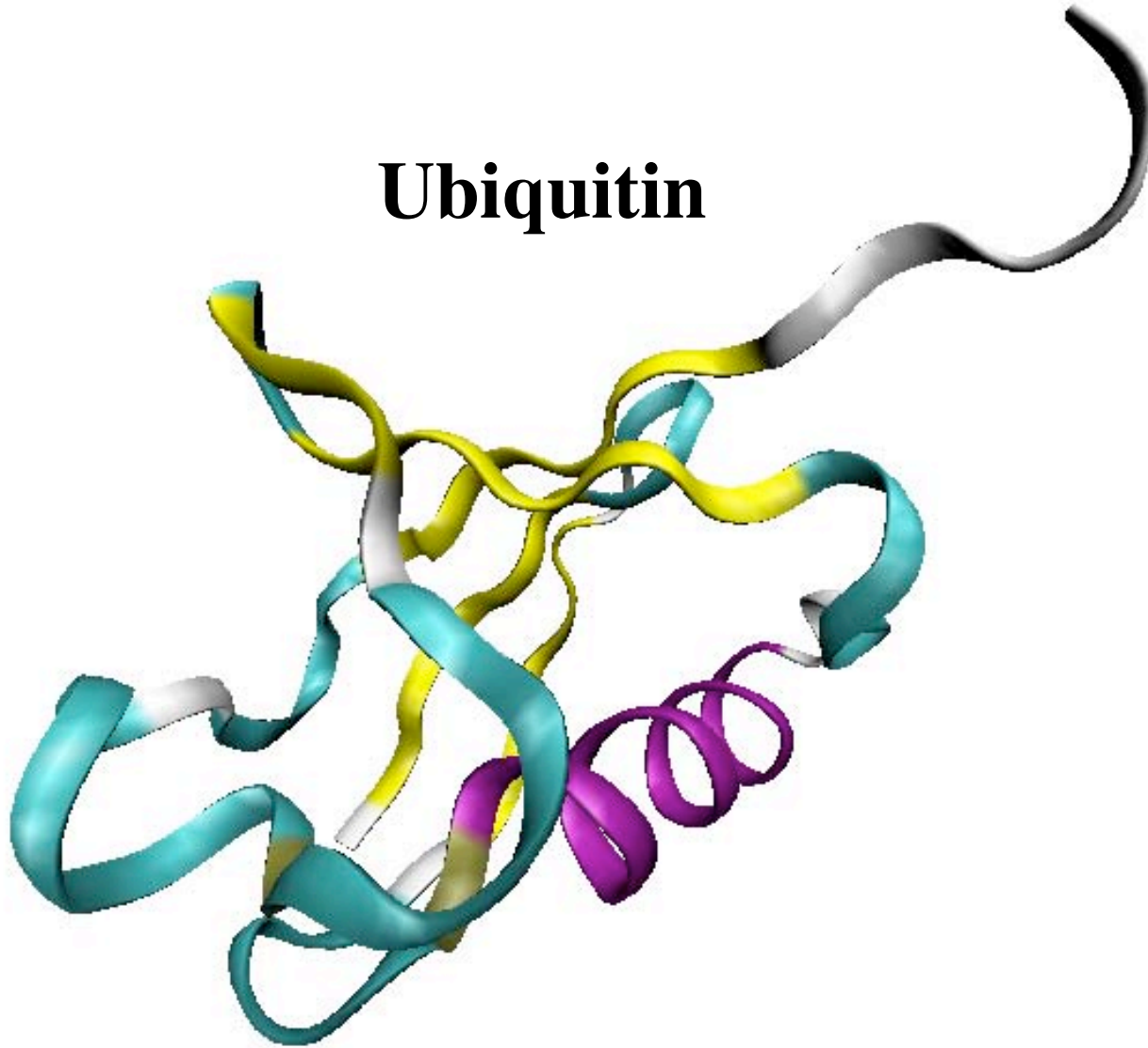


Molecular Dynamics of Proteins

Ubiquitin

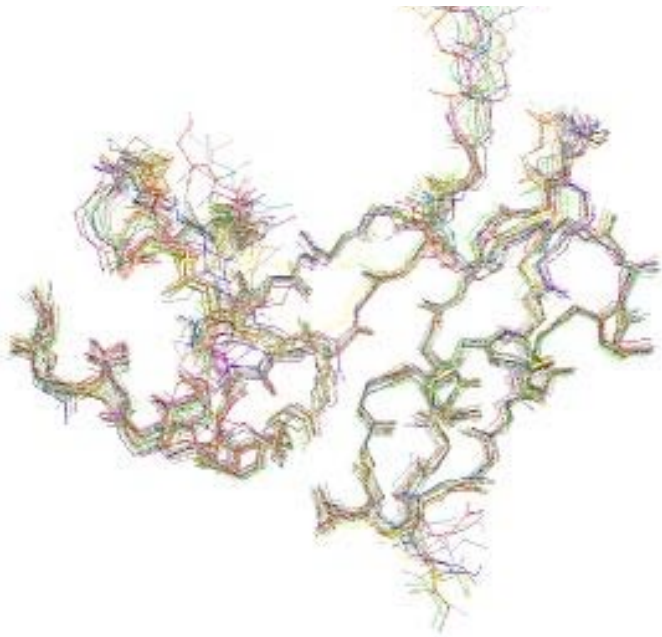
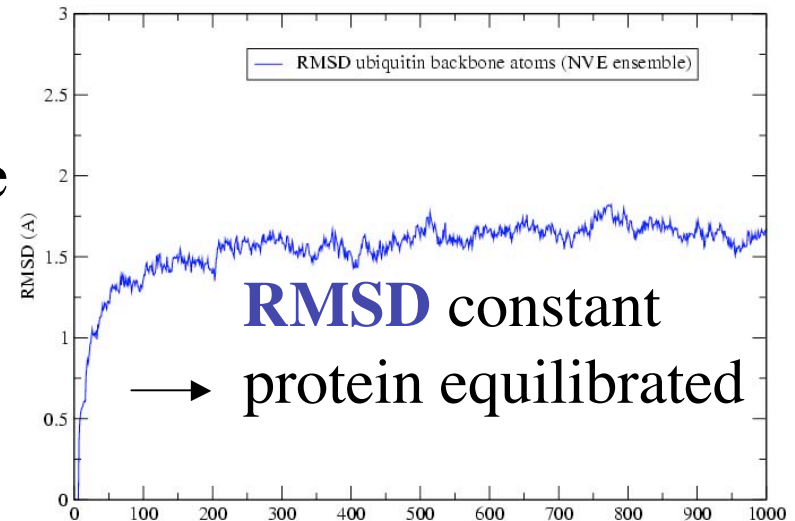


Equilibrium Properties of Proteins

Ubiquitin

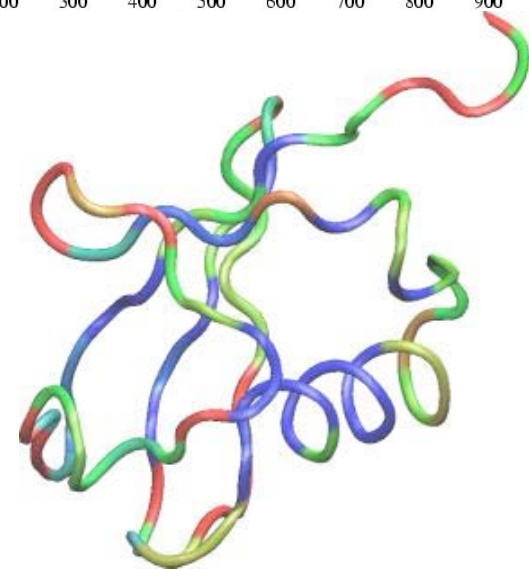
Root Mean Squared Deviation: measure for equilibration and protein flexibility

