

Quasielastic neutron scattering from soft matter

Adapted from HERCULES lectures 2003/4

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September 18, 2022

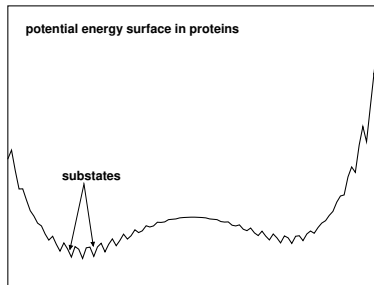
Contents

- Motivation
- Principles of neutron scattering
- Analytical models for protein dynamics
- Application of computer simulations
- Simulation-based models for protein dynamics

Motivation

- Flexibility and motion at the atomic level is important for protein function. Many proteins do not function below a transition temperature of $T \approx 200K$.
- At the transition temperature an onset of diffusive motions on the μs -timescale is observed by *quasielastic neutron scattering*.
- The onset of diffusive motions entails an increase of conformational disorder (entropy) and enables intramolecular transport processes.
- Understand relaxation and transport processes in proteins

Protein energy landscape



- Few principal minima and a large number of sub-minima (“conformational substates”).
- Thermally activated hopping between subminima may be described as a **diffusion process** \implies **quasielastic neutron scattering**.

Properties of neutrons

<i>Property</i>	<i>Symbol</i>	<i>Value</i>
Mass	m	$1.008 \text{ a.m.u.} \approx 1.6 \cdot 10^{-27} \text{ kg}$
Energy	E	$\approx 25 \text{ meV} = k_B T \text{ (} T = 300 \text{ K)}$
Charge	Q	0

Neutrons can be produced by

- controlled nuclear fission (reactors).
- by “evaporation” from heavy target atoms upon collision with energetic protons (spallation sources).

Particles and waves

- **Energy-momentum relation:**

$$E = \frac{\mathbf{p}^2}{2m} \quad (\text{non-relativistic particle}).$$

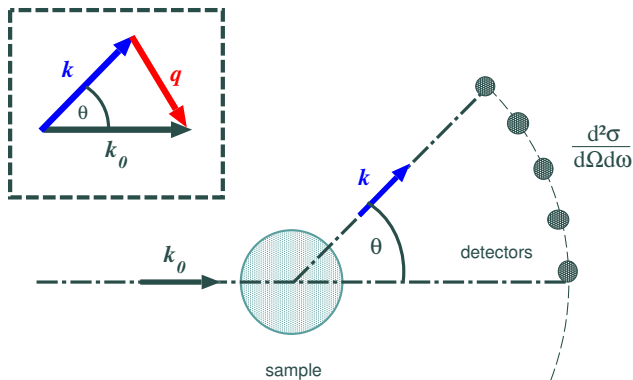
- **Wave properties:** (free particle = plane wave)

$$\begin{aligned} E &= \hbar\omega \\ \mathbf{p} &= \hbar\mathbf{k}, \quad \text{where } \mathbf{k} = \frac{2\pi}{\lambda}\mathbf{n}. \quad (\text{wave vector}) \end{aligned}$$

Here $\hbar = h/2\pi$, and $h = 6.626176 \cdot 10^{-34} \text{ Js}$.

$\lambda = 1.8 \text{ \AA}$ for $E = k_B T$ and $T = 300 \text{ K}$. Neutrons probe structure *and* dynamics of condensed matter on the atomic scale.

Neutron scattering experiment



Differential scattering X-section

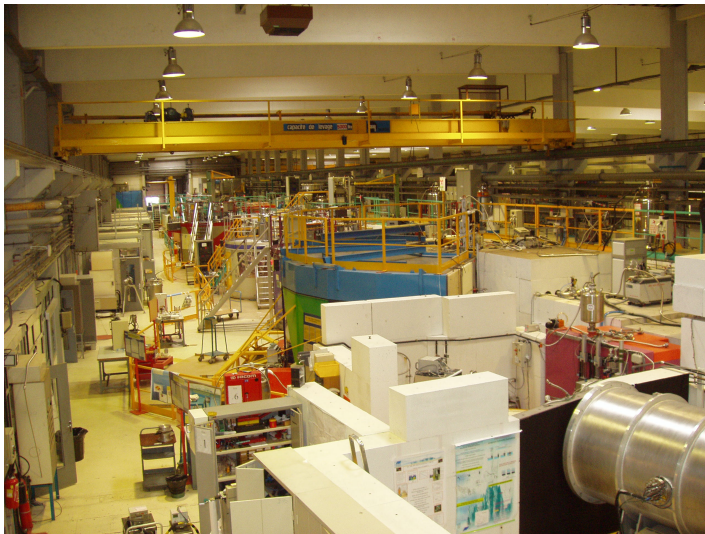
$$\frac{d^2\sigma}{d\Omega d\omega} = \frac{|\mathbf{k}|}{|\mathbf{k}_0|} \mathcal{S}(\mathbf{q}, \omega)$$

Here

$$\mathbf{q} = \mathbf{k}_0 - \mathbf{k}, \quad \omega = \frac{E_0 - E}{\hbar}$$

are the **momentum transfer** and **energy transfer**, respectively, and $\mathcal{S}(\mathbf{q}, \omega)$ is the **dynamic structure factor**.

Experimental hall at ILL



The IN5 spectrometer at ILL



Fermi potential

$$V = \sum_{\alpha} \frac{2\pi\hbar^2}{\mu_{\alpha}} b_{\alpha} \delta(\mathbf{r} - \mathbf{R}_{\alpha})$$

Neutrons see the nuclei. Here μ_{α} is the (reduced) mass of the target atom.

$$\sigma_{\alpha}^{\text{tot}} = 4\pi b_{\alpha}^2, \quad M_{\alpha} \gg m.$$

is the **total scattering cross section**. The *scattering lengths* b_{α} are of the order of fm ($10^{-15}m$).

Dynamic structure factor

$$\mathcal{S}(\mathbf{q}, \omega) = \frac{1}{2\pi} \int_{-\infty}^{+\infty} dt \exp(-i\omega t) \mathcal{I}(\mathbf{q}, t),$$
$$\mathcal{I}(\mathbf{q}, t) = \sum_{\alpha, \beta} \overline{b_{\alpha} b_{\beta}} \left\langle e^{i\mathbf{q}^T \cdot \mathbf{R}_{\beta}(t)} e^{-i\mathbf{q}^T \cdot \mathbf{R}_{\alpha}(0)} \right\rangle.$$

$\overline{b_{\alpha} b_{\beta}}$ = average over isotopes and relative spin orientations of neutron and nucleus. $\mathcal{I}(\mathbf{q}, t)$ is called the *intermediate scattering function*.

$\mathcal{S}(\mathbf{q}, \omega)$ is sensitive to structural and dynamical correlations of atomic positions.

