The laws of nature that we care about emerge through collective self-organization and really do not require knowledge of their component parts … they owe their reliability to principles of organization rather than to microscopic rules.

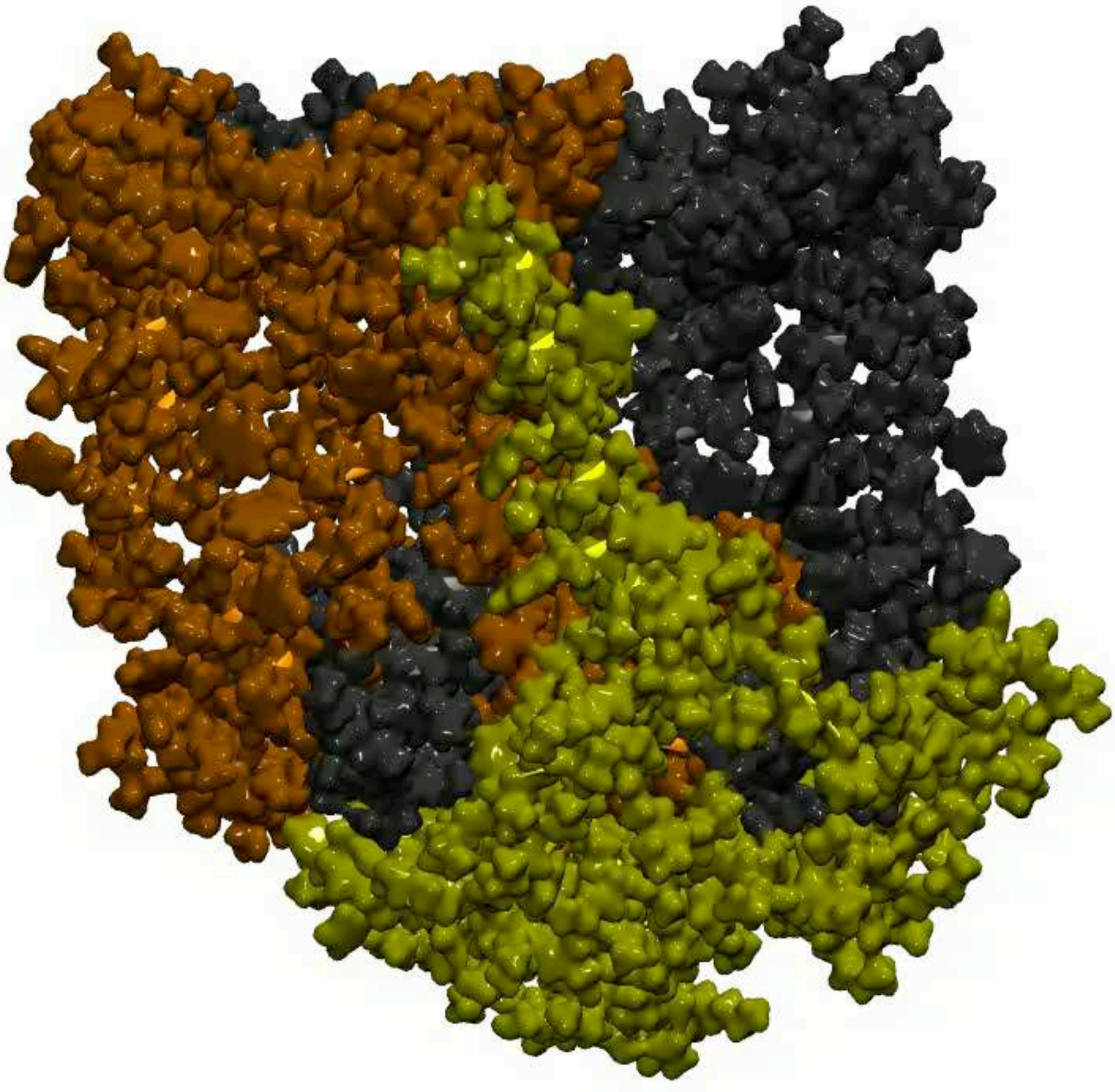
- Robert Laughlin

What can biology teach us about the condensed phase?

Tampa, Nov 13, 2014

Dmitry Matyushov
Center for Biological Physics
Department of Physics/Chemistry
Arizona State University

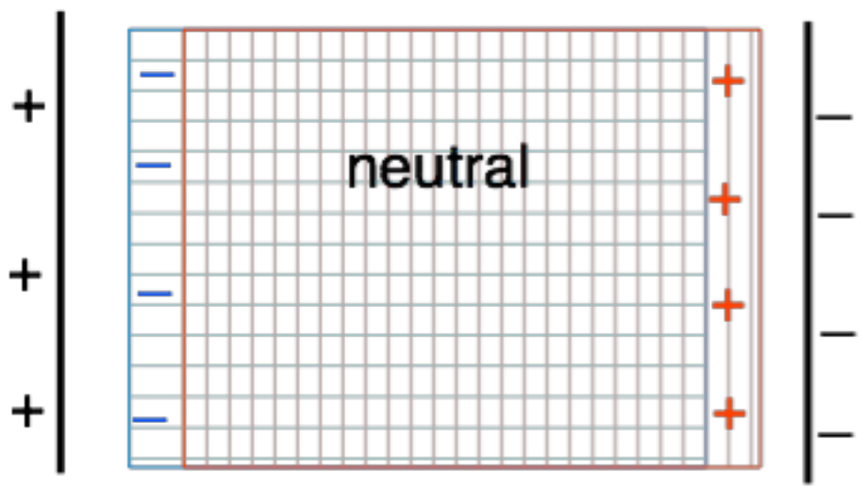
Bacterial reaction center: Are there certain general rules here?



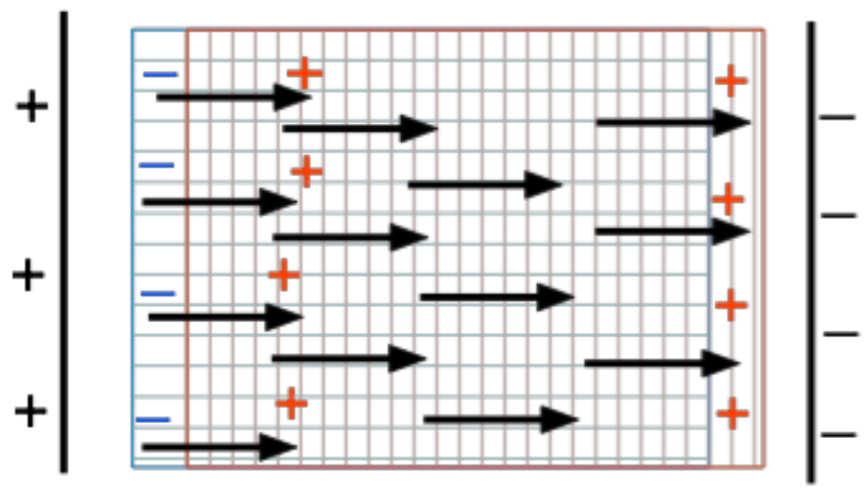
Electric Elasticity (Maxwell)

When an electromotive force acts on a dielectric, it puts every part of the dielectric into a polarized condition, in which its opposite sides are oppositely electrified.

"A dynamical Theory of Electromagnetic Field", Maxwell, 1865.



Maxwell: Elastic deformation of positive vs negative liquid

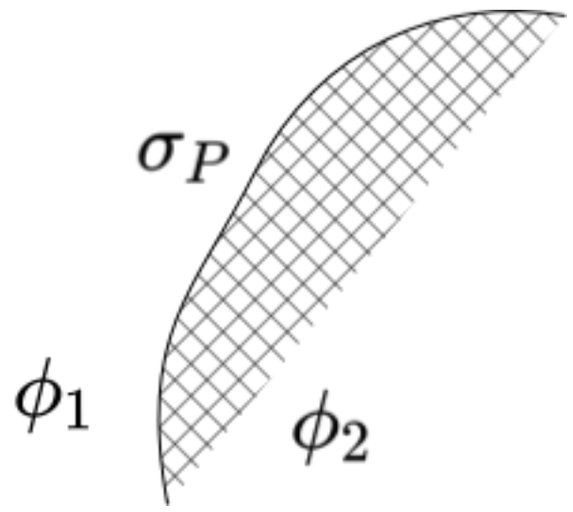


Debye: Picture of uniformly oriented dipoles

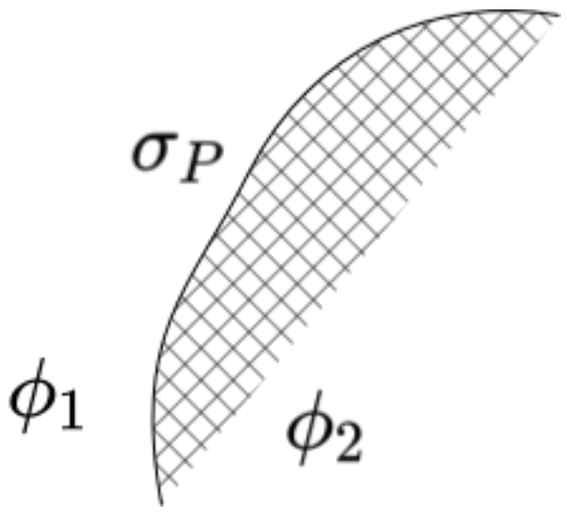
Boundary value problem:

$$\frac{\partial \Delta\phi}{\partial n} = -\Delta E_n = 4\pi\sigma_P$$

$$\Delta\phi = \phi_1 - \phi_2$$

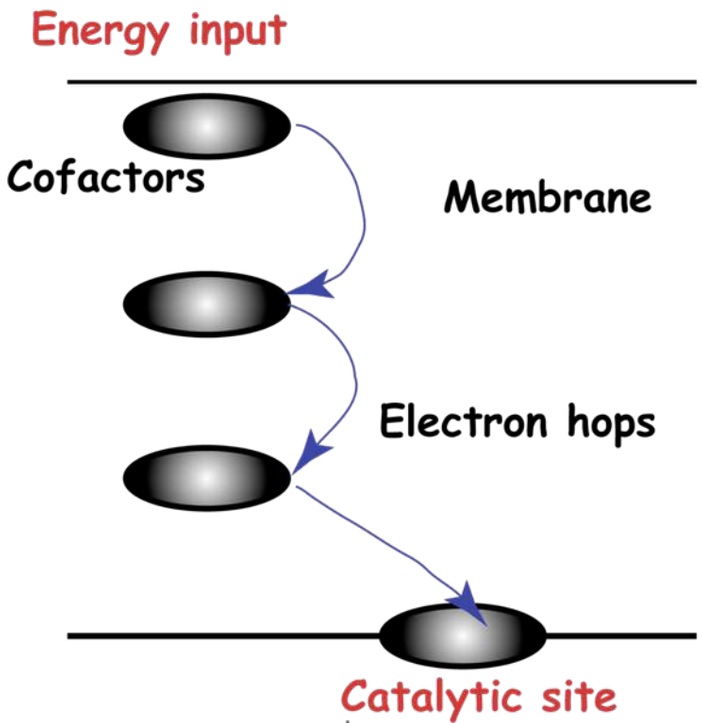


…the advancement of science depends on the discovery and development of exact ideas … to warrant the deductions we may draw by the application of mathematical reasoning. - J. C. Maxwell

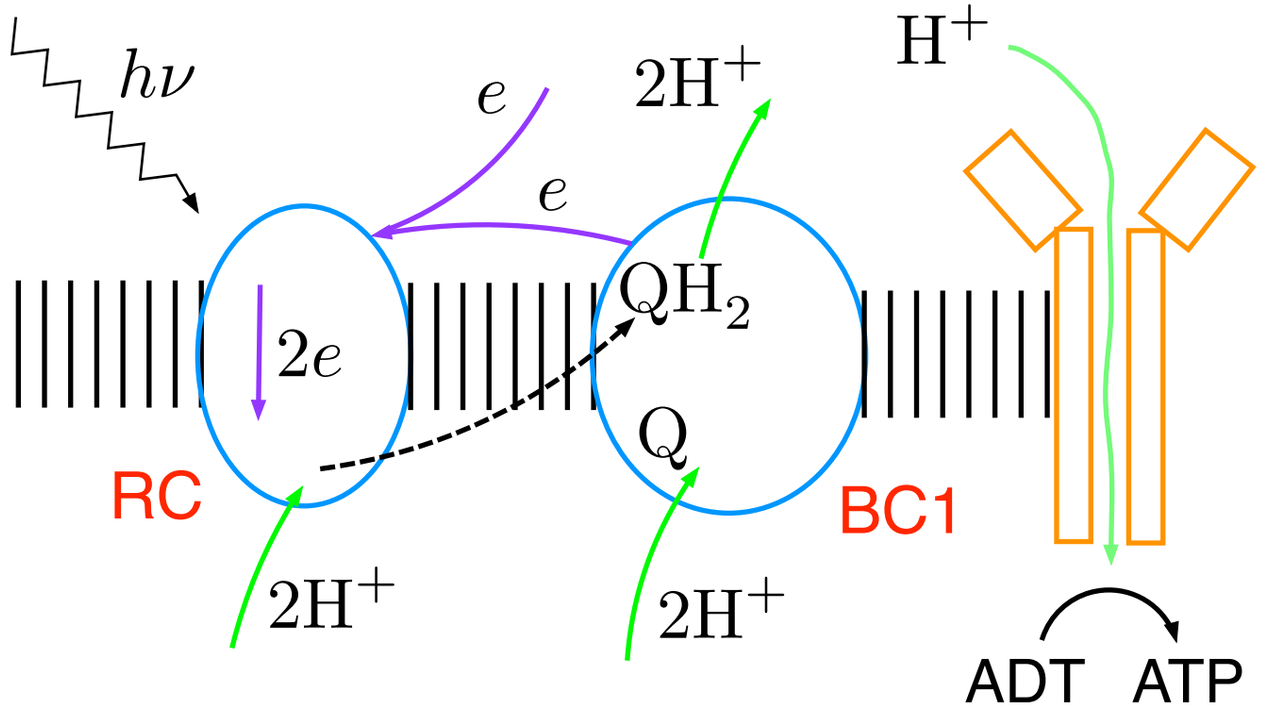


If the mathematics is universal, where do the specifics of the system come in?

Biology's energy chains

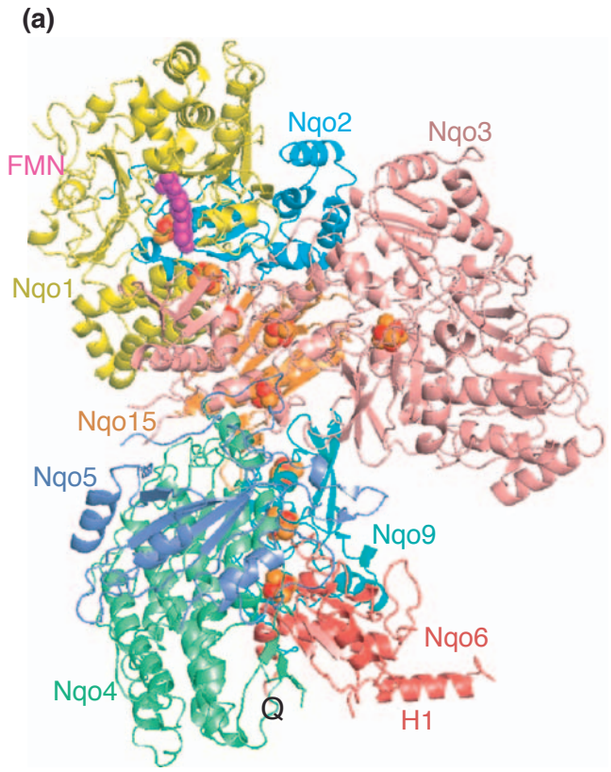


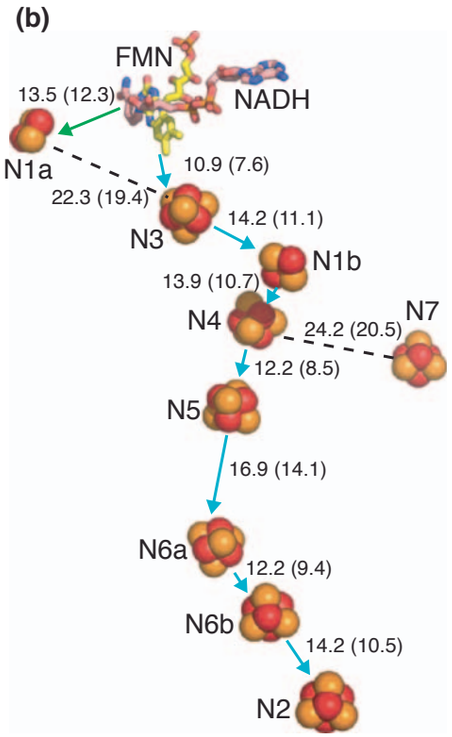
$$O_2 + 4H^+ + 4e^- \rightarrow 2H_2O$$



- 22 electron hops in mitochondria's membrane over the free energy span of 1.1 eV
- 8-9 electrons per one ATP produced
- ~25 kg of ATP produced daily in a human body

