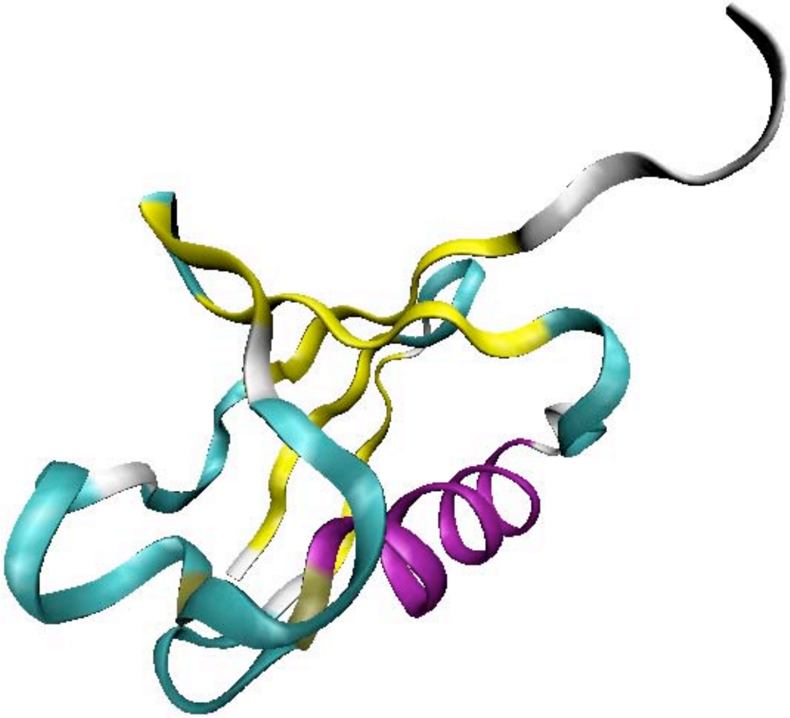
Statistical Mechanics of Proteins



Ubiquitin

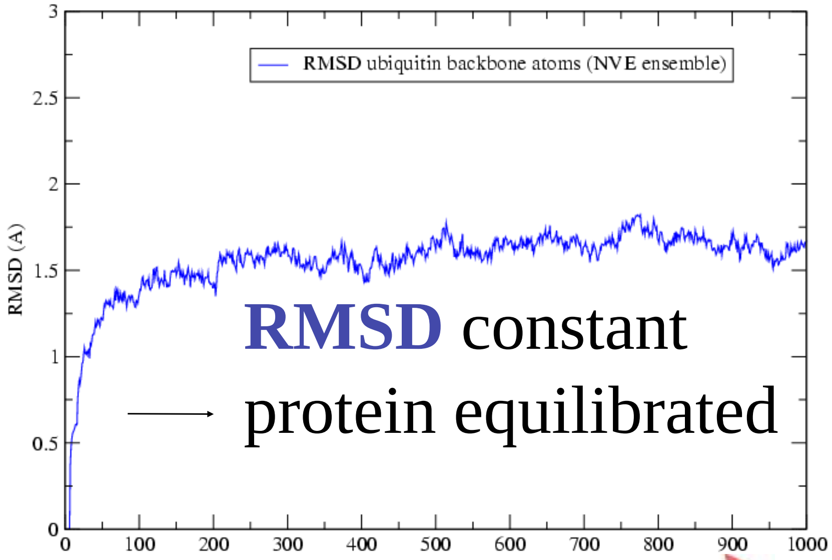
Show molecular dynamics trajectory in VMD

Equilibrium Properties of Proteins

Ubiquitin

Root Mean Squared Deviation: measure for equilibration and protein flexibility

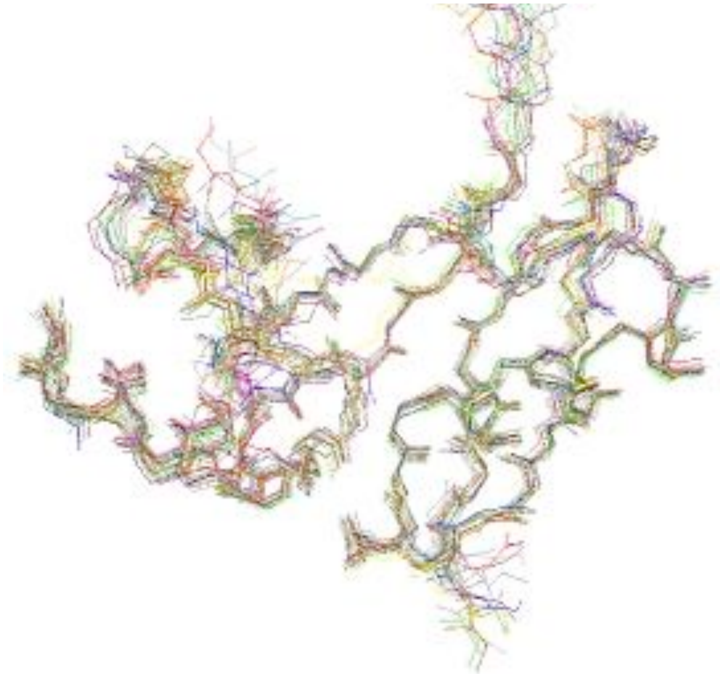
$$RMSD_\alpha = \sqrt{\frac{\sum_{j=1}^{N_t}\sum_{\alpha=1}^{N_\alpha}(\vec{r}_\alpha(t_j)-\langle\vec{r}_\alpha\rangle)^2}{N_\alpha}}$$



RMSD constant

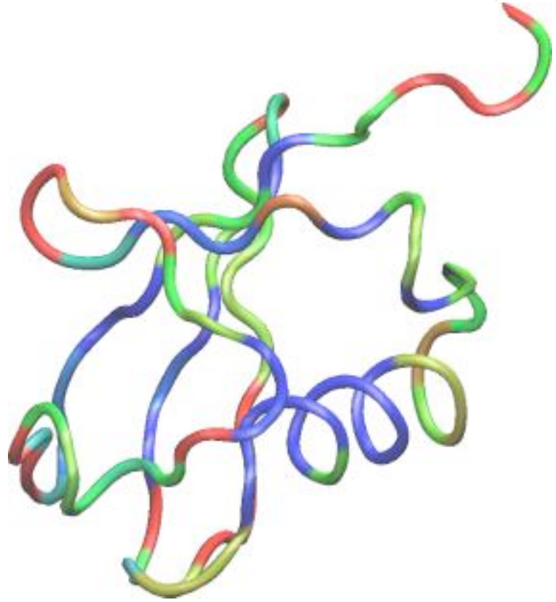
→ protein equilibrated

Protein sequence exhibits characteristic permanent flexibility!