Classical description

Intermediate scattering function

$$\mathcal{I}(\mathbf{q}, t) = \sum_{\alpha, \beta} \overline{b_{\alpha} b_{\beta}} \left\langle e^{i\mathbf{q}^T \cdot [\mathbf{R}_{\beta}(t) - \mathbf{R}_{\alpha}(0)]} \right\rangle$$

Here $\mathbf{R}_{\alpha}(t) \in \mathbb{R}^3$ are real-numbered vectors.

- The dynamics of the scattering system must evolve according to the laws of classical mechanics.
- The energy transfers must be small: $\frac{\hbar^2 \mathbf{q}^2}{2M} \ll k_B T$.

Accessible $(|\mathbf{q}|, \omega)$ -range:

Compute $q = \sqrt{(\mathbf{k}_0 - \mathbf{k})^2}$ and use that $E_0 = \hbar^2 |\mathbf{k}_0|^2 / 2m_n$ and $E = E_0 - \hbar\omega = \hbar^2 |\mathbf{k}|^2 / 2m_n$.

$$|\mathbf{q}| = k_0 \sqrt{2 - \frac{\hbar\omega}{E_0} - 2\sqrt{1 - \frac{\hbar\omega}{E_0}} \cos \theta}$$

Splitting $I(\mathbf{q}, t)$

Coherent and incoherent scattering:

$$\mathcal{I}(\mathbf{q}, t) = \mathcal{I}_{coh}(\mathbf{q}, t) + \mathcal{I}_{inc}(\mathbf{q}, t)$$

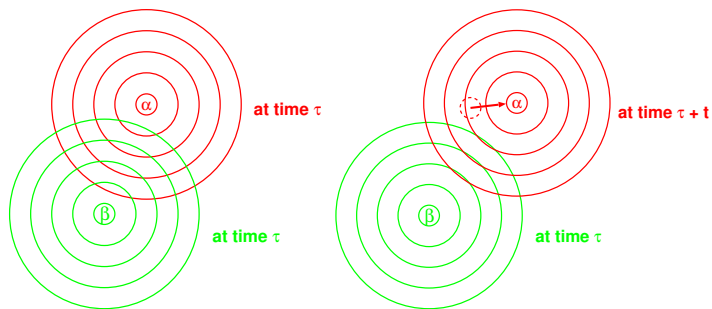
where

$$\mathcal{I}_{coh}(\mathbf{q}, t) = \sum_{\alpha, \beta} b_{\alpha, coh} b_{\beta, coh} \left\langle e^{i\mathbf{q}^T \cdot [\mathbf{R}_\beta(t) - \mathbf{R}_\alpha(0)]} \right\rangle,$$

$$\mathcal{I}_{inc}(\mathbf{q}, t) = \sum_{\alpha} b_{\alpha, inc}^2 \left\langle e^{i\mathbf{q}^T \cdot [\mathbf{R}_\alpha(t) - \mathbf{R}_\alpha(0)]} \right\rangle.$$

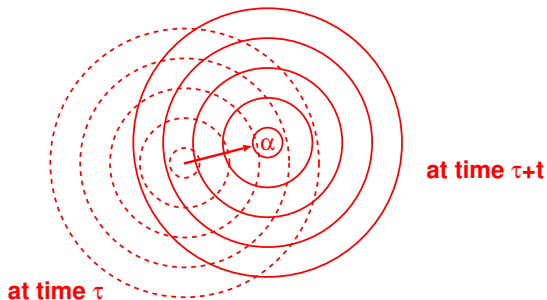
Here $b_{\alpha, coh} = \overline{b_\alpha}$ and $b_{\alpha, inc} = \sqrt{\overline{b_\alpha^2} - \overline{b_\alpha}^2}$

Distinct-scattering



A plane wave corresponding to an incident neutron hits the sample. The Huygens spherical waves emitted from *different* moving atoms at different times can interfere, giving rise to *distinct-scattering*.

Self-scattering



A plane wave corresponding to an incident neutron hits the sample. The Huygens spherical waves emitted from *the same* moving atom at different times can interfere, giving rise to *self-scattering*.

Hydrogen-rich samples

Incoherent scattering from hydrogen atoms dominates

Element	H	D	C	O	N	S
b_{coh}	-3.741	6.674	6.648	5.805	9.300	2.847
b_{inc}	25.217	4.022	0.285	0.000	2.241	0.188

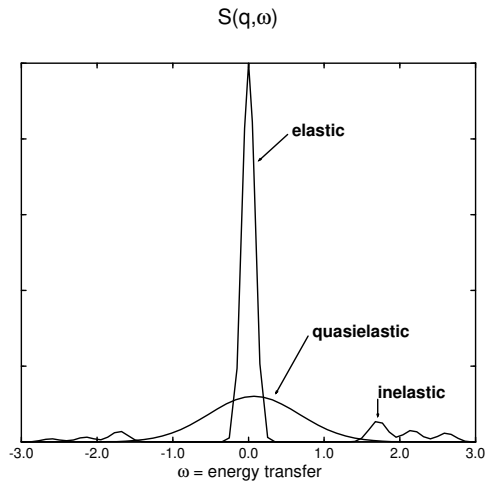
Scattering lengths of some elements in fm ($10^{-15} m$).

Approximation for $\mathcal{I}(\mathbf{q}, t)$

$$\begin{aligned}\mathcal{I}(\mathbf{q}, t) &\approx N b_{H,inc}^2 I_H(\mathbf{q}, t), \\ I_H(\mathbf{q}, t) &= \frac{1}{N} \sum_{\alpha \in \{H\}} \left\langle \exp\left(i\mathbf{q}^T \cdot [\mathbf{R}_\alpha(t) - \mathbf{R}_\alpha(0)]\right) \right\rangle.\end{aligned}$$

Biomolecules or solvent can be masked by substituting $H \rightarrow D$.

Neutron scattering spectrum



Van Hove correlation functions

$$G_H(\mathbf{r}, t) = \frac{1}{(2\pi)^3} \int d^3q \exp(i\mathbf{q}^T \cdot \mathbf{r}) I_H(\mathbf{q}, t)$$

In the classical limit one has

$$G_H^{cl}(\mathbf{r}, t) = \frac{1}{N} \sum_{\alpha \in \{H\}} \langle \delta(\mathbf{r} - [\mathbf{R}_\alpha(t) - \mathbf{R}_\alpha(0)]) \rangle$$

Probability for a displacement \mathbf{r} of a hydrogen atom within time t .

