Development of new methods to study molecular dynamics with neutron scattering

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Motivation

Why incoherent neutron scattering with bio-molecules?

- see atomic motions
  ⇒ information about internal dynamics
- high scattering cross section of H ($\sigma_{inc} \approx 80$ barn)
  ⇒ $\approx 50\%$ of biological sample & homogenously distributed
- high contrast in comparison to D ($\sigma_{inc} \approx 2$ barn)
- neutron scattering $\Rightarrow$ no destruction of bio. samples

$\Rightarrow$ Elastic (EINS) and quasi-elastic (QENS) incoherent neutron measurements of bio-molecules
Motivation

- Difference between myoglobin powder which is hydrated and in trehalose environment

- Mean force constant
  \[ \langle k \rangle = k_B \left( \frac{d\langle 3x^2 \rangle}{dT} \right)^{-1} \]
  \[ \rightarrow \] measure of resilience

\[ \langle 3x^2 \rangle : \text{harmonic mean square fluctuation from equilibrium} \]

Zaccai, Science, 2000
Neutron scattering - structure factor $S(Q, \omega)$

$\left( \frac{\sigma_{\text{total}}}{d\Omega dE} \right) = \frac{1}{4\pi} \frac{k}{k_0} N \left( \sigma_{\text{coh}} S_{\text{coh}}(Q, \omega) + \sigma_{\text{inc}} S_{\text{inc}}(Q, \omega) \right)$

$S_{\text{coh}}(Q, \omega) = \frac{1}{N} \frac{1}{2\pi\hbar} \sum_{j,j'} \int_{-\infty}^{\infty} \langle e^{-iQR_{j'}(0)} e^{iQR_j(t)} \rangle e^{-i\omega t}$

$S_{\text{inc}}(Q, \omega) = \frac{1}{N} \frac{1}{2\pi\hbar} \sum_{j} \int_{-\infty}^{\infty} \langle e^{-iQR_{j}(0)} e^{iQR_j(t)} \rangle e^{-i\omega t}$

- coherent: measure of structure
- incoherent: measure of dynamics

$\sigma$: scattering cross section
$R_j(t)$: location of atom $j$ at time $t$
$Q$: $k_0 - k$: momentum transfer (in units of $\hbar$)
$N$: # atoms
$\hbar\omega$: energy transfer
Incoherent neutron scattering

\[ S_{inc}(Q, \omega) = S_{inc}^{el}(Q) \delta(\omega) + S_{inc}^{in}(Q, \omega) \]
Motivation

- Gaussian approximation (Rahman et al., *Phys. Rev.*, 1962) for EINS only uses low Q values

\[ I_{\text{inc}} \propto \frac{I}{I_0} \propto \text{EISF} \propto \exp \left( -\frac{1}{6} Q^2 \langle r^2 \rangle \right), \text{ for } Q_{\text{max}}^2 \langle r^2 \rangle \leq 2 \]

\[ \langle r^2 \rangle : \text{mean square fluctuation} \]
• Gaussian approximation (Rahman et al., Phys. Rev., 1962) for EINS only uses low Q values

\[ l_{\text{inc}} \propto \frac{l}{l_0} \propto \text{EISF} \propto \exp \left(-\frac{1}{6} Q^2 \langle r^2 \rangle \right), \text{ for } Q^2_{\text{max}} \langle r^2 \rangle \leq 2 \]

• many data points are neglected for evaluation

⇒ extract more information by using all obtained information

\( \langle r^2 \rangle \): mean square fluctuation
• which Q range should be fitted (e.g. bound water at low Q)
Aim

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IN16 Acetylcholinesterase (AChE)

AChE data measured and published by J. Peters et al., 2012, M. Trapp et al., 2012 and M. Trovaslet et al., 2013
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- can we characterize Q ranges where certain effects are more pronounced
- what do we actually see at high Q values
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⇒ need for

- different samples
- conditions (hydration level, pressure)
- different instruments
- simulations
Different models - Elastic Incoherent Neutron Scattering