NMR structures

aligned together to see flexibility

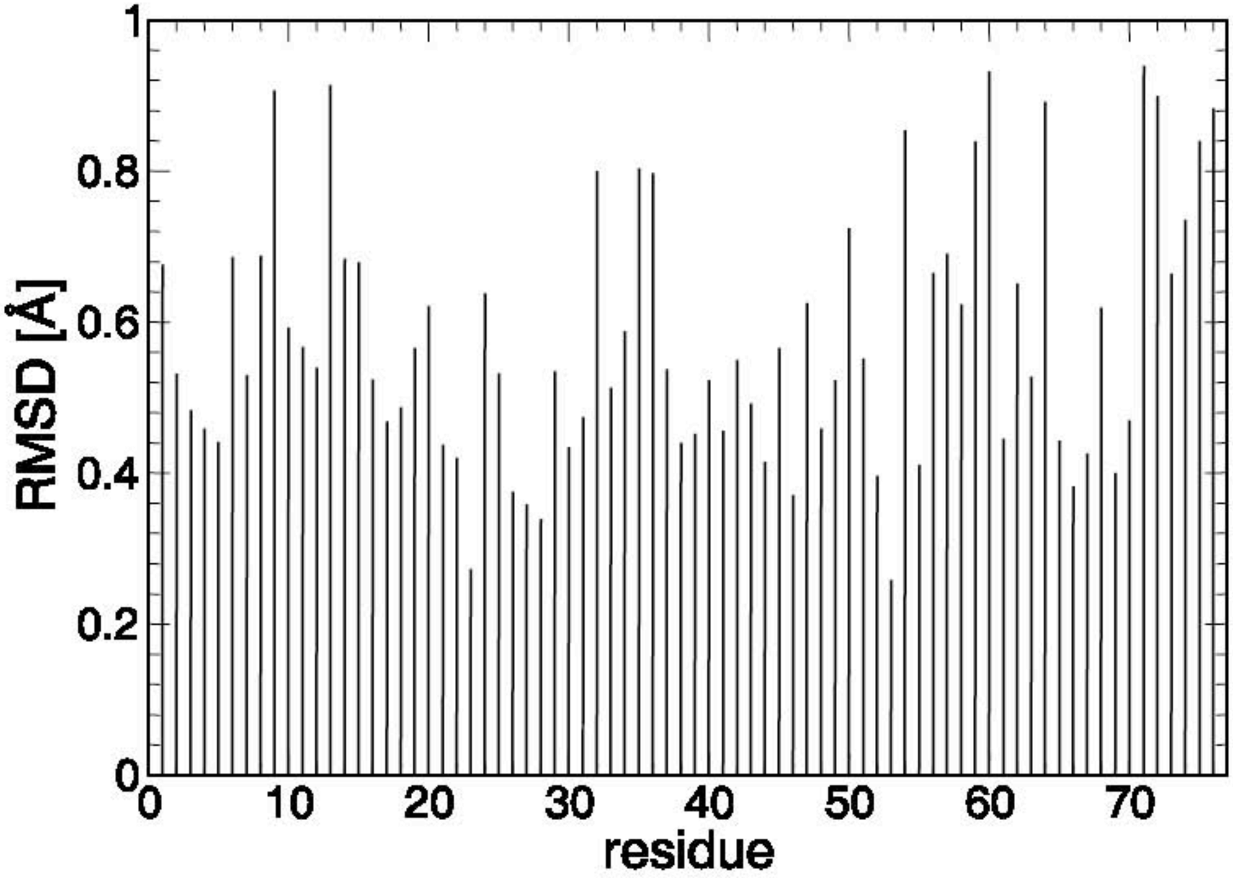


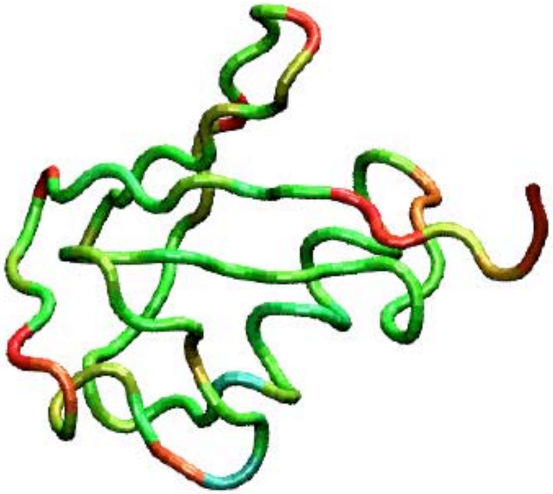
MD simulation

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

Thermal Motion of Ubiquitin from MD

RMSD values per residue



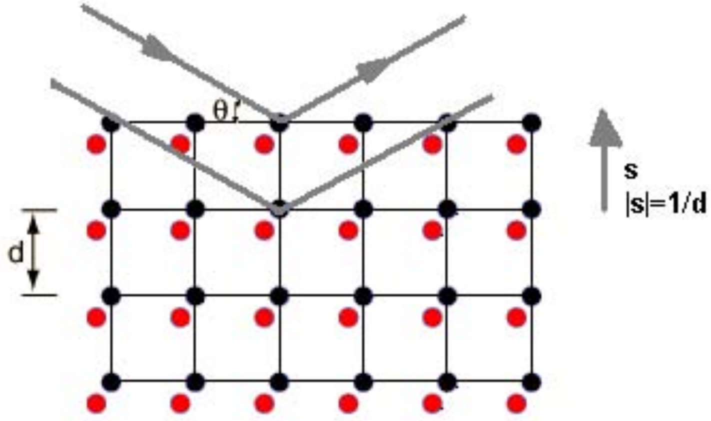


Thermal Motion of Ubiquitin from MD

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:

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

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

One can carry out the expansion further and show

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

Using for the thermal amplitude of the harmonic oscillator

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

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

?

temperature
dependence

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

Kinetic energy (quadratic)