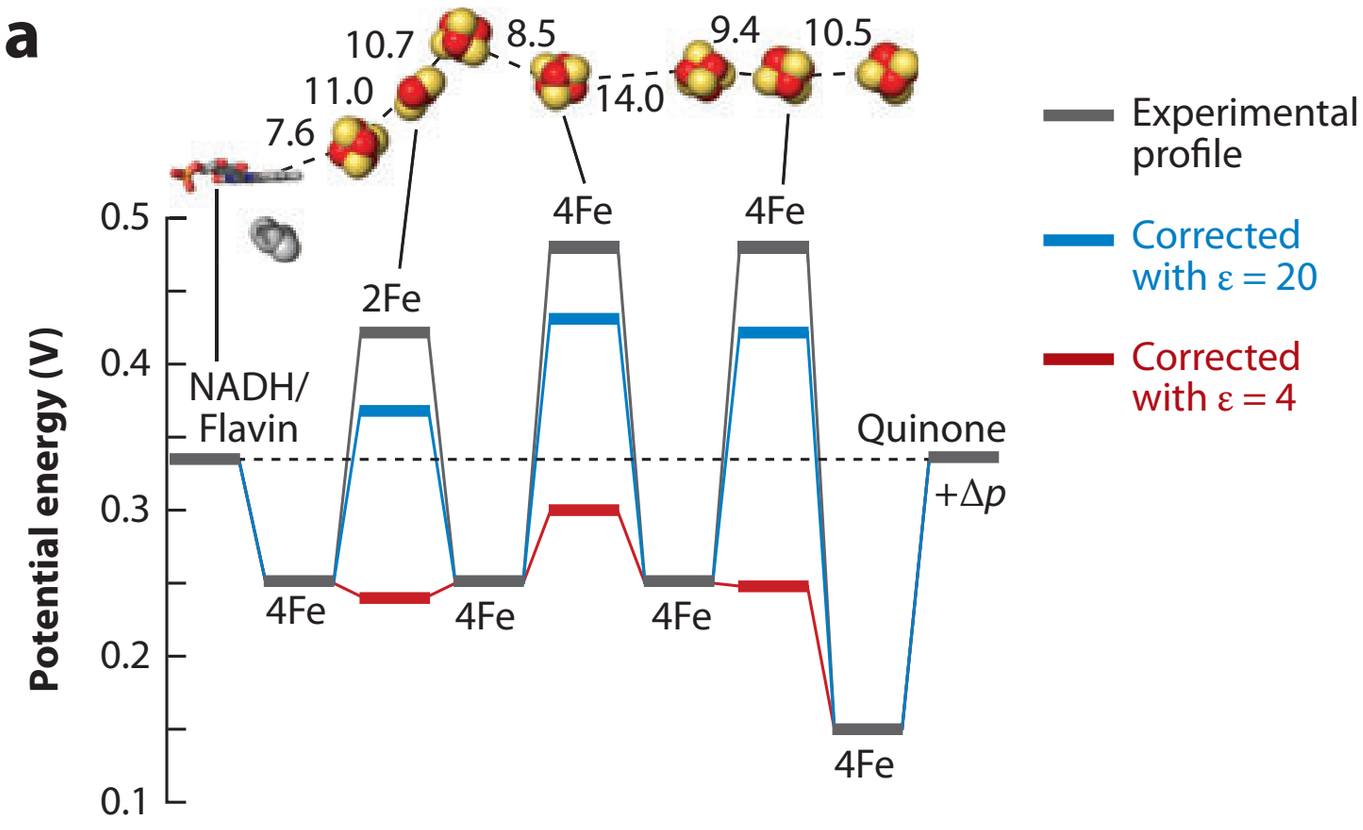
Mitochondria's Complex I





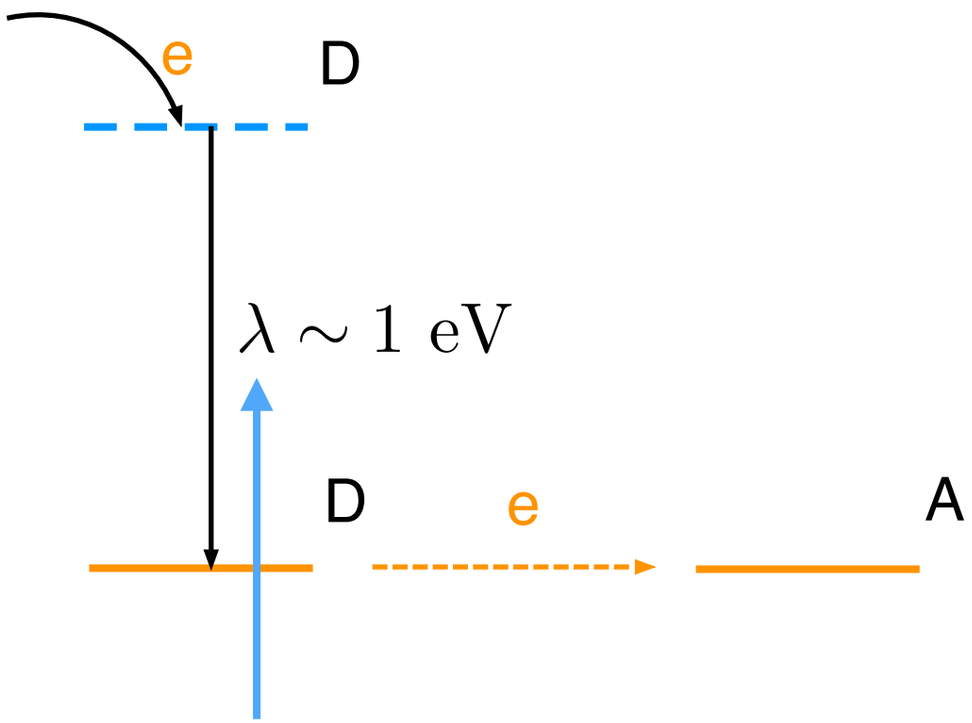
Efremov and Sazanov,

Curr. Opinion Struct. Biol. 2011, 21:532–540

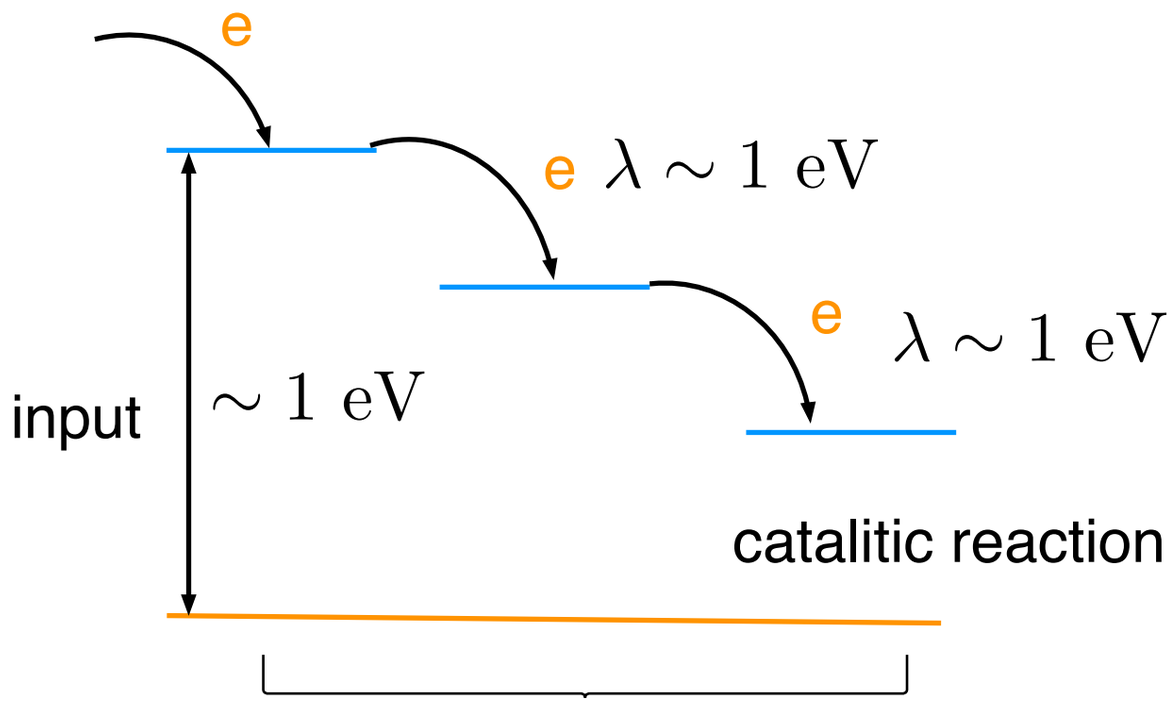


J. Hurst, Annu. Rev. Biochem. 2013. 82:551–75

Energy balance



Reorganization energy



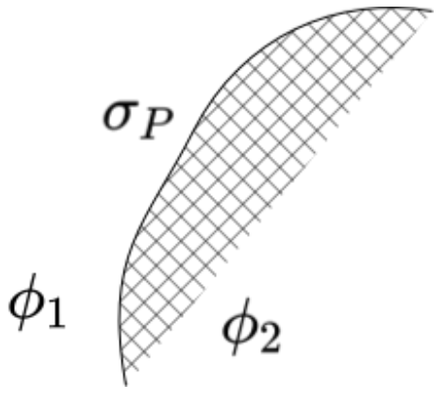
22 hops

How does biology produce energy?

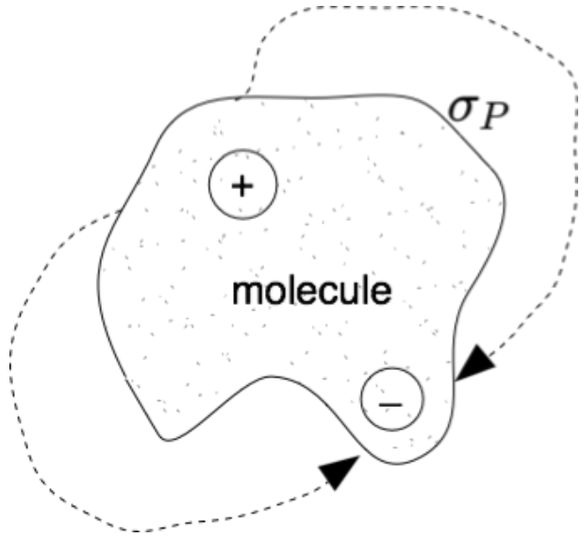
The mathematical framework seems to be OK, but we tend to put the “wrong” physics into it!

Is it thermodynamics only?

Can we view biological energy flow as a canonical ensemble problem?



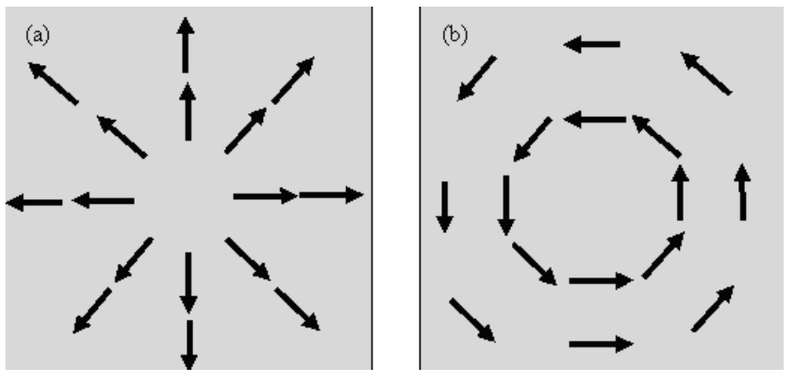
$$\frac{\partial \Delta\phi}{\partial n} = -\Delta E_n = 4\pi\sigma_P$$



Constitutive relation:

$$\mathbf{P} = \chi\mathbf{E}, \qquad \underbrace{\mathbf{D}}_{\text{transverse}} = \epsilon \underbrace{\mathbf{E}}_{\text{longitudinal}}$$

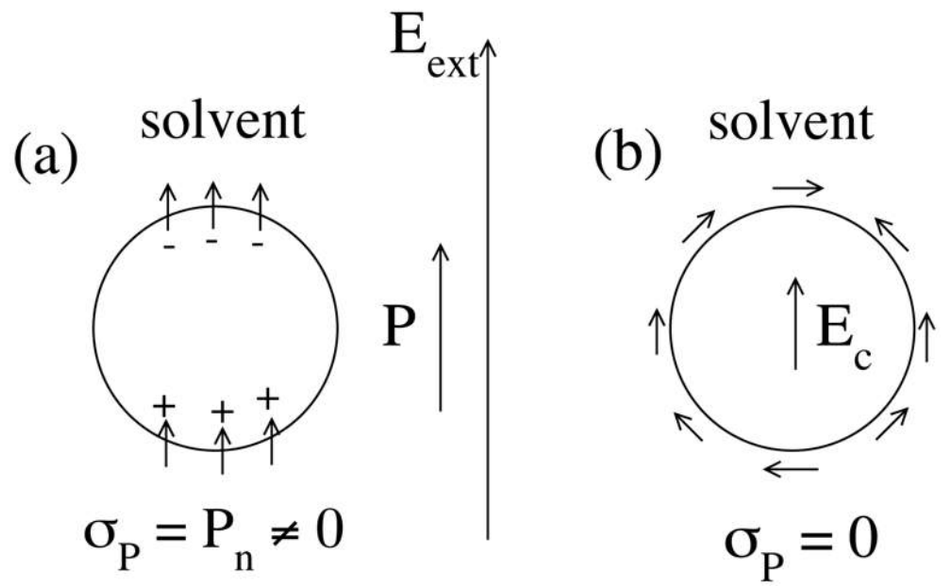
$$\nabla \cdot \mathbf{D} = 0$$



$$\nabla \times \mathbf{E} = 0$$

For non-uniform fields the constitutive relations connects fields of different symmetry

Cavity field



(a) Maxwell scenario:

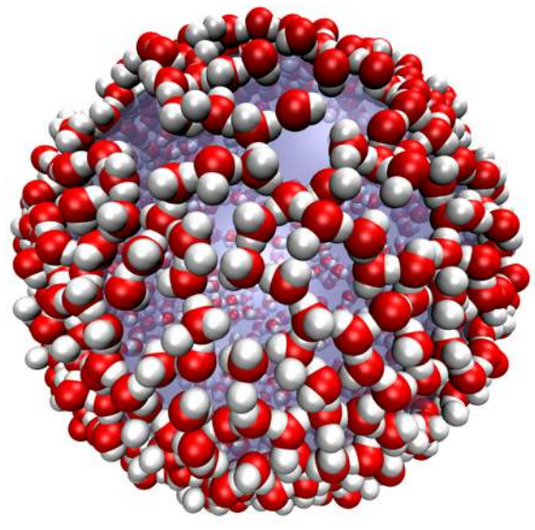
$$\frac{E_c}{E_{\rm ext}} = \frac{3}{2\epsilon + 1}$$

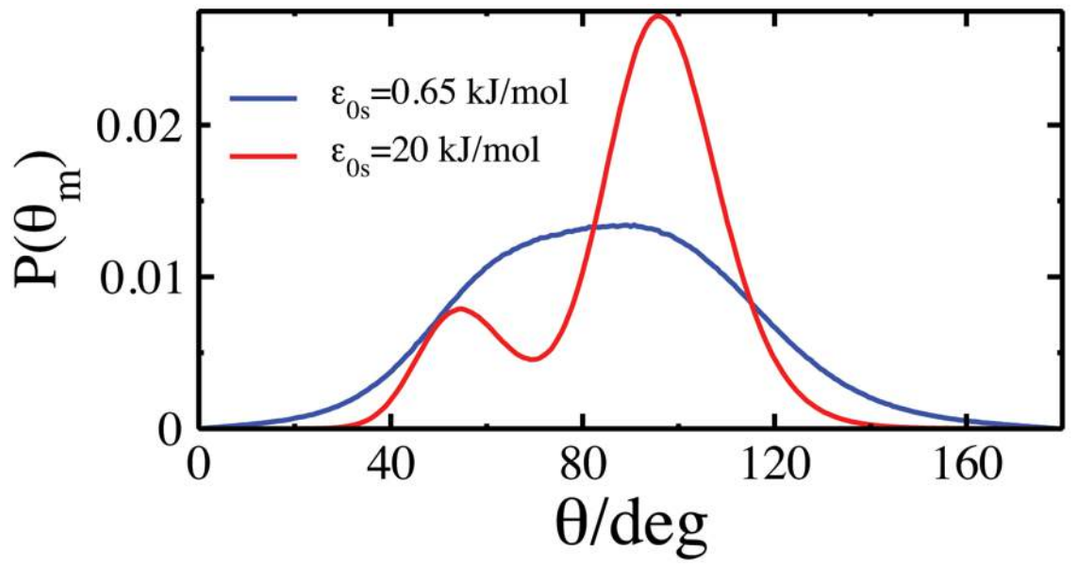
(b) Lorentz scenario:

$$\frac{E_c}{E_{\rm ext}} = \frac{\epsilon + 2}{3\epsilon}, \quad \sigma_P = 0$$

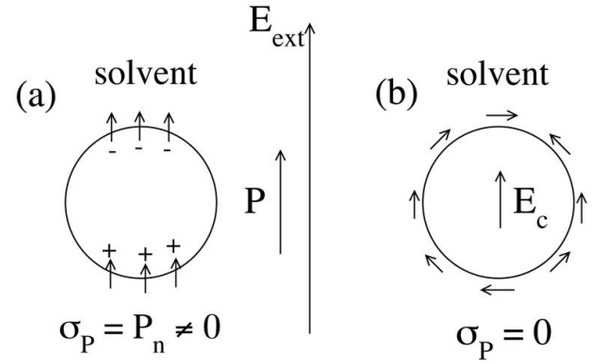
Kihara solute:

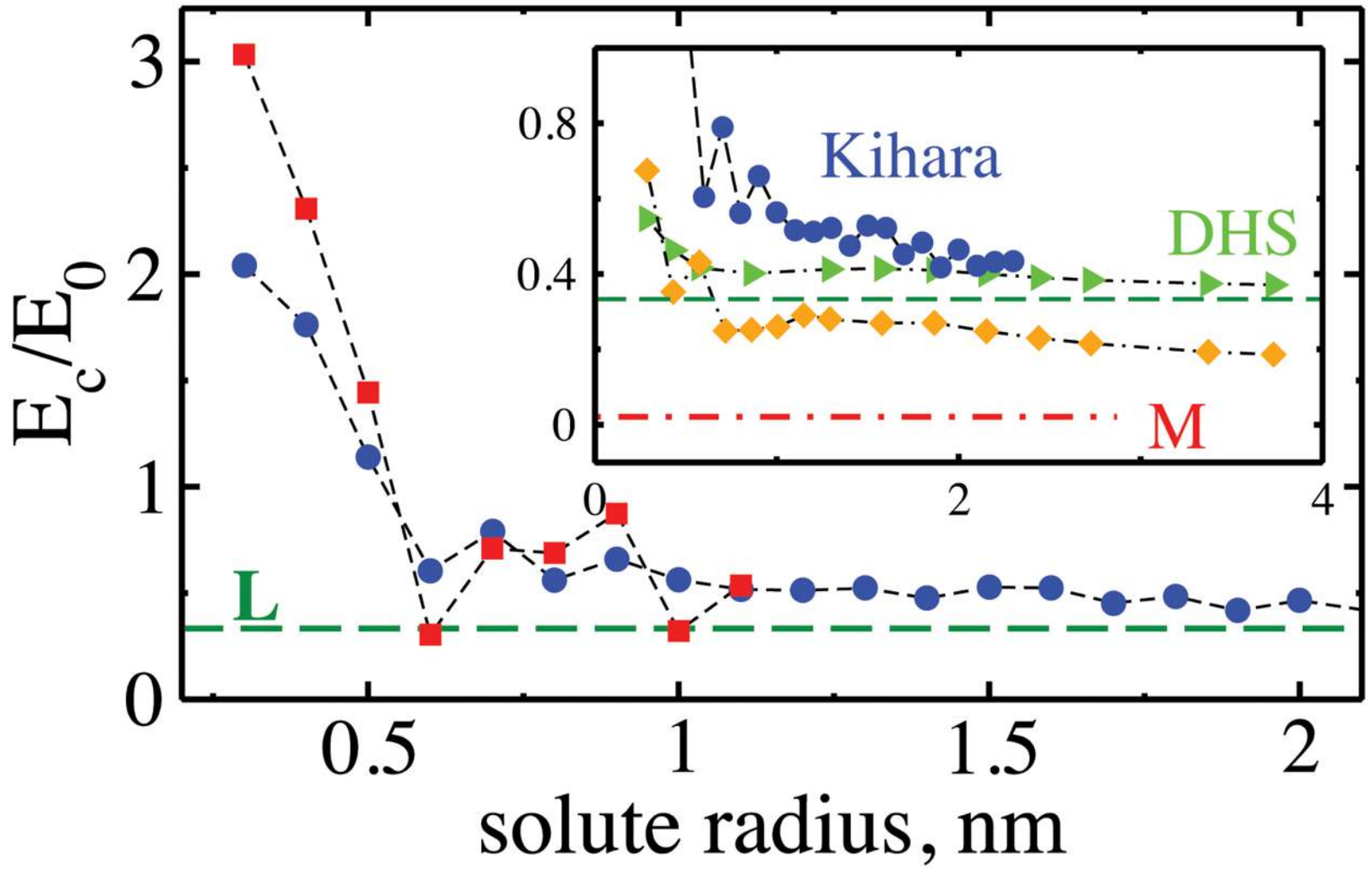
$$\phi_{0s}(r) = 4\epsilon_{0s}\left[\left(\frac{\sigma_{0s}}{r - R_{\rm HS}}\right)^{12} - \left(\frac{\sigma_{0s}}{r - R_{\rm HS}}\right)^{6}\right]$$





“Cavity” field inside a Kihara solute

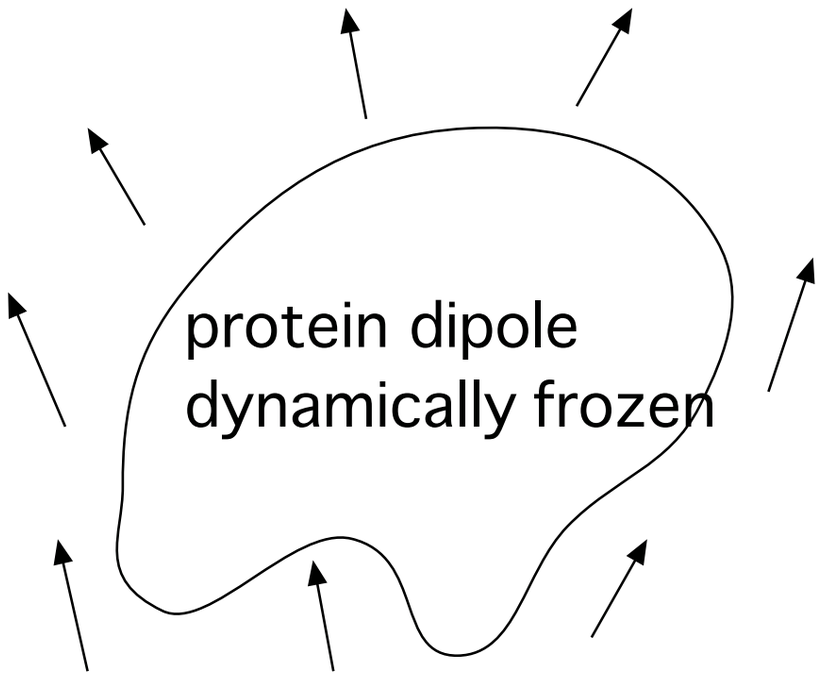




Lorentz scenario (no surface polarization) is more consistent with the data

Dipole of the interface

Total induced dipole of the hydration layer



$$\alpha = M_0^{\mathrm{int}} / M_0^{\mathrm{M}}$$

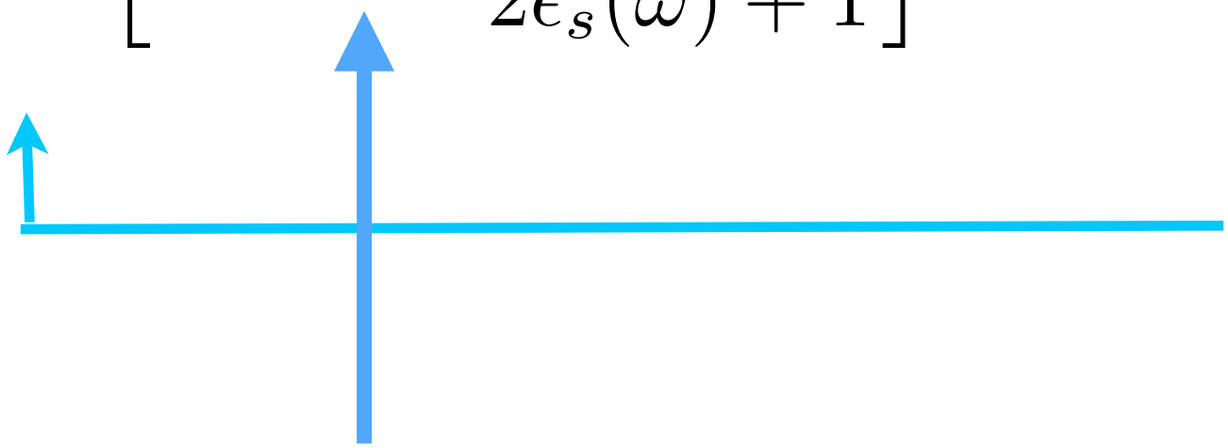
Parameter quantifying the deviation from the Maxwell scenario

