The Computational Microscope

Computational microscope views at atomic resolution ...

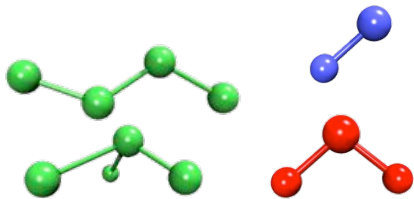Rs SER RER
E C
M GA
N
RER
L
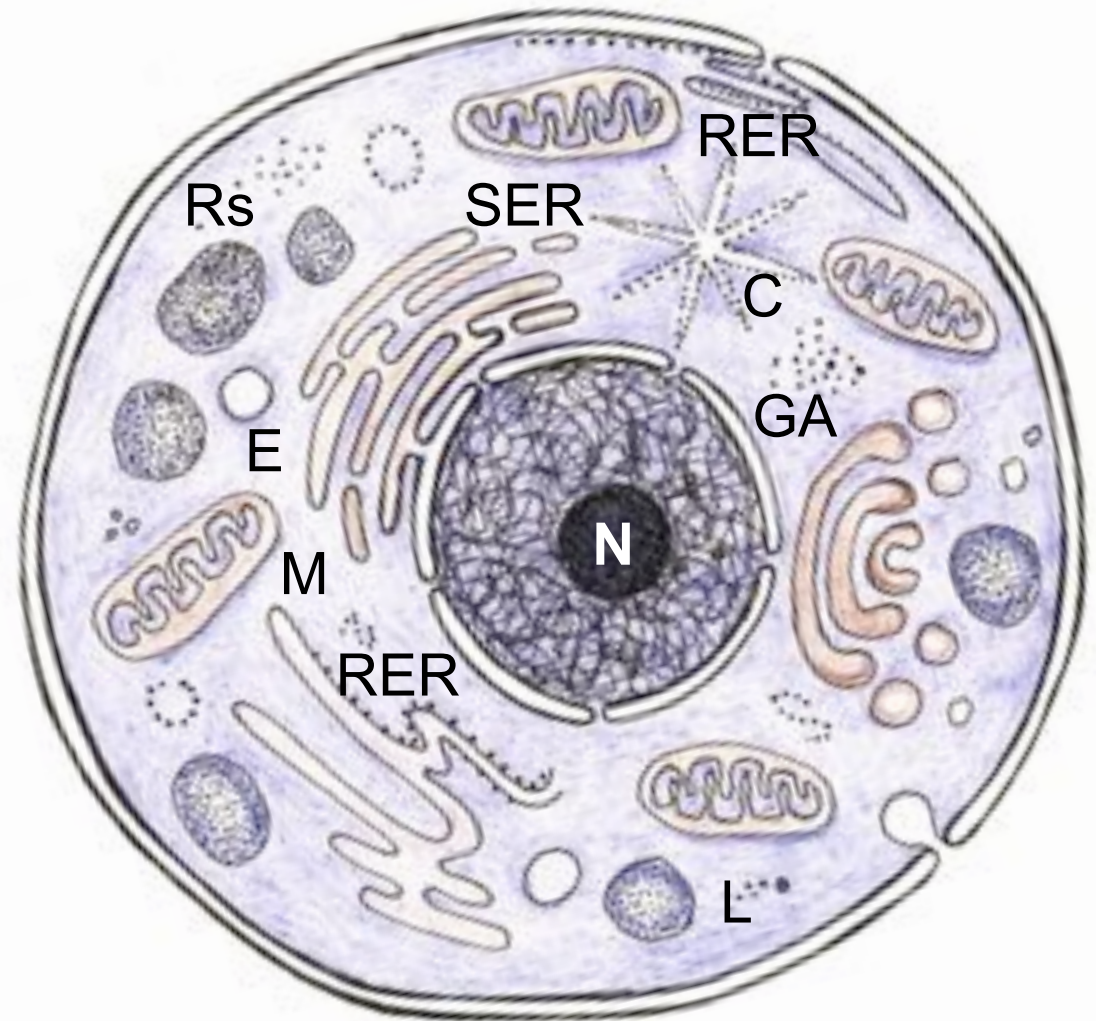
... how living cells maintain health and battle disease
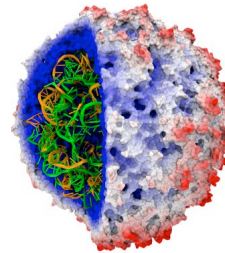
John Stone

Show videos from "Life on Earth" Chpt. 5

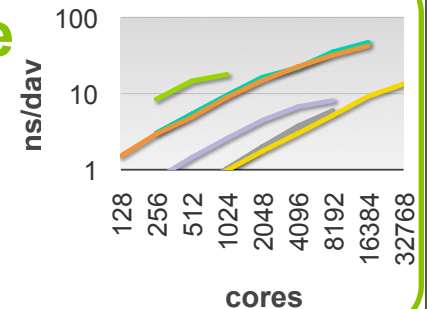# Our Microscope is Made of...

Chemistry

$$U(\vec{R}) = \underbrace{\sum_{bonds} k_i^{bond}(r_i - r_0)^2}_{U_{bond}} + \underbrace{\sum_{angles} k_i^{angle}(\theta_i - \theta_0)^2}_{U_{angle}} +$$

$$\underbrace{\sum_{dihedrals} k_i^{dihe}[1 + \cos(n_i\phi_i + \delta_i)]}_{U_{dihedral}} +$$

$$\underbrace{\sum_{i}\sum_{j \neq i} 4\epsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^6\right] + \sum_{i}\sum_{j \neq i}\frac{q_i q_j}{\epsilon r_{ij}}}_{U_{nonbond}}$$

NAMD Software

Virus

ns/day — 100, 10, 1

cores — 128 256 512 1024 2048 4096 8192 16384 32768

Physics

$$m_i \frac{d^2\vec{r}_i}{dt^2} = \vec{F}_i = -\vec{\nabla}U(\vec{R})$$

Math

$$\vec{r}_i(t + \Delta t) = 2\vec{r}_i(t) - \vec{r}_i(t - \Delta t) + \frac{\Delta t^2}{m_i}\vec{F}_i(t)$$

(repeat *one billion times* = microsecond)

..and Supercomputers

NAMD impact is broad and deep

- Comprehensive, industrial-quality software
  - Integrated with VMD for simulation setup and analysis
  - Portable extensibility through Tcl scripts (also used in VMD)
  - Consistent user experience from laptop to supercomputer

- Large user base – 51,000 registered users
  - 9,100 (18%) are NIH-funded; many in other countries
  - 14,100 have downloaded more than one version

- Leading-edge simulations
  - "most-used software" on NICS Cray XT5 (largest NSF machine)
  - "by far the most used MD package" at TACC (2nd and 3rd largest)
  - NCSA Blue Waters early science projects and acceptance test
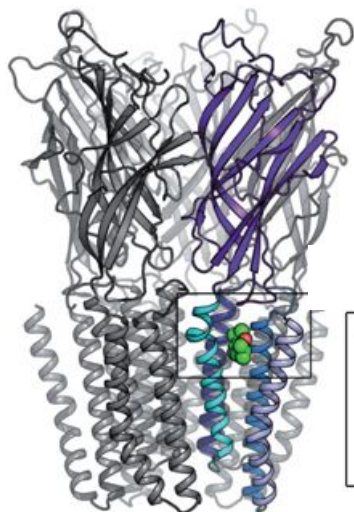 - Argonne Blue Gene/Q early science project
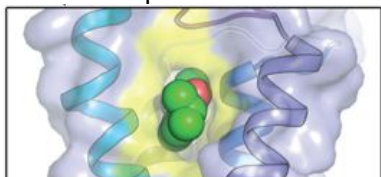
Outside researchers choose NAMD and succeed

2100 external citations since 2007

Corringer, et al., *Nature*, 2011

Voth, et al., *PNAS*, 2010

180K-atom 30 ns study of anesthetic binding to bacterial ligand-gated ion channel provided "complementary interpretations…that could not have been deduced from the static structure alone."

Bound Propofol Anesthetic

500K-atom 500 ns investigation of effect of actin depolymerization factor/cofilin on mechanical properties and conformational dynamics of actin filament.
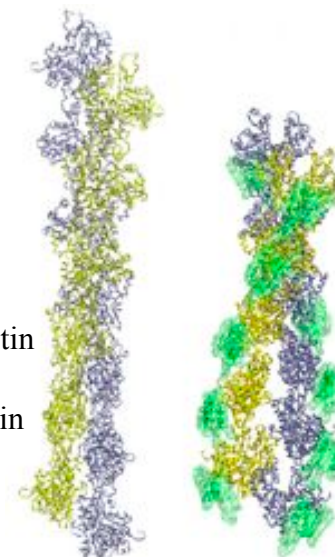
Bare actin   Cofilactin

Recent NAMD Simulations in *Nature*

- **M. Koeksal, et al.,** *Taxadiene synthase structure and evolution of modular architecture in terpene biosynthesis.* (2011)
- **C.-C. Su, et al.**, *Crystal structure of the CusBA heavy-metal efflux complex of Escherichia coli.* (2011)
- **D. Slade, et al.**, *The structure and catalytic mechanism of a poly(ADP-ribose) glycohydrolase.* (2011)
- **F. Rose, et al.,** *Mechanism of copper(II)-induced misfolding of Parkinson's disease protein.* (2011)
- **L. G. Cuello, et al.**, *Structural basis for the coupling between activation and inactivation gates in K(+) channels.* (2010)
- **S. Dang, et al.,**, *Structure of a fucose transporter in an outward-open conformation.* (2010)
- **F. Long, et al.**, *Crystal structures of the CusA efflux pump suggest methionine-mediated metal transport.* (2010)
- **R. H. P. Law, et al.**, *The structural basis for membrane binding and pore formation by lymphocyte perforin.* (2010)
- **P. Dalhaimer and T. D. Pollard**, *Molecular Dynamics Simulations of Arp2/3 Complex Activation.* (2010)
- **J. A. Tainer, et al.**, *Recognition of the Ring-Opened State of Proliferating Cell Nuclear Antigen by Replication Factor C Promotes Eukaryotic Clamp-Loading.* (2010)
- **D. Krepkiy, et al.,**, *Structure and hydration of membranes embedded with voltage-sensing domains.* (2009)
- **N. Yeung, et al.,**, *Rational design of a structural and functional nitric oxide reductase.* (2009)
- **Z. Xia, et al.**, *Recognition Mechanism of siRNA by Viral p19 Suppressor of RNA Silencing: A Molecular Dynamics Study.* (2009)

The Molecular Dynamics Simulation Process
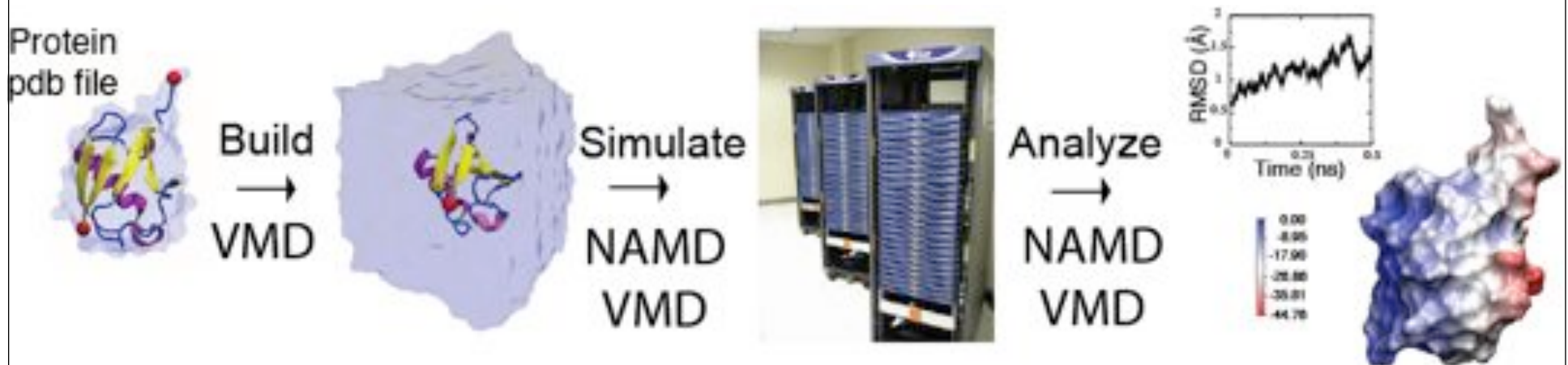
For textbooks see:

M.P. Allen and D.J. Tildesley. *Computer Simulation of Liquids.*Oxford University Press, New York, 1987.
D. Frenkel and B. Smit. *Understanding Molecular Simulations. From Algorithms to Applications.* Academic Press, San Diego, California, 1996.
A. R. Leach. *Molecular Modelling. Principles and Applications.*Addison Wesley Longman, Essex, England, 1996.
More at http://www.biomath.nyu.edu/index/course/99/textbooks.html

Classical Dynamics
at 300K

Energy function: $\quad U(\vec{r}_1, \vec{r}_2, \cdots \vec{r}_N) = U(\vec{R})$

used to determine the force on each atom:

$$m_i \frac{d^2 \vec{r}_i}{dt^2} = \vec{F}_i = -\vec{\nabla} U(\vec{R})$$

yields a set of 3N coupled 2nd-order differential equations that can be propagated forward (or backward) in time.

Initial coordinates obtained from crystal structure, velocities taken at random from Boltzmann distribution.

Maintain appropriate temperature by adjusting velocities.

Classical Dynamics
discretization in time for computing

$$m_i \frac{d^2 \vec{r_i}}{dt^2} = \vec{F_i} = -\vec{\nabla} U(\vec{R})$$

Use positions and accelerations at time t and the positions from time t-δt to calculate new positions at time t+δt.

$$\mathbf{r}(t + \delta t) \approx \mathbf{r}(t) + \mathbf{v}(t)\delta t + \frac{1}{2}\mathbf{a}(t)\delta t^2$$

$$+$$

$$\mathbf{r}(t - \delta t) \approx \mathbf{r}(t) - \mathbf{v}(t)\delta t + \frac{1}{2}\mathbf{a}(t)\delta t^2$$

"Verlet algorithm"

$$-\vec{\nabla} U(\vec{R}) \big/ m_i$$
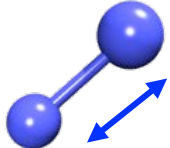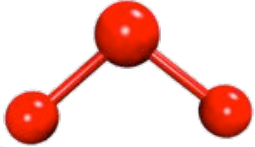
$$\boxed{\mathbf{r}(t + \delta t) \approx 2\mathbf{r}(t) - \mathbf{r}(t - \delta t) + \mathbf{a}(t)\delta t^2}$$

Potential Energy Function of Biopolymer

- Simple, fixed algebraic form for every type of interaction.

- Variable parameters depend on types of atoms involved.

heuristic

from physics

$$U(\vec{R}) = \underbrace{\sum_{bonds} k_i^{bond}(r_i - r_0)^2}_{U_{bond}} + \underbrace{\sum_{angles} k_i^{angle}(\theta_i - \theta_0)^2}_{U_{angle}} +$$

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Improving the Force Field

- Atomic polarizability increases computation by 2x…

- …but, the additional computations are perfectly suited to the GPU!

- For now, NAMD calculates atomic polarizability on CPUs only...soon we will also use GPUs

Atomic polarizability of water, highly accurately simulated through additional particles (shown in green)

NAMD CPU performance scaling

polarizable water

non-polarizable water

Seconds per step

CPU cores
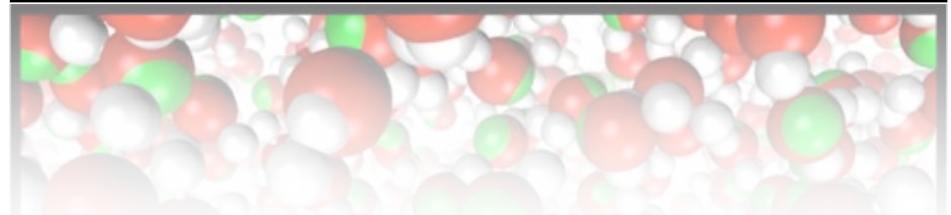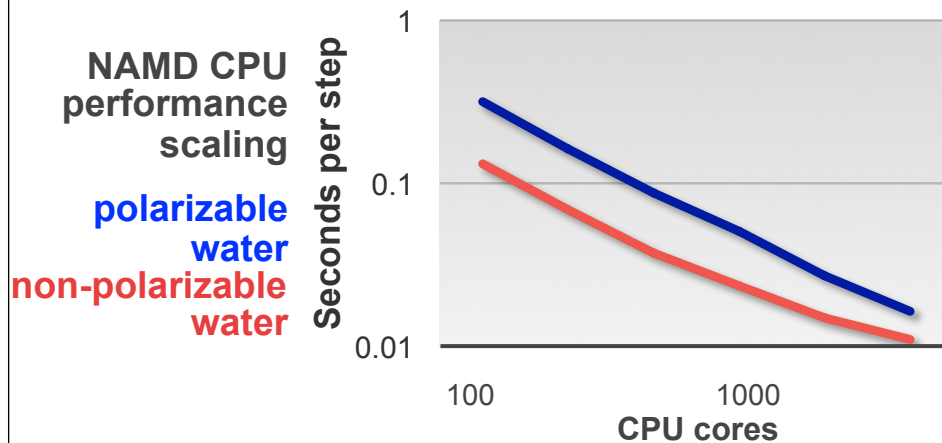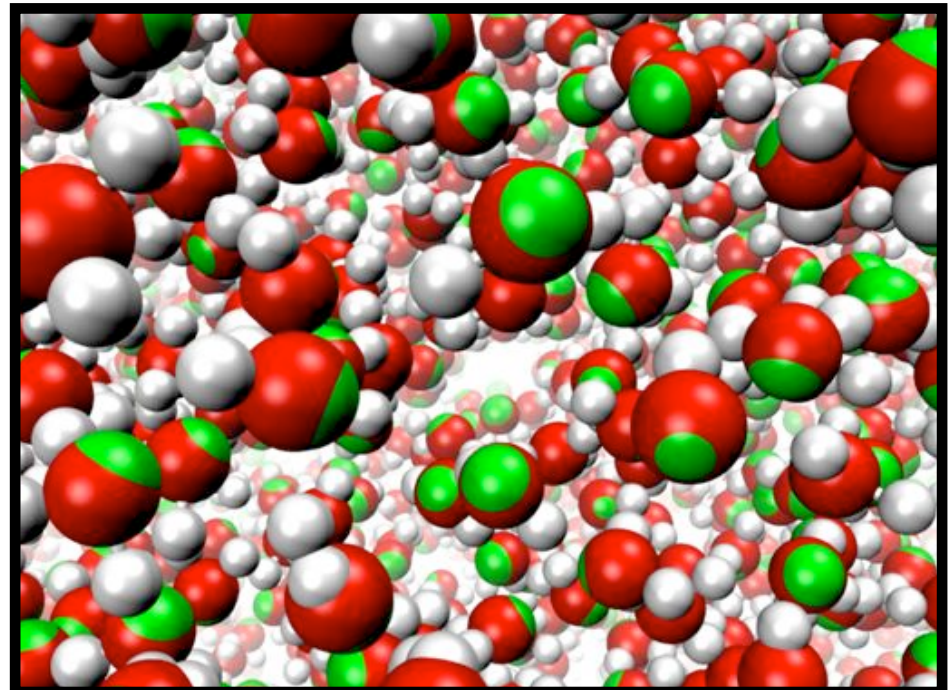
Molecular Dynamics Ensembles

Constant energy, constant number of particles (NE)

Constant energy, constant volume (NVE)

Constant temperature, constant volume (NVT)

Constant temperature, constant pressure (NPT)

Choose the ensemble that best fits your system and start the simulations, but use NE to check on accuracy of the simulation.