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

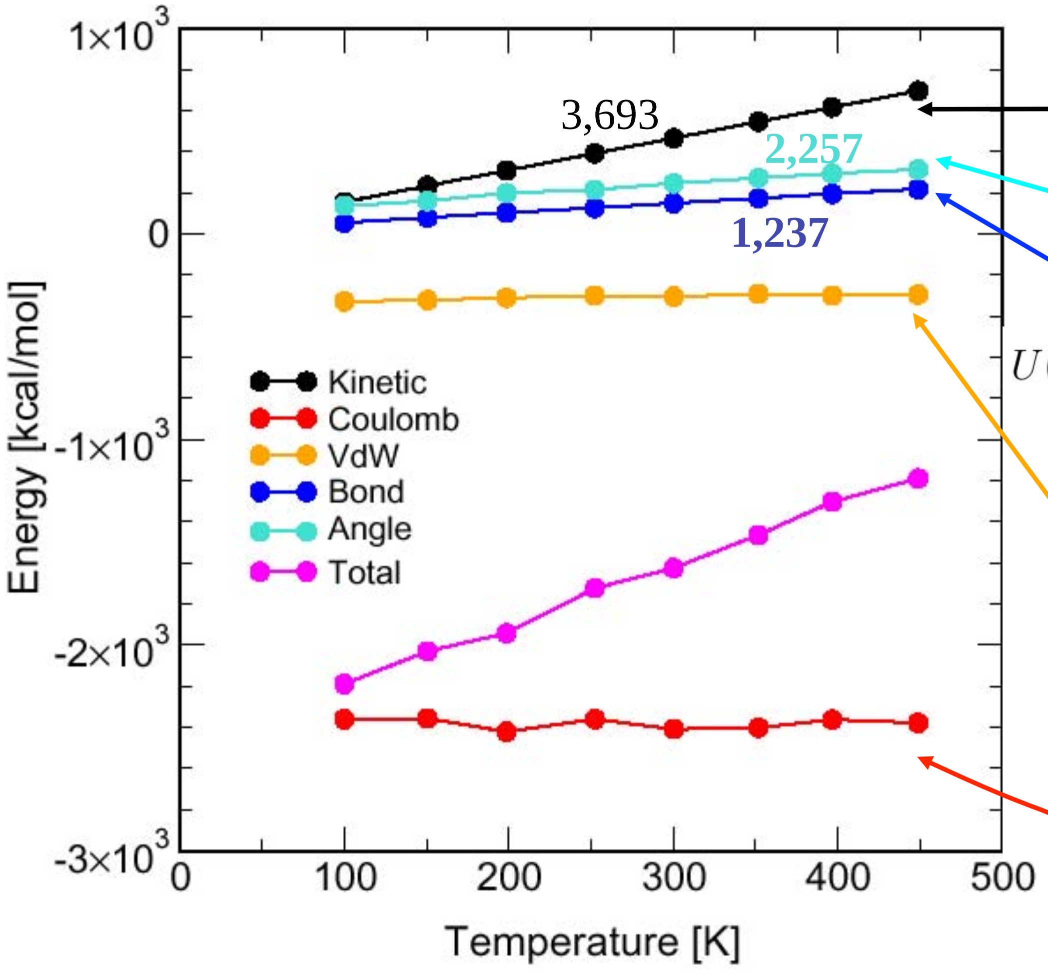
$$\underbrace{\sum_{dihedrals} k_i^{dihe}[1 + \cos(n_i\phi_i + \delta_i)]}_{U_{dihedral}} +$$

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

Potentialc energy (not all quadratic)

Equilibrium Properties of Proteins

Energies: kinetic and potential



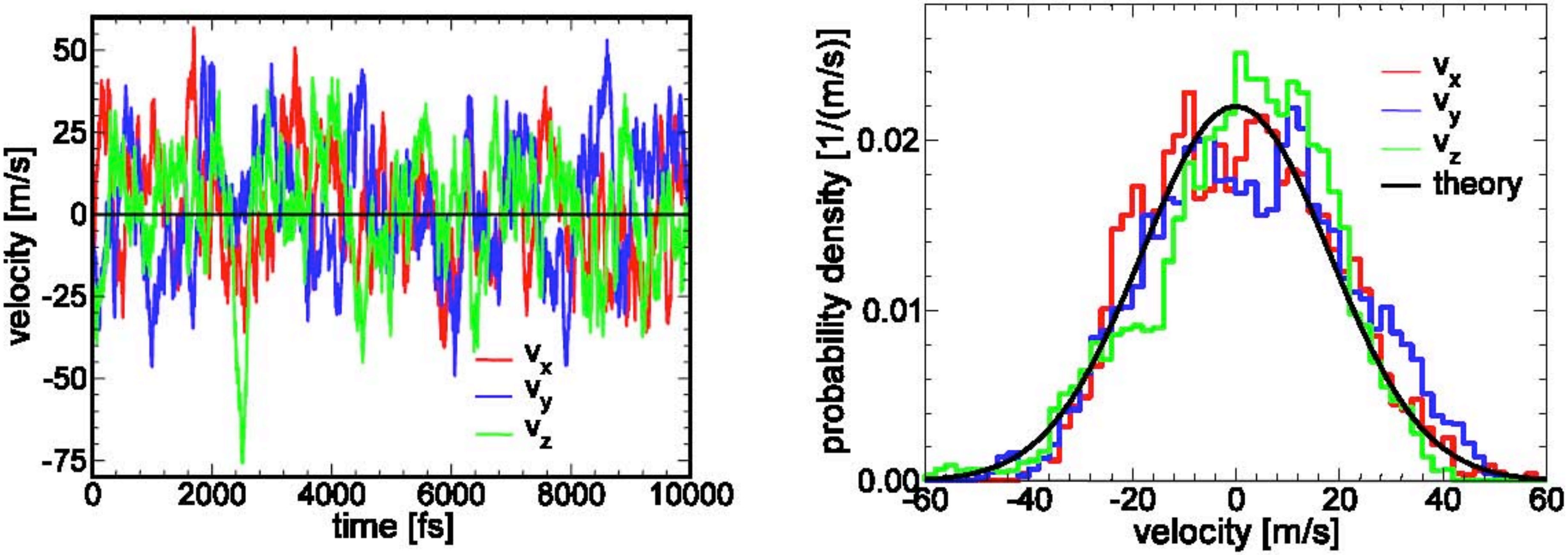
$$\langle \sum_j \frac{1}{2} m_j v_j^2 \rangle \;=\; \frac{3}{2} N\, k_B\, T$$

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)

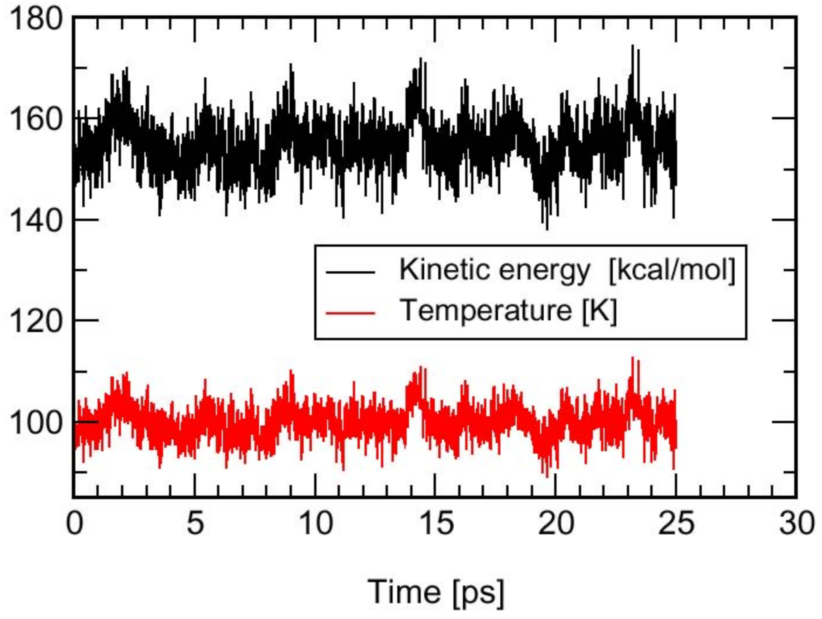
Maxwell Distribution of Atomic Velocities

