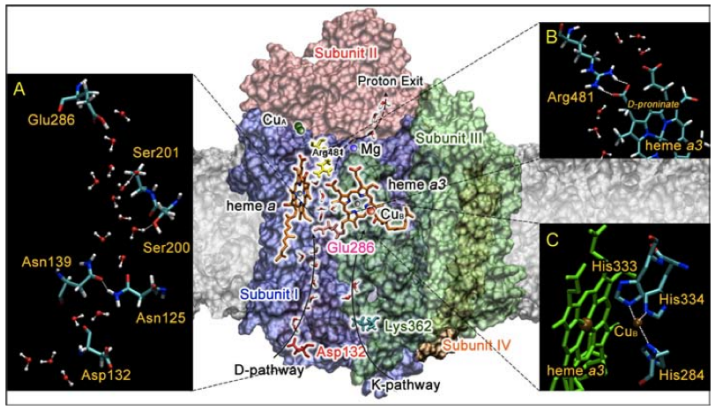
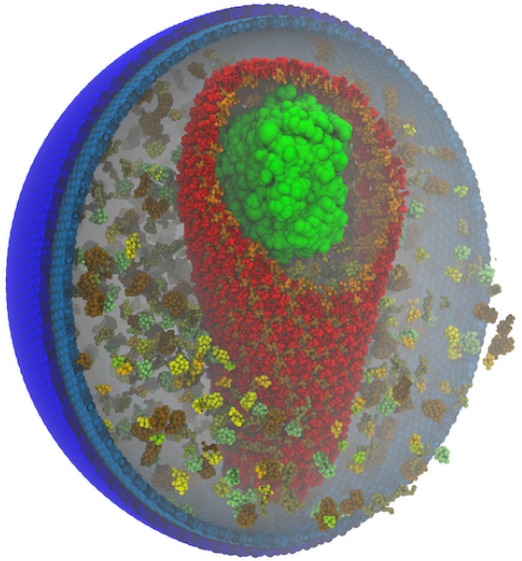
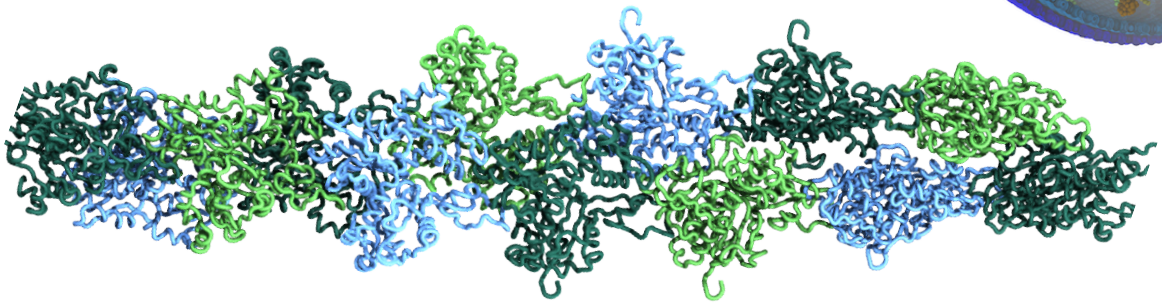
Multiscale Molecular Simulations at the Petascale







PI: Gregory A. Voth
Presenter: Chris Knight

5-16-2013

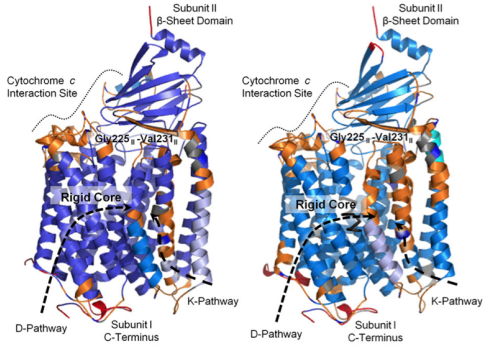
Argonne NATIONAL LABORATORY

THE UNIVERSITY OF CHICAGO

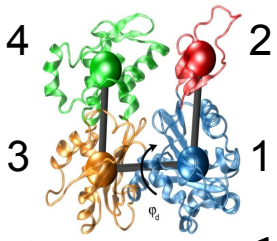
Computation Institute

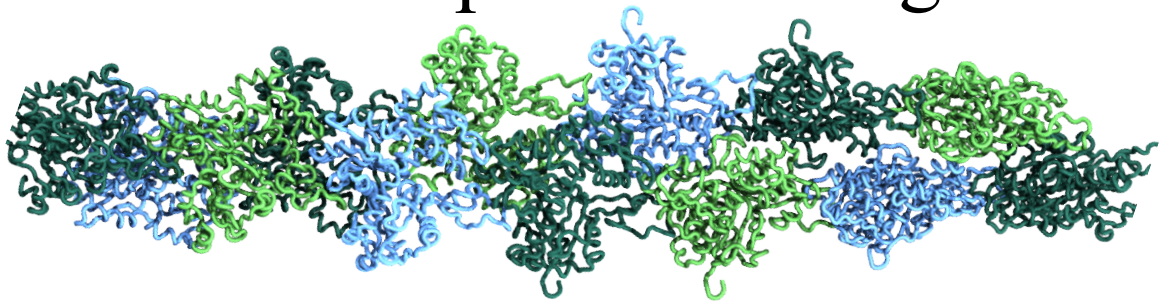
Outline

- Multiscale Reactive Molecular Dynamics
  - Cytochrome c Oxidase
  - Replica Exchange Umbrella Sampling