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



NMR structures
aligned together to see flexibility

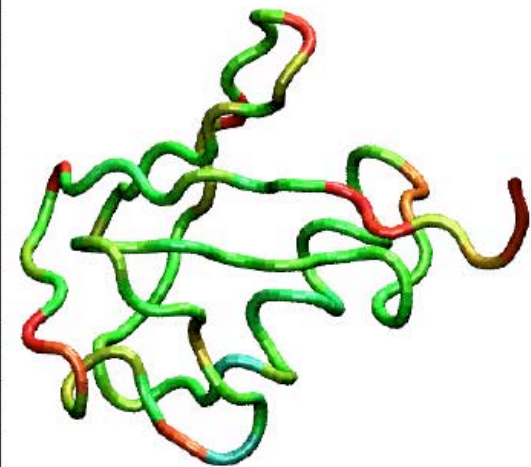
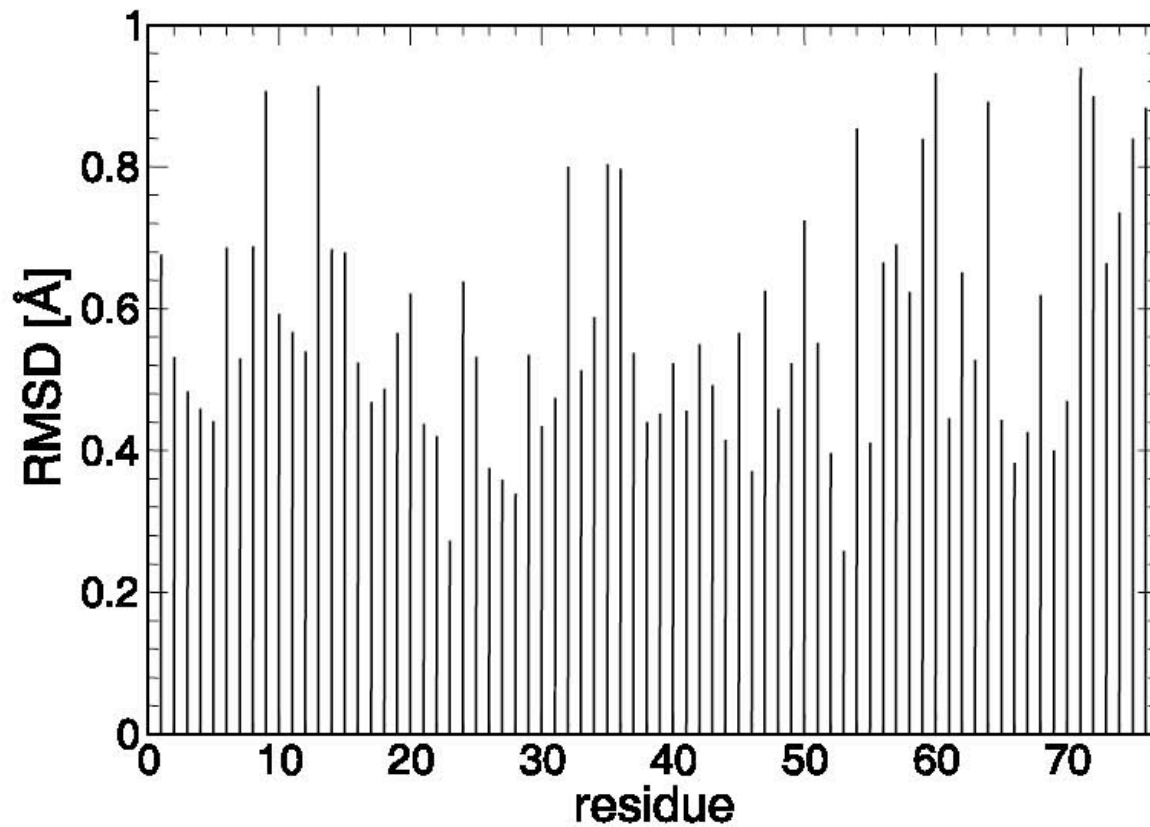
**Protein sequence
exhibits
characteristic
permanent
flexibility!**



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

Thermal Motion of Ubiquitin from MD

RMSD values per residue



Thermal Motion of Ubiquitin from MD

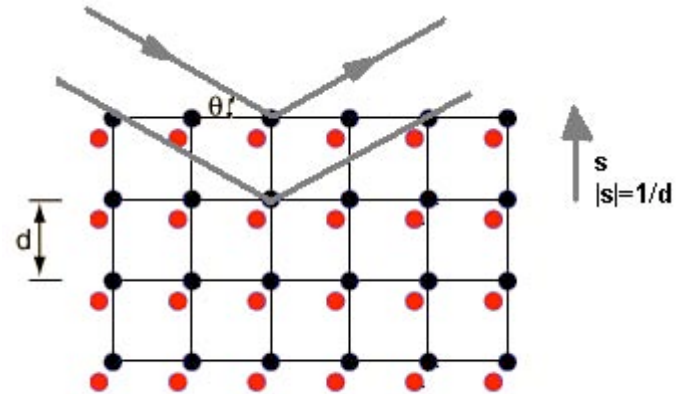
Temperature Dependence of Crystal Diffraction (Debye-Waller factor)

Bragg's law

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

structure factor

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



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:

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

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

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

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

Debye-Waller factor

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

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)

