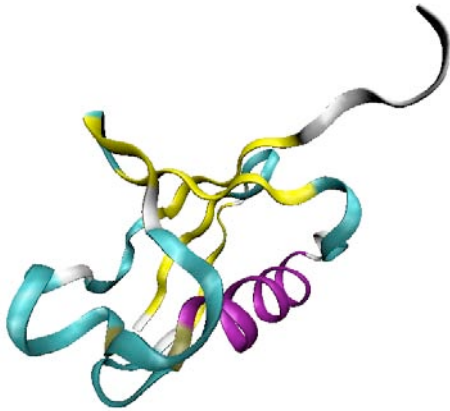
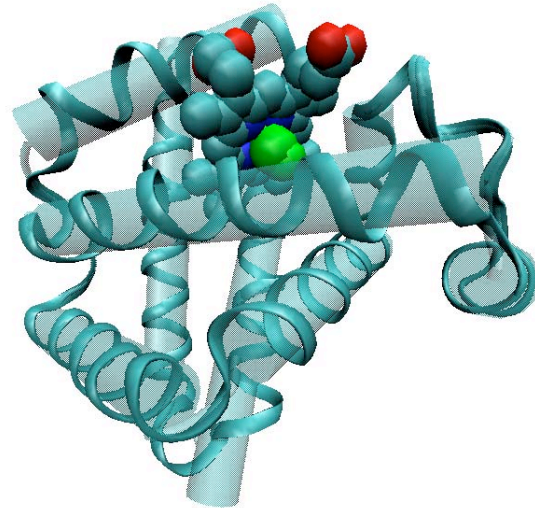


Molecular Dynamics of Proteins



Ubiquitin



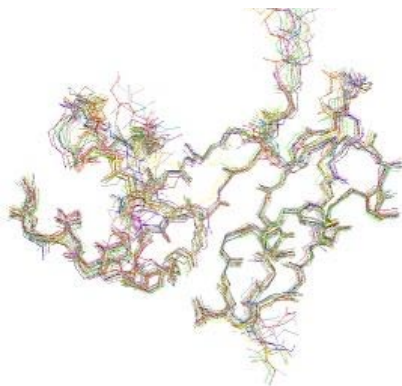
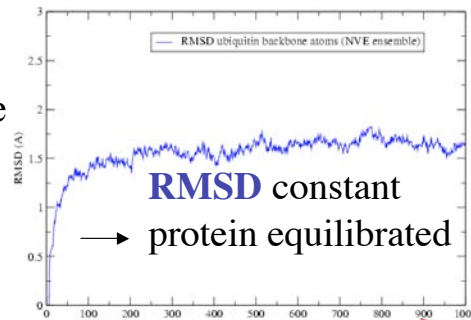
Myoglobin

Equilibrium Properties of Proteins

Ubiquitin

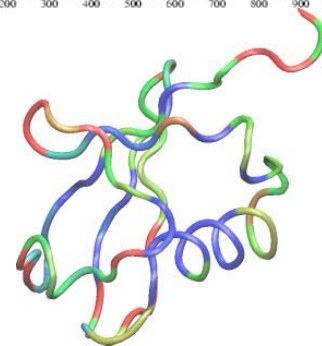
Root Mean Squared Deviation: measure for equilibration and protein flexibility

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



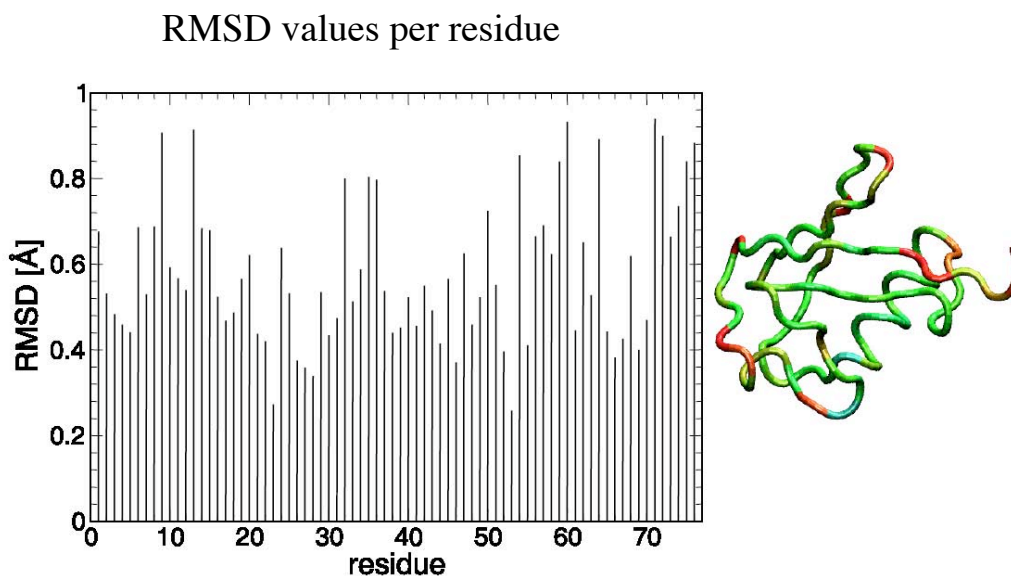
NMR structures
aligned together to see flexibility