EISF

- **Definition:**

$$EISF(\mathbf{q}) = \lim_{t \rightarrow \infty} I_H(\mathbf{q}, t)$$

- **Elastic line and the “rest”:**

$$S_H(\mathbf{q}, \omega) = EISF(\mathbf{q})\delta(\omega) + S'_H(\mathbf{q}, \omega)$$

- **Sum rule**

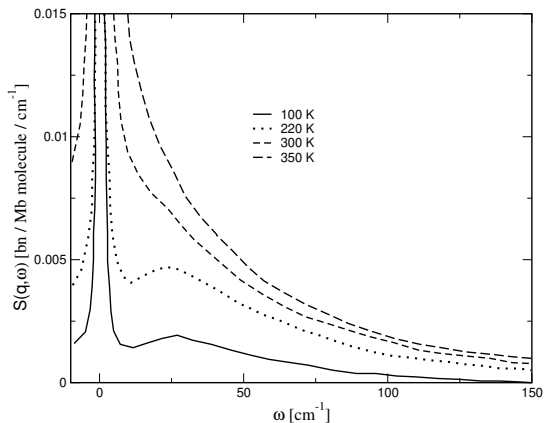
$$EISF(\mathbf{q}) + \int_{-\infty}^{+\infty} d\omega S'_H(\mathbf{q}, \omega) = 1$$

Information in the EISF

$$EISF(\mathbf{q}) = \int d^3q \exp(-i\mathbf{q}^T \cdot \mathbf{r}) G_H(\mathbf{r}, \infty)$$

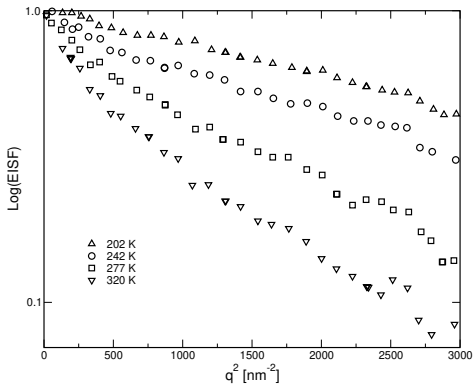
- The EISF gives information about the configurational space explored by the hydrogen atoms.
- Any dynamical process leads to a drop-off of the EISF (\implies “sum rule”). Processes which are too slow to be detected by a given instrument count as “elastic”.

A quasielastic spectrum



Temperature dependence of $S(q, \omega)$ for D_2O -hydrated myoglobin powders (Cusack & Doster, *Biophys. J.*, 1990).

Elastic scattering



Normalized elastic intensity of D_2O -deuterated myoglobin. The data are re-plotted from Doster *et al.*, *Nature*, 1989.

Probabilistic description

- $I(\mathbf{q}, t)$ in terms of a joint probability density

$$I(\mathbf{q}, t) = \int \int d\Omega d\Omega' P(\Omega, t; \Omega', t') e^{i\mathbf{q} \cdot [\mathbf{R}(\Omega) - \mathbf{R}(\Omega')]}$$

- $G(\mathbf{r}, t)$ in terms of a joint probability density

$$G(\mathbf{r}, t) = \int \int d\Omega d\Omega' P(\Omega, t; \Omega', t') \delta(\mathbf{r} - [\mathbf{R}(\Omega) - \mathbf{R}(\Omega')])$$

Ω and Ω' specify the state of the system at time t and $t' < t$, respectively.

Introducing models

- **Bayes's rule:**

$$P(\Omega, t; \Omega', t') = P(\Omega, t | \Omega', t') P(\Omega', t')$$

$P(\Omega, t | \Omega', t')$ is a *conditional probability density*. Models are introduced for $P(\Omega, t | \Omega', t')$.

- **Initial condition:** $P(\Omega, t' | \Omega', t') = \delta(\Omega - \Omega')$
- **Equilibrium:**

$$P(\Omega, t | \Omega', t') = P(\Omega, t - t' | \Omega', 0),$$

$$P(\Omega', t') = P_{eq}(\Omega') = \lim_{t \rightarrow \infty} P(\Omega, t | \Omega', t').$$

Motion types

Three motion types are considered

- molecular translations
- molecular rotations
- intramolecular motions

Correspondingly, the positions are decomposed as

$$\mathbf{R}_\alpha = \mathbf{R}_{CM} + \mathbf{r}_\alpha + \mathbf{u}_\alpha$$

Here α denotes a “representative” atom and CM the center of mass.

Decomposing $I(\mathbf{q}, t)$ and $S(\mathbf{q}, \omega)$

- **Assumption of uncorrelated motions:**

$$I(\mathbf{q}, t) = I_{CM}(\mathbf{q}, t)I_{rot}(\mathbf{q}, t)I_{int}(\mathbf{q}, t)$$

- **Convolution product for $S_H(\mathbf{q}, \omega)$:**

$$S(\mathbf{q}, \omega) = (S_{CM} * S_{rot} * S_{int})(\mathbf{q}, \omega)$$

Translational diffusion

Here $\Omega \equiv \{x, y, z\}$ and $\mathbf{R}(\Omega) = (x, y, z)^T$.

- **Diffusion equation**

$$\partial_t P = D \left(\frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2} \right) P$$

D is the *diffusion constant* ($[D] = \text{m}^2/\text{s}$).

- **Gaussian solution**

$$P(\mathbf{R}, t | \mathbf{R}', 0) = \frac{1}{\sqrt{4\pi Dt}^3} \exp\left(-\frac{|\mathbf{R} - \mathbf{R}'|^2}{4Dt}\right)$$

Translational diffusion (cont.)

- **Intermediate scattering function**

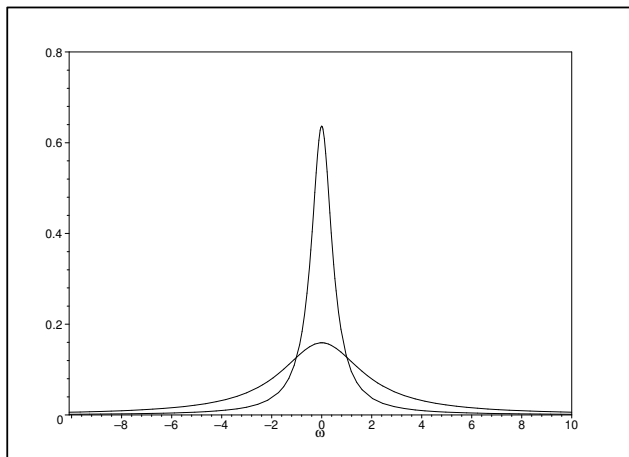
$$I(\mathbf{q}, t) = \exp(-D\mathbf{q}^2 t)$$

- **Dynamic structure factor**

$$S(\mathbf{q}, \omega) = \frac{1}{\pi} \frac{D\mathbf{q}^2}{(D\mathbf{q}^2)^2 + \omega^2}$$

Lorentzian quasielastic line.

Lorentz profile



Form of $S(\mathbf{q}, \omega)$ for translational diffusion. The widths of the the two Lorentzian profiles (on the ω -scale) are $\Gamma = 1$ (narrow line) and $\Gamma = 2$.

