Introduction to Molecular Dynamics

Day 2

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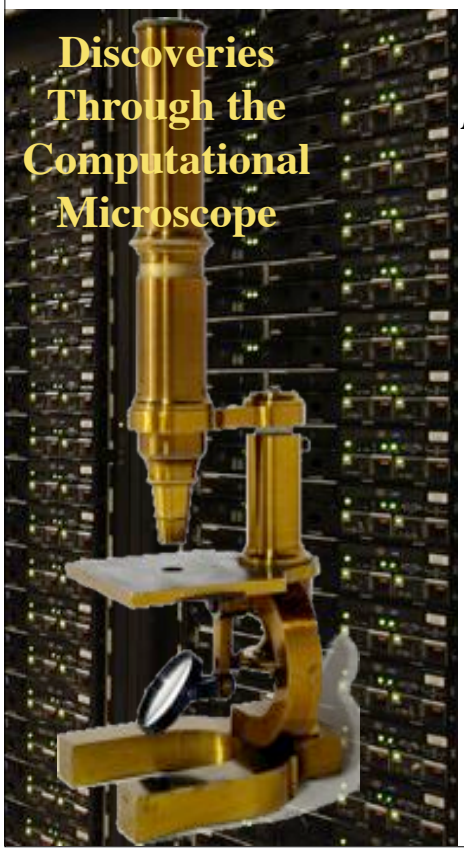
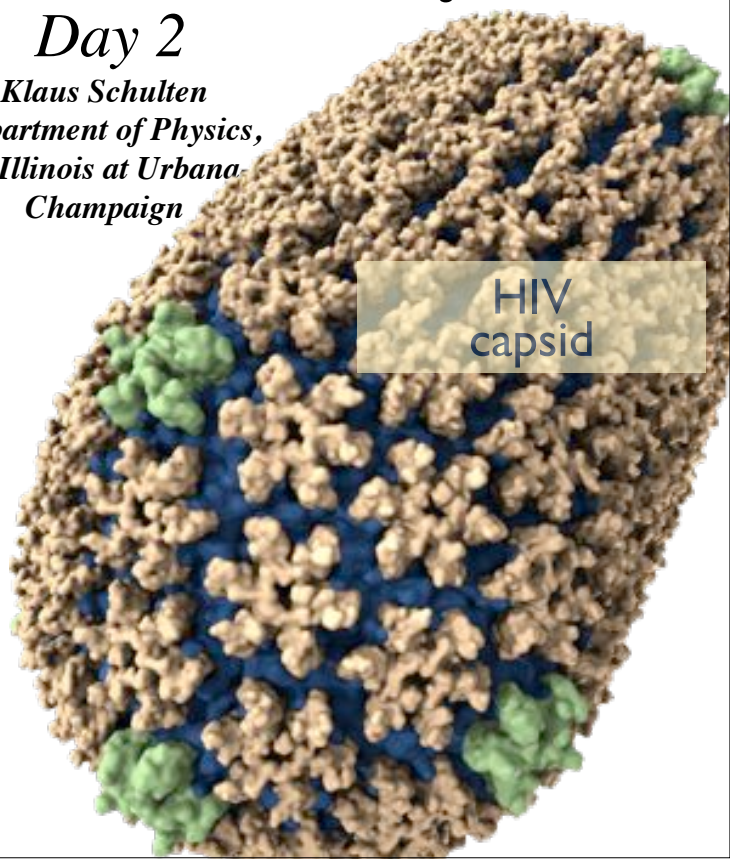
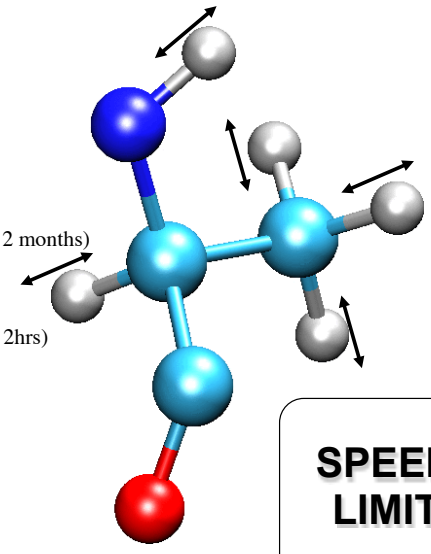




But long is still a problem!

biomolecular timescale and timestep limits

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



SPEED LIMIT

δt = 1 fs

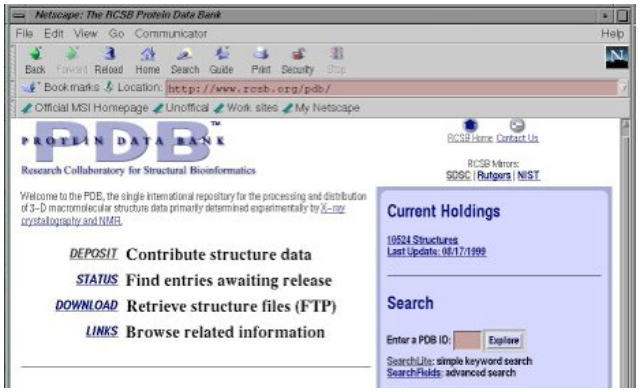
(NSF center, Shaw Res.)

PDB Files

gives one the structure and starting position

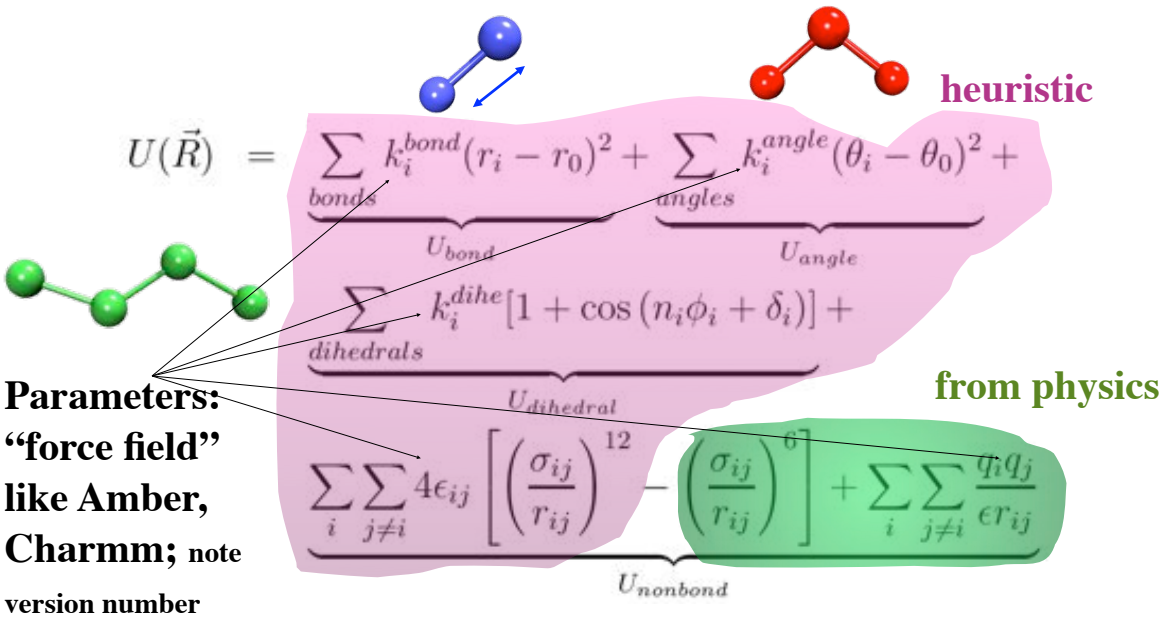
- Simulations start with a crystal structure from the Protein Data Bank, in the standard PDB file format.
- PDB files contain standard records for species, tissue, authorship, citations, sequence, secondary structure, etc.
- We only care about the atom records…
  - atom name (N, C, CA)
  - residue name (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.



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

Preparing Your System for MD

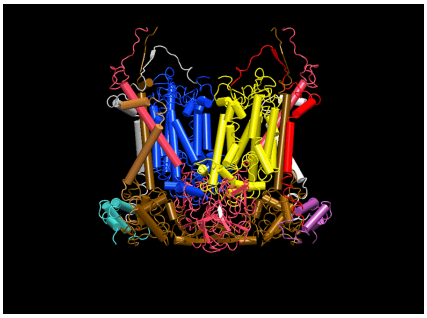
Solvation

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).

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

mitochondrial bc1 complex



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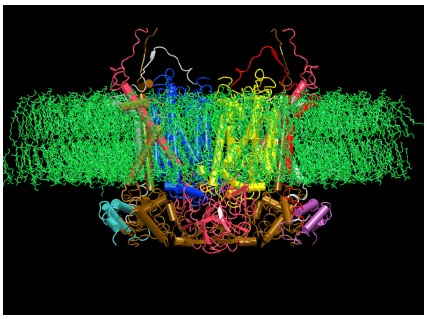

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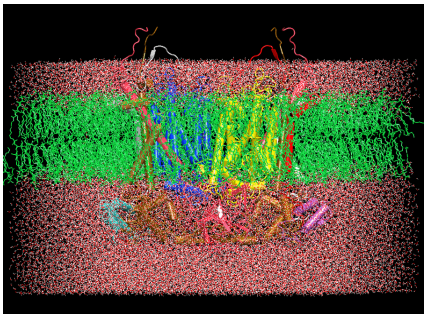
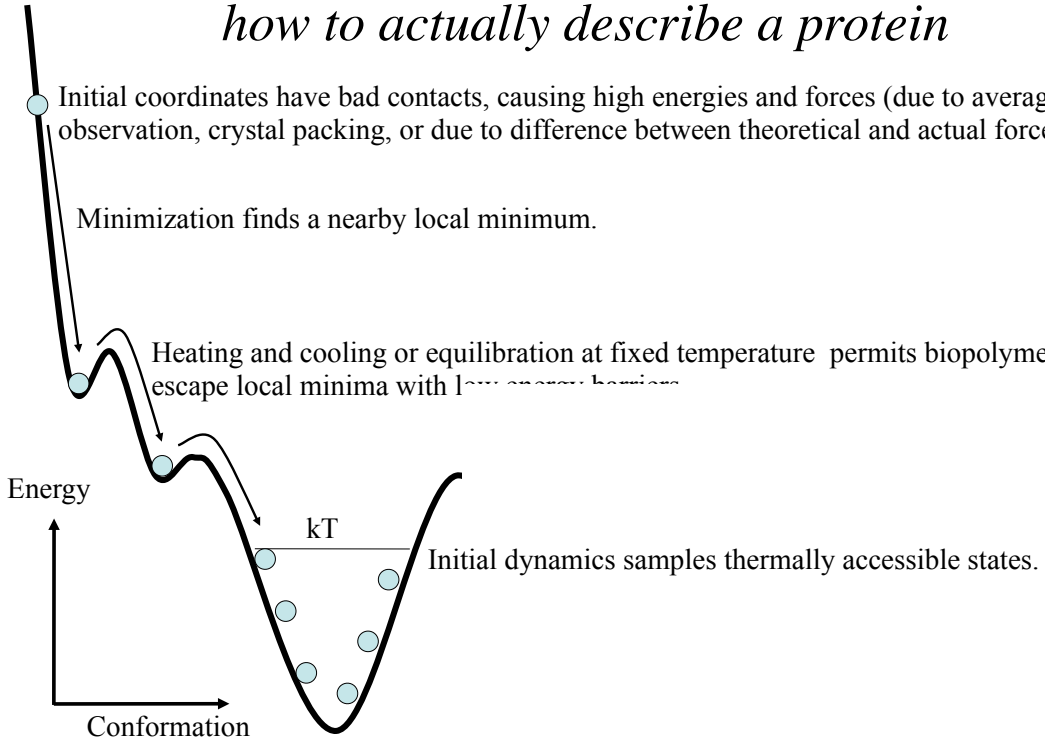