Maxwell interface dipole projected on x-axis of the external field

High-frequency (THz) absorption

$$\alpha_{\mathrm{abs}}(\omega) = \frac{4\pi\omega}{c}\frac{\chi''(\omega)}{\sqrt{1+4\pi\chi'(\omega)}}$$

$$\frac{\Delta\chi(\omega)}{\chi_s(\omega)} = -\eta_0\left[1+\alpha(\omega)\frac{\epsilon_s(\omega)-1}{2\epsilon_s(\omega)+1}\right]$$

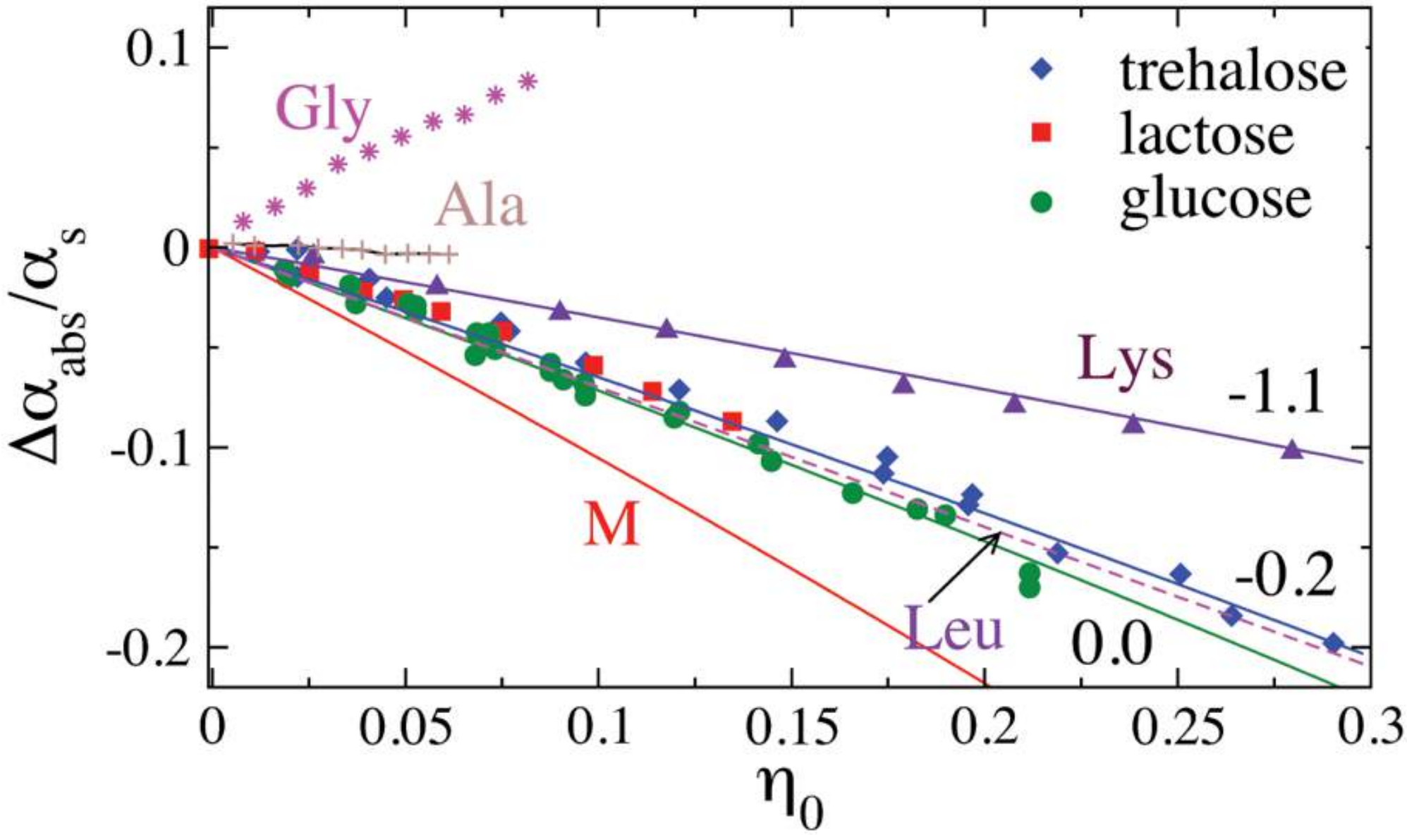


Volume fraction of solutes in solution

Deviation from the Maxwell prediction

THz absorption of sugars and amino acids (aq)

Rotations of a large solute are dynamically frozen on the THz time-scale, solutes are approximated by dielectric voids

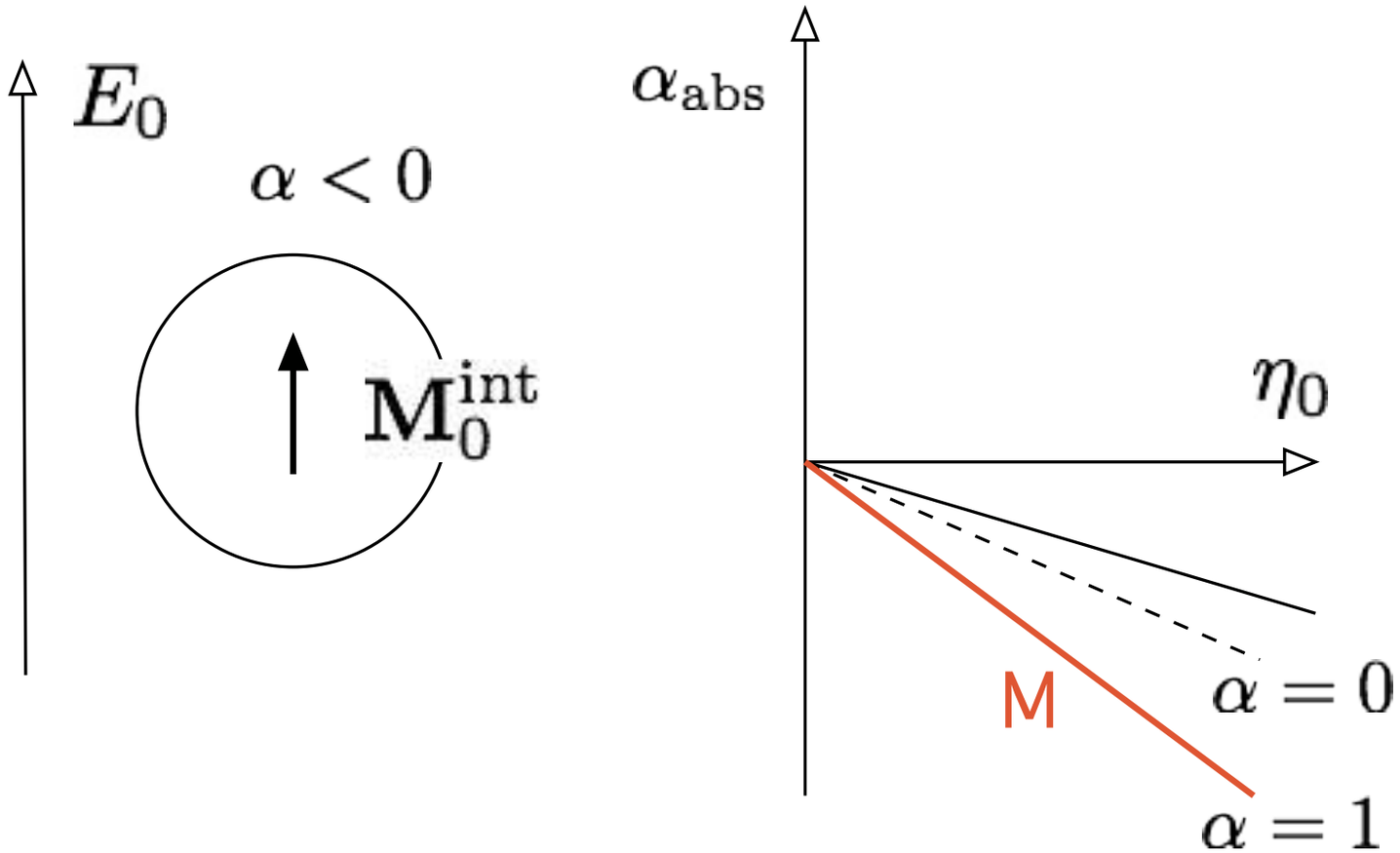


Heyden et al, JACS 130 (2008) 5773

Niehues et al. Farad. Disc. Chem. Soc. 150 (2011) 193

What does THz absorption tell us?

Maxwell: alpha = 1
Sugars: alpha = -0.2 - 0, **no interface dipole!**
Amino acids: alpha = -5 - -0.1, **interface dipole opposite to the field!**



Weakly **hydrophilic** solutes (glucose) leave no footprint, **hydrophilic** solute enhance the polarity relative to water.

Lysozyme: cavity field

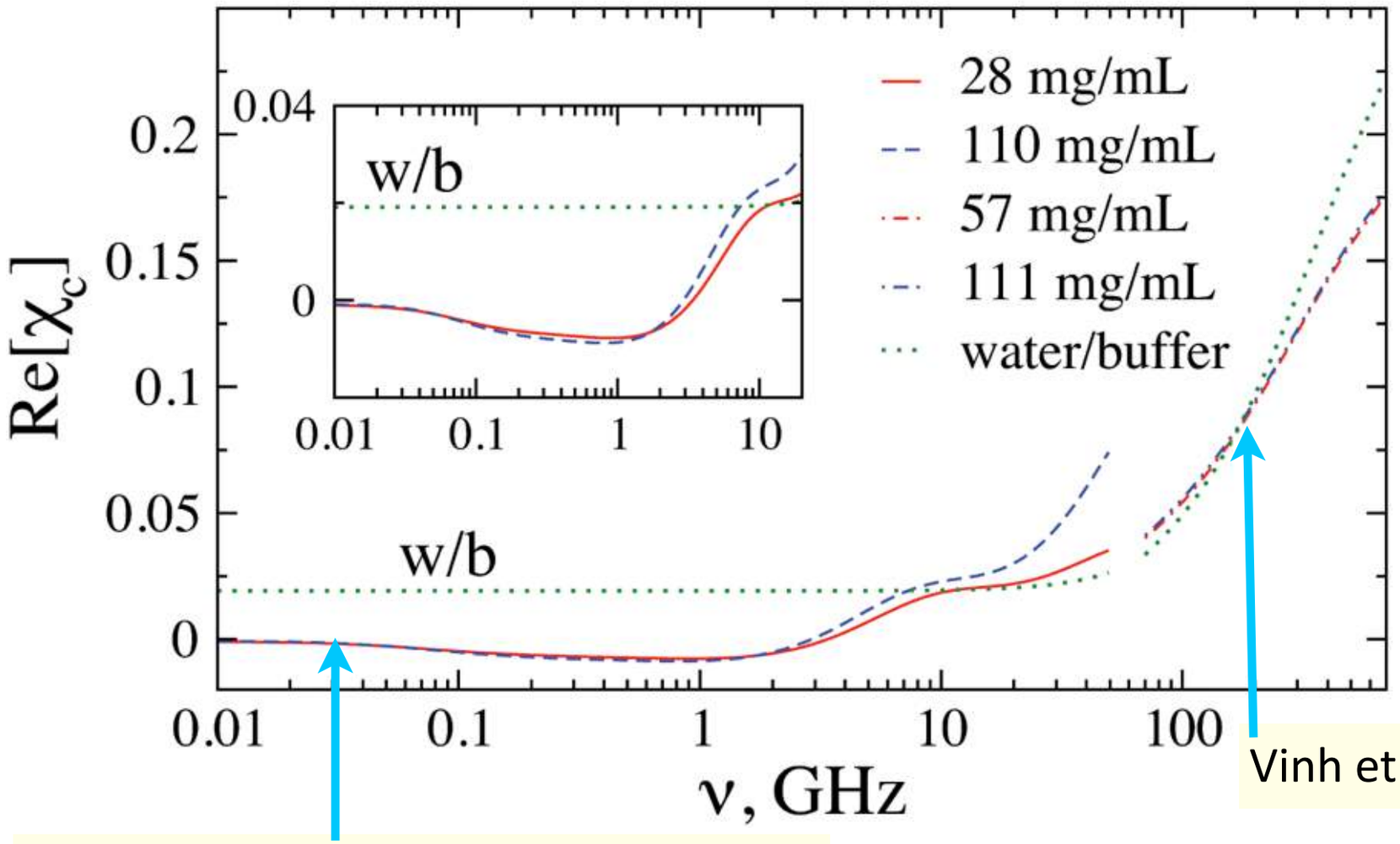
Cavity field response

$$\frac{\epsilon_s(\omega)}{\epsilon_{\rm mix}(\omega)} = 1 - 3\eta_0 + 3\eta_0\epsilon_s(\omega)\chi_c(\omega)\,(1 - y_0(\omega))$$

Experimental input

Volume fraction

Response of the lysozyme dipole, taken from MD



$$\chi_c^{\rm M} = \frac{3}{2\epsilon_s + 1}$$

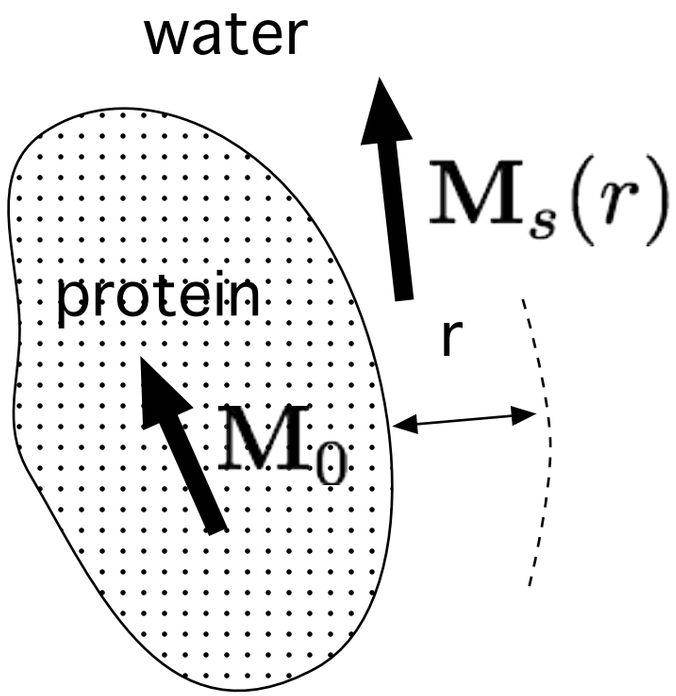
Maxwell scenario

Vinh et al, JACS 133 (2011) 8942

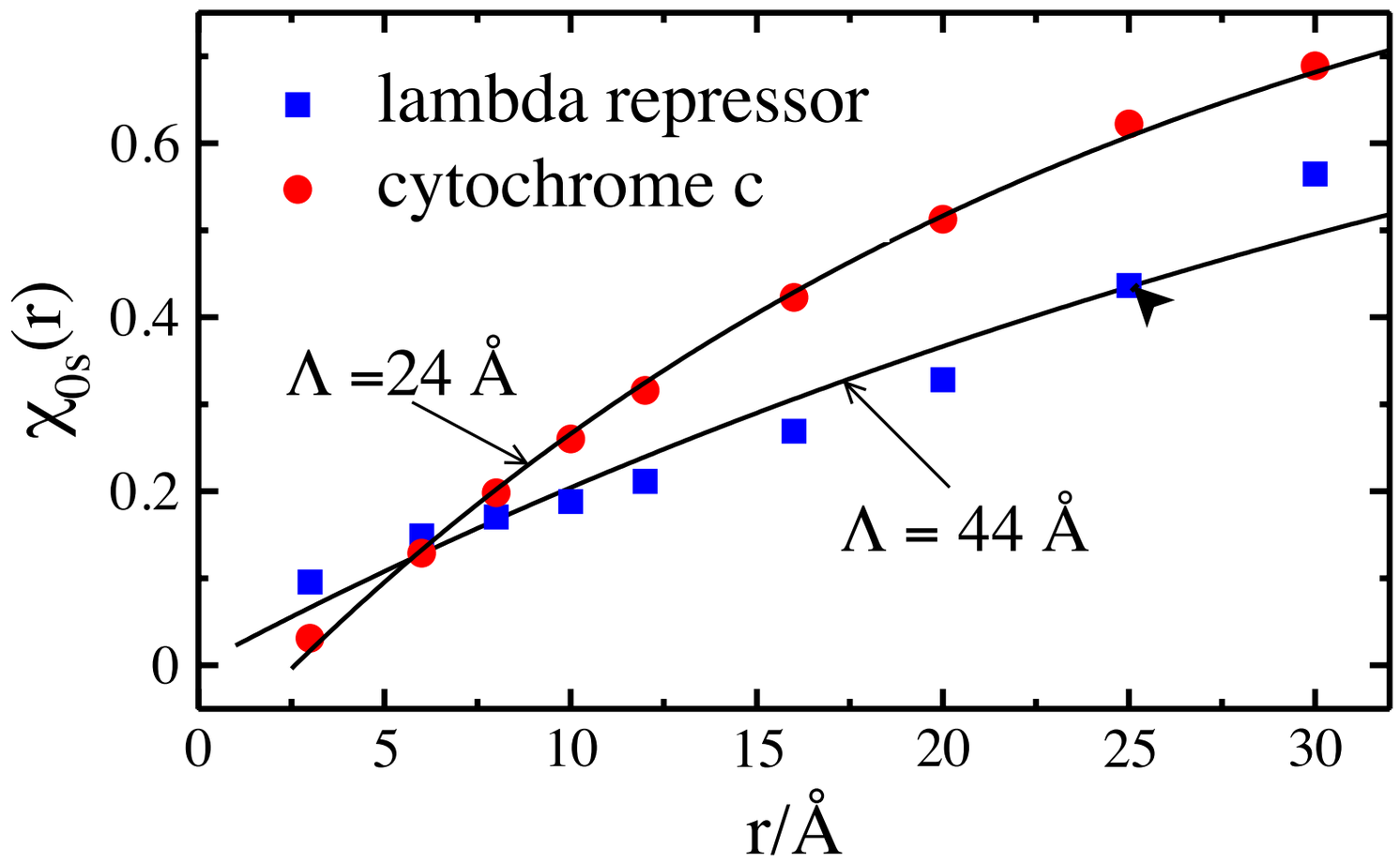
Cametti et al., JPCB 115 (2011) 7144

DVM, JPCM 24 (2012) 325105

Range of protein-water correlations

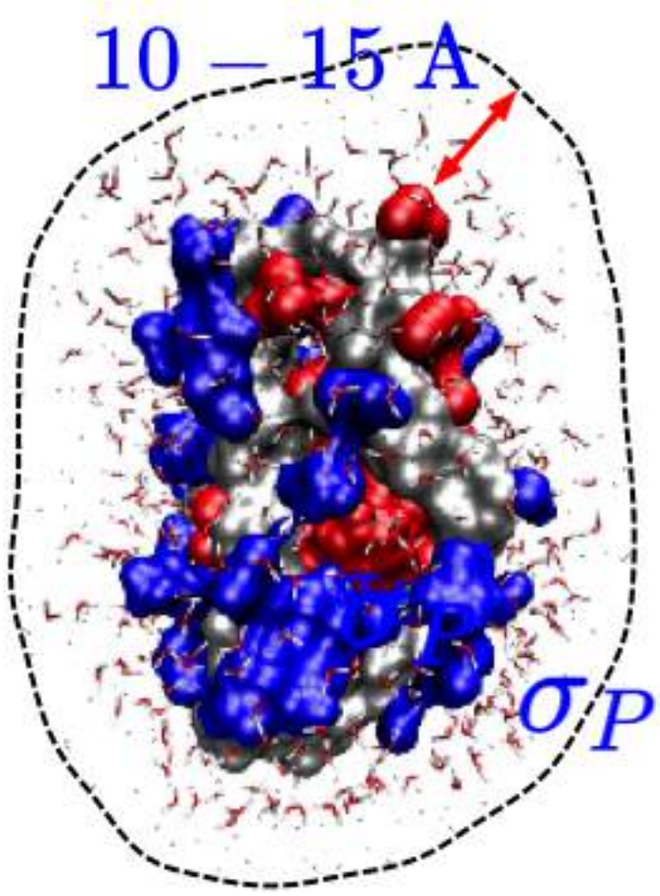


$$\chi_{0s}(r) \propto \langle \delta\mathbf{M}_0 \cdot \delta\mathbf{M}_s(r) \rangle$$