Translational diffusion (cont.)

- **van Hove correlation function**

$$G(\mathbf{r}, t) = \frac{1}{\sqrt{4\pi Dt}^3} \exp\left(-\frac{\mathbf{r}^2}{4Dt}\right)$$

Since $\lim_{t \rightarrow \infty} G(\mathbf{r}, t) = 0$, the EISF vanishes!

- **Mean square displacement**

$$\langle \mathbf{r}^2 \rangle(t) := \int_V d^3r \mathbf{r}^2 G(\mathbf{r}, t) = 6Dt$$


Stokes-Einstein relation:

$$D = \frac{k_B T}{6\pi\eta a}$$

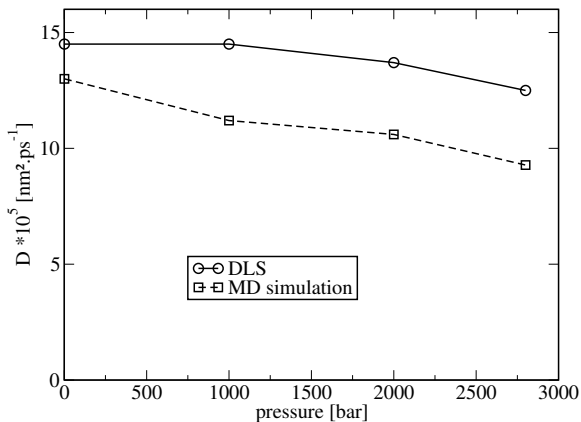
Here η is the viscosity of the solvent, and a is the hydrodynamic radius of the molecule.

- The diffusion coefficient for lysozyme is found to be $D \approx 7.2 \cdot 10^{-7} \text{ cm}^2/\text{s}$ by QENS¹ and $D \approx 14 \cdot 10^{-7} \text{ cm}^2/\text{s}$ by DLS²
- The diffusion coefficient of water is $2.5 \cdot 10^{-5} \text{ cm}^2/\text{s}$.

¹J. Perez, J.M. Zanotti, D. Durand, *Biophys. J.* **77**, 454-469 (1999)

²Nystrom & Roots, *Makromol. Chem.* **185**, 1441-1447 (1984) 

D_{CM} from MD and DLS



D_{CM} of lysozyme from dynamic light scattering (Nystrom & Roots, 1984) and MD (Véronique Hamon, thesis Univ. Orléans 2004).

Rotational diffusion

We consider first *rotational diffusion on a sphere*. Here $\Omega = (\alpha, \beta, \gamma)$ are the Euler angles describing the orientation of the molecule.

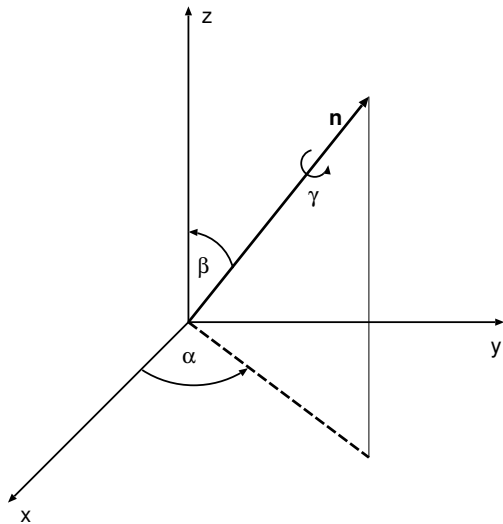
The intermediate scattering function is found to be³

$$I(\mathbf{q}, t) = \sum_{l=0}^{\infty} (2l+1) j_l^2(|\mathbf{q}|a) \exp(-l(l+1)D_r t)$$

Here D_r is the *rotational Diffusion constant* ($[D_r] = 1/s$), a is the radius of the molecule, and $j_l(z)$ are the spherical Bessel functions.

³See lecture notes for the solution of the rotational diffusion equation for $P(\Omega, t|\Omega', 0)$.

Euler angles



Rotational diffusion (cont.)

Average over spheres of a spherical molecule, assuming a *homogenous distribution of hydrogen atoms*,

$$I(\mathbf{q}, t) = \sum_{l=0}^{\infty} (2l + 1) A_l(qa) \exp(-l(l + 1)D_r t)$$

Here

$$A_l(qa) = \frac{3}{a^3} \int_0^a dR R^2 j_l^2(qR)$$

Rotational diffusion (cont.)

- **EISF:**

$$EISF(\mathbf{q}) = A_0(qa) = \frac{3[2qa - \sin(2qa)]}{4q^3 a^3}$$

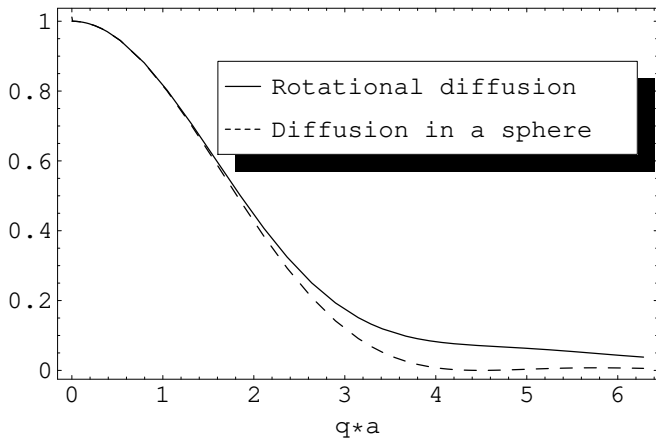
- **Dynamic structure factor:**

$$S_{rot}(\mathbf{q}, \omega) = A_0(qa)\delta(\omega) + \frac{1}{\pi} \sum_{l=1}^{\infty} (2l+1)A_l(qa) \frac{\Gamma_l}{\Gamma_l^2 + \omega^2}$$

where

$$\Gamma_l = l(l+1)D_r.$$

Rotational EISF



Stokes-Einstein relation:

For rotational motion (B. Cichocki et al., 1988)

$$\gamma_r = \frac{k_B T}{4\pi\eta a^3}$$

- Rotational diffusion of whole proteins is *slow* : For $a = 1.45 \text{ nm}$ one obtains

$$\tau_r \approx 10 \text{ ns}$$

- Comparison for *translational* diffusion :

$$\tau_{CM} \approx 70 \text{ ps}$$

Damped vibrations (1-dim.)

Here $\Omega = (x, v)$, where $v = \dot{x}$.

- **Harmonic force:**

$$F(x) = -M\omega_0^2 x$$

- **Langevin equation:**

$$\frac{d^2 x}{dt^2} + \gamma_0 \frac{dx}{dt} + \omega_0^2 x = \frac{1}{M} F_s$$

Here F_s is white noise with zero mean. Underdamped motion for $\omega_0 > \frac{\gamma_0}{2}$ overdamped motion for $\omega_0 \leq \frac{\gamma_0}{2}$.

