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Model of Large Scale Conformation Mobility in Proteins

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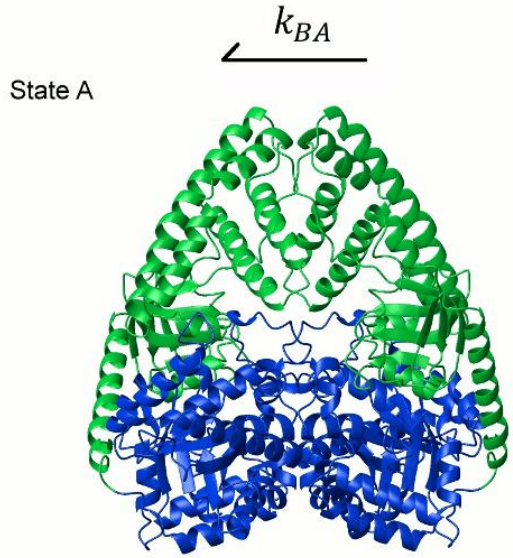
Outline

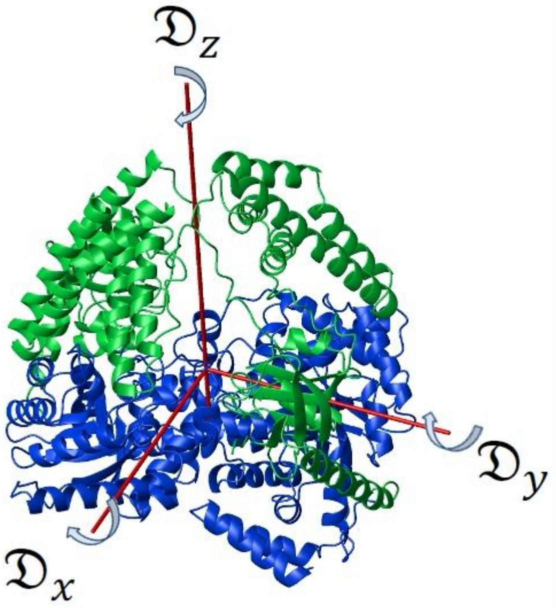
- Conformational transitions on different time scales
- Model of conformation transitions between discrete states
- Closed form expression for correlation function
  Time domain vs. Frequency domain
- What to expect: Illustrative calculations