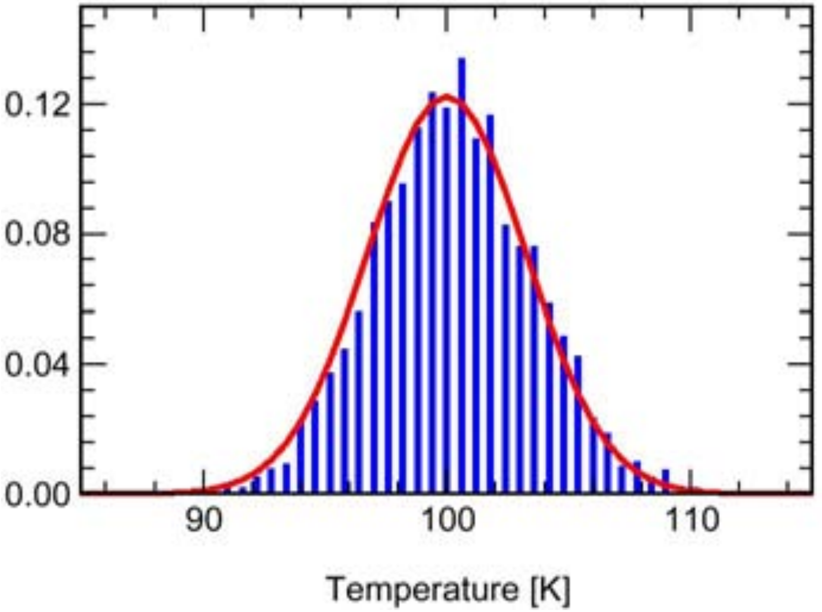


$$p(v_\sigma) = \sqrt{\frac{m}{2\pi k_B T}} \exp\left[-\frac{m v_\sigma^2}{2 k_B T}\right]$$

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

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





Definition of Temperature

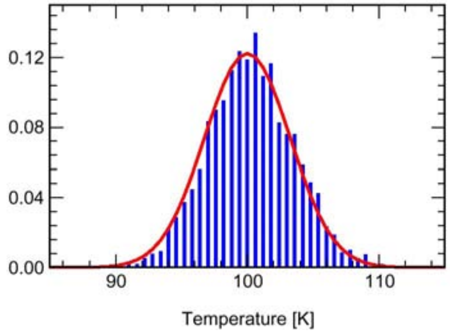
$$\langle\sum_j \frac{1}{2} m_j v_j^2\rangle = \frac{3}{2} N\, k_B\, T$$

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

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

Temperatur Fluctuations

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



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

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

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

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

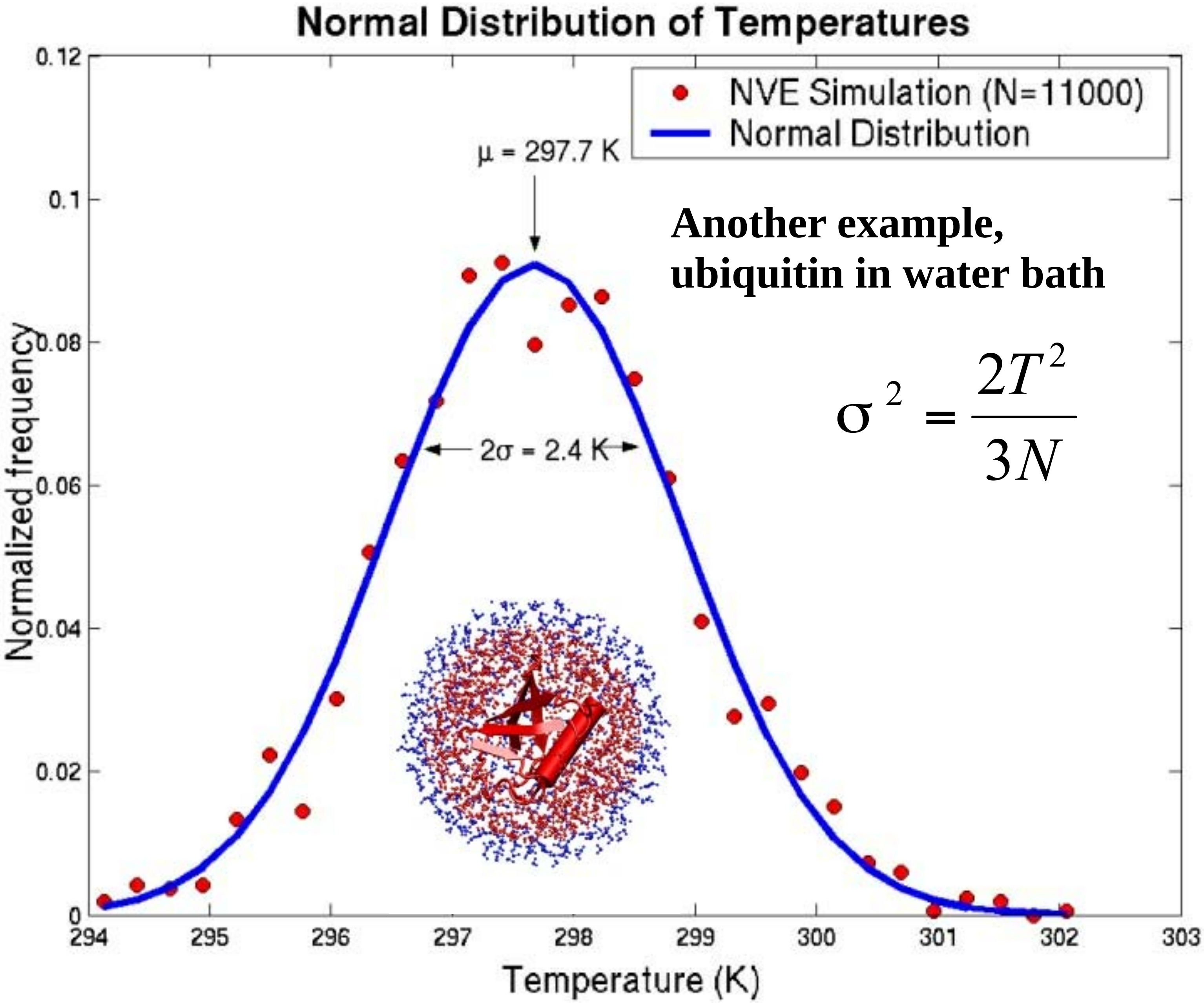
The distribution of the total kinetic energy $E_{kin} = \sum_j \frac{1}{2}m_jv_j^2$, according to the central limit theorem, is approximately Gaussian