Damped vibrations (cont.)

- **Intermediate scattering function:**⁴

$$I(q, t) = \exp\left(-\frac{q^2}{2} W(t)\right)$$

- **Mean square displacement:**

$$W(t) = \langle [x(t) - x(0)]^2 \rangle$$

⁴See lecture notes for the solution of the Fokker-Planck equation for $P(\Omega, t | \Omega', 0)$.

Damped vibrations (cont.)

- **Analytical form for MSD:**

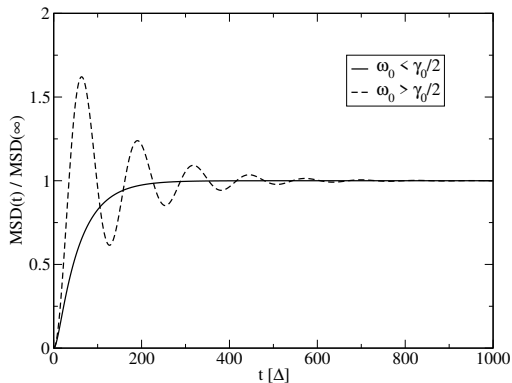
$$W(t) = \begin{cases} \frac{2k_B T}{M\omega_0^2} \left(1 - \exp\left(-\frac{\gamma_0 t}{2}\right) \left\{\cos \Omega t + \frac{\gamma_0}{2\Omega} \sin \Omega t\right\}\right) \\ \frac{2k_B T}{M\omega_0^2} \left(1 - \exp\left(-\frac{\gamma_0 t}{2}\right) \left\{\cosh |\Omega| t + \frac{\gamma_0}{2|\Omega|} \sinh |\Omega| t\right\}\right) \end{cases}$$

for underdamped and overdamped motion, respectively.

- **Plateau value:**

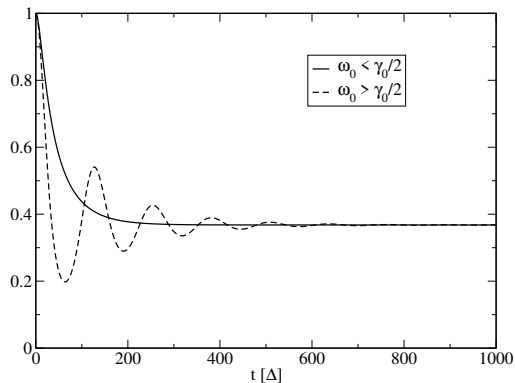
$$\lim_{t \rightarrow \infty} W(t) = \frac{2k_B T}{M\omega_0^2} = 2\langle x^2 \rangle$$

Mean square displacement



MSD for the Langevin oscillator in the underdamped regime (dashed line) and in the overdamped regime (solid line).

Intermediate scattering function



$I(q, t)$ for the Langevin oscillator in the underdamped regime (dashed line) and in the overdamped regime (solid line).

EISF

The EISF of a Langevin oscillator is given by

$$EISF(q) = \exp(-q^2 \langle x^2 \rangle)$$

where

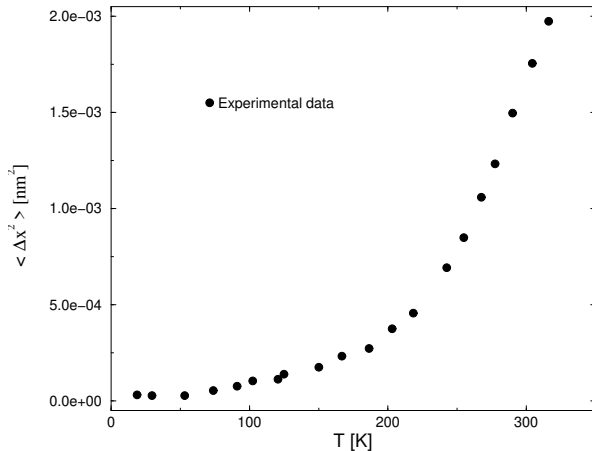
$$\langle x^2 \rangle = \frac{k_B T}{M\omega_0^2}$$

is the *position fluctuation* of the oscillator.

Within the harmonic model, the EISF allows to measure force constants.⁵

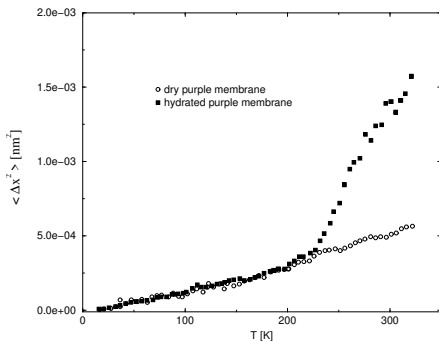
⁵Zaccai, G., *Science*, 288:1604-1607, 2000.

Example #1:



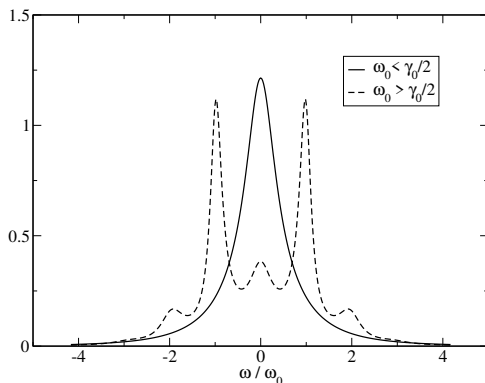
Position fluctuations of H -atoms in D_2O -hydrated Myoglobin as a function of temperature (W. Doster *et al.*, *Nature*,1989).

Example #2:



Position fluctuations of *H*-atoms in bacteriorhodopsin (BR) in purple membranes (PM). A) Dry PM (circles) and B) D_2O -hydrated PM (full squares) (M Ferrand et al., *PNAS*, 1993). Below 220K BR cannot perform a complete photocycle.

Dynamic structure factor



Numerical calculation of $S'(q, \omega)$ for the Langevin oscillator in the underdamped regime (dashed line) and in the overdamped regime (solid line).