**Protein sequence
exhibits
characteristic
permanent
flexibility!**



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

Thermal Motion of Ubiquitin from MD



Thermal Motion of Ubiquitin from MD

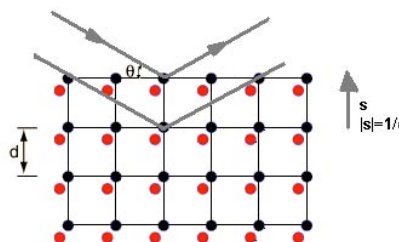
Temperature Dependence of Crystal Diffraction (Debye-Waller factor)

Bragg's law

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

structure factor

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



The diffraction signal is the sum of the structure factors of all atoms in the crystal.

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:

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

Spatial average: $\langle (\vec{s} \cdot \vec{u}_j)^2 \rangle = \frac{1}{3} s^2 \langle u_j^2 \rangle$

One can carry out the expansion further and show

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

Using for the thermal amplitude of the harmonic oscillator

$$\frac{1}{2} m \omega^2 u_j^2 = \frac{3}{2} k_B T$$

one obtains

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

Equilibrium Properties of Proteins

Energies: kinetic and potential



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

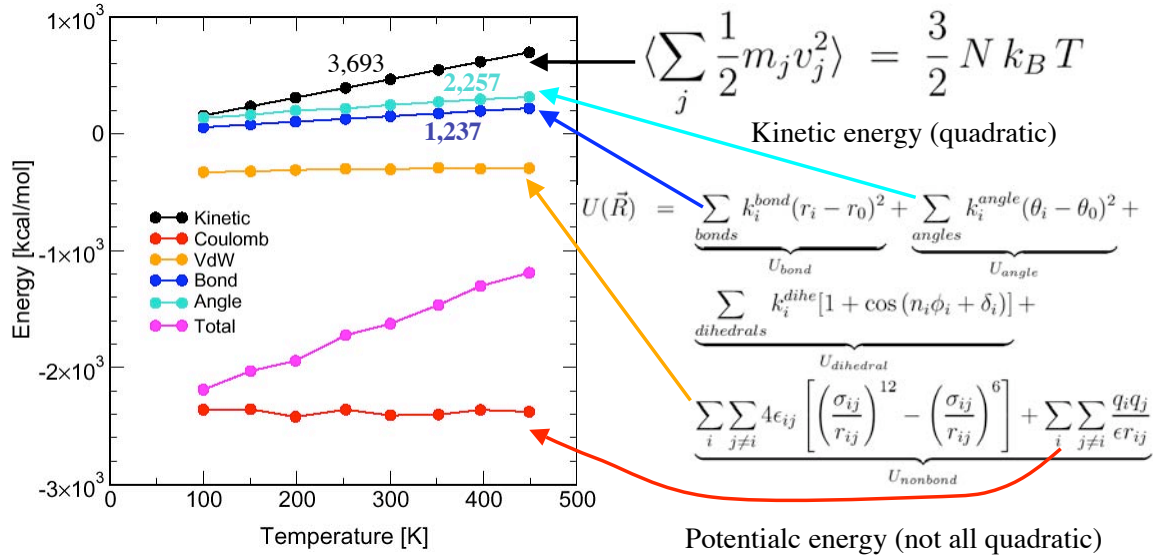
Kinetic energy (quadratic)

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

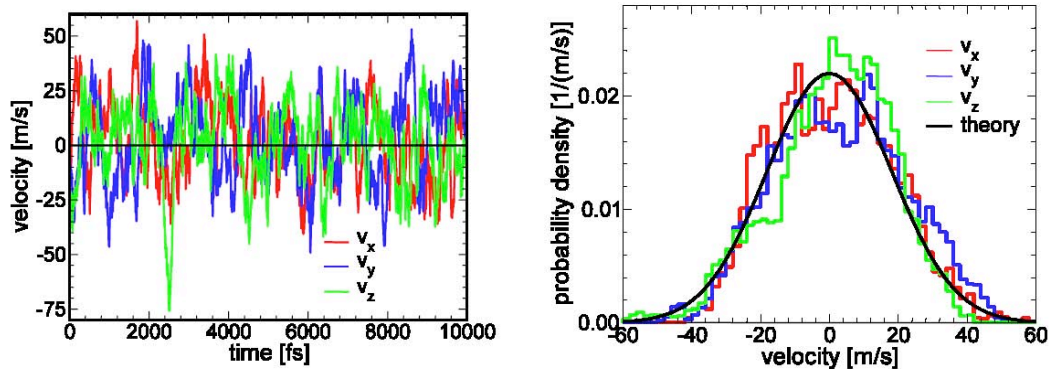
Potential energy (not all quadratic)