1. Heterogeneity

  → dominant non-Gaussian contribution to the EISF due to motional heterogeneity and "true" non-Gaussian effects are small
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Different models - **Elastic Incoherent Neutron Scattering**

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  \[ \text{Gaussian approximation for individual atoms, but representing the distribution of atomic position fluctuations by a gamma distribution} \]

  \[ \text{correction term to describe heterogeneity} \]
  \[ \sigma^2 = \frac{1}{N} \sum_{\alpha=1}^{N} (\langle \Delta r_{\alpha}^2 \rangle - \langle \Delta^2 \rangle)^2 \]
Different models - Elastic Incoherent Neutron Scattering

1. Heterogeneity

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  \[ \Rightarrow \text{Gaussian approximation for individual atoms, but representing the distribution of atomic position fluctuations by a gamma distribution} \]

  \[ \Rightarrow \text{\(q^4\sigma^2\) correction term to describe heterogeneity} \]
  \[ \left( \sigma^2 = \frac{1}{N} \sum_{\alpha=1}^{N} (\langle \Delta r_{\alpha}^2 \rangle - \langle \Delta r^2 \rangle)^2 \right) \]
  \[ \Rightarrow \text{using entire Q range and solving problem of heterogeneity} \]
2. No isotropy

  → solving problem of different motions on different directions ($\langle u^2 \rangle \neq 1/3(\langle u_x^2 \rangle + \langle u_y^2 \rangle + \langle u_z^2 \rangle)$)
Different models - Elastic Incoherent Neutron Scattering

2. No isotropy

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  \[ \langle u^2 \rangle \neq 1/3(\langle u_x^2 \rangle + \langle u_y^2 \rangle + \langle u_z^2 \rangle) \]

3. Long-Time Mean Square Displacements

  → solving problem of instrument resolution
Different fitting models

- Gaussian approximation:
  \[ \propto \exp\left(-\frac{1}{6} Q^2 \langle r \rangle^2 \right) \]

- Peters and Kneller, 2012:
  \[ \propto \frac{1}{\left(1 + \frac{Q^2 \langle r \rangle^2}{\beta} \right)^\beta} \]

- Yi et al., 2012:
  \[ \propto \exp\left(-\frac{1}{6} Q^2 \langle r \rangle^2 \right) \left(1 + \frac{Q^4}{72} \sigma^2 \right) \]
Example - AChE IN6, 50 $\mu$eV $\rightarrow t_{obs} \approx 20$ ps

Fits:
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Fits:

MSD:
Example - AChE IN13, $8 \mu eV \rightarrow t_{obs} \approx 100 \text{ ps}$

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MSD:
Example - AChE IN16, $0.9 \mu eV \rightarrow t_{obs} \approx 1 \text{ ns}$

Fits:
Example - AChE IN16, 0.9 $\mu$eV $\rightarrow t_{\text{obs}} \approx 1$ ns

Fits:

MSD:
Example - AChE IN16, 0.9 $\mu$eV $\rightarrow$ $t_{obs} \approx 1$ ns

Fits:

Zoom 300K:

MSD:
**Example - AChE IN16, 0.9 $\mu$eV $\rightarrow t_{obs} \approx 1$ ns**

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Example - AChE IN16, 0.9 \( \mu \text{eV} \rightarrow t_{\text{obs}} \approx 1 \text{ ns} \)

Fits:

MSD:
Problems with experimental data:

- Bragg peak of surrounding water, sample holder (coherent scattering)
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- effects of normalization, corrections
- Multi-scattering effects at low Q values

Problems with models:

- stable fitting routine
- distinguish between fitting artefacts and real behaviour

⇒ comparison to simulations are needed
Outlook

- Further investigation of AChE → simulations
- "Complete" study of α-lactalbumin (4 instruments, Simulations, diff. hydration)
- gathering data of already measured system, e.g. β-lactoglobulin
- investigation of other small protein systems, e.g. insulin
  ⇒ Developing new methods to characterize data and populate nDDB (neutron Dynamics Data Bank\(^1\))

\(^{1}\)Rusevich et al., *Eur. Phys. J. E*, 36, 80, 2013