Time scale of Conformational transitions

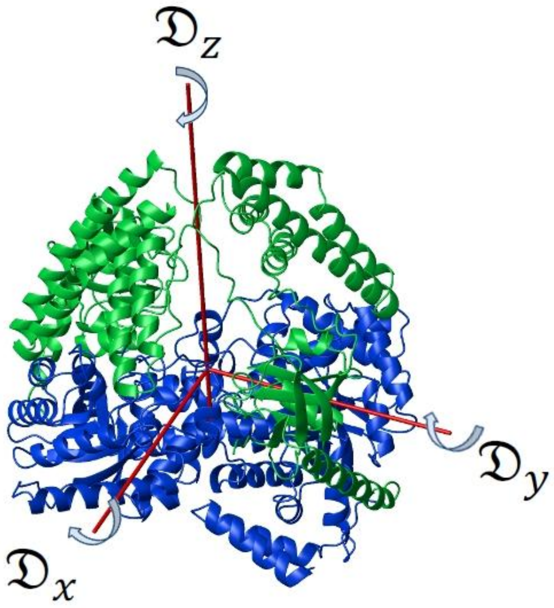


$$\tau_c = \frac{1}{k_{AB} + k_{BA}}$$

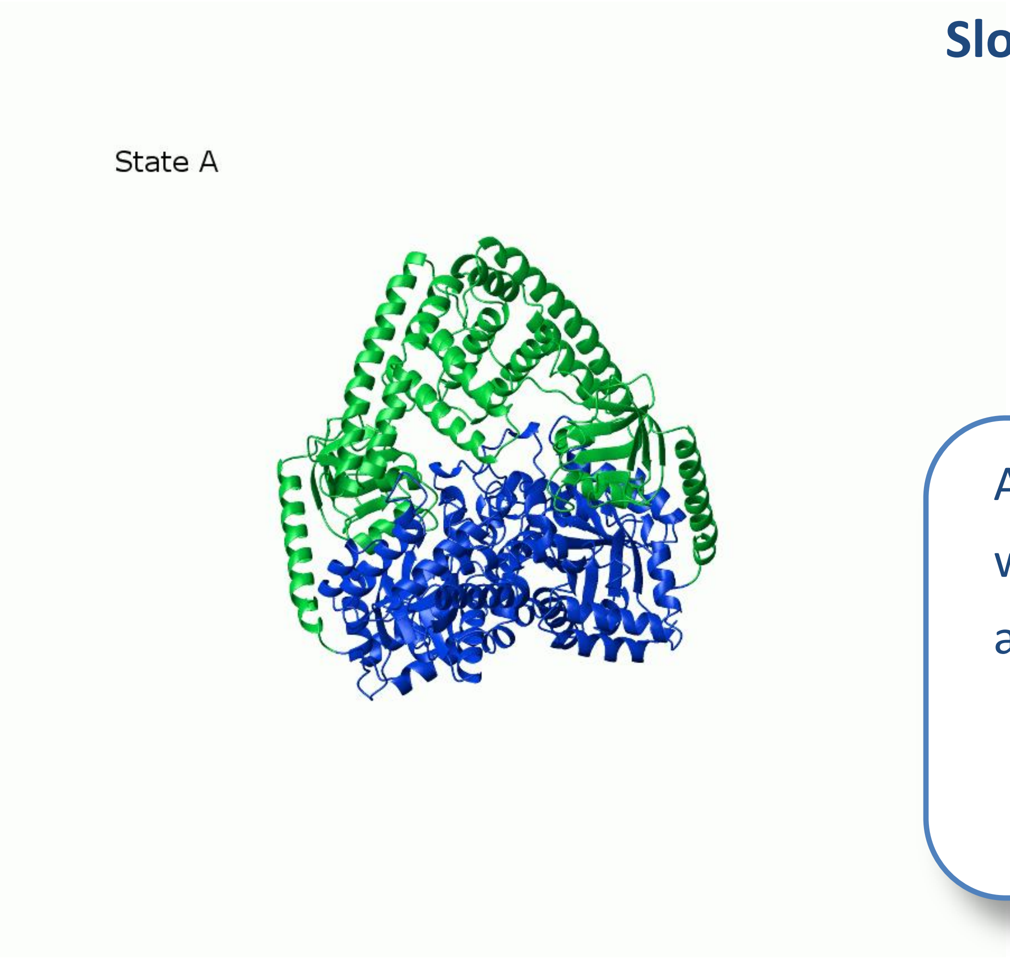
Time scale of Rotational diffusion



$$\tau_{\mathfrak{D}} = \frac{1}{2\left(\mathfrak{D}_x + \mathfrak{D}_y + \mathfrak{D}_z\right)}$$