(Usually periodic! Avoids surface effects)

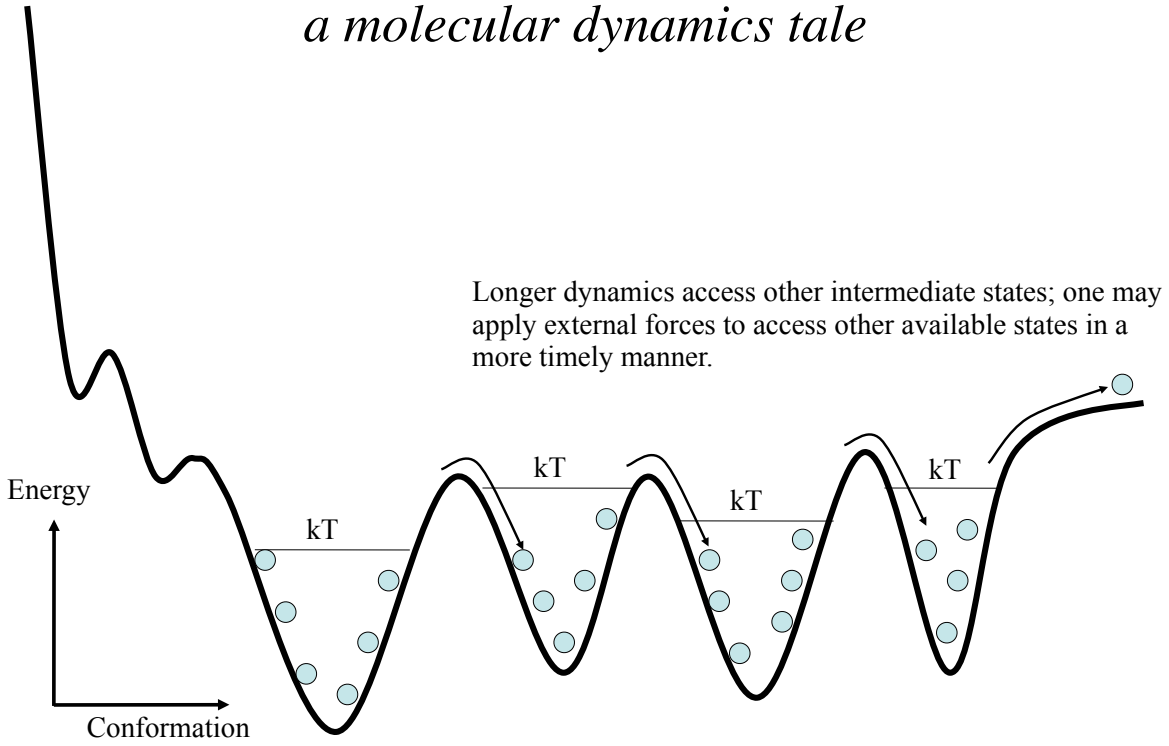
From the Mountains to the Valleys

how to actually describe a protein



From the Mountains to the Valleys

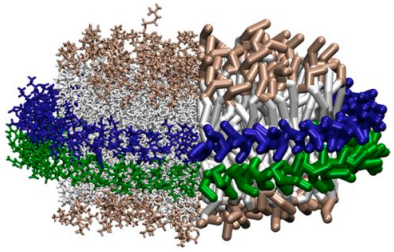
a molecular dynamics tale



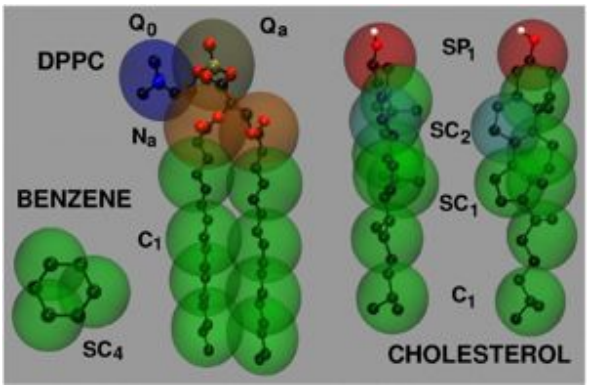
Cutting Corners

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

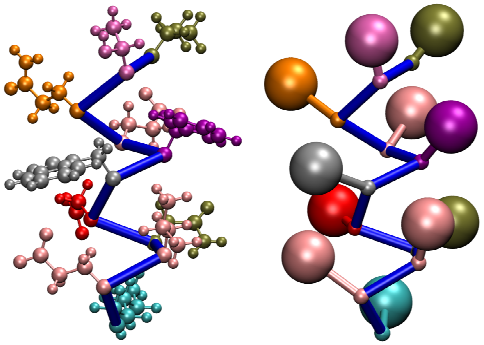


Residue-Based Coarse-Grained Model



- 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

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

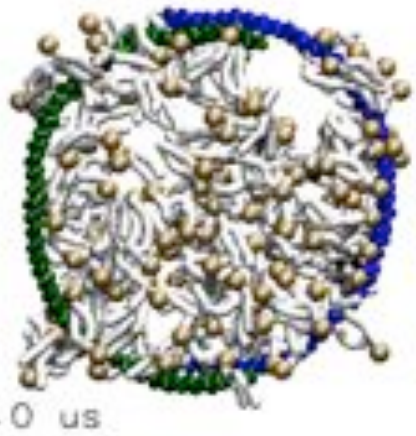


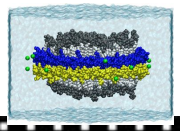
All-atom peptide CG peptide

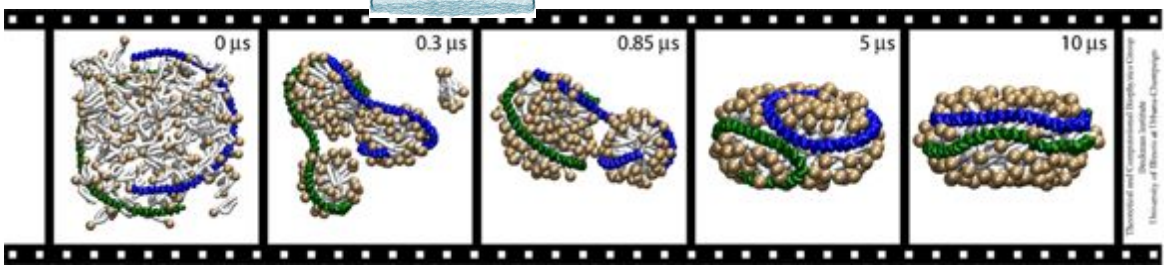
Peter L. Freddolino, Anton Arkhipov, Amy Y. Shih, Ying Yin, Zhongzhou Chen, and Klaus Schulten. **Application of residue-based and shape-based coarse graining to biomolecular simulations.** In Gregory A. Voth, editor, *Coarse-Graining of Condensed Phase and Biomolecular Systems*, chapter 20, pp. 299-315.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



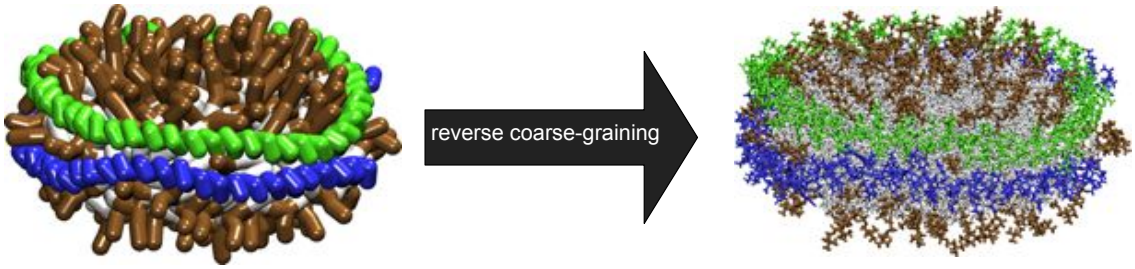




A. Shih, A. Arkhipov, P. Freddolino, and K. Schulten. *J. Phys. Chem. B*, 110:3674–3684, 2006; A. Shih, P. Freddolino, A. Arkhipov, and K. Schulten. *J. Struct. Biol.*, 157:579–592,2007; A. Shih, A. Arkhipov, P. Freddolino, S. Sligar, and K. Schulten. *Journal of Physical Chemistry B*, 111: 11095 - 11104,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