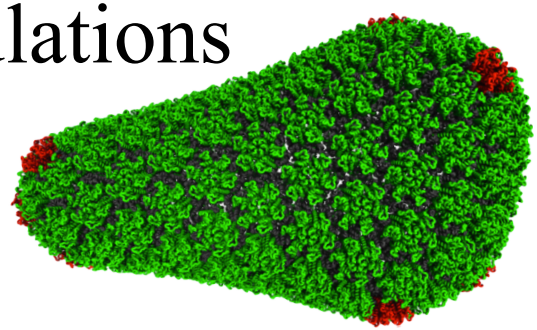


- "Hot-Beads" Hamiltonian Replica Exchange
  - Actin filaments

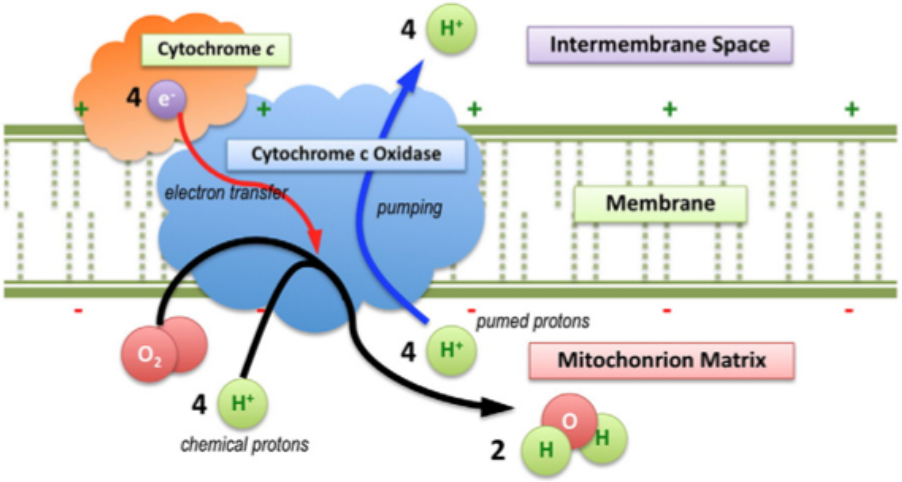


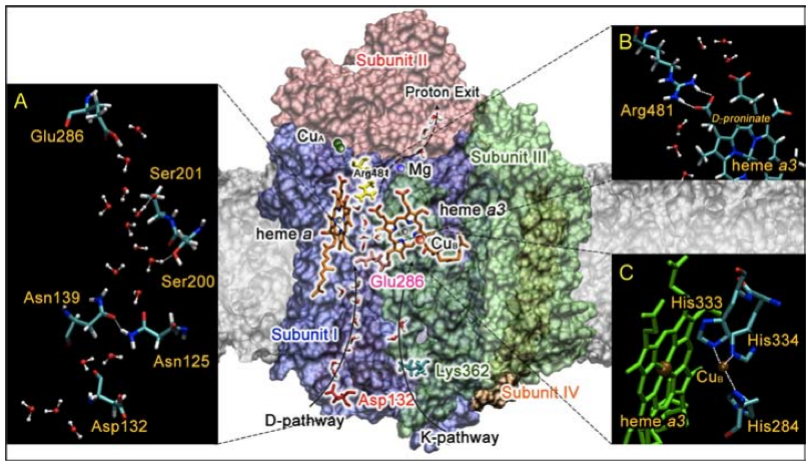


- Cellular-scale Molecular Simulations
  - HIV virion maturation



Biological Perspective on Cytochrome c Oxidase



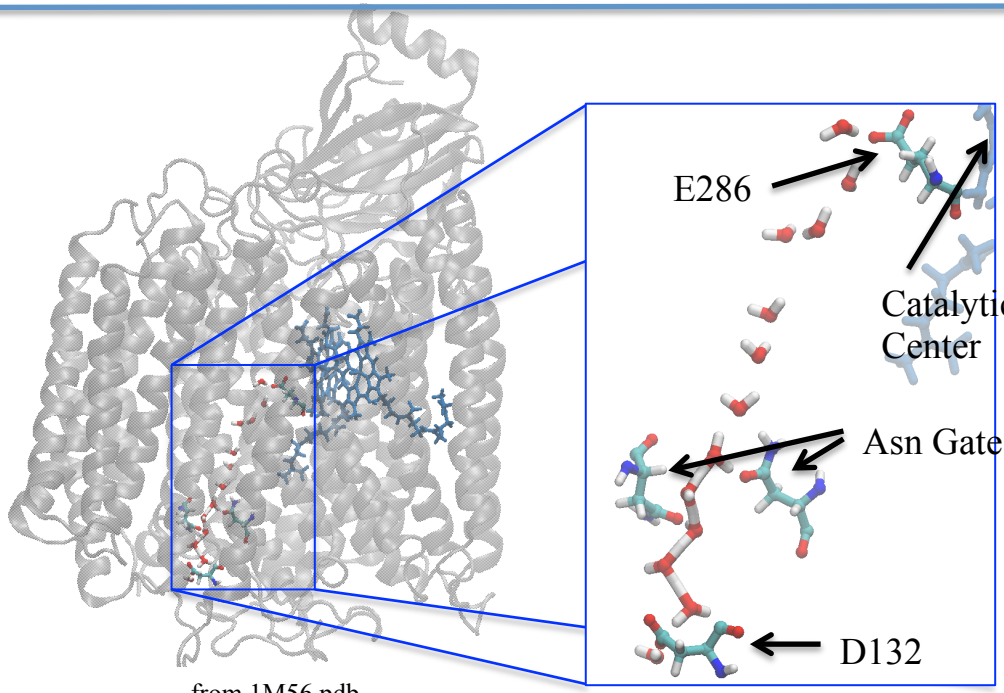


Peng and Voth. Biochim. Biophys. Acta (2011), doi:10.1016/j.bbabio.2011.11.017

- Cytochrome c Oxidase (CcO) couples the formation of water to H+ pumping
- Large transmembrane protein and terminal enzyme in the electron transport chain
- Two important questions
  - How is proton pumping coupled to redox states?
  - How are two proton transfer processes regulated?

Gard Nelson, Yuxing Peng

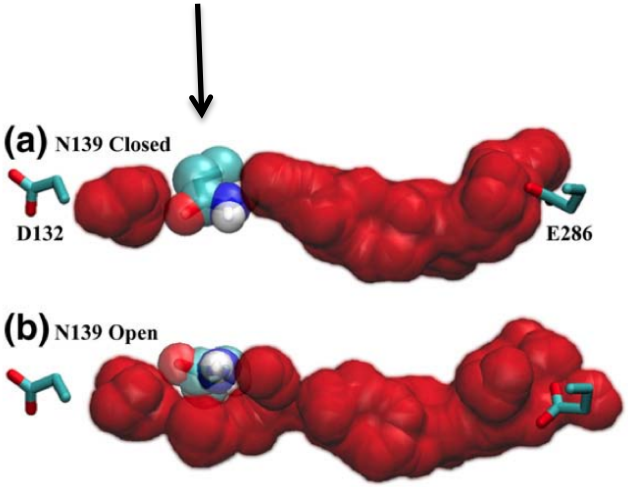
Proton Uptake in the D-Channel



from 1M56.pdb

D-Channel

Asparagine (Asn) gate



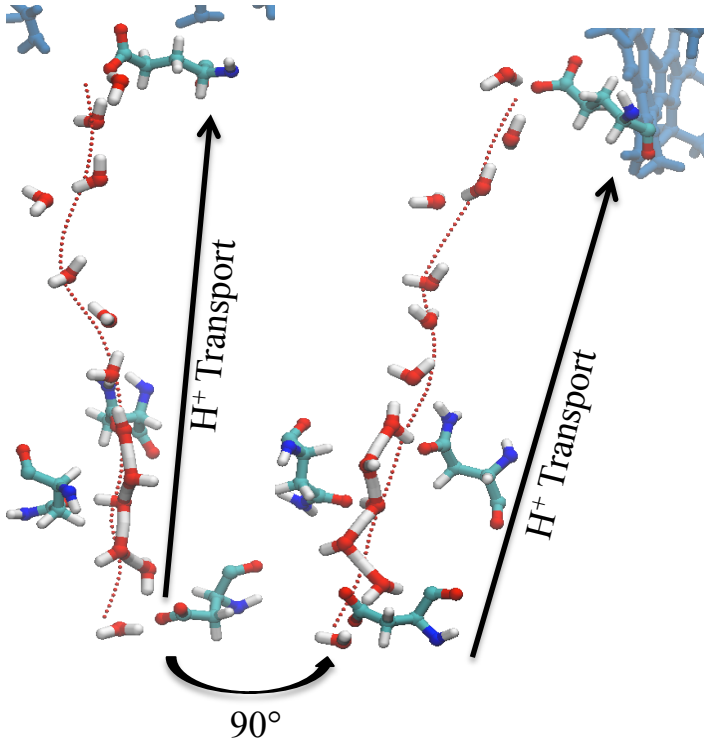
Henry et al. J. Mol. Biol. (2009) 387, 1165–1185

- Path with highest proton conductance; largest effect on productivity.
- Water wire, 10-13 molecules, many of which are x-ray resolved.
- e-/H+ transport driven by heme redox states

Gard Nelson, Yuxing Peng

The Challenges

- Need an accurate reactive model for proton transport.
- Water dynamics slow through Asn gate.
- Curvilinear path sampling in free energy calculations.



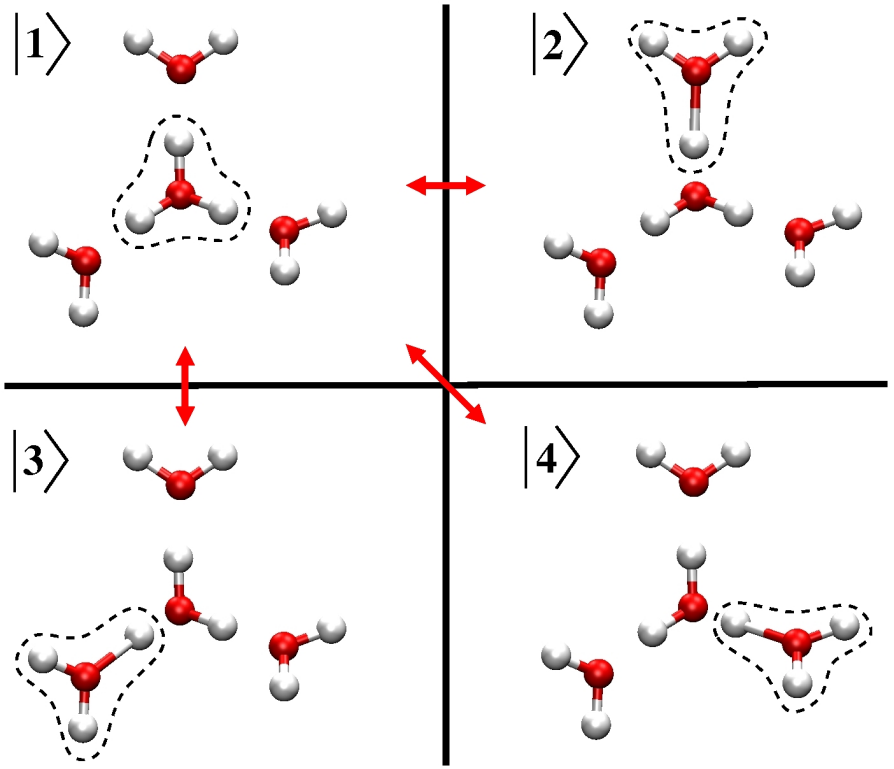
The solution:

- Reactive simulations using multistate methodology
- Well-Tempered Metadynamics to approximate path
- Replica Exchange Umbrella Sampling along curved path

Multiscale Reactive Molecular Dynamics

- A linear combination of bonding topologies can be used to describe the variable bond topology of a reactive complex.

$$\mathbf{H} = \begin{pmatrix} V_{11} & V_{12} & V_{13} & V_{14} \\ V_{12} & V_{22} & 0 & 0 \\ V_{13} & 0 & V_{33} & 0 \\ V_{14} & 0 & 0 & V_{44} \end{pmatrix}$$



- Diabatic States: $V_{jj} = V_{MM} + V_{CORR}$
- Couplings: $V_{ij} = \left(V_{CONST} + V_{EX}\right) A_{GEO}$

All interactions are parameterized by fitting to QM or AIMD data.

*Swanson et al., J. Phys. Chem. B, **111**, 4300 (2007)*
*Knight and Voth, Acc. Chem. Res., **45**, 101 (2012)*

Computationally Efficient Reactive Simulations

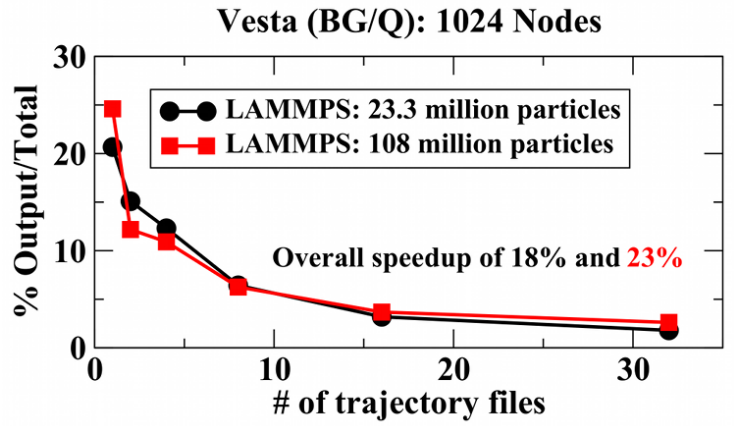
RAPTOR optimization in LAMMPS

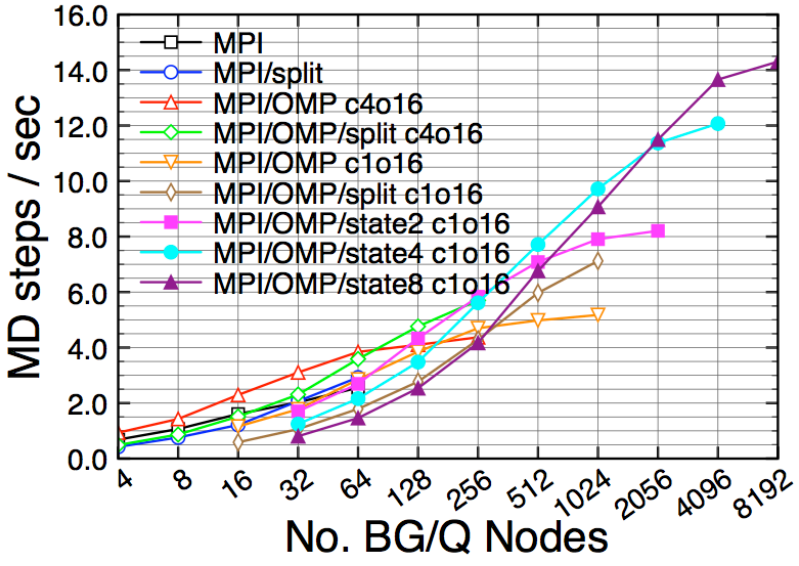
- Multithreading with OpenMP
- Parallel I/O
- State-decomposition parallelization

$$\mathbf{H} = \begin{pmatrix} V_{11} & V_{12} & V_{13} & V_{14} \\ V_{12} & V_{22} & 0 & 0 \\ V_{13} & 0 & V_{33} & 0 \\ V_{14} & 0 & 0 & V_{44} \end{pmatrix}$$