$$\chi_{0s}(r) \propto (1 - \exp[-(r - r_0)/\Lambda])$$

Protein-Water Interface

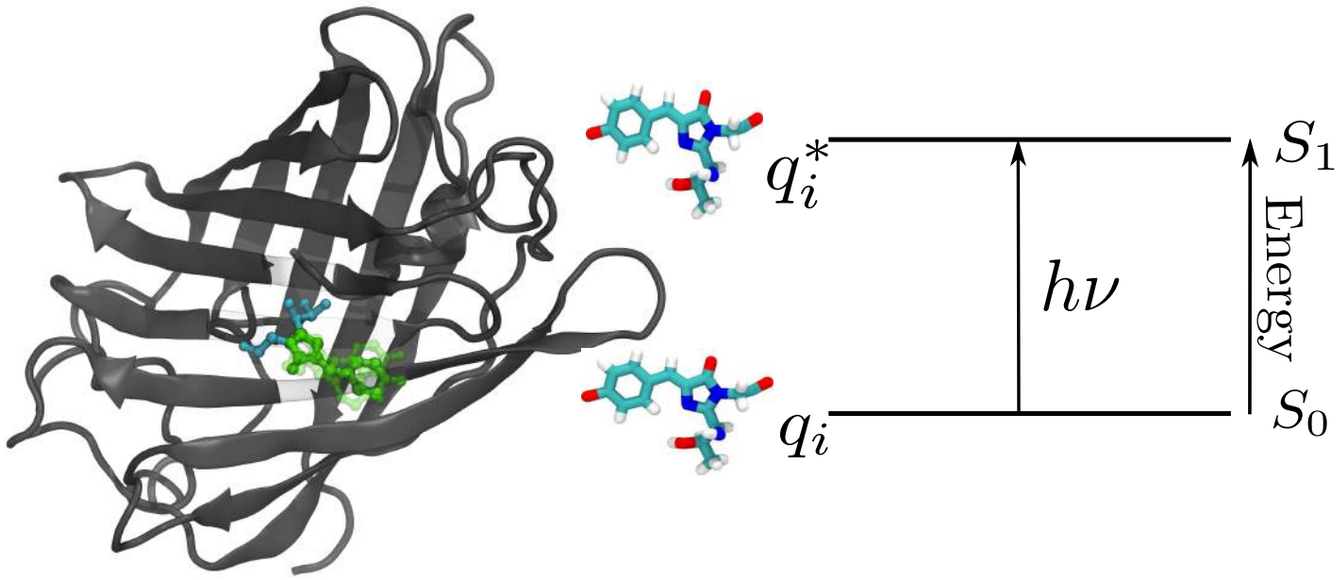


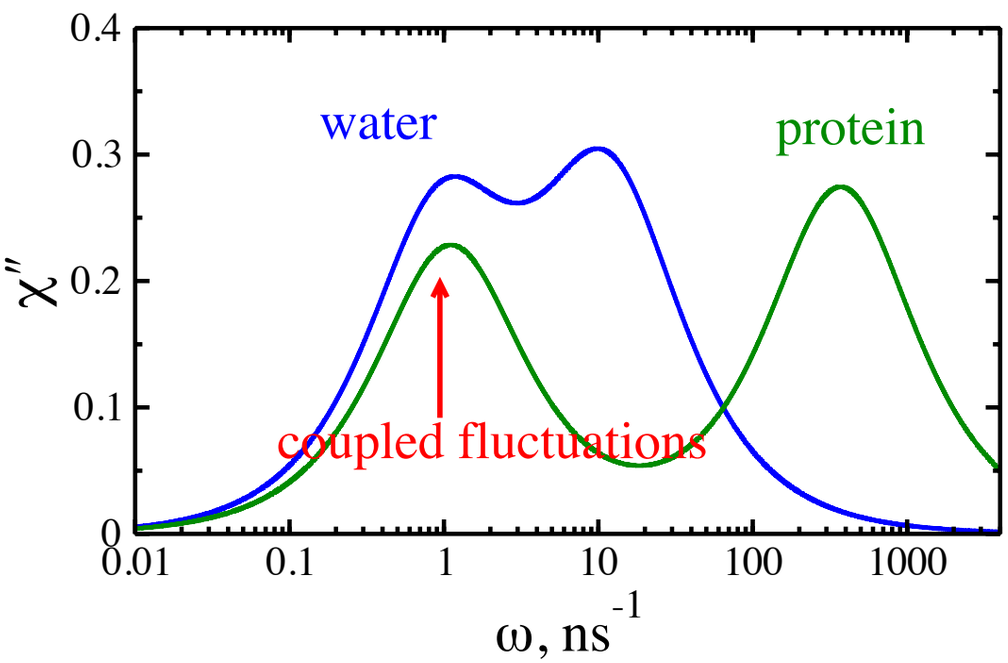
Water structure is locally broken: surface polarization is determined by the residue

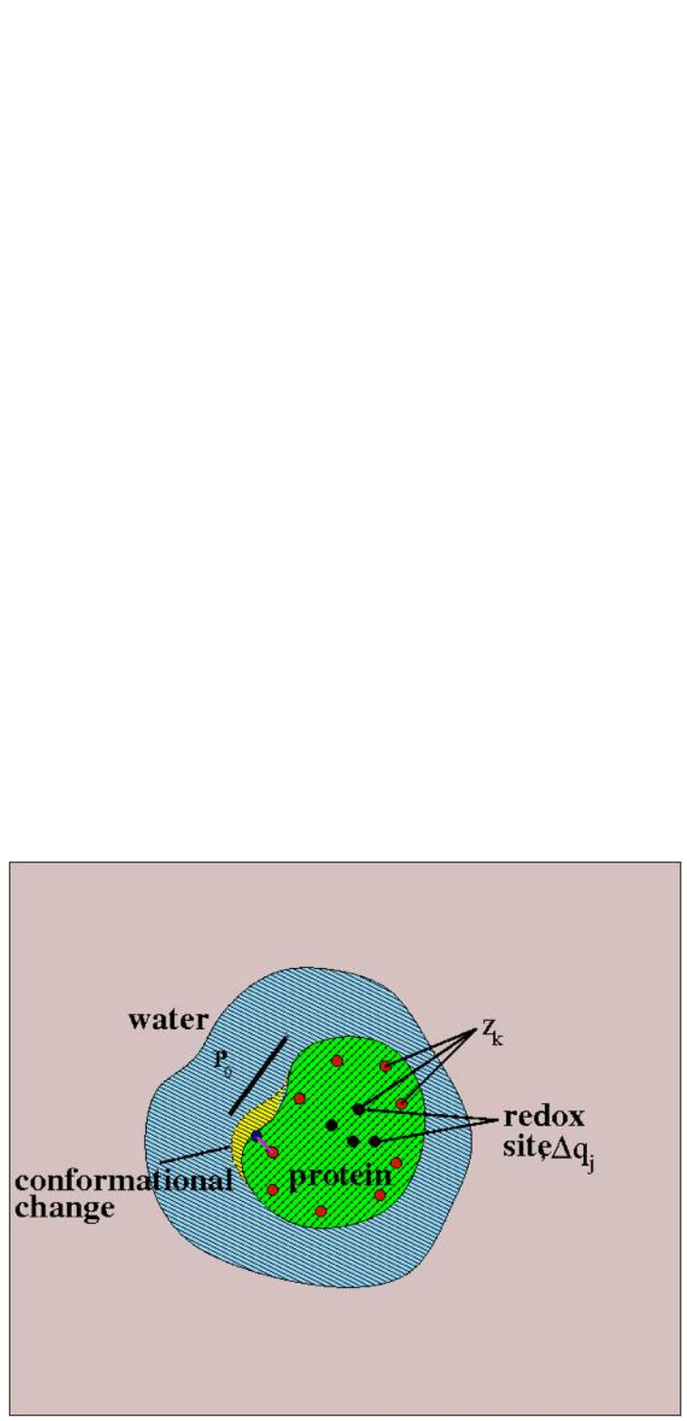
Frustration of surface polarized domains: long propagation into the bulk

Heterogeneous dynamics of the interfacial polarization

Coupled protein-water fluctuations (GFP)

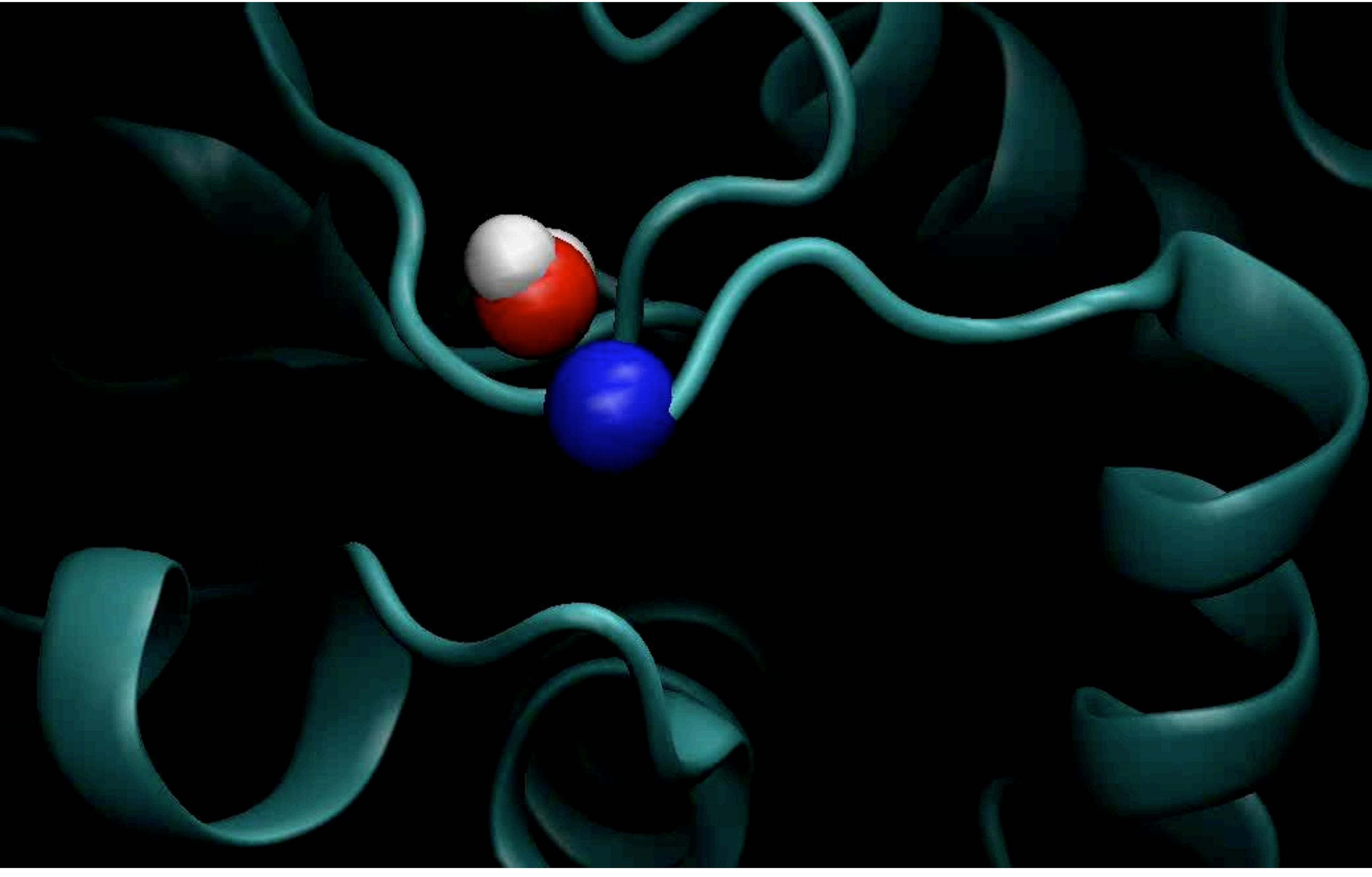






Low-frequency motions of the protein move both the ionized surface residues and the water shells polarized by them.

JPCB 116 (2012) 10294

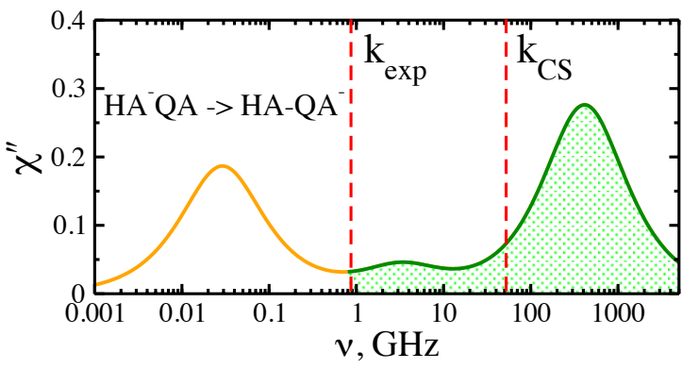


Proteins:

Large-scale electrostatic fluctuations (lots of surface charges)

Slow modes

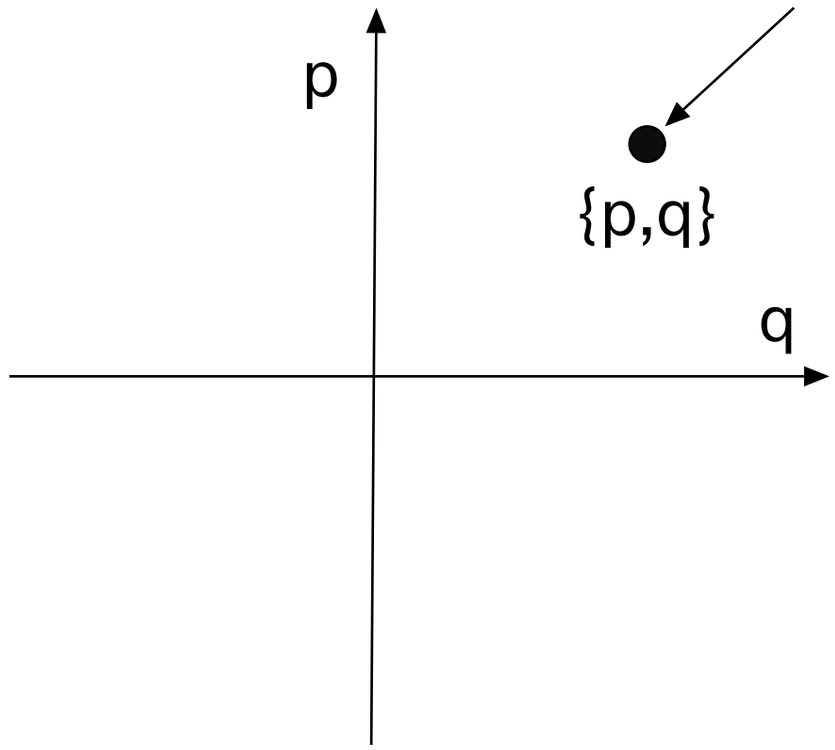
What if the rate of the reactions is faster than the fluctuations?



?

Ergodicity

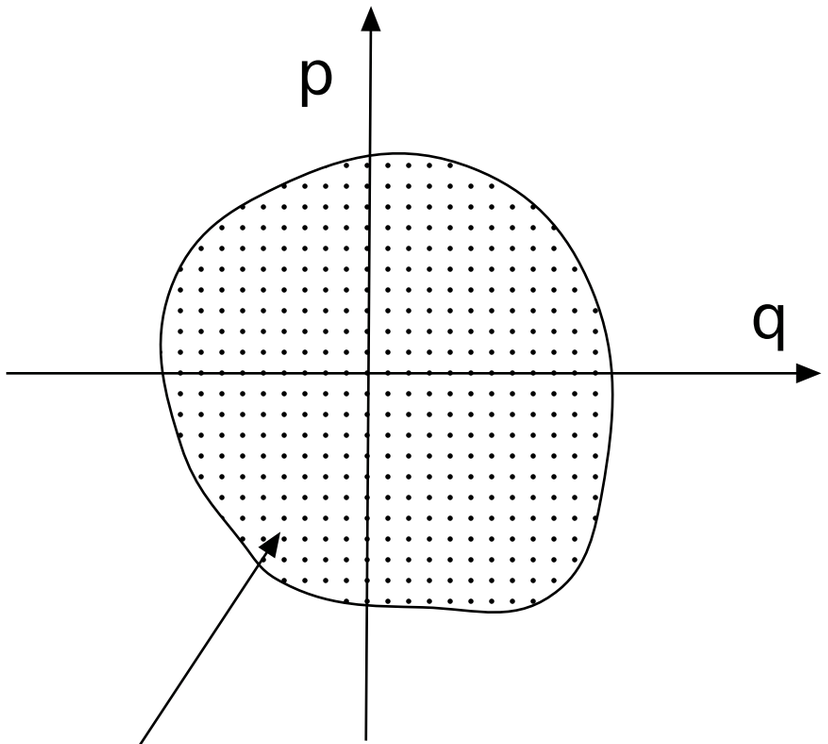
$$P \propto e^{-\beta H(p,q)}, \quad \beta = 1/(k_{\mathrm{B}}T)$$

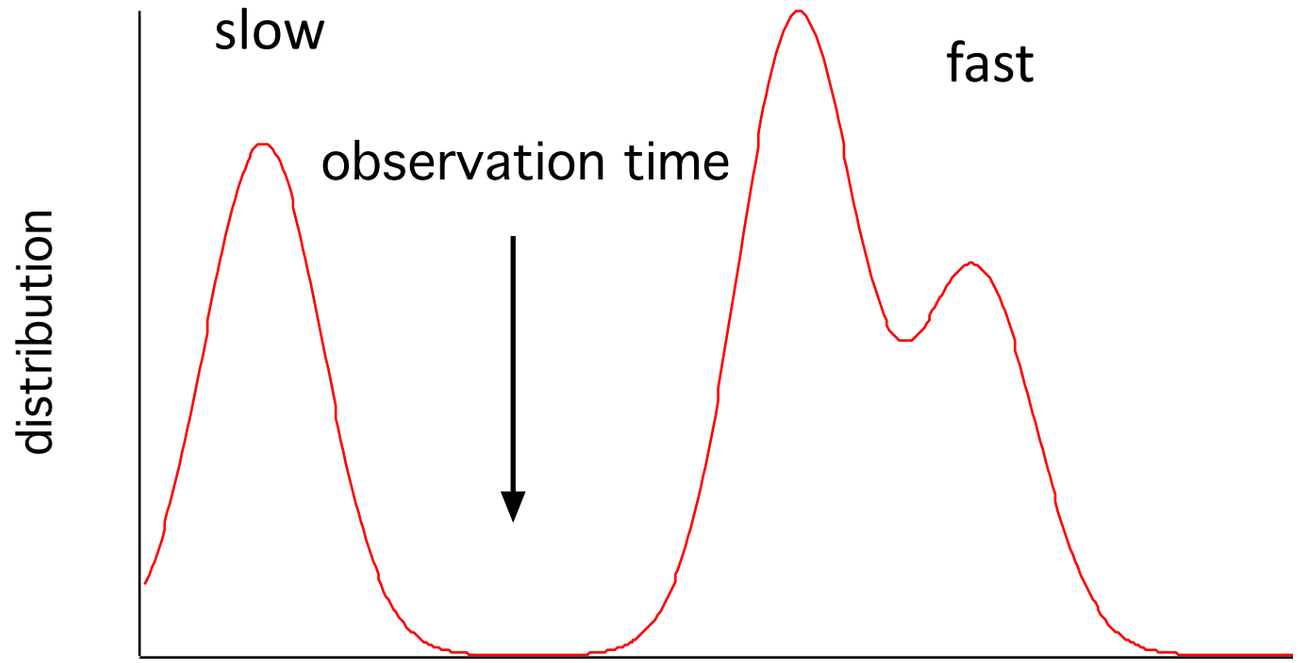


Mathematical abstraction: $\tau_{\mathrm{obs}} \to \infty$

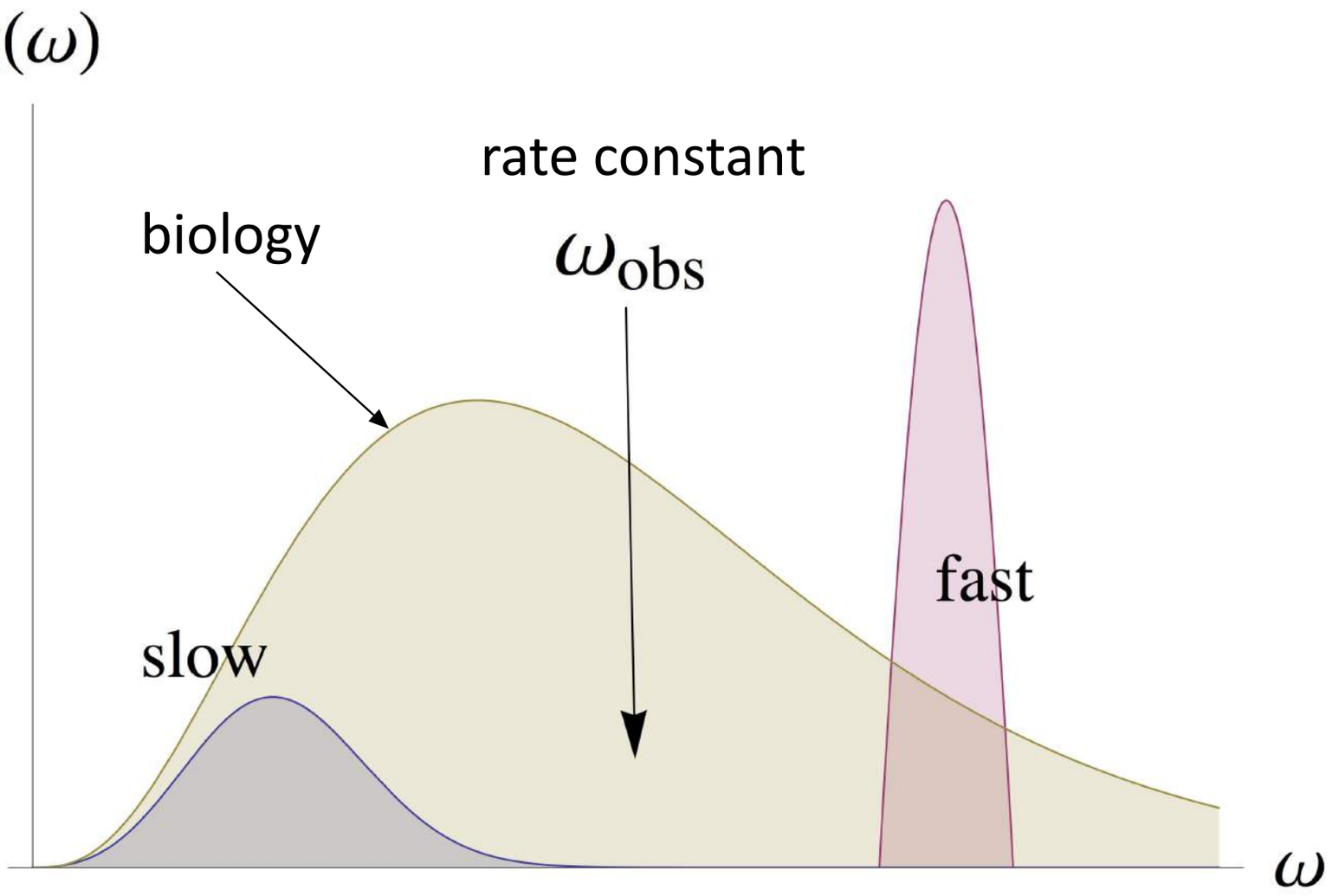
Canonical ensemble: “All the ‘fast’ things have happened and all the ‘slow’ things have not”