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

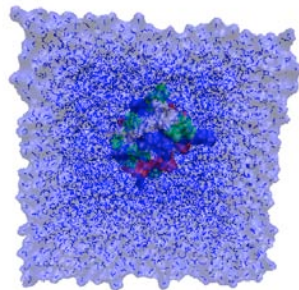
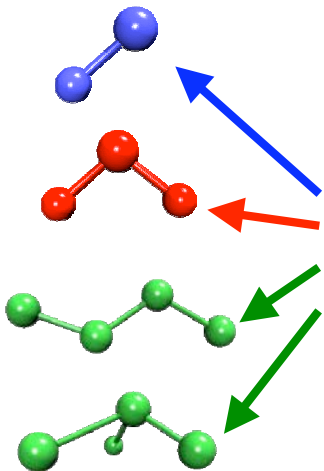
$$\underbrace{\sum_{\text{dihedrals}} k_i^{\text{dihe}} [1 + \cos(n_i \phi_i + \delta_i)]}_{U_{\text{dihedral}}} +$$

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

Potential energy (not all quadratic)

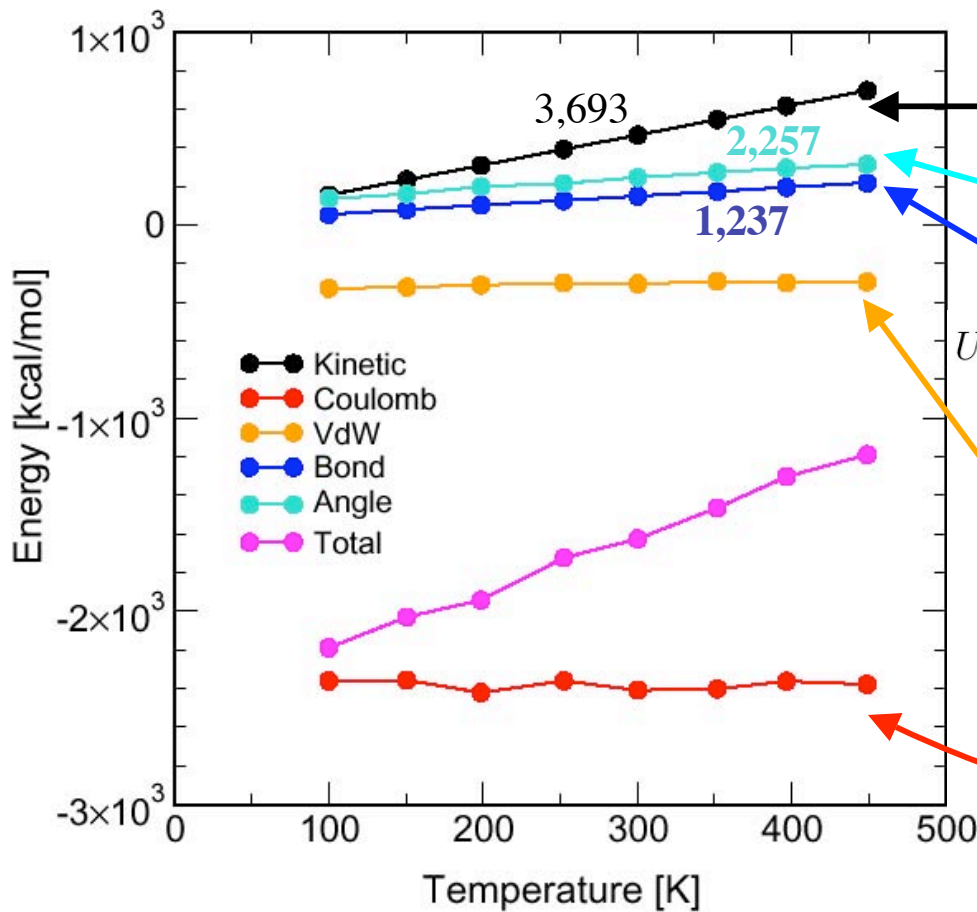
from ubiquitin.psf

26190	!NATOM:	atoms
17867	!NBOND:	bonds
10572	!NTHETA:	angles
3293	!NPHI:	dihedrals
204	!NIMPHI:	impropers



