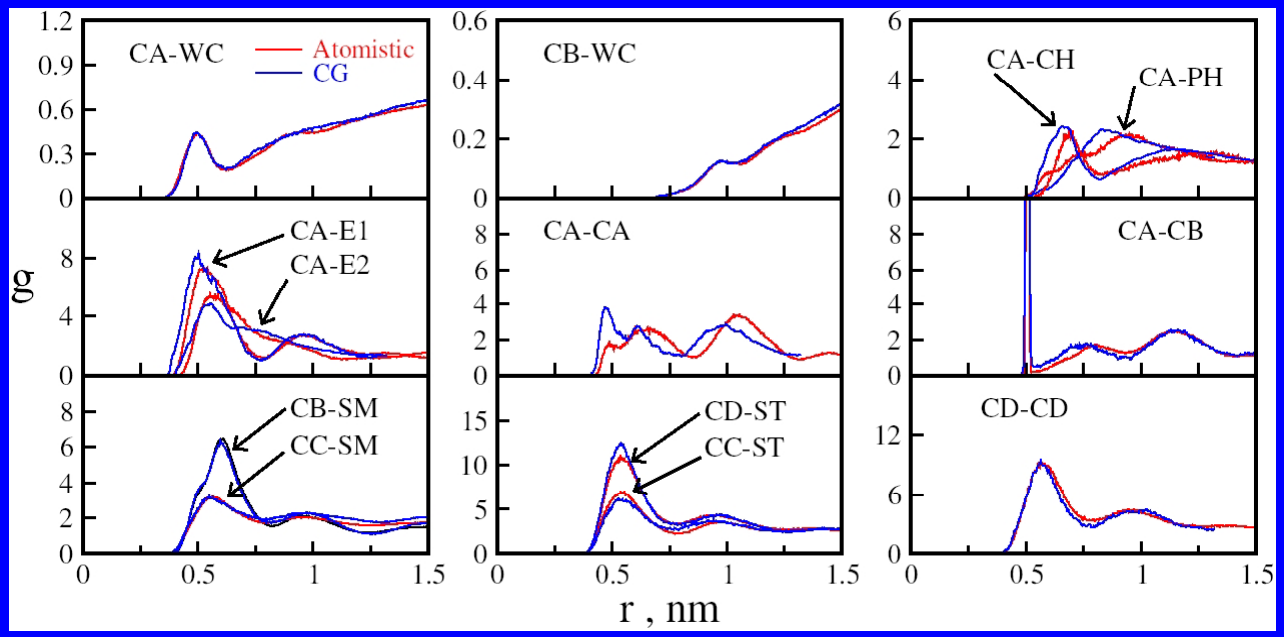
A Multiscale Coarse-Grained Model for Mixed Lipid/Cholesterol Bilayers



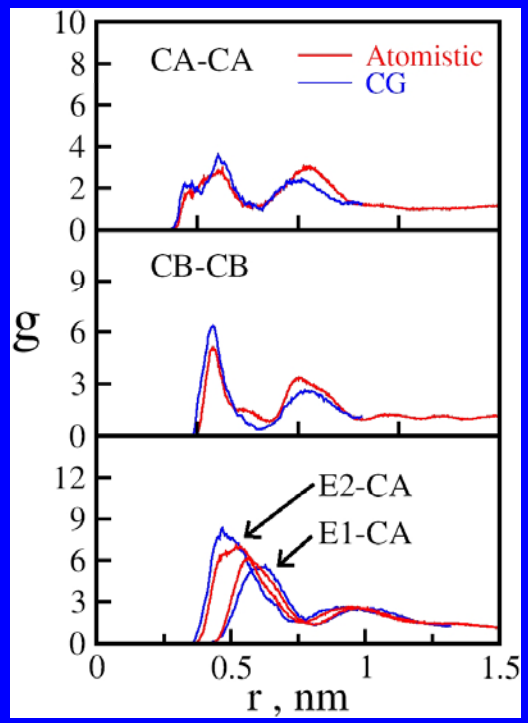
Protocol: trajectories+forces from atomistic simulation → trajectories+forces for c.o.m CG interaction sites → Force-Matching

Chol-Water , Chol-Chol , Chol-Lipid RDFs

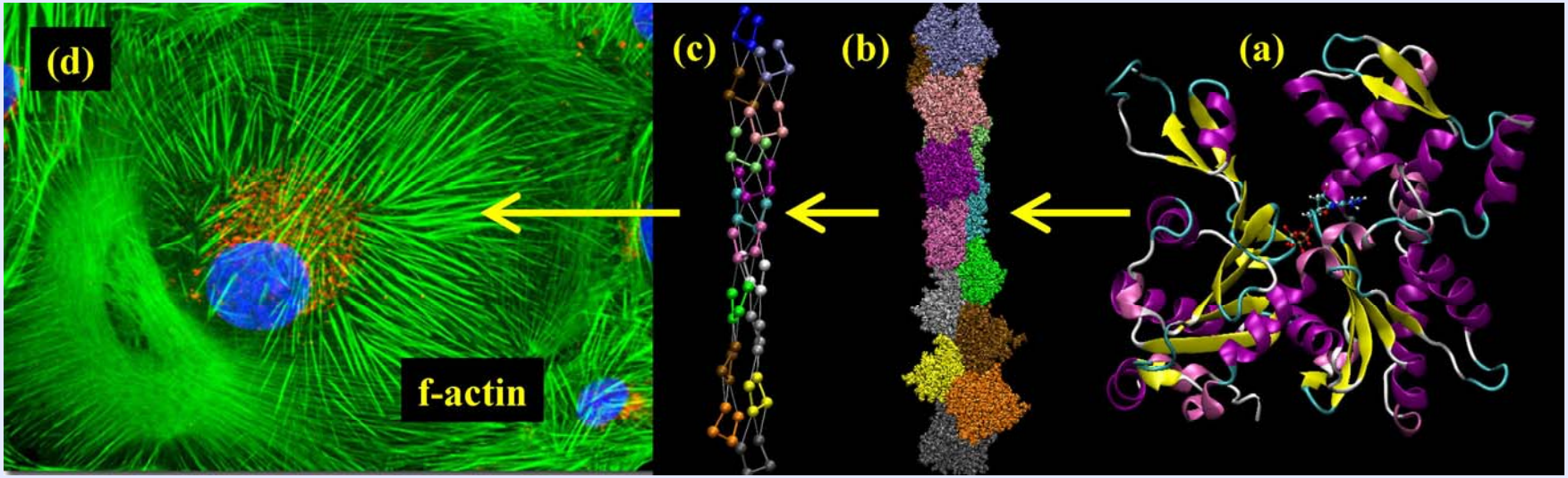
4-Site Chol



7-Site Chol



The Multiscale Challenge for Large Proteins



<u>Needed</u>: Good theoretical descriptions at each scale, proper information transfer between the scales, and (finally) concurrent multiscale simulation where required.

Two Big Problems to Solve First

- **Eliminate the Solvent Entirely**
- **Define "Large" CG Sites for Proteins**

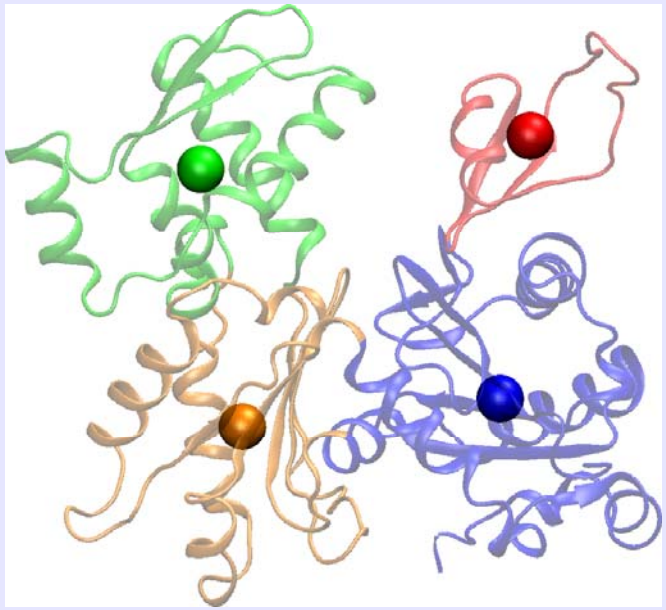
Second Big Problem: Defining "Large Coarse-Grained Sites of Proteins

$$\exp(-\beta F) \propto \int d\mathbf{r} \exp[-\beta V(\mathbf{r})] \qquad (\beta = 1/k_B T)$$

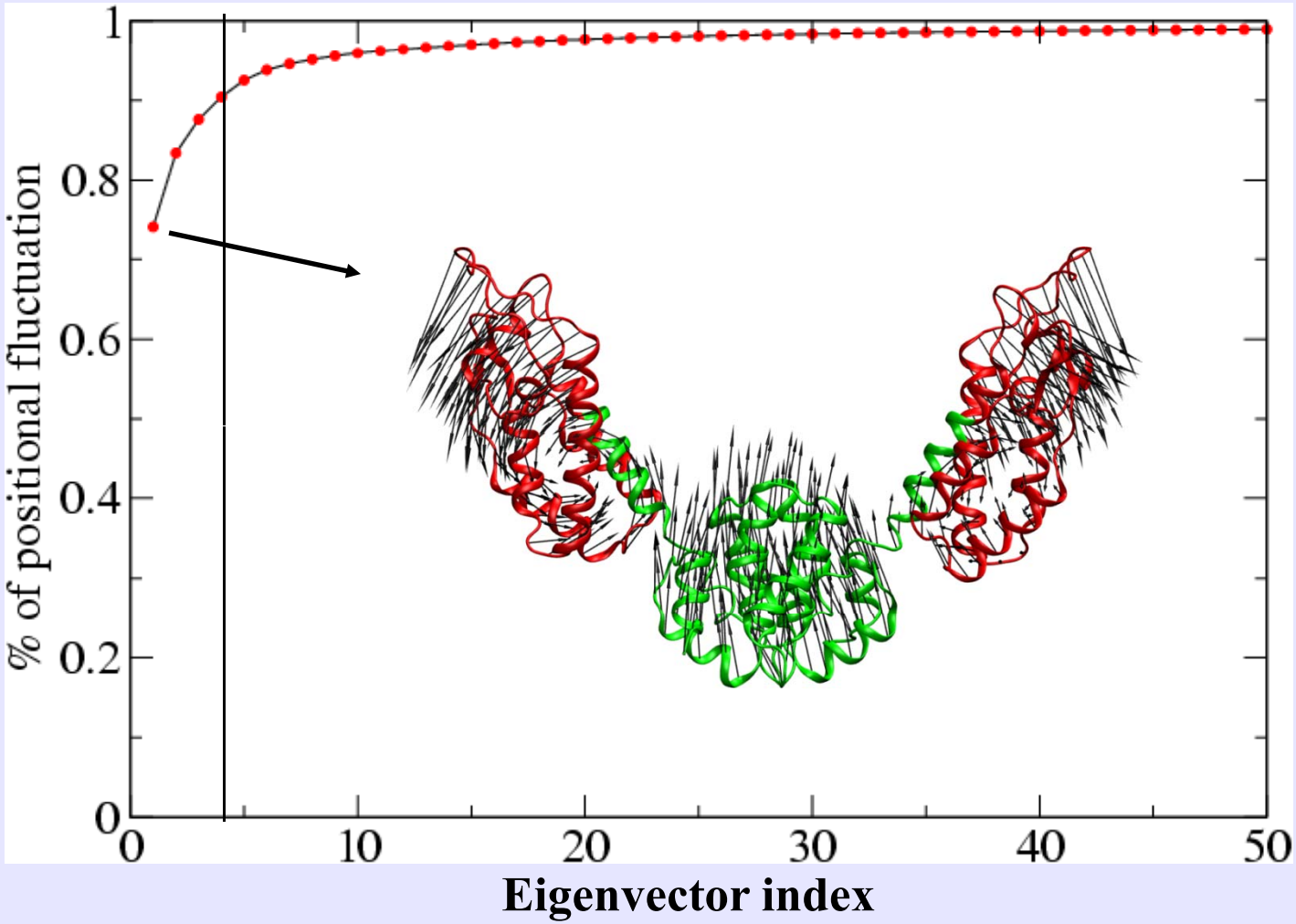
$$\int d\mathbf{r} \exp[-\beta V(\mathbf{r})] \equiv \int d\mathbf{R}_{CG} \exp[-\beta V_{CG}(\mathbf{R}_{CG})] \qquad \left(N_{\mathbf{R}_{CG}} << N_{\mathbf{r}}\right)$$

How best to define $\mathbf{R}_{CG}$?

How to determine $V_{CG}(\mathbf{R}_{CG})$?



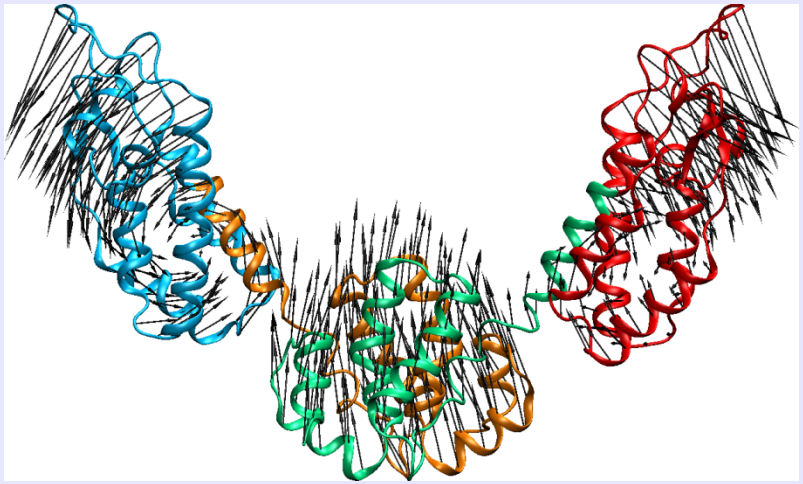
Essential Dynamics of Proteins



Essential subspace: the first few modes represent the most important protein dynamics

CG sites that reflect essential dynamics (ED-CG)

Essential Dynamics Coarse-graining (ED-CG)*



As identified by ED, a "dynamic domain" is a group of atoms that move together in a highly correlated fashion. If the atom j moves in a correlated fashion with the atom i, their displacement difference should be small, and they should be allocated in the same CG site I, which leads to a variational minimization of the residual:

$$\chi^2 = \frac{1}{3N}\sum_{I=1}^{N}\frac{1}{n_t}\sum_{t=1}^{n_t}\left(\sum_{i\in I}\sum_{j\geq i\in I}\left|\Delta r_i^{ED}(t)-\Delta r_j^{ED}(t)\right|^2\right)$$

$$\downarrow$$

$$\chi^2 = \frac{1}{3N}\sum_{I=1}^{N}\left(\sum_{i\in I}\sum_{j\geq i\in I}\left(C_{ii}^{ED}-2C_{ij}^{ED}+C_{jj}^{ED}\right)\right)$$

$$C_{ij}^{ED} \equiv \frac{1}{n_t}\sum_{t=1}^{n_t}\Delta r_i^{ED}(t)\cdot\Delta r_j^{ED}(t)$$

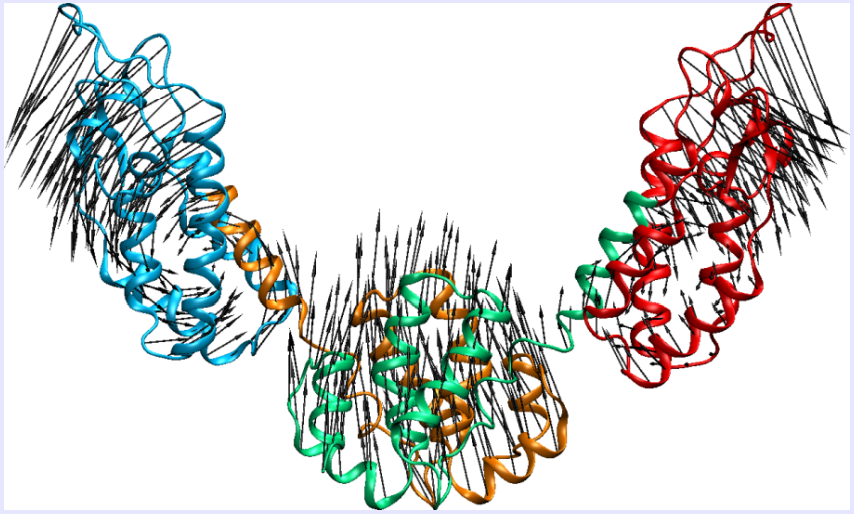
$$= \sum_{h=1}^{3} C^{ED}(i_h, j_h)$$

$$= \sum_{h=1}^{3}\left(\sum_{q=1}^{n_{ED}}\psi_q^{i_h}\lambda_q\psi_q^{j_h}\right)$$

*Z. Zhang, L. Lu, W. G. Noid, V. Krishna, J. Pfaendtner, and G. A. Voth, Biophys. J. **95**, 5073 (2008).

ED-CG Methodology

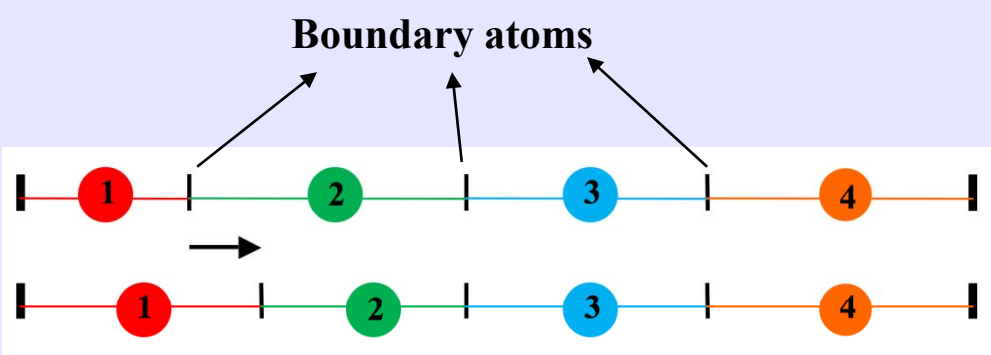
- Numerical Algorithm



(1) Each atom is involved in only one dynamic domain;

(2) Dynamic domains are contiguous in sequence space.