- R. Feynman

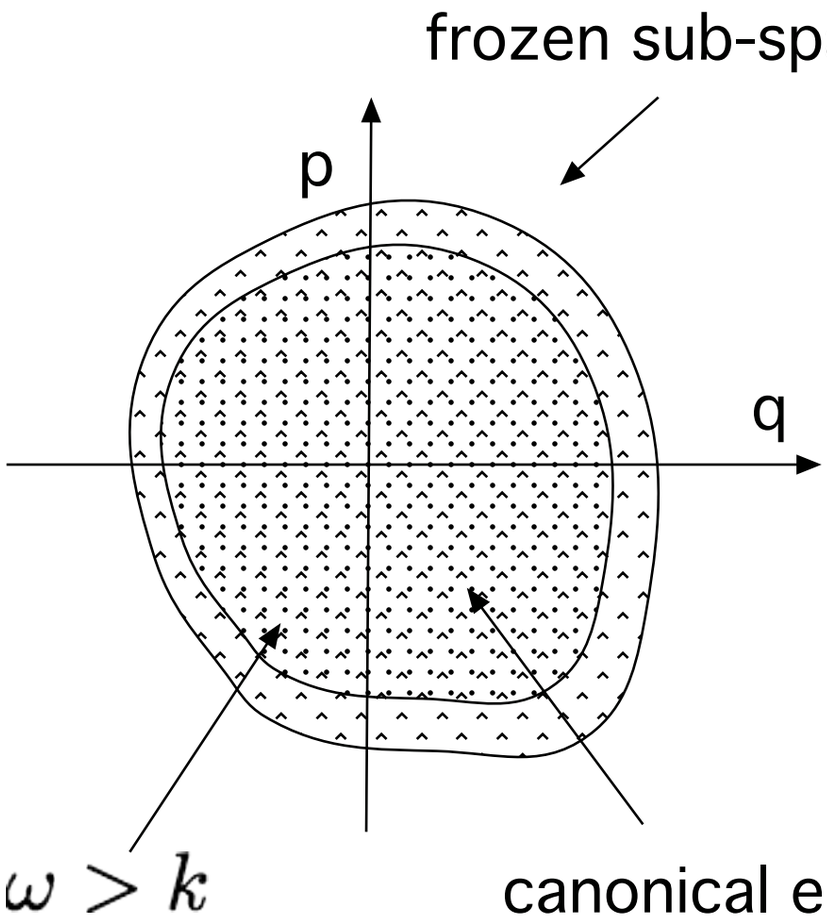




Biology: continuous ergodicity breaking



Dynamically **restricted** ensemble



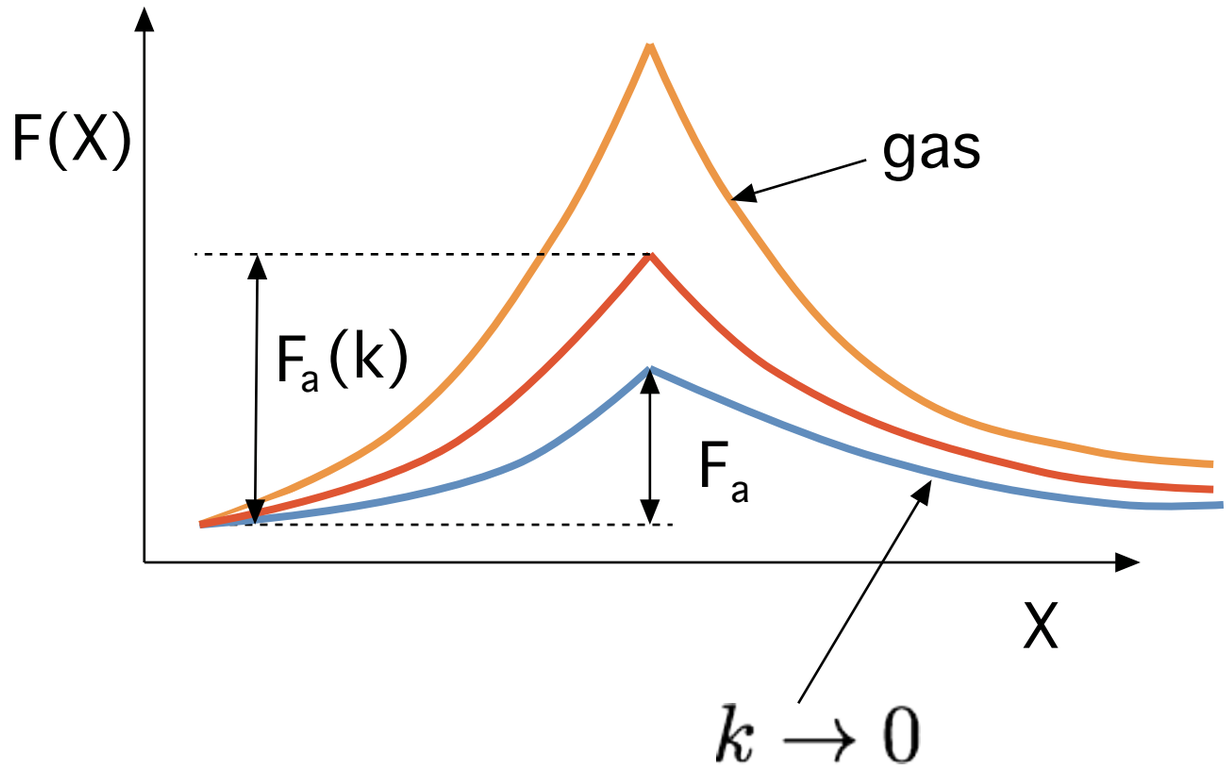
Canonical (Gibbs) average over motions

faster than the rate

$$k < \omega$$

Nonergodic kinetics

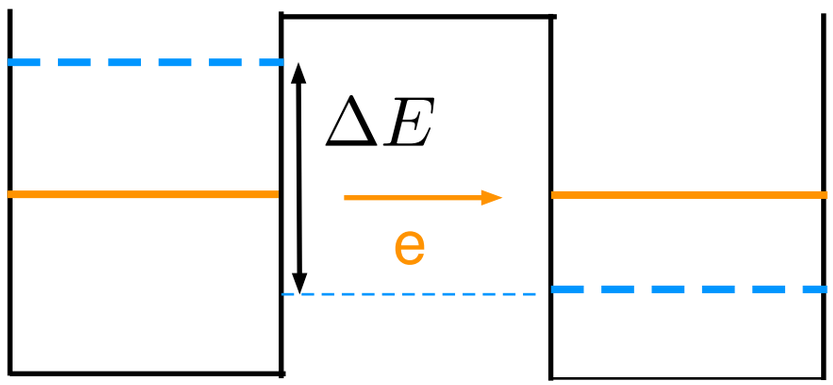
Activation barrier depends on the rate



$$\underbrace{\mathbf{k} \propto \exp[-\beta F_a(\mathbf{k})]}_{\text{self-consistent solution for } \mathbf{k}}$$

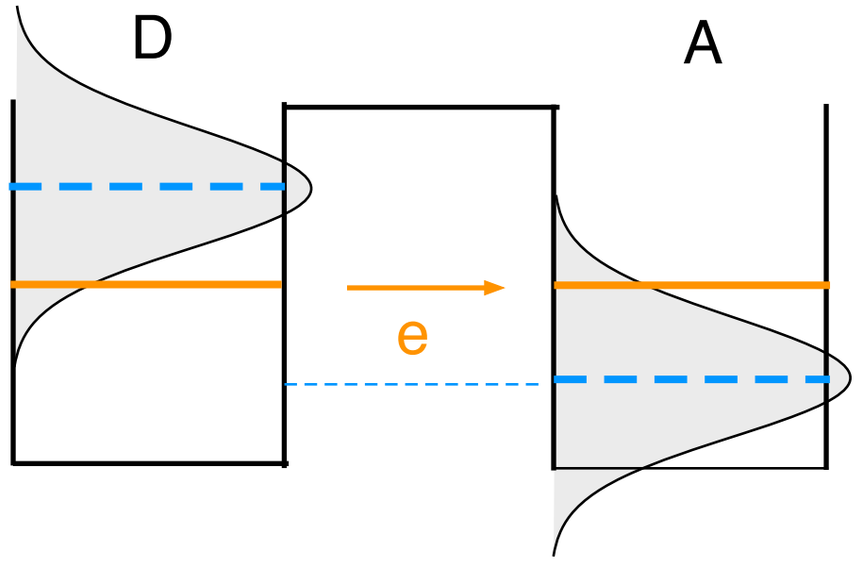
Electron tunneling (hopping conductivity)

gas



$X = \Delta E$

condensed matter



$X = \Delta E$

$$F(X) = -k_{\mathrm{B}} T \ln P(X) = \frac{(X - X_0)^2}{4\lambda}$$

Reorganization energy (extent of medium deformation)

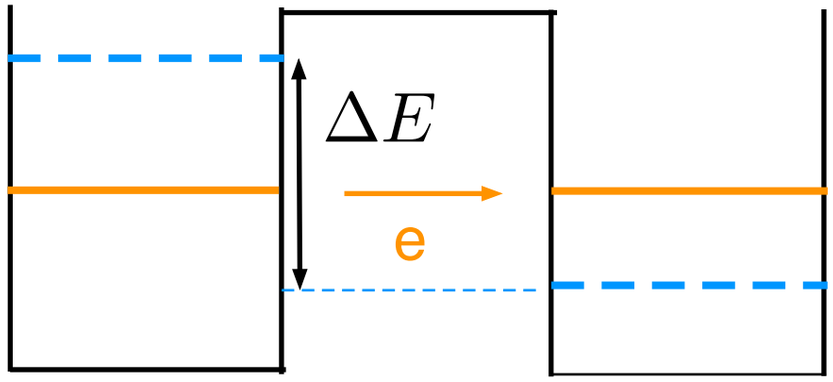
Dynamics vs thermodynamics

Stokes-shift time correlation function:

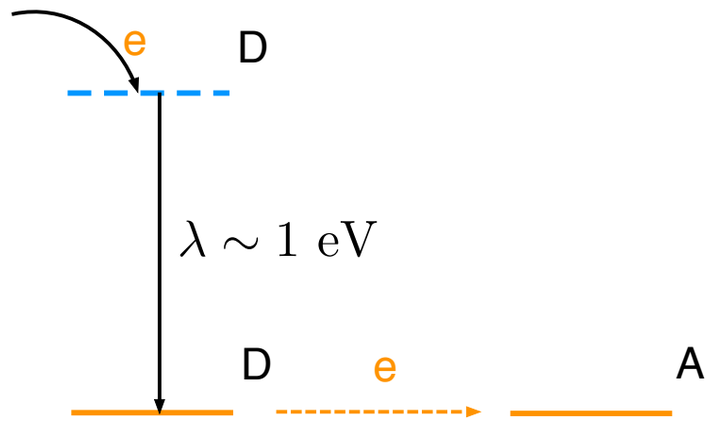
$$C_i(t) = \langle \delta X(t) \delta X(0) \rangle_i$$

$$\chi_i''(\omega) = (\beta\omega/2) C_i(\omega)$$

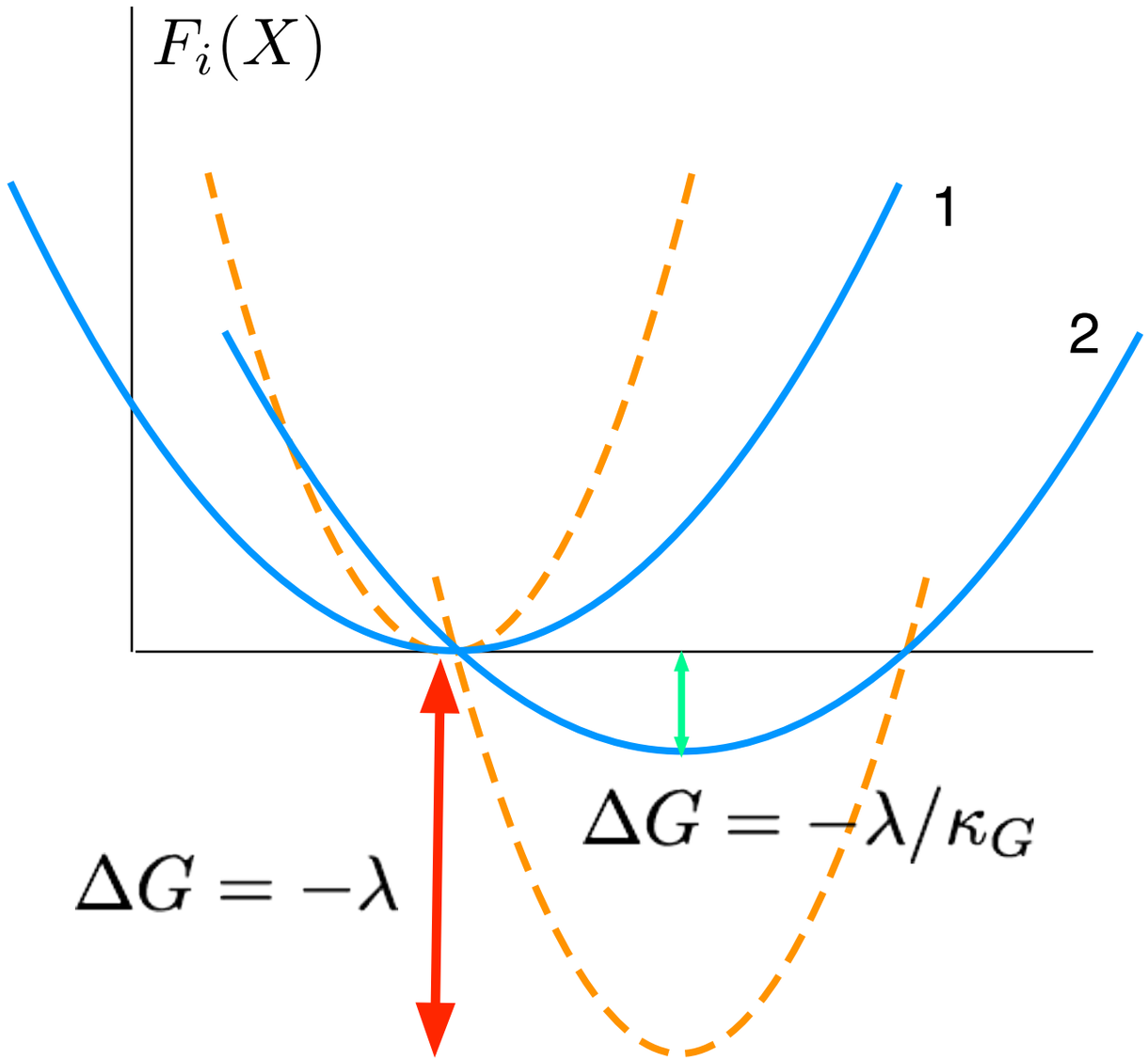
$$\boxed{\lambda_s(k) \propto \int_{k=\omega_{\rm obs}}^{\infty} \chi''(\omega)(d\omega/\omega)}$$



$$X = \Delta E$$

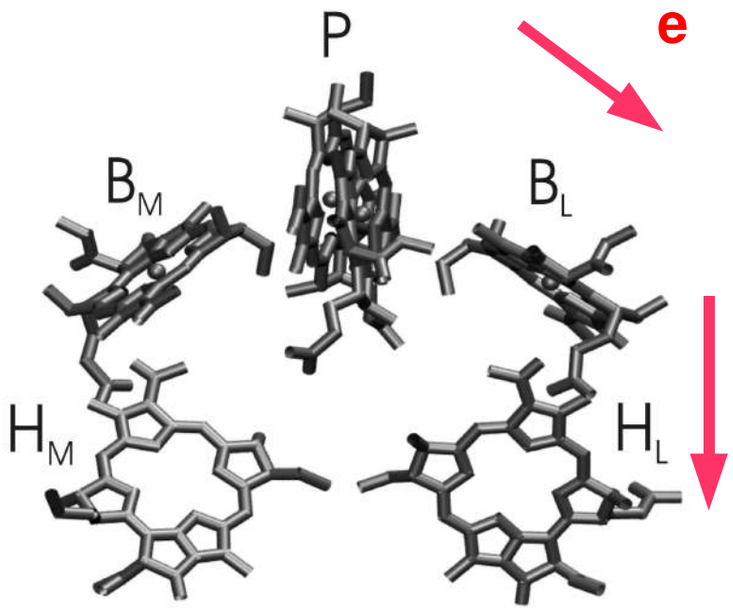


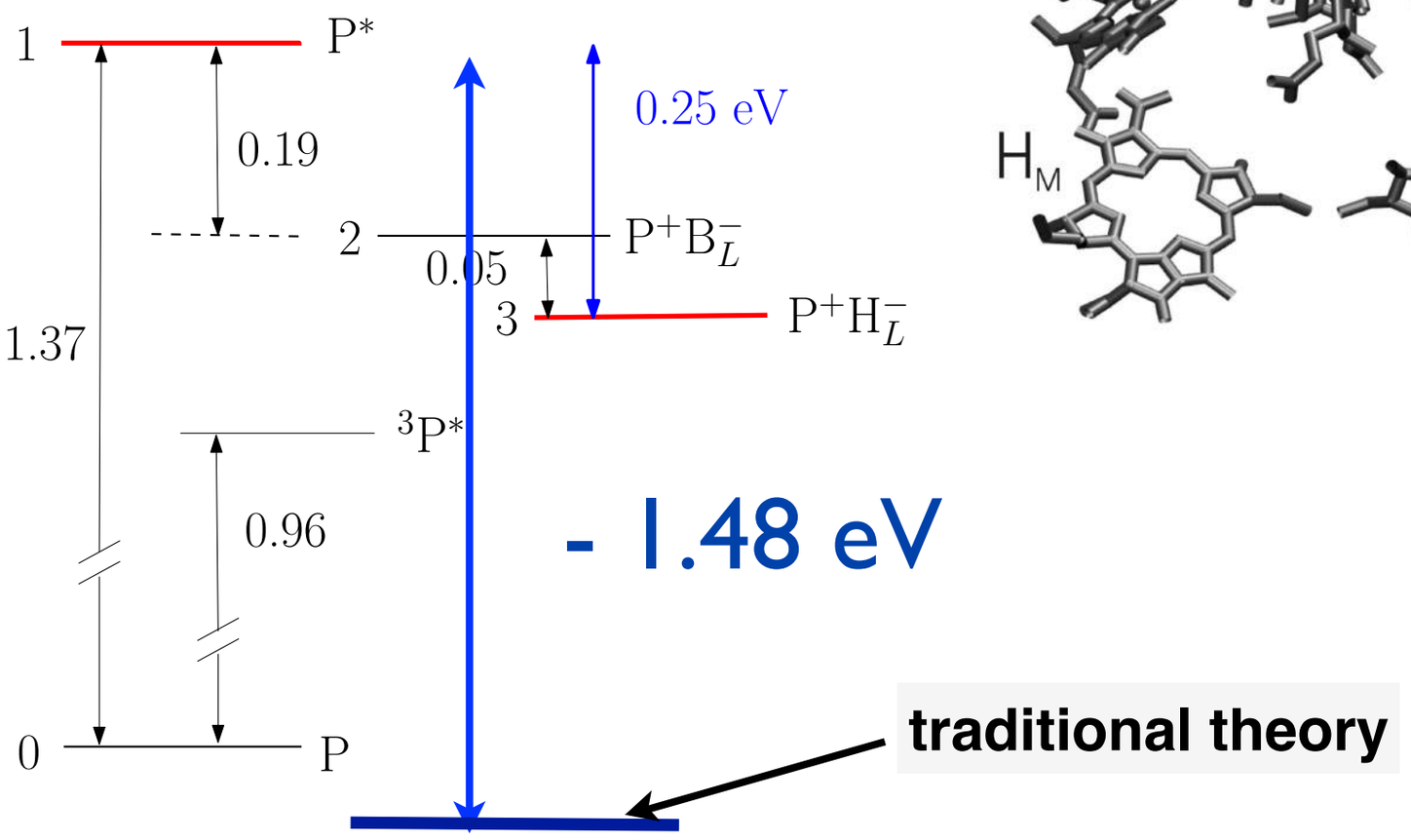
Reaction free energy & activation barrier