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

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

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

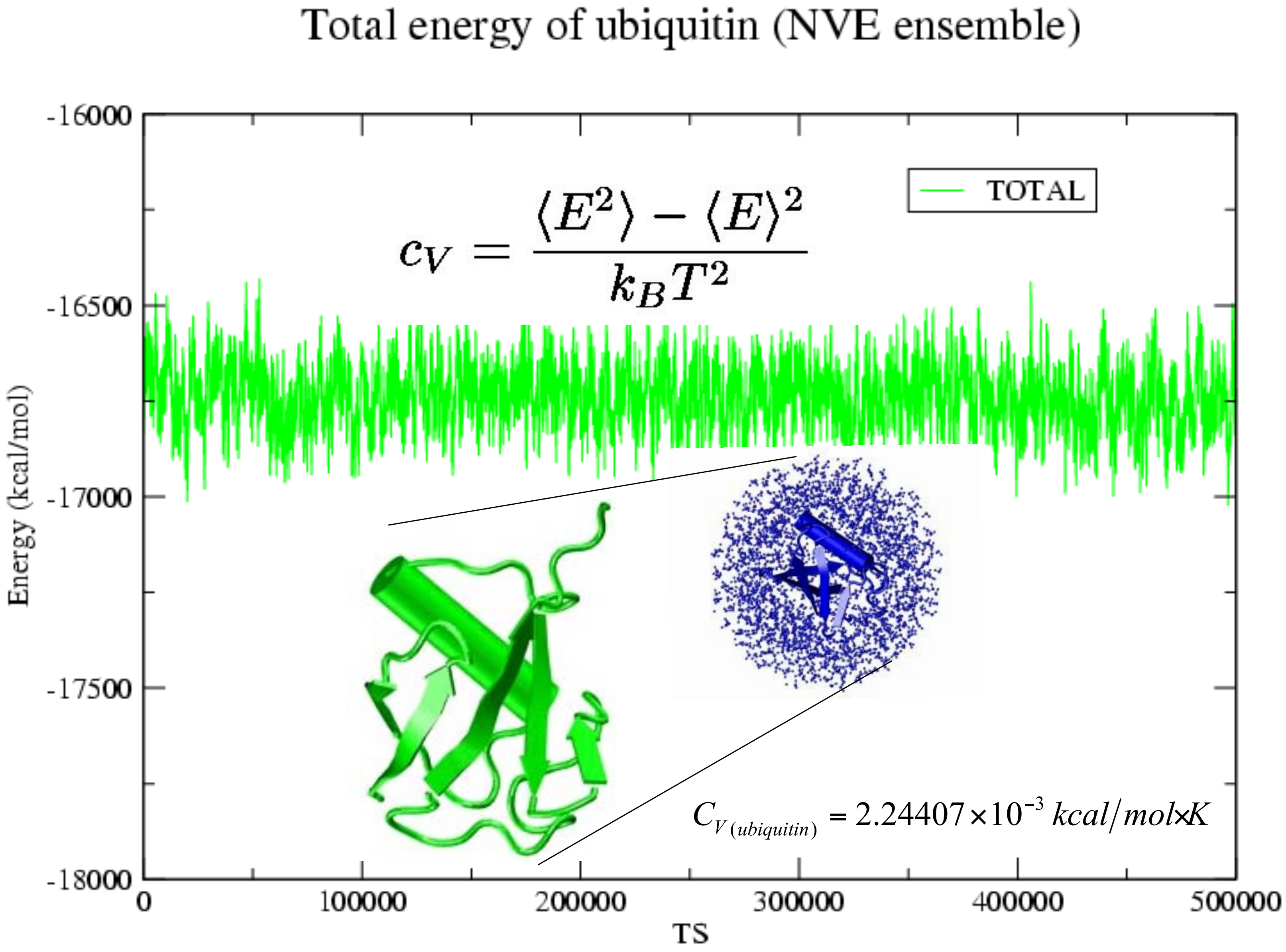
For $T_0 = 100\text{K}$ and $N = 557$, this gives $\sigma = 3.6$.