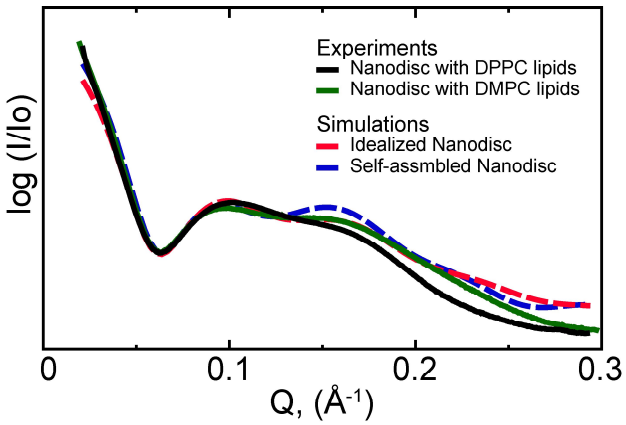
Validation of Simulations

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

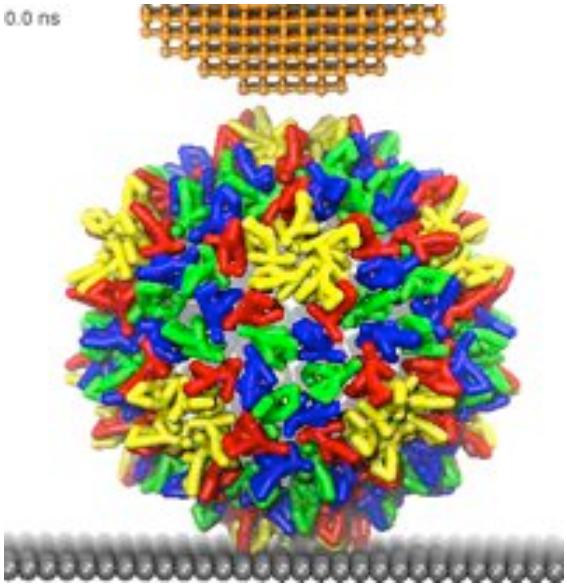


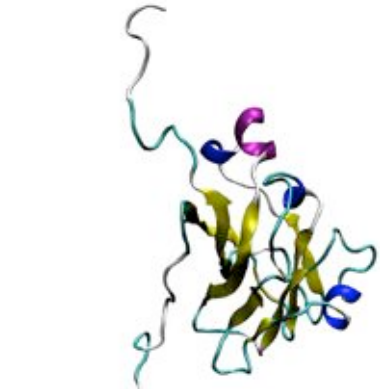
Reverse coarse-graining:
1. Map center of mass of the group of atoms represented by a single CG bead to that beads location
2. MD minimization, simulated annealing with restraints, and equilibration to get all-atom structure

Small-angle X-ray scattering:
Calculated from reverse coarse-grained all-atom model and compared with experimental measurements



Shape-Based Coarse-Grained (CG) model





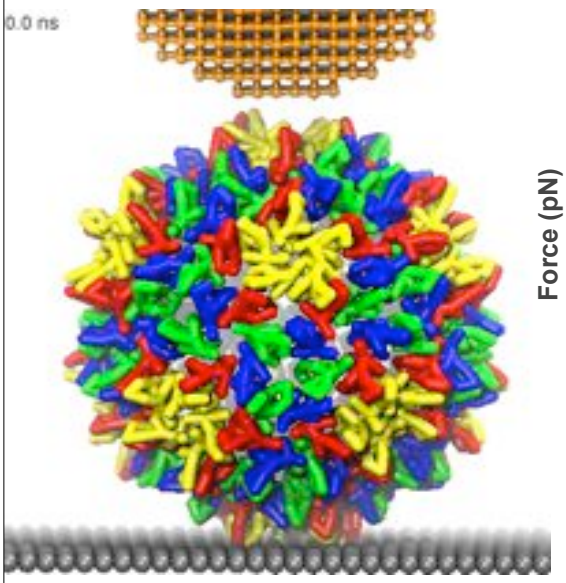
Anton Arkhipov, Wouter H. Roos, Gijs J. L. Wuite, and Klaus Schulten. **Elucidating the mechanism behind irreversible deformation of viral capsids.** *Biophysical Journal*, 97, 2009. In press.

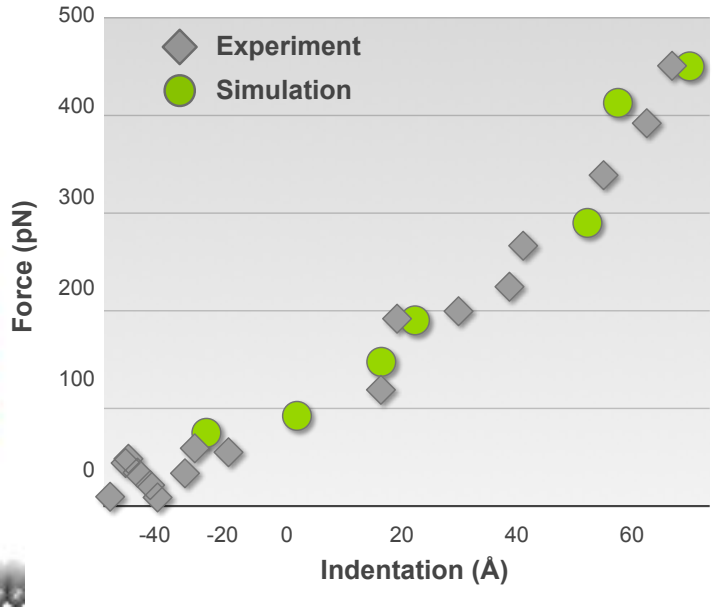
- **Fully automatic**
- **Number of CG beads is chosen by a user (we used ~200 atoms per CG bead)**

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 —

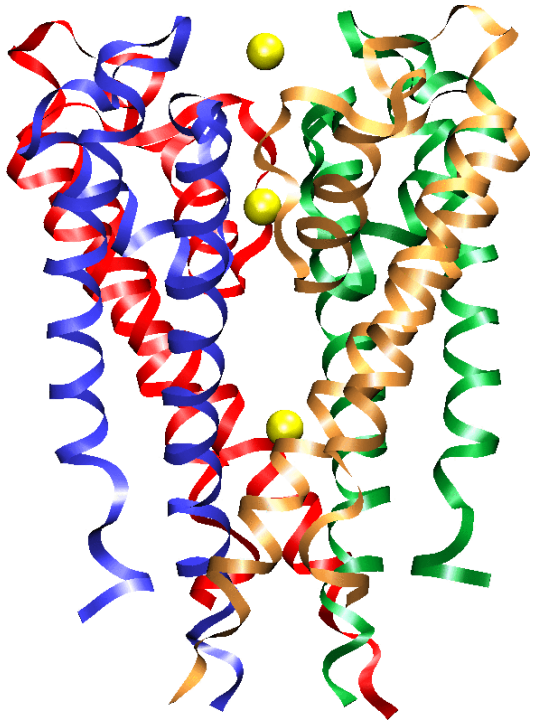




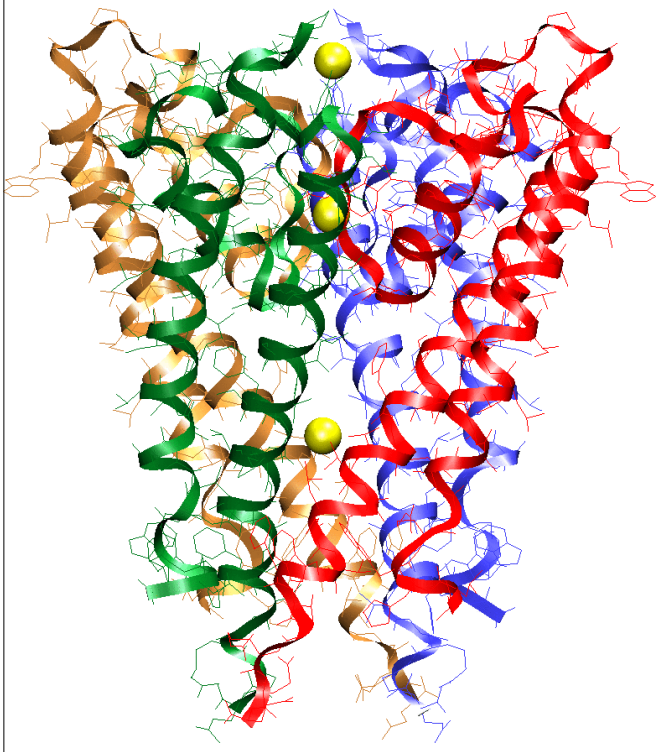
Example: MD Simulations of the K^+ Channel Protein

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.

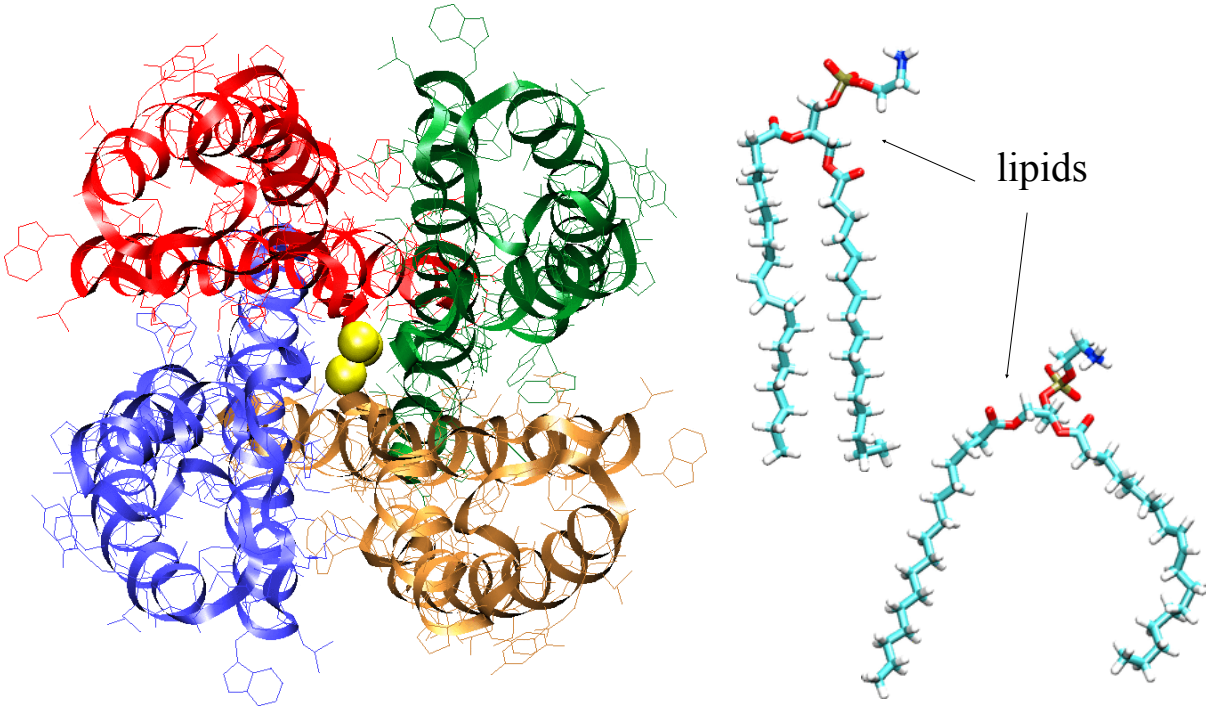


Setting up the system (1)