Langevin Dynamics
for temperature control

Langevin dynamics deals with each atom separately, balancing a small friction term with Gaussian noise to control temperature:

$$m\,\ddot{\vec{r}} = \vec{F}(\vec{r}) - \gamma\,m\,\dot{\vec{r}} + \vec{R}(t)$$

$$\langle \vec{R}(t) \cdot \vec{R}(t') \rangle = 6 k_B T \gamma \, \delta(t - t')$$

Langevin Dynamics
for pressure control

**Underlying Langevin-Hoover barostat equation for all atoms:
Equations solved numerically in NAMD**

$$\frac{d^2V(t)}{dt^2} = \frac{1}{W_{bs}}\left[P(t) - P_{\text{target}}\right] - \frac{1}{\tau_{\text{bs}}}\frac{dV(t)}{dt} + R_{\text{bs}}(t)$$

$$P = \rho k_B T + \frac{1}{Vd}\sum_{i<j}\langle r_{ij}\frac{dU_{tot}(r_{ij})}{dr_{ij}}\rangle \qquad d = \text{dimension}$$

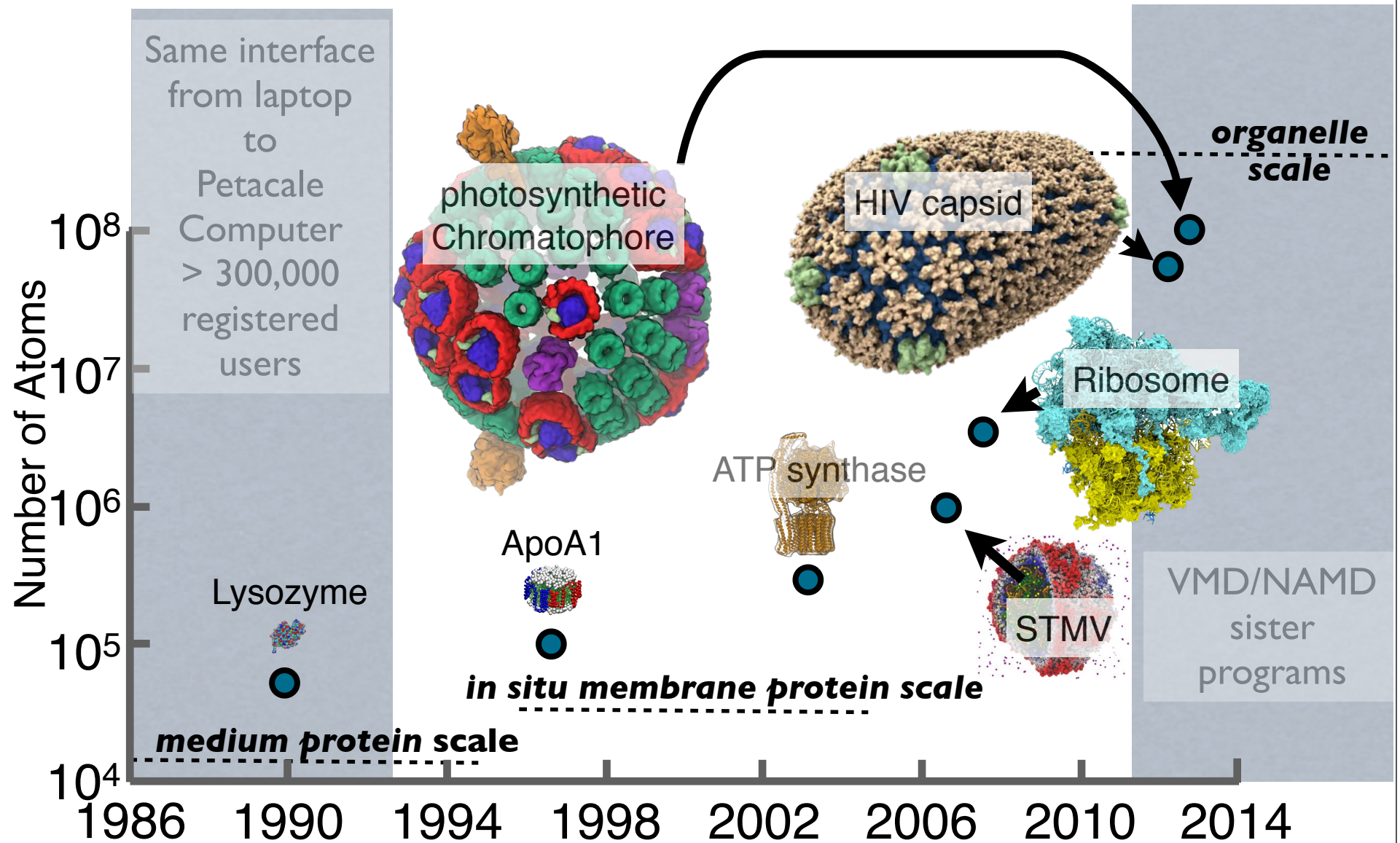$$\langle R_{\text{bs}}(t)\,R_{\text{bs}}(t')\rangle = \frac{2\,k_{\text{B}}\,T_{\text{target}}\,\delta(t-t')}{W_{\text{bs}}\,\tau_{\text{bs}}} \qquad W_{\text{bs}} = d\,N_{\text{atoms}}\,k_{\text{B}}T_{\text{target}}\,\tau_{period}^2$$

$$\dot{\mathbf{r}}_i = \mathbf{v}_i + s\mathbf{r}_i \qquad\qquad \dot{\mathbf{v}}_i = \mathbf{F}_i\,/\,m_i - s\mathbf{v}_i$$
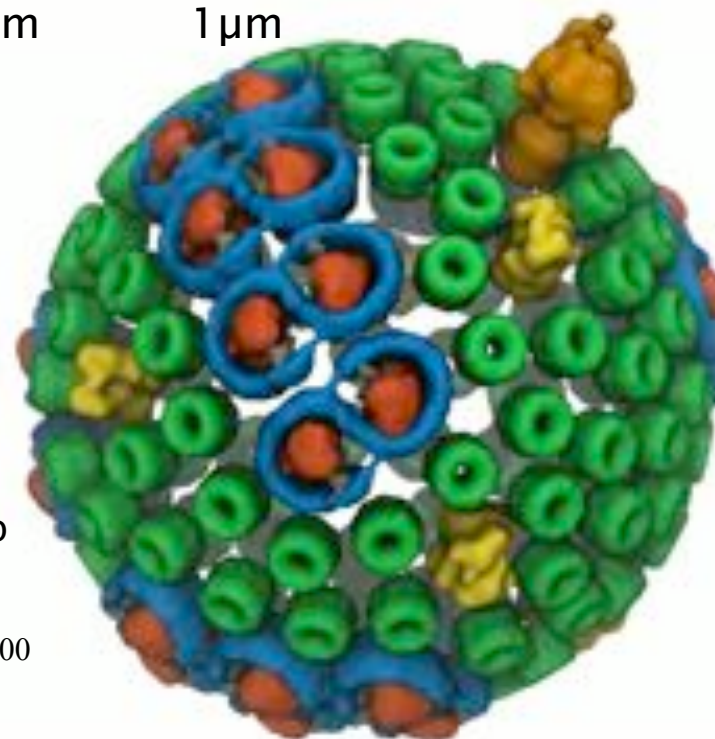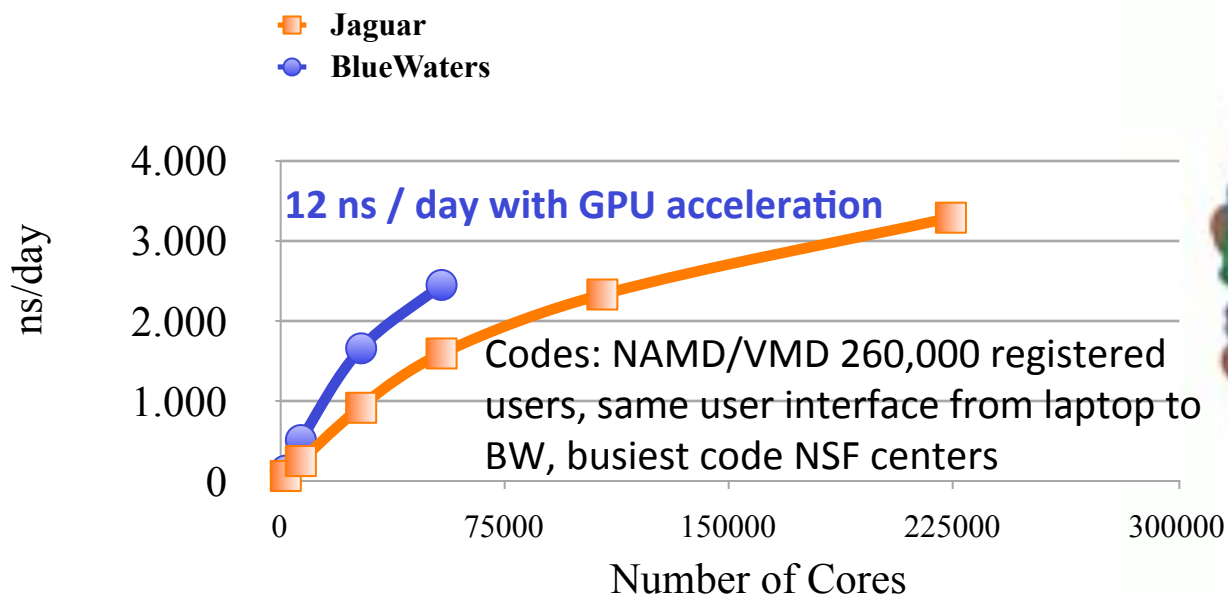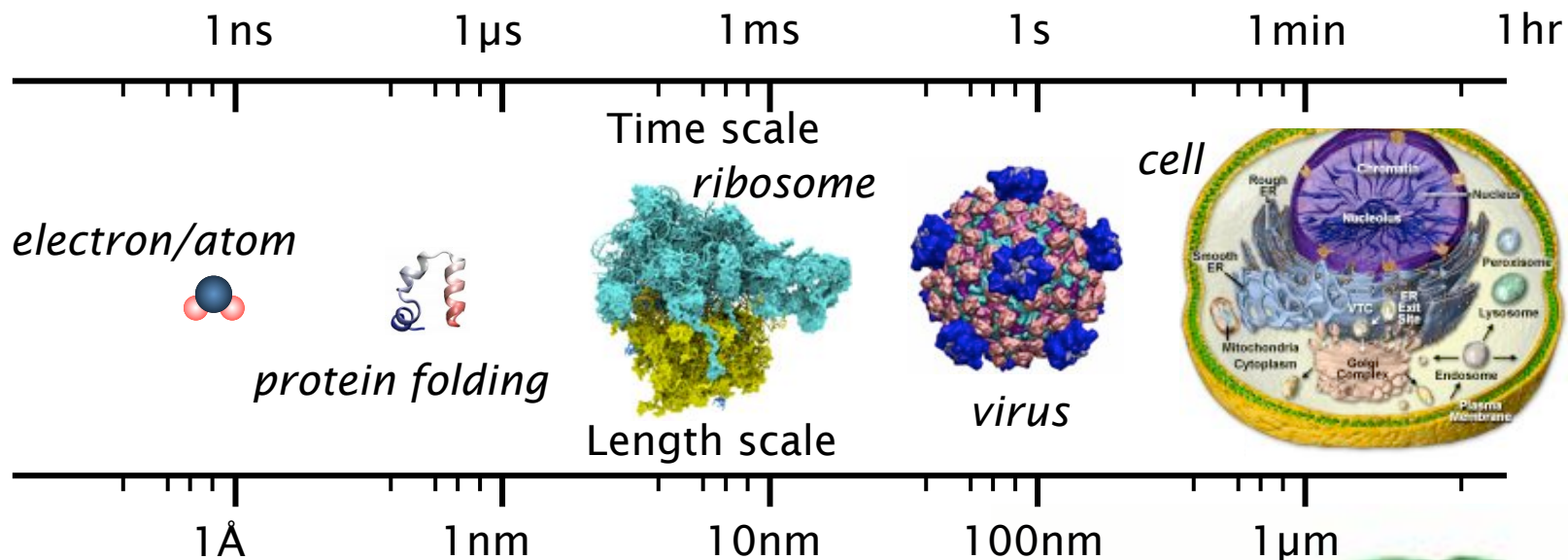
$$\dot{V} = dVs \qquad \dot{s} = dV(P - P_{\text{target}})\,/\,W - s\,/\,\tau_{\text{bs}} \quad + R(t)$$

d - dimension

All-Atom Molecular Dynamics Extends Today to Small Cellular Organelle (100nm)^3 Scale

Same interface from laptop to Petacale Computer > 300,000 registered users

10^8

10^7

Number of Atoms

10^6

10^5

10^4

photosynthetic Chromatophore

HIV capsid

organelle scale

Ribosome

ATP synthase

ApoA1

STMV

Lysozyme

in situ membrane protein scale

medium protein scale

VMD/NAMD sister programs

1986   1990   1994   1998   2002   2006   2010   2014

NAMD Increases Biological Realism Towards the Cell Scale

1ns   1μs   1ms   1s   1min   1hr

Time scale

ribosome

electron/atom

cell

protein folding

virus

Length scale

1Å   1nm   10nm   100nm   1μm

- Jaguar
- BlueWaters

12 ns / day with GPU acceleration

Codes: NAMD/VMD 260,000 registered users, same user interface from laptop to BW, busiest code NSF centers

ns/day

4.000
3.000
2.000
1.000
0

Number of Cores

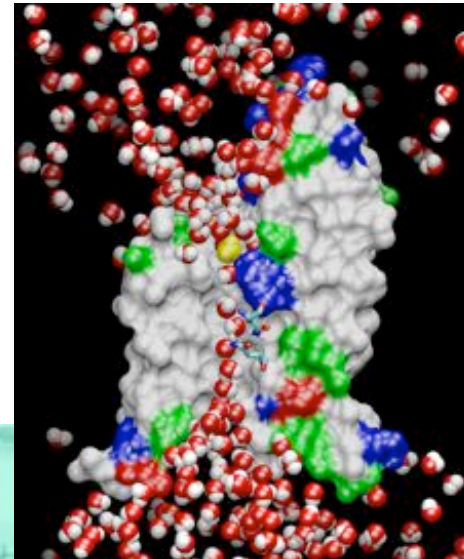0   75000   150000   225000   300000

**100 M atom simulation**

From 10,000 to 100,000 Atom MD in 2000

100k atom MD reached in 2000
- then a factor 10 increase in computation;
- **needed to describe membrane processes;**
- was achieved through cluster computing;
- produced good quality results for aquaporin;
- **is now standard.**

E.Tajkhorshid,
P. Nollert,
M. Jensen,
L. Miercke,
J. O'Connell,
and K. Schulten.
Science, **296:**525-530,
2002.