Conformation transitions on different time scales



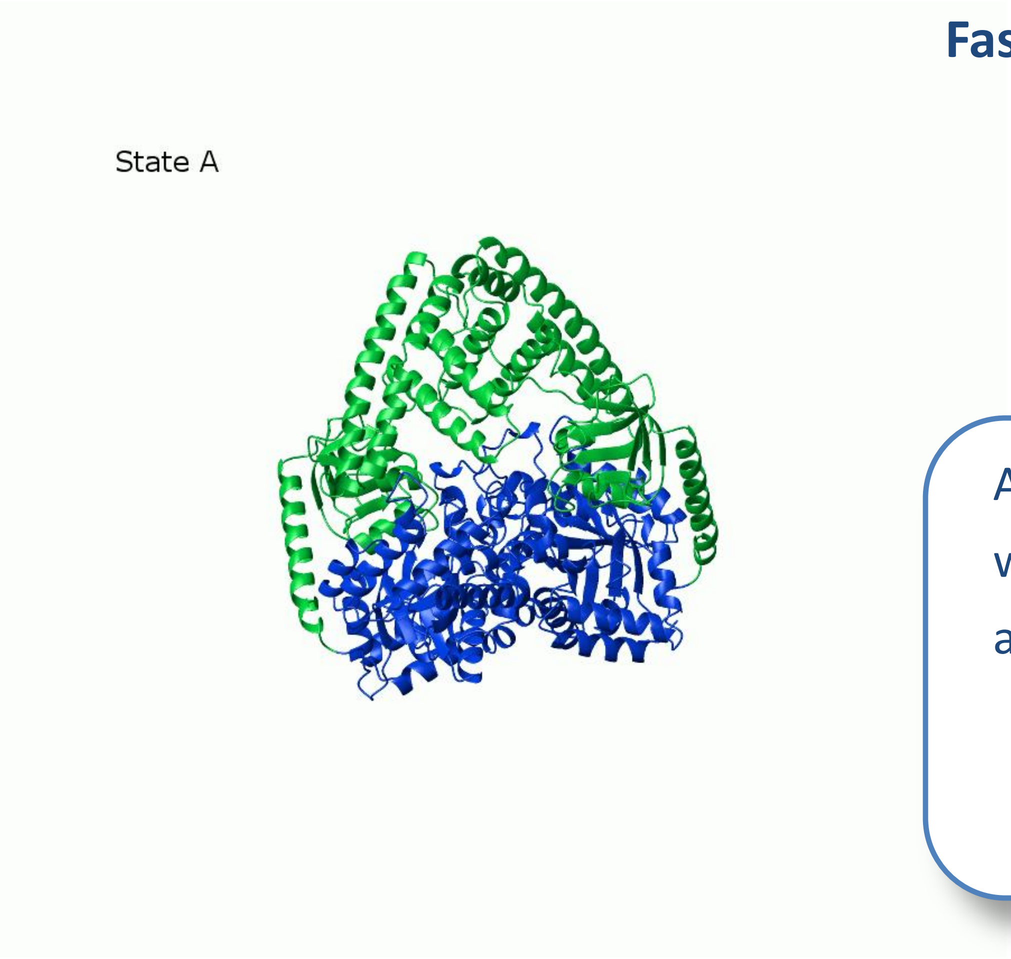
Slow Exchange

$$\tau_c \gg \tau_{\mathfrak{D}}$$

Approximation of **two species** with **two different structures** and **two diffusion tensors**

$\mathfrak{D}^A$ and $\mathfrak{D}^B$

Conformation transitions on different time scales



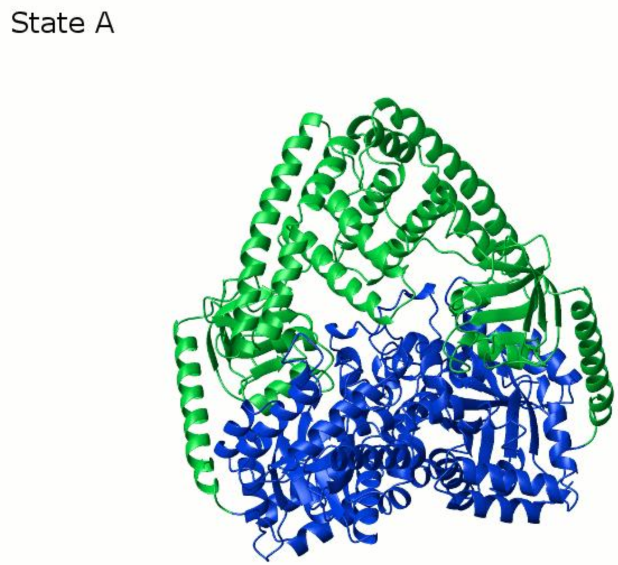
Fast Exchange

$$\tau_c \ll \tau_{\mathfrak{D}}$$

Approximation of **single conformer** with **one averaged structure** and **one averaged diffusion tensor**