- 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 better than available in Charmm to describe well the ions
- minimize the protein structure using NAMD2

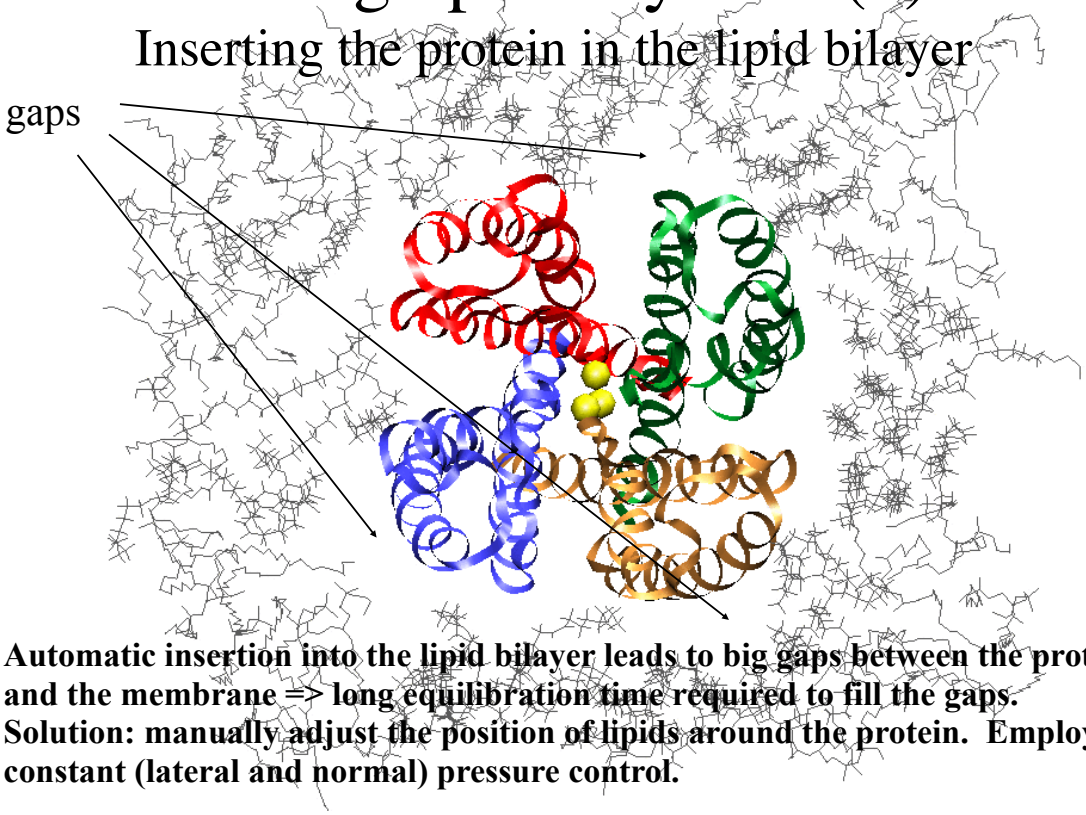
Setting up the system (2)



Simulate the protein in its natural environment: solvated lipid bilayer

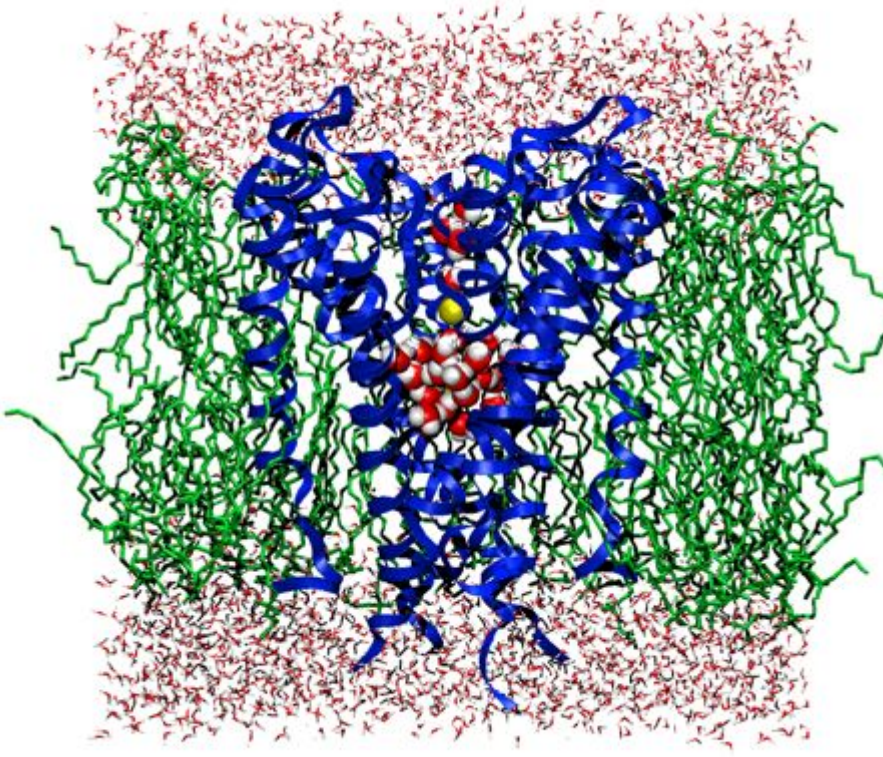
Setting up the system (3)

Inserting the protein in the lipid bilayer



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



solvent

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

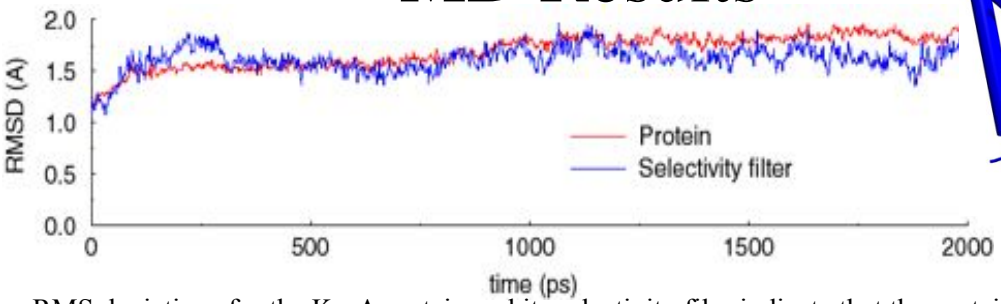
Simulating the system: Free MD

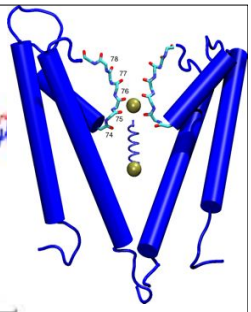
Summary of simulations:
• protein/membrane system contains 38,112 atoms, including 5117 water molecules, 100 POPE and 34 POPG lipids, plus K^+ counterions
• CHARMM26 forcefield
• periodic boundary conditions, PME electrostatics
• 1 ns equilibration at 310K, NpT
• 2 ns dynamics, NpT

Program: NAMD2

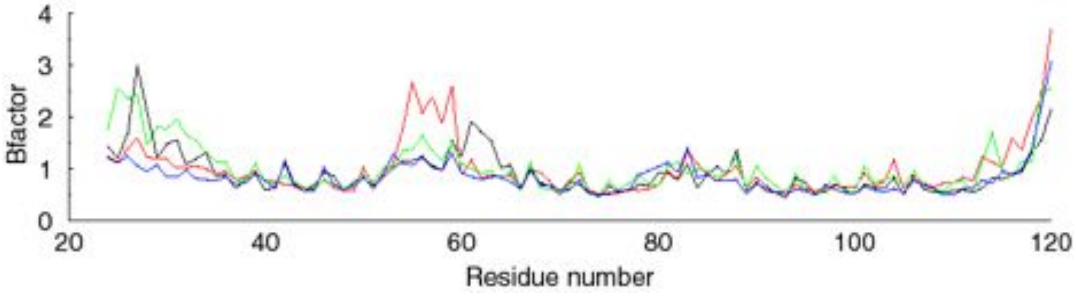
Platform: Cray T3E (Pittsburgh Supercomputer Center) or local computer cluster; choose ~1000 atoms per processor.

MD Results



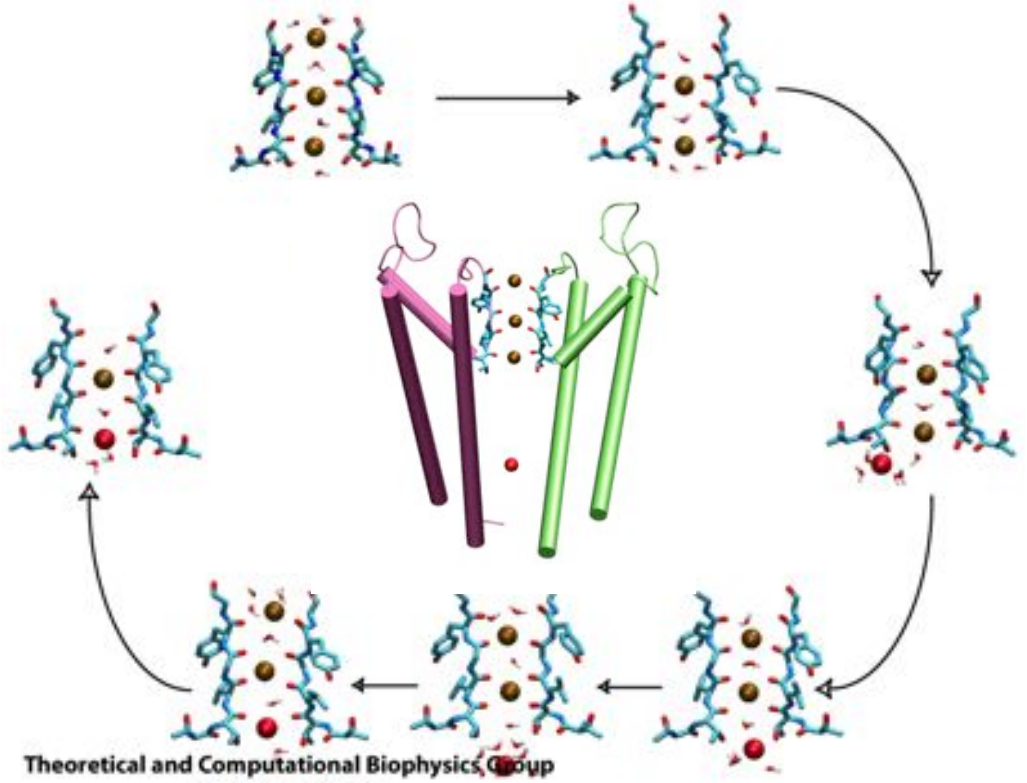


RMS deviations for the KcsA protein and its selectivity filer indicate that the protein is stable during the simulation with the selectivity filter the most stable part of the system.