(3) A CG site is the COM of a group of atoms (a dynamic domain);

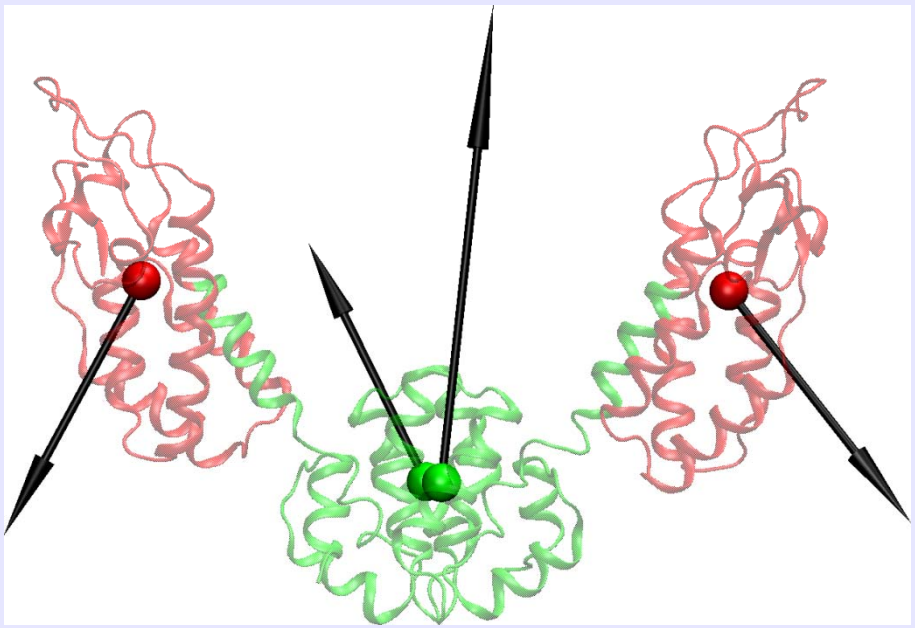


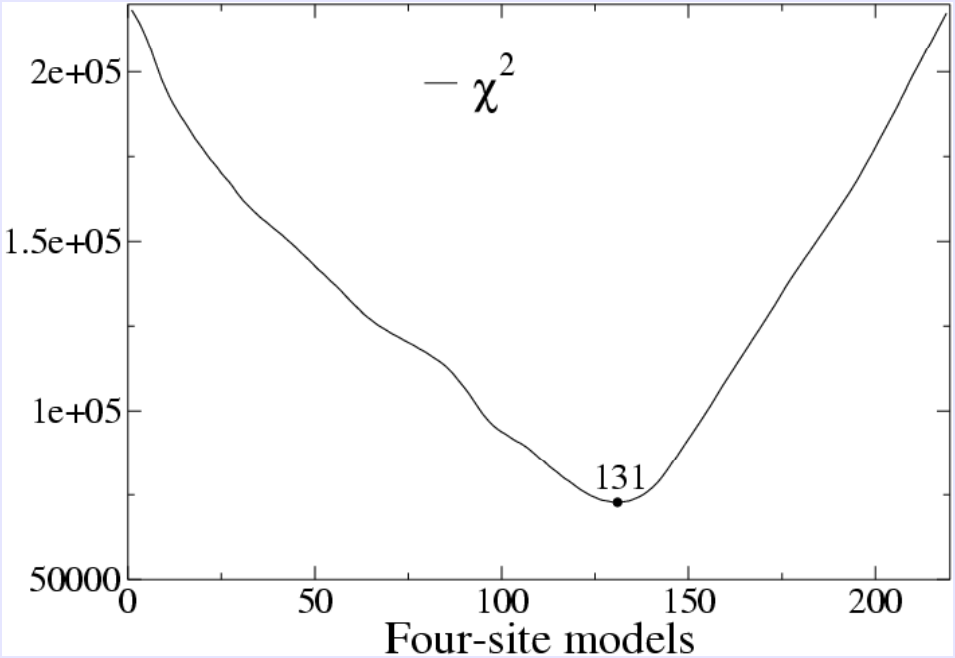
Simulated Annealing and Steepest Descent

CG Sites for the HIV-1 CA Protein Dimer

- Symmetric four-site model

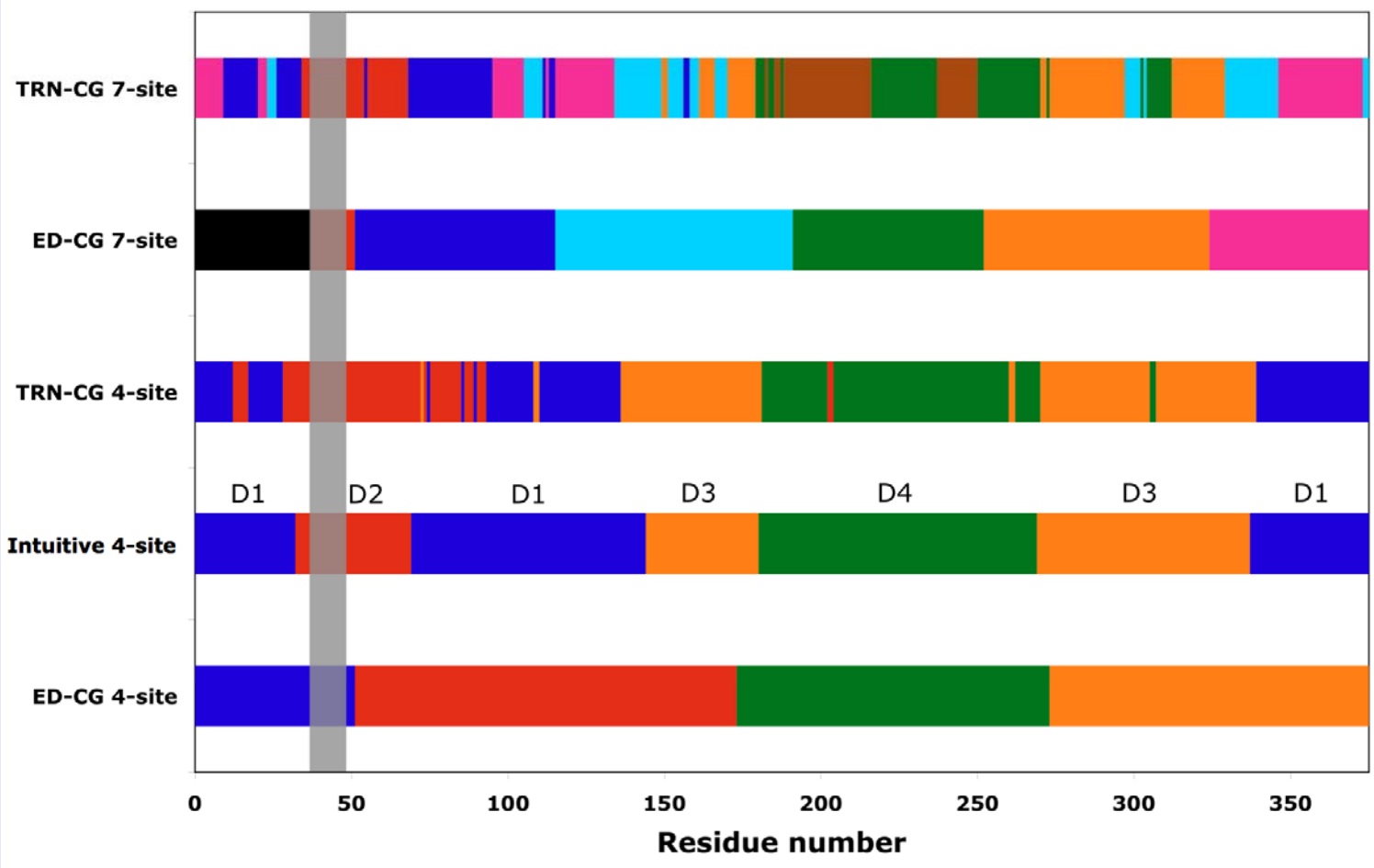
There is only one boundary atom in the symmetric four-site model, which is from positions 1-219





Results for G-actin

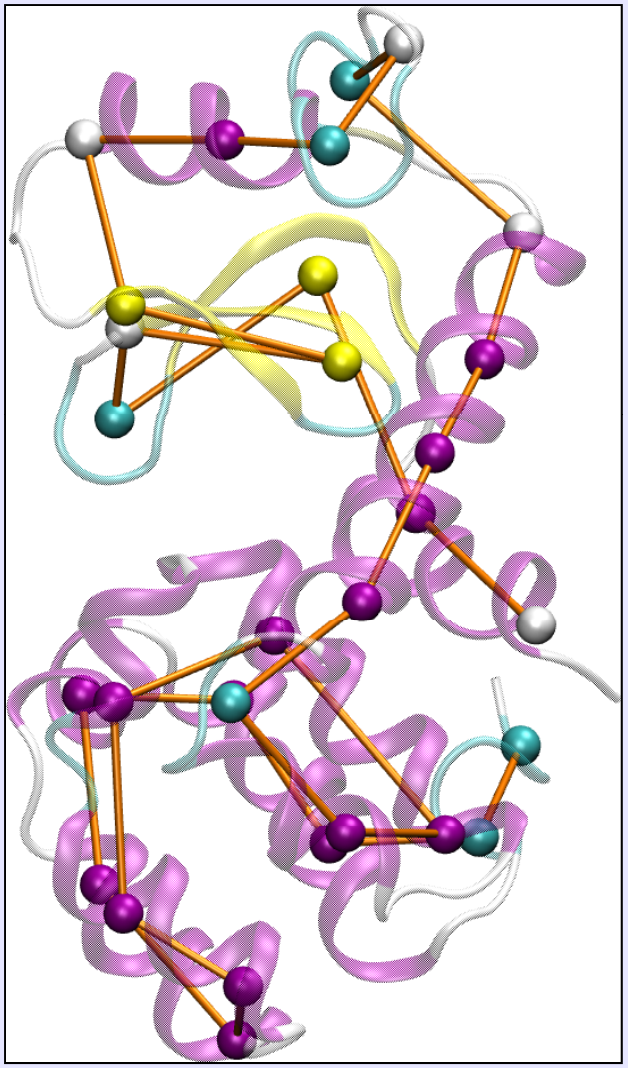
- Comparison of different models



The x-axis is the residue number of the protein, and the DNase binding loop region is marked with a vertical grey box

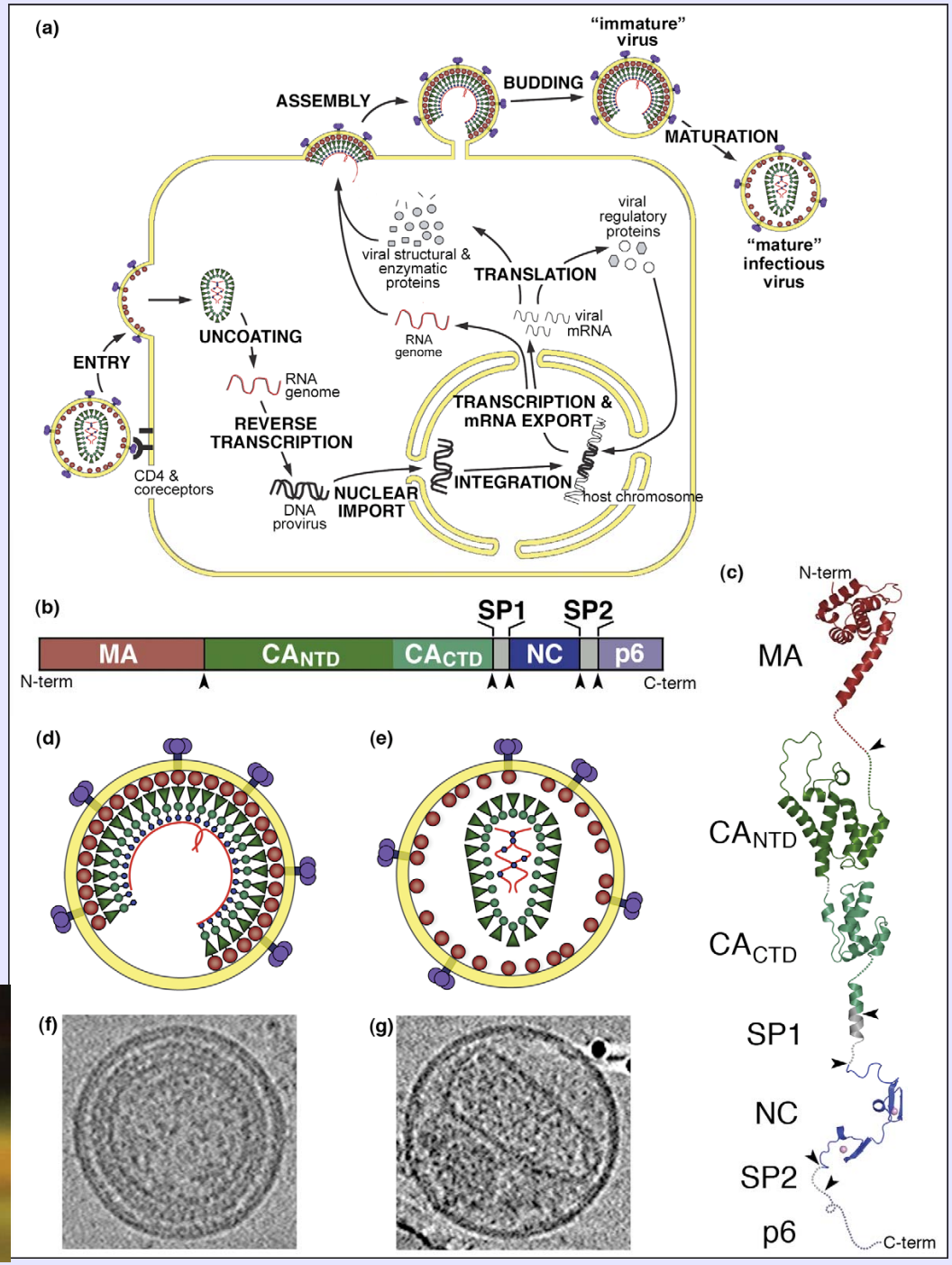
Features of the ED-CG Method

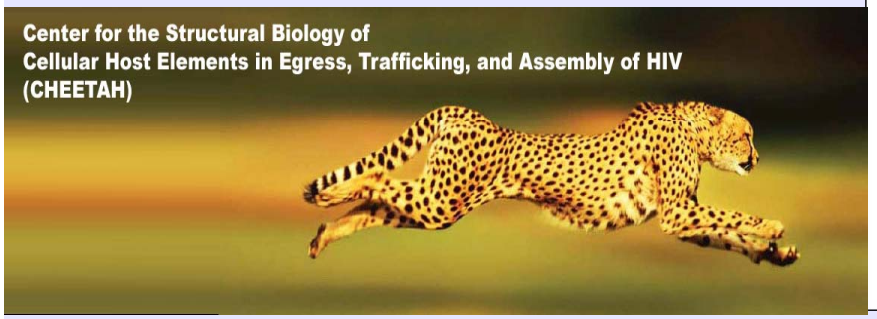
- A quantitative method to place CG sites that reflects important dynamics
- The ED-CG method is suitable to identify relatively few CG sites in large biomolecules
- The ED-CG method can use input from massively parallel MD simulations at the atomistic level.
- CG force fields for the ED-CG models can then be developed



Bacteriophage T4 lysozyme

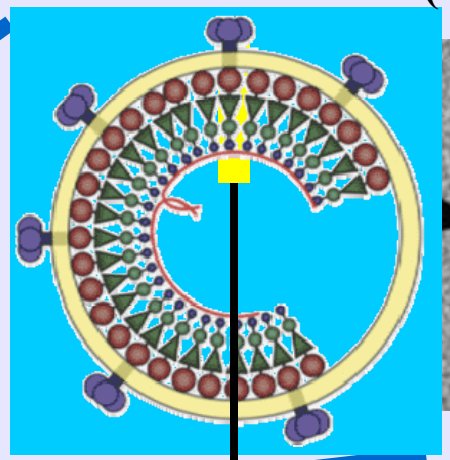
Multiscale Simulation of the HIV-1 Virion

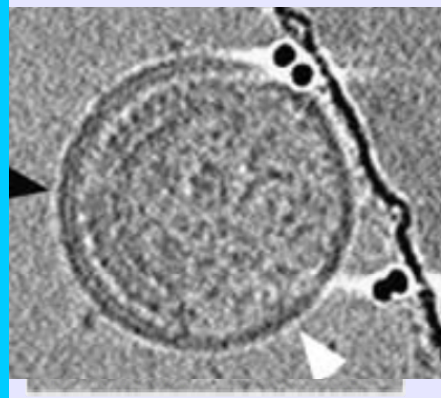




The Immature HIV-1 Virion

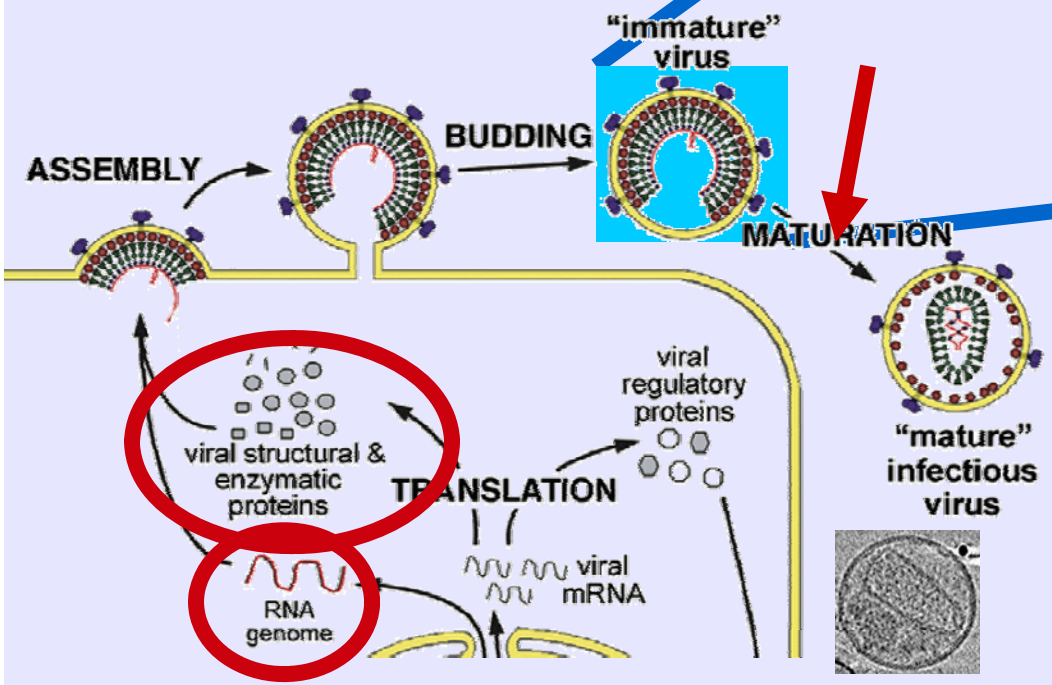
The immature virion (130 nm in diameter)