$\kappa_G \sim 3 - 20$ from MD of redox proteins

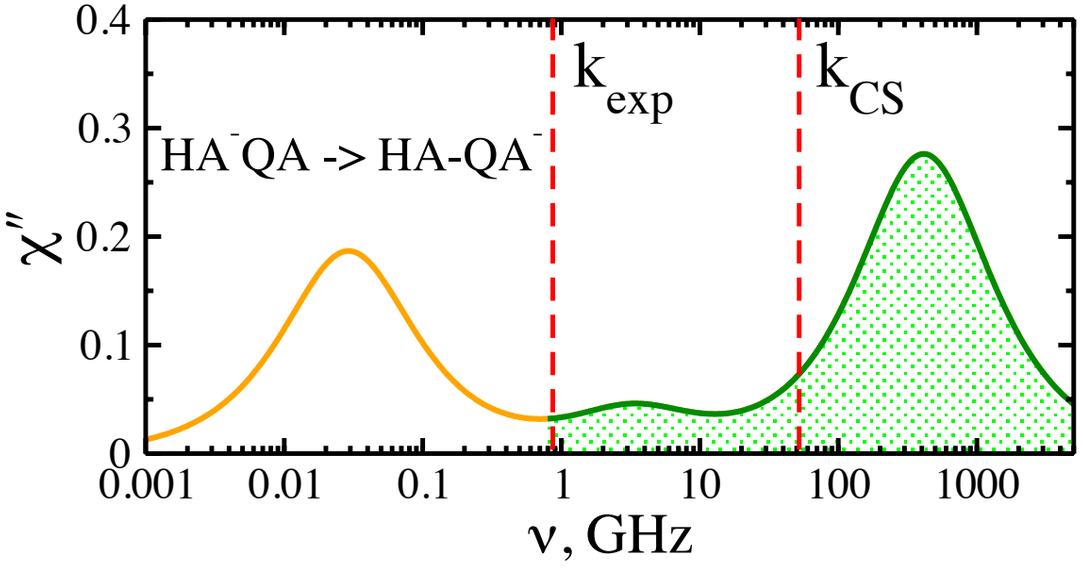
Bacterial photosynthesis: Energetics

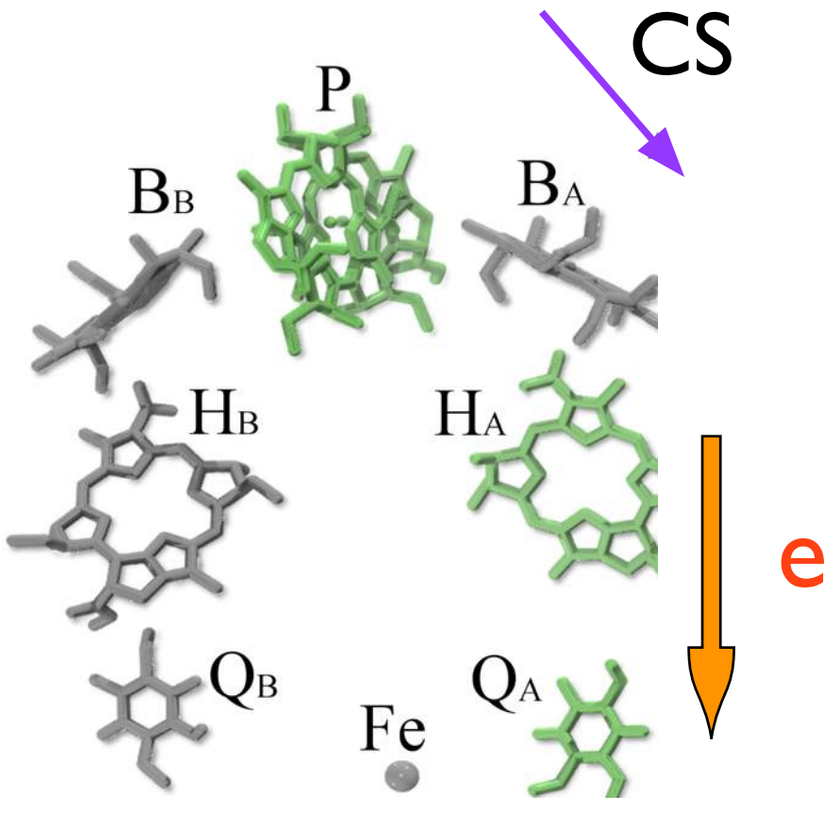


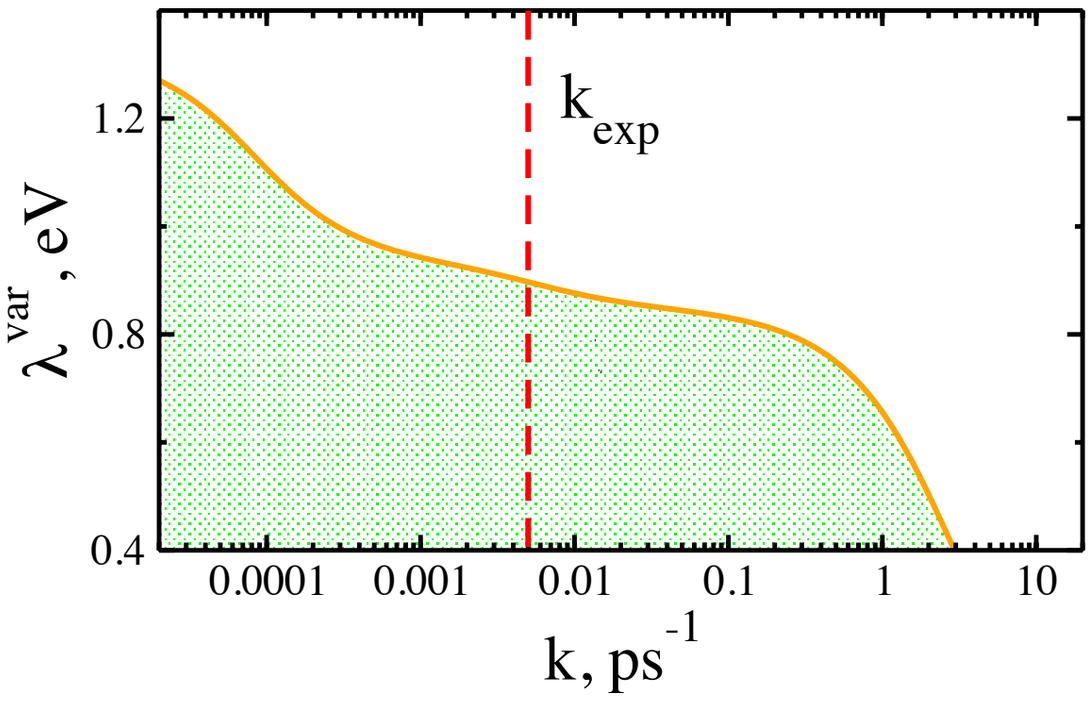


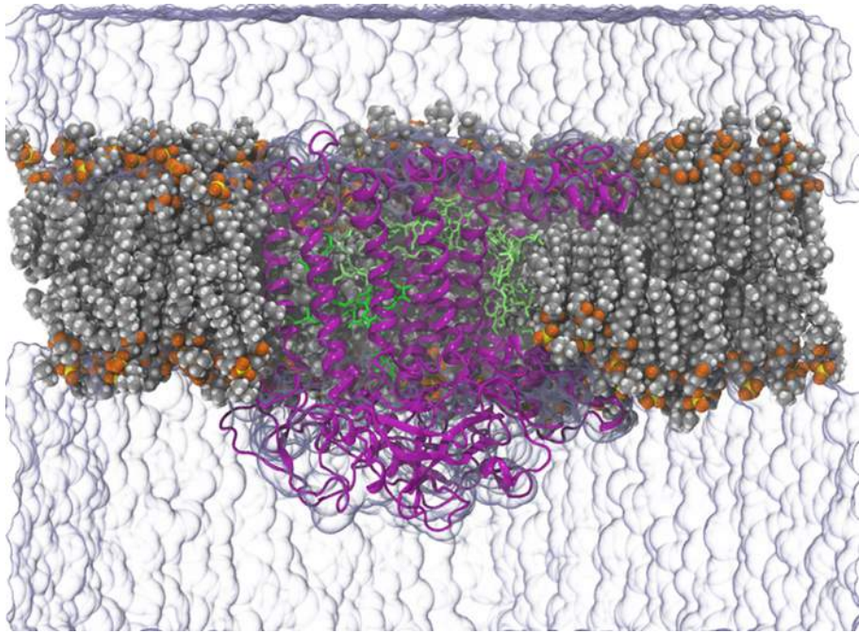
$$\lambda_{12} \simeq 0.77 \text{ eV}, \ \lambda_{23} = 0.71 \text{ eV}$$
$$-\Delta G_{13} = \lambda_{12} + \lambda_{23} = 1.48 \text{ eV}$$

HA to QA


0.4
0.3
0.2
0.1
0
χ''
HA-QA -> HA-QA-
k exp
k CS
0.001
0.01
0.1
1
10
100
1000
ν, GHz

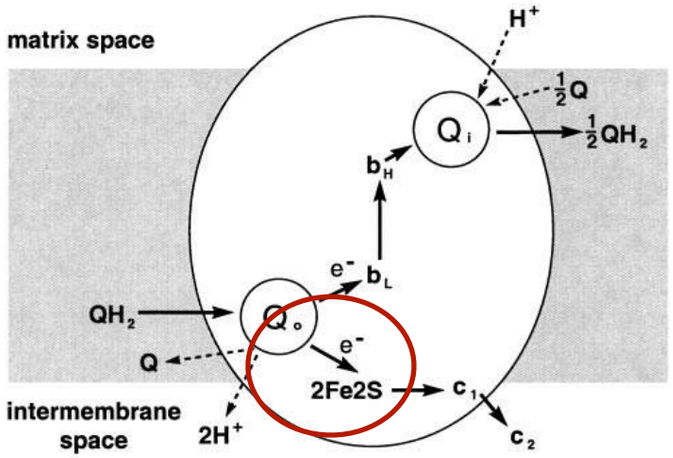

CS
P
BB
BA
HB
HA
e
QB
Fe
QA


1.2
0.8
0.4
λ var, eV
k exp
0.0001
0.001
0.01
0.1
1
10
k, ps-1

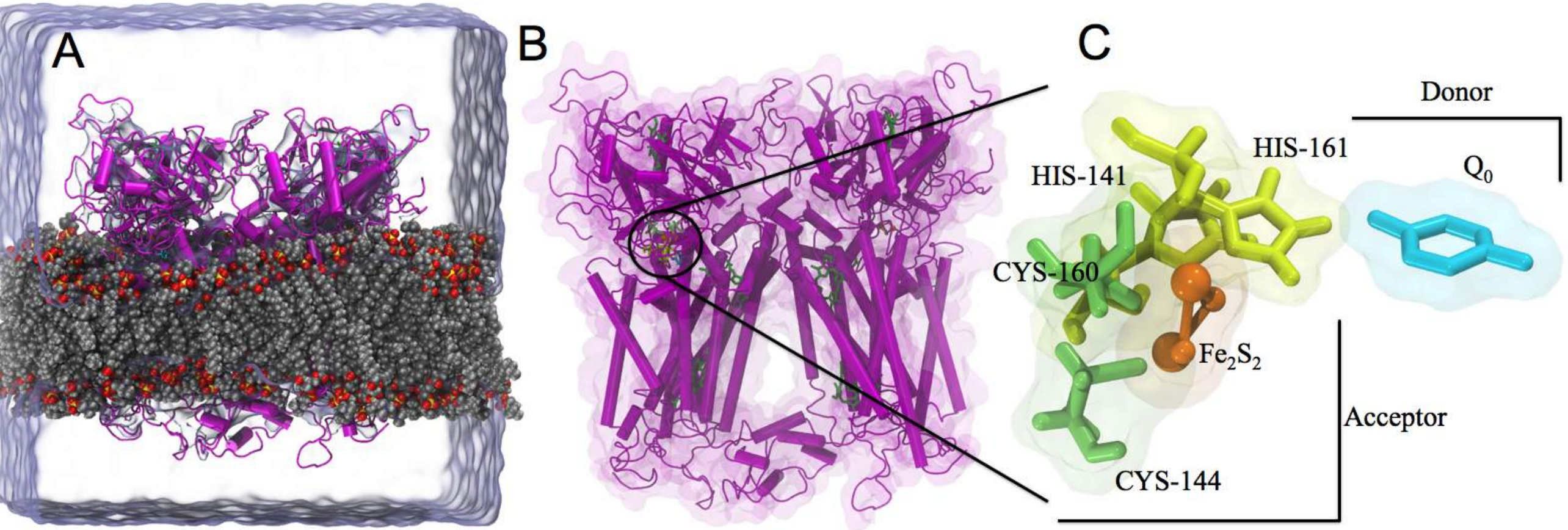


bc1 complex of respiratory chains

Reaction rate ~ 1 ms



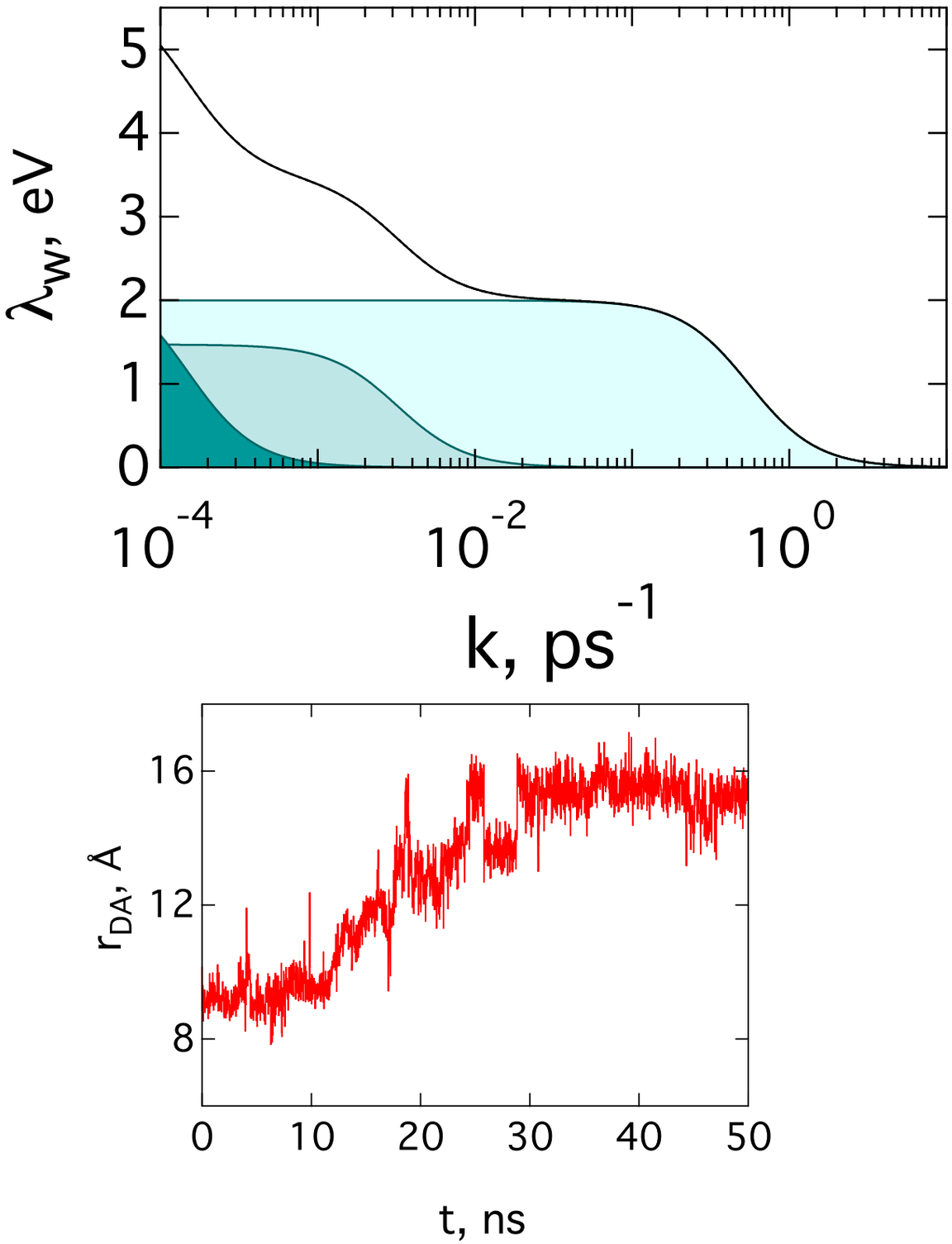
Izrailev et al., Biophys. J. '99

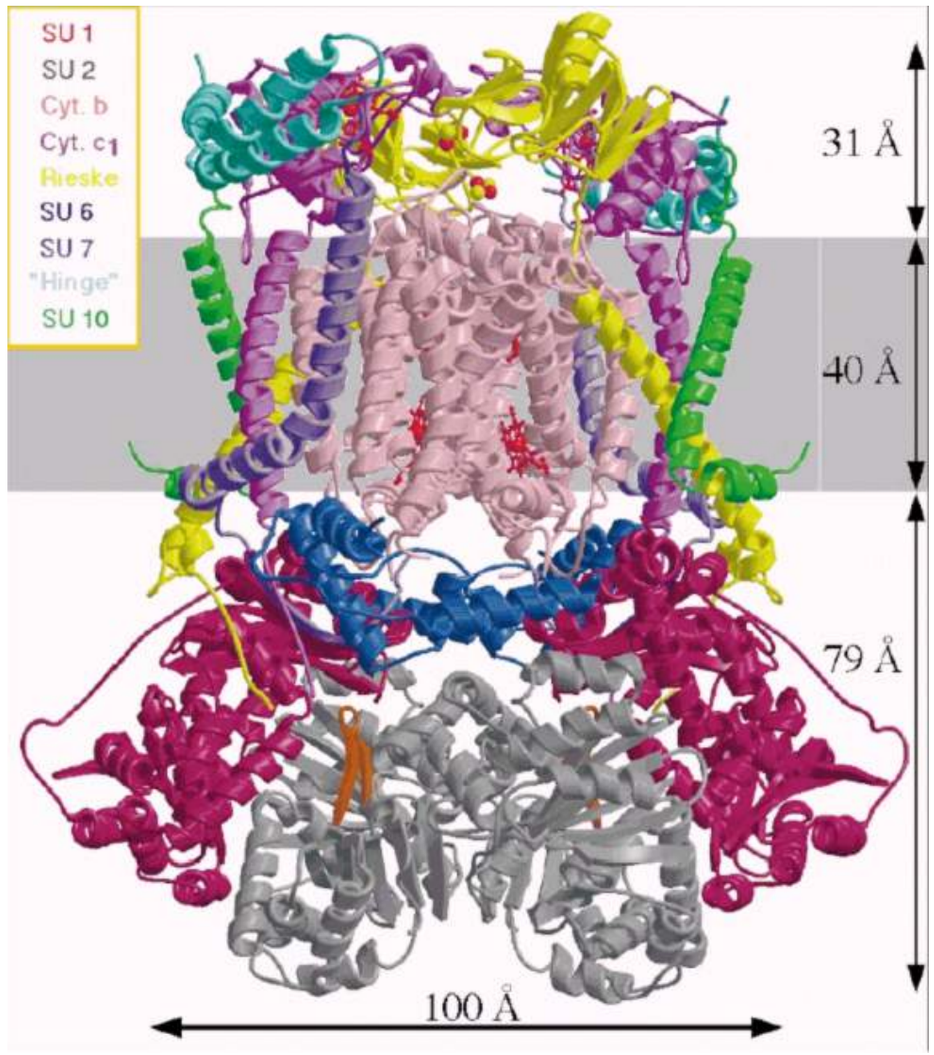


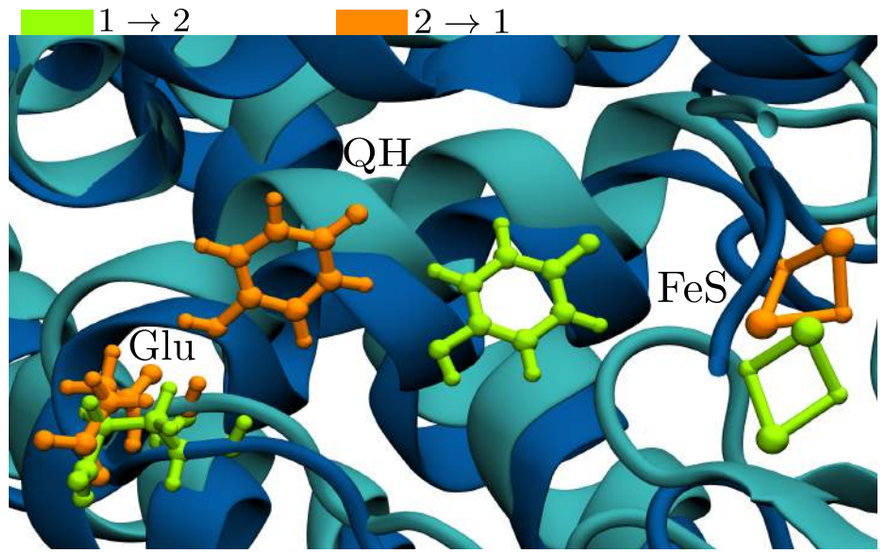
Martin, LeBard, DVM, JPCL 4 (2014) 3602.

bc1 complex: lambda(k)

200 ns simulation





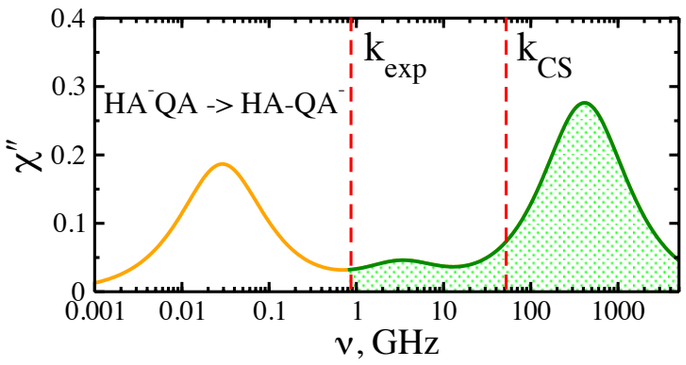


Why are enzymes big?