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)



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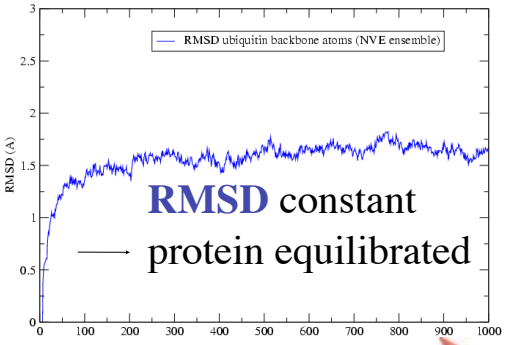
Beckman Institute
University of Illinois at Urbana-Champaign

Equilibrium Properties of Proteins

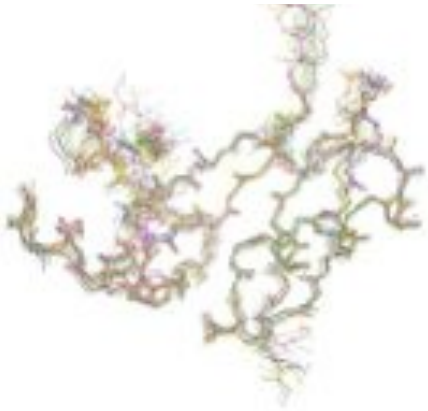
Ubiquitin

Root Mean Squared Deviation: measure for equilibration and protein flexibility

$$RMSD_\alpha = \sqrt{\frac{\sum_{j=1}^{N_t} \sum_{\alpha=1}^{N_\alpha} (\vec{r}_\alpha(t_j) - \langle \vec{r}_\alpha \rangle)^2}{N_\alpha}}$$

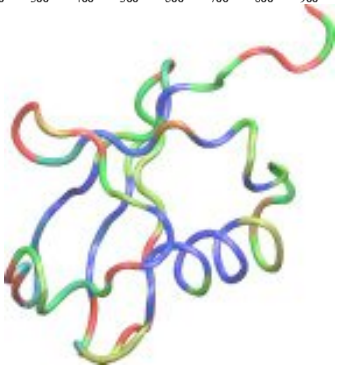


RMSD constant
protein equilibrated



NMR structures
aligned together to see flexibility

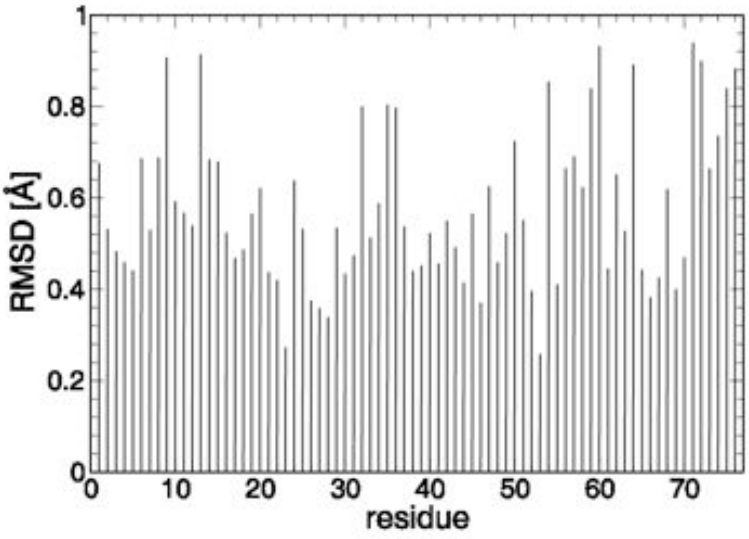
Protein sequence exhibits characteristic permanent flexibility!

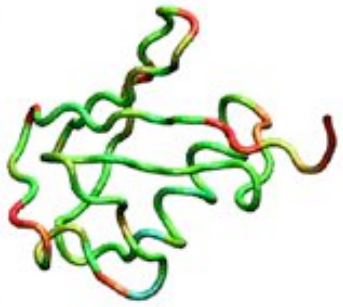


MD simulation
The color represents mobility of the protein per residue through simulation (red = more flexible)

Thermal Motion of Ubiquitin from MD

RMSD values per residue



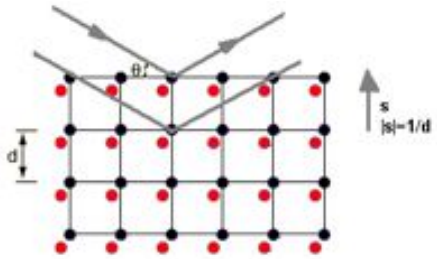


Thermal Motion of Ubiquitin from MD

Temperature Dependence of Crystal Diffraction (Debye-Waller factor)

Bragg's law

$$2\,d\,\sin\theta \;=\; \lambda$$



structure factor

$$f_j \exp[-i\vec{s}\cdot\vec{r}_j]$$

But the atom carries out thermal vibrations around equilibrium position $\vec{x}_j$

$$\vec{r}_j(t) \;=\; \vec{x}_j \;+\; \vec{u}_j(t)$$

Accordingly:

$$\langle f_j \exp[-i\vec{s}\cdot\vec{r}_j]\rangle \;=\; f_j \exp[-i\vec{s}\cdot\vec{x}_j]\,\langle \exp[-i\vec{s}\cdot\vec{u}_j]\rangle$$

Thermal Motion of Ubiquitin from MD

Temperature Dependence of Crystal Diffraction (Debye-Waller factor)

One can expand:

$$\langle \exp[-i\vec{s}\cdot\vec{u}_j]\rangle \;=\; 1 \;-\; i\underbrace{\langle \vec{s}\cdot\vec{u}_j\rangle}_{=0} \;-\; \tfrac{1}{2}\langle(\vec{s}\cdot\vec{u}_j)^2\rangle \;\; + \ldots$$

Spatial average for harmonic oscillator: $\langle(\vec{s}\cdot\vec{u}_j)^2\rangle \;=\; \tfrac{1}{3}s^2\langle u_j^2\rangle$

One can carry out the expansion further and show

$$\langle \exp[-i\vec{s}\cdot\vec{u}_j]\rangle \;=\; \exp\left[-\tfrac{1}{6}s^2\langle\langle u_j^2\rangle\right]$$

Using for the thermal amplitude of the harmonic oscillator

$$\tfrac{1}{2}m\omega^2 u_j^2 \;=\; \tfrac{3}{2}k_BT$$

one obtains

$$\langle f_j \exp\left[-i\vec{s}\cdot\vec{r}_j\right]\rangle \;=\; f_j \overbrace{\exp[-s^2k_BT/2m\omega^2]}^{\text{Debye-Waller factor}} \exp[-i\vec{s}\cdot\vec{x}_j]$$

Equilibrium Properties of Proteins

Energies: kinetic and potential

?

temperature dependence

$$\longleftarrow \langle \sum_j \frac{1}{2}m_j v_j^2\rangle$$

Kinetic energy (quadratic)

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

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

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

Potentialc energy (not all quadratic)

Equilibrium Properties of Proteins

Energies: kinetic and potential

?

temperature dependence

$$\langle \sum_j \frac{1}{2} m_j v_j^2 \rangle = \frac{3}{2} N k_B T$$

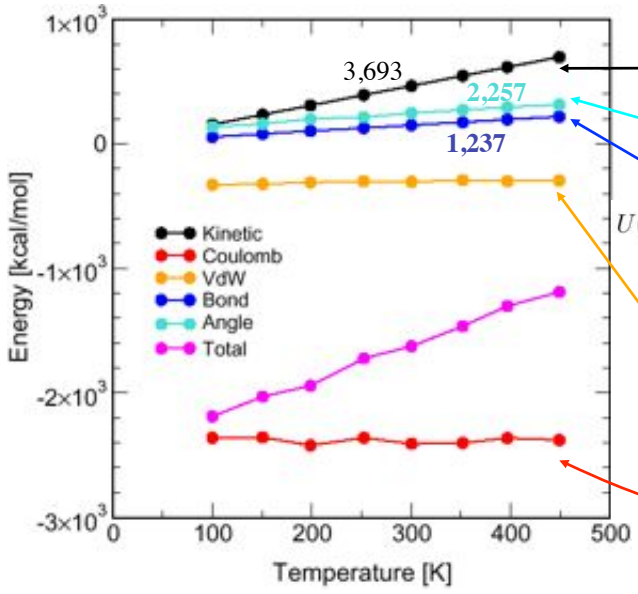
Kinetic energy (quadratic)

$$U(\vec{R}) = \underbrace{\sum_{bonds} k_i^{bond}(r_i - r_0)^2}_{U_{bond}} + \underbrace{\sum_{angles} k_i^{angle}(\theta_i - \theta_0)^2}_{U_{angle}} + \underbrace{\sum_{dihedrals} k_i^{dihe}[1 + \cos(n_i\phi_i + \delta_i)]}_{U_{dihedral}} + \underbrace{\sum_i \sum_{j \neq i} 4\epsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \sum_i \sum_{j \neq i} \frac{q_i q_j}{\epsilon r_{ij}}}_{U_{nonbond}}$$

Potentialc energy (not all quadratic)

Equilibrium Properties of Proteins

Energies: kinetic and potential



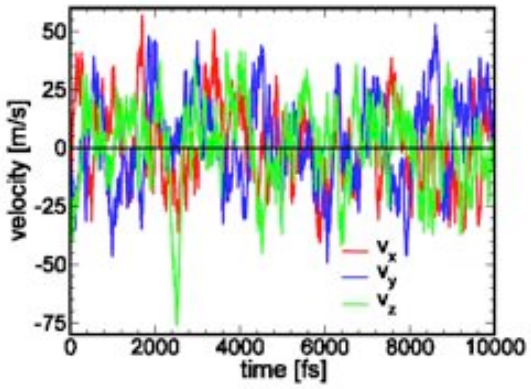
$$\langle \sum_j \frac{1}{2} m_j v_j^2 \rangle = \frac{3}{2} N k_B T$$