$$\bar{\mathfrak{D}}$$

Conformation transitions on different time scales



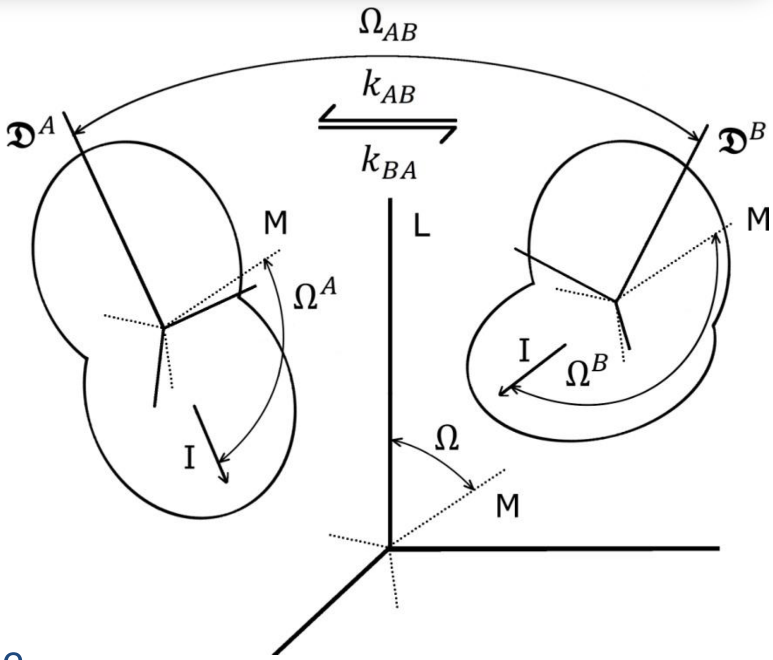
Intermediate Exchange

$$\tau_{c} \sim \tau_{\mathfrak{D}}$$

?

Rotational diffusion of semi-Rigid molecule

Conformation transition between discrete set of states



- Molecule tumbles in isotropic solvent
- Molecule exchanges between discrete conformations $\varepsilon = A, B, \ldots$
- In each conformation state molecule is rigid and has diffusion tensor $\mathfrak{D}^{\varepsilon}$
- The transition time is much shorter than the time which molecule spends in any conformation

Berne, Pecora (1968); Wong, Case and Szabo (2009)

Relationships between experimental observables and theoretical calculations

Orientation correlation function

$$C_l(t) = \langle P_l[\boldsymbol{n}(t)\cdot\boldsymbol{n}(0)]\rangle$$

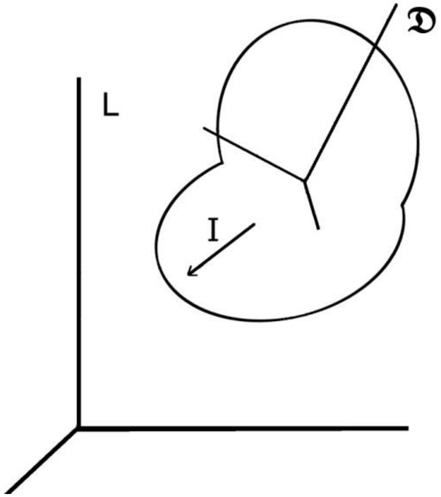
Fourier transform

Spectral density

$$J_l(\omega)$$

Linear Combination

Experimental observables: R1, R2 etc.



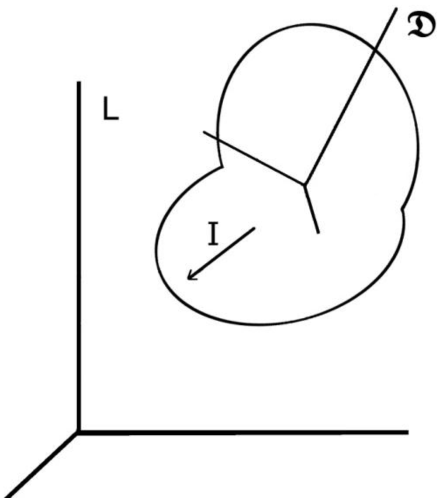
Solution in time domain cannot be represented in closed forms due to **Abel impossibility theorem (1824)**