- Complex-decomposition parallelization

$$\mathbf{H}_1 = \begin{pmatrix} V_{11} & V_{12} & V_{13} & V_{14} \\ V_{12} & V_{22} & 0 & 0 \\ V_{13} & 0 & V_{33} & 0 \\ V_{14} & 0 & 0 & V_{44} \end{pmatrix}, \ldots, \mathbf{H}_N = \begin{pmatrix} V_{11} & V_{12} & V_{13} & V_{14} \\ V_{12} & V_{22} & 0 & 0 \\ V_{13} & 0 & V_{33} & 0 \\ V_{14} & 0 & 0 & V_{44} \end{pmatrix}$$

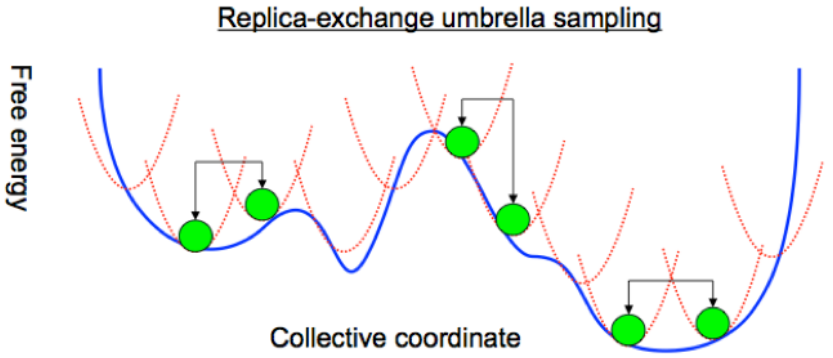


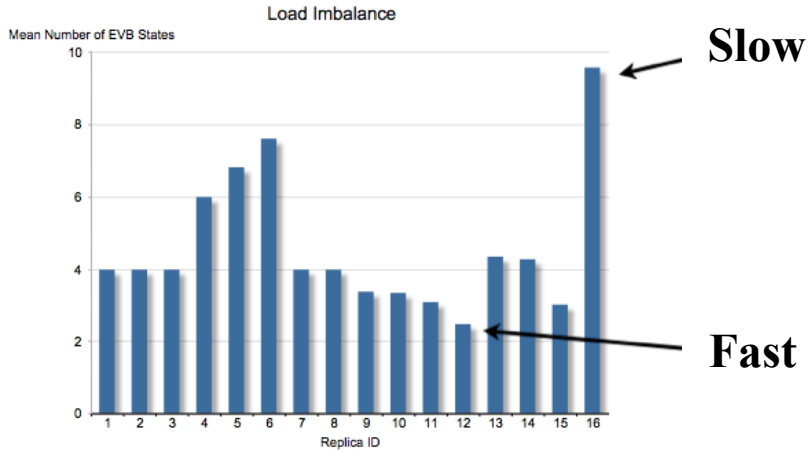


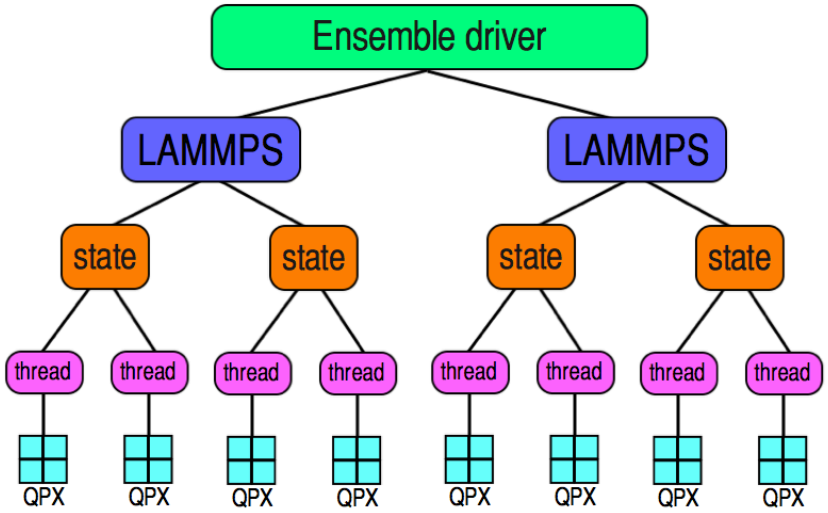
Adrian Lange, Chris Knight, Yuxing Peng

Replica Exchange Umbrella Sampling

- Periodically attempt to swap restraint between neighboring windows.
- Subcommunicators create own instance of LAMMPS
- Replica exchange between subcomms
- Dynamic load-balance



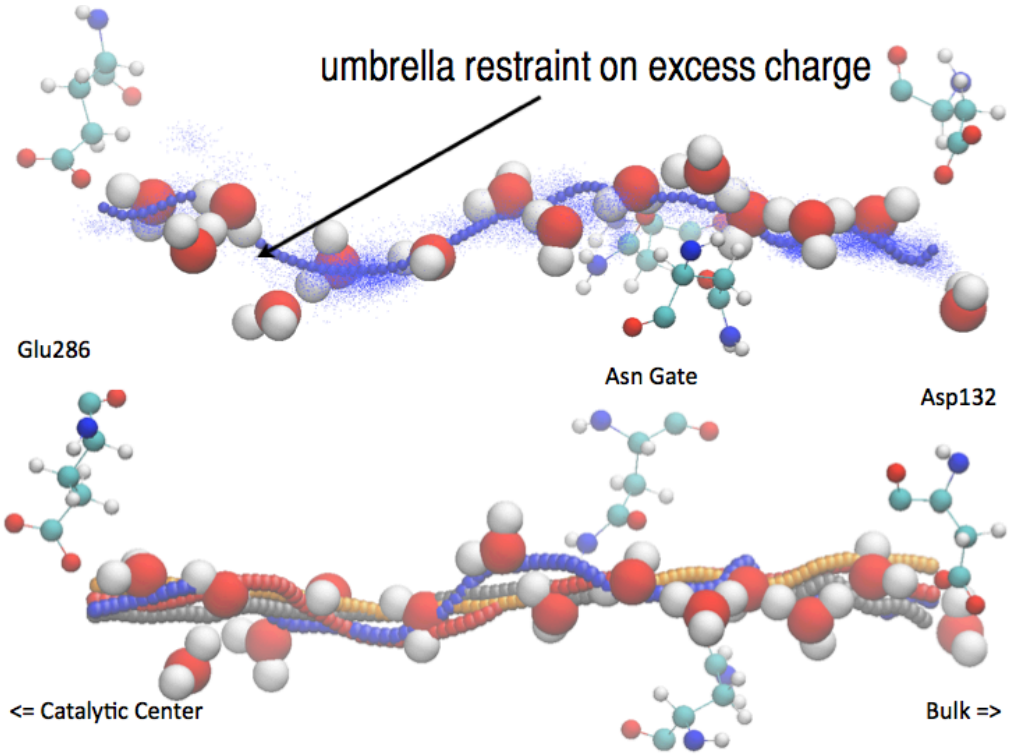


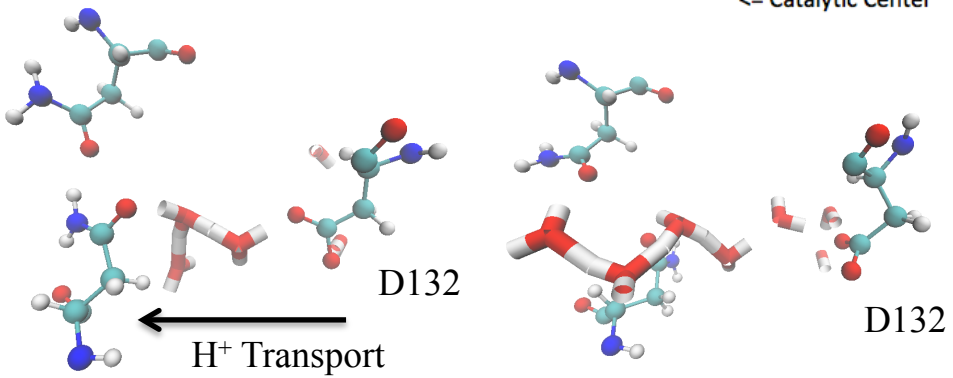


Adrian Lange, Jeff Hammond

Enhanced Sampling Along D-channel

- Umbrella sampling at 96 points along curvilinear path
- Enhanced sampling of Asn gate open/closed observed.
- Paths are mostly conserved amongst heme redox states.