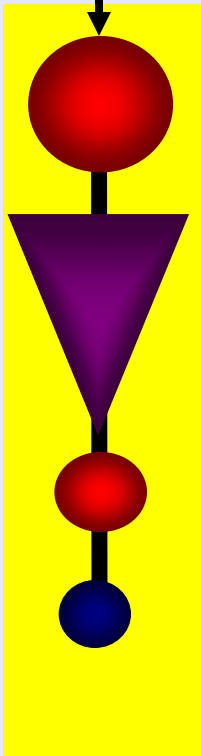


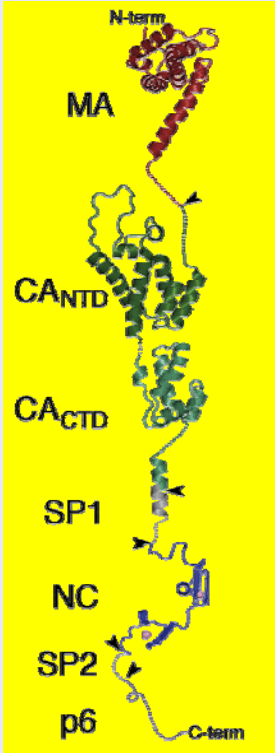
Cryoelectron tomography imaging

Gag and RNA assembly and budding



a small part of the HIV-1 infection pathway

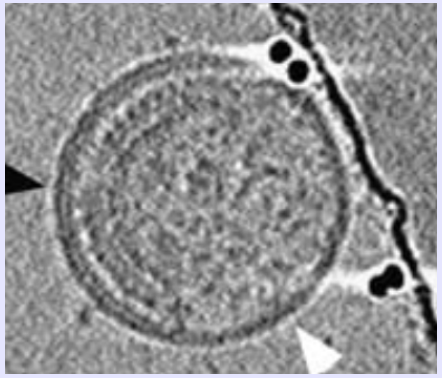




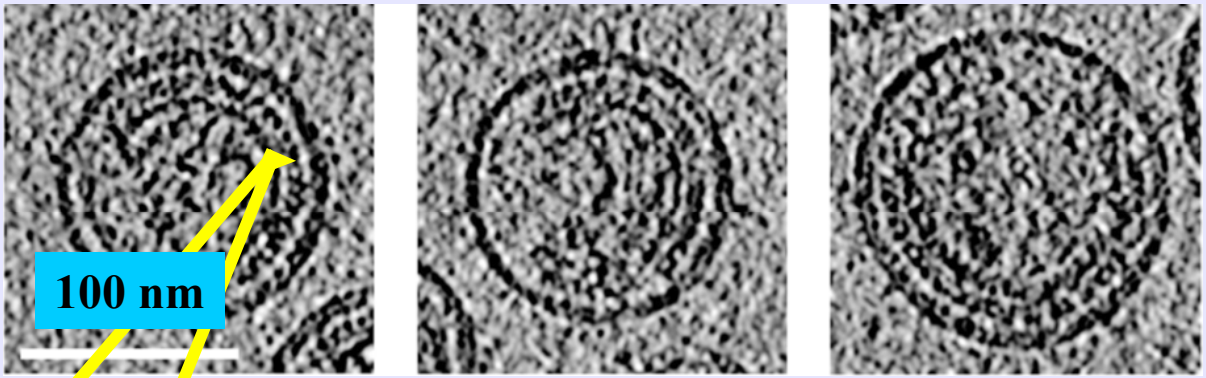
About 10^9 atoms: FAR beyond atomistic molecular dynamics capabilities

Ganser-Pornillos, Yeager, Sundquist, COSB, **18**, 203, 2008

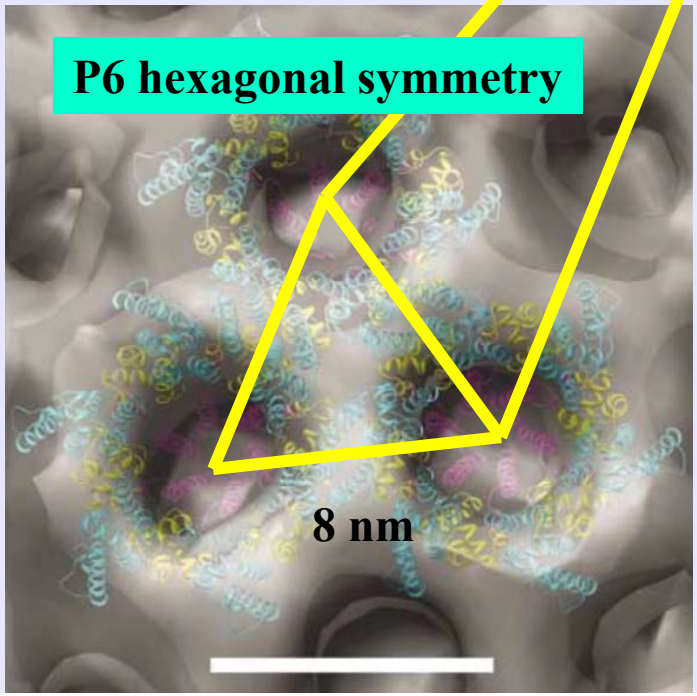
Cryotomography Suggests Structure in the CA Domain



Wright, Schooler, Ding, Kieffer, Fillmore, Sundquist, Jenson, EMBO, 26, 2218, 2007



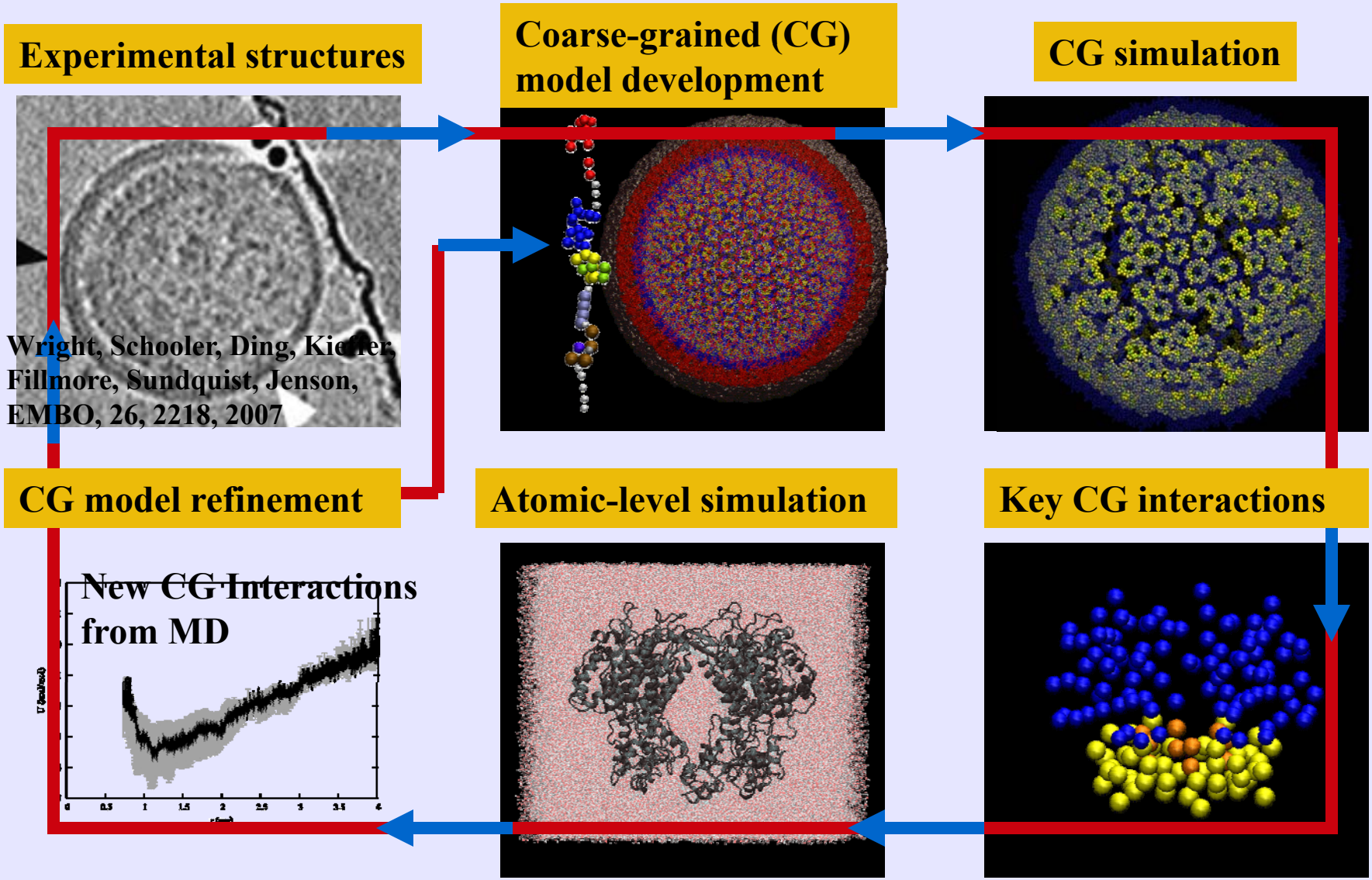
Briggs, Riches, Glass, Bartonova, Zanetti, Krausslich, PNAS, 106, 11090, 2009



An incomplete Gag lattice- only part of the virion is occupied

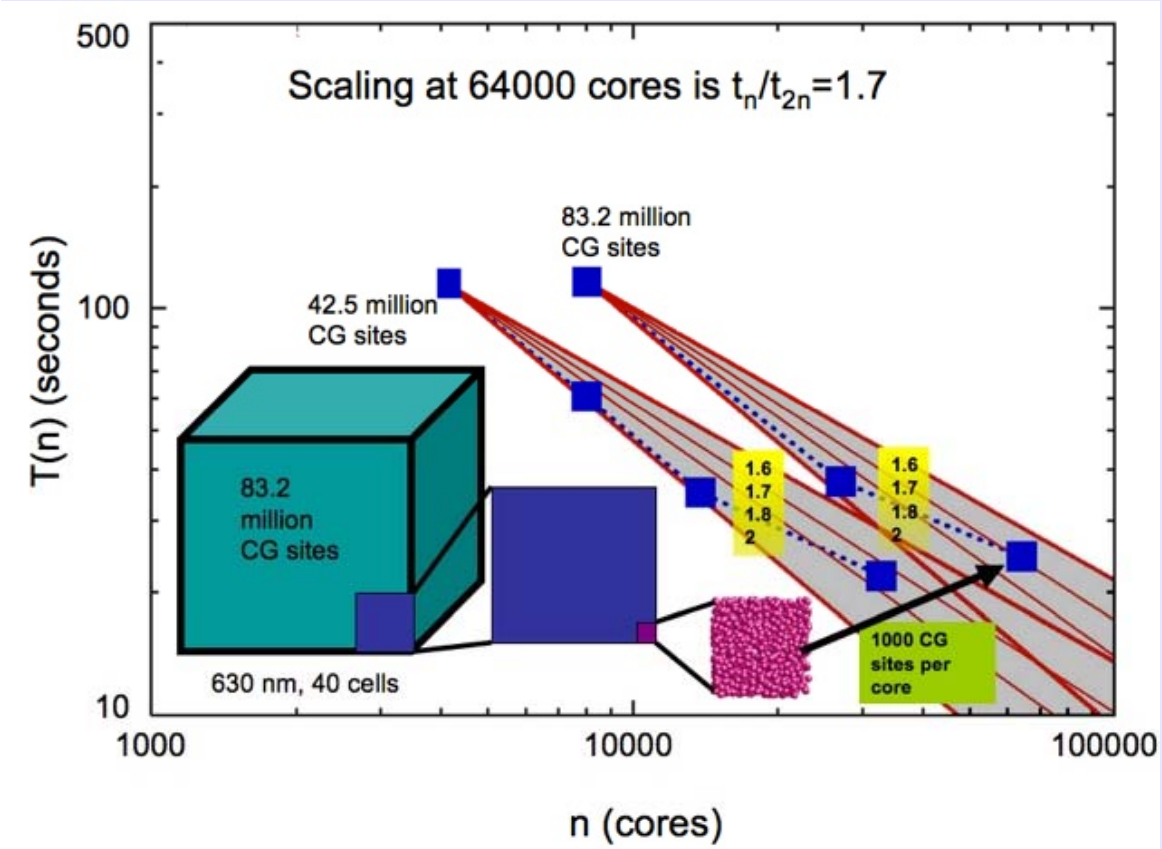
P6 hexagonal lattice in the immature virion is DIFFERENT from the p6 lattice in the infectious viral capsid

A New Direction: Hybrid Multiscale Simulation



An iterative modeling approach combining experimental imaging (cryotomography), coarse-grain (CG) simulation and atomic-level molecular dynamics (MD)

Highly Parallel Multiscale Simulations for the Future



All simulations performed at the National Institute for Computational Sciences (NICS)

Presently good parallel scaling over as many as 64,000 cores

Coarse-grained Model of Gag

DOPC/DOPS 50/50
CG bilayer, screened charges

MA domain: elastic network, screened charge and dipolar interactions

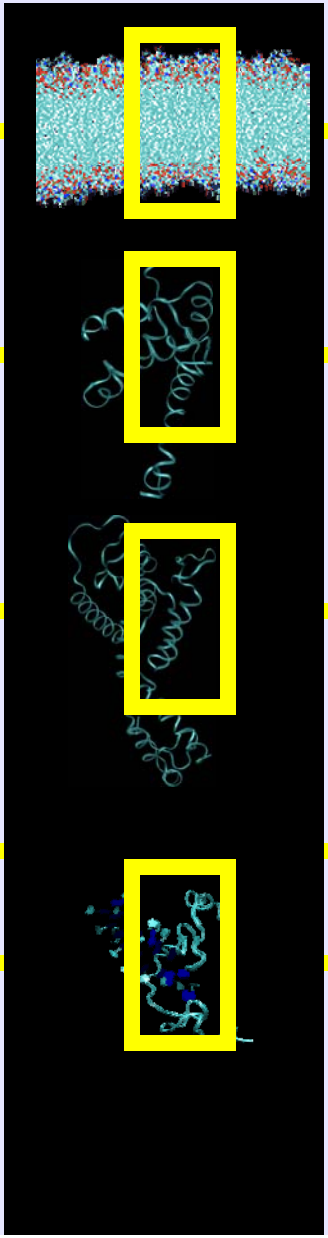
CA NTD-CTD domain: elastic network, screened charge and dipolar interactions

SP1 domain: elastic chain, screened charge and dipolar interactions

NC/SP2 domains: elastic network, charged CG sites, effective binding to RNA

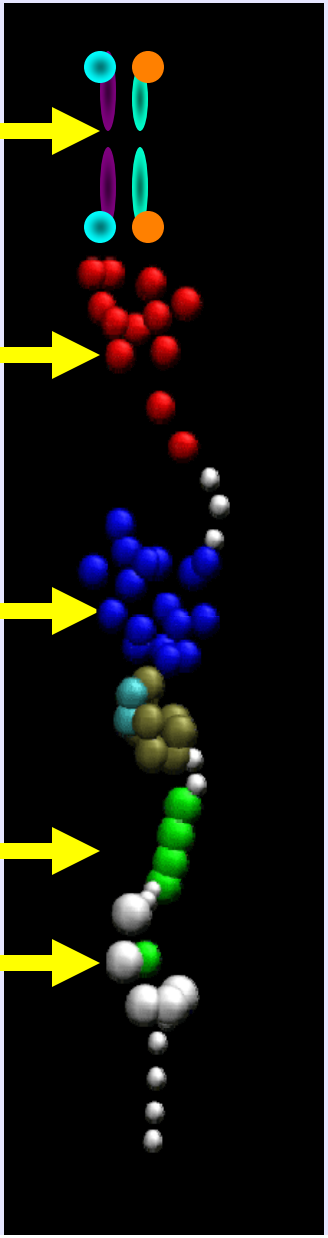
P6: elastic flexible chain

High resolution atomic structures



Coarse-grain the system

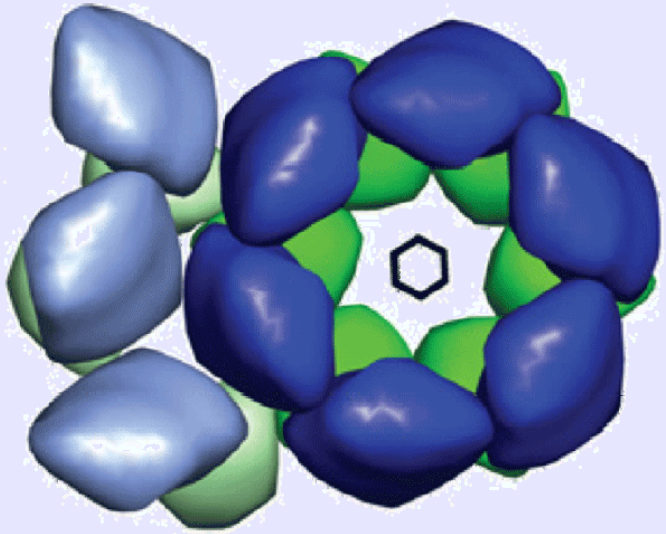
New CG representation



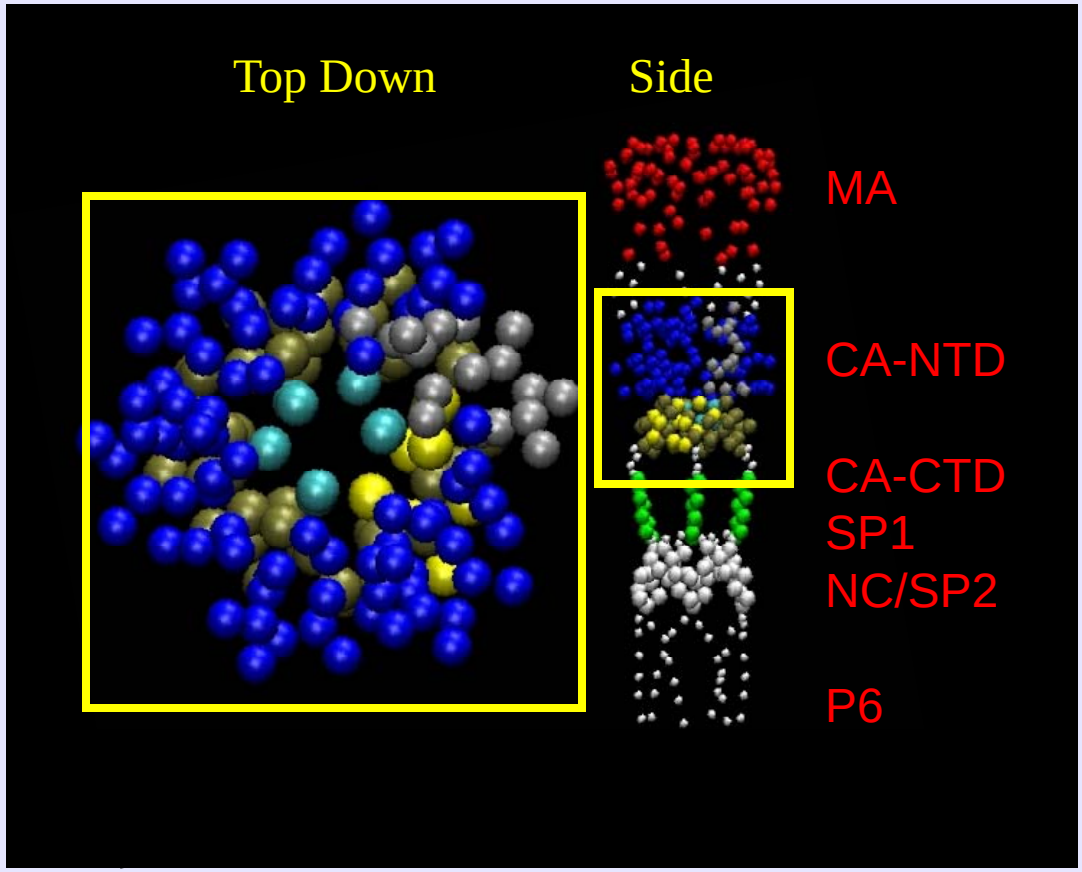
Starting Structure: The Gag "Bundle"