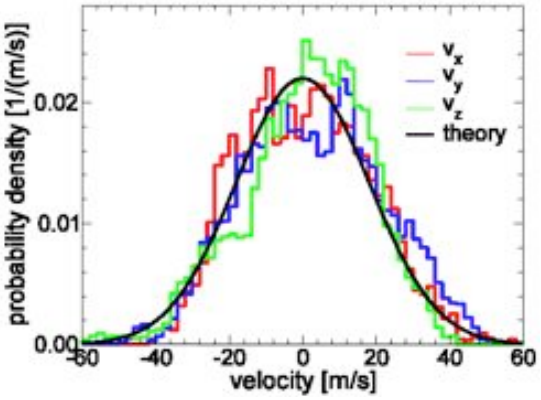
Kinetic energy (quadratic)

$$U(\vec{R}) = \underbrace{\sum_{bonds} k_i^{bond}(r_i - r_0)^2}_{U_{bond}} + \underbrace{\sum_{angles} k_i^{angle}(\theta_i - \theta_0)^2}_{U_{angle}} + \underbrace{\sum_{dihedrals} k_i^{dihe}[1 + \cos(n_i\phi_i + \delta_i)]}_{U_{dihedral}} + \underbrace{\sum_i \sum_{j \neq i} 4\epsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \sum_i \sum_{j \neq i} \frac{q_i q_j}{\epsilon r_{ij}}}_{U_{nonbond}}$$

Potentialc energy (not all quadratic)

Maxwell Distribution of Atomic Velocities

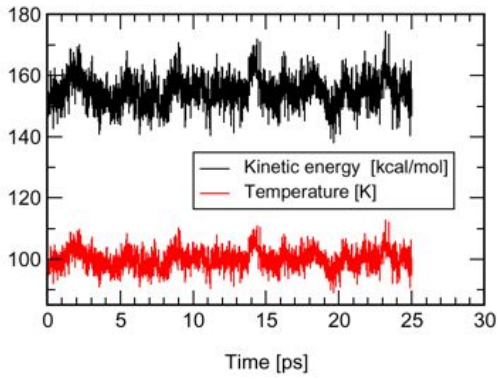


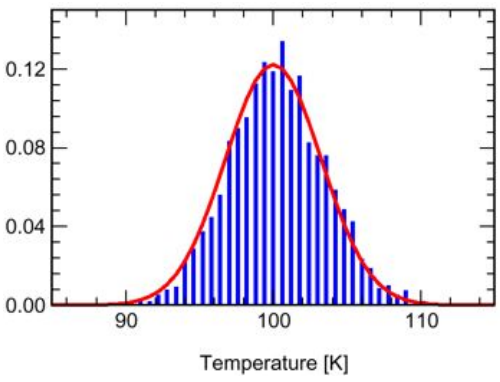


$$p(v_\sigma) = \sqrt{\frac{m}{2\pi k_B T}} \exp\left[-\frac{m v_\sigma^2}{2 k_B T}\right]$$

$$\sigma = x,\ y,\ z$$

Analysis of E_{kin}, T (free dynamics)





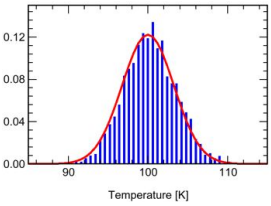
Definition of Temperature

$$\langle \sum_j \frac{1}{2} m_j v_j^2 \rangle = \frac{3}{2} N k_B T$$

$$T = \frac{2}{3N k_B} \langle \sum_j \frac{1}{2} m_j v_j^2 \rangle$$

The atomic velocities of a protein establish a thermometer, but is it accurate?

The atomic velocity thermometer is inaccurate due to the finite size of a protein!



Temperatur Fluctuations

Maxwell distribution

$$dP(v_n) = c\,\exp(-m\,v_n^2/2k_BT)\,dv_n \tag{7}$$

Individual kinetic energy $\epsilon_n = mv_n^2/2$

$$dP(\epsilon_n) = (\pi T_0\epsilon_n)^{-1/2}\exp(-\epsilon_n/k_BT_0)\,d\epsilon_n \tag{8}$$

One can derive (temperature T_0 in units k_B)

$$\langle\epsilon_n\rangle = T_0/2 \tag{9}$$

$$\langle\epsilon_n^2\rangle = 3\,T_0^2/4 \tag{10}$$

$$\langle\epsilon_n^2\rangle - \langle\epsilon_n\rangle^2 = T_0^2/2 \tag{11}$$

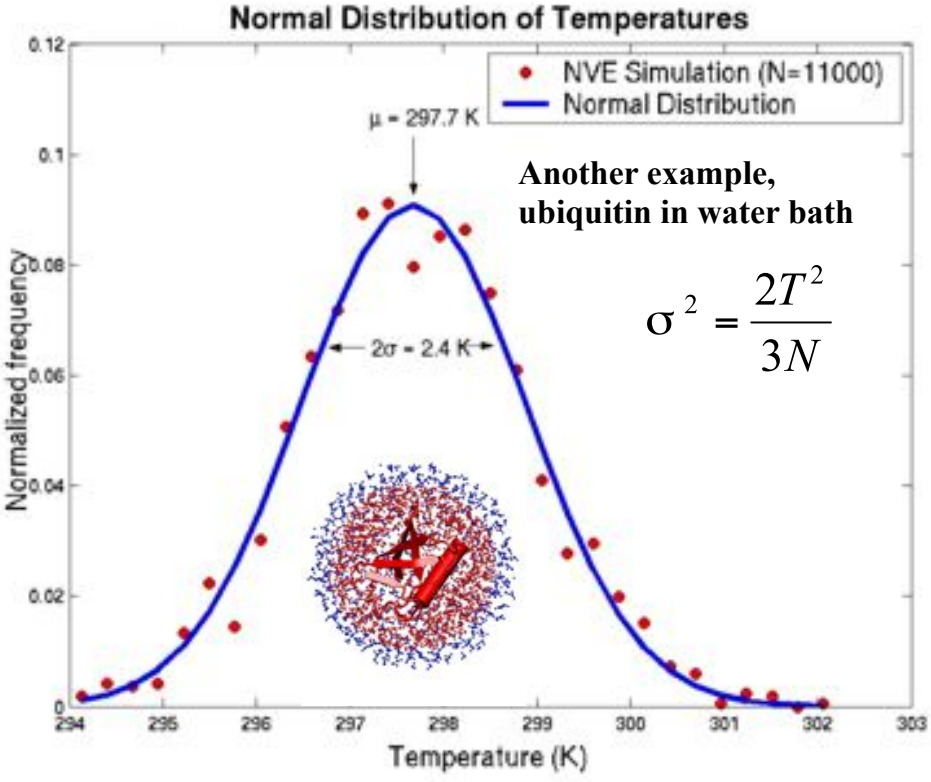
The distribution of the total kinetic energy $E_{kin} = \sum_j \frac{1}{2}m_jv_j^2$, according to the central limit theorem, is approximately Gaussian

$$P(E_{kin}) = c\,\exp\left(\frac{-(E_{kin}-\langle E_{kin}\rangle)^2}{2\left(\frac{3Nk_B^2T_0^2}{2}\right)}\right) \tag{12}$$

The distribution function for the temperature ($T = 2E_{kin}/3k_B$) fluctuations $\Delta T = T - T_0$ is then

$$P(\Delta T) = c\,\exp[-(\Delta T)^2/2\sigma^2]\,, \qquad \sigma^2 = 2\,T^2/3N \tag{13}$$

For $T_0 = 100$K and $N = 557$, this gives $\sigma = 3.6$.

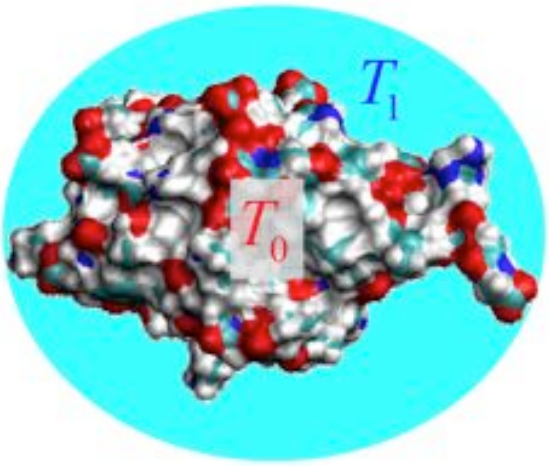


Another example, ubiquitin in water bath

$$\sigma^2 = \frac{2T^2}{3N}$$

Simulated Cooling of Ubiquitin

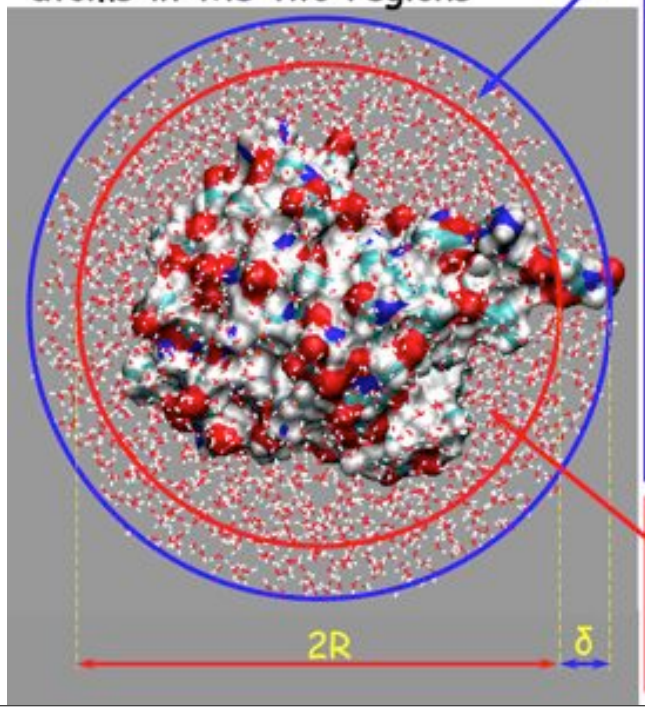
- Proteins function in a narrow (physiological) temperature range. What happens to them when the temperature of their surrounding changes significantly (temperature gradient) ?
- Can the heating/cooling process of a protein be simulated by molecular dynamics ? If yes, then how?



- What can we learn from the simulated cooling/heating of a protein ?

How to simulate cooling ?