Equilibrium Properties of Proteins

Energies: kinetic and potential



Maxwell Distribution of Atomic Velocities



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

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

Mean Kinetic Energy

Exercise in Statistics

$$\begin{aligned}
 \langle \frac{1}{2}mv^2 \rangle &= \int_{-\infty}^{\infty} dv \left(\frac{1}{2}mv^2 \right) p(v) \\
 &= \sqrt{\frac{m}{2\pi k_B T}} \int_{-\infty}^{\infty} dv \left(\frac{1}{2}mv^2 \right) \exp \left[-\frac{mv^2}{2k_B T} \right] \\
 &= k_B T \sqrt{\frac{1}{\pi}} \int_{-\infty}^{\infty} \sqrt{\frac{m}{2k_B T}} dv \left(\frac{mv^2}{2k_B T} \right) \exp \left[-\frac{mv^2}{2k_B T} \right] \\
 &= k_B T \sqrt{\frac{1}{\pi}} \int_{-\infty}^{\infty} dy y^2 \exp -y^2]
 \end{aligned}$$

Use formula below: $\langle \frac{1}{2}mv^2 \rangle = \frac{1}{2}k_B T$

$$\begin{aligned}
 \int_0^{\infty} dy y^m \exp[-y^2] &= \frac{1}{2} \Gamma \left(\frac{m+1}{2} \right) \\
 \Gamma(x+1) &= x \Gamma(x), \quad \Gamma \left(\frac{1}{2} \right) = \sqrt{\frac{1}{2}}
 \end{aligned}$$

Maxwell Kinetic Energy Distribution

Second Exercise in Statistics

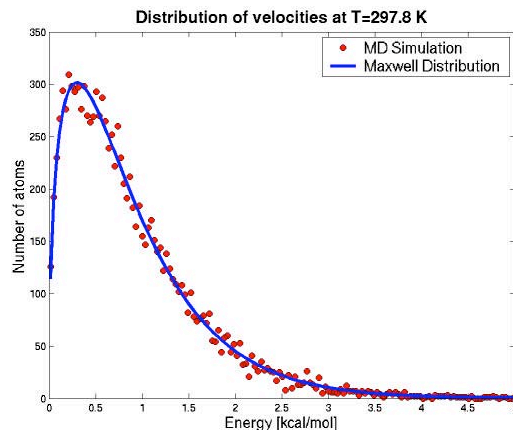
One-dimensional kinetic energy: $\epsilon_k = \frac{1}{2}mv_{\sigma}^2$

$$\tilde{p}(\epsilon_k) = p(v_{\sigma}) \frac{dv_{\sigma}}{d\epsilon_k} \rightarrow \tilde{p}(\epsilon_k) = \sqrt{1/\pi k_B T} \sqrt{1/\epsilon_k} \exp[-\epsilon_k/k_B T]$$

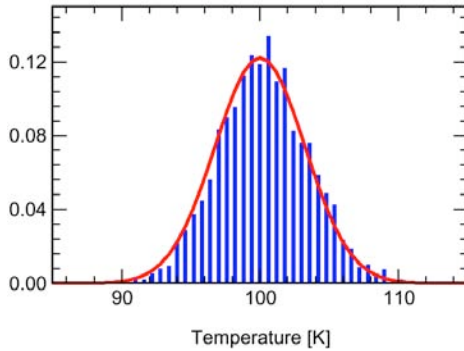
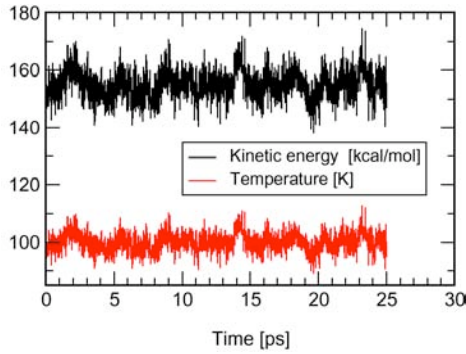
(factor 2 from restriction of integration to positive values)

For the total kinetic energy
(in three dimensions)
holds then

$$\tilde{p}(\epsilon_k) = \frac{4}{\sqrt{\pi}} (k_B T)^{-\frac{3}{2}} \sqrt{\epsilon_k} \exp[-\epsilon_k/k_B T]$$