100,000 atoms, 12 ns
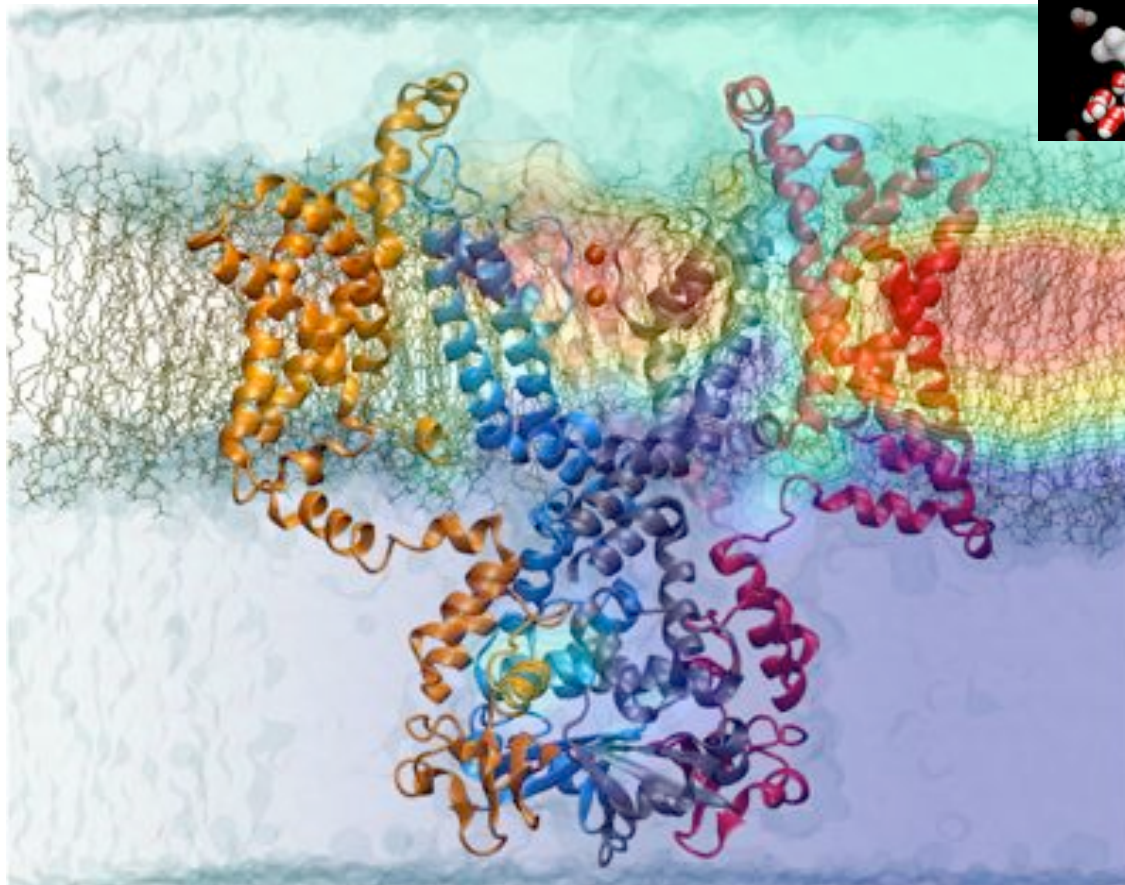
F. Khalili-Araghi, V. Jogini,
V. Yarov-Yarovoy,
E. Tajkhorshid,
B. Roux, and K. Schulten.
**Calculation of the gating charge for the
Kv1.2 voltage-activated potassium
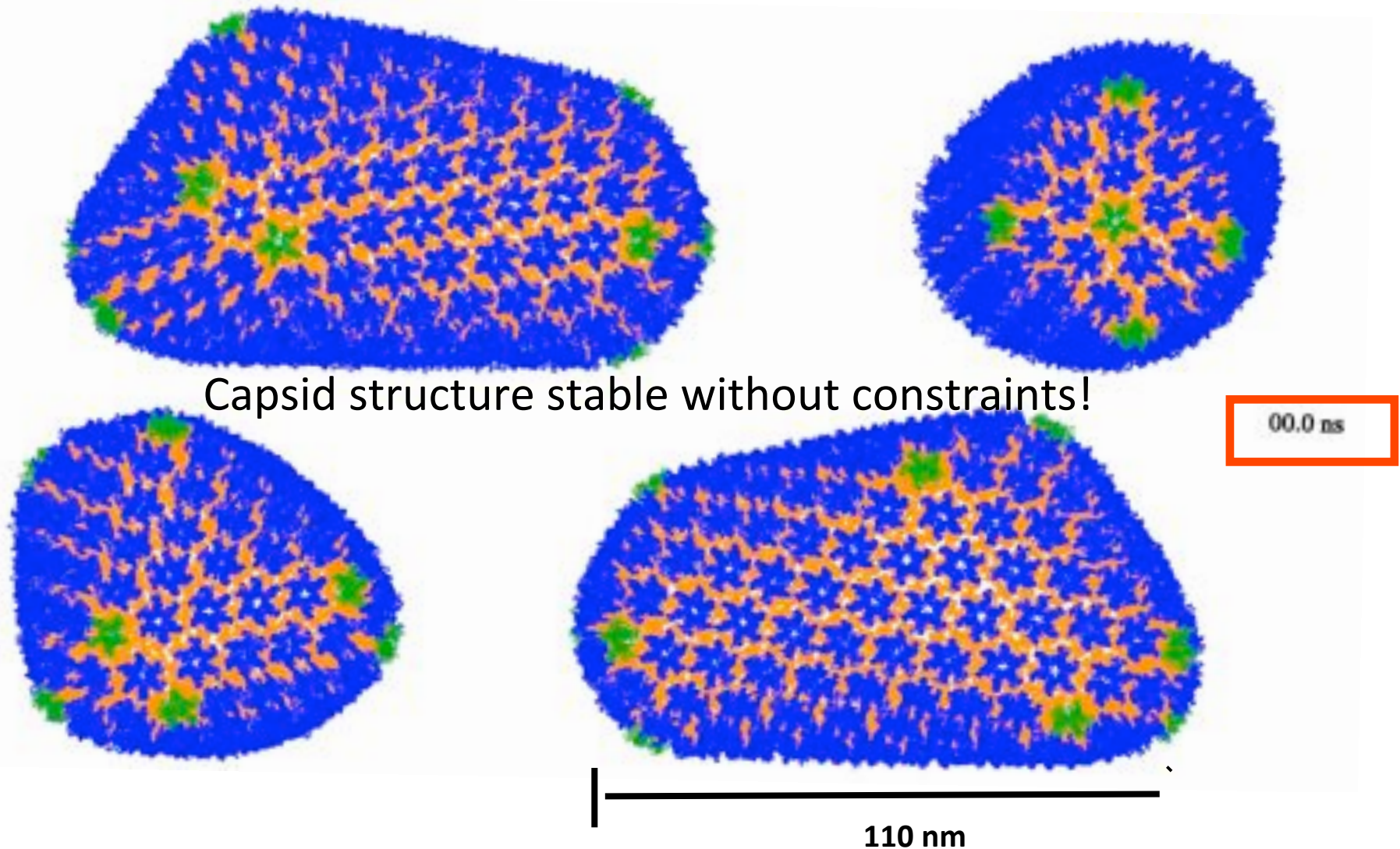channel.** *Biophysical Journal*,
98:2189-2198, 2010.

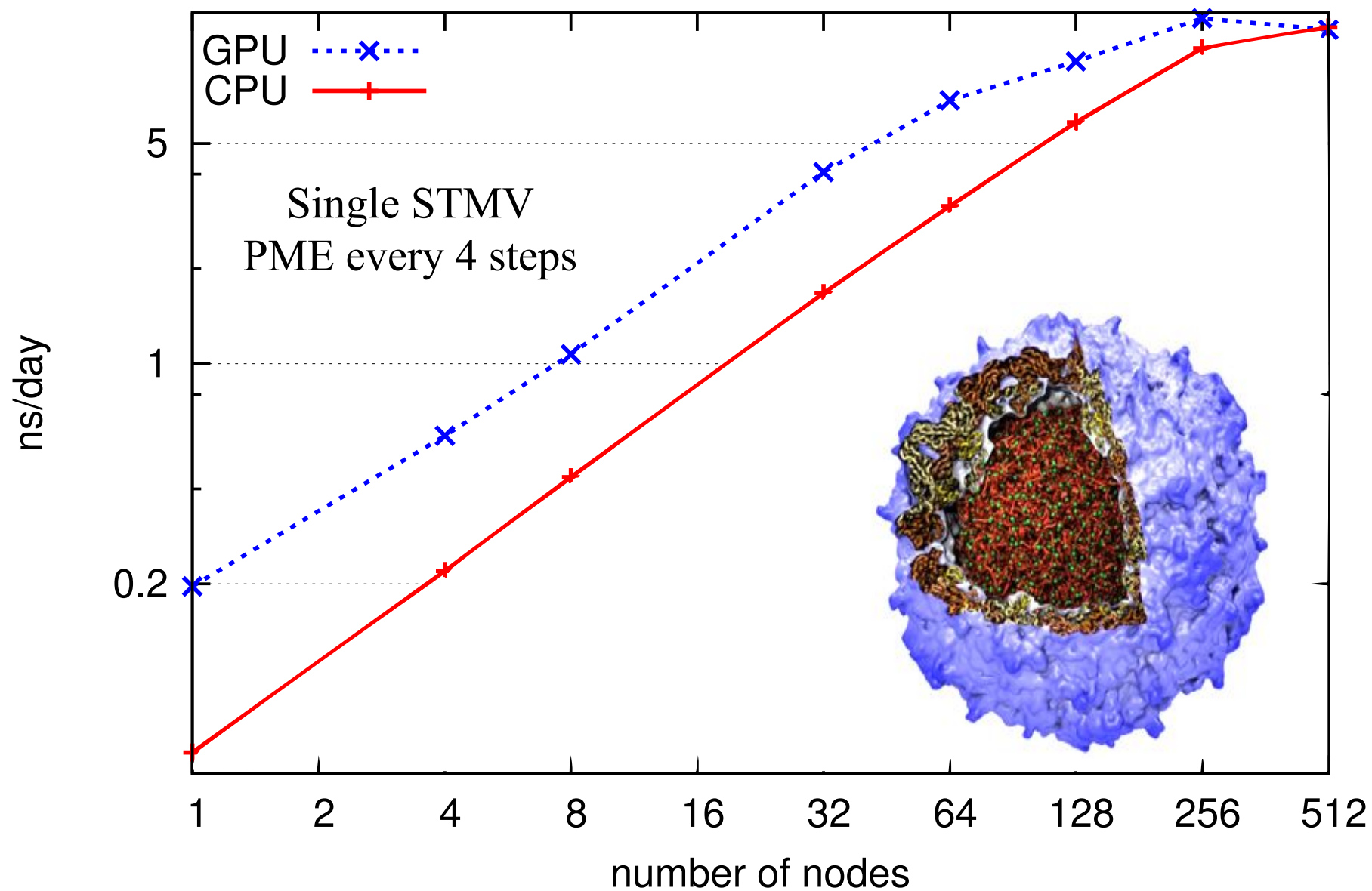350,000 atoms, 0.5 μs

From 100,000 to 64,000,000 Atom MD Now

- **all-atom structure of mature HIV capsid**
- **216 hexamers +12 pentamers, pdb 3J3Q**
- **64 million atoms total**
- **run on 2000 Cray-XK nodes (GPU accelerated) at 12 ns / day**

All-atom MD Simulation of HIV-1 Capsid

Capsid structure stable without constraints!

00.0 ns

110 nm

- 216 hexamers +12 pentamers, pdb 3J3Q (available May 29)
- 64 million atoms total
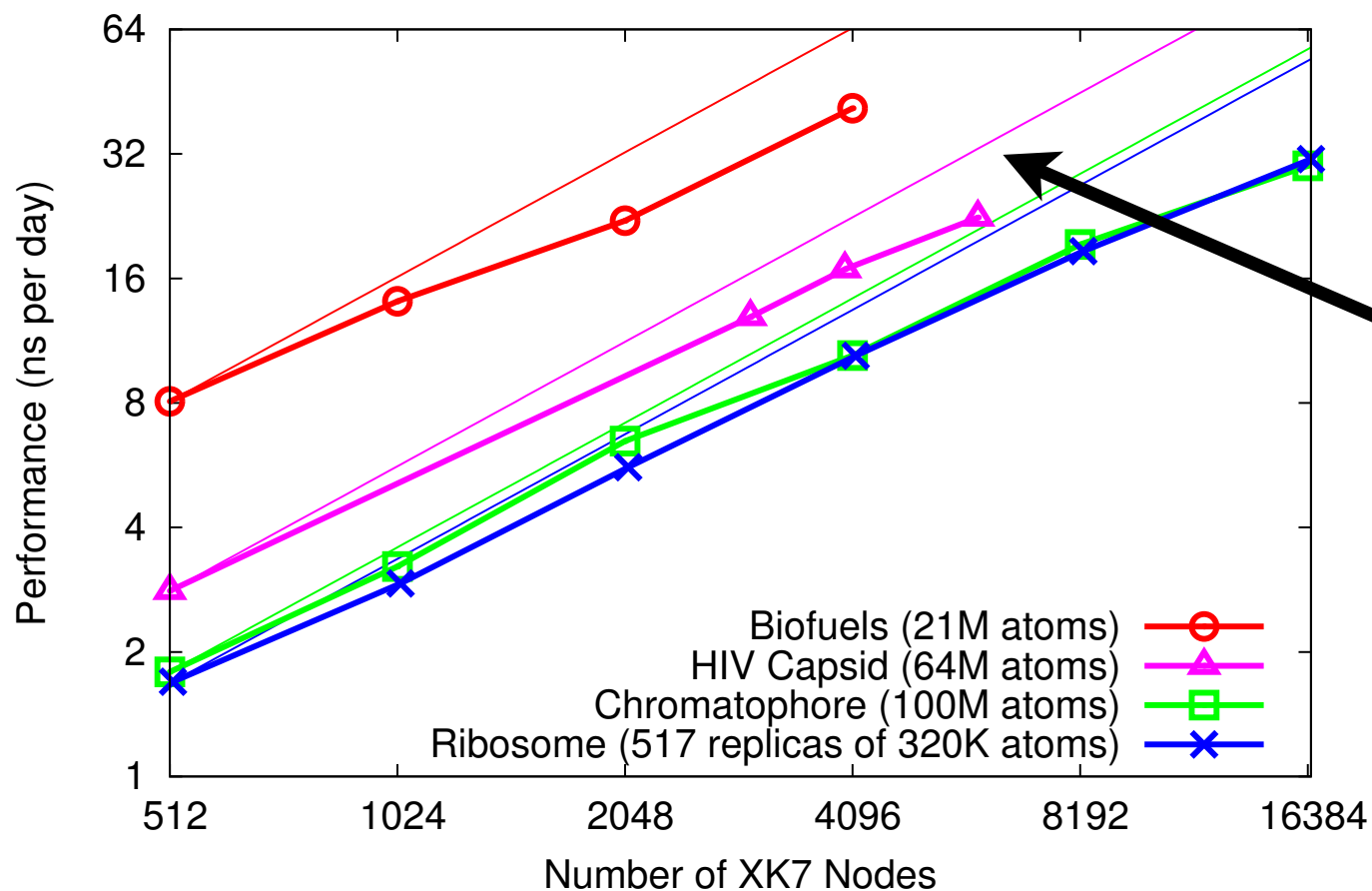- Over 100 ns of MD on NSF Blue Waters – 5000 Nodes, 160,000 cores - 10ns/day

1M Atom Virus on TitanDev GPU

GPU ····×····
CPU ——+——

Single STMV
PME every 4 steps

ns/day

5

1

0.2

1 2 4 8 16 32 64 128 256 512

number of nodes

NAMD Enables very Large Simulations on Titan Cray XK7 (2013)

NAMD on Titan Cray XK7 (2fs timestep with PME)