Proposed model of the CA domains

Briggs et al., PNAS, 106, 11090, 2009



Initial simulation Gag starting structure



This proposed model gives an experimentally inspired starting structure. However, the simulation is not bound to this, and can explore other structures

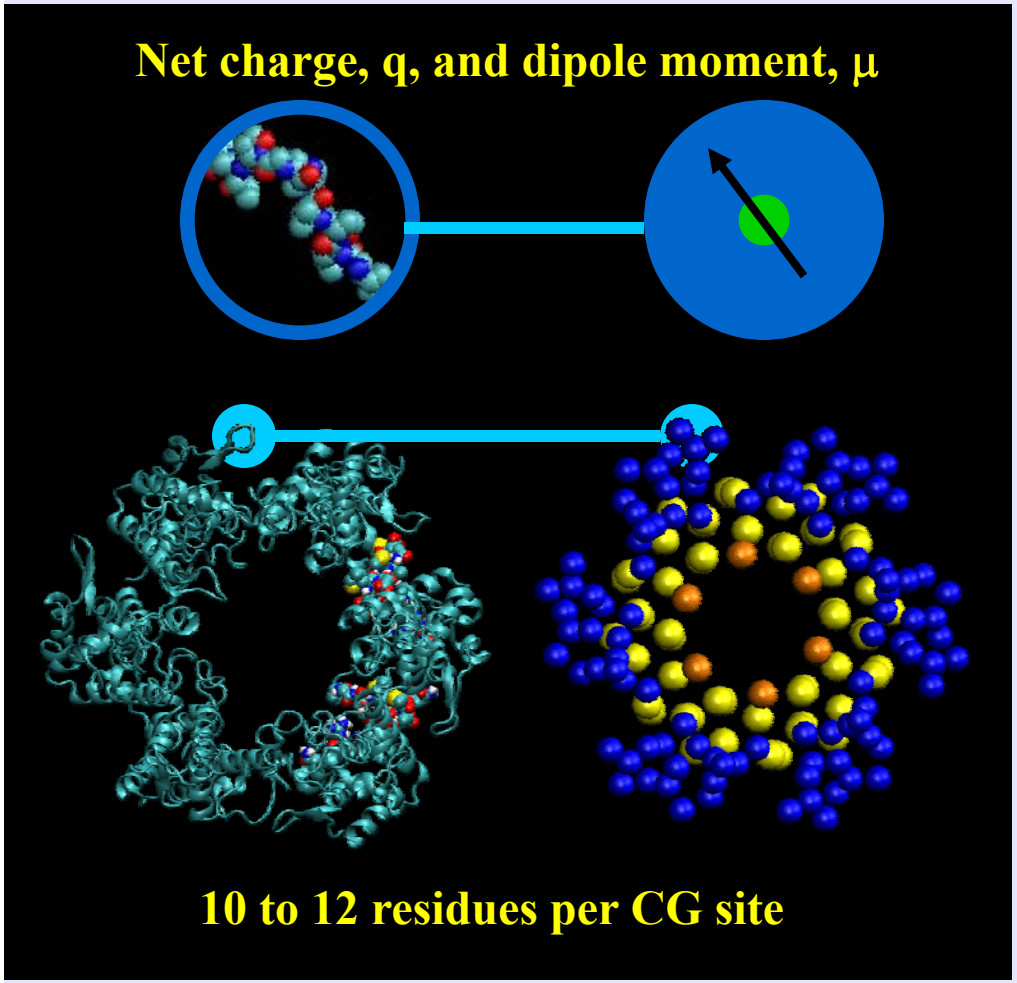
The Gags are NOT bound together!

They are free to fall apart, stay bound, anneal into something else

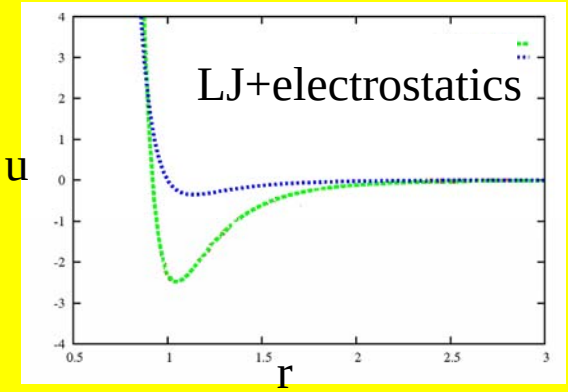
Modeling CG Interactions: Electrostatics and Excluded Volume

A single atomic structure is used for the initial CG parameterization

Initial Atomic Structure **CG model**



Initial CG potential



Well depth scanned between 1 and 5 kcal/mol

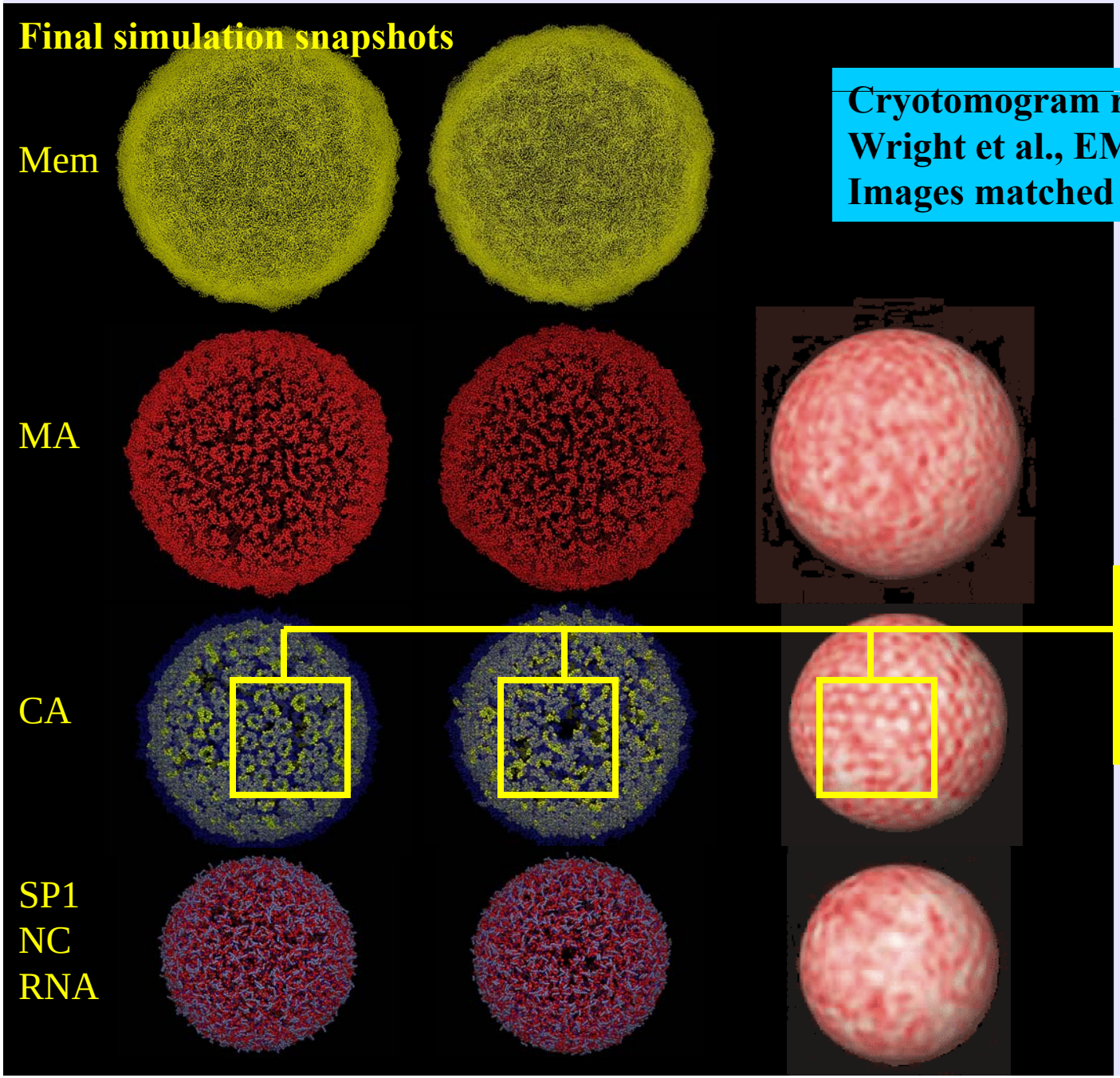
Screened electrostatics:

$$\Psi(\alpha_Y, r) = \exp[-\alpha_Y r]/r$$

$$u^{(4)}_{i_\alpha j_\beta} = \Big(q_{i_\alpha} q_{j_\beta} - q_{i_\alpha} \mu_{j_\beta} \mathbf{e}_{j_\beta} \bullet \nabla_{\mathbf{r}} + \mu_{i_\alpha} q_{j_\beta} \mathbf{e}_{i_\alpha} \bullet \nabla_{\mathbf{r}} - \mu_{j_\beta} \mu_{i_\alpha} \mathbf{e}_{i_\alpha} \bullet \nabla_{\mathbf{r}} \mathbf{e}_{j_\beta} \bullet \nabla_{\mathbf{r}}\Big) \Psi(\alpha_Y, r)$$

The CG simulation then directs the next round of CG model refinement

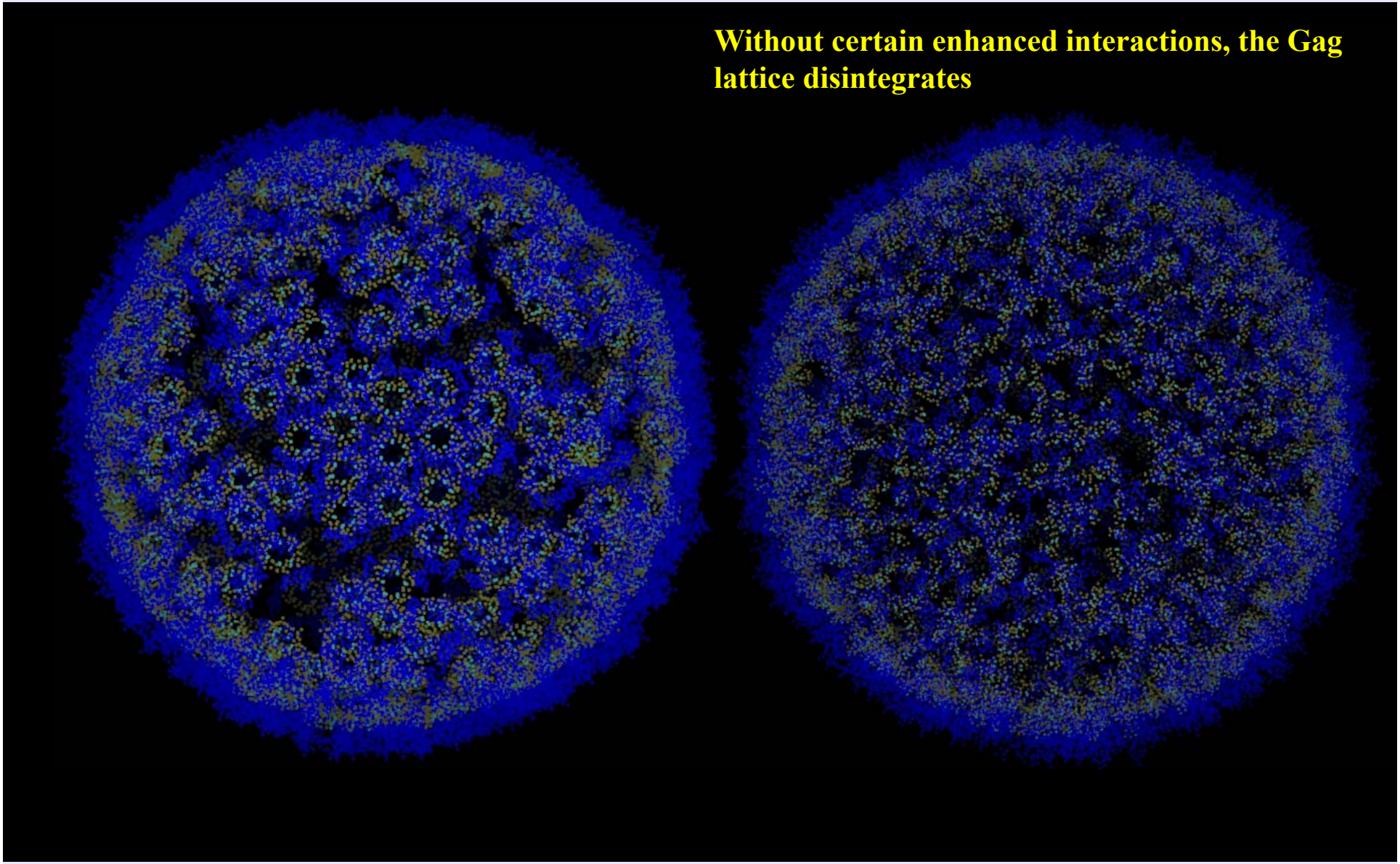
Interactions in the CA_{CTD} Domain Stabilize p6 Hexagonal Order



Cryotomogram reconstructions from Wright et al., EMBO, 26, 2218, 2007. Images matched to the same scale

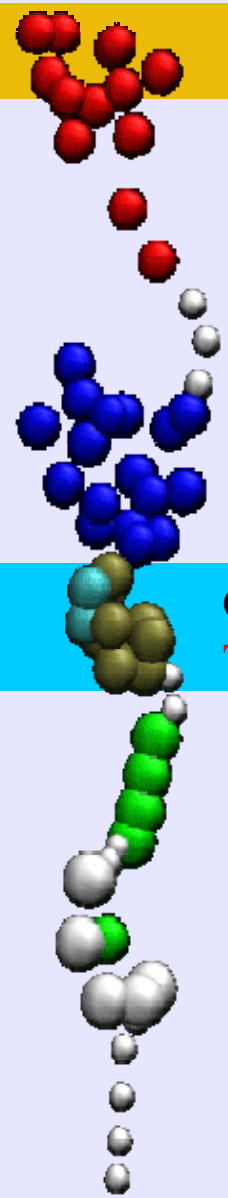
Only a few interactions in the entire Gag stabilize this hexagonal structure

Snapshots of the CA Domains in the Immature Virion



With CA-CTD interfacial interactions **Without**

No Other Interactions Stabilize p6 Hexagonal Order



MA domain binding to the membrane (2-5 kcal/mol + electrostatics)

Inter-domain interactions (0.25 - 1 kcal/mol + electrostatics)

No effect on p6 hexagonal order, but can affect aggregation

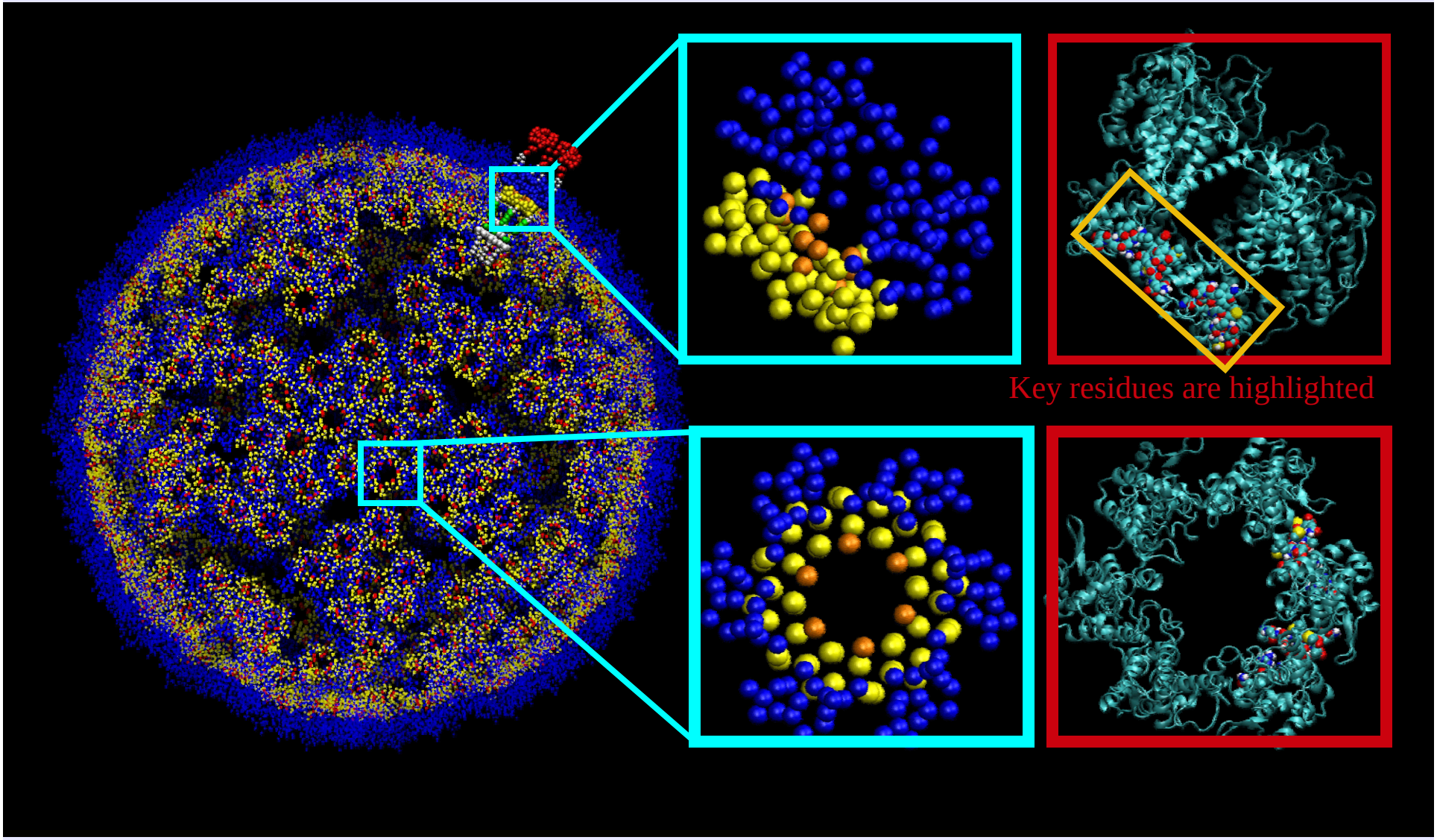
CA-CTD interfacial interactions (enhanced by 2-4 kcal/mol)
These are the only interactions that generate p6 hexagonal order

SP1, NC interactions, (0.25-1 kcal/mol + electrostatics)