Heat transfer through mechanical coupling between atoms in the two regions



coolant layer of atoms

motion of atoms is subject to stochastic Langevin dynamics

$$m\ddot{\boldsymbol{r}} = \boldsymbol{F}_{FF} + \boldsymbol{F}_H + \boldsymbol{F}_f + \boldsymbol{F}_L$$

$\boldsymbol{F}_{FF} \rightarrow$ force field
$\boldsymbol{F}_H \rightarrow$ harmonic restrain
$\boldsymbol{F}_f \rightarrow$ friction
$\boldsymbol{F}_L \rightarrow$ Langevin force

atoms in the inner region follow Newtonian dynamics

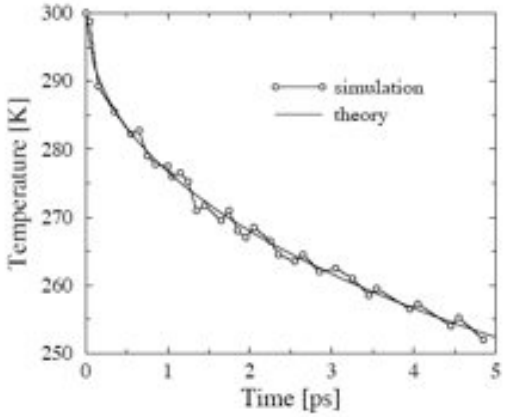
$$m\ddot{\boldsymbol{r}} = \boldsymbol{F}_{FF}$$

Simulated Cooling - Result

t	$\langle T_{sim}\rangle$	t	$\langle T_{sim}\rangle$	t	$\langle T_{sim}\rangle$	t	$\langle T_{sim}\rangle$
0.05	298.75	1.05	276.00	1.95	267.00	3.25	261.00
0.15	289.25	1.15	276.50	2.05	268.50	3.45	258.50
0.35	285.50	1.25	275.25	2.25	266.50	3.55	259.50
0.55	282.25	1.35	271.00	2.35	264.50	3.95	256.50
0.65	282.75	1.45	271.75	2.55	263.50	4.05	257.25
0.75	279.00	1.65	269.50	2.65	264.50	4.45	254.00
0.85	277.75	1.75	271.00	2.85	262.00	4.55	255.25
1.00	277.50	1.85	268.00	3.05	262.50	4.85	252.00

Table 1: Mean temperature $\langle T_{sim}\rangle$ [K] of the protein as a function of time t [ps].

Result from simulation



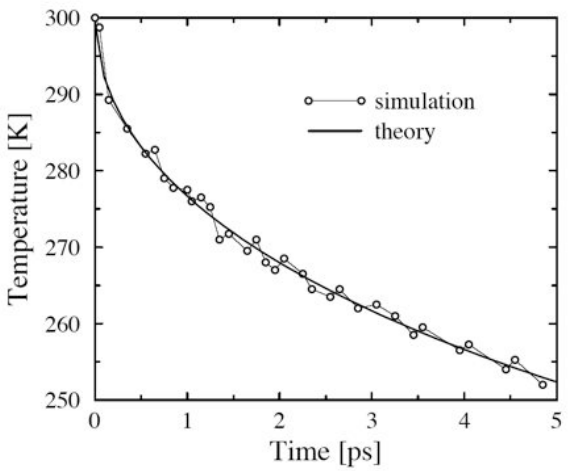
Solution of the Heat Equation

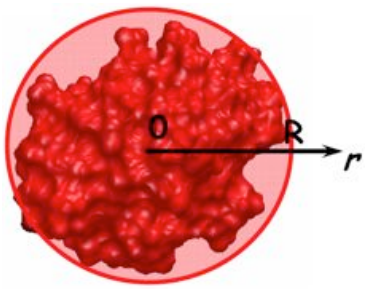
Temperature averaged over volume

$$\langle T\rangle(t) = \left(\frac{4\pi R^3}{3}\right)^{-1}\int d^3\mathbf{r}\,T(\mathbf{r},t) = \frac{3}{R^3}\int_0^R r^2 dr\,T(r,t)$$

$$= T_{bath} + \sum_{n=1}^{\infty} a_n \exp\left[-\left(\frac{n\pi}{R}\right)^2 D\,t\right]\frac{3}{R^3}\int_0^R r dr\,\sin\left(\frac{n\pi r}{R}\right)$$

$$= T_{bath} + 6\frac{\Delta T}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp\left[-\left(\frac{n\pi}{R}\right)^2 D\,t\right]$$

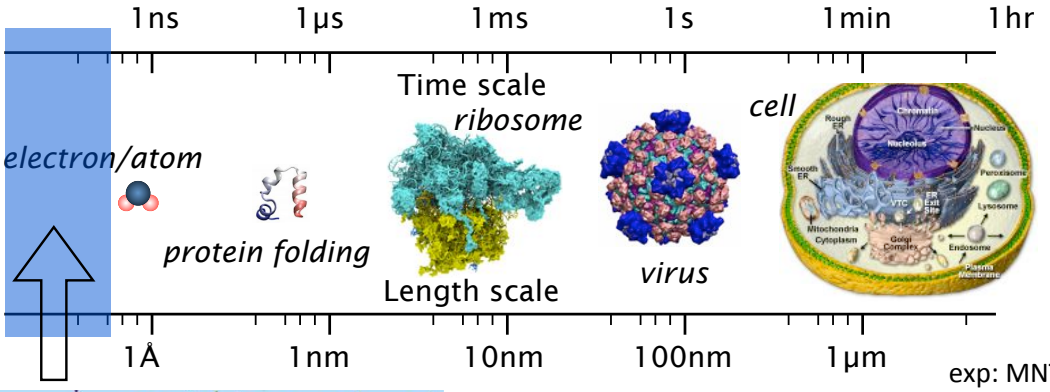




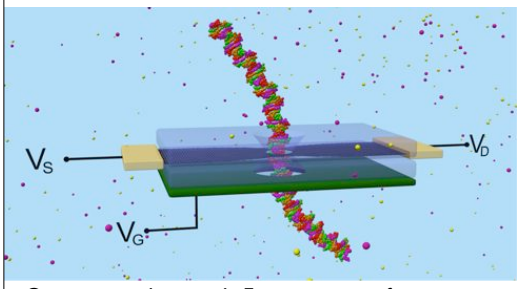
$D \approx 0.38 \times 10^{-3}\mathrm{cm}^2\mathrm{s}^{-1}$

water $1.4 \times 10^{-3}\mathrm{cm}^2\mathrm{s}^{-1}$

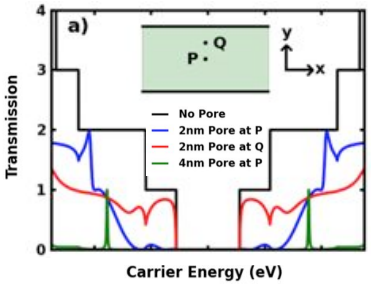
Increasing Biological Realism in Theory and Computation

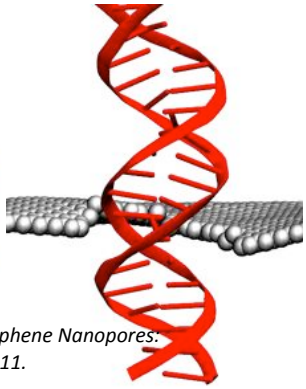


exp: MNTL



Gate terminal controls Fermi energy of conduction electrons and also slows down translocating DNA





Computational investigation of DNA detection using Graphene Nanopores: C. Sathe, X. Zou, J. P. Leburton, K. Schulten. ACS Nano 2011.

Aksimentiev: Advanced Functional Materials 21:1040-1050 (2011); ACS Nano, 5: 9345–9353 (2011); Nano Letters 12: 1038–1044 (2012).
Schulten: ACS Nano 5: 8842-8851 (2011); Nucleic Acids Res. 39: 8740-8751 (2011); ACS Nano: 6: 8847- 8856 (2012); Scientific Reports 3: 1389 - 1397 (2013).

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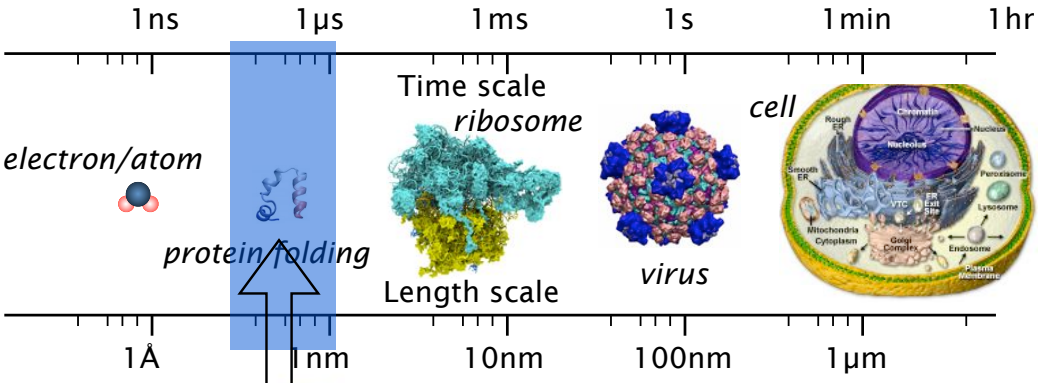

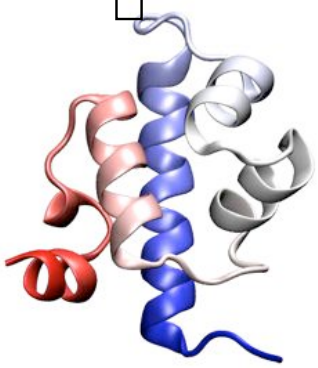

with experimentalist Martin Gruebele

lambda repressor, 80 amino acids, 100 μs

Proceedings of the National Academy of Sciences, USA, In press, 2013.