Performance (ns per day) vs Number of XK7 Nodes
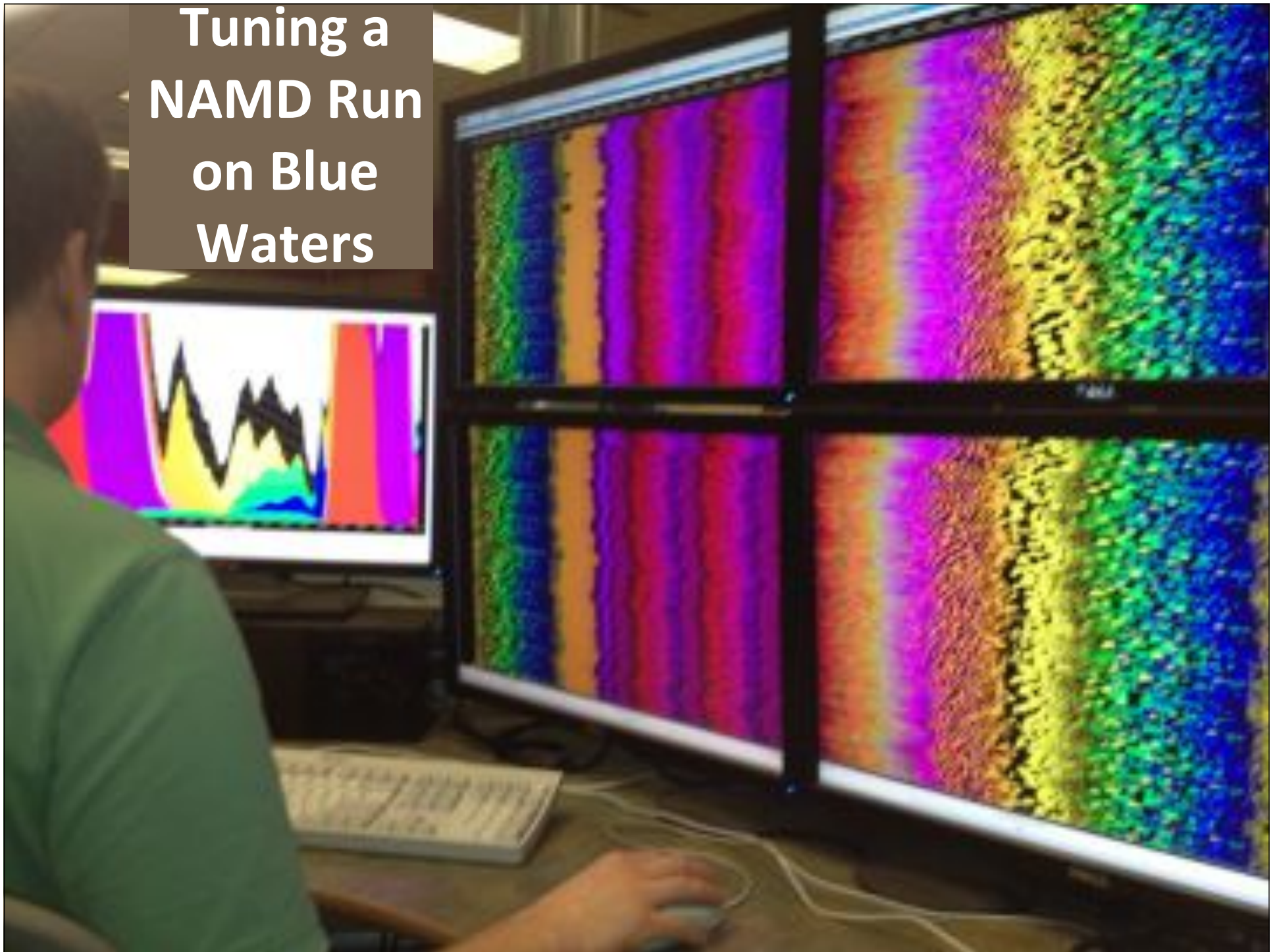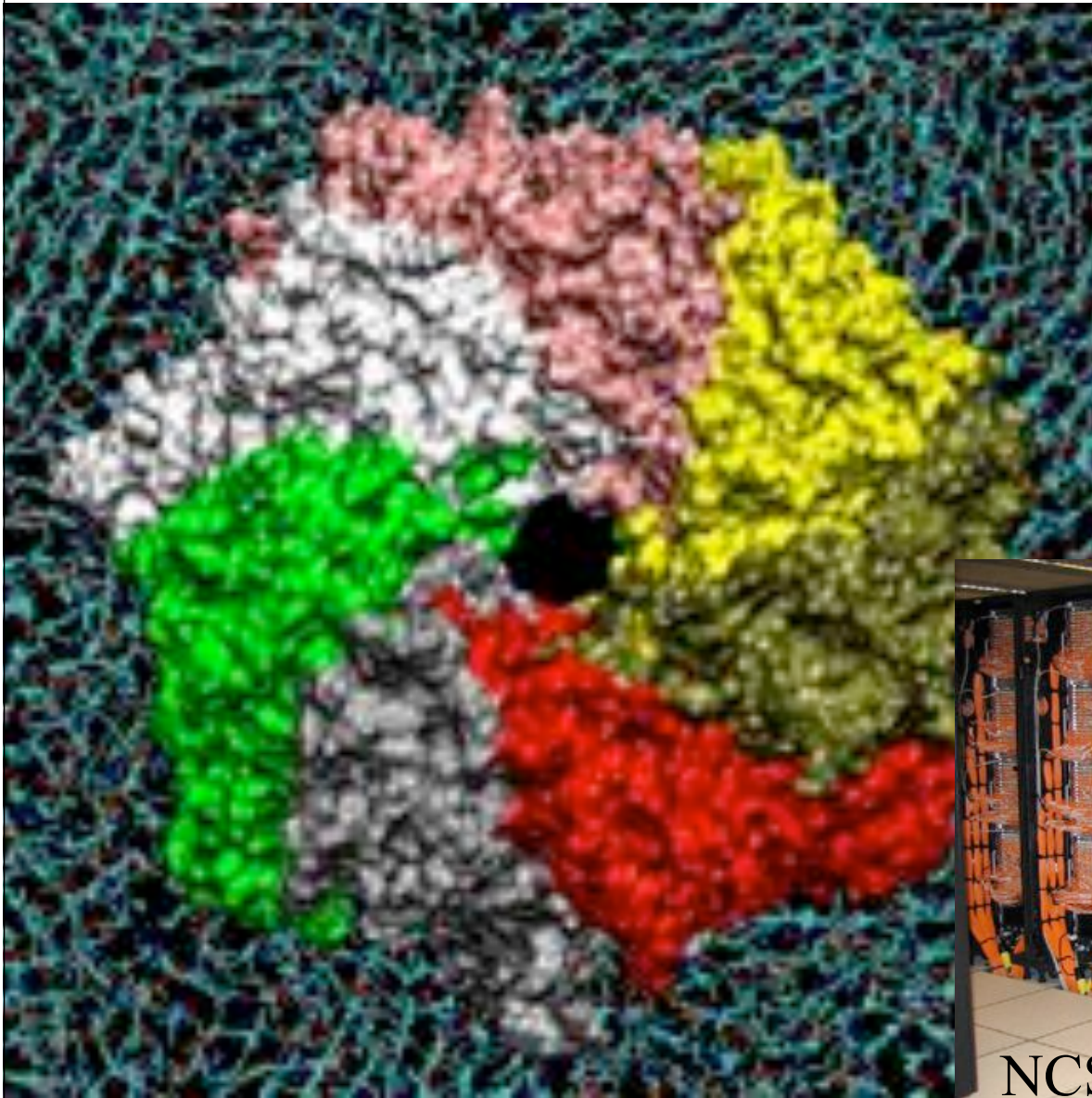
Legend:
- Biofuels (21M atoms) — red circles
- HIV Capsid (64M atoms) — magenta triangles
- Chromatophore (100M atoms) — green squares
- Ribosome (517 replicas of 320K atoms) — blue x

HIV

(2fs timestep)

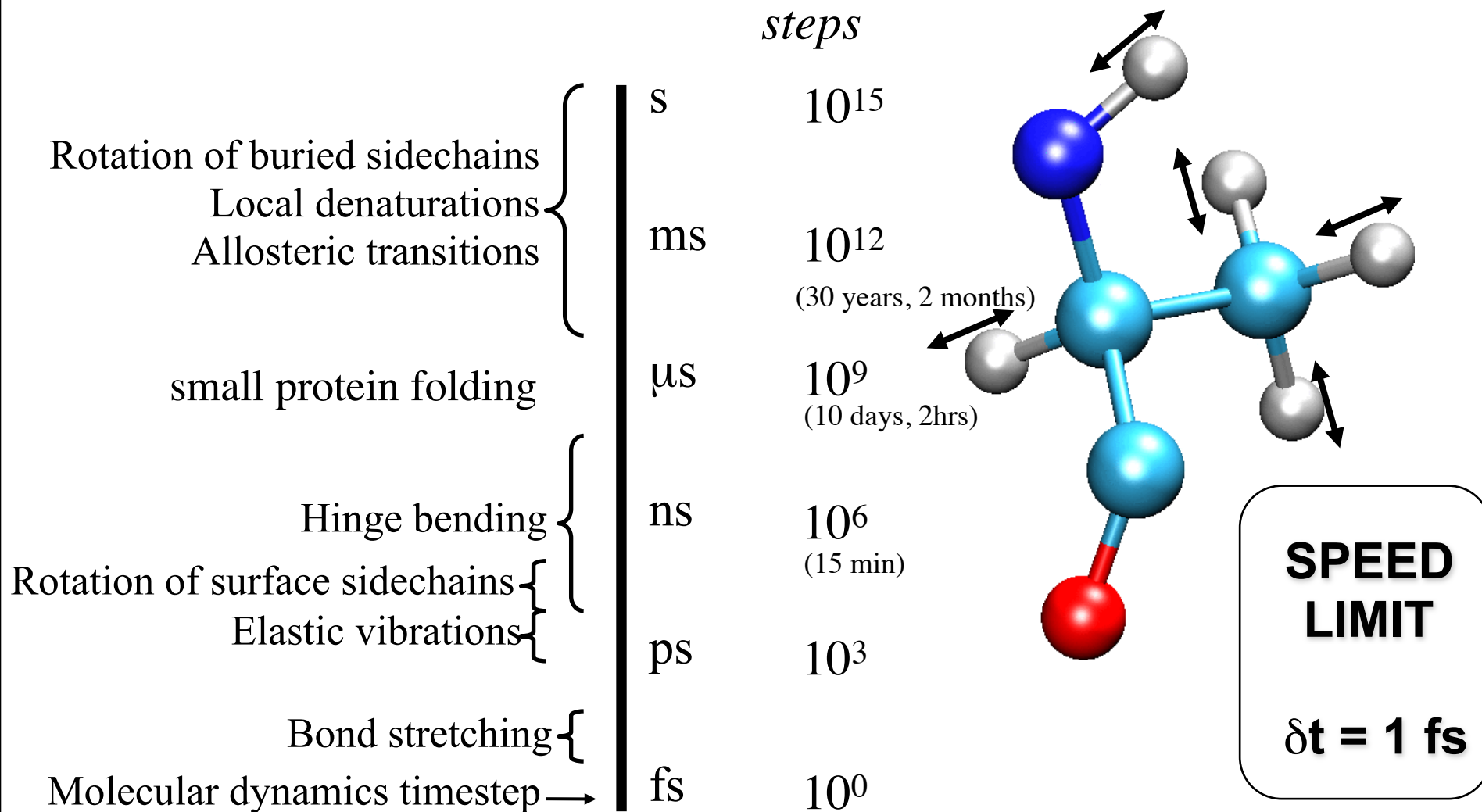Tuning a NAMD Run on Blue Waters

Large is no problem. But …

Molecular dynamics simu-
lation of alpha-hemolysin
with about 300,000 atoms;
10 million atom
simulations are routine
today, 200 million atom
simulations are possible.



NCSA machine room

But long is still a problem!
biomolecular timescale and timestep limits

steps

Rotation of buried sidechains	s	10^{15}
Local denaturations		
Allosteric transitions	ms	10^{12}
		(30 years, 2 months)
small protein folding	μs	10^9
		(10 days, 2hrs)
Hinge bending	ns	10^6
Rotation of surface sidechains		(15 min)
Elastic vibrations	ps	10^3
Bond stretching		
Molecular dynamics timestep $\rightarrow$	fs	10^0

SPEED LIMIT

δ**t = 1 fs**

(NSF center, Shaw Res.)

Protein Folding

- Protein **misfolding** responsible for diseases:
  - Alzheimer's
  - Parkinson's
  - Huntington
  - Mad cow
  - Type II diabetes
  - ...
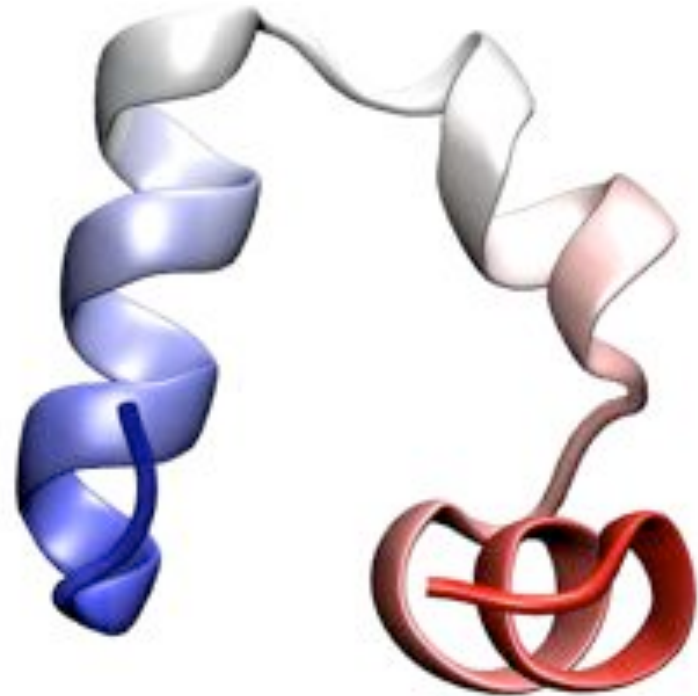
**villin headpiece
3 months on 329 CPUs**

Observe folding process in unprecedented detail
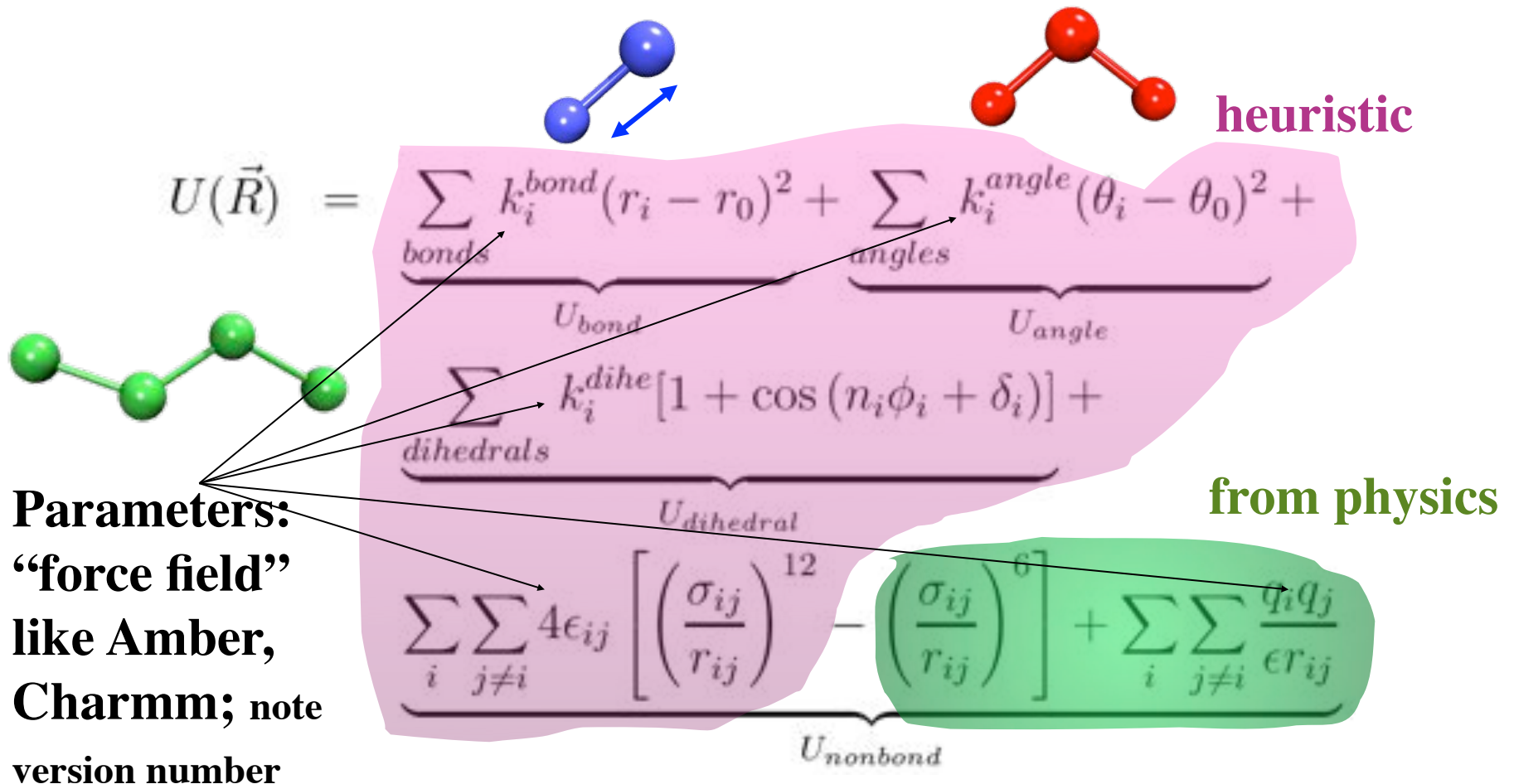
PDB Files

gives one the structure and starting position

- Simulations start with a crystal structure from the Protein Data Bank, in the standard PDB file format.

- PDB files contain standard records for species, tissue, authorship, citations, sequence, secondary structure, etc.

- We only care about the atom records…

  – atom name (N, C, CA)

  – residue name (ALA, HIS)

  – residue id (integer)

  – coordinates (x, y, z)

  – occupancy (0.0 to 1.0)

  – temp. factor (a.k.a. beta)

  – segment id (6PTI)

- No hydrogen atoms!