Need to go back down to the molecular interactions that might be involved

CG Simulation Indicates Important Atomic Level Domains

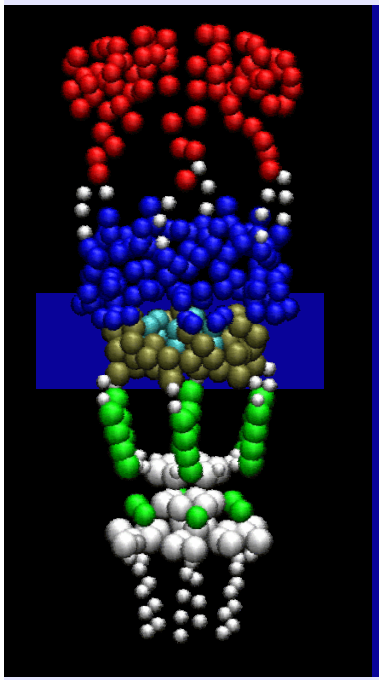
(only the CA domain shown)



Enhanced CG Interactions Stabilize p6 Hexagonal Order

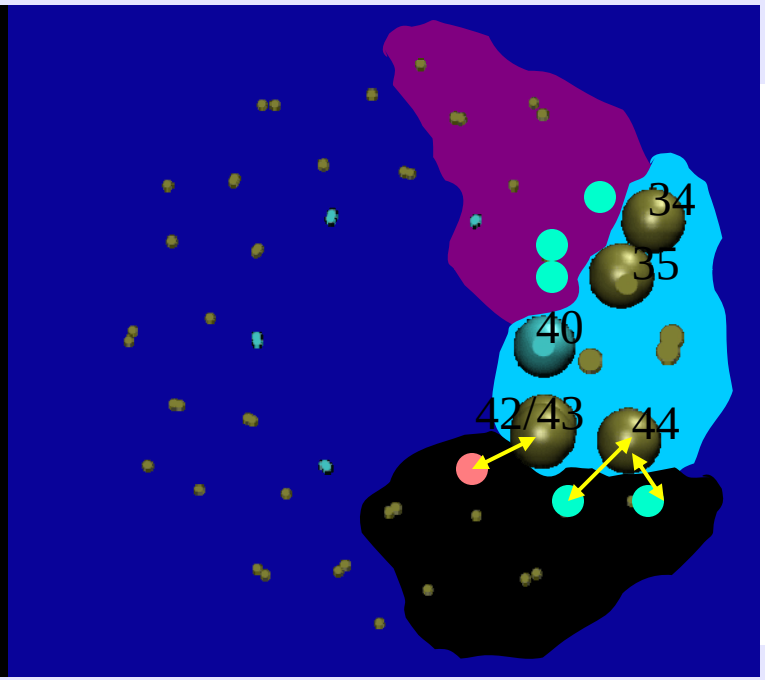
Specific CG sites in the CA_{CTD} domain require very strong attractive interactions

Side view

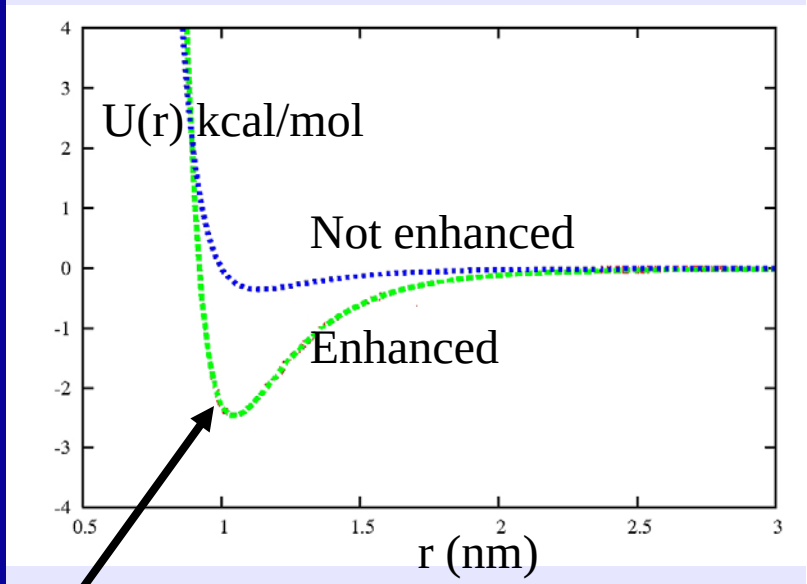


CA_{CTD} domain bundle highlighted

Top Down (CG sites shown)



Interaction potential between different CG sites



The enhanced interactions have a deeper attractive well

Yellow arrows indicate CG sites with enhanced interactions

Coarse-grain Interactions Identify Key Atomic-level Interactions

Enhanced Interaction List

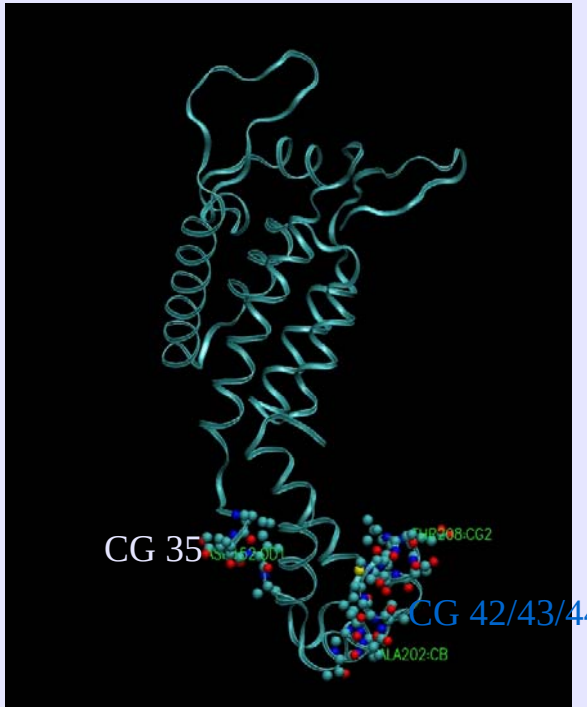
CG label	C_α Carbons	Residues in CG site
35	**150-154**	ILE150 LEU151 **ASP152** ILE153 **ARG154**
40	182-187	ALA182 ALA183 THR184 GLU185 THR186 LEU187
42	198-204	THR198 ILE199 LEU200 **LYS201** ALA202 LEU203 GLY204
43	205-208	PRO205 GLY206 ALA207 THR208
44	**209-217**	LEU209 GLU210 GLU211 MET212 MET213 THR214 ALA215 CYS216 GLN217

The "bottom-up" approach allows us to re-trace our steps

Experimental:

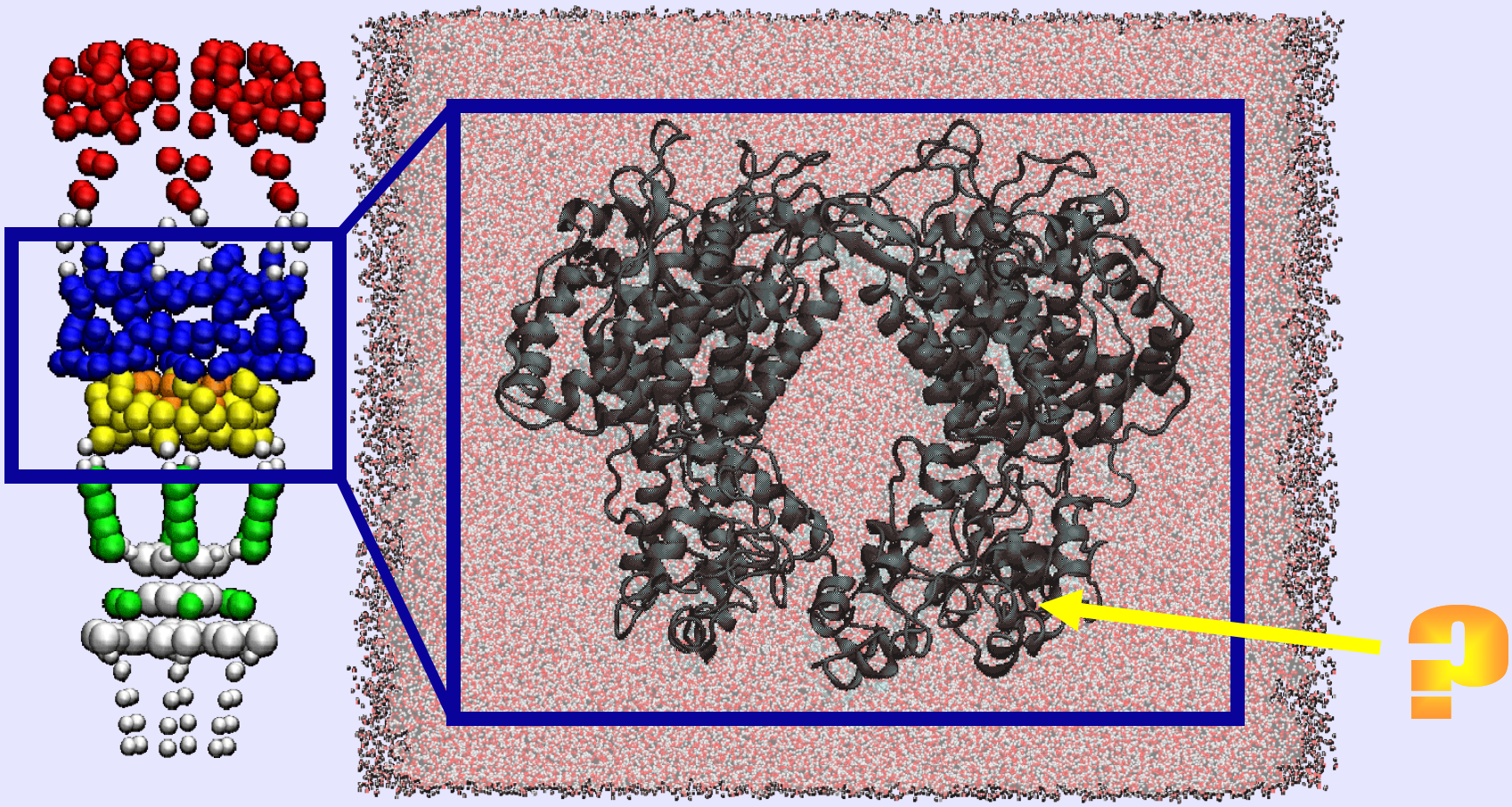
EM: Residues **153-159** most likely interact with **212-219** (Briggs, Riches, Glass, Bartonova,Zanetti, Kräusslich, PNAS, **106**, 2009)

Residue mutations K**158**A, K158D, K158Q, and D**197**A, D197N inhibited mature particle production (von Schwedler, Stray, Garrus, Sundquist, J. Virol., **77**, 2003)



All Atom Simulation of the CA Domains in the Hexamer

The previous CG virion simulations have pin-pointed a candidate for all atom MD. Atomic-level simulations must now validate the CG interactions

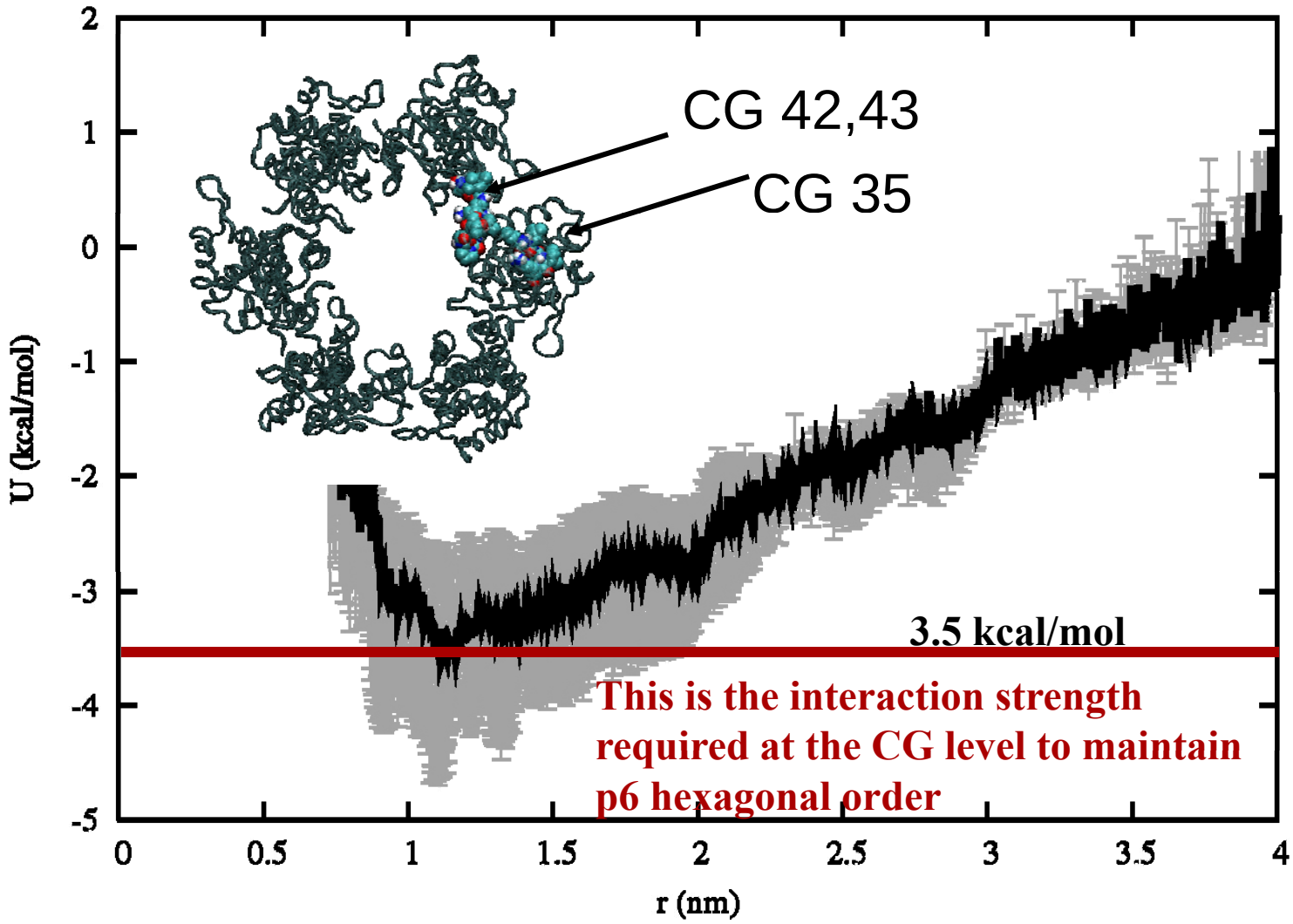


CG CA hexamer
390 CG sites

Atomic level fully solvated CA hexamer
GROMOS/SPC force field
176,330 atoms in total

Estimate the Contact Binding Strength From MD

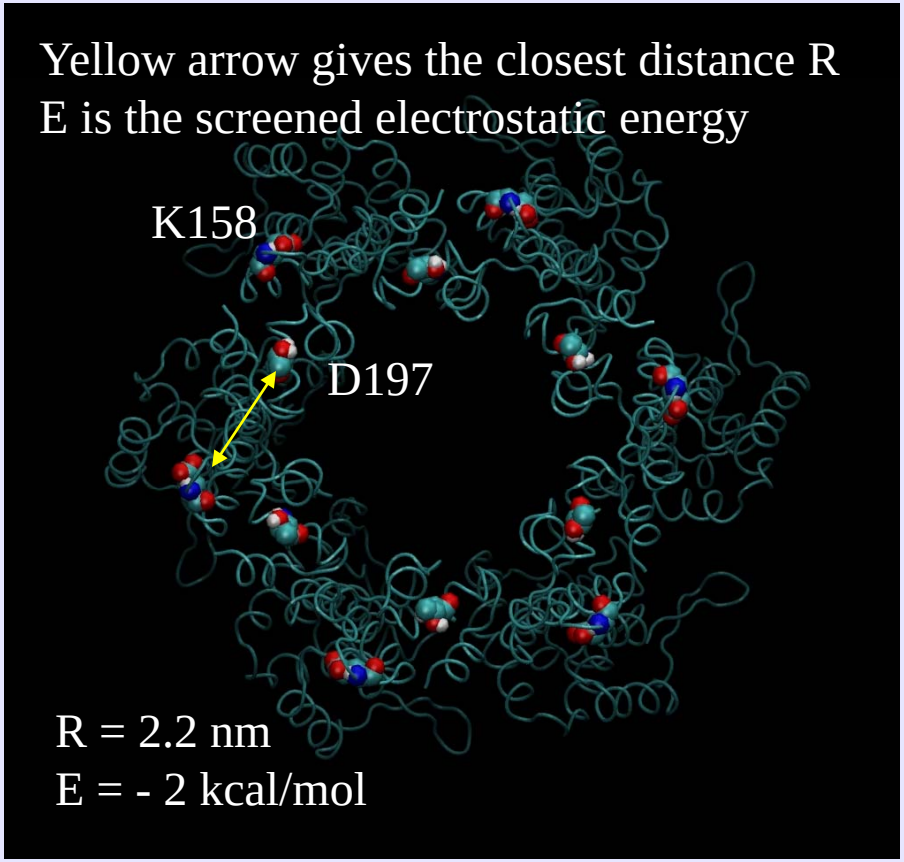
MD simulations indicate an enhanced interaction strength in the CA_{CTD} subunits! These residues appear to be holding the entire assembly together



Some Possible Mutations

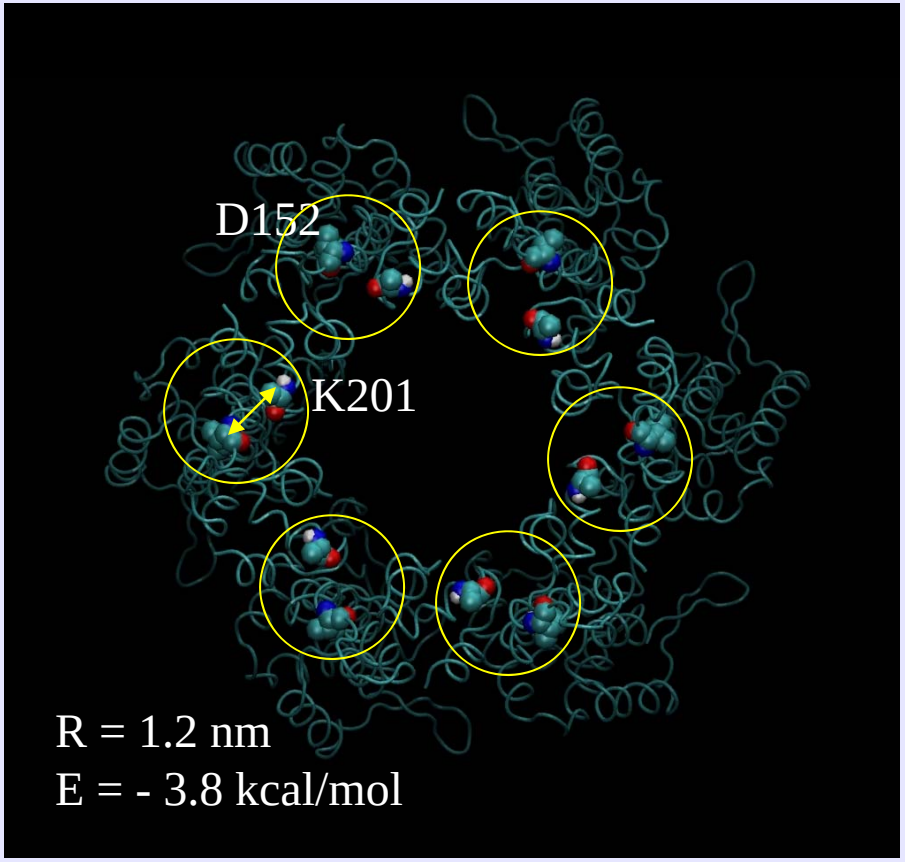
Looking from the CA_{CTD} domain up to the CA_{NTD} domain. Physiological pH is assumed