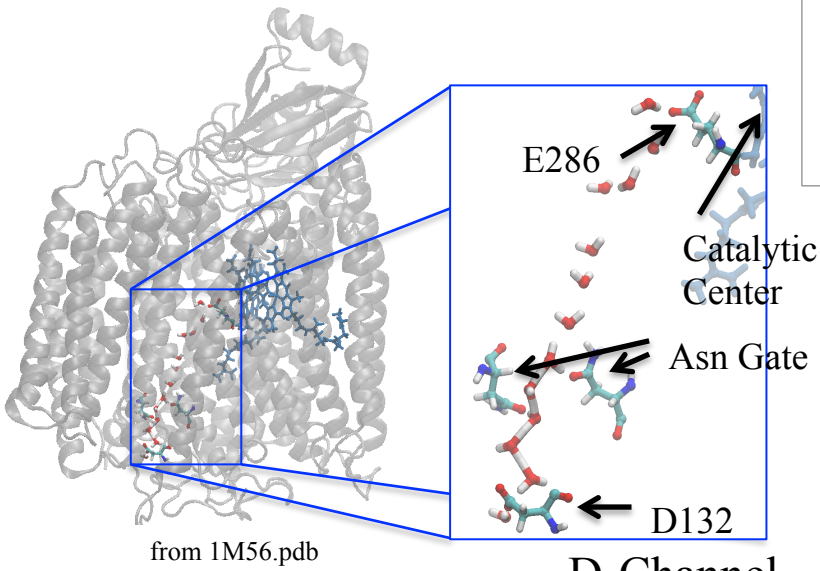
Gate closed

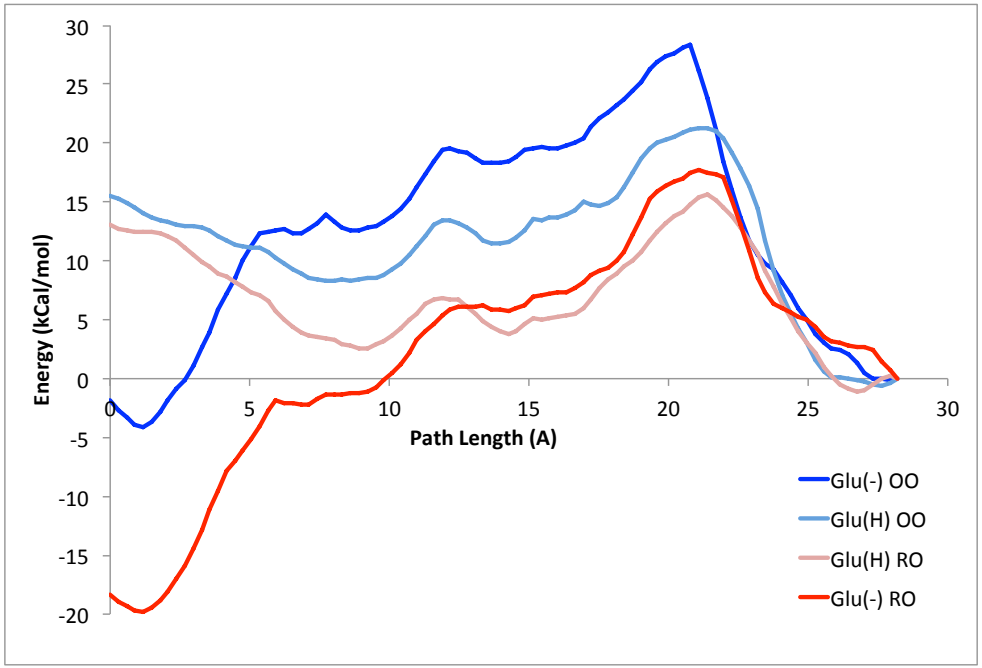
Gate open

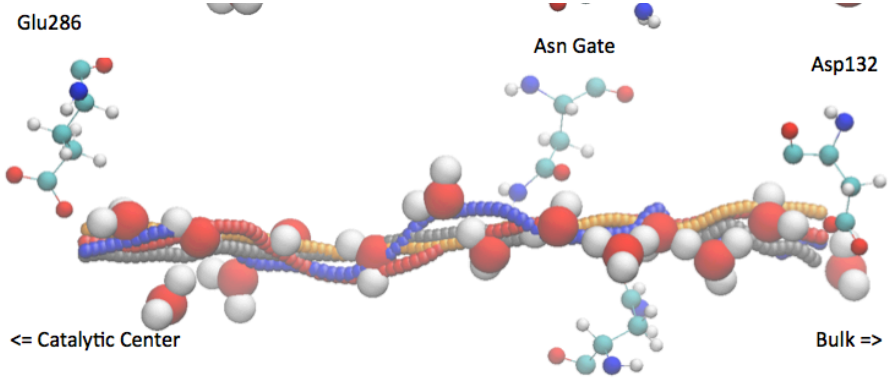
Gard Nelson, Adrian Lange

H+ Uptake Along D-channel

- Redox state dependence observed in model.
- Good estimate of H+ uptake barrier in transporting state.
- H+ uptake blocked in all other states.







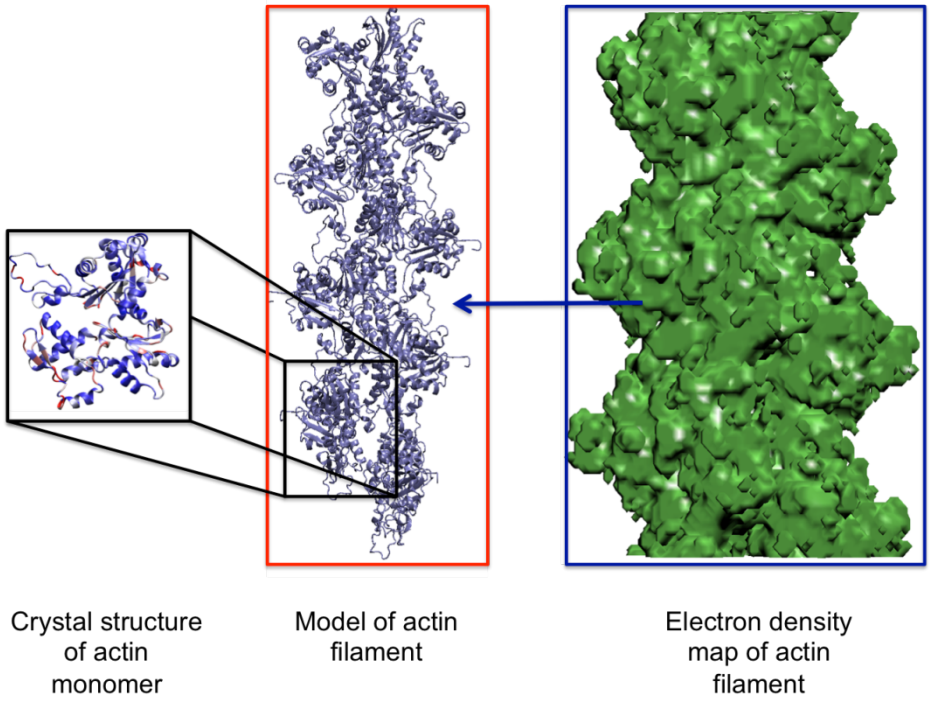
Gard Nelson, Adrian Lange

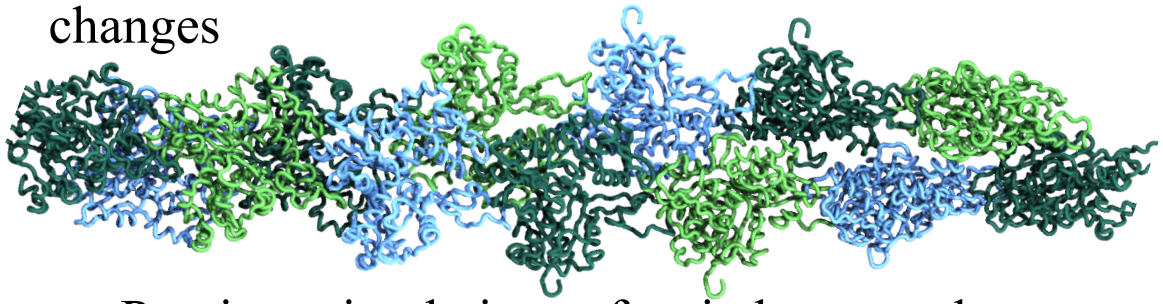
Reactive REUS of Proton Transfer in CcO

- Development of Computational Machinery
  - Significant optimization of reactive simulations in LAMMPS
  - Driver script for replica-exchange algorithms
- Molecular insight into proton pumping
  - First time reactive simulations on complete CcO system
  - Redox state dependence
  - Gating mechanism
- How to sample important transitions between protein conformations?
  - Large portions of CcO effectively rigid (membrane), but important for other proteins

Actin Filaments

- Found in all eukaryotic cells
- Part of a dynamic network, performing motive functions
  - Cell motility
  - Cell attachment
  - Cytokinesis
  - Endocytosis
  - Intracellular Signaling
- Treadmilling; many conformational changes





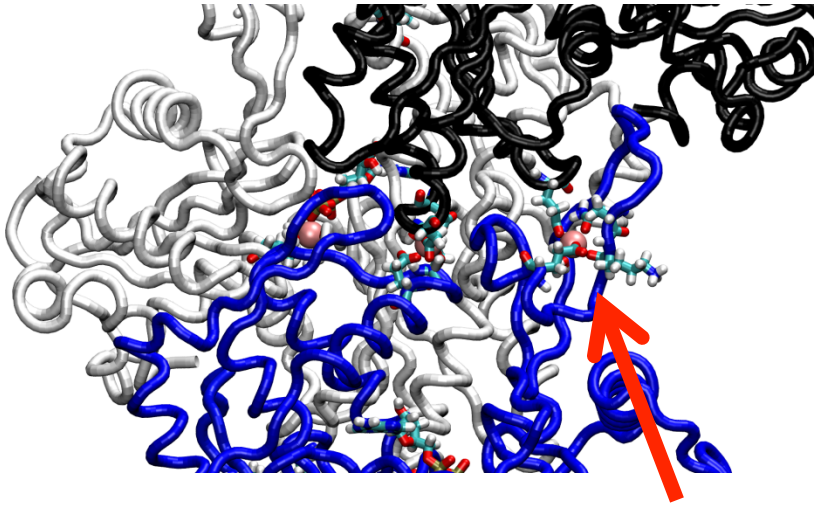
Previous simulations of actin have used a half-period (13 monomers) actin filament