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



Definition of Temperature

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

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

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

Temperatur Fluctuations

Maxwell distribution

$$dP(v_n) = c \exp(-m v_n^2 / 2k_B T) dv_n \quad (7)$$

Individual kinetic energy $\epsilon_n = m v_n^2 / 2$

$$dP(\epsilon_n) = (\pi T_0 \epsilon_n)^{-1/2} \exp(-\epsilon_n / k_B T_0) d\epsilon_n \quad (8)$$

One can derive

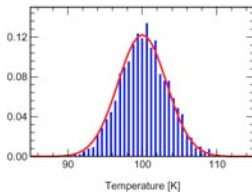
$$\langle \epsilon_n \rangle = T_0 / 2 \quad (9)$$

$$\langle \epsilon_n^2 \rangle = 3 T_0^2 / 4 \quad (10)$$

$$\langle \epsilon_n^2 \rangle - \langle \epsilon_n \rangle^2 = T_0^2 / 2 \quad (11)$$

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

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

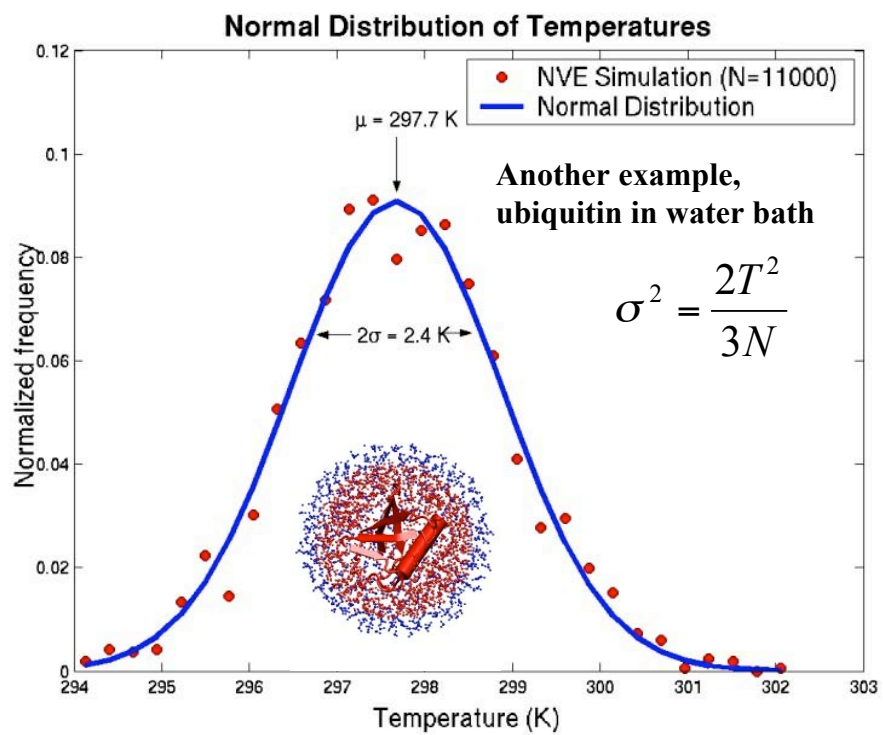


The distribution function for the temperature ($T = 2E_{kin}/3k_B$) fluctuations $\Delta T = T - T_0$ is then

