Model of Large Scale Conformation Mobility in Proteins

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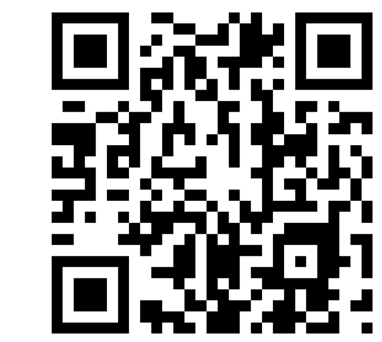

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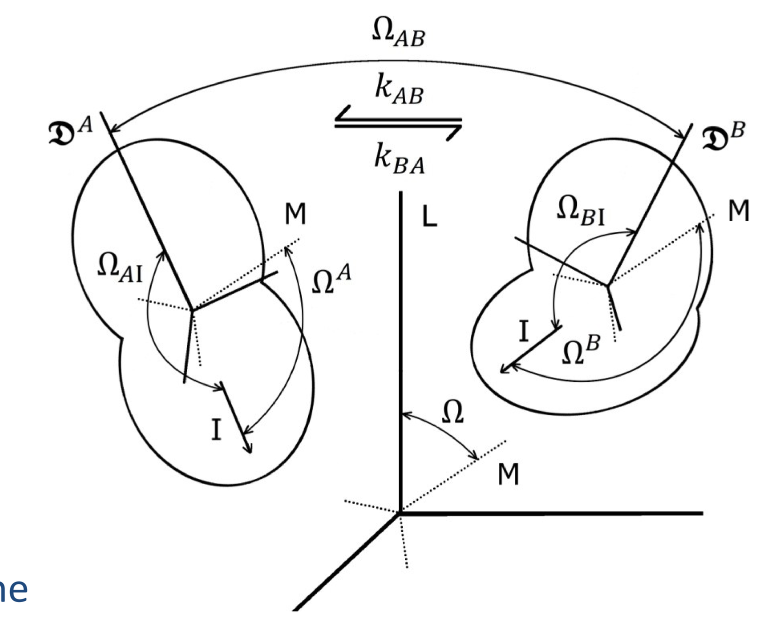
Conformation transition between discrete set of states

- 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
- Molecular reference frame **M** is some reference frame which reorients only due to rotational diffusion



Two characteristic times

Conformation exchange

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

Rotational diffusion

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

Fast exchange	Intermediate exchange	Slow exchange
$\tau_c \ll \tau_{\mathfrak{D}}$	$\tau_c \sim \tau_{\mathfrak{D}}$	$\tau_c \gg \tau_{\mathfrak{D}}$
$\bar{\mathfrak{D}}$	?	$\mathfrak{D}^A$ and $\mathfrak{D}^B$

Set of Partial Differential Equations for Green's functions

$$\frac{\partial p^{\varepsilon\eta}(\Omega, t|\Omega^0)}{\partial t} = -\hat{L}^{\mathrm{T}}\mathfrak{D}^{\varepsilon}\hat{L}\, p^{\varepsilon\eta}(\Omega, t|\Omega^0) + \sum_{\mu\neq\varepsilon} K_{\varepsilon\mu}\, p^{\mu\eta}(\Omega, t|\Omega^0)$$

Conformation exchange

$$\boldsymbol{K} = \begin{pmatrix} -\sum_{\varepsilon\neq A} k_{\varepsilon A} & k_{AB} & \vdots \\ k_{BA} & -\sum_{\varepsilon\neq B} k_{\varepsilon B} & \vdots \\ \ldots & \ldots & \end{pmatrix}$$

Initial conditions

$$p^{\varepsilon\eta}(\Omega, t|\Omega^0)|_{t=+0} = \delta_{\varepsilon\eta}\delta(\Omega - \Omega^0)$$

B.J. Berne, R. Pecora *J. Chem. Phys.* 50(2): 783-791 (1969)

Eigen functions of $\hat{L}^{\mathrm{T}}\mathfrak{D}\hat{L}$

$$\hat{L}^{\mathrm{T}}\mathfrak{D}\hat{L}\,\Psi^{l}_{mn}(\Omega) = E^{l}_{n}\Psi^{l}_{mn}(\Omega)$$

$$\hat{L}^{\mathrm{T}} = \{L_x, L_y, L_z\}$$

$$\hat{L} = i[\vec{r}\times\vec{\nabla}] \qquad \vec{\nabla} = \left\{\frac{\partial}{\partial x}, \frac{\partial}{\partial y}, \frac{\partial}{\partial z}\right\}$$