Orientation correlation function

$$C_l(t) = \langle P_l[\boldsymbol{n}(t) \cdot \boldsymbol{n}(0)] \rangle$$

Poster # 396

Chopin Ballroom, **Thursday 2:00 -3:45 pm**



Ryabov, Clore, Schwieters, JCP **136** (2012) 034108

Rotational diffusion of semi-Rigid molecule

Correlation function in frequency domain

Ryabov, Clore, Schwieters (2012)

$$\hat{C}_l(i\omega) = \frac{4\pi}{2l+1}\sum_{\varepsilon,\eta} \mathbf{Y}_l^T(\Omega_{\varepsilon \mathrm{I}})\mathbf{A}^{\varepsilon,l\dagger}\mathbf{R}^{l,\varepsilon\eta}(i\omega)\,\mathbf{A}^{\eta,l}\mathbf{Y}_l^*(\Omega_{\eta \mathrm{I}})P_{eq}^{\eta}$$

Spectral density

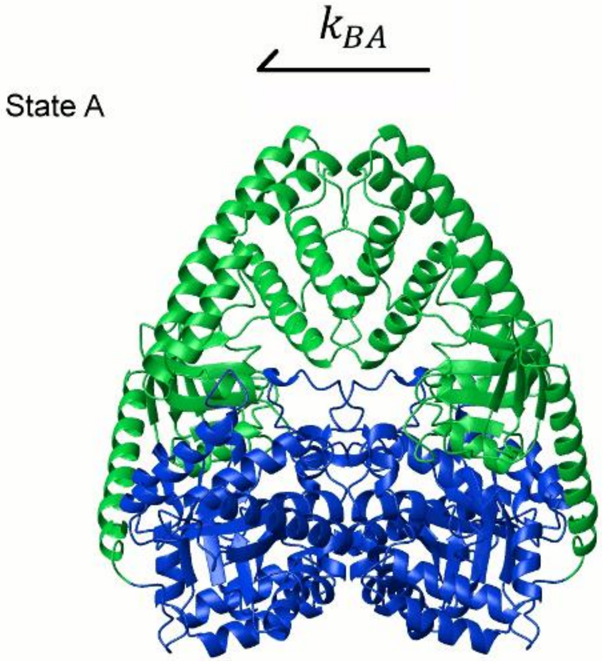
$$J(\omega) = Re\{\hat{C}(i\omega)\}$$

$$\hat{C}_l(i\omega) = \frac{4\pi}{2l+1}\sum_{m=-l}^{l}\sum_{\varepsilon,\eta} f_{l,m}^{\varepsilon\eta}(i\omega)Y_{l,m}(\Omega^{\varepsilon})Y_{l,m}^*(\Omega^{\eta})P_{eq}^{\eta}$$

Berne, Pecora (1968); Wong, Case and Szabo (2009)

Illustrative calculations

EI dimer



Estimations of XplorNIH @ 300 K

$$\mathfrak{D}_x^A = 29.16 \times 10^7\ [s^{-1}] \qquad \tau_{\mathfrak{D}}^A = 53.73\ \ [ns]$$

$$\mathfrak{D}_y^A = 31.47 \times 10^7\ [s^{-1}]$$

$$\mathfrak{D}_z^A = 32.43 \times 10^7\ [s^{-1}]$$

$$\mathfrak{D}_x^B = 15.71 \times 10^7\ [s^{-1}] \qquad \tau_{\mathfrak{D}}^B = 79.99\ \ [ns]$$