Equilibrium Properties of Proteins

Energies: kinetic and potential



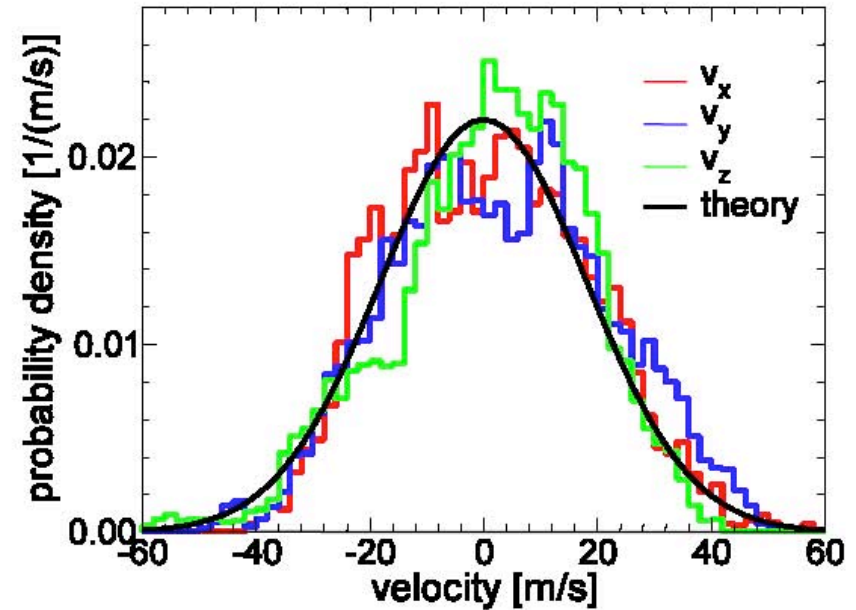
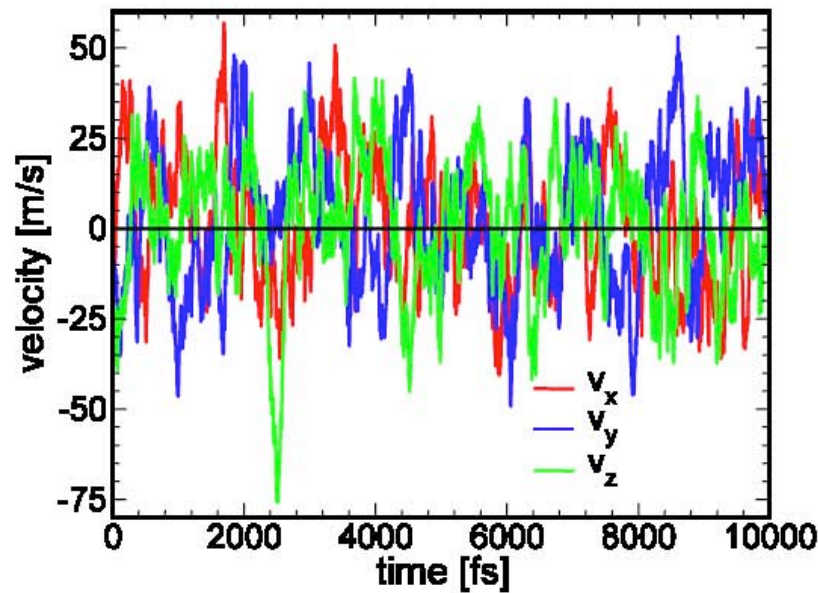
$$\left\langle \sum_j \frac{1}{2} m_j v_j^2 \right\rangle = \frac{3}{2} N k_B T$$

Kinetic energy (quadratic)

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

Potential energy (not all quadratic)

