Water fluctuations at the protein interface: Gigantic reorganization energy

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Plastocyanin — electron carrier that connects photosystem I and photosystem II

On average, 60% of protein surface is hydrophobic, 33% is polar, and 7% is charged.

9/-8- charge is made by 9 Glu and 6 Asp, 6 Lys, and Cu⁺
Patchy (hydrophobic/hydrophilic) interface

Weak dewetting on hydrophobic patches (large fluctuations according to Chandler!)
The reason for the dynamical transition is either in the bulk (Widom line) or interfacial (hydrophobic interface) effects.
Expectations from linear response, solvation of difference charges

\( V_{0s} \)

Coulomb solute–solvent interaction potential

\[-\langle V_{0s} \rangle = \frac{\langle (\delta V_{0s})^2 \rangle}{k_B T} = 2\lambda_s \]

Stokes shift

Reorganization energy

\( \lambda^{St} = -\langle V_{0s} \rangle / 2 \)

Linear response

Standard expectations for the energetics of protein redox reactions (Marcus theory)
Protein electron transfer

linear response paradigm

Why does nature rely on multiple electron jumps if each of them is energetically unfavorable by the reorganization energy?

Should we try to mimic this design if it does not provide energetic efficiency?
GIGANTIC reorganization energy in proteins

Breadth of fluctuations much exceeding that for typical small molecules (inset)

Reorganization energy on the level 5 eV

Significant splitting between the reorganization energy and Stokes shift/2

~300-500 ps is the scale of losing ergodicity
Trying to calculate it

SolvMol
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http://theochemlab.asu.edu/codes.html

Input: PDB file
Calculates:
• Solvation free energy
• Solvation entropy
• Stokes shift dynamics

Solute

Structure:
X-ray, NMR, Molecular mechanics

Charge Distribution:
Empirical Force Field, QM calculations

\[ E_0(r) \]

\[ \tilde{E}_0(k) \]

\[ \int |\tilde{E}_0(k)|^2 S(k)dk \rightarrow \text{Solvation Free Energy} \]

Solvent

Polarization structure factors:
Liquid-state theories, Computer Simulations
We can understand the first moment of the potential

\[ \lambda^{St} = -\langle V_{0s} \rangle / 2 \quad \lambda_s = \lambda^{St} - \left( \frac{1}{2k_B T} \right) \langle \delta V_{0s} \delta V_{OP} \rangle \]

Fluctuations of the potential created by protein's charges

Cross-correlations of water and protein are not sufficient to account for the gigantic reorganization energy from fluctuations!
GIGANTIC reorganization energy in proteins

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~300-500 ps is the scale of loosing ergodicity
Temperature dependence

Reorganization energy shoots up to its gigantic values from the «normal» magnitude seen at low temperatures.

What is the nuclear mode that unfreezes at the dynamical transition?

Spike at 220 K: Crossing of the Widom line?

\[ \lambda = \lambda_s + \lambda_p + \lambda_{s,p} \]
Dynamical features: Stokes shift dynamics

\[ S(t) = \frac{\langle \delta V_{0s}(t) \delta V_{0s}(0) \rangle}{\langle \delta V_{0s}^2 \rangle} \]

\[ S(t) = A_G e^{-(t/t_G)^2} + (1 - A_G) e^{-(t/\tau_E)\beta} \]
Dynamics of orientational fluctuations

Density manifold:

\[ C_N(t) = \langle \delta N_I(t) \delta N_I(0) \rangle \]

Orientational manifold:

\[ C_M(t) = \langle N_I \rangle^{-1} \langle \delta M_I(t) \cdot \delta M_I(0) \rangle \]

Fragile-strong transition at 220 K and strong-strong transition at 160 K
Only one strong-to-strong (Arrhenius-to-Arrhenius) dynamical transition is observed when diffusivity is averaged over the waters in the simulation box: the dynamical transition is the property of the interface.

Experimentally, fragile-to-strong transition is not observed in the primary relaxation of the protein-water mixture!
Density fluctuations at the hydrophobic interface

Does dynamical arrest imply the formation of the hydrophobic interface?

The change in the number of first shell particles is consistent with the mean-squared displacements.

Average number and variance of the number of first shell waters

The hydration shell becomes softer and more noisy with increasing temperature!
Length-scale of fluctuations

Dependence of the first and second cumulants on the cutoff distance from the protein surface

Different length-scale for the first and second cumulants!
Broad application to electron transport in biology

The standard notion: electronic transitions sacrifice the reaction Gibbs energy to achieve near-zero activation barrier

The new paradigm: multiple electron jumps are possible due to a significant asymmetry between the breadth and the average of the electrostatic fluctuations
Conclusions

Gigantic reorganization energy of electrostatic solvation, splitting between the reorganization energy and the Stokes shift.

Transition in the breadth of electrostatic fluctuations coinciding with the traditional dynamical transition of atomic displacements. Critical slowing down and spike in the reorganization energy at 220 K, fragile-strong (220K) and strong-strong (ca 160 K) dynamical transitions of the first-shell dynamics.

Density fluctuations behind large electrostatic fluctuations.

A possibility that the protein dynamical transition is linked to the creation of the high-temperature hydrophobic interface.

If YES, prediction: it should disappear at some lengthscale below 1nm.

Recent dielectric measurements (Markelz): no dynamical transition for polypeptides below certain length.
Proteins are not just big molecules!
David LeBard, graduates December '08

$\$ NSF

JPCB 2008, 112, 5218

JCP, 2008, 128, 155106 (solvation theory)
PRE, submitted (temperature dependence of PC's reorg. energy)
Non-ergodic reorganization energy

If the Stokes shift correlation function is known:

\[ C_X(t) = \langle X(t)X(0) \rangle \]

The non-ergodic reorganization energy becomes a step-wise filter of the Stokes shift frequency spectrum:

\[ \lambda(\tau_{\text{obs}}) = \beta \int_{1/\tau_{\text{obs}}}^{\infty} C_X(\omega) d\omega \]

For a Debye relaxation spectrum:

\[ \lambda(\tau_{\text{obs}}, T) = \lambda_{eq} \frac{2}{\pi} \cot^{-1}\left(\frac{\tau(T)}{\tau_{\text{obs}}}\right) \]