$$\mathfrak{D}_y^B = 15.82 \times 10^7\ [s^{-1}]$$

$$\mathfrak{D}_z^B = 30.99 \times 10^7\ [s^{-1}]$$

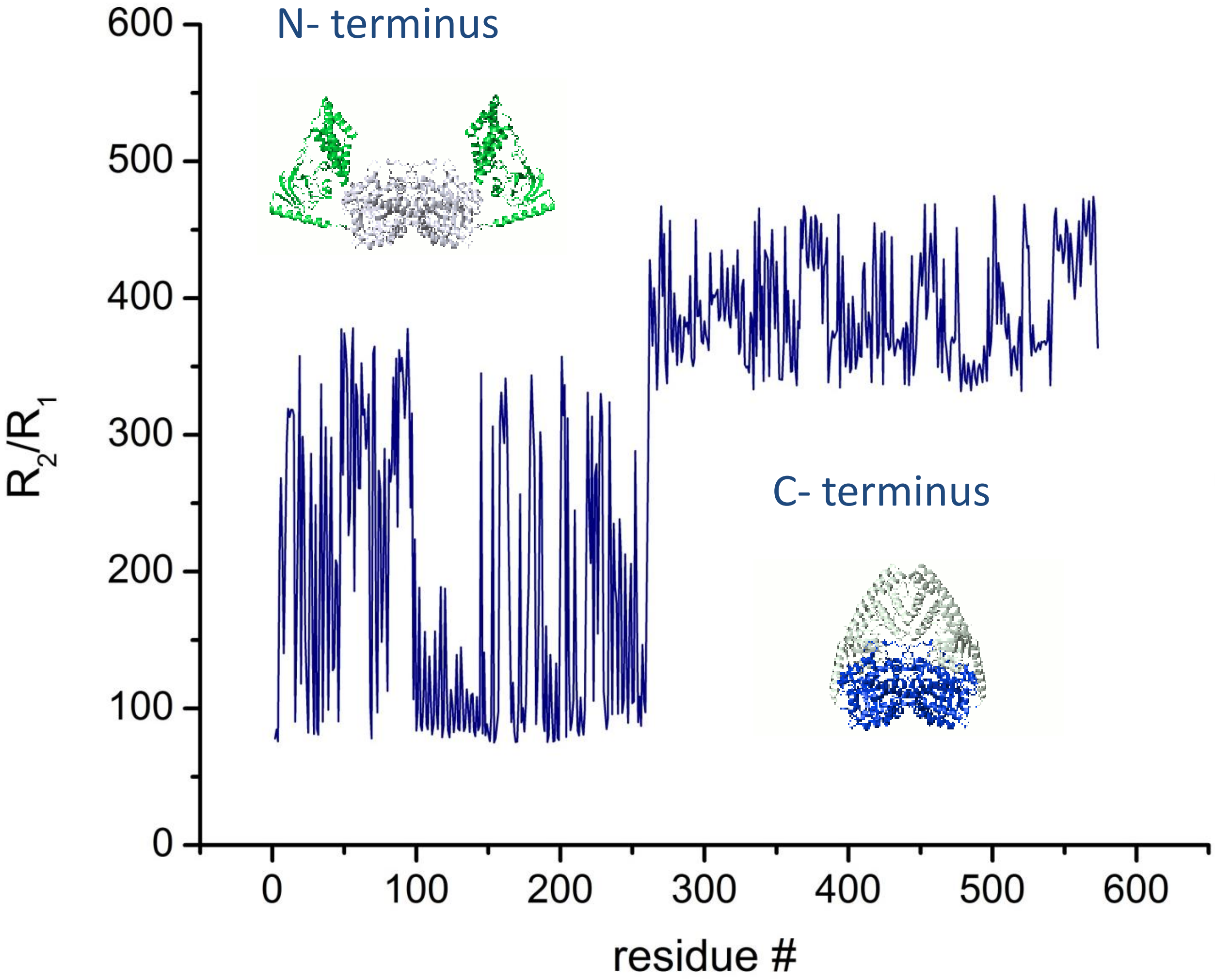
Assumptions

Symmetric motions $\Omega_{\mathrm{AB}}\colon \{\alpha_{\mathrm{AB}} = 0, \beta_{\mathrm{AB}} = 0, \gamma_{\mathrm{AB}} = 0\}$