  (We must add them ourselves.)
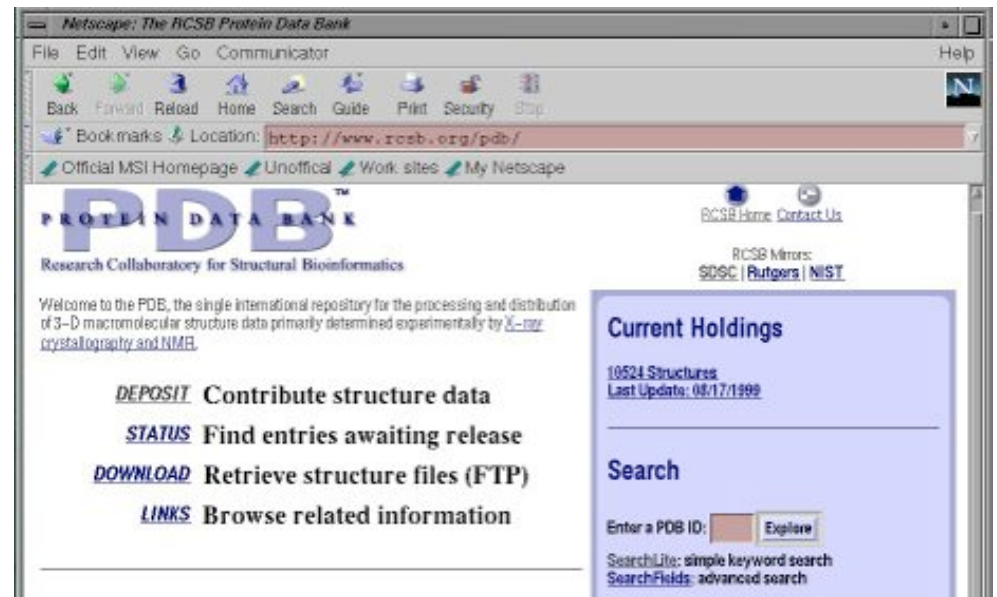
Potential Energy Function
of Biopolymer

- Simple, fixed algebraic form for every type of interaction.
- Variable parameters depend on types of atoms involved.

heuristic

$$U(\vec{R}) = \underbrace{\sum_{bonds} k_i^{bond}(r_i - r_0)^2}_{U_{bond}} + \underbrace{\sum_{angles} k_i^{angle}(\theta_i - \theta_0)^2}_{U_{angle}} +$$

$$\underbrace{\sum_{dihedrals} k_i^{dihe}[1 + \cos(n_i\phi_i + \delta_i)]}_{U_{dihedral}} +$$

from physics

$$\underbrace{\sum_i \sum_{j \neq i} 4\epsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^6\right] + \sum_i \sum_{j \neq i} \frac{q_i q_j}{\epsilon r_{ij}}}_{U_{nonbond}}$$

Parameters: "force field" like Amber, Charmm; note version number

PSF Files

- Every atom in the simulation is listed.
- Provides all static atom-specific values:
  - atom name (N, C, CA)
  - atom type (NH1, C, CT1)
  - residue name (ALA, HIS)
  - residue id (integer)
  - segment id (6PTI)
  - atomic mass (in atomic mass units)
  - partial charge (in electronic charge units)
- What is not in the PSF file?
  - coordinates (dynamic data, initially read from PDB file)
  - velocities (dynamic data, initially from Boltzmann distribution)
  - force field parameters (non-specific, used for many molecules)

Ala

HN

N

HB1

CB

HB2

CA

HA

C

HB3

O
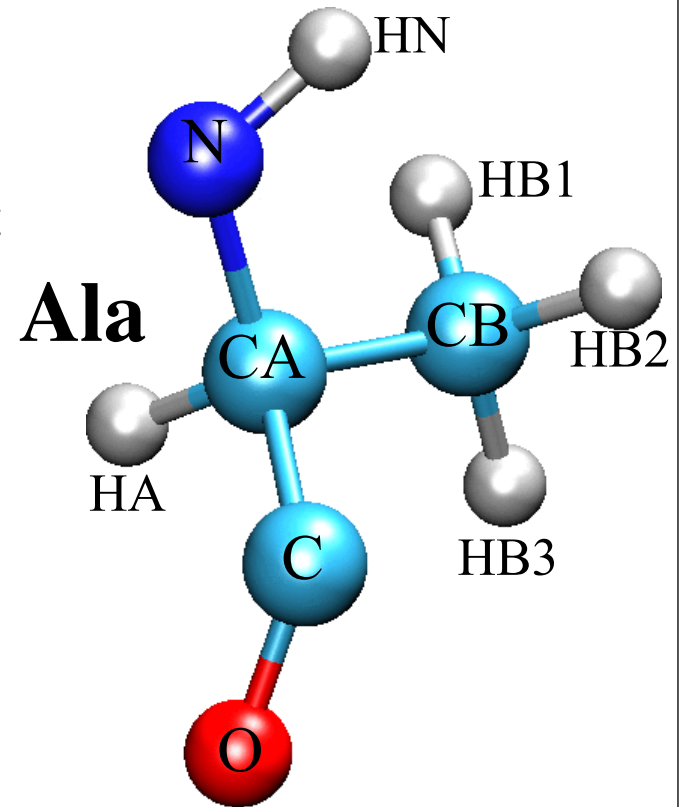
PSF Files
molecular structure (bonds, angles, etc.)
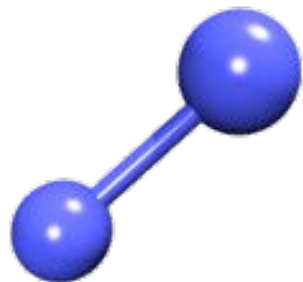
Bonds: Every pair of covalently bonded atoms is listed.

Angles: Two bonds that share a common atom form an angle. Every such set of three atoms in the molecule is listed.
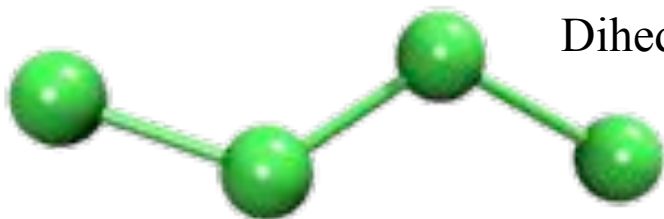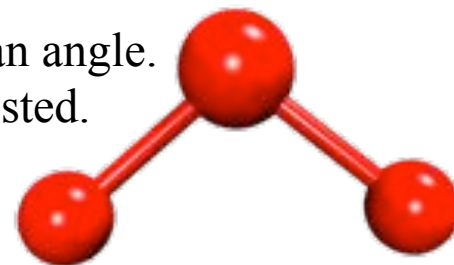
Dihedrals: Two angles that share a common bond form a dihedral. Every such set of four atoms in the molecule is listed.

Impropers: Any *planar* group of four atoms forms an improper. Every such set of four atoms in the molecule is listed.
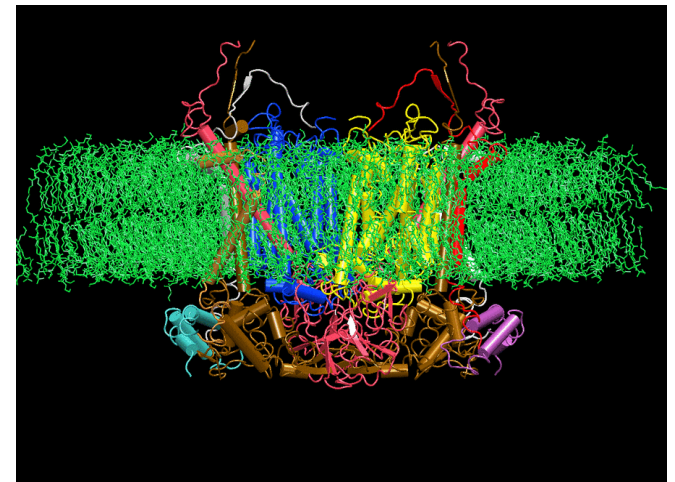
Preparing Your System for MD
Solvation

Biological activity is the result of interactions between molecules and occurs at the interfaces between molecules (protein-protein, protein-DNA, protein-solvent, DNA-solvent, etc).

mitochondrial bc1 complex

Why model solvation?
• many biological processes occur in aqueous solution
• solvation effects play a crucial role in determining molecular conformation, electronic properties, binding energies, etc

How to model solvation?
• explicit treatment: solvent molecules are added to the molecular system
• implicit treatment: solvent is modeled as a continuum dielectric or so-called implicit force field

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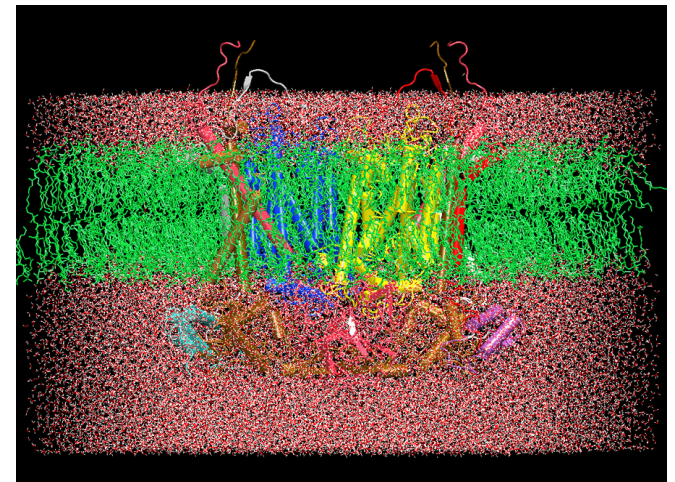
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mitochondrial bc1 complex

(Usually periodic! Avoids surface effects)

From the Mountains to the Valleys
how to actually describe a protein

Initial coordinates have bad contacts, causing high energies and forces (due to averaging in observation, crystal packing, or due to difference between theoretical and actual forces)

Minimization finds a nearby local minimum.

Heating and cooling or equilibration at fixed temperature permits biopolymer to escape local minima with

Energy

kT

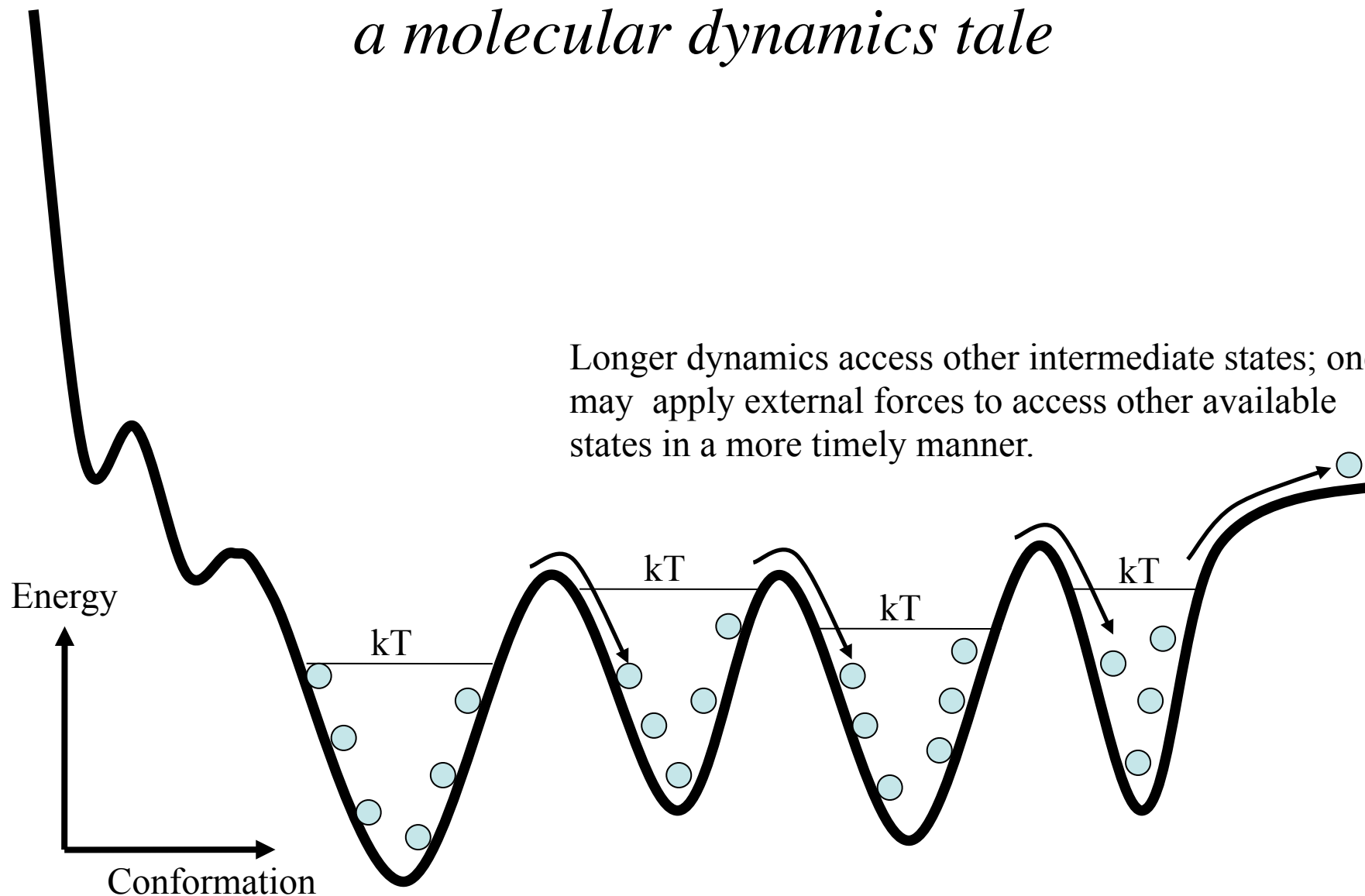Initial dynamics samples thermally accessible states.

Conformation
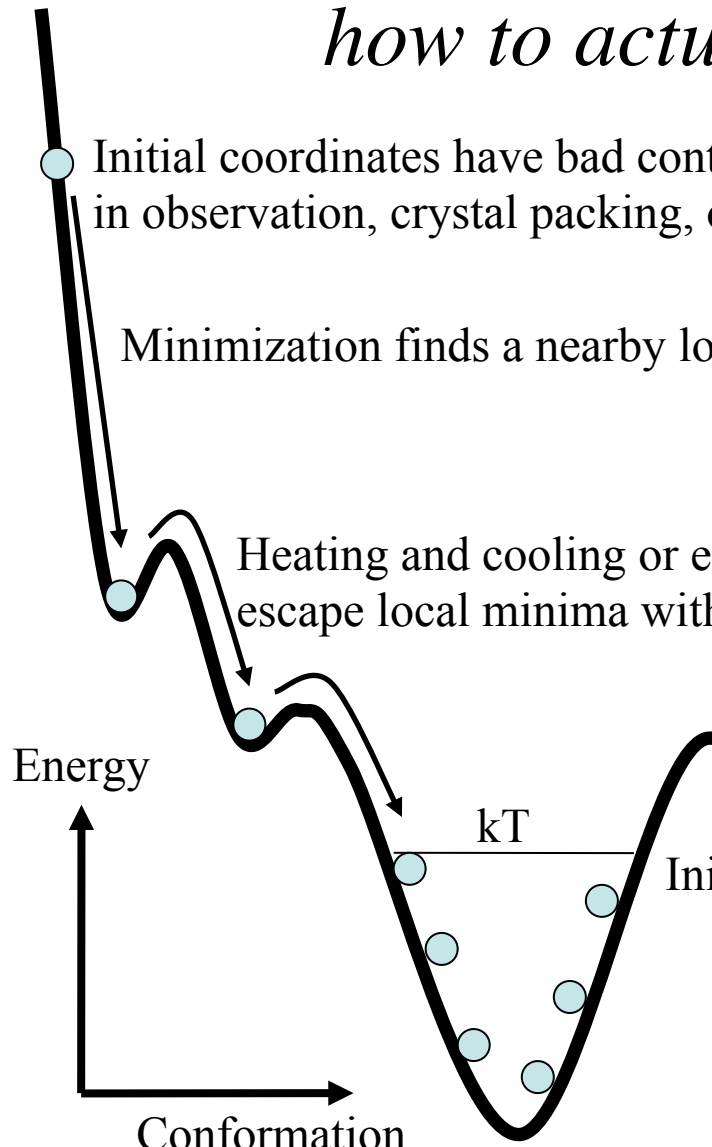
From the Mountains to the Valleys
a molecular dynamics tale

Longer dynamics access other intermediate states; one may apply external forces to access other available states in a more timely manner.

Energy

Conformation

kT

kT

kT

kT

kT

Cutting Corners
cutoffs, PME, rigid bonds, and multiple timesteps

- Nonbonded interactions require order N^2 computer time!

    - Truncating at R_{cutoff} reduces this to order $N\ R_{cutoff}^3$

    - Particle mesh Ewald (PME) method adds long range electrostatics at order $N \log N$, only minor cost compared to cutoff calculation.

- Can we extend the timestep, and do this work fewer times?

    - Bonds to hydrogen atoms, which require a 1fs timestep, can be held at their equilibrium lengths, allowing 2fs steps.

    - Long range electrostatics forces vary slowly, and may be evaluated less often, such as on every second or third step.

- Coarse Graining
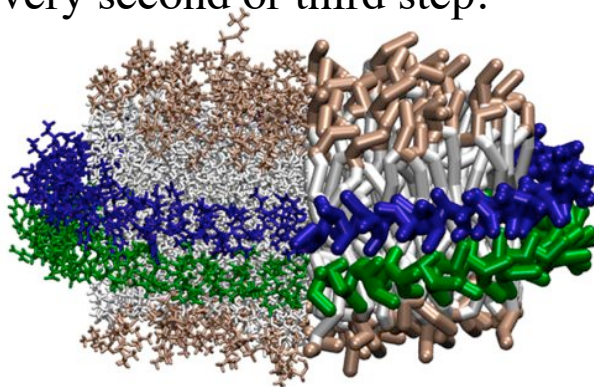
Residue-Based Coarse-Grained Model

- Protein model uses two CG beads per residue
- One CG bead per side chain another for backbone
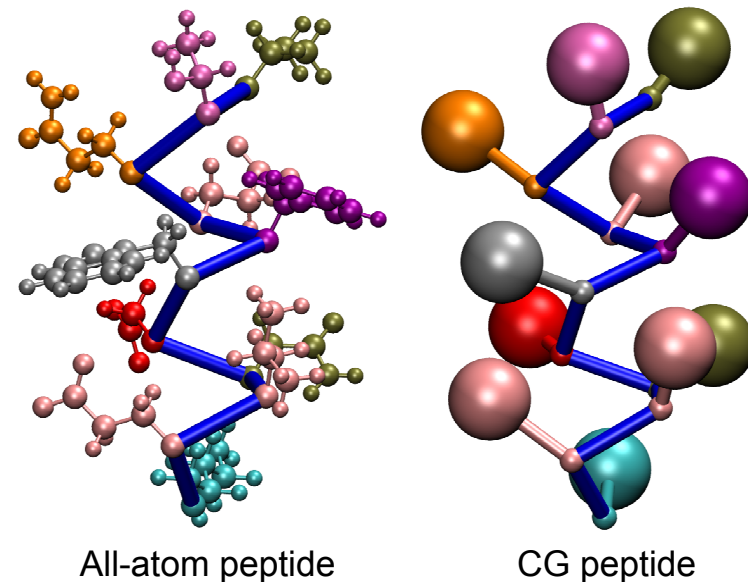
All-atom peptide   CG peptide