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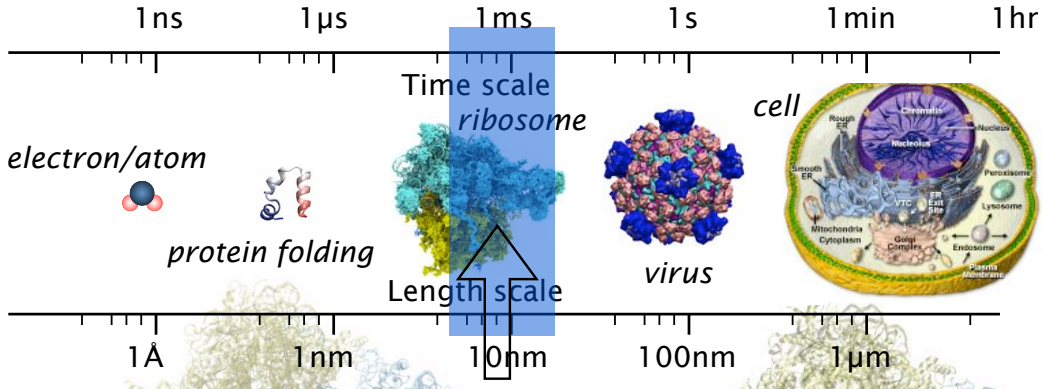
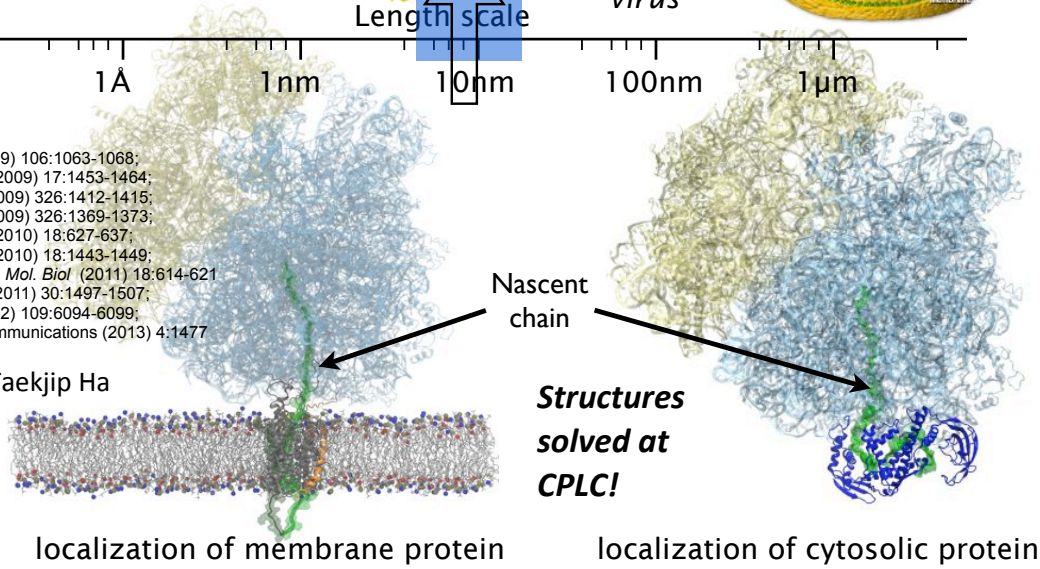




PNAS (2009) 106:1063-1068;
Structure (2009) 17:1453-1464;
Science (2009) 326:1412-1415;
Science (2009) 326:1369-1373;
Structure (2010) 18:627-637;
Structure (2010) 18:1443-1449;
Nat. Struct. Mol. Biol (2011) 18:614-621
EMBO J. (2011) 30:1497-1507;
PNAS (2012) 109:6094-6099;
Nature Communications (2013) 4:1477

Nascent chain

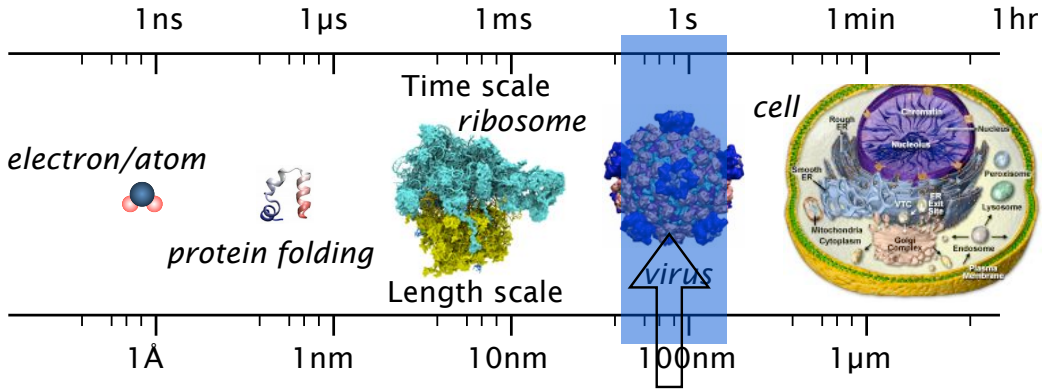
exp: Taekjip Ha

Structures solved at CPLC!

localization of membrane protein

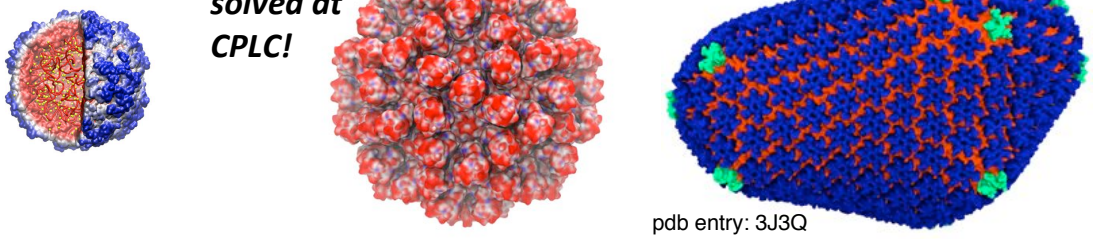
localization of cytosolic protein (new)

Increasing Biological Realism in Theory and Computation



Structures solved at CPLC!

exp: U Pittsburgh



pdb entry: 3J3Q

Satellite Tobacco Mosaic Virus
17 nm in diameter
1 millions atoms (2006)

Structure, 14:437-449, 2006.
Structure, 14:1767-1777, 2006.

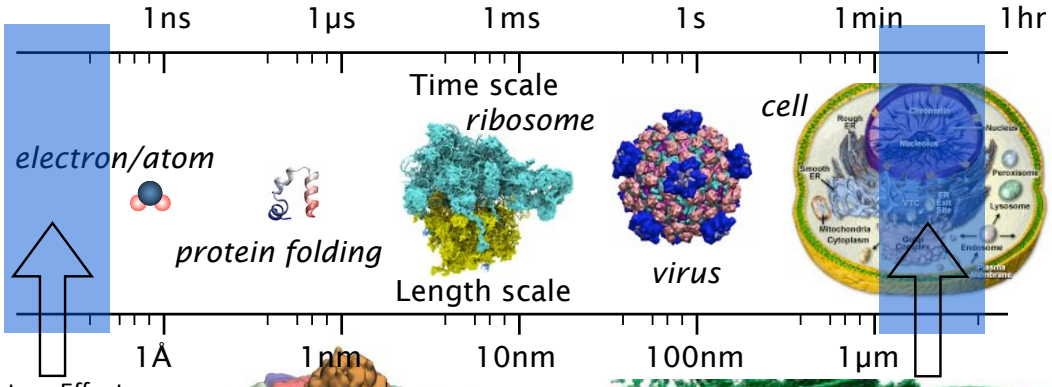
Rabbit Hemorrhagic Disease Virus
45 nm in diameter
10 millions atoms (2012)

PLoS Pathogens, 9:e1003132, 2013.

HIV-1
70 nm in length
64 millions atoms (2013)

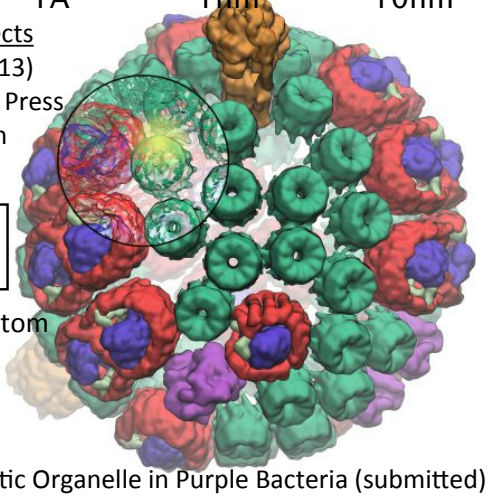
Nature, in press, 2013.

Increasing Biological Realism in Theory and Computation

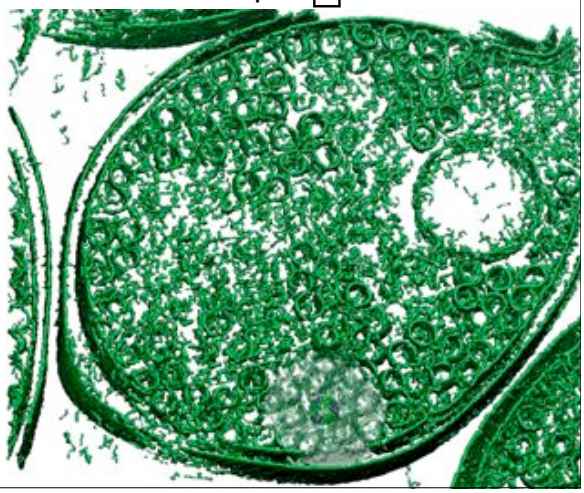


Quantum Effects in Biology (2013) Cambridge U. Press + 10 articles in 2011-2013

exp: several labs

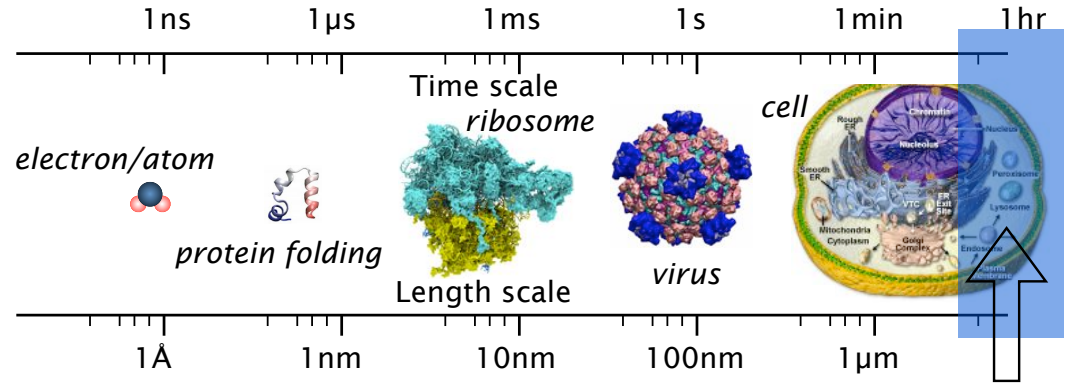


100 million atom simulation Blue Waters (Oct. 2012)



Photosynthetic Organelle in Purple Bacteria (submitted)

Increasing Biological Realism in Theory and Computation



whole cell simulation

Luthey-Schulten, presents later

Theoretical and Computational Biophysics Group Developers

NIH Center for Research Resources

Funding: NIH, NSF

- focus on systems biology
- focus on quantum biology
- theoretical biophysics
- computational biophysics
- develops renewable energy
- guides bionanotechnology