Chu and Voth, PNSA (2005)
Chu and Voth, BiophysJ (2006)
Pfaendtner, Lyman, Pollard, and Voth, JMB (2010)
Saunders and Voth, JMB (2011)
Fan, Saunders, and Voth, BiophysJ (2012)
Saunders and Voth, Structure (2012)

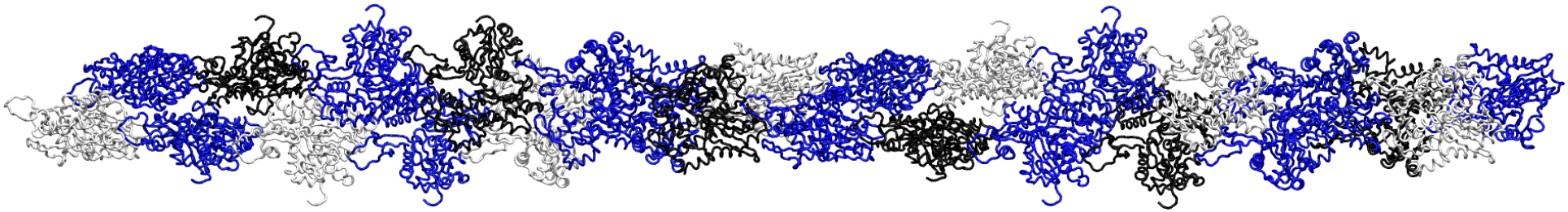
Joe Baker, Jun Fan, Marissa Saunders

Actin Filaments: A full period

- How faithfully do MD simulations of a full period of the actin filament represent important filament properties? (persistence length, torsional rigidity)
- Have incorporated specific Mg2+ ions at experimentally predicted locations in the filament to understand influence on filament dynamics
- Full period simulation plus presence of site-specific cations will represent the most accurate simulation model of eukaryotic actin to date



Site specific Mg2+ ions may significantly modulate filament properties[1]



One full period of actin filament (26 monomers)

1. Kang H, Bradley MJ, McCullough BR, Pierre A, Grintsevich EE, Reisler E, De La Cruz EM. PNAS (2012)

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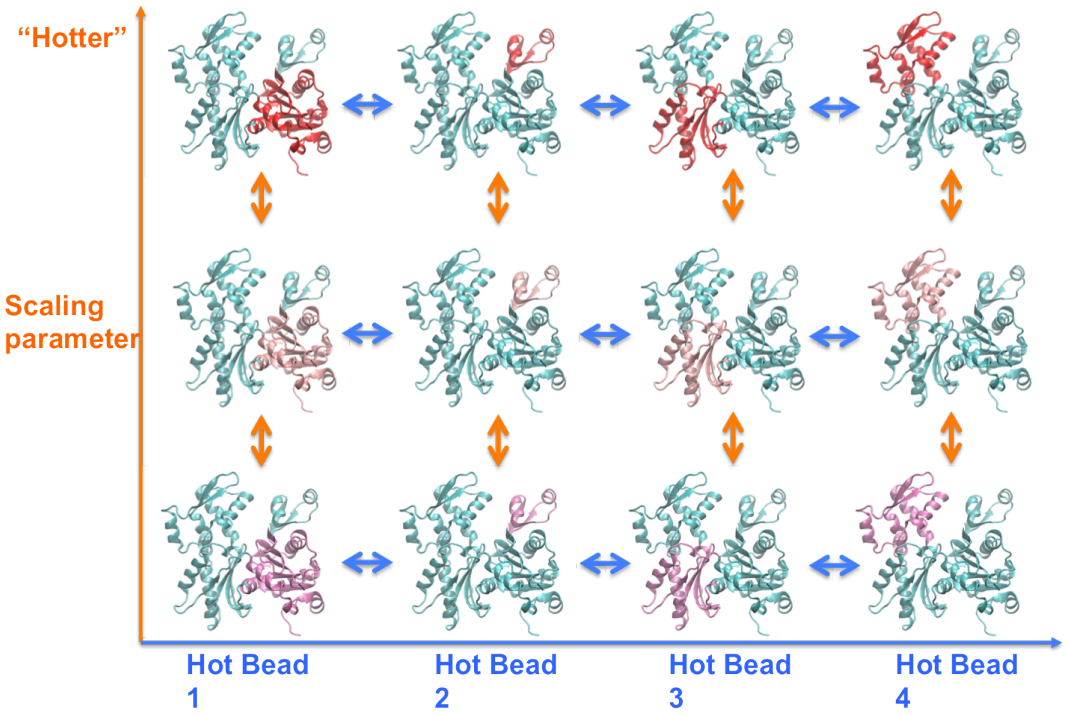
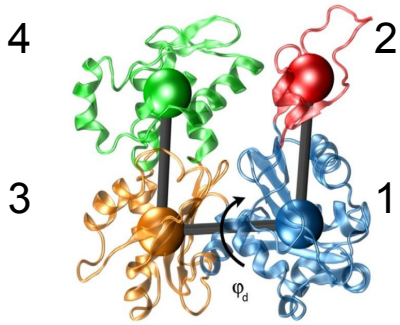
“Hot-Beads” Hamiltonian Replica Exchange

- Sampling large configurational changes in proteins is difficult with brute-force techniques.
- Locally enhance sampling (colored regions of protein)
- Choice of regions guided by coarse-graining studies.
- Along x-axis, separate regions are selected for enhanced sampling.
- Along y-axis, “temperature” of region is scaled.

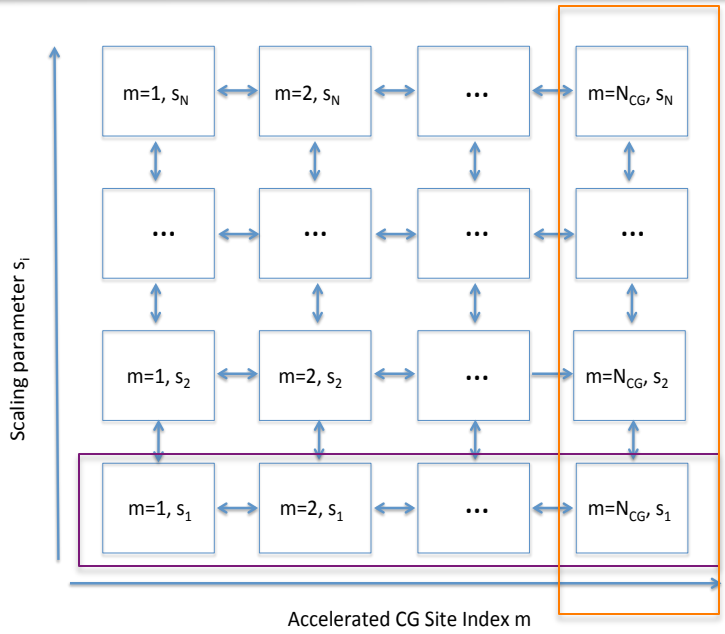




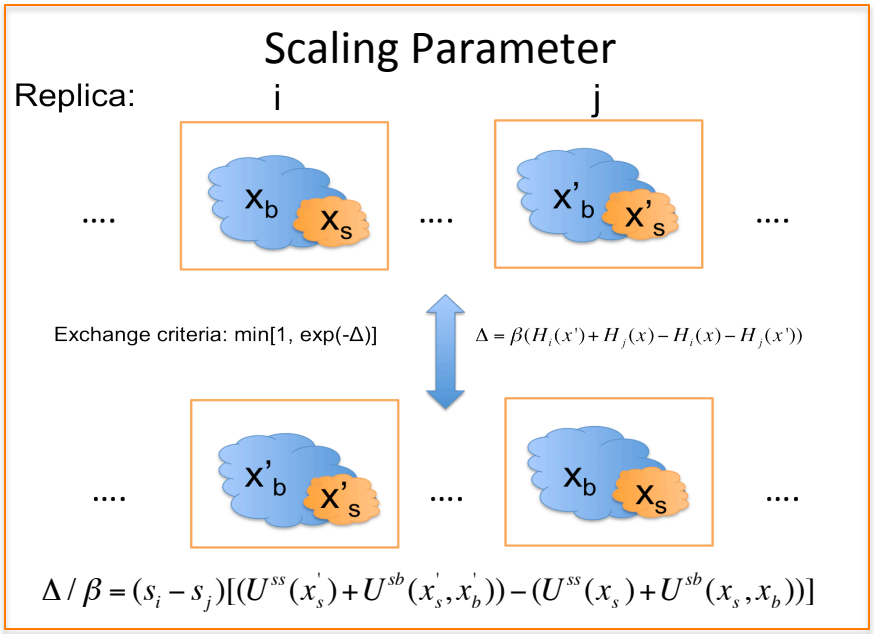
4 CG domains (Hot Beads)

Jun Fan, Wei Jiang

“Hot-Beads” Hamiltonian Replica Exchange

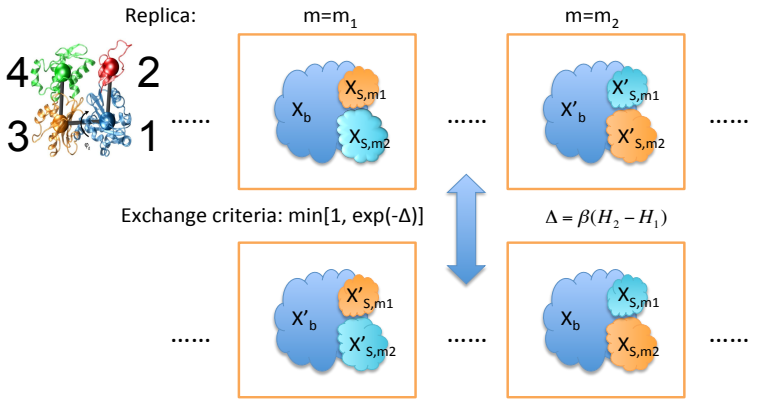


Scaling Parameter

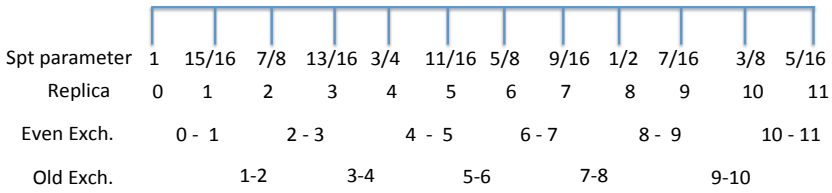


$$\Delta/\beta = (s_i - s_j)[(U^{ss}(x_s^{'}) + U^{sb}(x_s^{'}, x_b^{'})) - (U^{ss}(x_s) + U^{sb}(x_s, x_b))]$$