K**158**A (+ to n), D**197**A (- to n)



von Schwedler, Stray, Garrus, Sundquist, J. Virol., 77, 5439, 2003 (favorable electrostatics not obvious in WT)

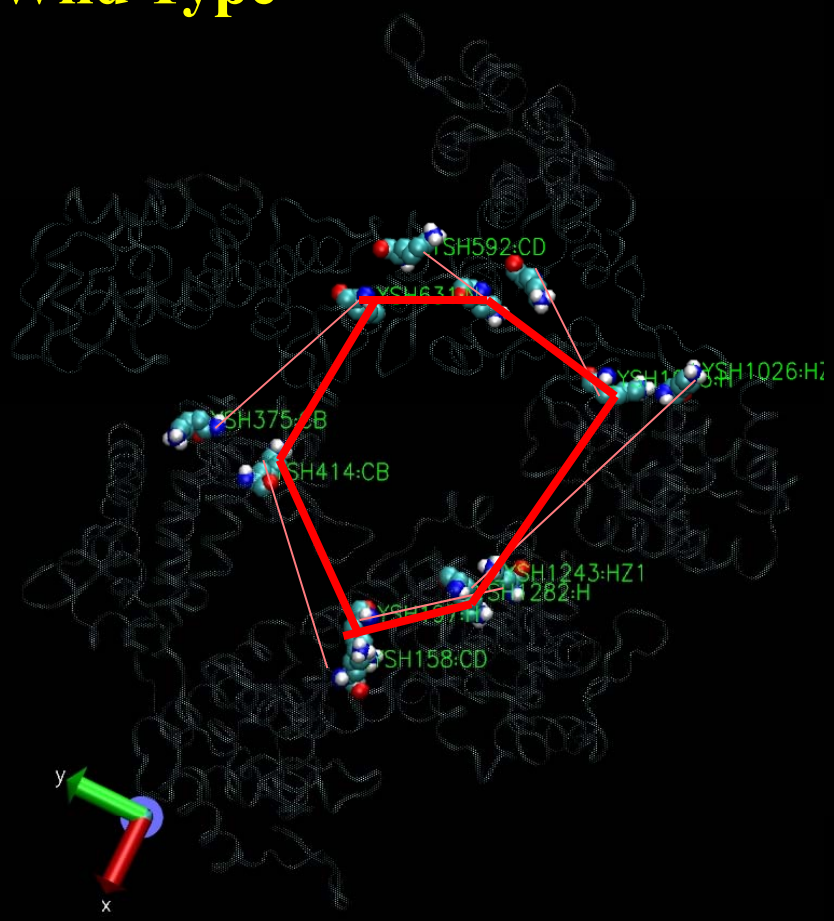
D**152**A (- to n), K**201**A (+ to n)



Briggs et al., PNAS, 2009 (possible favorable electrostatics in the WT)

Some Mutations Cause Collapse of Hexameric Structure

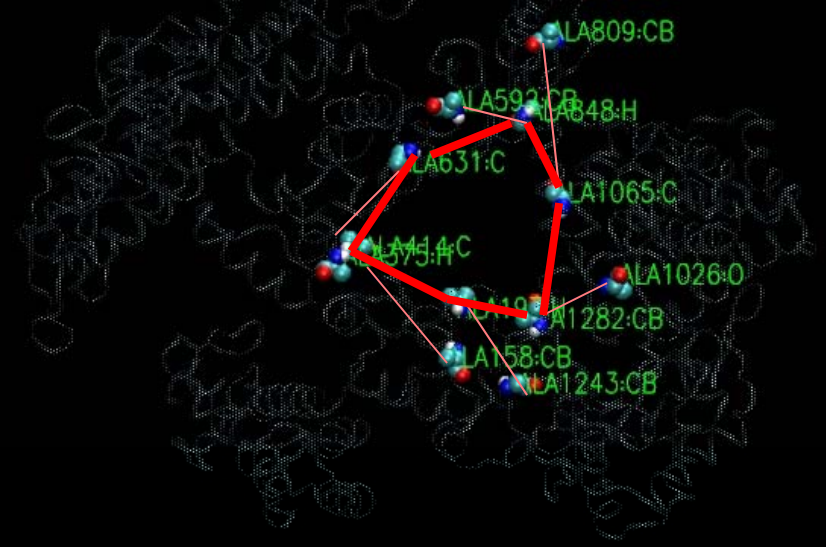
Wild Type



9.5 nm

K158A-D197A (von Schwedler, Stray, Garrus, Sundquist, J. Virol., 77, 5439, 2003)

Hexamer structure over-stabilized: Consistent with the experimental observations of an altered virion?

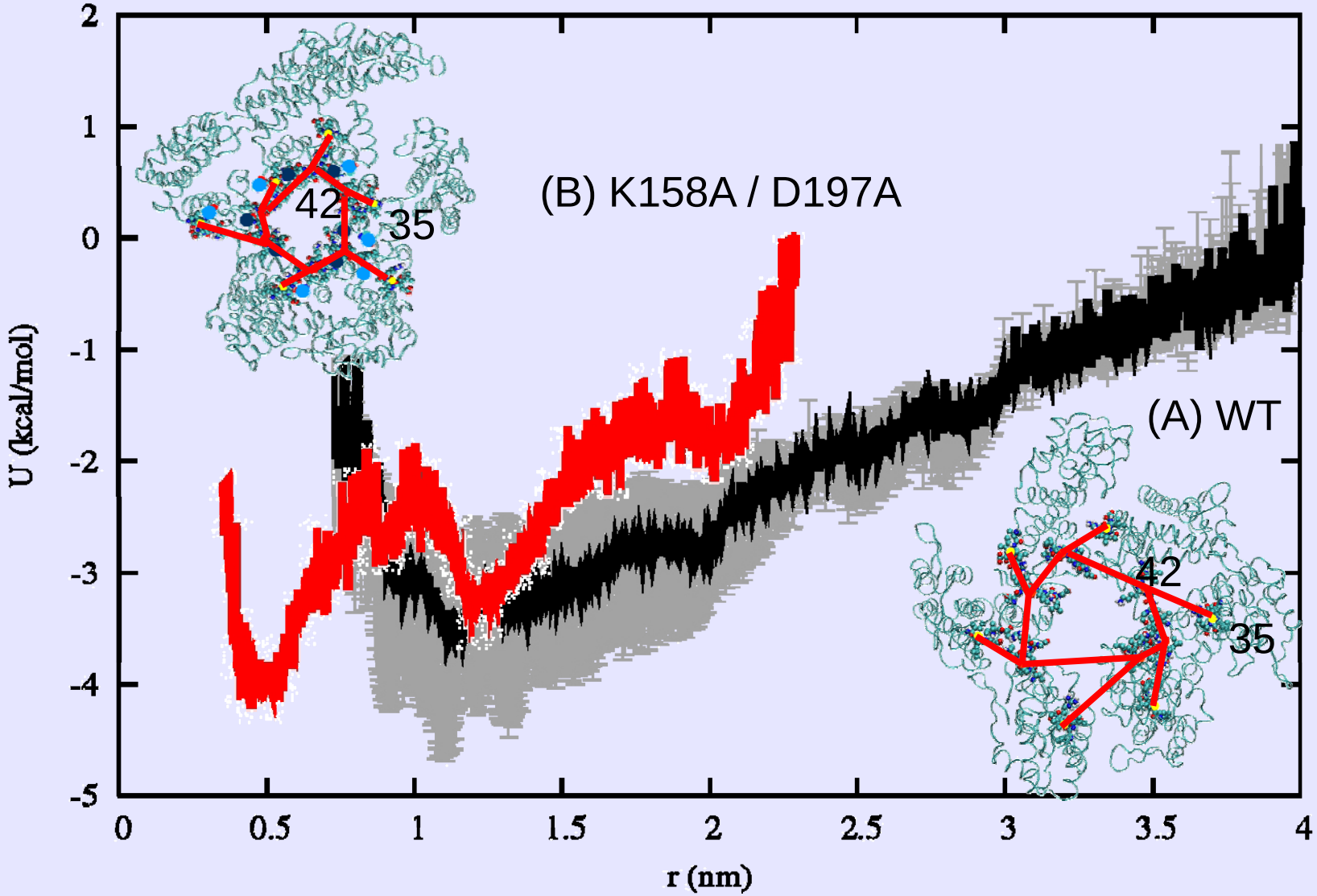


9.5 nm

Grey lines designate pairs of residues on adjacent domains

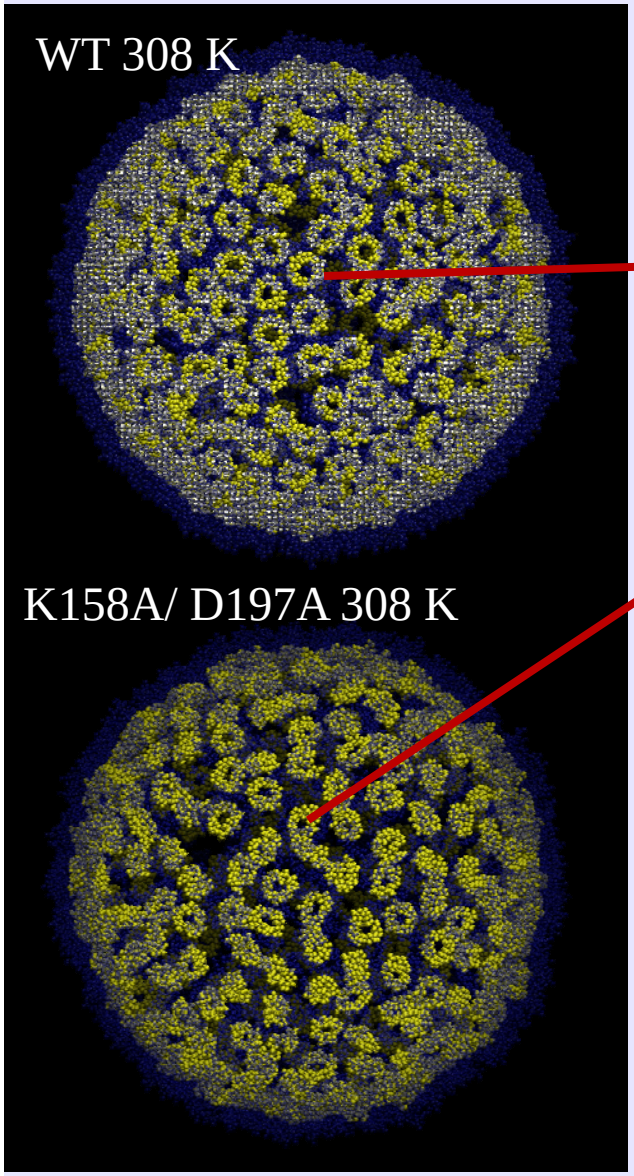
Red lines connect like residues

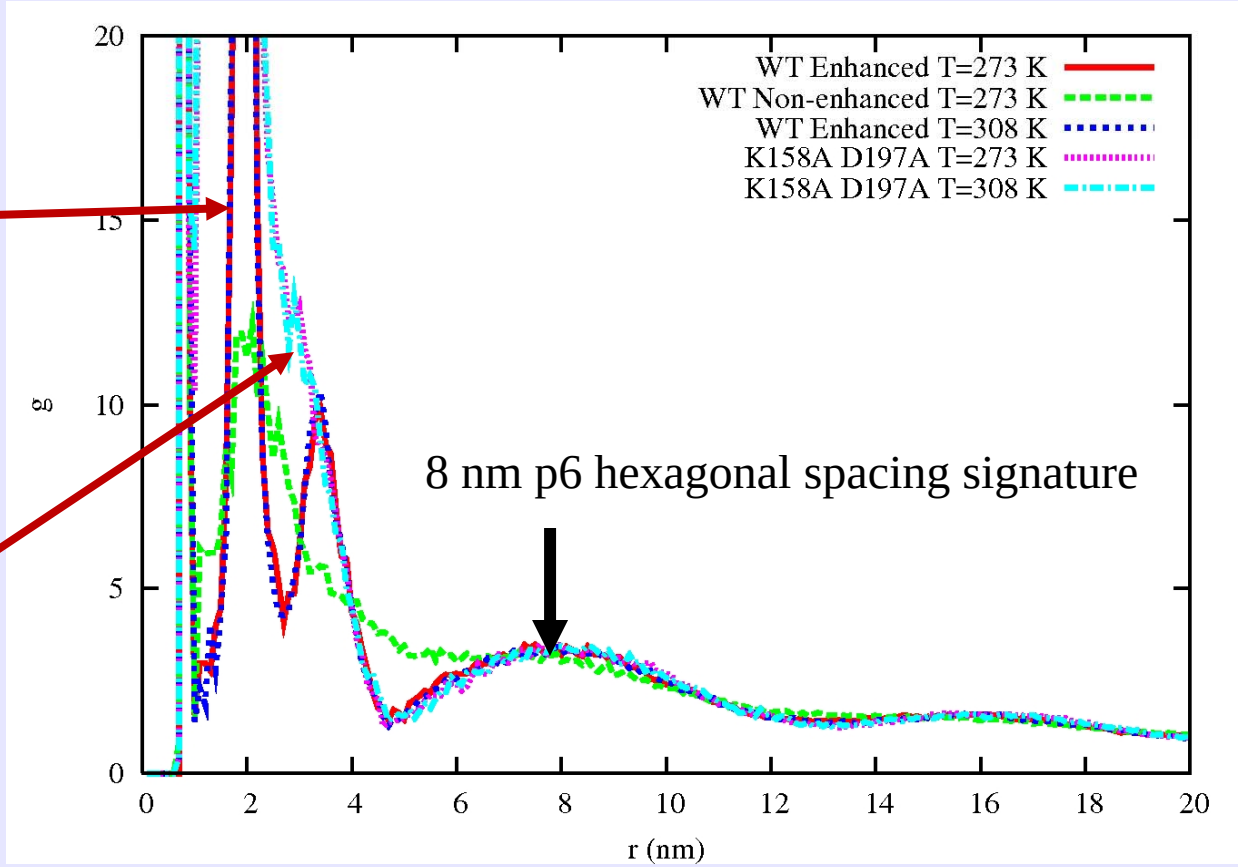
The Mutant PMF is Altered Compared to the WT



Red curve is the mutant PMF: The collapse is evident

Local Structure and Correlations are Quite Different in the WT and Mutants





Peaks at less than 4 nm indicate well-defined local p6 hexagonal order. WT shows distinct peaks; mutant is much more disordered

Some Concluding Remarks

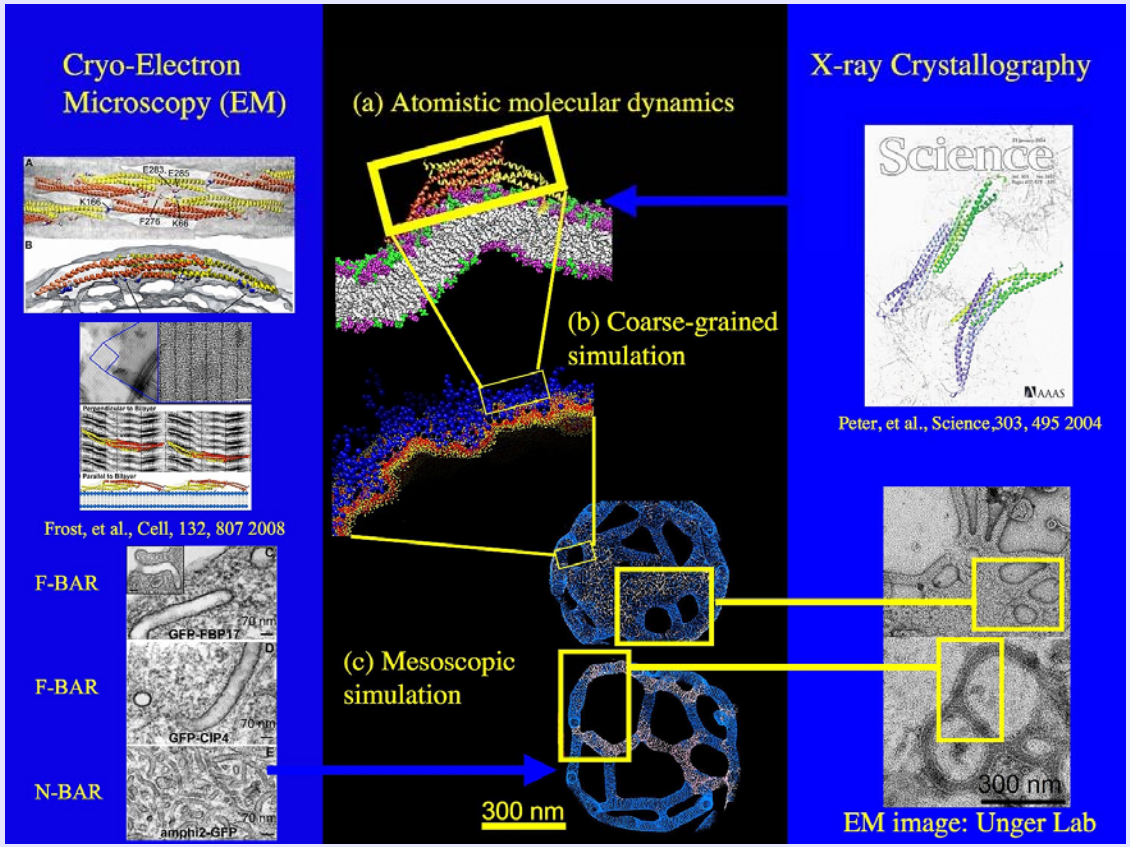
- **We approach coarse-graining of biomolecular systems and soft matter as a fundamental challenge in statistical mechanics (rather than an exercise in computer modeling).**

- **We have shown that CG models can be developed in a thermodynamically consistent fashion and thereby systematically created and refined.**

- **For large proteins it becomes an additional challenge to define the optimal CG sites, as well as their effective interactions.**

- **Bridging to the cellular scale is a future critical priority. This is clearly a good target for extreme scale computing.**

Acknowledgements



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- Jian Zhou (SCUT)