Another example, ubiquitin in water bath

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

Specific Heat of a Protein

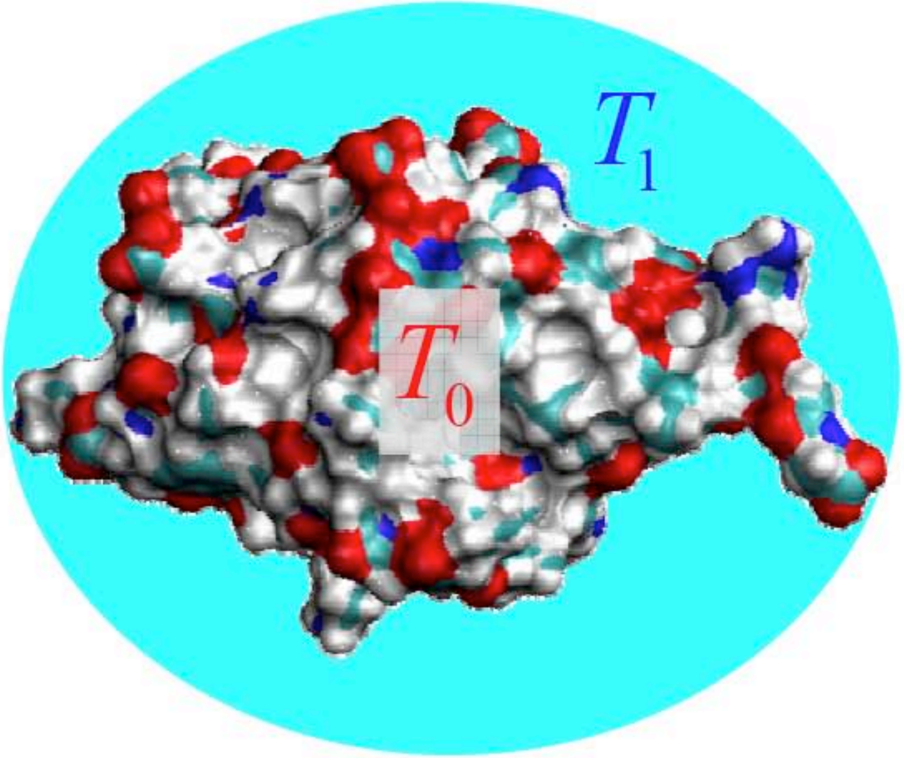


$$c_V = \frac{\langle E^2 \rangle - \langle E \rangle^2}{k_B T^2}$$

$$C_{V\,(ubiquitin)} = 2.24407 \times 10^{-3}\ kcal/mol \times K$$

Simulated Cooling of Ubiquitin

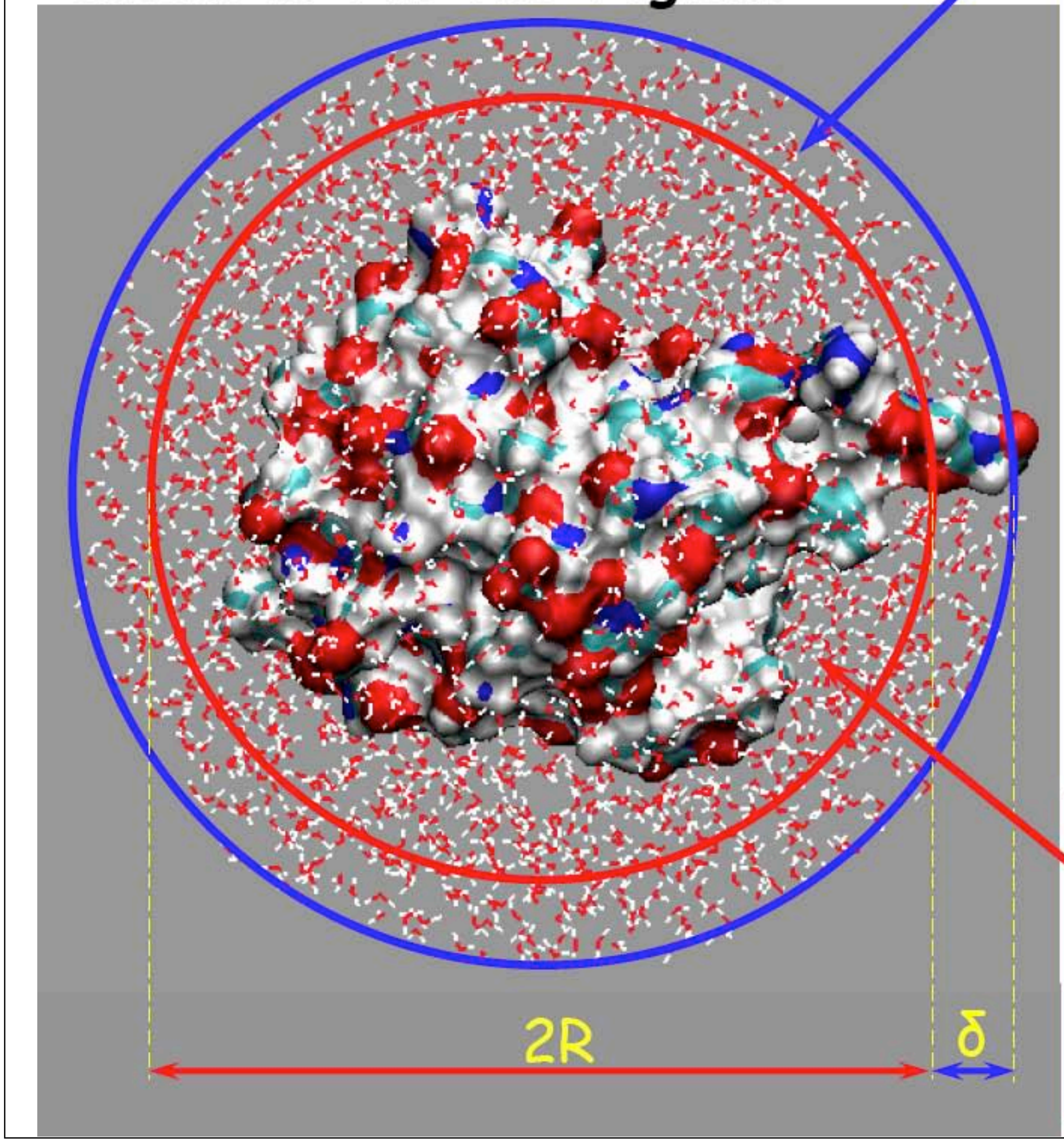
- Proteins function in a narrow (physiological) temperature range. What happens to them when the temperature of their surrounding changes significantly (temperature gradient) ?
- Can the heating/cooling process of a protein be simulated by molecular dynamics ? If yes, then how?



- 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

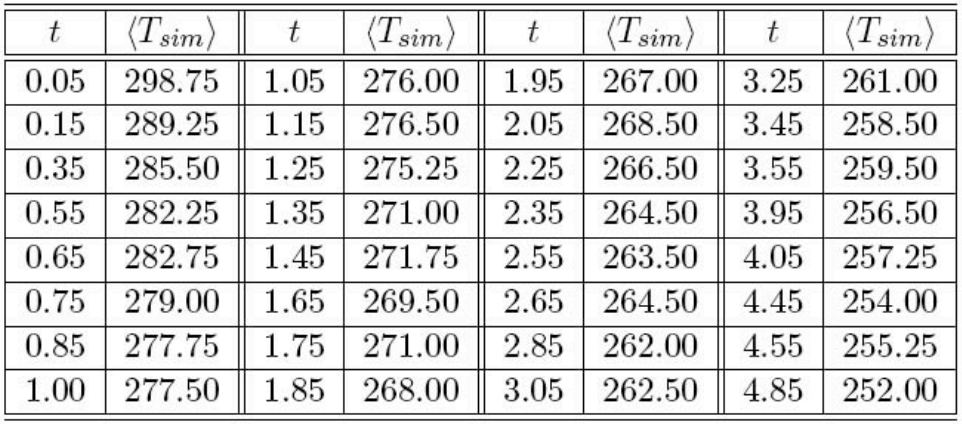
$\boldsymbol{F}_{f} \rightarrow$ friction

$\boldsymbol{F}_{L} \rightarrow$ Langevin force

atoms in the inner region follow Newtonian dynamics

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

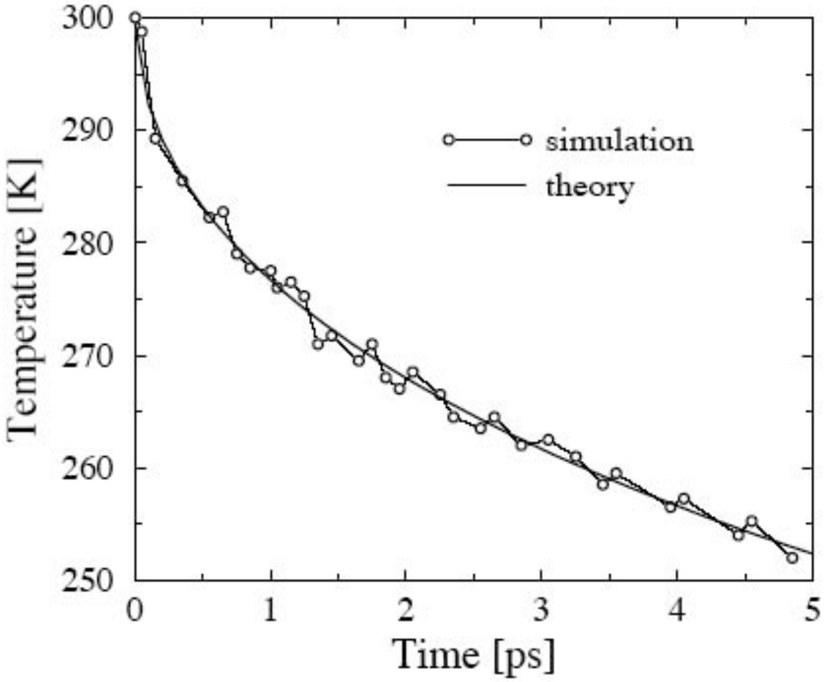
Simulated Cooling - Result



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



Heat Conduction Equation

$$\boxed{\frac{\partial T(\mathbf{r},t)}{\partial t} = D\nabla^2 T(\mathbf{r},t)}$$