- Lipid model: MARTINI
- Level of coarse-graining: ~4 heavy atoms per CG bead
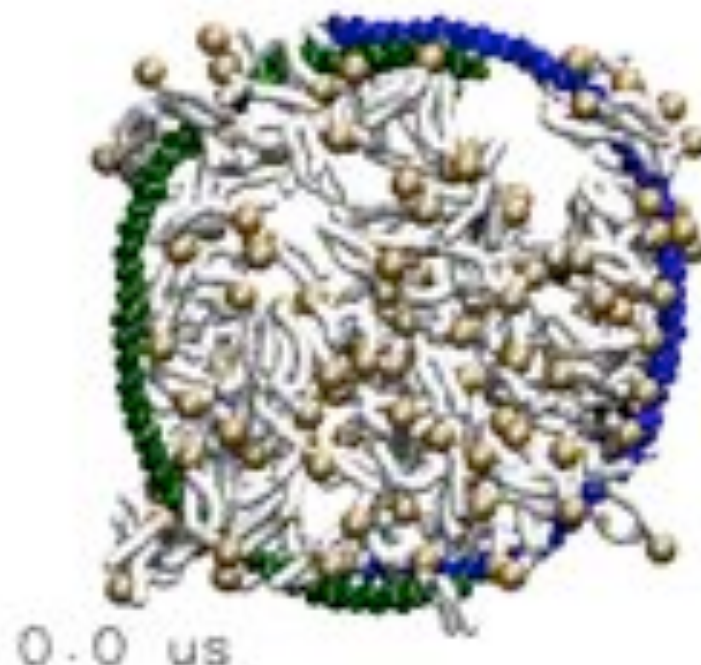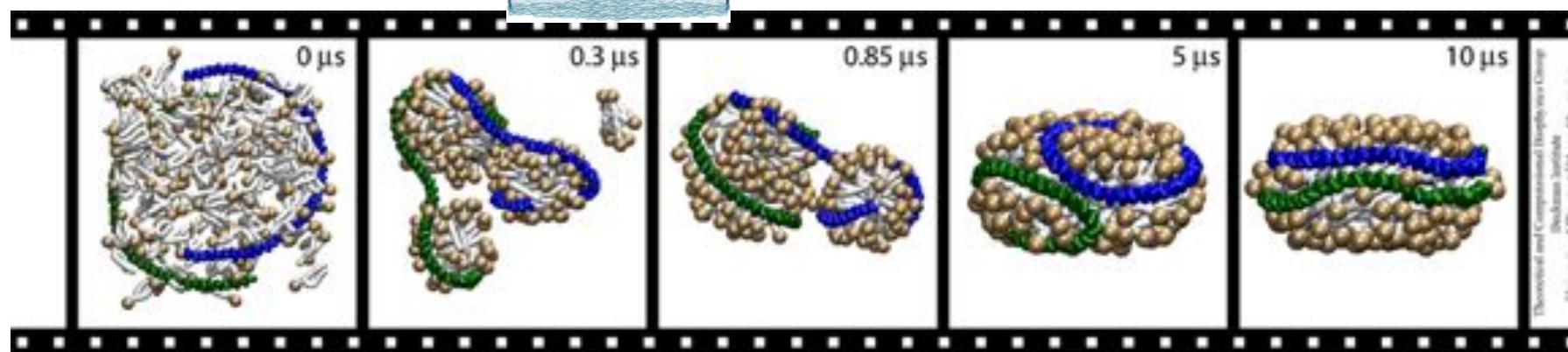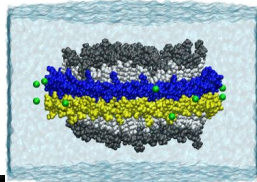- Interactions parameterized based on experimental data and thermodynamic properties of small molecules

Peter L. Freddolino, Anton Arkhipov, Amy Y. Shih, Ying Yin, Zhongzhou Chen, and Klaus Schulten. **Application of residue-based and shape-based coarse graining to biomolecular simulations.** In Gregory A. Voth, editor, *Coarse-Graining of Condensed Phase and Biomolecular Systems*, chapter 20, pp. 299-315. Chapman and Hall/CRC Press, Taylor and Francis Group, 2008.

Nanodisc Assembly CG MD Simulation

- 10 μs simulation

- Assembly proceeds in two steps:
  - Aggregation of proteins and lipids driven by the hydrophobic effect
  - Optimization of the protein structure driven by increasingly specific protein-protein interactions

- Formation of the generally accepted double-belt model for discoidal HDL

Fully hydrated

0.0 us

| 0 μs | 0.3 μs | 0.85 μs | 5 μs | 10 μs |

A. Shih, A. Arkhipov, P. Freddolino, and K. Schulten. *J. Phys. Chem. B*, 110:3674–3684, 2006; A. Shih, P. Freddolino, A. Arkhipov, and K. Schulten. *J. Struct. Biol.*, 157:579–592,2007; A. Shih, A. Arkhipov, P. Freddolino, S. Sligar, and K. Schulten. *Journal of Physical Chemistry B*, 111: 11095 - 11104, 2007; A. Shih, P. Freddolino, S. Sligar, and K. Schulten. *Nano Letters*, 7:1692-1696, 2007.

Validation of Simulations

reverse coarse-graining and small-angle X-ray scattering

reverse coarse-graining
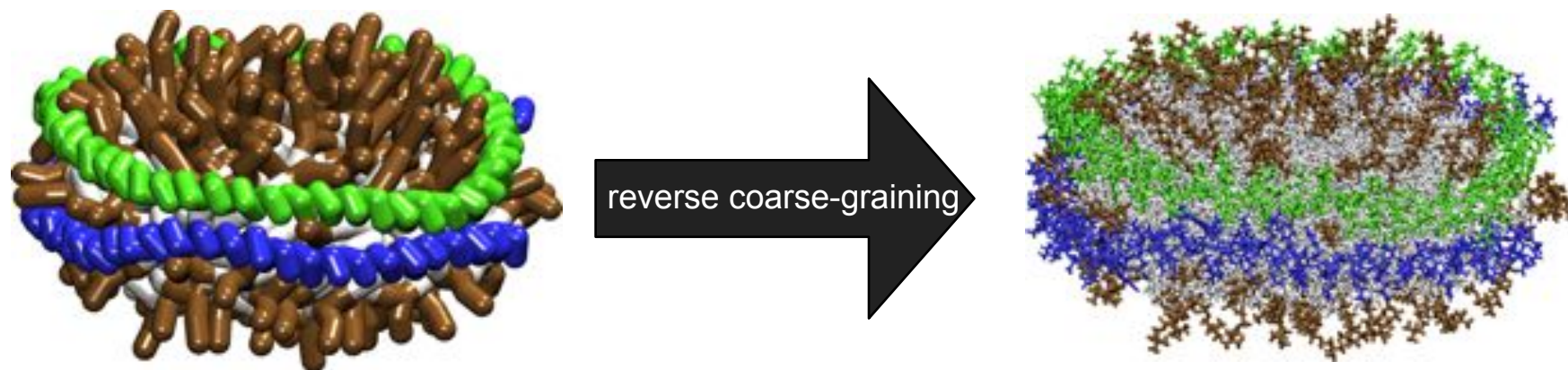
Reverse coarse-graining:
1. Map center of mass of the group of atoms represented by a single CG bead to that beads location
2. MD minimization, simulated annealing with restraints, and equilibration to get all-atom structure
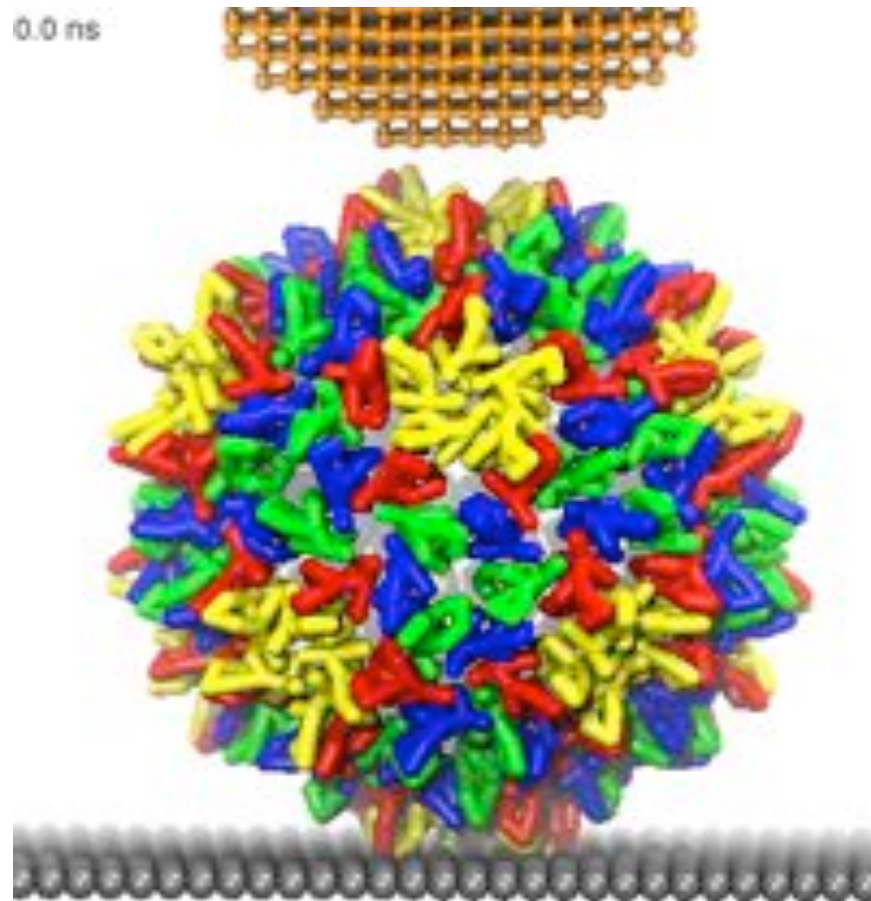
Small-angle X-ray scattering:
Calculated from reverse coarse-grained all-atom model and compared with experimental measurements

Experiments
— Nanodisc with DPPC lipids
— Nanodisc with DMPC lipids

Simulations
-- Idealized Nanodisc
-- Self-assmbled Nanodisc

$\log (I/I_o)$

Q, (Å^{-1})
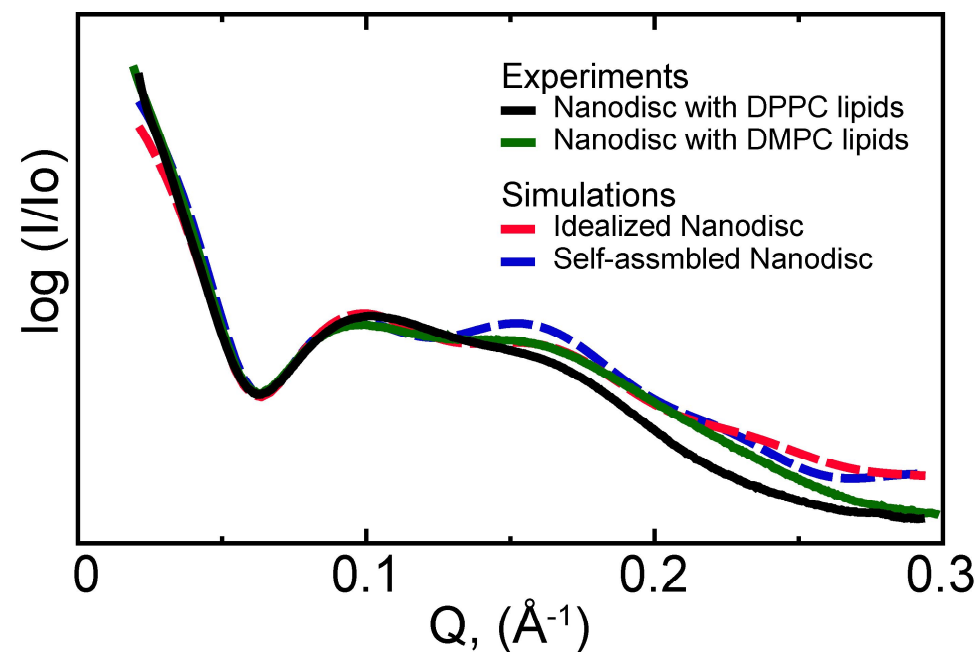
Shape-Based Coarse-Grained (CG) model

0.0 ns

Anton Arkhipov, Wouter H. Roos, Gijs J. L. Wuite, and Klaus Schulten. **Elucidating the mechanism behind irreversible deformation of viral capsids.** *Biophysical Journal*, 97, 2009. In press.
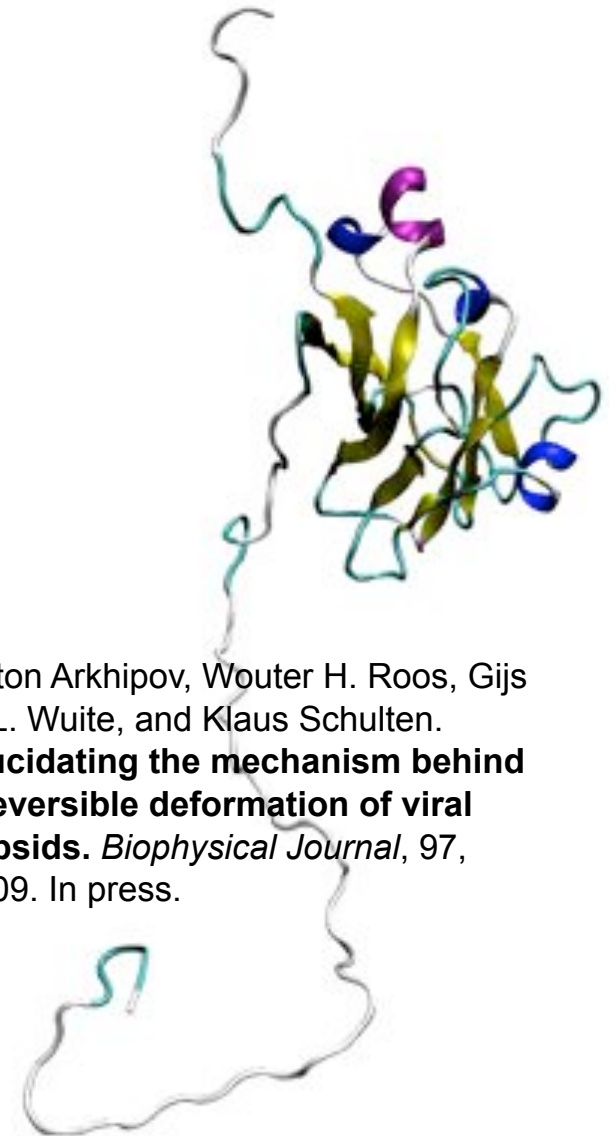
- **Fully automatic**
- **Number of CG beads is chosen by a user (we used ~200 atoms per CG bead)**

Peter L. Freddolino, Anton Arkhipov, Amy Y. Shih, Ying Yin, Zhongzhou Chen, and Klaus Schulten. **Application of residue-based and shape-based coarse graining to biomolecular simulations.** In Gregory A. Voth, editor, *Coarse-Graining of Condensed Phase and Biomolecular Systems*, chapter 20, pp. 299-315. Chapman and Hall/CRC Press, Taylor and Francis Group, 2008.

Virus Capsid Mechanics
Atomic Force Microscope

— **Hepatitis B Virus** —
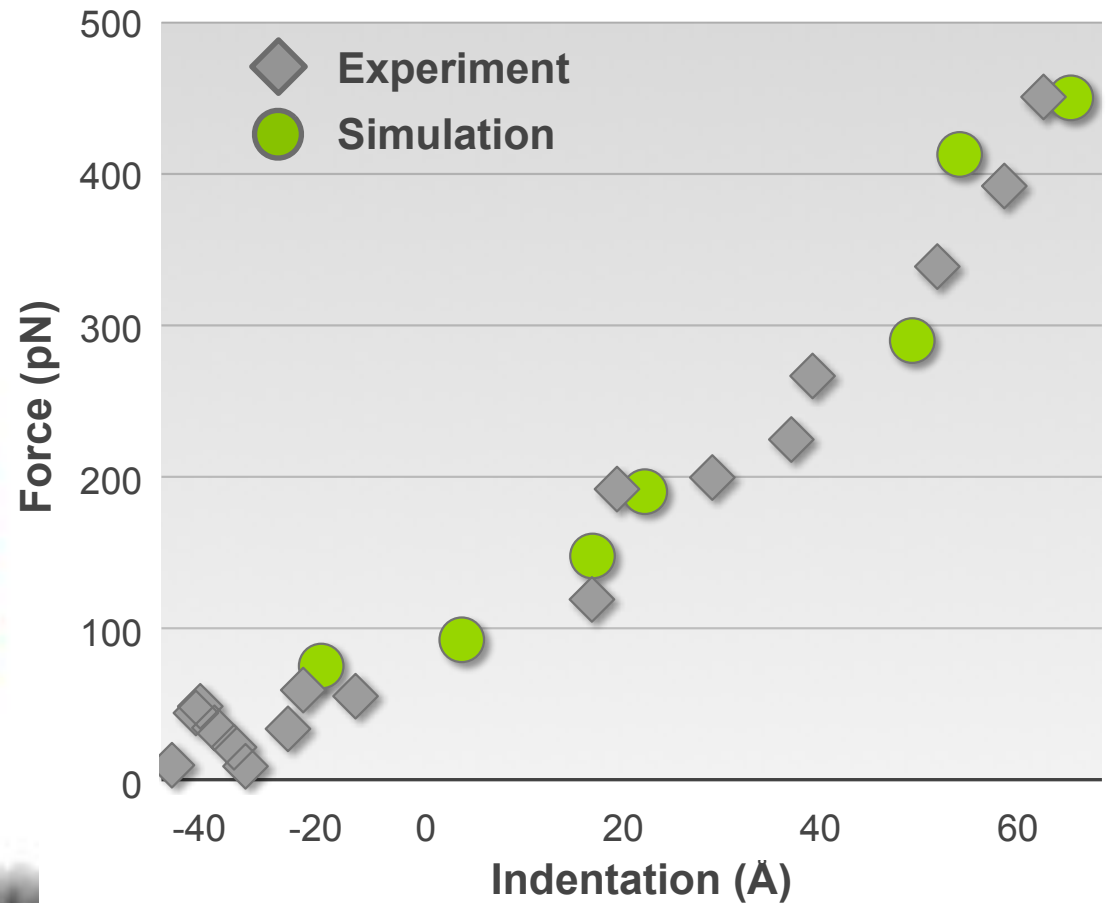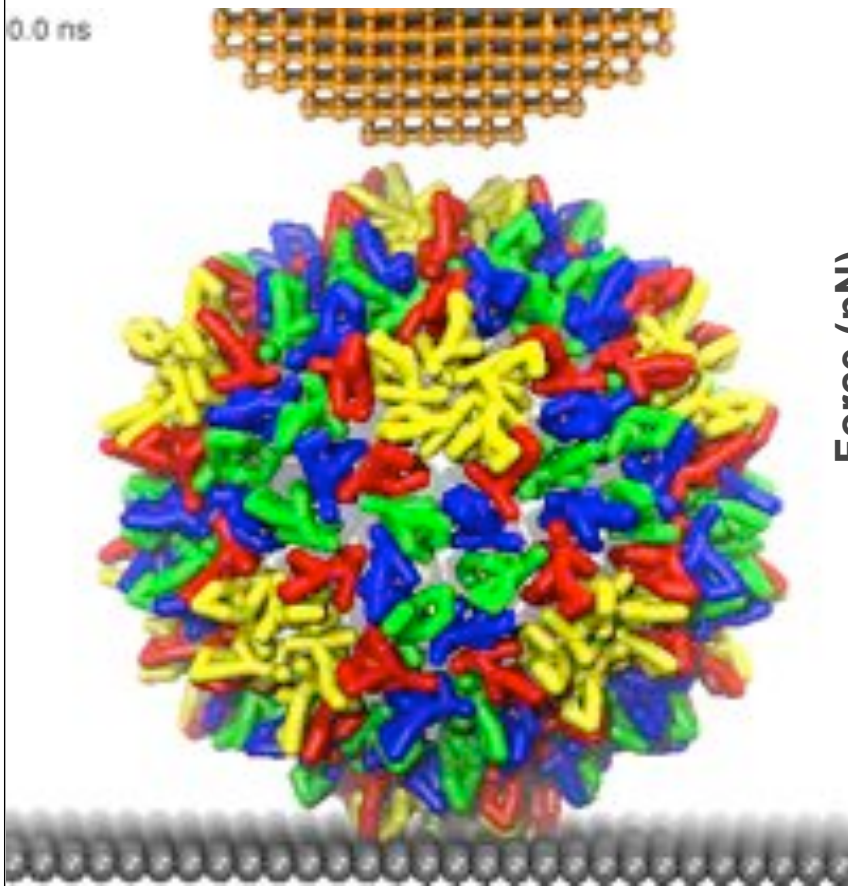
# Example: MD Simulations of the K+ Channel Protein