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

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

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

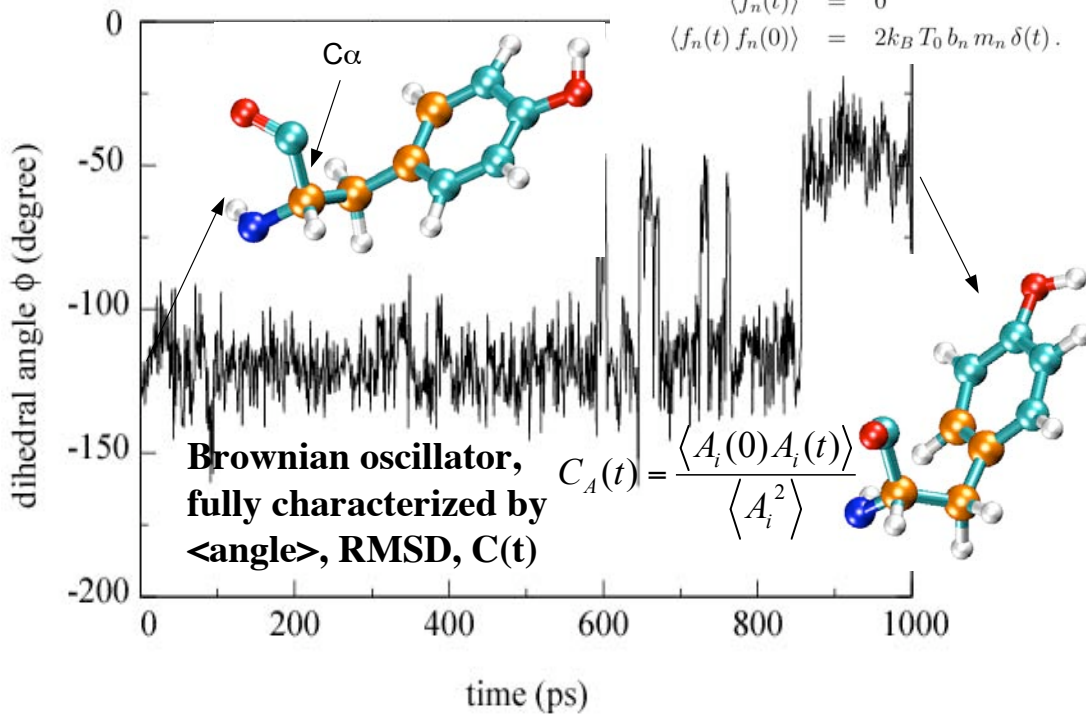


Show BPTI trajectory

$$m_n \frac{d^2 x_n(t)}{dt^2} = -\nabla_{x_n} V - m_n b_n \frac{dx_n(t)}{dt} + f_n(t)$$

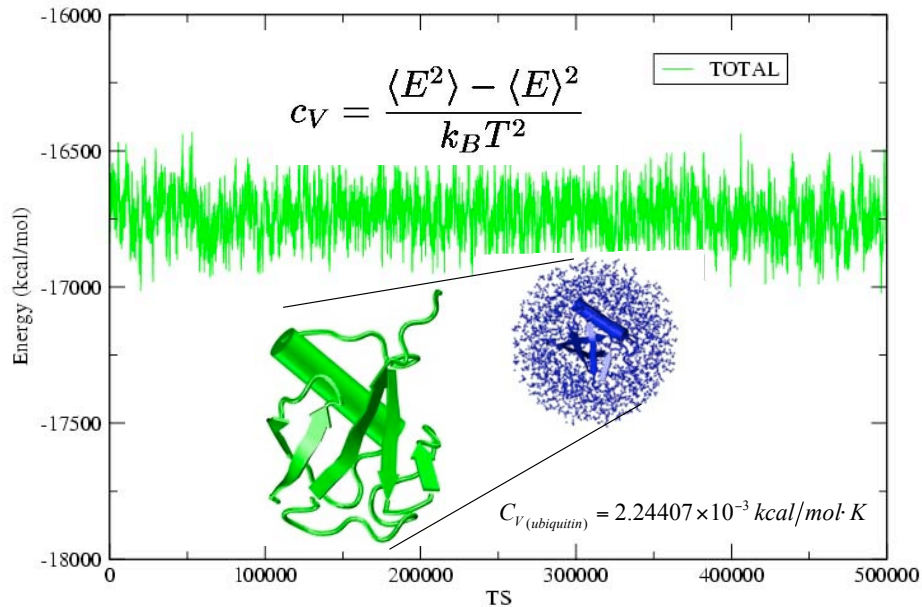
Dihedral Angle

Langevin dynamics in strong friction limit

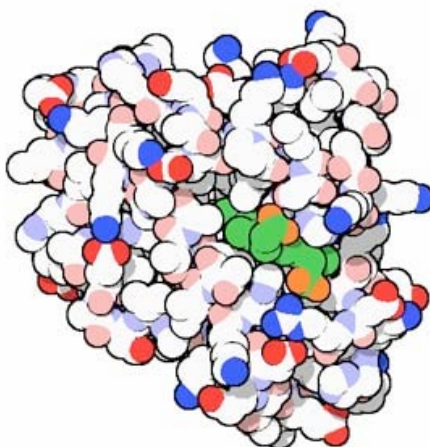


Specific Heat of a Protein

Total energy of ubiquitin (NVE ensemble)



Myoglobin

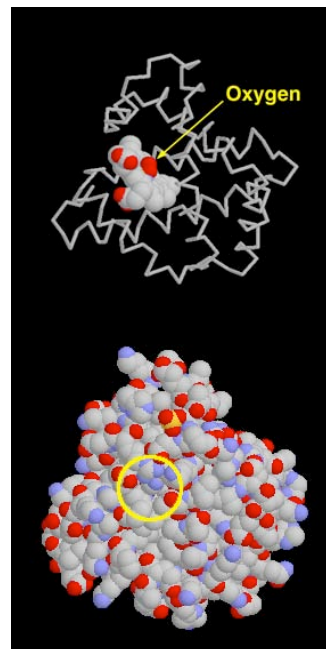


Myoglobin is a small, bright red protein. It is very common in muscle cells, and gives meat much of its red color. Its job is to store oxygen, for use when muscles are hard at work. If you look at John Kendrew's PDB file, you will notice that the myoglobin that he used was taken from sperm whale muscles. As you can imagine, marine whales and dolphins have a great need for myoglobin, so that they can store extra oxygen for use in their deep dives undersea.