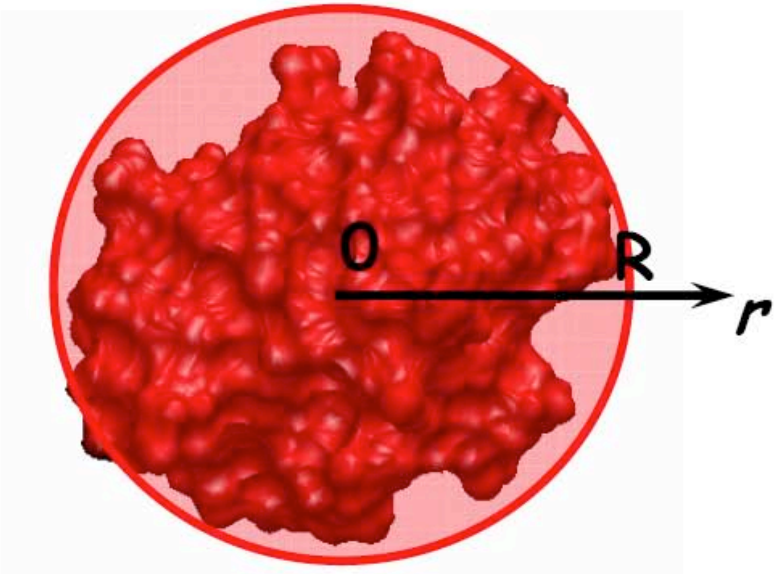
mass density

thermal diffusion coefficient

$$D = K/\rho c$$

specific heat

thermal conductivity



- approximate the protein with a homogeneous sphere of radius R~20 Å
- calculate *T(r,t)* assuming initial and boundary conditions:

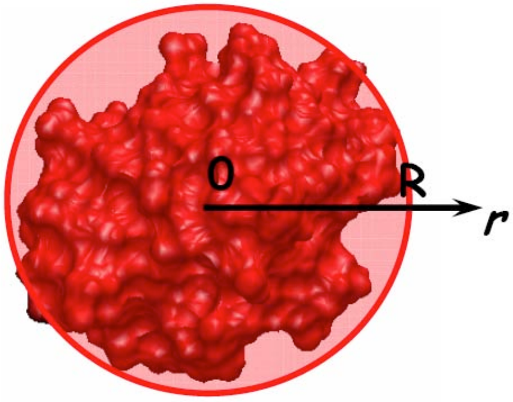
$$T(r,0) = T_0 \;\; for \;\; r < R$$

$$T(R,t) = T_{bath}$$

Solution of the Heat Equation

$$\frac{\partial T(\mathbf{r},t)}{\partial t} = D\,\nabla^2 T(\mathbf{r},t)\ ,$$

$$D = K/\rho c\ ,$$



Initial condition

$$T(\mathbf{r},0) = \langle T_{sim}\rangle(0) \qquad \text{for}\ \ r < R\ ,$$

Boundary condition

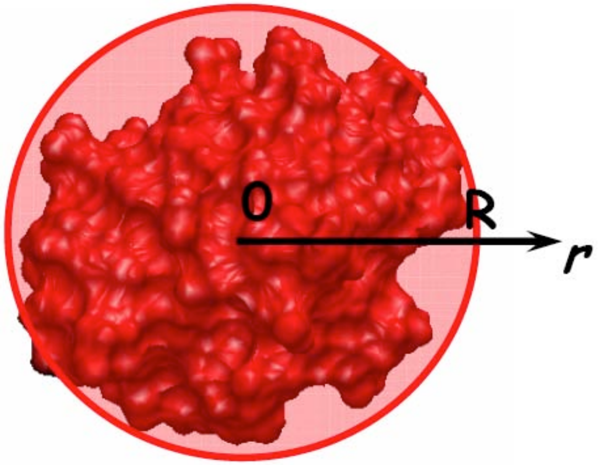
$$T(R,t) = T_{bath}\ .$$

Solution of the Heat Equation

Spherical symmetry

$$\frac{\partial T(r,t)}{\partial t} \;=\; D\,\frac{1}{r}\partial_r^2 r\,T(r,t)$$

$$T_{bath}$$



We assume

$$T(r,t) \;=\; T_{bath} + \sum_{n=1}^{\infty} a_n e^{\lambda_n t} u_n(r)$$

difference from bath

Here u_n are the eigenfunctions of the spherical diffusion operator

$$L \;\equiv\; \frac{D}{r}\frac{d^2}{dr^2} r$$

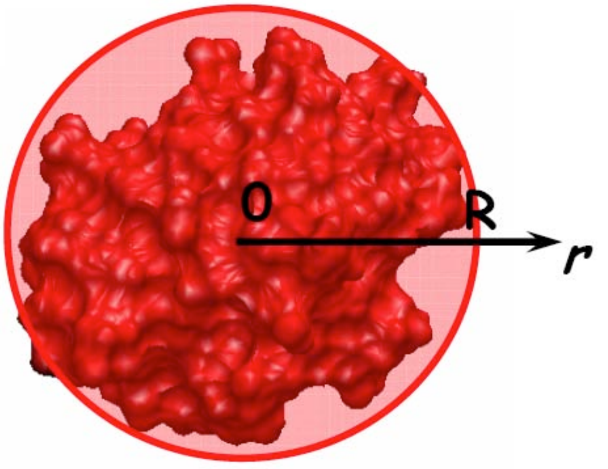
$$\frac{D}{r}\frac{d^2}{dr^2} r u_n(r) \;=\; \lambda_n\, u_n(r) \quad , \quad u_n(0) \;=\; \text{finite}\,, \quad u_n(R) \;=\; 0$$