Ion channels are membrane - spanning proteins that form a pathway for the flux of inorganic ions across cell membranes.

Potassium channels are a particularly interesting class of ion channels, managing to distinguish with impressive fidelity between K^+ and Na^+ ions while maintaining a very high throughput of K^+ ions when gated.
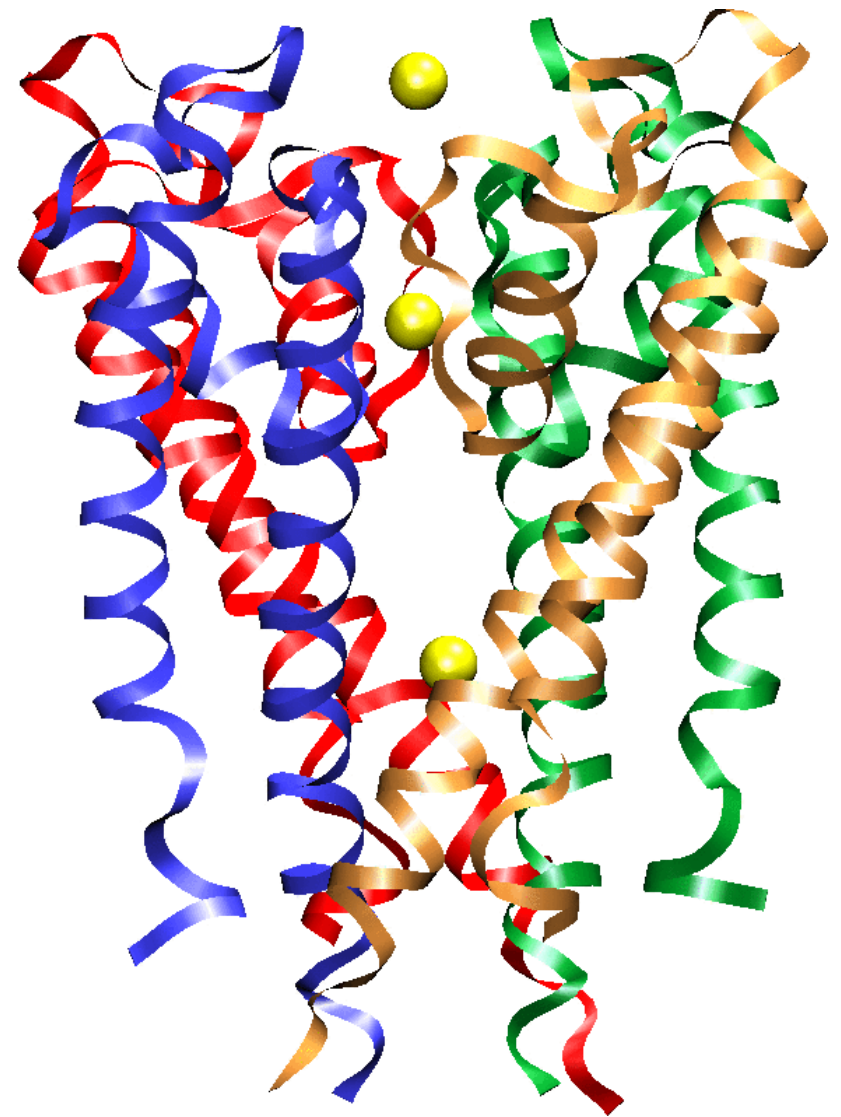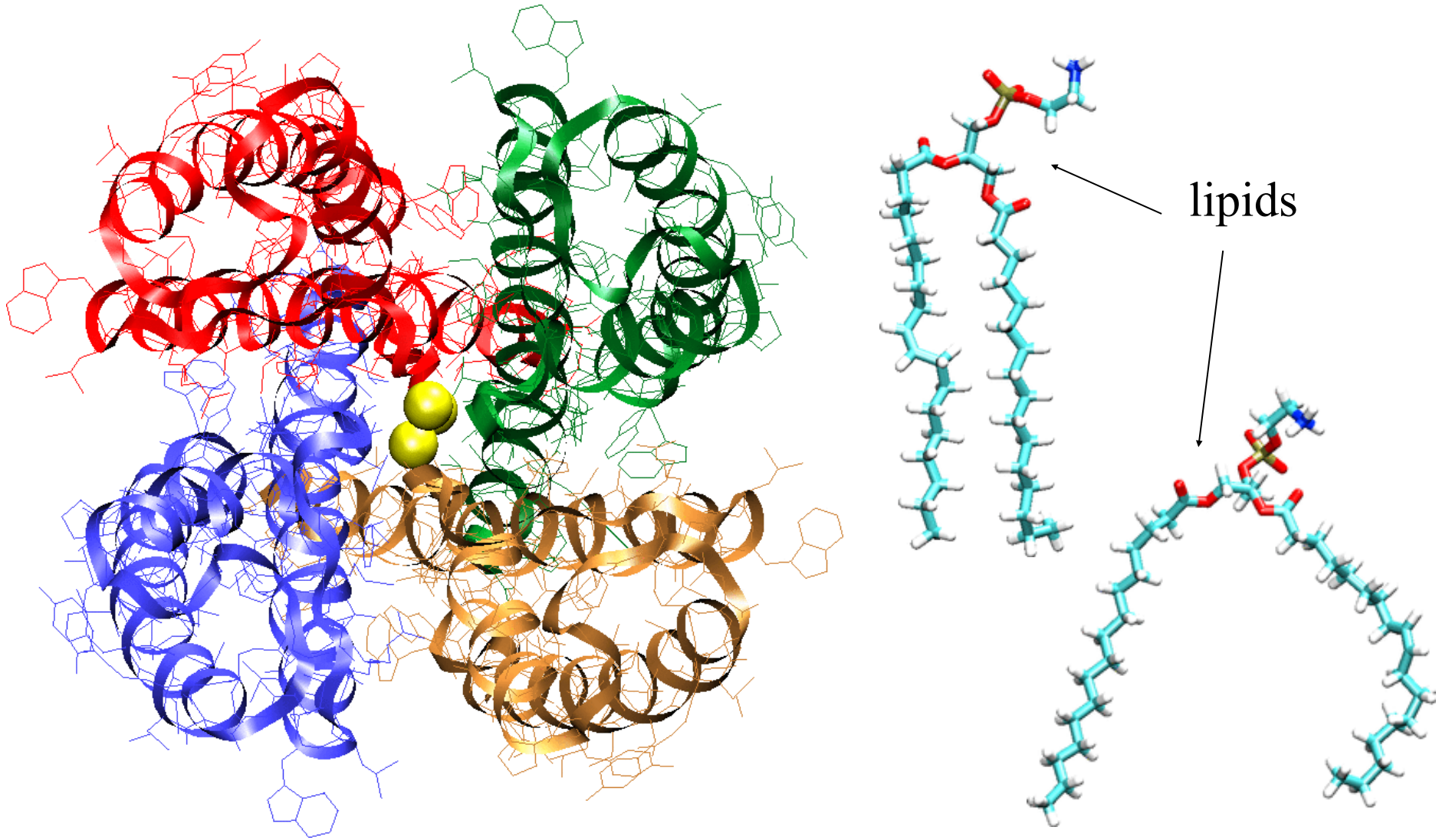
Setting up the system (1)
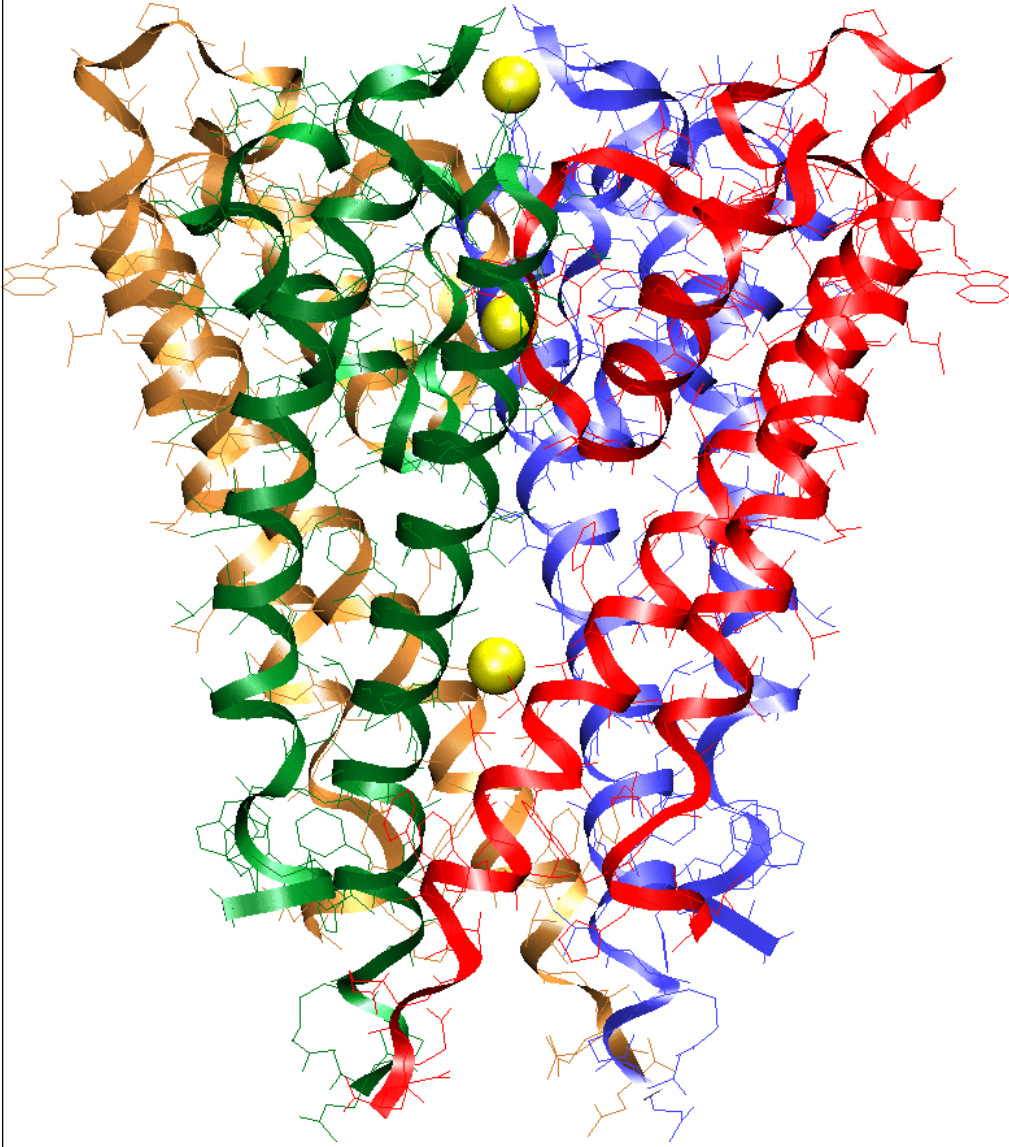
• retrieve the PDB (coordinates) file from the Protein Data Bank

• add hydrogen atoms using PSFGEN

• use psf and parameter files to set up the structure; needs to be better than available in Charmm to describe well the ions, e.g., K/Na ion selectivity or Ca^{++} ion

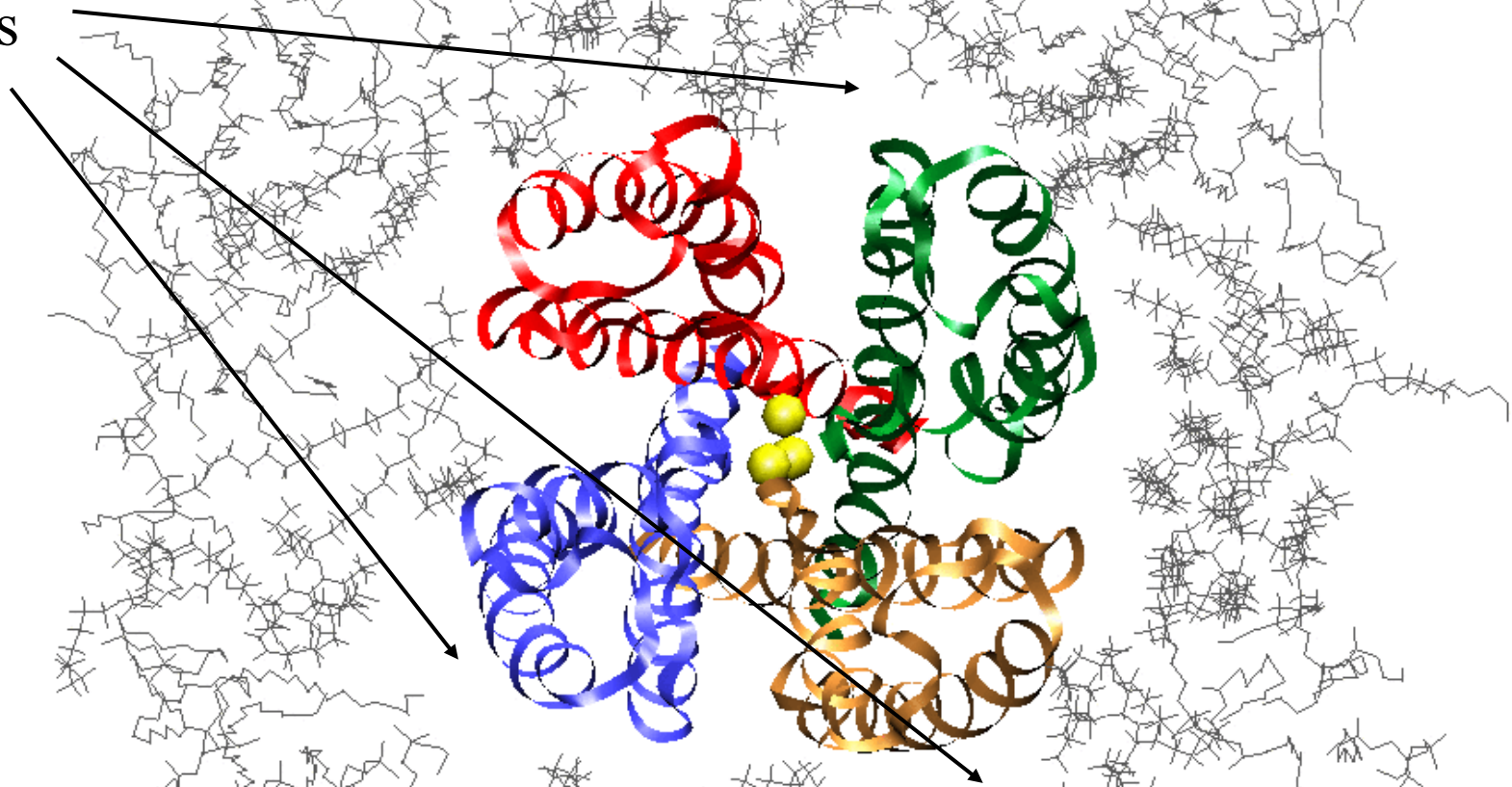• minimize the protein structure using NAMD2