Brownian motion

For strongly overdamped motion, $\gamma \gg \omega_0$, and observation times $t \gg 1/\gamma_0$,

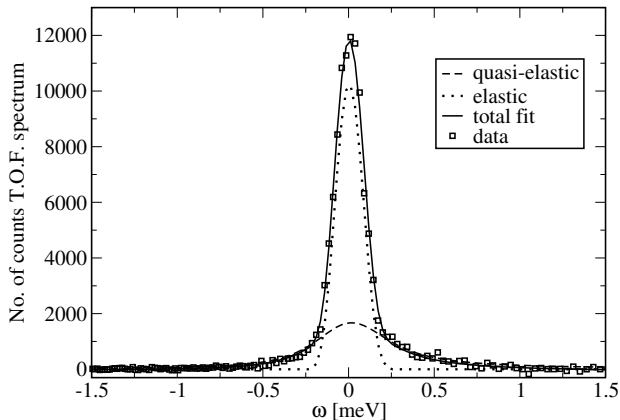
$$I(q, t) = \exp \left[-q^2 \frac{k_B T}{M\omega_0^2} (1 - \exp(-\gamma_0^{-1}\omega_0^2 t)) \right]$$

Approximation for small q

$$I'(q, t) \propto \exp(-\gamma_0^{-1}\omega_0^2 t), \quad q^2 \langle x^2 \rangle \ll 1.$$

$S'(q, \omega)$ is a Lorentzian.

QES from lysozyme



Fitted quasielastic spectrum (Lorentzian) of lysozyme in aqueous solution at 300 K (Véronique Hamon, thesis Univ. Orléans 2004) – see lecture notes.

MD simulations

- Numerical Integration of Newton's equation of motion,

$$m_{\alpha} \ddot{\mathbf{R}}_{\alpha} = - \frac{\partial U}{\partial \mathbf{R}_{\alpha}}$$

- Compute time correlations functions

$$\langle A(0)B(m) \rangle = \frac{1}{N_t - m} \sum_{k=0}^{N_t - m - 1} A(k)B(k + m)$$

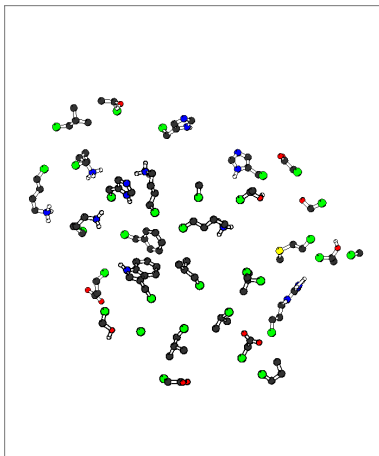
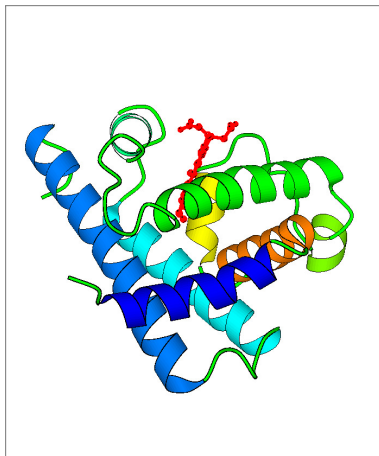
- Analyse MD trajectories to extract details not accessible to experiments.

MD force field

$$\begin{aligned} U = & \sum_{\text{bonds } ij} k_{ij} \left(r_{ij} - r_{ij}^{(0)} \right)^2 \\ & + \sum_{\text{angles } ijk} k_{ijk} \left(\phi_{ijk} - \phi_{ijk}^{(0)} \right)^2 \\ & + \sum_{\text{dihedrals } ijkl} k_{ijkl} \cos \left(n_{ijkl} \theta_{ijkl} - \delta_{ijkl} \right) \\ & + \sum_{\text{all pairs } ij} 4\epsilon_{ij} \left(\left[\frac{\sigma_{ij}}{r} \right]^{12} - \left[\frac{\sigma_{ij}}{r} \right]^6 \right) \\ & + \sum_{\text{all pairs } ij} \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}}. \end{aligned}$$

Two groups of terms: **bonded** and **non-bonded** interactions.

Myoglobin



Left: Backbone of myoglobin. **Right:** 31 selected side-chains.

Motions seen by QENS

- **Question:**

What are the internal motions in proteins seen by QENS?
(Jump diffusion, small-step diffusion,...)

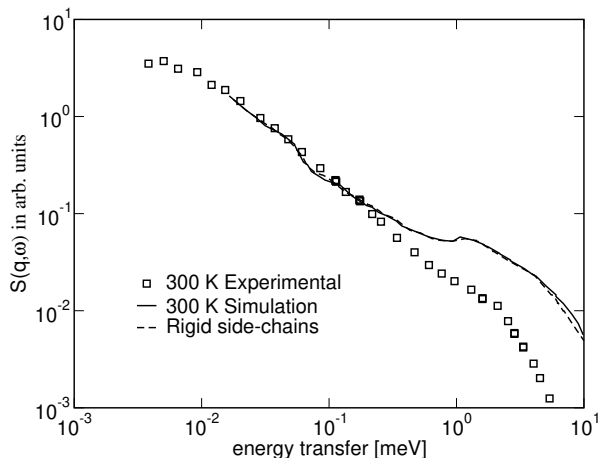
- **Hypothesis:**

QENS is produced by “liquid-like” rigid-body motions of the protein side-chains.

- **Verification:**

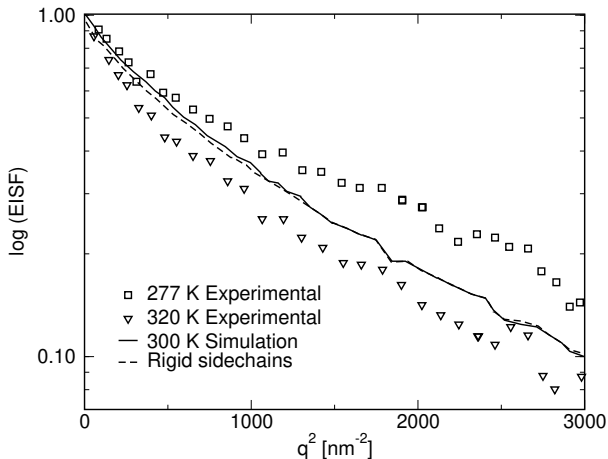
Use MD simulations and the possibility to “filter” the trajectories: Remove internal side-chain motions *a posteriori* by rigid-body fits.

QENS from myoglobin:



Neutron QENS from myoglobin from MD simulation (Kneller & Smith, 1994) and experiment (Doster *et al.*, *Nature*, 1989).

EISF for myoglobin:



EISF of myoglobin from MD simulation (Kneller & Smith, 1994) and experiment (Doster *et al.*, *Nature*, 1989).

Gaussian approximation

- **Definition (here one atom, 1-d):**

$$I(q, t) \approx \exp\left(-\frac{q^2}{2} W(t)\right)$$

- **MSD and VACF:**

$$W(t) = \langle [x(t) - x(0)]^2 \rangle = 2 \int_0^t d\tau (t - \tau) c_{ww}(\tau)$$

The GA represents a considerable simplification – it is always valid for small q .