Hot Region



$$H_2 - H_1 = (1 - s_i)[(V(x_{si,m1}, x_{si,m1}) + V(x_{si,m1}, x_b) + V(x'_{si,m2}, x'_{si,m2}) + V(x'_{si,m2}, x'_b)) - (V(x_{si,m2}, x_{si,m2}) + V(x_{si,m2}, x_b) + V(x'_{si,m1}, x'_{si,m1}) + V(x'_{si,m1}, x'_b))]$$

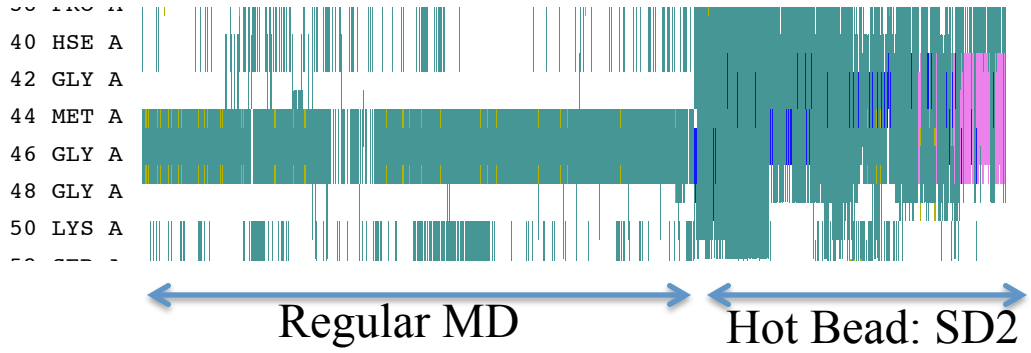


Wei Jiang, et al., JCTC, 5, 2583 (2009)
Wei Jiang, et al., JCTC, 8, 4672 (2012)

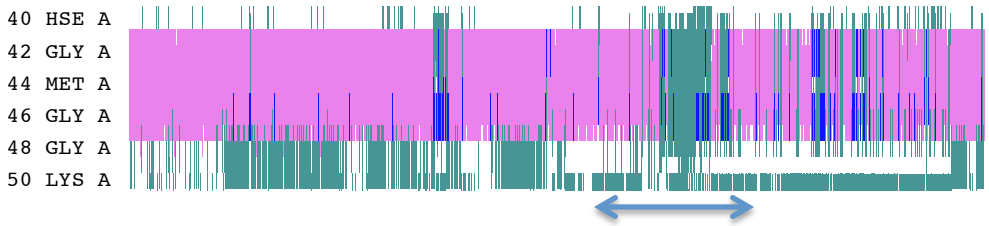
Jun Fan, Wei Jiang

Enhanced Sampling of Actin Conformations

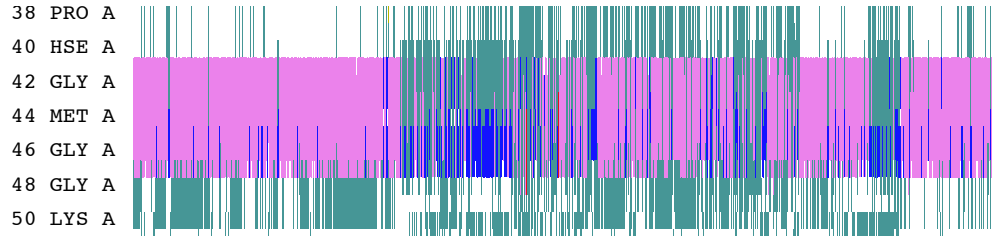
- ATP-uf Secondary Structure of D-loop



- ADP-f

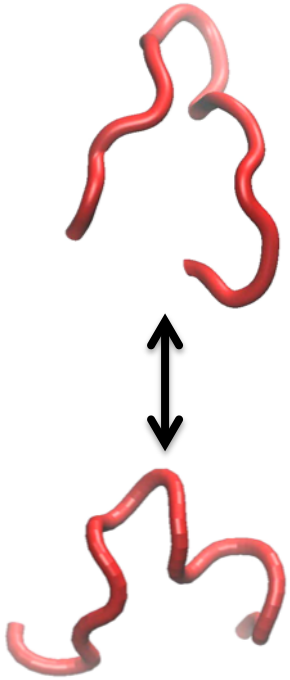


- ATP-f



T: hydrogen bonded turn
G: 3-turn helix
H: 4-turn helix

Regular transitions between folded and unfolded states



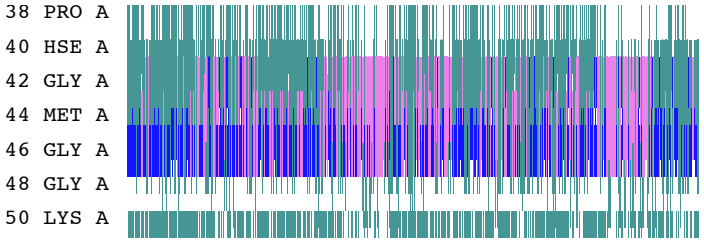
Jun Fan, Wei Jiang

Enhanced Sampling of Actin Conformations

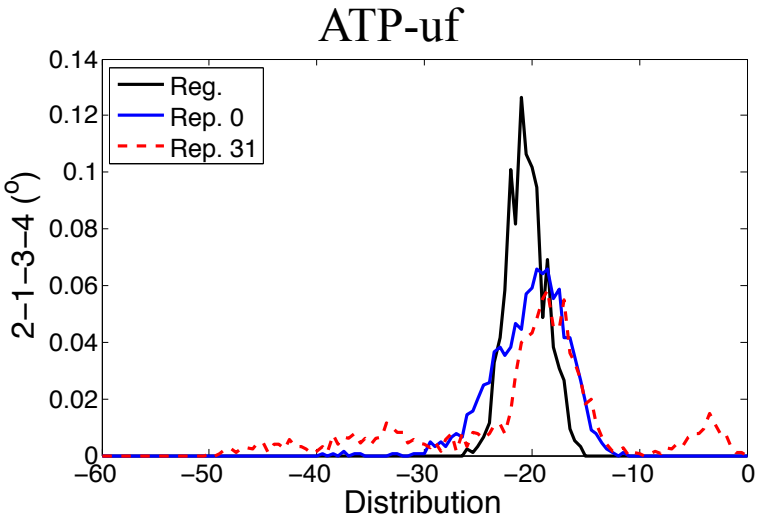
- Secondary Structure

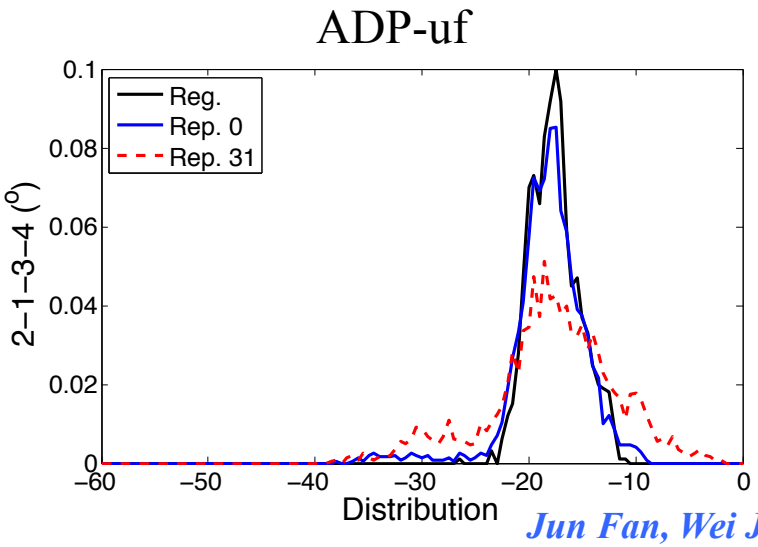
T: hydrogen bonded turn
G: 3-turn helix
H: 4-turn helix