Setting up the system (2)

lipids

Simulate the protein in its natural environment: solvated lipid bilayer

Setting up the system (3)
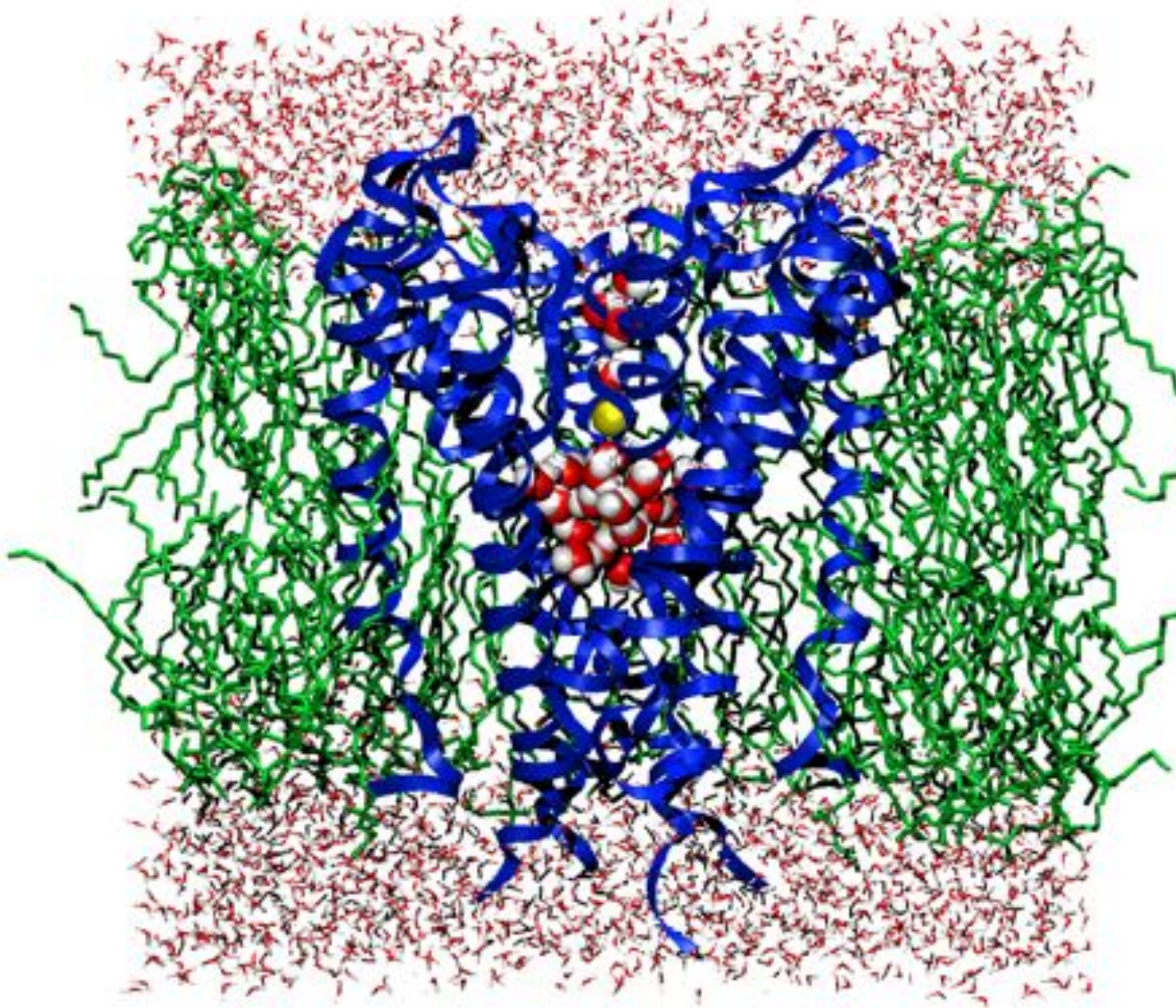## Inserting the protein in the lipid bilayer

gaps

Automatic insertion into the lipid bilayer leads to big gaps between the protein and the membrane => long equilibration time required to fill the gaps. Solution: manually adjust the position of lipids around the protein. Employ constant (lateral and normal) pressure control.

The system

Kcsa channel protein (in blue) embedded in a (3:1) POPE/POPG lipid bilayer. Water molecules inside the channel are shown in vdW representation.

solvent
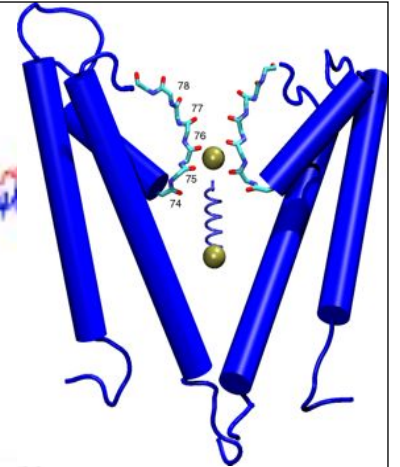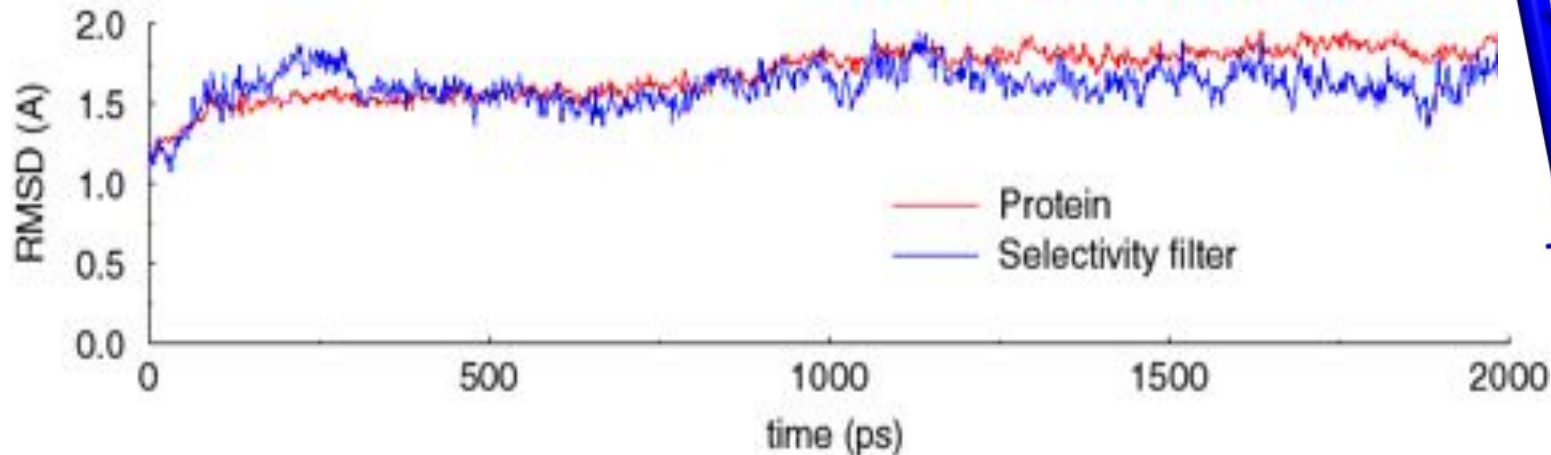
Simulating the system:
Free MD

Summary of simulations:
• protein/membrane system contains 38,112 atoms, including 5117 water molecules, 100 POPE and 34 POPG lipids, plus K^+ counterions
• CHARMM26 forcefield
• periodic boundary conditions, PME electrostatics
• 1 ns equilibration at 310K, NpT
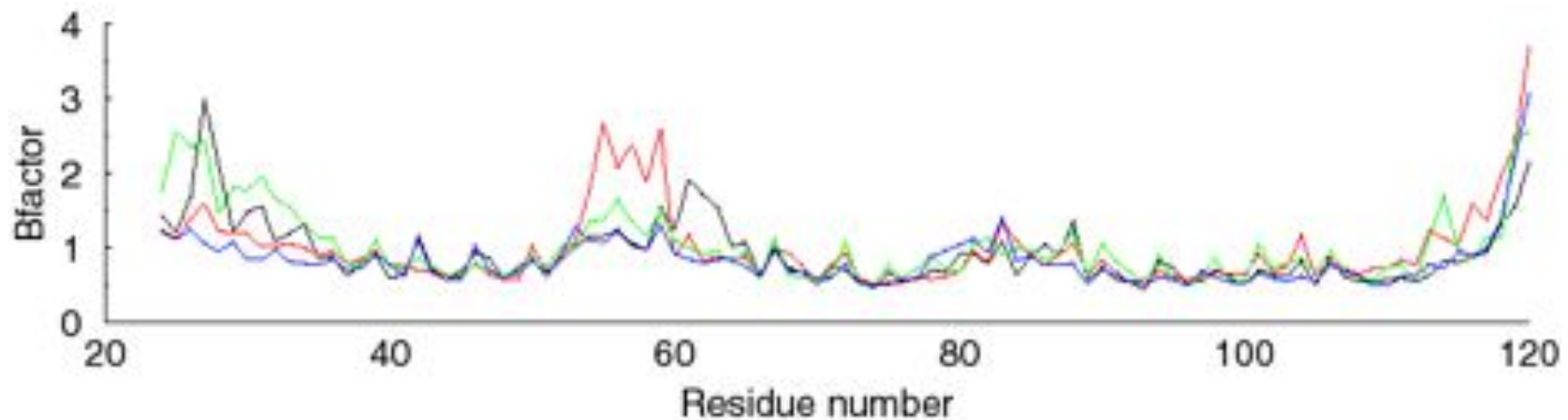• 2 ns dynamics, NpT

Program: NAMD2

Platform: Cray T3E (Pittsburgh Supercomputer Center) or local computer cluster; choose ~1000 atoms per processor.

MD Results

RMS deviations for the KcsA protein and its selectivity filer indicate that the protein is stable during the simulation with the selectivity filter the most stable part of the system.

Temperature factors for individual residues in the four monomers of the KcsA channel protein indicate that the most flexible parts of the protein are the N and C terminal ends, residues 52-60 and residues 84-90. Residues 74-80 in the selectivity filter have low temperature factors and are very stable during the simulation.
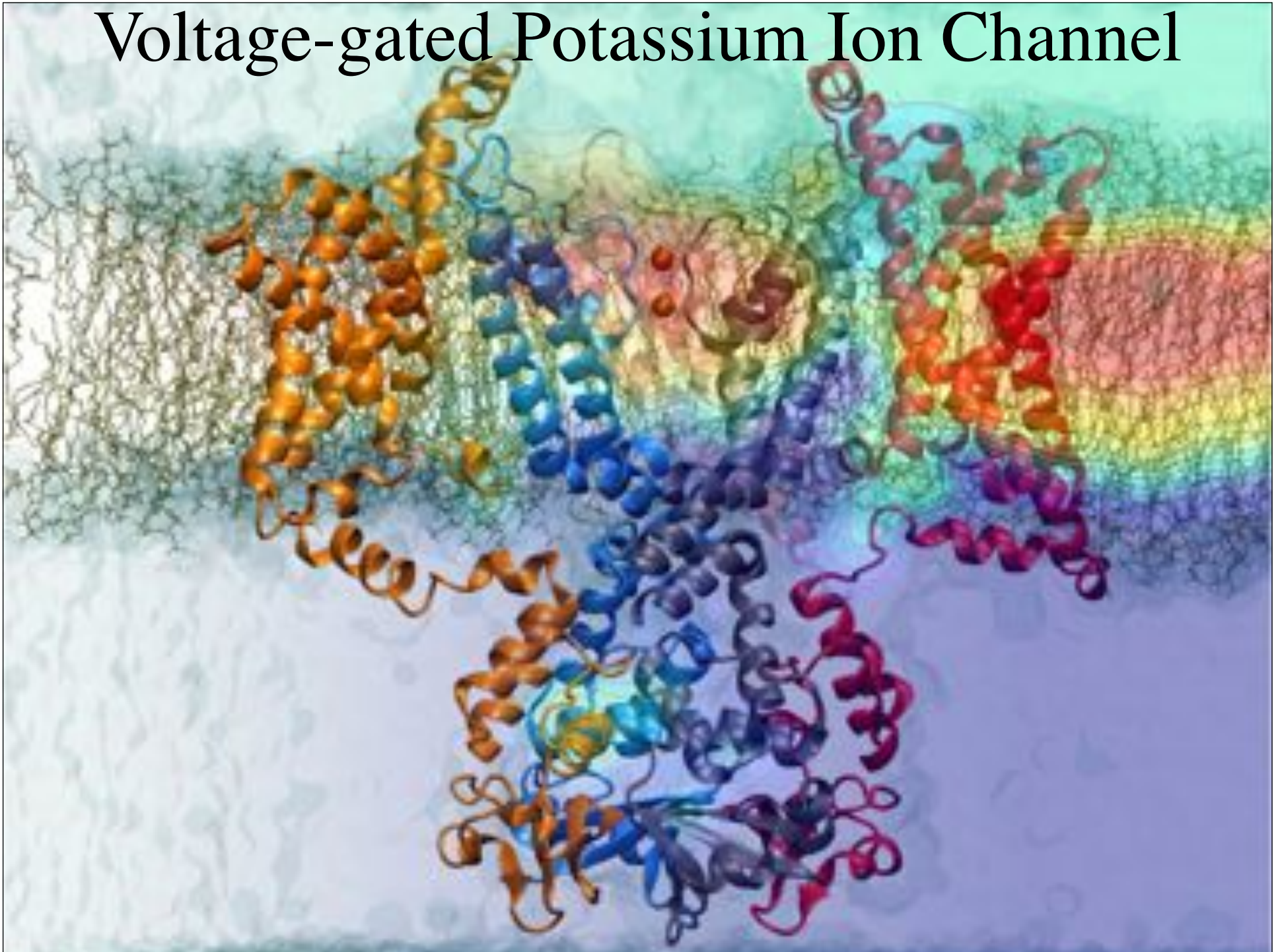
Simulation of Ion Conduction (here for Kv1.2)
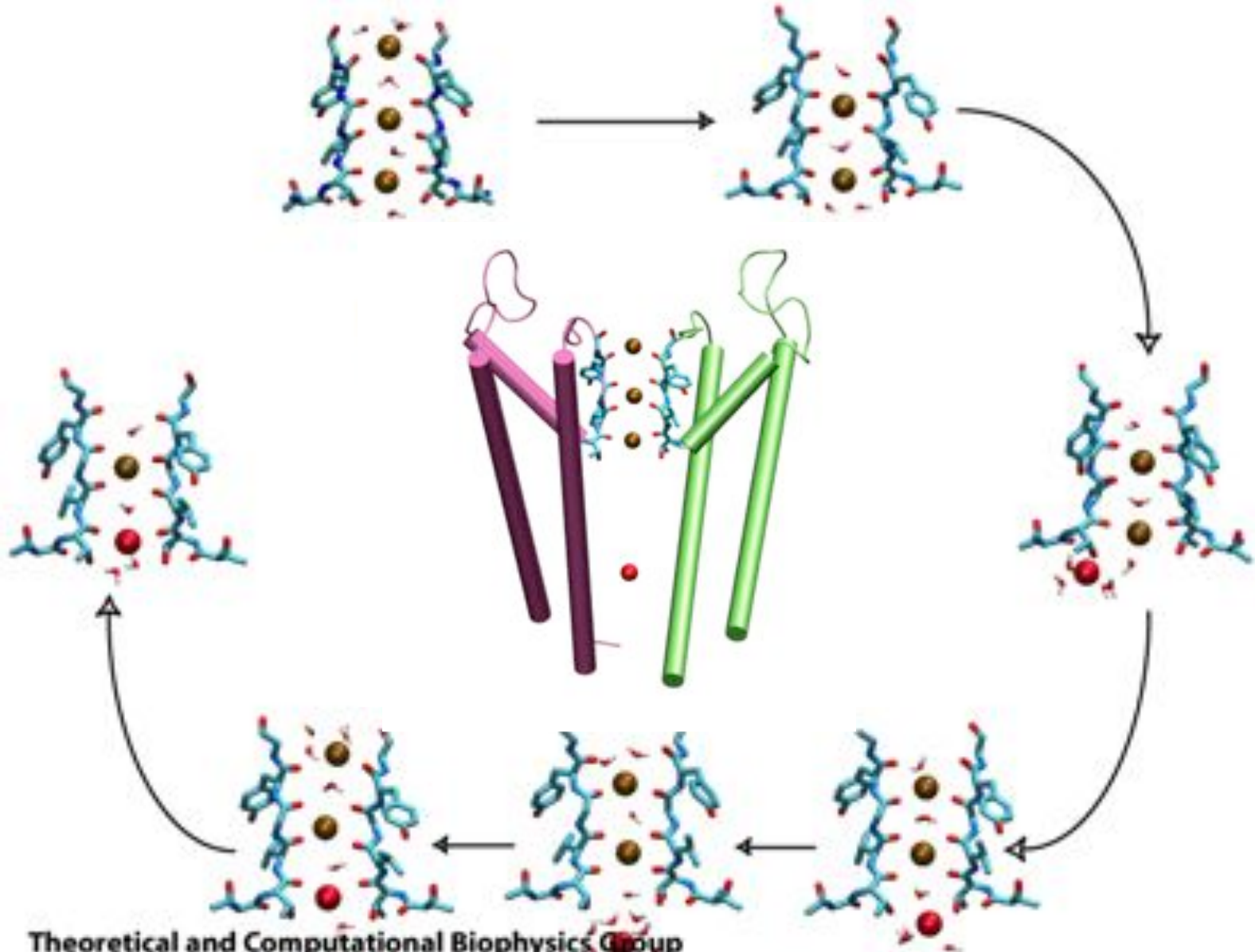
Theoretical and Computational Biophysics Group
Beckman Institute
University of Illinois at Urbana-Champaign

Voltage-gated Potassium Ion Channel

Voltage-gated Potassium Ion Channel