EISF and GA

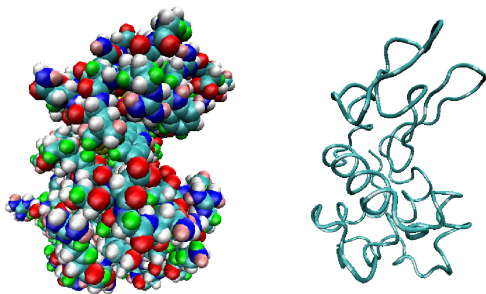
- Plateau for the MSD:

$$\lim_{t \rightarrow \infty} W(t) = 2 \langle x^2 \rangle$$

- EISF:

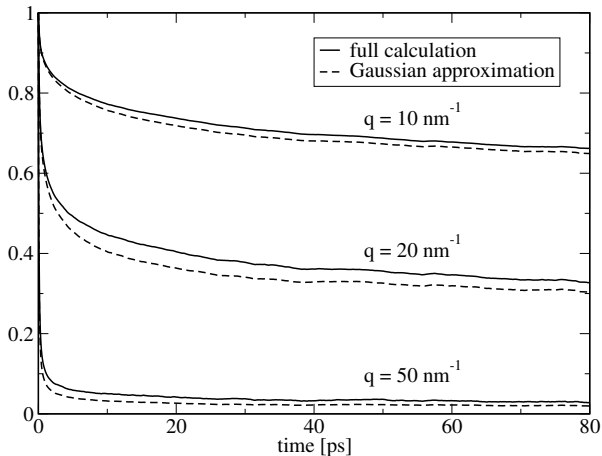
$$EISF(q) = \lim_{t \rightarrow \infty} I(q, t) = \exp(-q^2 \langle x^2 \rangle)$$

Lysozyme



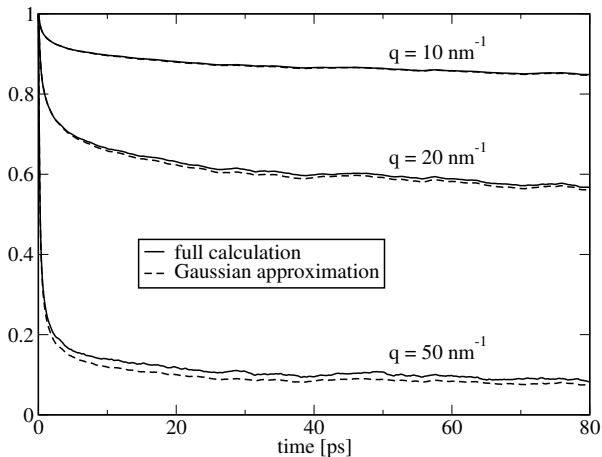
Left: The lysozyme molecule. Each atom is represented by a van der Waals sphere. **Right:** Protein backbone.

The GA for the H -atoms



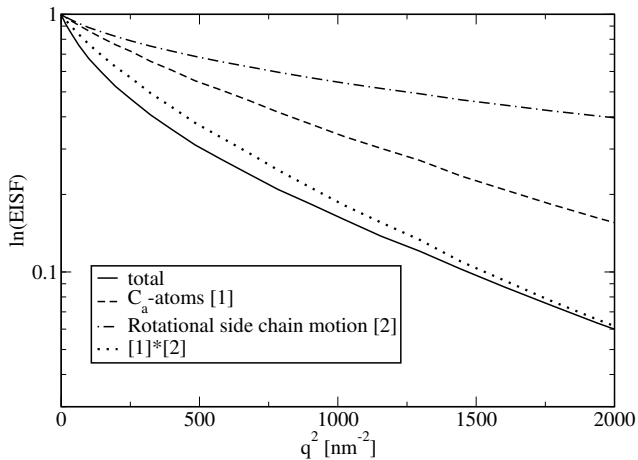
$I(q, t)$ for the H -atoms in lysozyme by direct calculation and GA.

The GA for the C_{α} -atoms



$I(q, t)$ for the C_{α} -atoms in lysozyme by direct calculation and GA.

Decomposing the EISF



Decomposition of the EISF of lysozyme.

Motional heterogeneity

Non-linear behaviour of $\ln(EISF)$ as a function of q^2 can be due to

- Truly non-gaussian behavior (rotation of the side-chains)
- Motional heterogeneity of the atoms: Averaging Gaussians with different widths leads to a non-gaussian function.

Coarse-grained harmonic model

EISF:⁶⁷

$$EISF(\mathbf{q}) = \sum_{\alpha=1}^N w_{\alpha} \exp \left(-k_B T \sum_{k=1}^{3N} \frac{1}{\tilde{\omega}_j^2} (\mathbf{q}^T \cdot \mathbf{d}_{j\alpha})^2 \right)$$

Normal modes:⁸

$$\mathbf{K} \cdot \mathbf{d}_j = \omega_j^2 \mathbf{d}_j$$

$$\mathbf{K} = \mathbf{M}^{-1/2} \cdot \left(\frac{\partial^2 U}{\partial x_i \partial x_j} \right) \Big|_{\min.} \cdot \mathbf{M}^{-1/2}$$

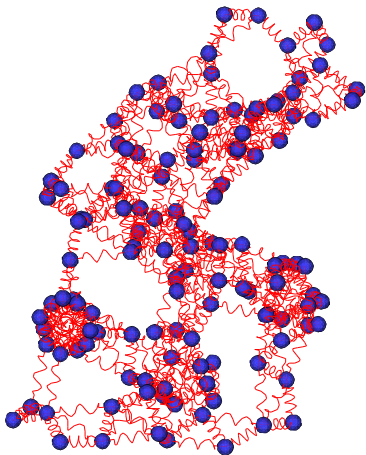
Scaled frequencies: $\tilde{\omega}_j = \eta \omega_j$ ($0 < \eta < 1$).

⁶Kneller, *Chem. Phys.* (2000); Hinsen *et al.*, *Chem. Phys.* (2000).

⁷The w_{α} are effective scattering lengths with $\sum_{\alpha} w_{\alpha} = 1$.

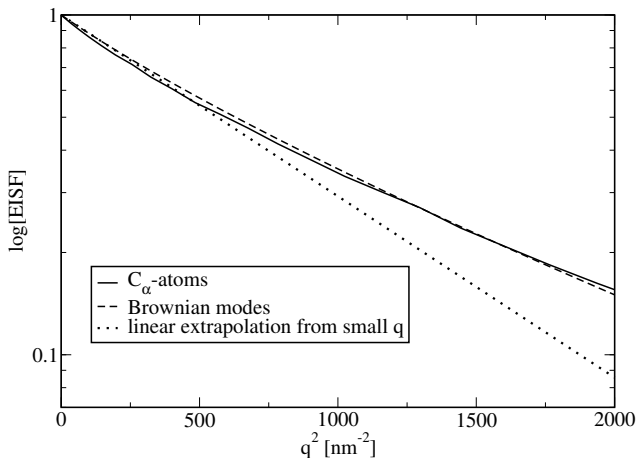
⁸ \mathbf{M} is the mass matrix of “point-like” residues.