[PDB Molecule of the Month: Myoglobin](#)

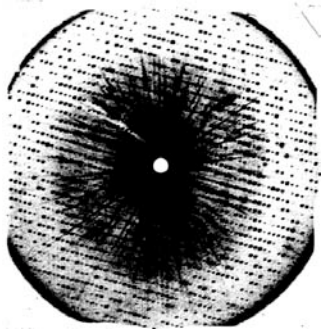
Oxygen Bound to Myoglobin

This structure of myoglobin, with the accession code **1mbo**, shows the location of oxygen. The iron atom at the center of the heme group holds the oxygen molecule tightly. Compare the two pictures. The first shows only a set of thin tubes to represent the protein chain, and the oxygen is easily seen. But when all of the atoms in the protein are shown in the second picture, the oxygen disappears, buried inside the protein. So how does the oxygen get in and out, if it is totally surrounded by protein? In reality, myoglobin (and all other proteins) are constantly in motion, performing small flexing and breathing motions. Temporary openings constantly appear and disappear, allowing oxygen in and out. The structure in the PDB is merely one snapshot of the protein, caught when it is in a tightly-closed form. Looking at the static structure held in the PDB, we must imagine the dynamic structure that actually exists in nature. The two pictures above were created with RASMOL. You can create similar pictures by accessing the PDB file **1mbo**, and then clicking on "View Structure." Try switching between the two types of pictures shown above, to prove to yourself that the oxygen is buried in this structure!



[PDB Molecule of the Month: Myoglobin](#)

Myoglobin, the first protein with known structure



Diffraction pattern observed



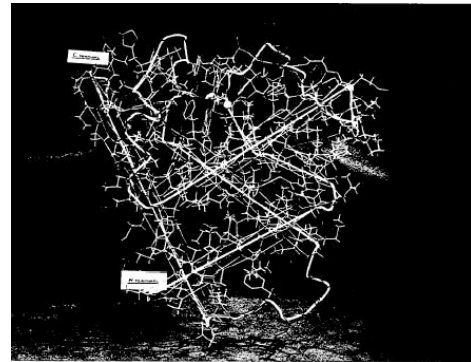
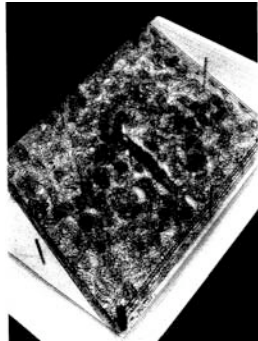
John Cowdery Kendrew
Nobel Prize in Chemistry
Jointly with Max Perutz



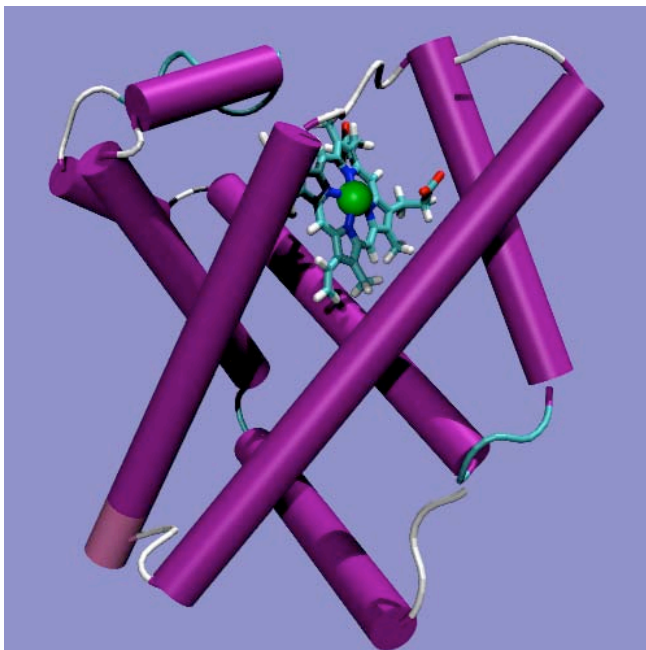
Structure model at 6 Å resolution

Higher resolution
Model:

- 1) Construct electron density map
- 2) Build model

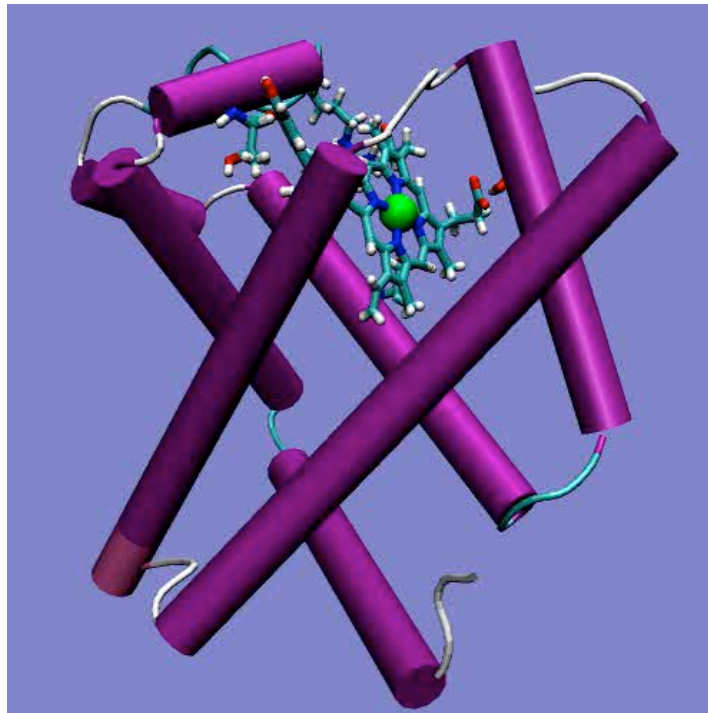


Myoglobin with heme group



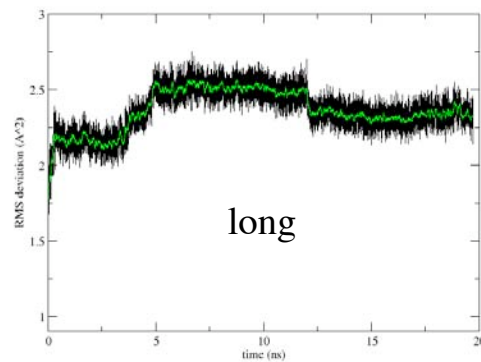
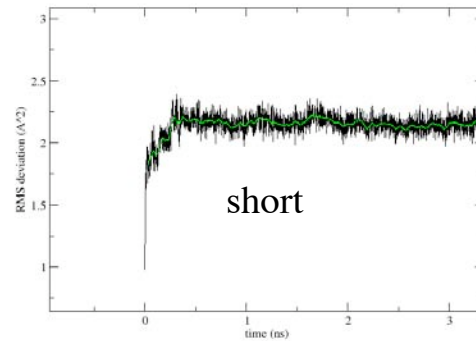
- Myoglobin from PDB structure 1A6M
- X-ray crystal structure at 1.00 Å resolution.
- Steps seen in RMSD are due primarily to tilting of the helix to the upper right of the heme in the picture...

Myoglobin Dynamics to Probe Motion of Fe



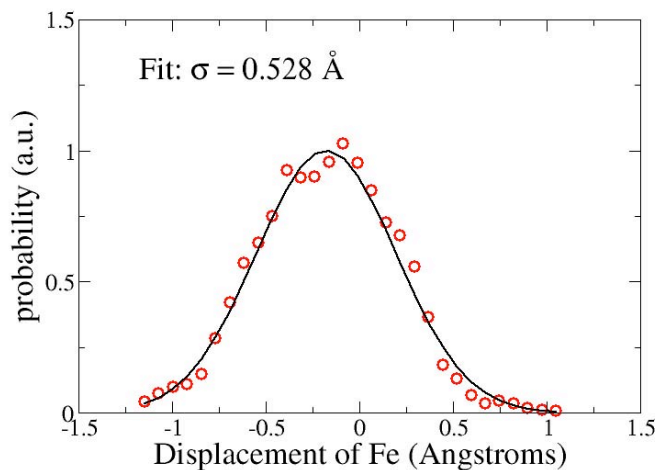
Setup and Equilibration

- Remove oxygen liganded to Fe
- Minimize 1000 steps, fixing the C_{α} atoms.
- Heat for 5 ps with Langevin dynamics at 300 K, fixed C_{α} atoms.
- Simulate in NVT ensemble for 19 ns, saving coordinates every ps.