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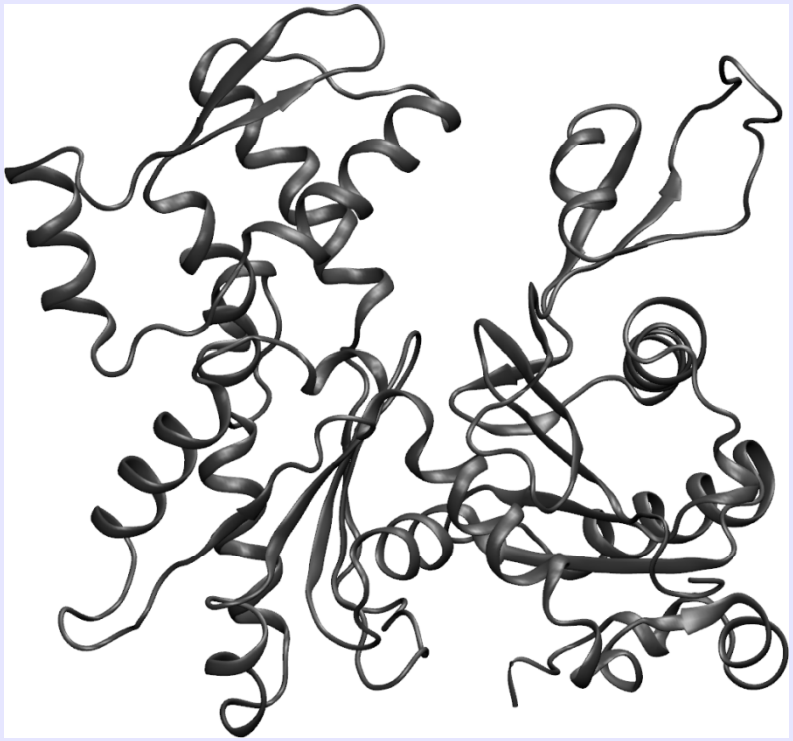
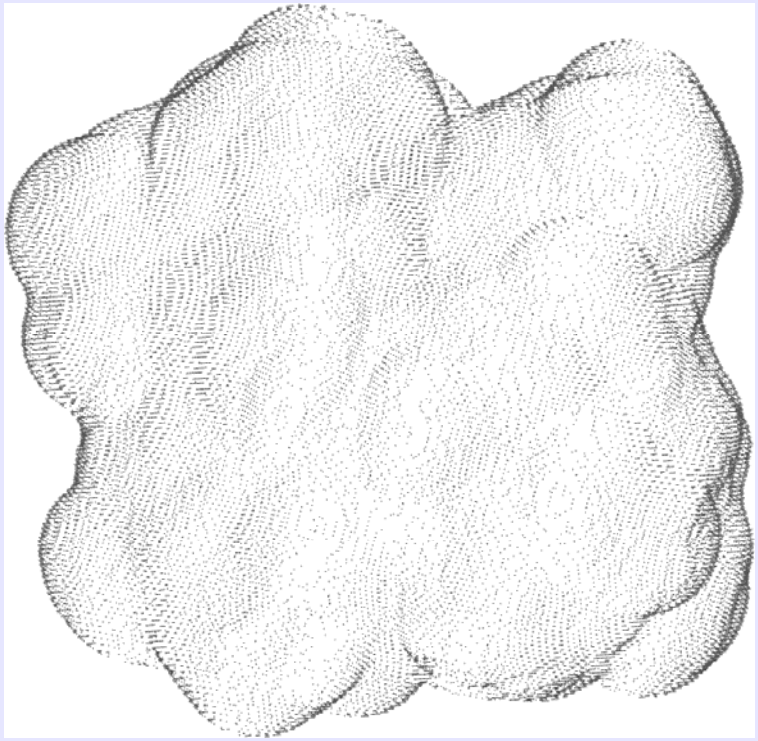
ENM-ED-CG on Low-resolution Density Map



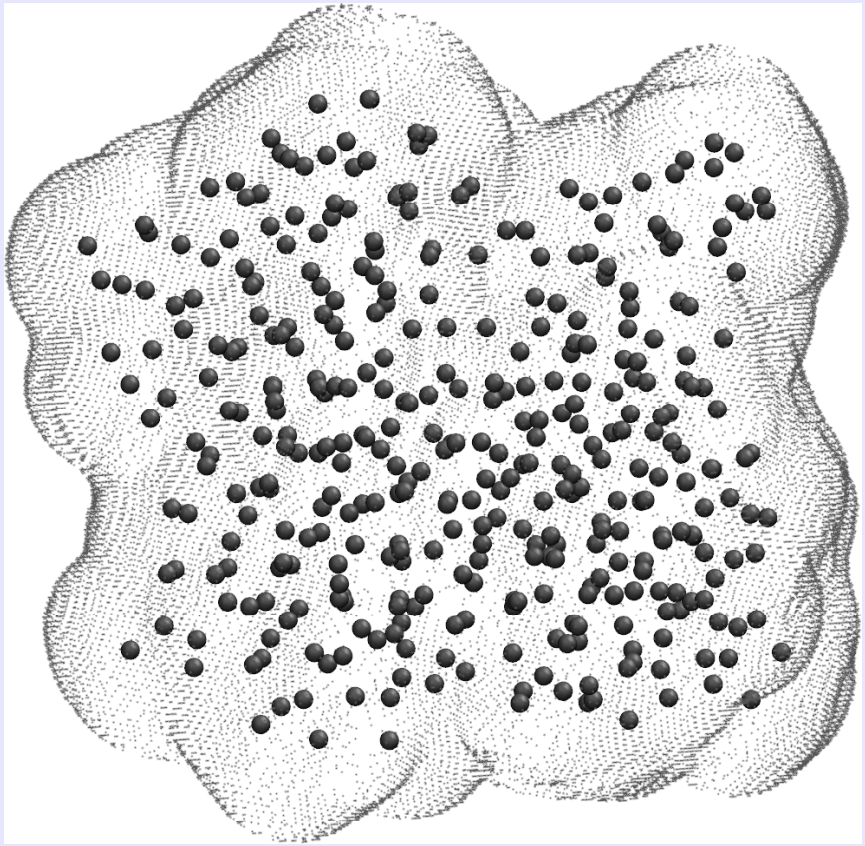


Atomistic structure of G-actin

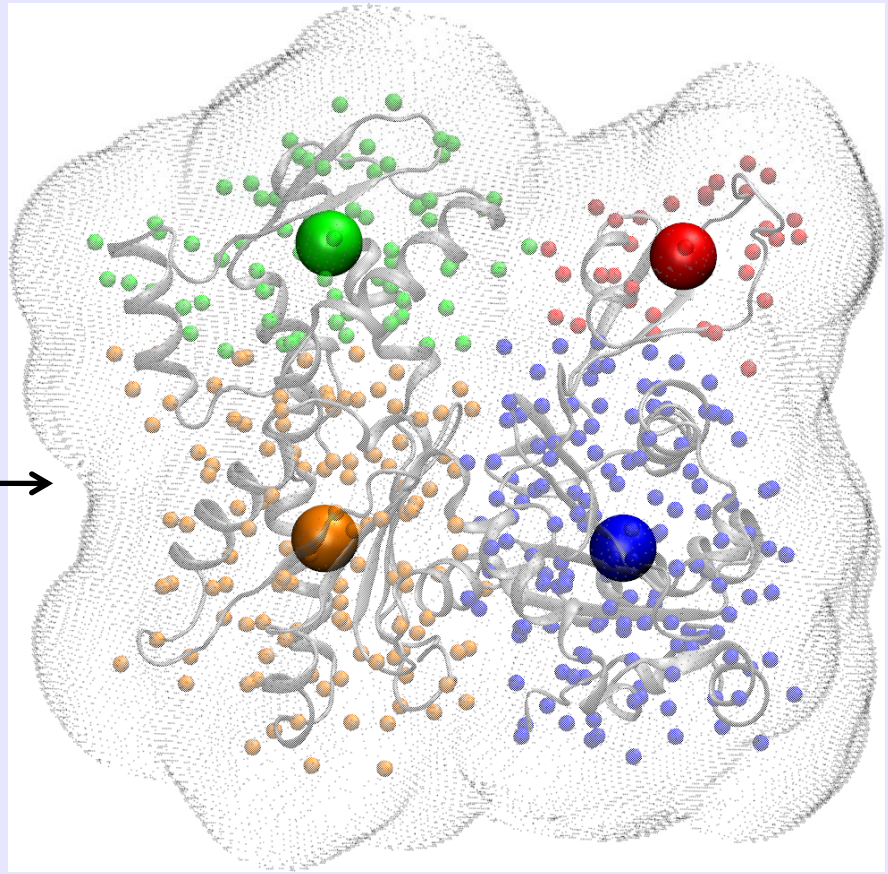
A density map with 10 Angstrom resolution
Generated by Situs (http://situs.biomachina.org)

Can we identify ED-CG models from low-resolution structures without atomistic details and sequence information?

A Space-based ENM-ED-CG Method



375 CG sites were defined from the density map, by a shape-base CG tool in VMD.

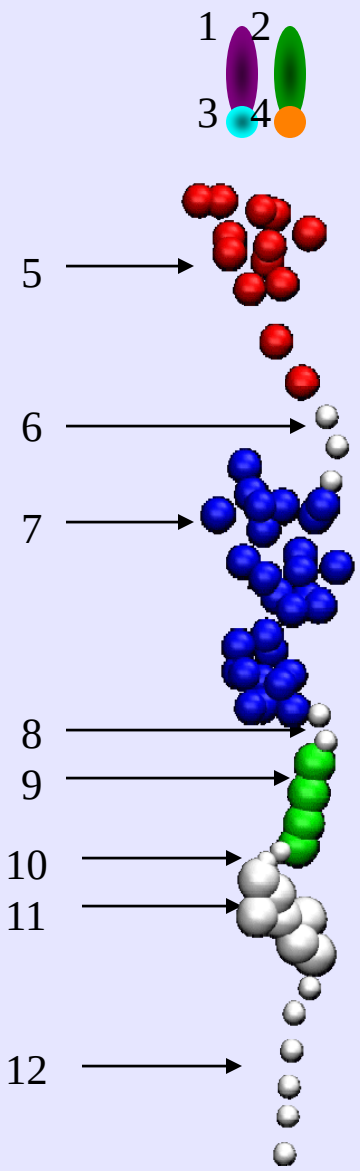


An ENM was build by the 375 CG sites, then a space-based ENM-ED-CG method was used to define a four-site CG model.

The four-site model from the low-resolution density map is similar to the intuitive four-site model from the atomic structure of G-actin.

Expressed Mathematically

12 CG types



$$U = \frac{1}{2}\underbrace{\sum_{\alpha}^{12}\sum_{\beta}^{12}}_{\text{Summation over CG types}}\underbrace{\sum_{i_\alpha}^{N_\alpha}\sum_{j_\beta *}^{N_\beta}}_{\text{Summation over each CG site of a different type. The * excludes self terms.}} u_{i_\alpha j_\beta}^{\alpha\beta}$$

$$U = \frac{1}{2}\sum_{\alpha=1}^{2}\sum_{\beta=1}^{2}\sum_{i_\alpha}^{N_\alpha}\sum_{j_\beta *}^{N_\beta} u_{i_\alpha j_\beta}^{\alpha\beta} + \frac{1}{2}\sum_{\alpha=5}^{12}\sum_{\beta=5}^{12}\sum_{i_\alpha}^{N_\alpha}\sum_{j_\beta *}^{N_\beta} u_{i_\alpha j_\beta}^{\alpha\beta} + \frac{1}{2}\sum_{\alpha'}^{12}\sum_{\beta'}^{12}\sum_{i_{\alpha'}}^{N_\alpha}\sum_{j_{\beta'} *}^{N_\beta} u_{i_\alpha j_\beta}^{\alpha\beta}$$

$$= U_{mem} + U_{Gag} + U_{cross}$$

The prime includes only those terms not in the first two summations

Important Functional Forms

U_{mem}

$$u_{ij}^{\alpha\beta} = u_{ij}^{GB}\left(\mathbf{r}_{ij}, \mathbf{e}_i, \mathbf{e}_j\right) + \Delta u\left(r_{ij}\right)$$

Lipid-lipid interaction employs the HAS approach: a pair-wise interaction that employs an analytic component, and a systematic part. **The systematic part employs atomic MD simulation data.**

The present model does a 50/50 mixture of DOPS and DOPE. Other mixtures and compositions are possible.

U_{Gag}

$$u_{ij}^{\alpha\beta} = \begin{cases} k\left(r_{ij} - r_0\right)^2 & \alpha = \beta, \beta+1, \beta+2 \\ 4\varepsilon\left(\left(\frac{\sigma}{r_{ij}}\right)^{10} - \left(\frac{\sigma}{r_{ij}}\right)^{6}\right) + \frac{q_i q_j e^{-a r_{ij}}}{r_{ij}} & \text{otherwise} \end{cases}$$

The Gag interaction employs an elastic network for each domain, and then a soft repulsion/attraction term ALONG with **a Yukawa interaction for charged CG sites**.

$k = 100,\ 500,\ 1000\ \text{amu ps}^{-2}$

U_{cross}

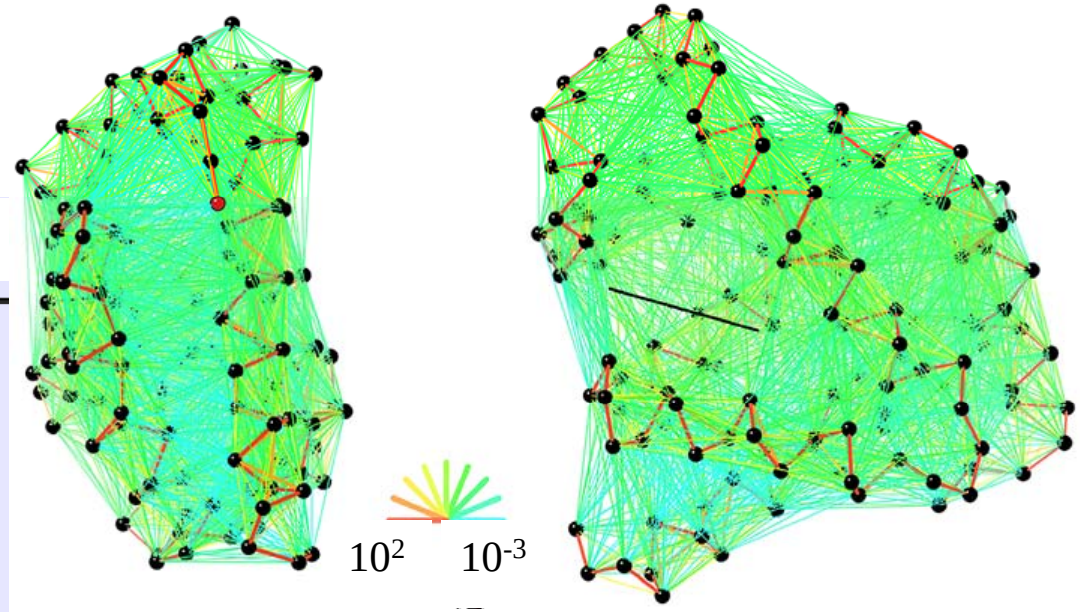
$$u_{ij}^{\alpha\beta} = \begin{cases} u_{ij}^{GB}\left(\mathbf{r}_{ij}, \mathbf{e}_i, \mathbf{e}_j\right) & \alpha, \beta \neq 3, 4 \\ 4\varepsilon\left(\left(\frac{\sigma}{r_{ij}}\right)^{10} - \left(\frac{\sigma}{r_{ij}}\right)^{6}\right) + \frac{q_i q_j e^{-a r_{ij}}}{r_{ij}} & \text{otherwise} \end{cases}$$

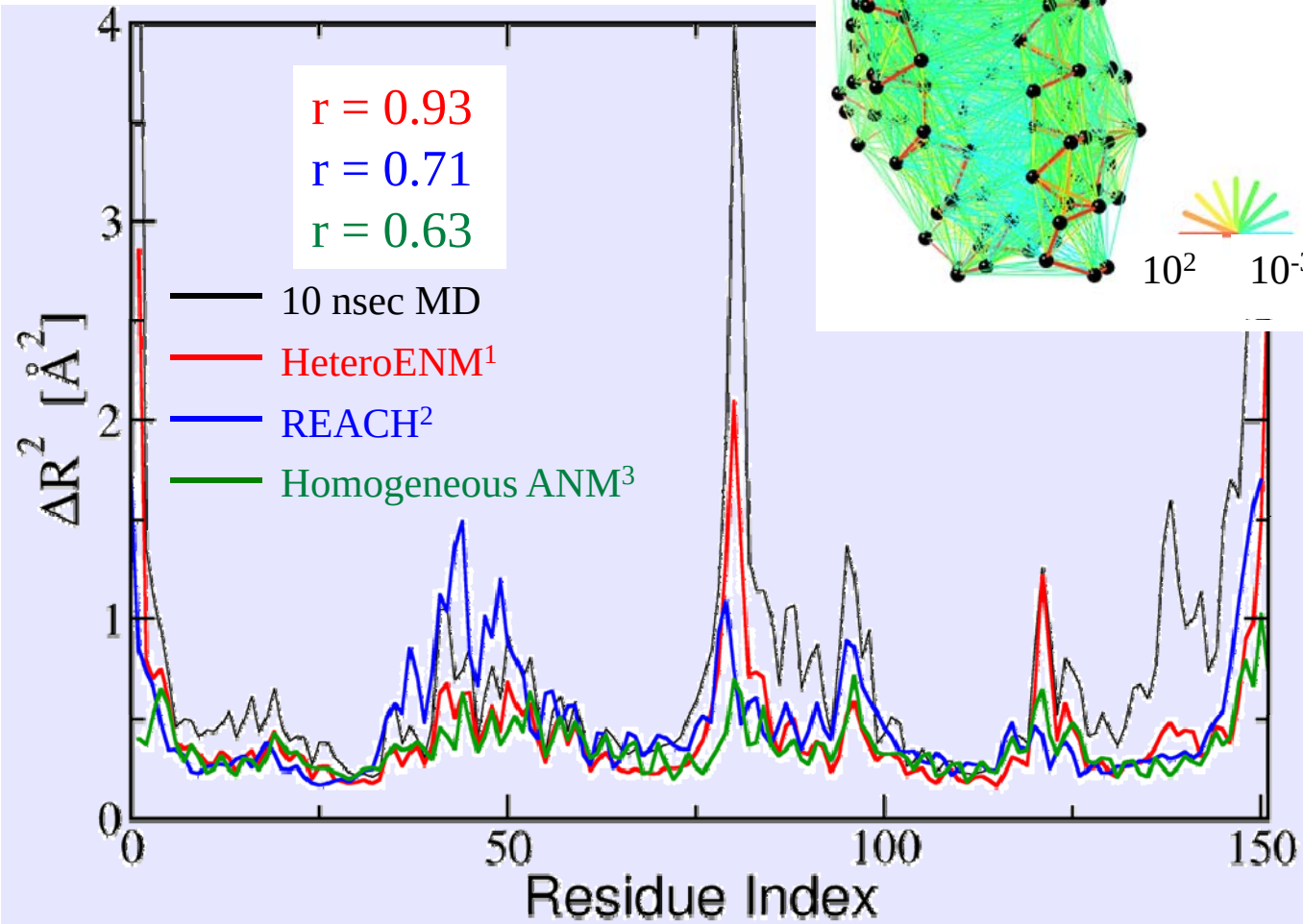
Membrane-Gag interactions employ both a lipid-Gag interaction (GB), and a head-group Gag interaction which also employs a Yukawa interaction for charges CG species.