Lysozyme at the residue level



Coarse-grained harmonic model for lysozyme. Each residue is represented by an “effective C_{α} -atom”.

Harmonic EISF and MD



EISF for the C_α -atoms in lysozyme compared to an (effective) harmonic model with motional heterogeneity.

Multiscale relaxation

- **Memory function equation** (Zwanzig, 1961)

$$\partial_t I(\mathbf{q}, t) = - \int_0^t d\tau \xi(\mathbf{q}, t - \tau) I(\mathbf{q}, \tau)$$

Here $\xi(\mathbf{q}, t)$ is the *memory function*.

- **Short-time memory** ($q = |\mathbf{q}|$)

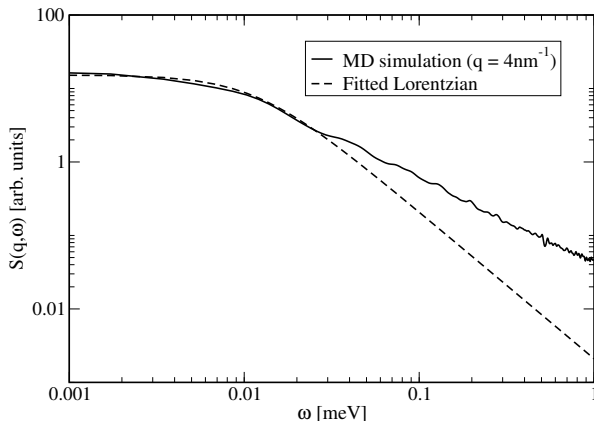
$$\xi(\mathbf{q}, t) = Dq^2 \delta(t) \implies I(\mathbf{q}, t) = \exp(-Dq^2 t)$$

Short-time memory corresponds to free Brownian motion, characterized by an exponential correlation function.

Relaxation in proteins

- Proteins have an enormous range of characteristic time scales (sub-picosecond to seconds).
- Correlation functions are *multiexponential* – with a broad distribution of relaxation time. There is no “characteristic time scale”.
- Memory functions are long-ranged.

Non-Lorentzian spectrum



Incoherent $S(q, \omega)$ for the internal dynamics of lysozyme from simulation and fit of a Lorentzian.

Fractional Brownian Dynamics

- **Spectrum**

$$S_{fBD}(\omega) = \frac{2\tau \sin(\beta\pi/2)}{|\omega\tau| (|\omega\tau|^\beta + 2 \cos(\beta\pi/2) + |\omega\tau|^{-\beta})}$$

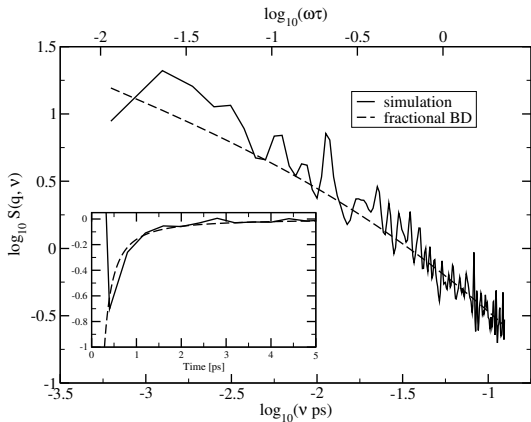
for $0 < \beta \leq 1$.

- **Memory function**

$$\xi(t) \propto (\beta - 1) \left(\frac{t}{\tau}\right)^{\beta-2}$$

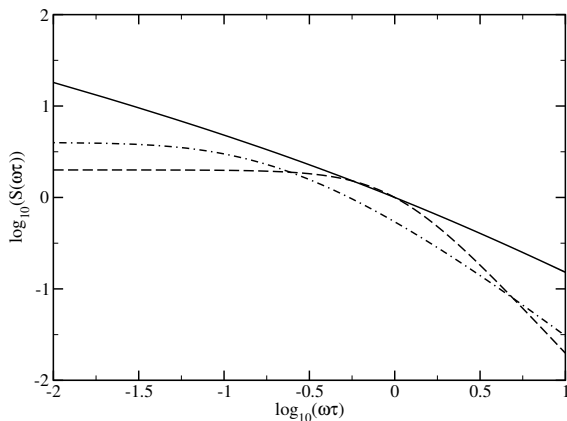
Long-ranged memory function with $\int_0^\infty dt \xi(t) = 0$.

Model and simulation



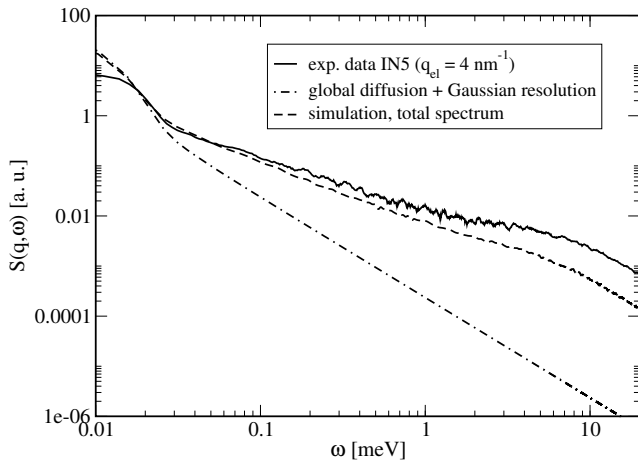
Dynamic structure factor and memory function for lysozyme at $q = 10 \text{ nm}^{-1}$ from MD and fBD model.

Different scattering laws



Solid line = fBD model with $\beta = 1/2$, **dashed line** = Lorentzian,
dot-dashed line = and stretched exponential with $\beta = 1/2$.

Simulation / Experiment



EISF and global diffusion

- **CM diffusion and internal motions**

$$S(\mathbf{q}, \omega) = (S_{CM} * S_{int})(\mathbf{q}, \omega).$$

- **Internal motions**

$$S_{int}(\mathbf{q}, \omega) = EISF(\mathbf{q})\delta(\omega) + S'_{int}(\mathbf{q}, \omega).$$

- **Resulting scattering law**

$$S(\mathbf{q}, \omega) = EISF(\mathbf{q})S_{CM}(\mathbf{q}, \omega) + (S_{CM} * S')(\mathbf{q}, \omega)$$

Summary

- MD simulation is a reliable tool for complementary numerical experiments to neutron scattering.
- Simulation-based modeling of protein dynamics is a powerful method to develop simple, but realistic models:
 - The Gaussian approximation is very reasonable. Rotational motions account only for a small fraction of the EISF.
 - Due to long-time memory effects, quasielastic spectra cannot be modeled with one or a few Lorentzians.