D-loop (40-51) in G-ATP-f



- 2-1-3-4 Dihedral Angle Distribution after 5 ns



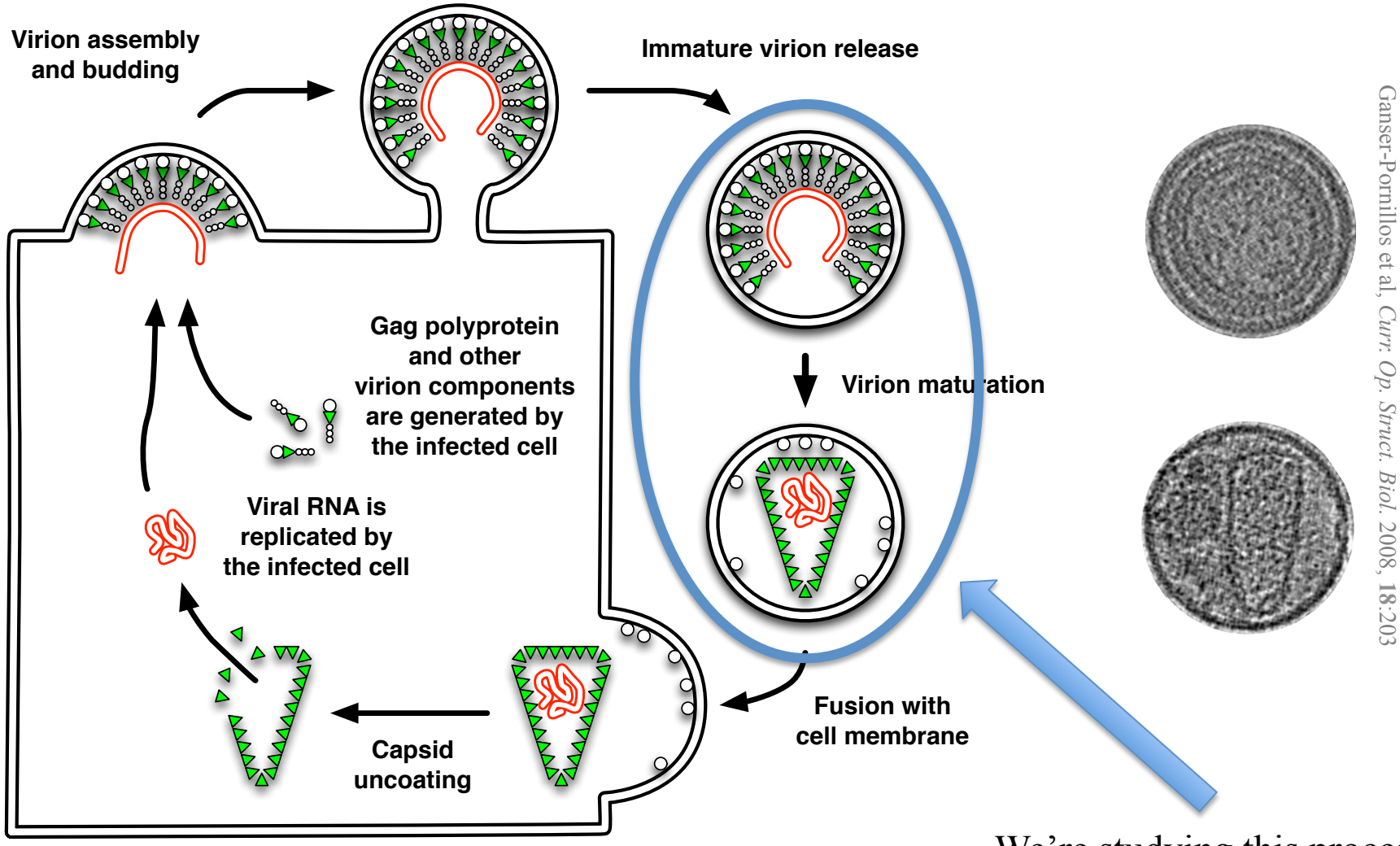


Jun Fan, Wei Jiang

Enhanced Sampling with "Hot-Beads"

- Development of Computational Machinery
  - "Hot-Beads" enhanced sampling implemented in NAMD
- Large-scale simulations of G- and F-Actin
  - First simulations of complete period of filaments
  - Enhanced sampling of large-scale protein conformations w/ actin binding proteins and nucleotides
- What about sampling larger scale phenomena?

The HIV "lifecycle"



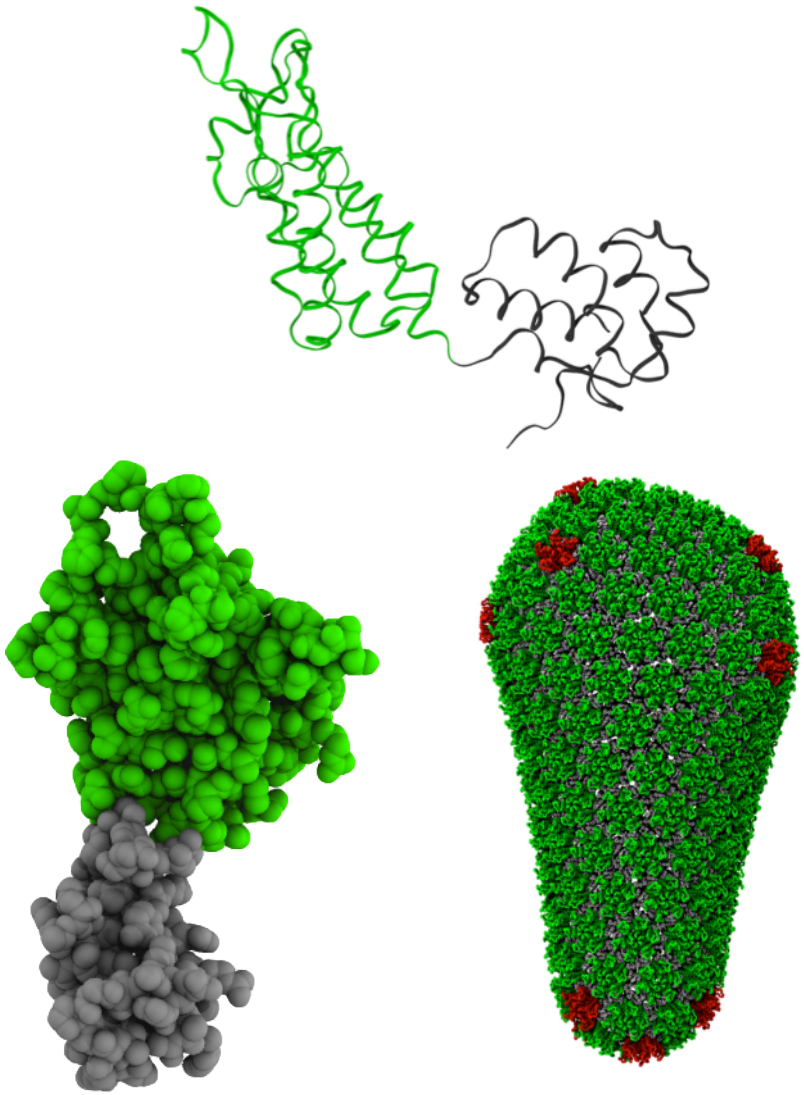
Ganser-Pornillos et al, *Curr. Op. Struct. Biol.* 2008, 18:203

We're studying this process!

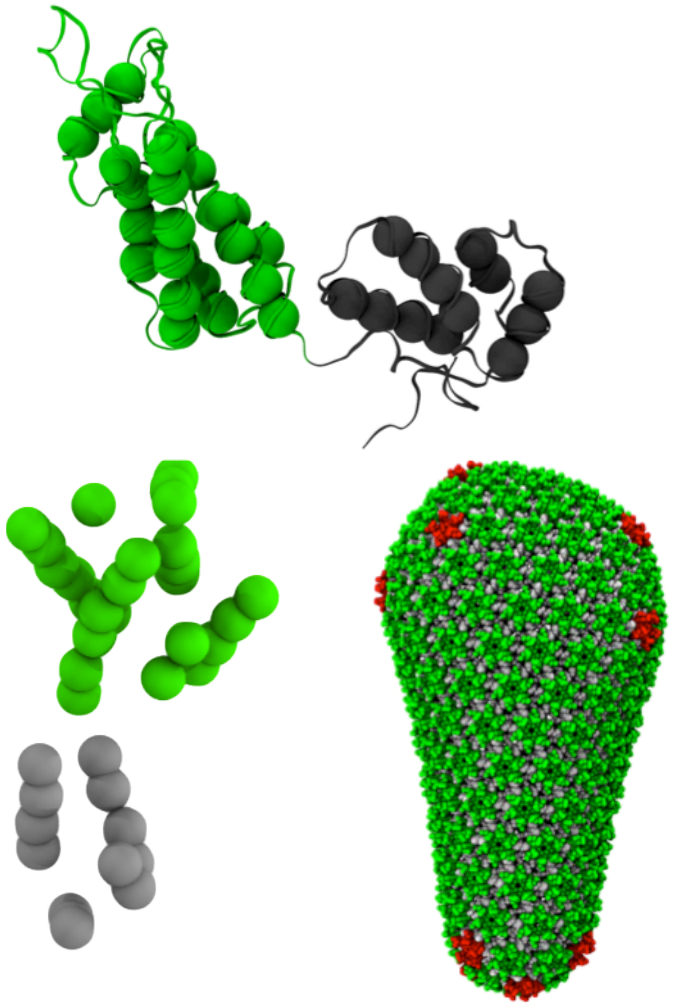
John Grime

Coarse-grained model of “capsid protein”

Atomistic



Coarse-grained

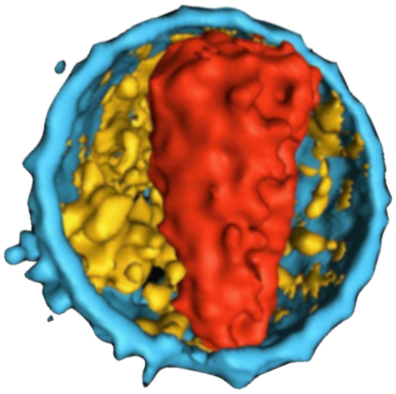


John Grime

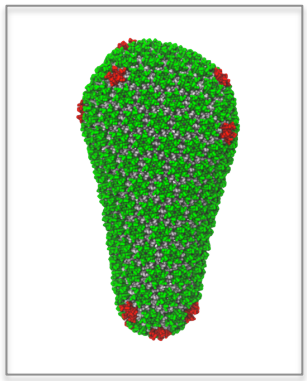
The Challenges

Implicit solvent for large scale ultra-CG: introduces large, dynamic areas of low particle density:

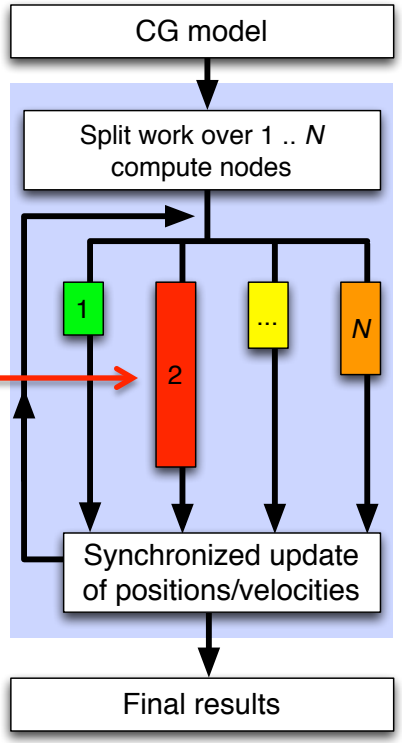
- *Load balancing*: MD simulation proceeds at pace of **slowest node**



HIV capsid[1]



Ultra-CG model

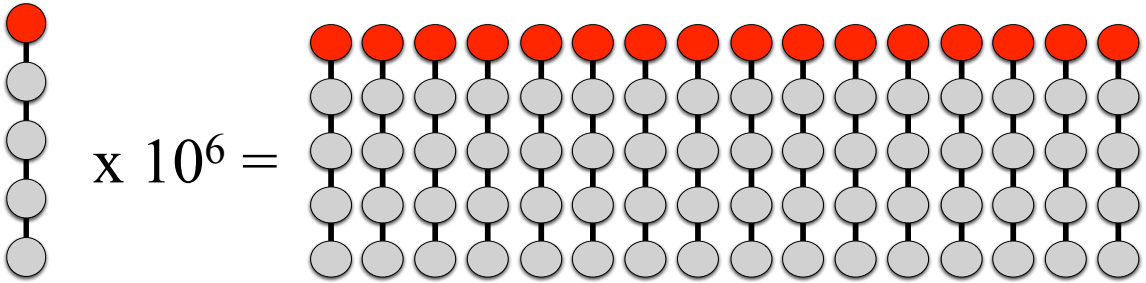


- *Memory requirements*: memory needed even for empty regions of simulation

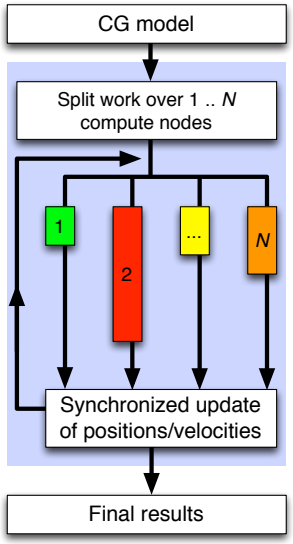
[1]Tom Goddard 2009, UCSF

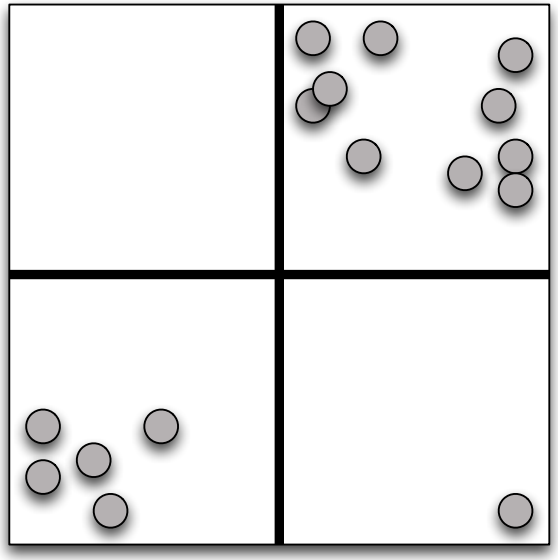
John Grime

…and their solution

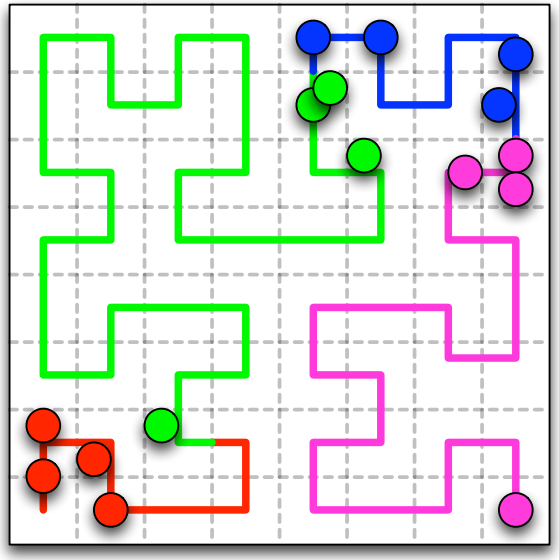


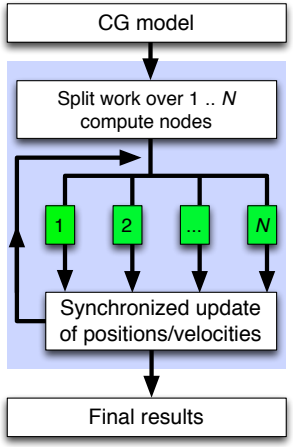
No need to store redundant information on topology





Naïve, uniform spatial decomposition





Hilbert curve spatial decomposition

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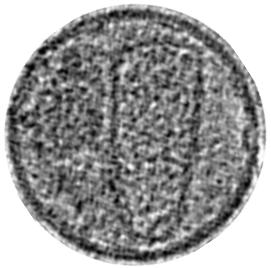
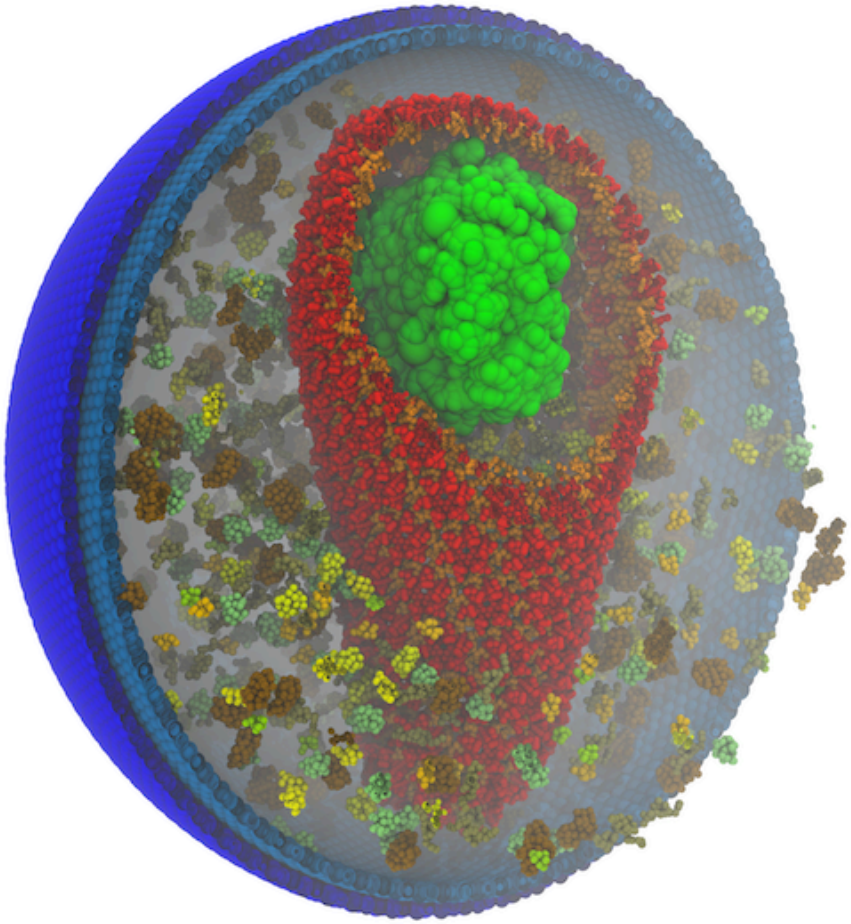
Cellular-scale Molecular Dynamics



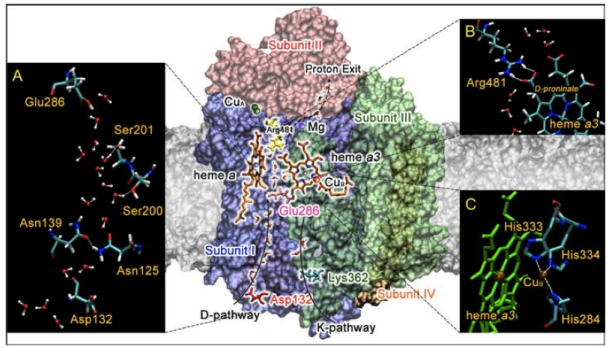


Hopefully, new CG-MD code & Mira allows us to study the full HIV virion maturation process

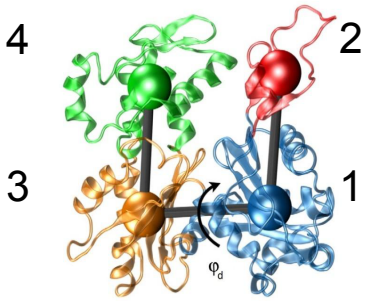
John Grime

A Look Towards the Future…

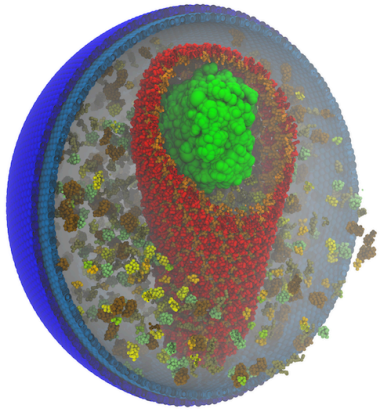
- Leadership-scale code for reactive simulations
  - Biophysics (proteins, membranes)
  - Energy Storage (batteries, fuel cells)



- Enhanced Sampling Methods
  - REUS in LAMMPS
  - "Hot-Beads" in NAMD



- Cellular-scale Molecular Simulations
  - Algorithms that scale: load-balancing, memory



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