We are all familiar with the systems like software (or government legislation) … can grow rapidly in size over a number of years. Enzyme evolution is a great deal slower - but it has been going for million of years…

“From Enzyme Models to Model Enzymes”, Kirby & Hollfelder

Maybe because slow reactions require slower elastic deformations of the interface



…the advancement of science depends on the discovery and development of exact ideas …
to warrant the deductions we may draw by the application of mathematical reasoning.

- J. C. Maxwell

Biological interfaces are "different"

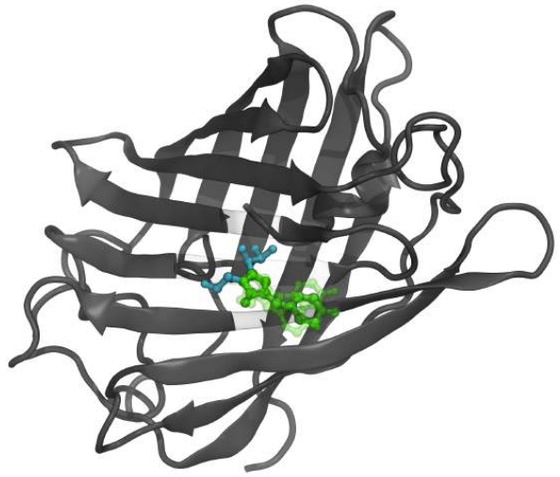
Nonergodicity introduces timescales to where previously only (free) energy has ruled.

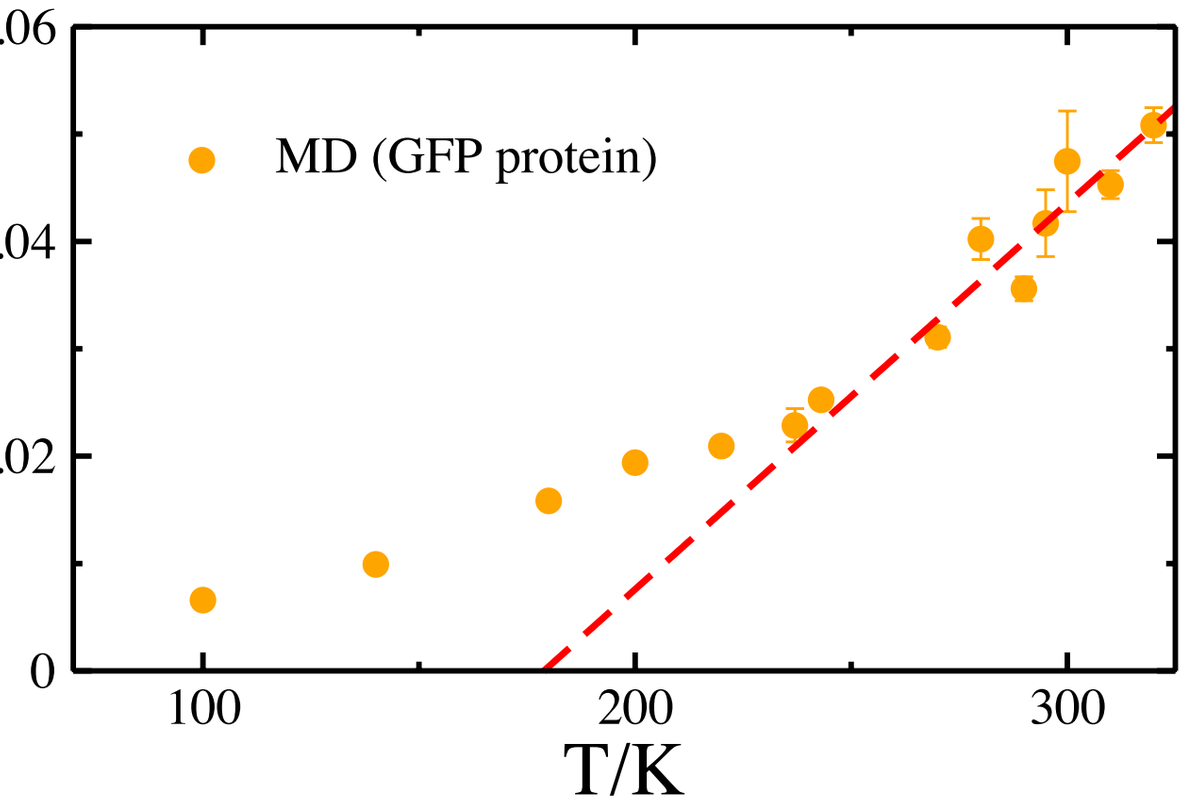
Prof David LeBard

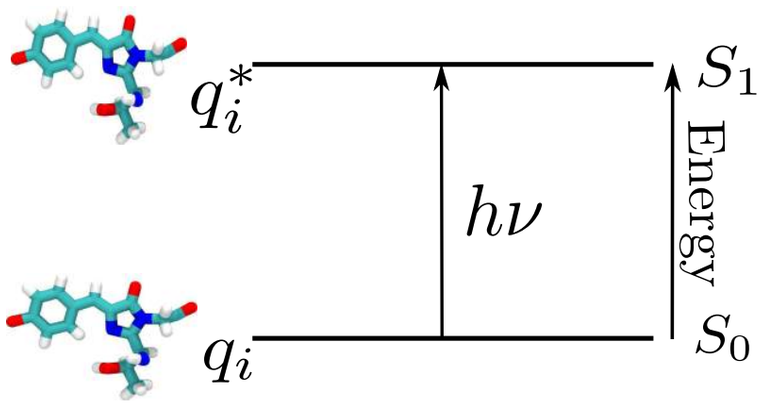
Dr Daniel Martin

$$ NSF

Lambda: dynamical transition





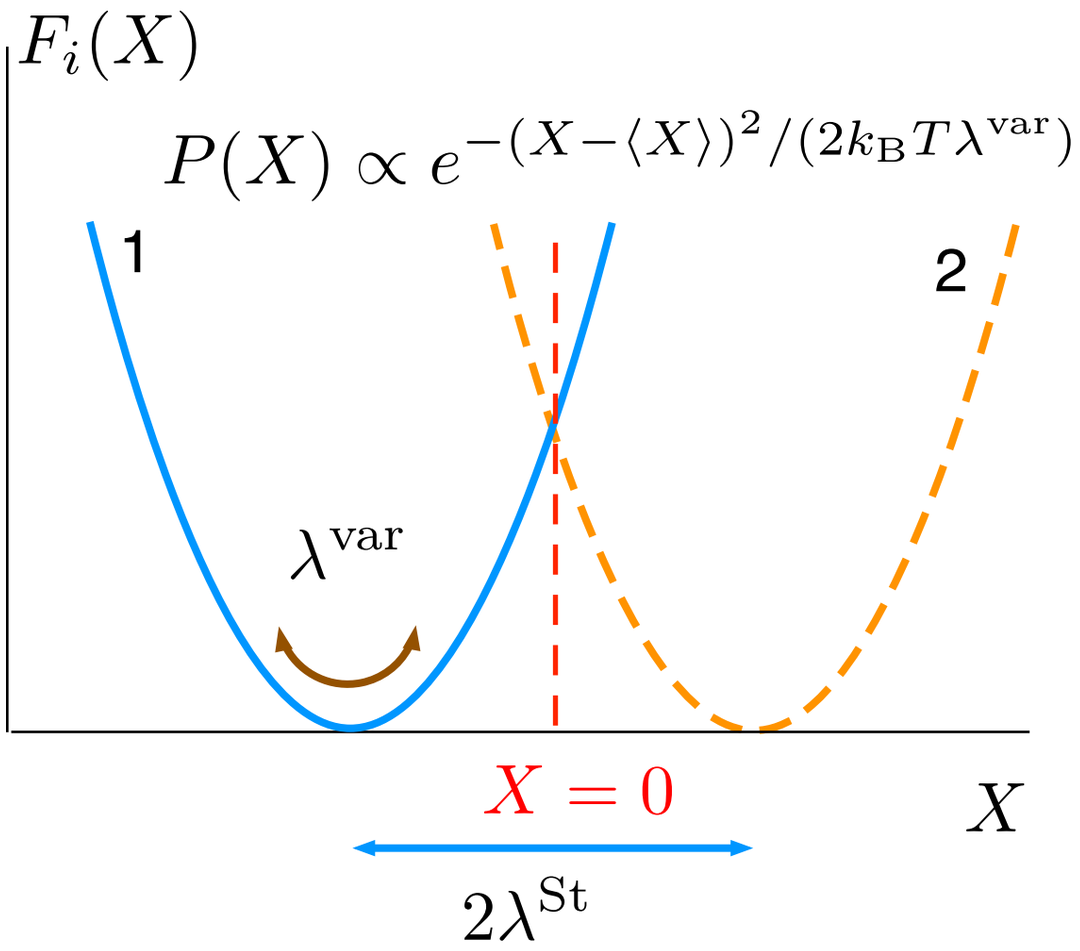


Standard picture: $\sigma(T)^2 = 2\lambda^{\mathrm{var}} k_{\mathrm{B}} T \propto T$

Proteins: $2k_{\mathrm{B}} T\lambda^{\mathrm{var}} \propto T - T_0$

JPCB 116 (2012) 10294

Glassy kinetics



$$k_{\mathrm{ET}} \propto P(0)$$

$$2k_{\mathrm{B}}T\lambda^{\mathrm{var}} \propto T - T_0$$

High-temperature rate constant:

$$k_{\mathrm{ET}} \propto \exp\left(-\frac{A}{T - T_0}\right)$$

Fogel-Fulcher-Tammann high-temperature kinetics

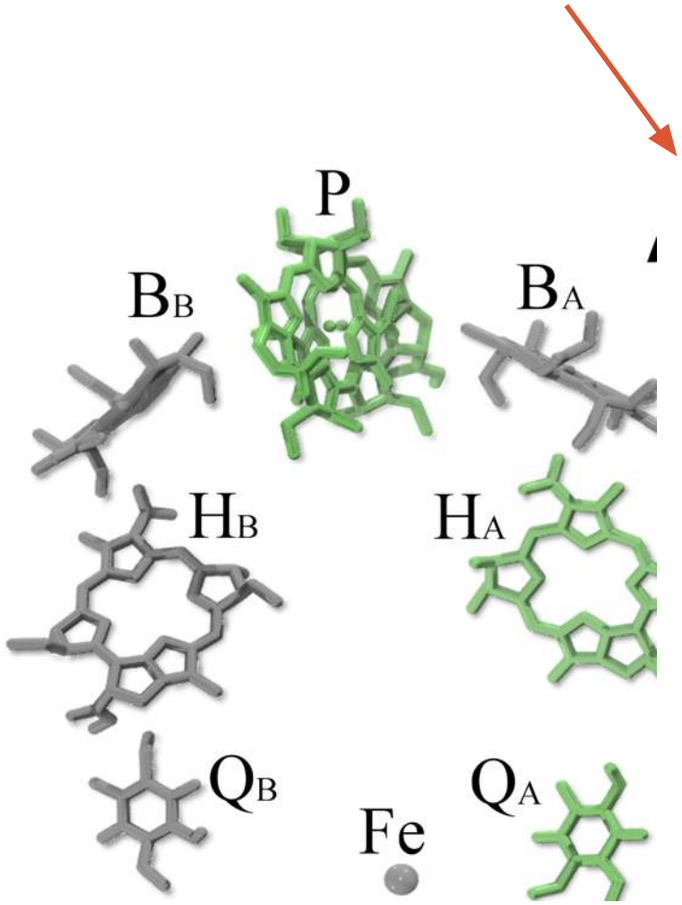
Bacterial charge separation (3 ps reaction time!)

$$\lambda(k) \propto \int_k^\infty \chi''(\omega)(d\omega/\omega)$$

$$\underbrace{\mathbf{k} \propto \exp[-\beta F_a(\mathbf{k})]}_{\text{self-consistent solution for } \mathbf{k}}$$

$$\lambda(k = 0.3\ \text{ps}^{-1}) = 0.35\ \text{eV}$$

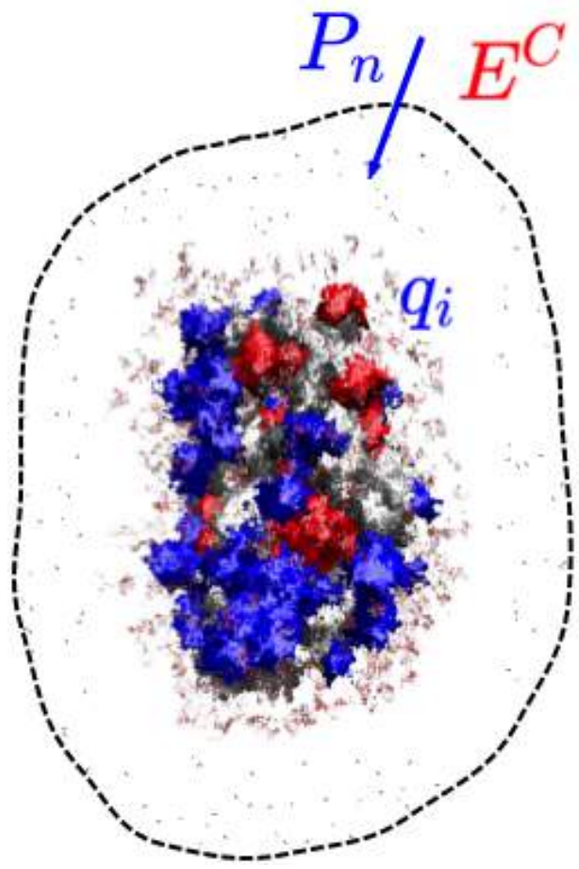
$$\lambda(k \to 0) = 2.4\ \text{eV}$$

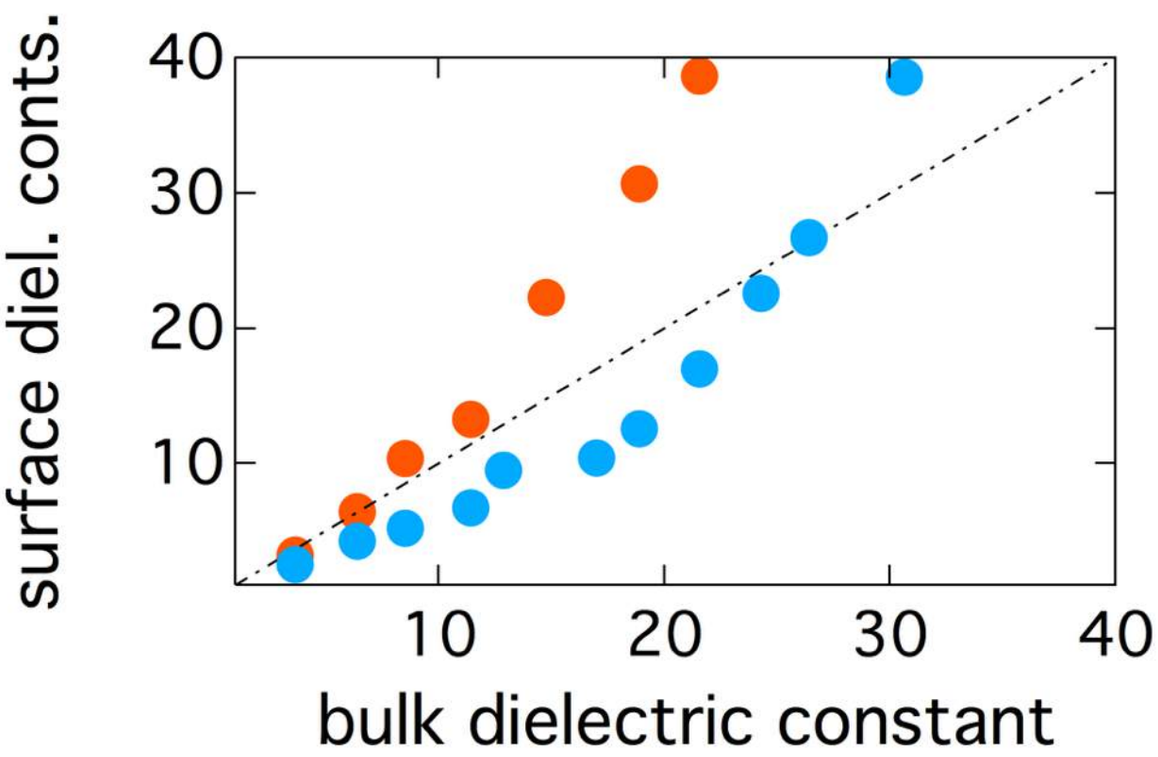


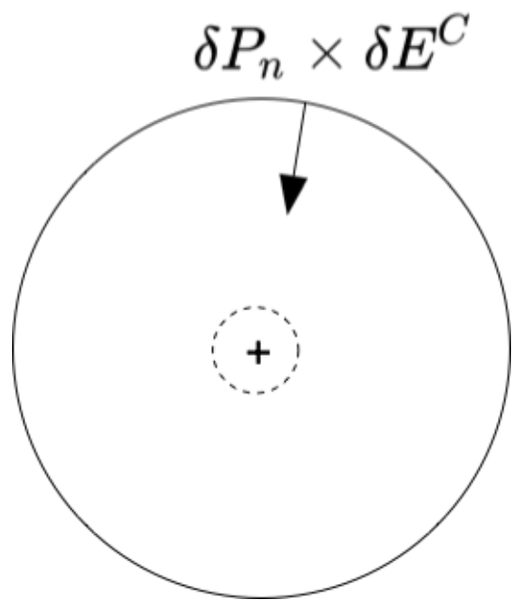
“Surface” dielectric constant

$$E^C(\mathbf{r}) = \sum_i q_i \underbrace{\Phi_s(\mathbf{r})}_{\text{solvent potential}}$$

$$\sigma_P = \frac{1}{k_B T} \langle \delta P_n \delta E^C \rangle$$

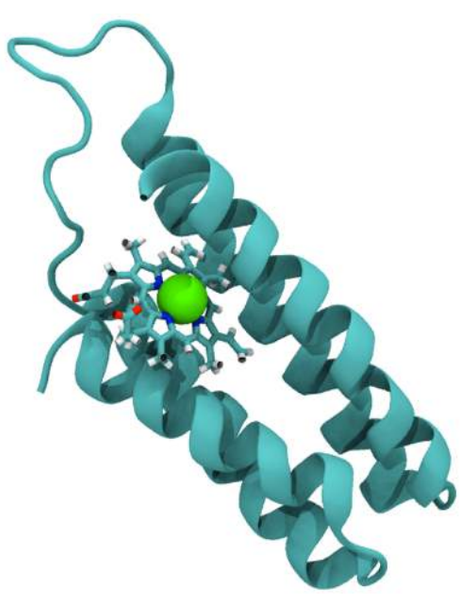


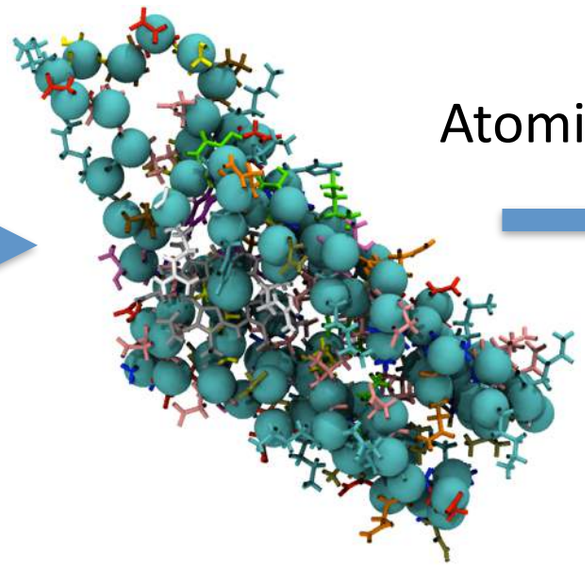




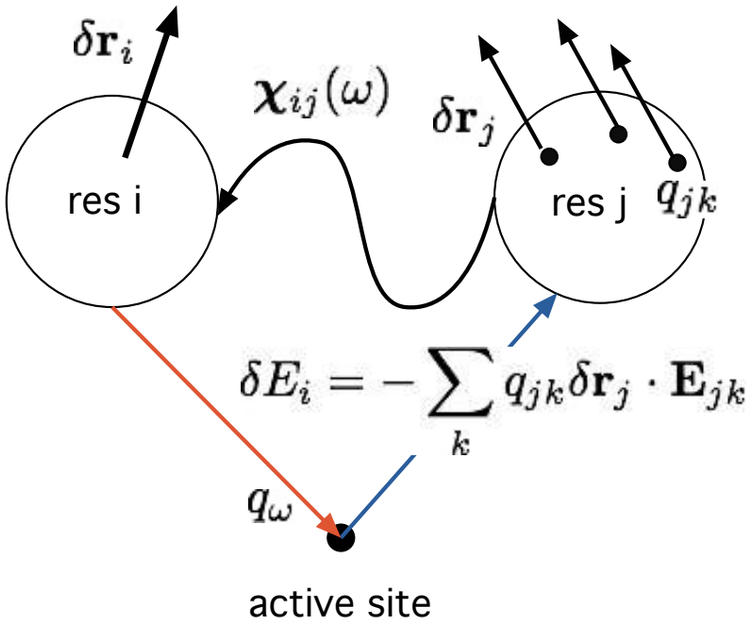
JCP **140**, 224506 (2014)