Obtain “f” from position distribution

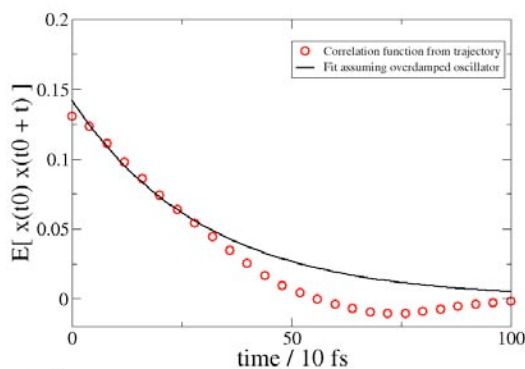
- Best fit “by eye” is $\sigma=0.528 \text{ \AA}$.
- However: standard deviation gives $\sigma=0.36$ ($f=kT/\sigma^2$) = 319 pN/Å; this is what we use below.



Obtain diffusion coefficient from position autocorrelation function

Once we know the restoring force, the diffusion coefficient can be obtained from the position autocorrelation function:

$$\langle x(t)x(0) \rangle = \frac{k_B T}{2f} \exp[-Dft/k_B T]$$



$$D f/kT = .0321$$

$$D = 0.0042 \text{ \AA}^2/10 \text{ fs}$$

$$= 0.42 \text{ \AA}^2/\text{ps.}$$

$$\text{Compare: } D_{\text{water}} = 0.24 \text{ \AA}^2/\text{ps}$$

Position autocorrelation: underdamped case

The Langevin equation governing underdamped motion is

$$\ddot{x} + b\dot{x} + \omega^2 x = \eta(t)$$

The position correlation function is given by

$$\langle x(t)x(0) \rangle = \langle x(0)^2 \rangle e^{-bt/2} \left[\cos \Omega(t) + \frac{b}{2\Omega} \sin \Omega(t) \right]$$

Using $\Omega = \sqrt{\omega^2 + b^2/4}$

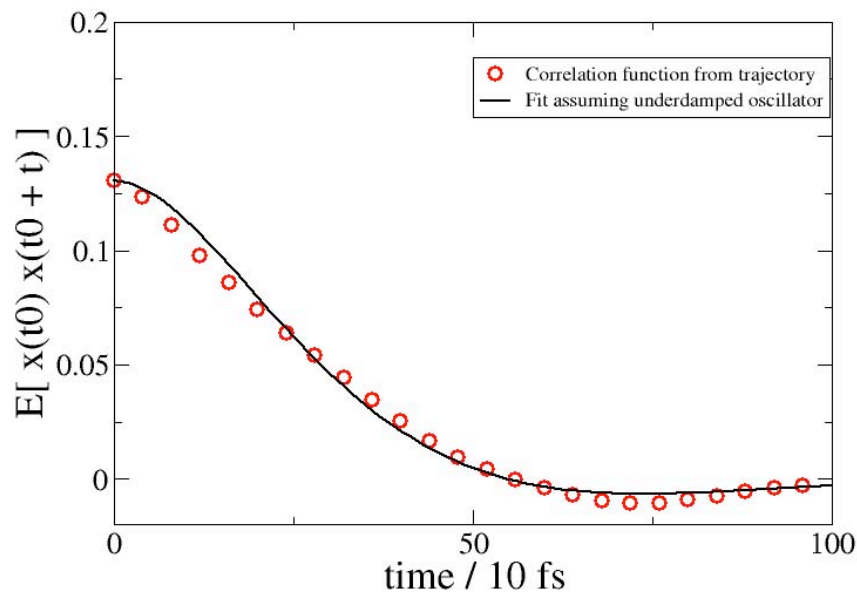
$$m = f/\omega^2 \quad (\text{from } F = ma)$$

$$\gamma = mb$$

$$D = k_B T / \gamma = \frac{k_B T \omega^2}{f b}$$

we can solve for D.

Diffusion coefficient from underdamped oscillator



Fitting parameters: $\Omega = 0.0426$; $b = 0.0811$; $\omega^2 = \Omega^2 + b^2/4 = 34.59/\text{ps}^2$. $D = 0.556 \text{ \AA}^2/\text{ps}$.

Mossbauer line shape function

The lineshape $I(\omega)$ we are trying to calculate is given by

$$I(\omega) = \frac{\sigma_0 \Gamma}{4} \int_{-\infty}^{\infty} dt e^{-i\omega t - \frac{1}{2}\Gamma|t|} G(\mathbf{k}, t) \quad (1)$$

where $G(\mathbf{k}, t)$ is given by

$$G(\mathbf{k}, t) = \int d\mathbf{r} \int d\mathbf{r}_o e^{i\mathbf{k} \cdot (\mathbf{r} - \mathbf{r}_o)} p(\mathbf{r}, t | \mathbf{r}_o, 0) p_0(\mathbf{r}_o) \quad (2)$$

Notice that $G(\mathbf{k}, t)$ is just the autocorrelation function of $\exp(-i\mathbf{k} \cdot \mathbf{r})$.

Moessbauer Line Shape Function - Sampled and Matched to Analytical Formula