Maxwell Distribution of Atomic Velocities



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

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

Mean Kinetic Energy

Exercise in Statistics

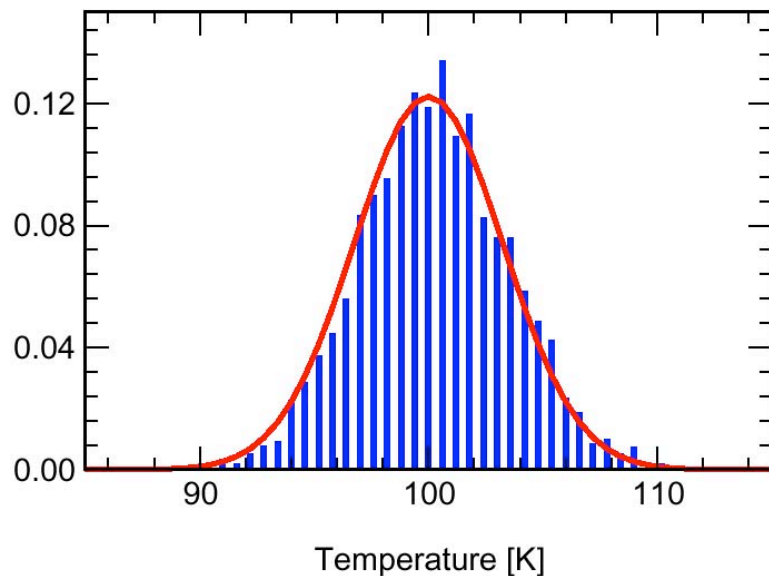
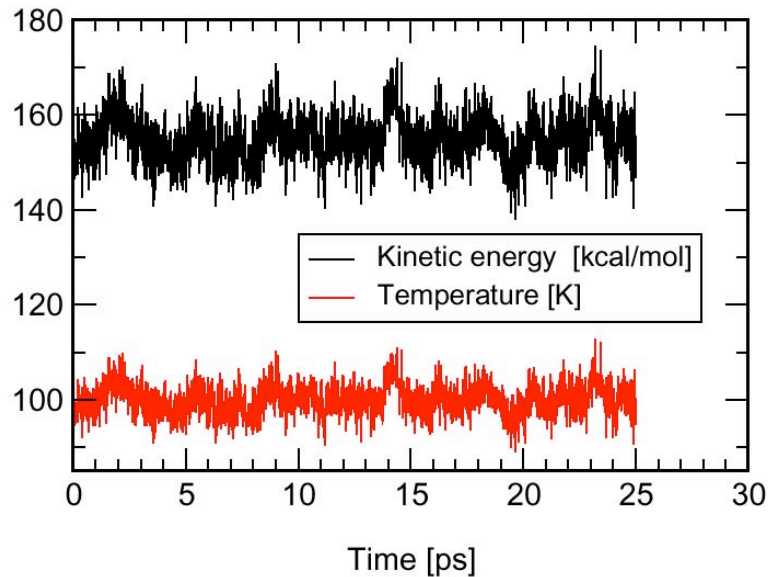
$$\begin{aligned}\langle \frac{1}{2}mv^2 \rangle &= \int_{-\infty}^{\infty} dv \left(\frac{1}{2}mv^2 \right) p(v) \\ &= \sqrt{\frac{m}{2\pi k_B T}} \int_{-\infty}^{\infty} dv \left(\frac{1}{2}mv^2 \right) \exp \left[-\frac{mv^2}{2k_B T} \right] \\ &= k_B T \sqrt{\frac{1}{\pi}} \int_{-\infty}^{\infty}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

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

$$\int_0^{\infty} dy y^m \exp[-y^2] = \frac{1}{2} \Gamma \left(\frac{m+1}{2} \right)$$

$$\Gamma(x+1) = x \Gamma(x), \quad \Gamma\left(\frac{1}{2}\right) = \sqrt{\frac{1}{2}}$$

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?

Maxwell Kinetic Energy Distribution

Second Exercise in Statistics

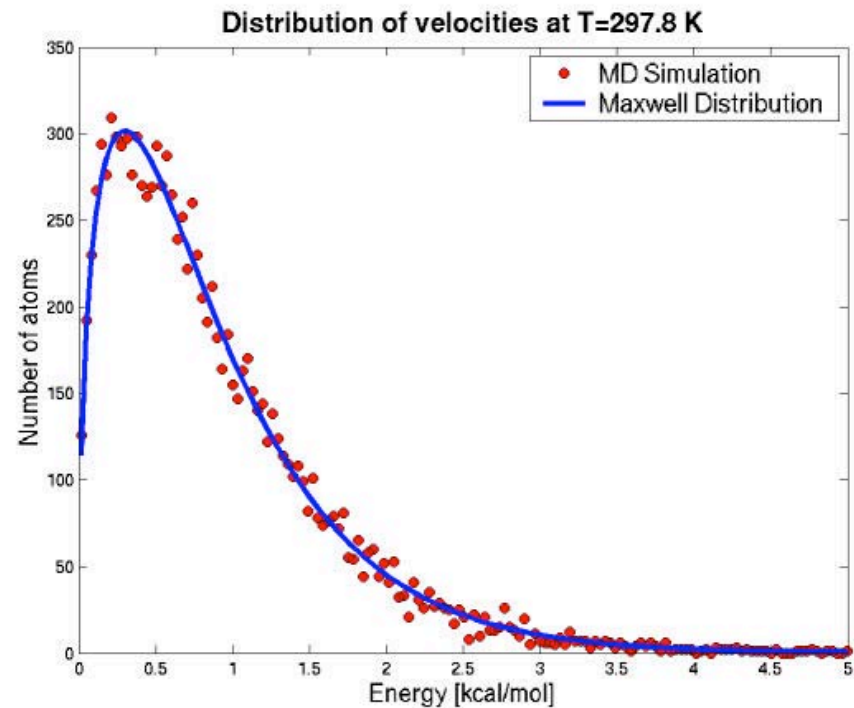
One-dimensional kinetic energy: $\epsilon_k = \frac{1}{2}mv_\sigma^2$

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

(factor 2 from restriction of integration to positive values)