Ansatz of non-eigen decomposition

$$p^{\varepsilon\eta}(\Omega, t|\Omega^0, 0) = \sum_{l=0}^{\infty}\sum_{g,q=-l}^{l} c^{\varepsilon\eta}_{l,gq}(t) D^{(l)}_{gq}(\Omega)$$

$$\Psi^{\varepsilon,l}_{mn}(\Omega) = \sum_{k,p=-l}^{l} A^{\varepsilon,l}_{mp} D^{(l)}_{pk}(\Omega^{\varepsilon}_{\mathfrak{D}}) D^{(l)}_{kn}(\Omega)$$

L.D. Favro *Phys. Rev.* 119: 53-62 (1960)

Unitary transition between two sets of

$$\Psi^{\varepsilon,l}_{nk}(\Omega) \text{ and } D^{(l)}_{kn}(\Omega)$$

$$U^{\varepsilon,l}_{pk} = \sum_{n=-l}^{l} D^{(l)*}_{np}(\Omega)\Psi^{\varepsilon,l}_{nk}(\Omega)$$

Set of Linear Differential Equations

$$\frac{\partial c^{\varepsilon\eta}_{l,mn}(t)}{\partial t} = -\sum_{s,q=-l}^{l} U^{\varepsilon,l}_{ns}E^{\varepsilon,l}_{s}U^{\varepsilon,l\dagger}_{sq}c^{\varepsilon\eta}_{l,mq}(t) + \sum_{\mu\neq\varepsilon} K_{\varepsilon\mu}\, c^{\mu\eta}_{l,mn}(t)$$

Initial conditions

$$c^{\varepsilon\eta}_{l,mn}(t)\big|_{t=+0} = \frac{2l+1}{8\pi^2} D^{(l)*}_{mn}(\Omega^0)\delta_{\varepsilon\eta}$$

In matrix form

$$\frac{\partial \boldsymbol{c}^{\eta}_{l,m}(t)}{\partial t} = \mathbf{M}_l \boldsymbol{c}^{\eta}_{l,m}(t) \qquad [\boldsymbol{c}^{\eta}_{l,m}(t)]_{\varepsilon} = \begin{pmatrix} c^{\varepsilon\eta}_{l,ml}(t) \\ \vdots \\ c^{\varepsilon\eta}_{l,m-l}(t) \end{pmatrix}$$