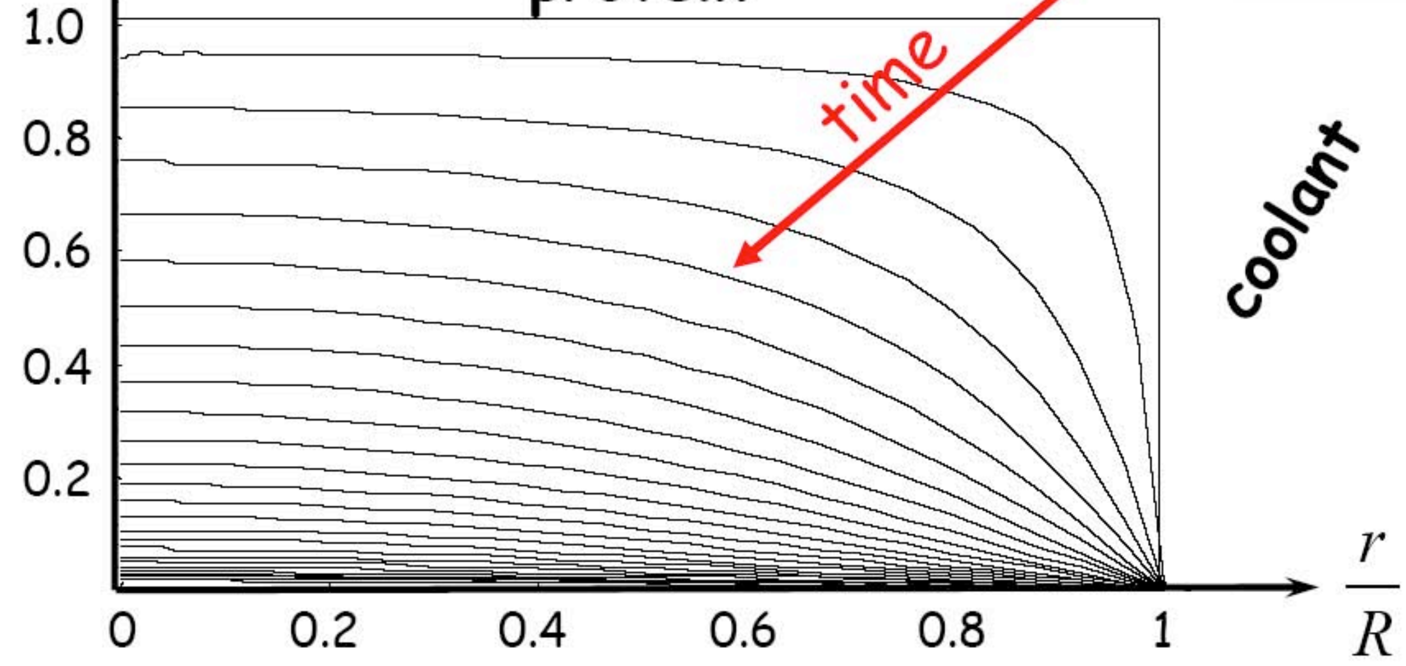
Solution of the Heat Equation

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

$$a_m \;=\; \frac{2R}{m\pi}\,\Delta T\,(-1)^{m+1}$$

T_{bath}

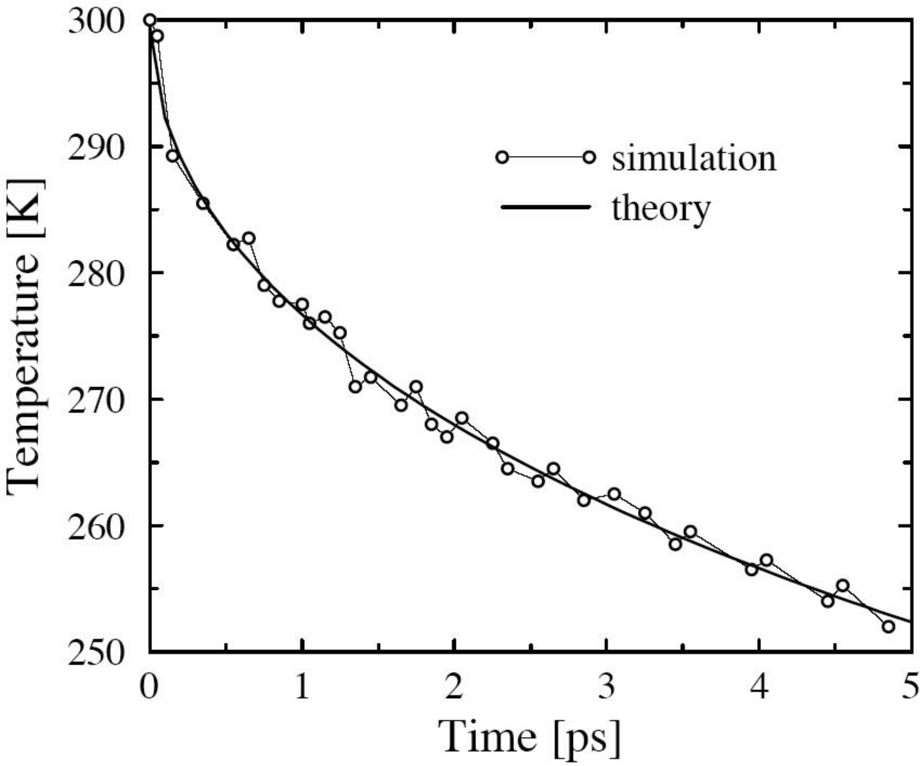


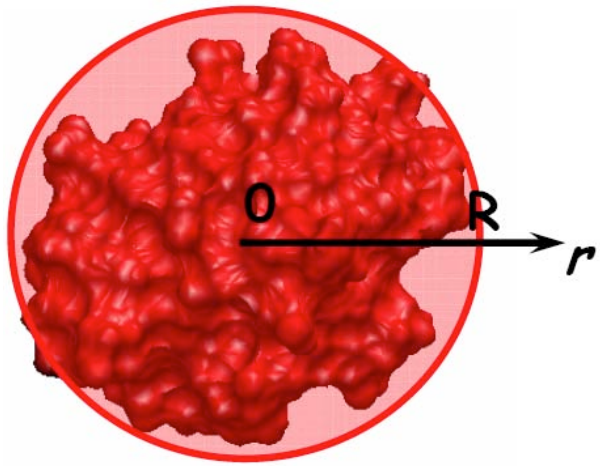


Solution of the Heat Equation

Temperature averaged over volume

$$
\begin{aligned}
\langle T\rangle(t) &= \left(\frac{4\pi R^3}{3}\right)^{-1}\int d^3\mathbf{r}\,T(\mathbf{r},t) \;=\; \frac{3}{R^3}\int_0^R r^2 dr\,T(r,t)\\
&= T_{bath} + \sum_{n=1}^{\infty} a_n \exp\left[-\left(\frac{n\pi}{R}\right)^2 D\,t\right]\frac{3}{R^3}\int_0^R r dr\,\sin\left(\frac{n\pi r}{R}\right)\\
&= T_{bath} + 6\frac{\Delta T}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp\left[-\left(\frac{n\pi}{R}\right)^2 D\,t\right]
\end{aligned}
$$





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

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