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

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



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

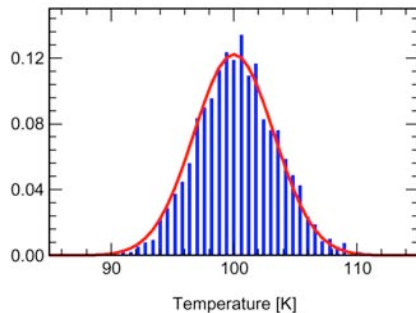
$$P(E_{kin}) = c \exp\left(\frac{-(E_{kin} - \langle E_{kin} \rangle)^2}{2 \left(\frac{3Nk_B^2 T_0^2}{2}\right)}\right) \quad (12)$$

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

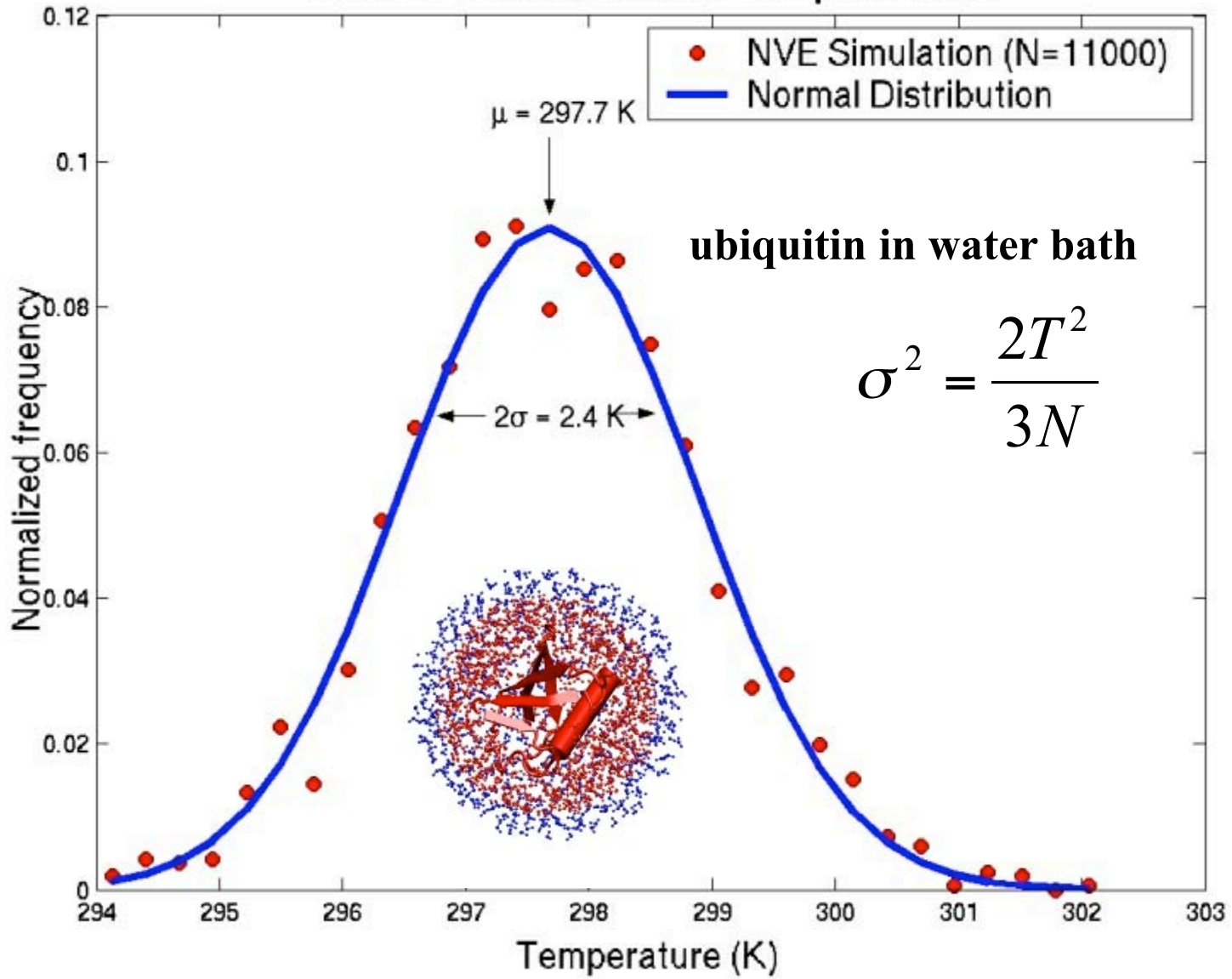
$$P(\Delta T) = c \exp[-(\Delta T)^2/2\sigma^2], \quad \sigma^2 = 2T^2/3N \quad (13)$$

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!