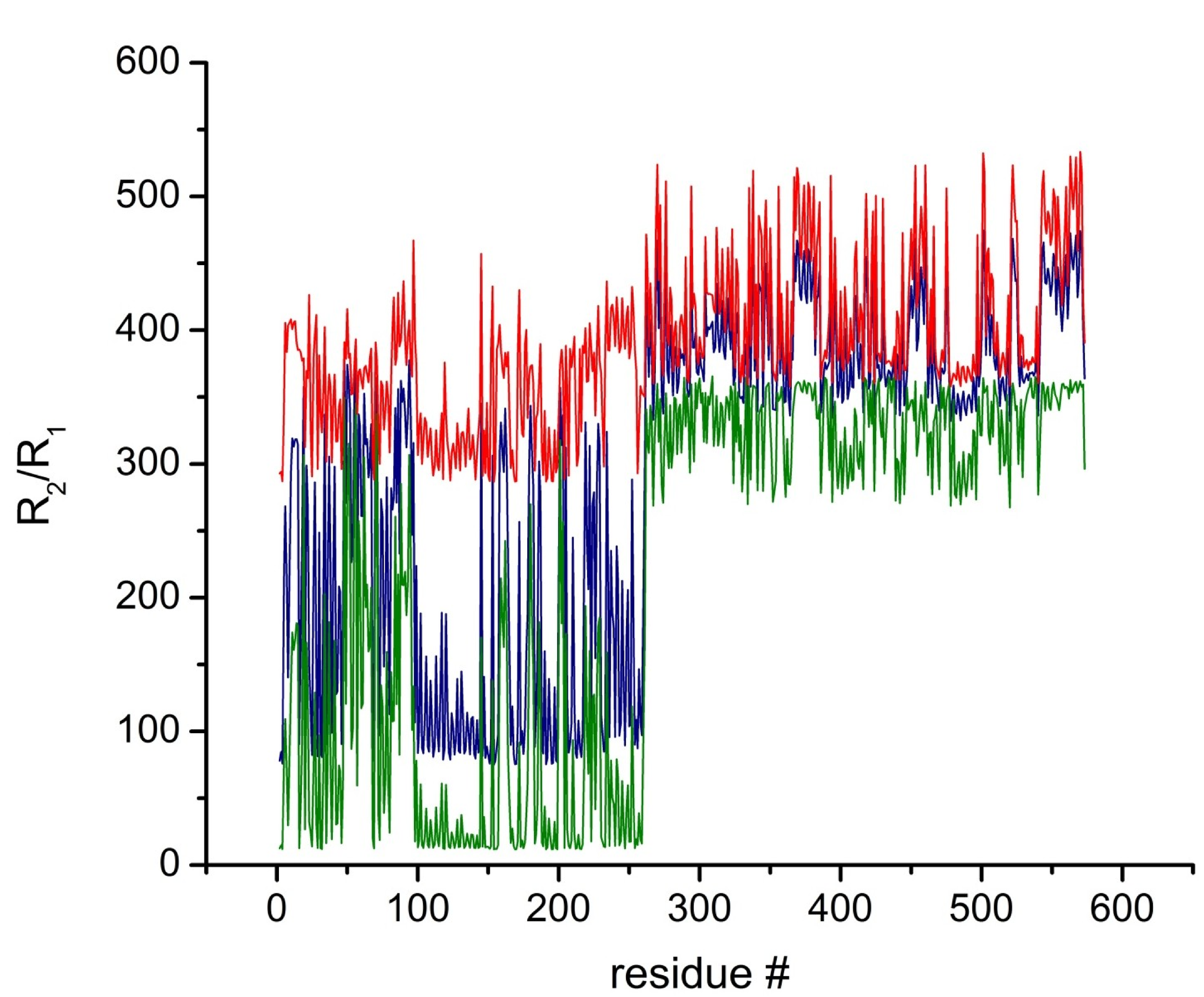
$$\mathbf{M}_l = \begin{pmatrix} \mathbf{U}^{A,l}\mathbf{E}^{A,l}\mathbf{U}^{A,l\dagger} - k^A\mathbf{I}_{2l+1} & k_{AB}\mathbf{I}_{2l+1} & \vdots \\ k_{BA}\mathbf{I}_{2l+1} & \mathbf{U}^{B,l}\mathbf{E}^{B,l}\mathbf{U}^{B,l\dagger} - k^B\mathbf{I}_{2l+1} & \vdots \\ \ldots & \ldots & \end{pmatrix}$$

$\mathbf{M}_l$ dimension $N_{states}(2l+1)$

No closed form for $\boldsymbol{c}^{\eta}_{l,m}(t)$ when $l \geq 1$ and $N_{states} \geq 2$

Due to **Abel impossibility theorem (1824)**

Illustrative simulations



$$k_{AB} = k_{BA}$$

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

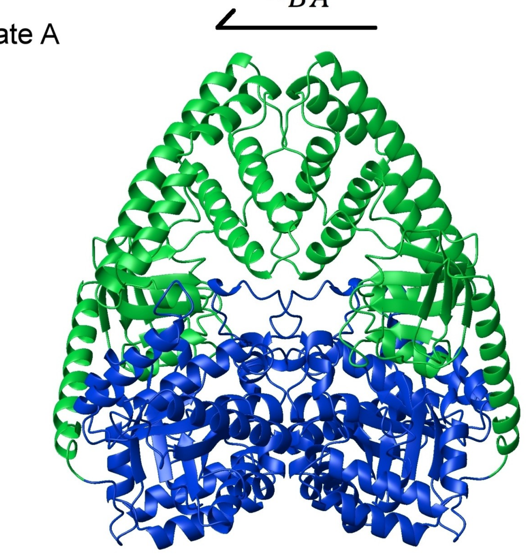
$$k = \frac{2}{\tau^A_{\mathfrak{D}} + \tau^B_{\mathfrak{D}}} = 155.57 \ [ns^{-1}]$$