Equal occupation $P_{eq}^A = P_{eq}^B = 1/2 \qquad k_{AB} = k_{BA}$

Illustrative calculations

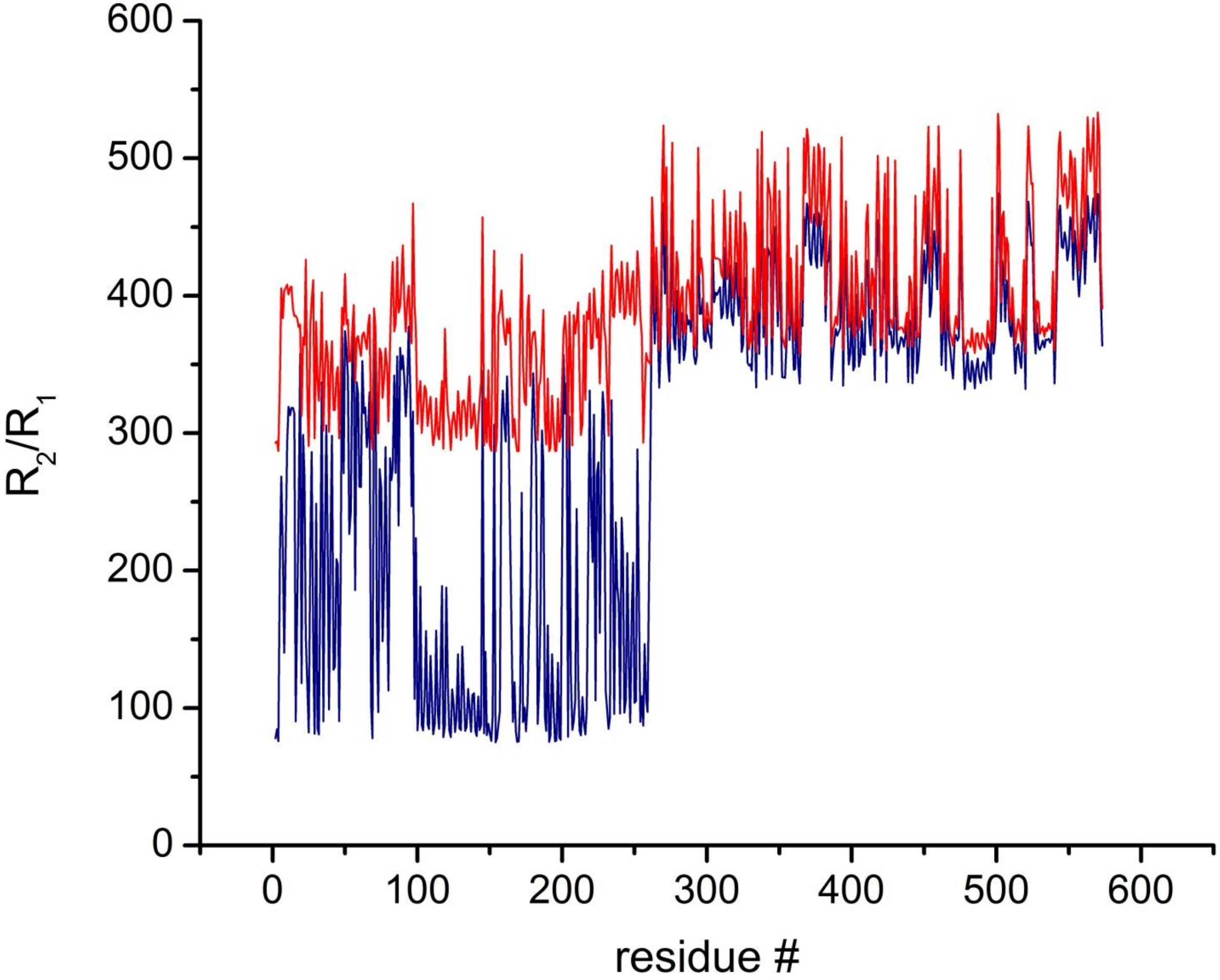
NMR relaxation rates for 600 MHz @ 300 K



$$k = \frac{2}{\tau_{\mathfrak{D}}^{A} + \tau_{\mathfrak{D}}^{B}} = 155.57 \;\; [ns^{-1}]$$