Normal Distribution of Temperatures

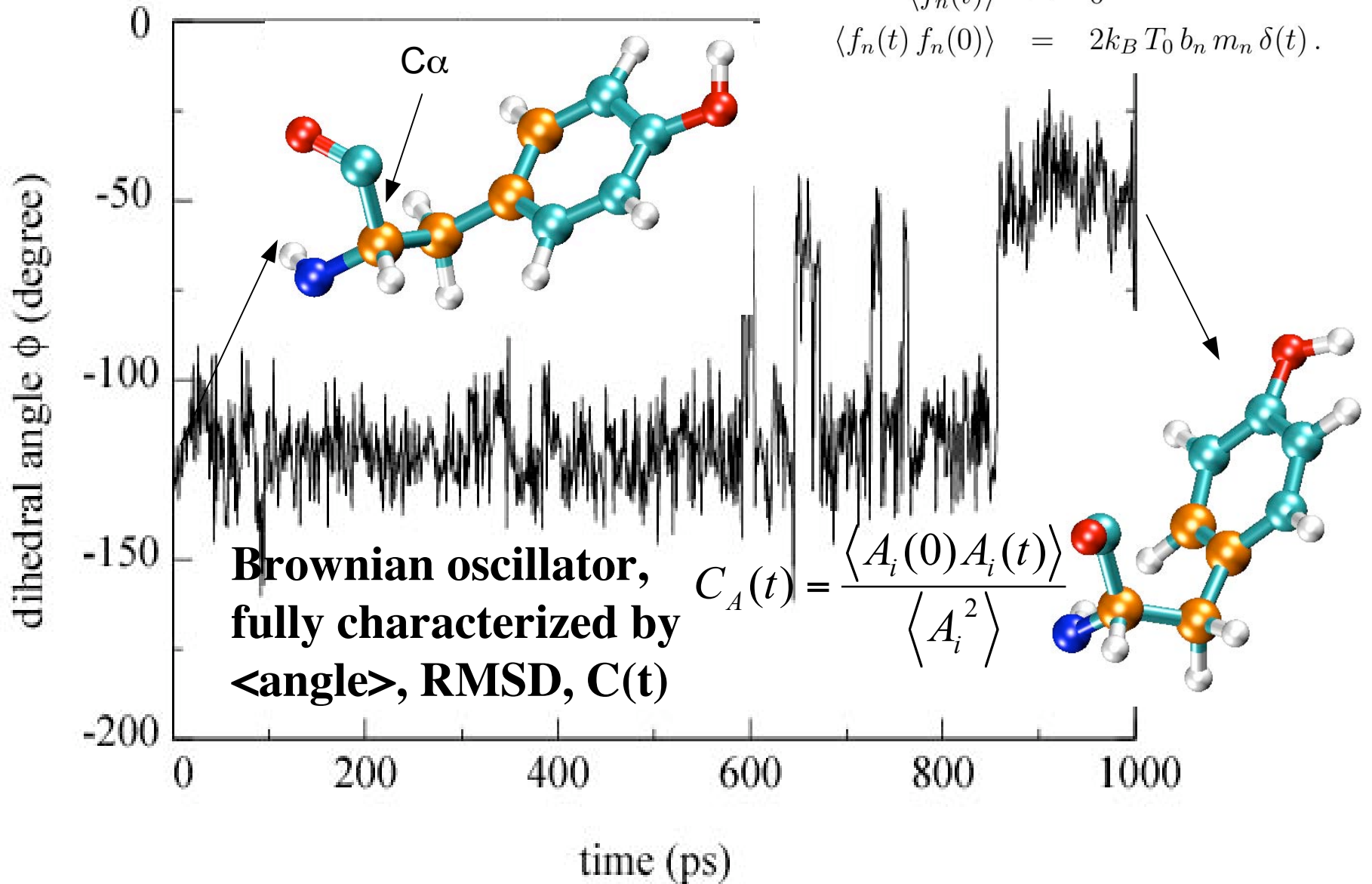


Dihedral Angle

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

Langevin dynamics in strong friction limit

$$\begin{aligned} \langle f_n(t) \rangle &= 0 \\ \langle f_n(t) f_n(0) \rangle &= 2k_B T_0 b_n m_n \delta(t) . \end{aligned}$$



Specific Heat of a Protein

Total energy of ubiquitin (NVE ensemble)