$\varepsilon = 2K\ 10\ k_B T$

A number of values for $\sum$ and k were tested: The results hold across a fairly broad range

HeteroENM: Systematic Parameterization of Elastic ED-CG Models





Target:

$$\sigma^2_{sim}(r_i) = \overline{\left(r_i - \bar{r}_i\right)^2}$$

$$\sigma^2_{ENM}(r_i) = \left\langle \left(r_i - \langle r_i \rangle\right)^2 \right\rangle$$

Iterate

$$\frac{1}{4k_i^{n+1}} = \frac{1}{4k_i^{n}} - \alpha\left(\sigma^2_{ENM}(r_i) - \sigma^2_{SIM}(r_i)\right)$$

[1]Lyman et. al., *Biophys. J.* **95**:4183(2008)

[2]Moritsugu and Smith *Biophys. J.* **93**:3460(2007)

[3]Atilgan, et. al. *Biophys. J.* **80**:505(2001)

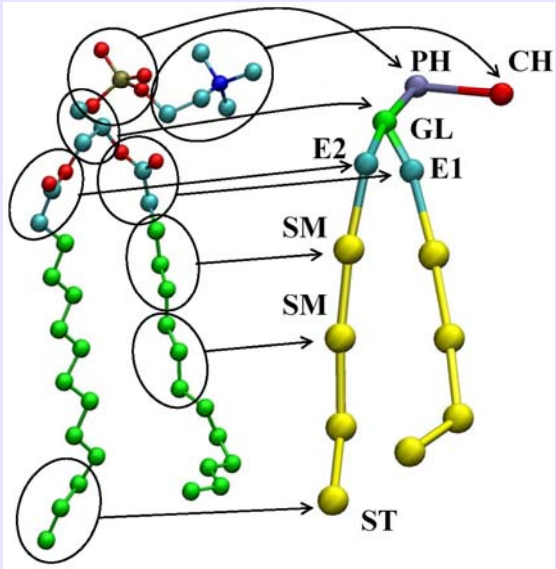
First Big Problem: Multiscale Coarse-Graining as a Means to "Eliminate" the Solvent from the Problem

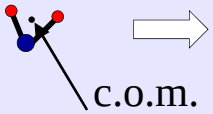
$$\exp(-\beta F) \propto \int d\mathbf{r} \exp[-\beta V(\mathbf{r})] \qquad (\beta = 1/k_B T)$$

$$\int d\mathbf{r} \exp[-\beta V(\mathbf{r})] \equiv \int d\mathbf{R}_{CG} \exp[-\beta V_{CG}(\mathbf{R}_{CG})] \qquad \left(N_{\mathbf{R}_{CG}} << N_{\mathbf{r}}\right)$$

The set of coordinates $\mathbf{R}_{CG}$ can be chosen to <u>eliminate</u> the solvent.

The resulting renormalized effective potential $V_{CG}(\mathbf{R}_{CG})$ will have the effects of the environment <u>folded</u> <u>into</u> <u>it</u>.

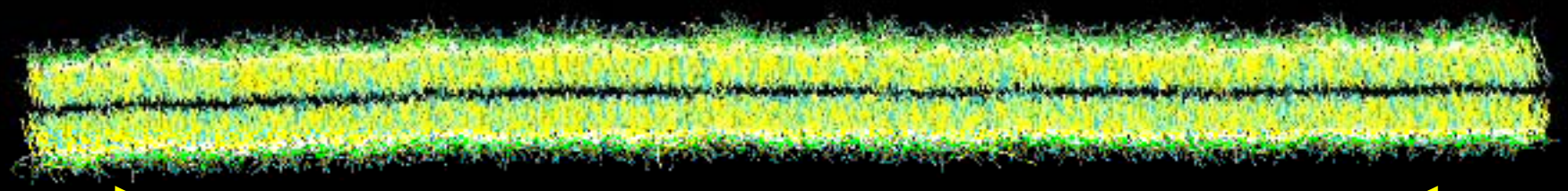




Gone!

The Solvent Can Be Completely Removed
Example: Solvent Free MS-CG Bilayer

400 Angstroms , 6400 DMPC & Chol Mol, Solvent-Free Model



NPxPyT

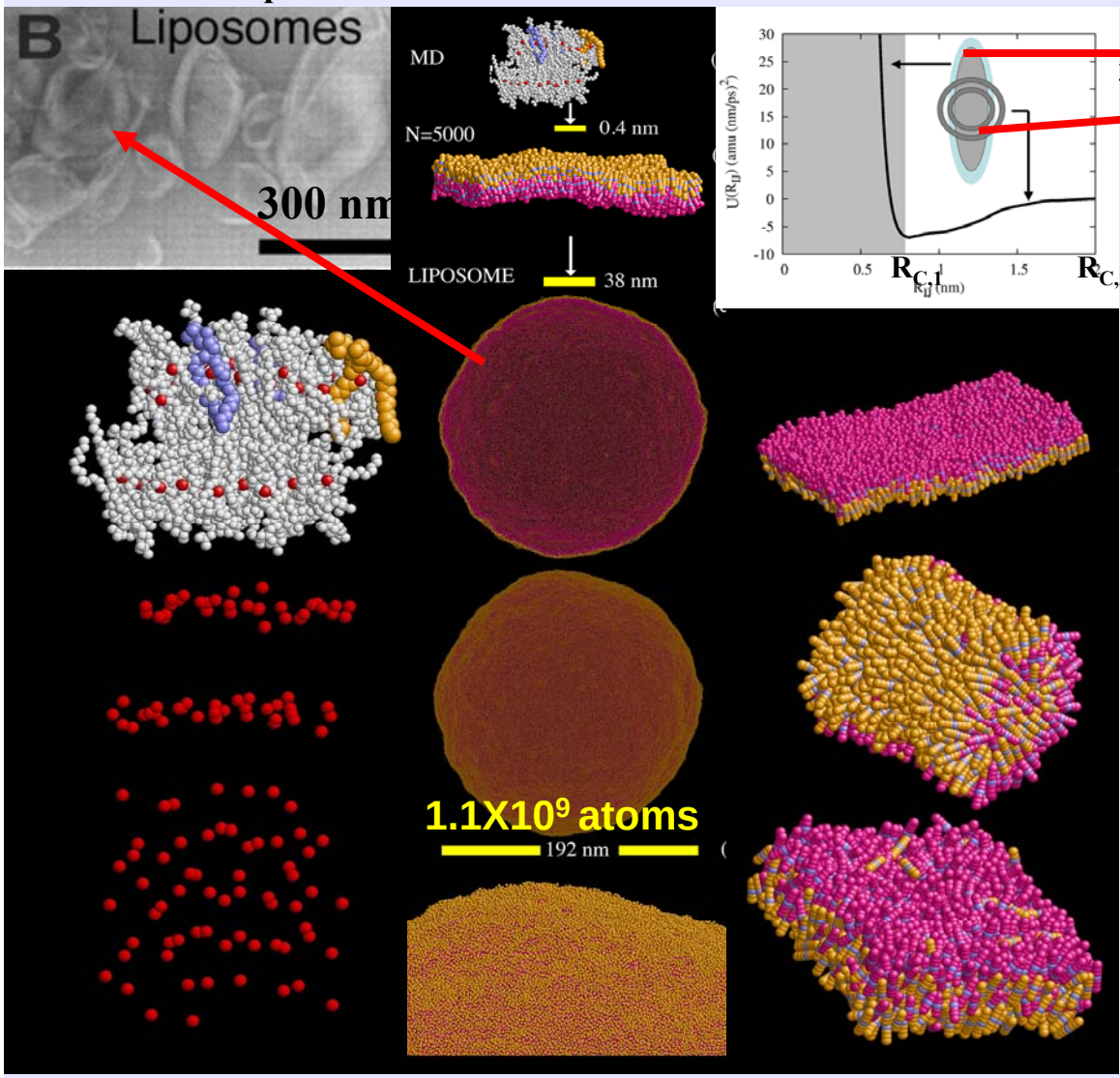
NPxPyT

~ 10 ns, effectively ~ 10^7 atoms

	Bulk Modulus	Area Compressibility	Bending Modulus
Atomistic MD	3.5×10^8 Pa	2.6 J/m^2	2.6×10^{-19} J
CG (Explicit Solvent)	2.1×10^8 Pa	2.3 J/m^2	2.5×10^{-19} J
CG (Solvent Free)	-''-	5.5 J/m^2	3.0×10^{-19} J
Experiment	3.0×10^8 Pa (1:1)	6.0 J/m^2 (3:2)	5.0×10^{-19} J (1:1) 3.8×10^{-19} J (3:1)

The Need for Efficient but Semi-Systematic Membrane Models: The Hybrid Analytic-Systematic (HAS) Approach*

Biologically relevant length-scales:
Half a million lipids



ΔU is found from MS-CG

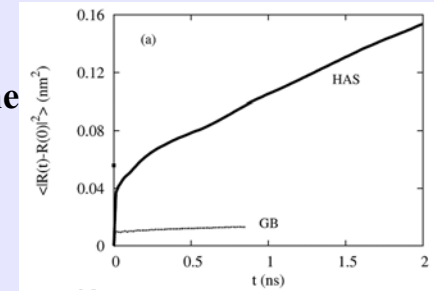
$$U_{IJ}(\mathbf{R}_I,\mathbf{R}_J,\mathbf{e}_I,\mathbf{e}_J) = \begin{cases} U_{IJ}^{GB}(\mathbf{R}_I,\mathbf{R}_J,\mathbf{e}_I,\mathbf{e}_J) & R_{IJ} < R_{C,1} \\ U_{IJ}^{GB}(\mathbf{R}_I,\mathbf{R}_J,\mathbf{e}_I,\mathbf{e}_J) + \Delta U(R_{IJ}) & R_{C,1} \le R_{IJ} \le R_{C,2} \\ 0 & R_{IJ} > R_{C,2} \end{cases}$$

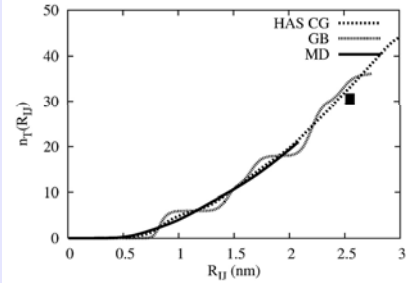
The HAS Approach:
Use force-matching (MS-CG) for well sampled MD configurations and an analytic component otherwise.
Also eliminate solvent completely.

The HAS interaction melts the otherwise solid membrane

Area per lipid is correct

Bending modulus and area compressibility is good for this lipid

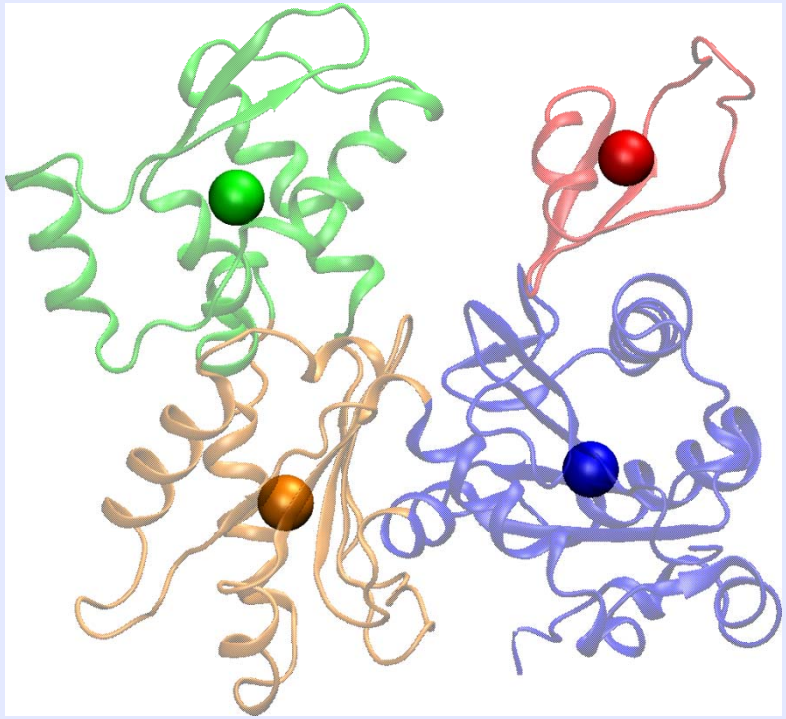


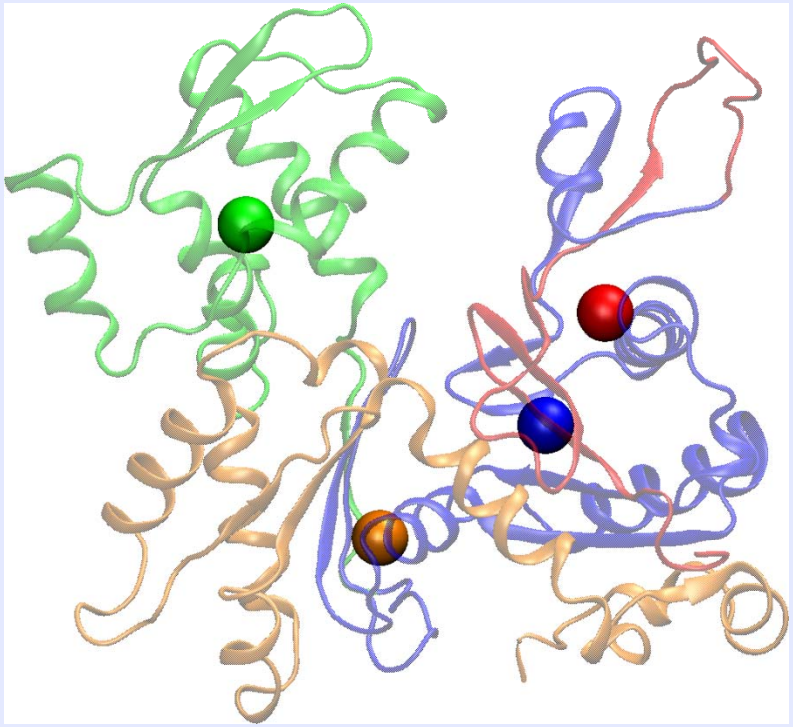


*G. S. Ayton and G. A. Voth, J. Phys. Chem. B 113, 4413 (2009).

CG Sites for ATP-bound G-actin

- four-site models





"Intuitive" four-site model: residual 7128

D1 (1-32, 70-144, and 338-375): blue

D2 (33-69): red

D3 (145-180, and 270-337): orange

D4 (181-269): green

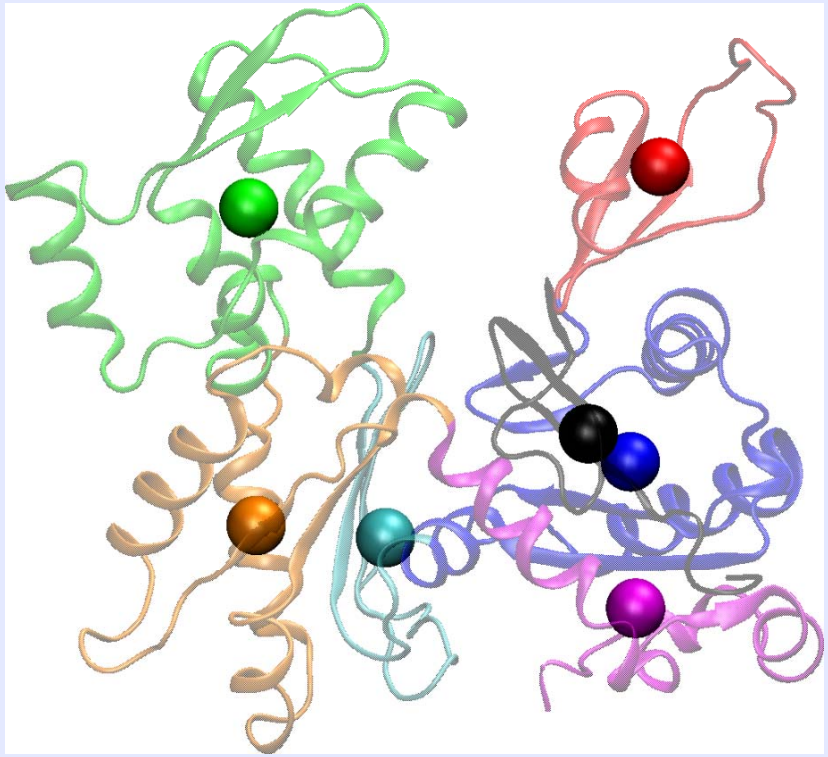
ED-CG four-site model: residual 6211

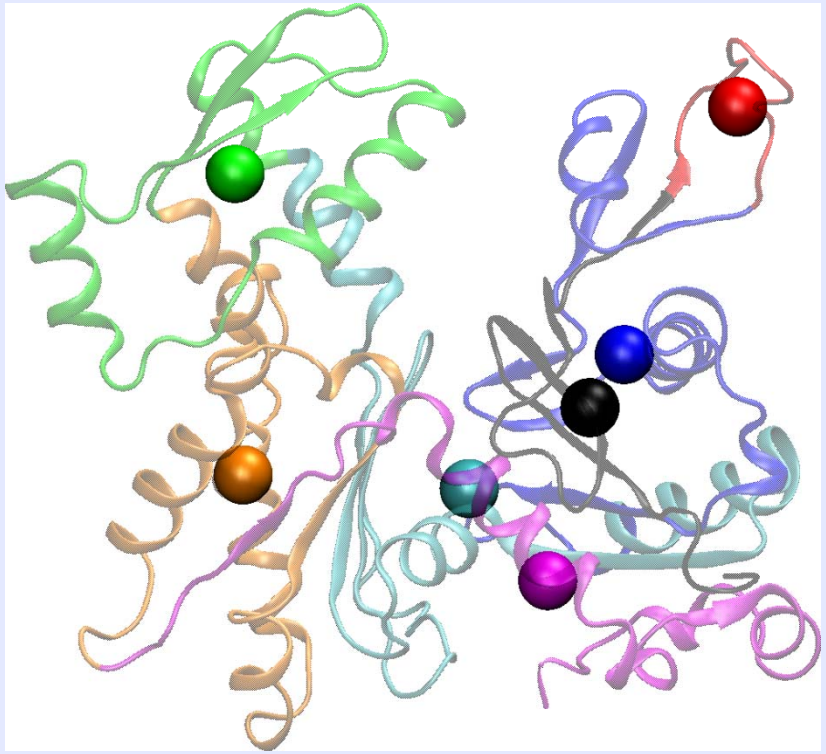
1-51: red, 52-173: blue

174-273: green, 274-375: orange

CG Sites for G-actin

- seven-site models





"Intuitive" seven-site model: residual 2448

1-32: black, 33-69: red, 70-144: blue

145-180: cyan, 181-269: green

270-337: orange, 338-375: magenta

ED-CG seven-site model: residual 2088

1-37: black, 38-51: red, 52-115: blue

116-191: cyan, 192-252: green

253-324: orange, 325-375: magenta