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

$$\tau^A_{\mathfrak{D}} = 53.73 \ [ns]$$

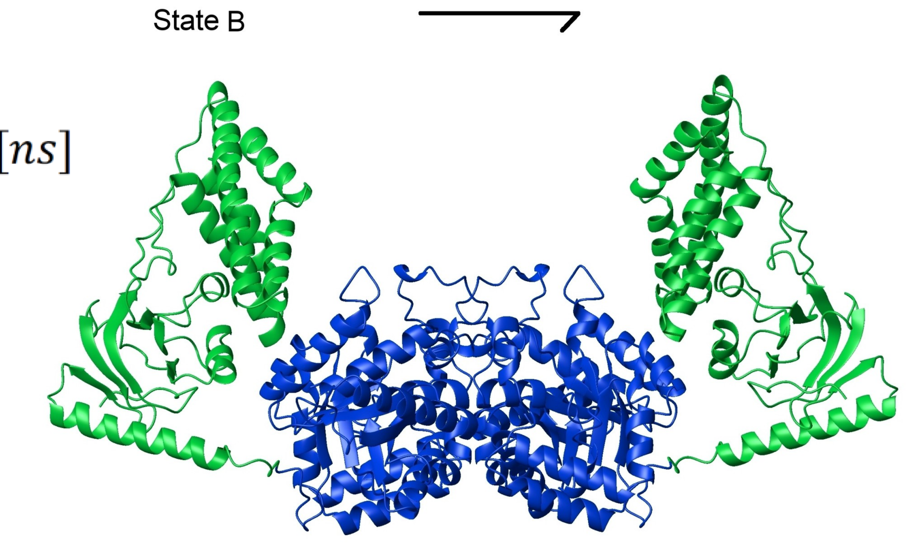
State A

k_{BA}



State B

k_{AB}



$$\tau^B_{\mathfrak{D}} = 79.99 \ [ns]$$

In frequency domain

Set of Linear Equations

$$\sigma\tilde{\boldsymbol{c}}^{\eta}_{l,m}(\sigma) - \boldsymbol{c}^{\eta}_{l,mn}(t)\big|_{t=+0} = \mathbf{M}_l\tilde{\boldsymbol{c}}^{\eta}_{l,m}(\sigma) \qquad \sigma = \gamma + i\omega$$

$$[\boldsymbol{c}^{\eta}_{l,mn}(t)|_{t=+0}]_{\varepsilon} = \delta_{\varepsilon\eta}\frac{2l+1}{8\pi^2}\begin{pmatrix} D^{(l)*}_{m,l}(\Omega^0) \\ \vdots \\ D^{(l)*}_{m,-l}(\Omega^0) \end{pmatrix} \qquad \tilde{\boldsymbol{c}}^{\eta}_{l,m}(\sigma) \coloneqq \mathcal{L}[\boldsymbol{c}^{\eta}_{l,m}(t)]$$

No restrictions from Abel theorem in frequency domain

Closed form solutions

$$C(t) = \iint p(\Omega_{\mathrm{LM}}, t|\Omega^0_{\mathrm{LM}}, 0) p_{eq}(\Omega^0_{\mathrm{LM}}) \times$$

$$\times \sum_{m,k,k'=-l}^{l} D^{l*}_{mk}(\Omega_{\mathrm{LM}}) D^{l}_{mk'}(\Omega^0_{\mathrm{LM}}) D^{l*}_{k0}(\Omega_{\mathrm{MI}}) D^{l}_{k'0}(\Omega_{\mathrm{MI}})\, d\Omega_{\mathrm{LM}} d\Omega^0_{\mathrm{LM}}$$

$$\tilde{C}_l(\sigma) = \frac{4\pi}{2l+1}\sum_{\varepsilon,\eta} \mathbf{Y}^{T}_{l}(\Omega_{\varepsilon I})\mathbf{A}^{\varepsilon,l\dagger}\mathbf{R}^{\varepsilon\eta}(\sigma)\mathbf{A}^{\eta,l}\mathbf{Y}^{*}_{l}(\Omega_{\eta I})P^{\eta}_{eq}$$

Spectral density

$$J(\omega) = Re\{\hat{C}(\omega)\} = Re\left\{\tilde{C}(\sigma)\big|_{\sigma=i\omega}\right\}$$

R_1 R_2 Experimental observables