Illustrative calculations

NMR relaxation rates for 600 MHz @ 300 K

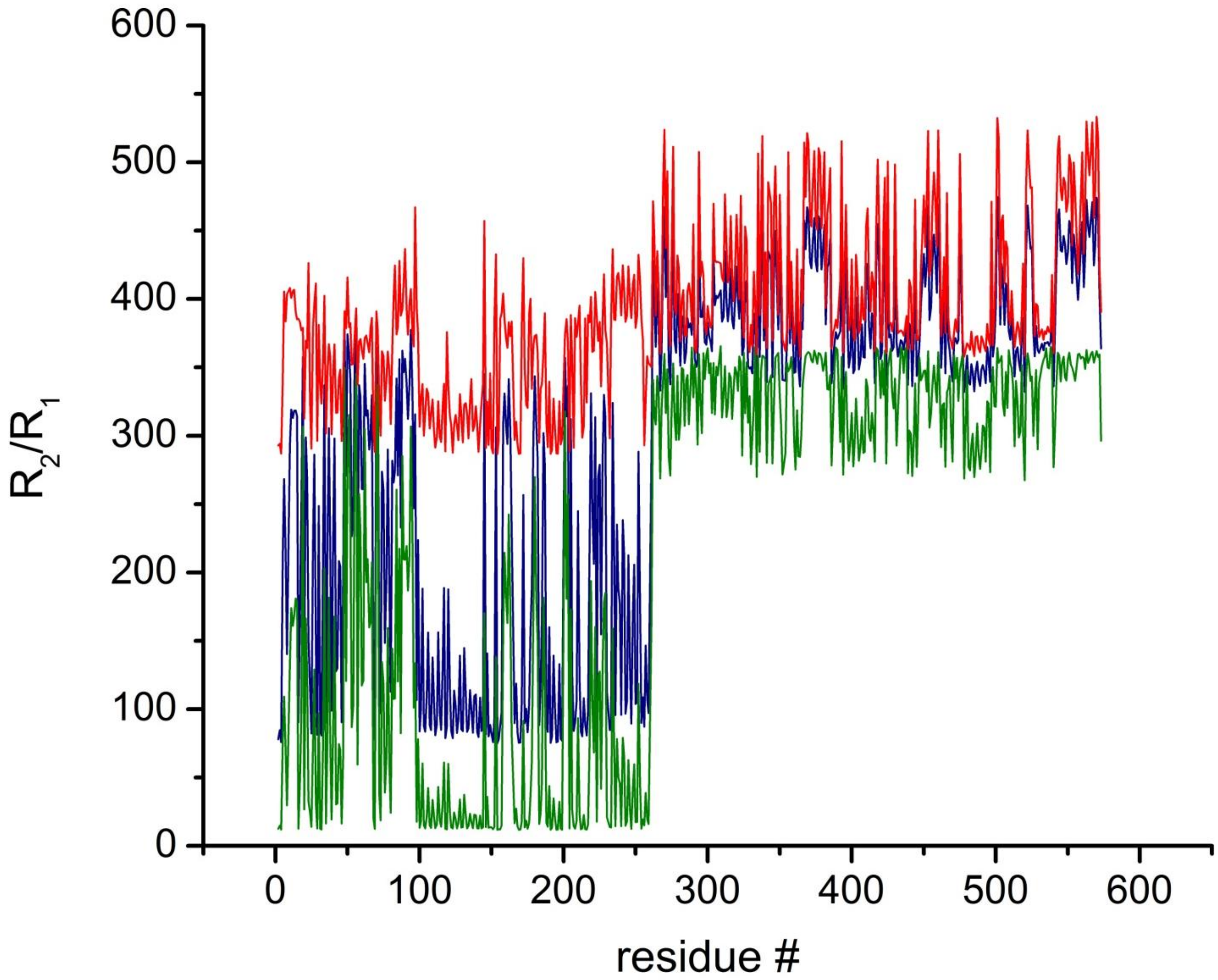


$$k_{slow} = 0.1 \times k$$

$$k = \frac{2}{\tau_{\mathfrak{D}}^{A} + \tau_{\mathfrak{D}}^{B}} = 155.57 \;\; [ns^{-1}]$$

Illustrative calculations

NMR relaxation rates for 600 MHz @ 300 K



$$k_{slow} = 0.1 \times k$$

🟥

$$k = \frac{2}{\tau_{\mathfrak{D}}^{A} + \tau_{\mathfrak{D}}^{B}} = 155.57 \ \ [ns^{-1}]$$

🟦

$$k_{fast} = 10 \times k$$

🟩

Concluding notes

Our Model

- Provides closed form solutions in frequency domain ready for evaluation of spectral density etc.
- Provides known limiting cases and is reproduced by Monte Carlo simulations
- Not universal: discusses only the transitions between discrete states
- However, accounts for arbitrary symmetry of diffusion tensors, arbitrary reorientation of molecules upon conformation transition, and coupling between diffusion tumbling and conformation exchange

Acknowledgments

Co-Authors

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- G. Marius Clore

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