Dissipative Electro-Elastic Network Model (DENM)





Atomic charges



Spring Constant $\delta r = r - r_0$

$$E = \frac{C}{2} \sum_{i,j} H_{ij}^{\alpha\beta} \delta r_i^\alpha \delta r_j^\beta$$

Hessian Matrix

$$\int_0^t \zeta(t-t') \dot{\mathbf{q}}_m(t') dt' + \lambda_m \mathbf{q}_m = \mathbf{F}(t) + \mathbf{R}(t)$$

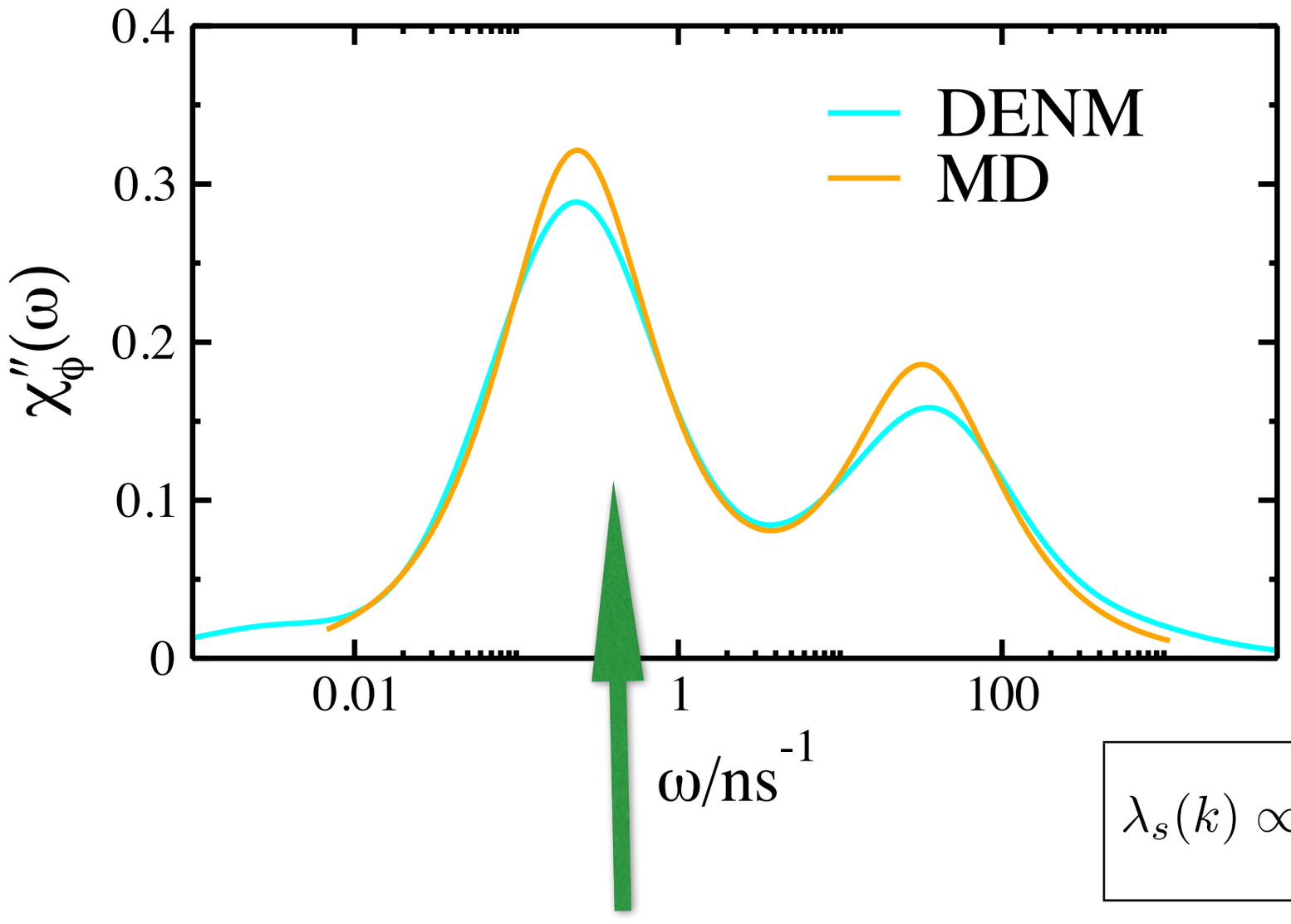
$$\chi_{ij}^{\alpha\beta}(\omega) = C^{-1} \sum_m U_{mi}^{\gamma\alpha} \left[\lambda_m + i\omega\zeta(\omega)\right]^{-1} U_{mj}^{\gamma\beta}$$

$$\chi_\phi(\omega) = -\sum_{i,j} E_{0j}^\alpha \chi_{ij}^{\alpha\beta}(\omega) E_{0i}^\beta$$

JCP 137 (2012) 165101

CytB: potential response

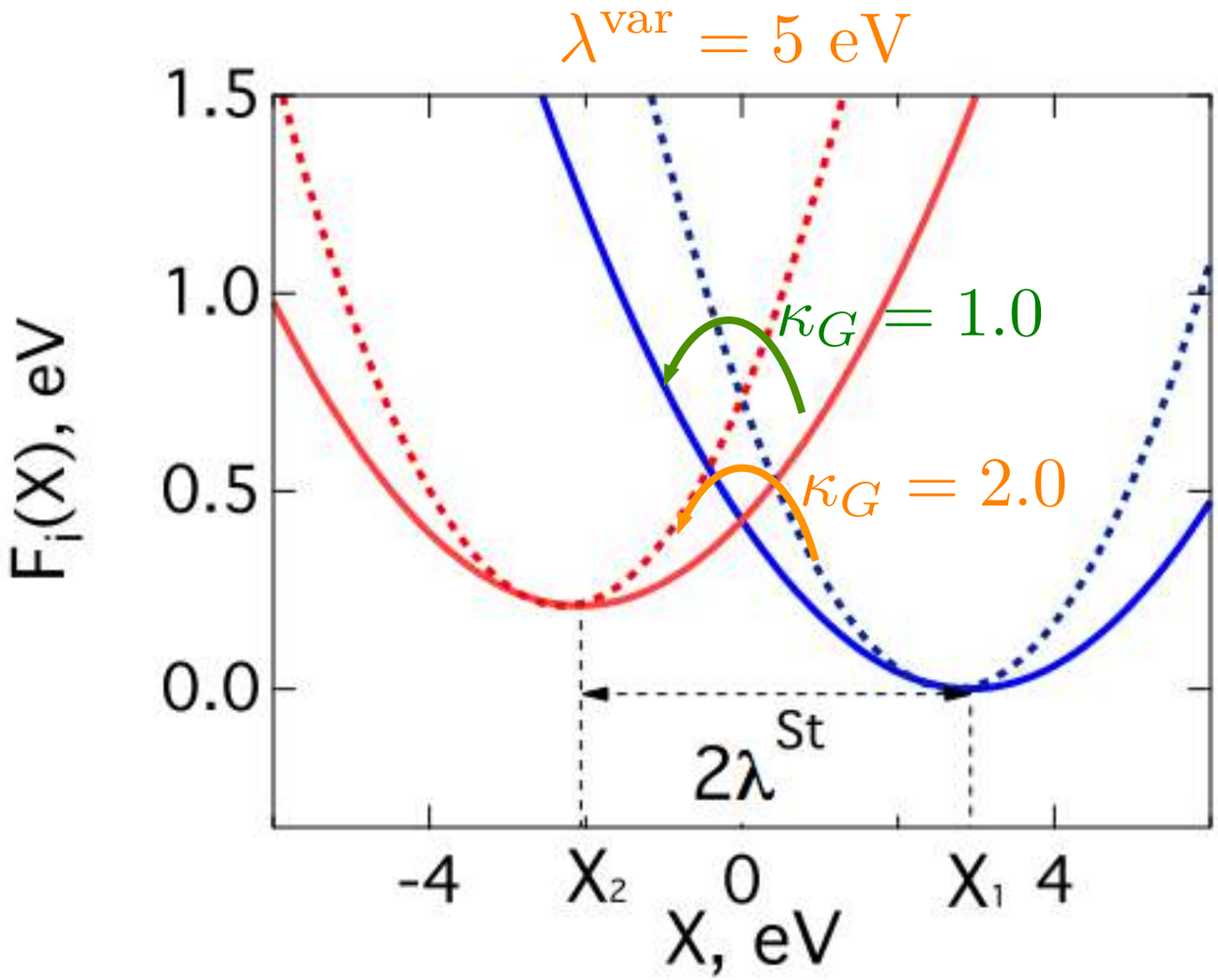
$$\chi_\phi(\omega) = -\sum_{i,j} E_{0j}^{\alpha} \chi_{ij}^{\alpha\beta}(\omega) E_{0i}^{\beta}$$



$$\lambda_s(k) \propto \int_{k=\omega_{\rm obs}}^{\infty} \chi''(\omega)(d\omega/\omega)$$

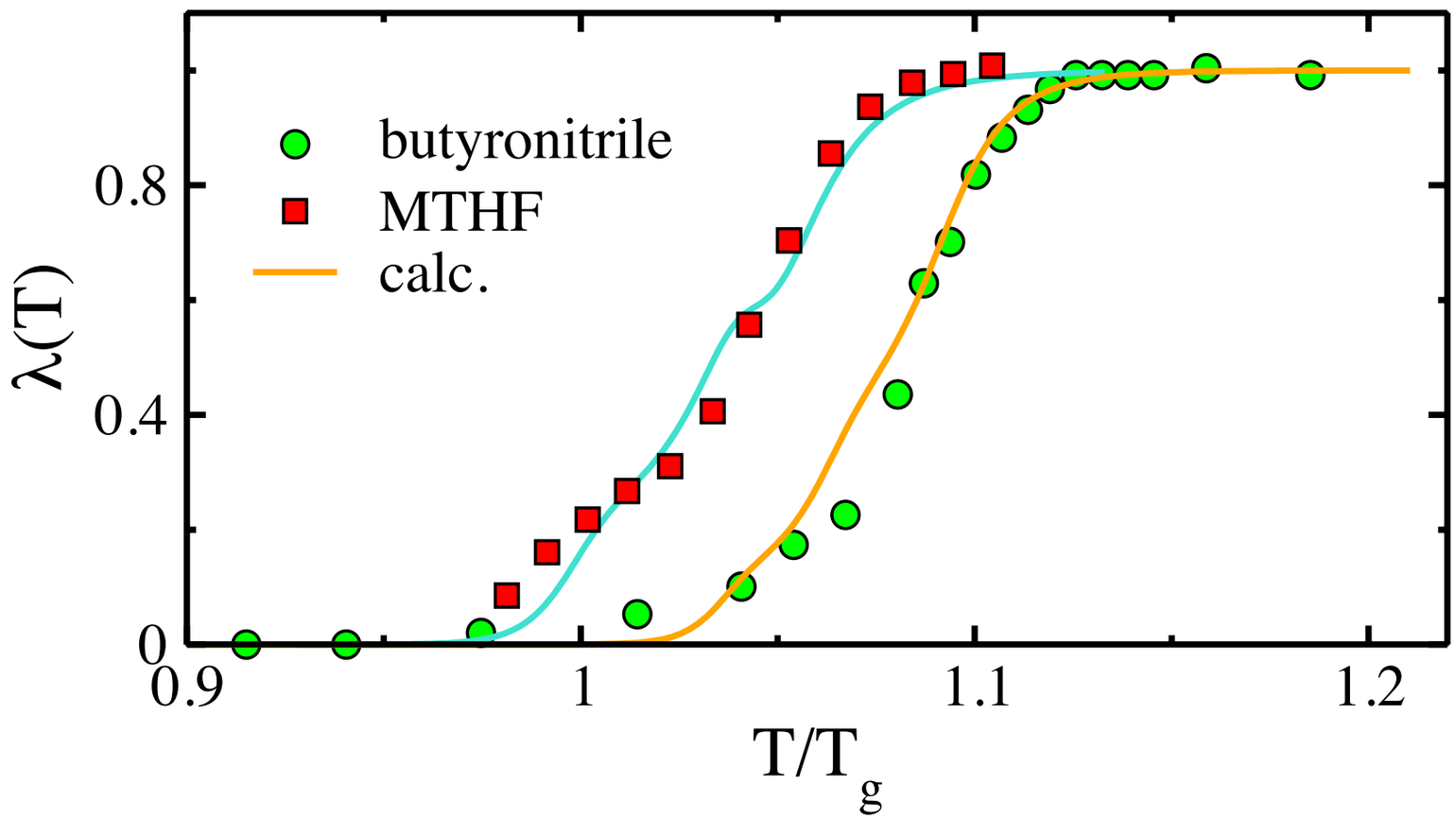
Elastic deformations of the protein shape

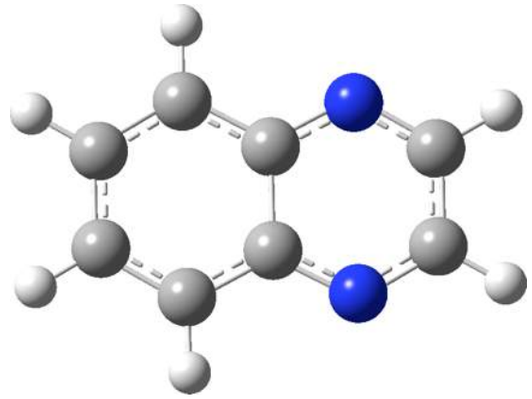
Nonergodic free energy surfaces



Spectroscopy in super-cooled liquids

$$\omega_{\rm obs} = 1/\tau_{\rm em}$$





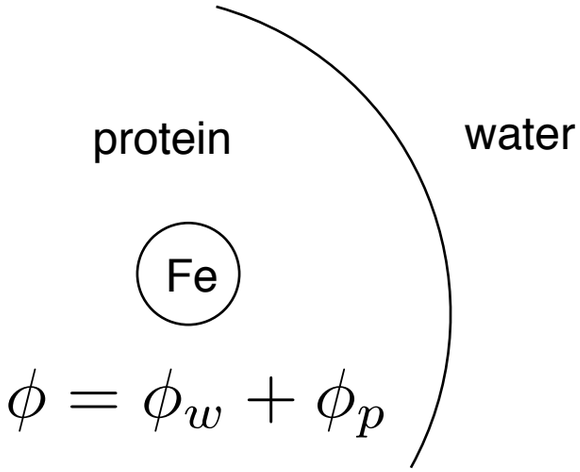
quinoxaline dye,

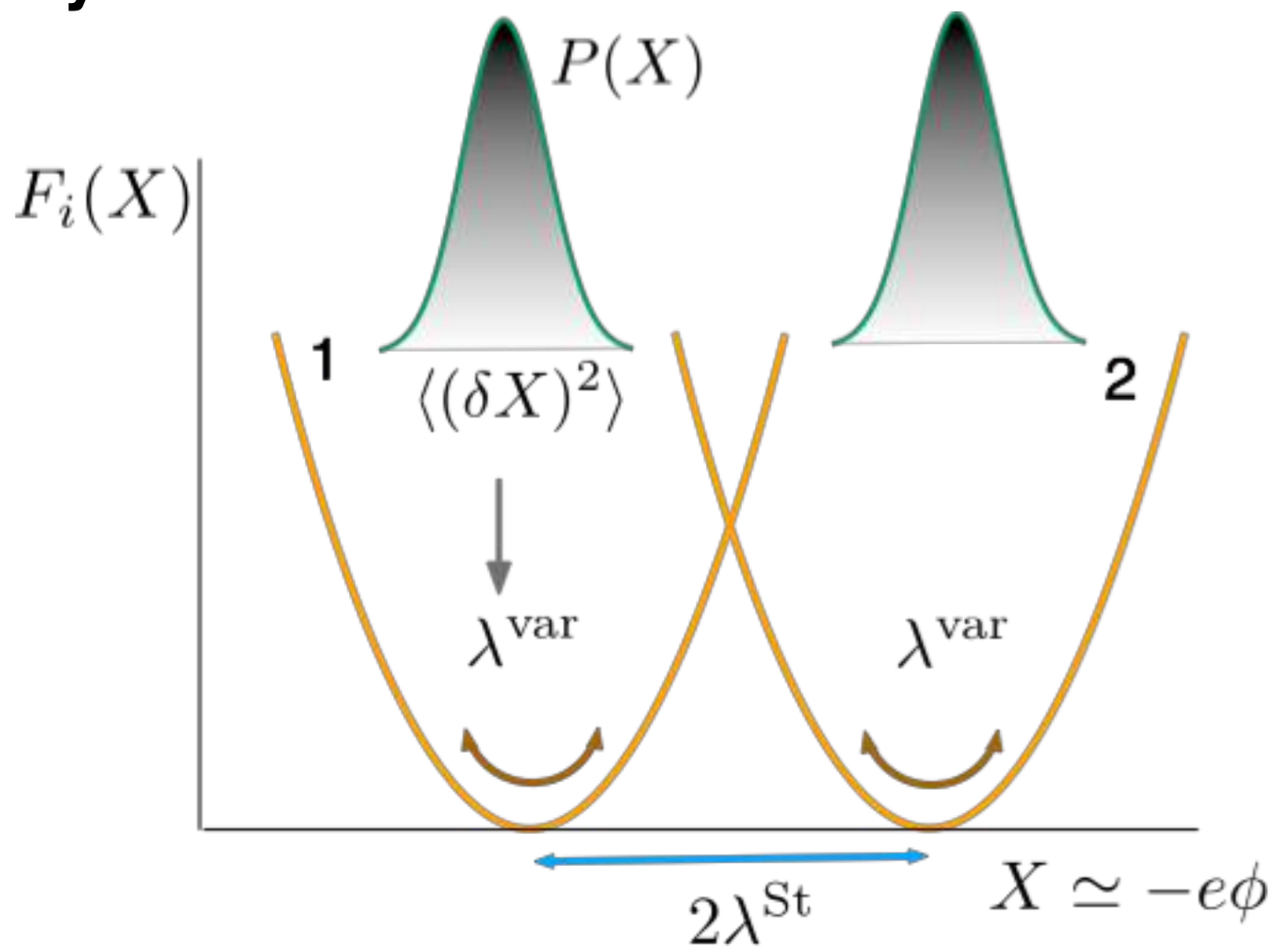
R. Richert, ASU

Freezing out of nuclear degrees of freedom on the time-scale of phosphorescence

DVM, Acc.Chem.Res'07

Signature of nonergodicity





$$\lambda^{\rm var} = \beta\langle(\delta X)^2\rangle/2$$

$$2\lambda^{\rm St} = X_1 - X_2$$

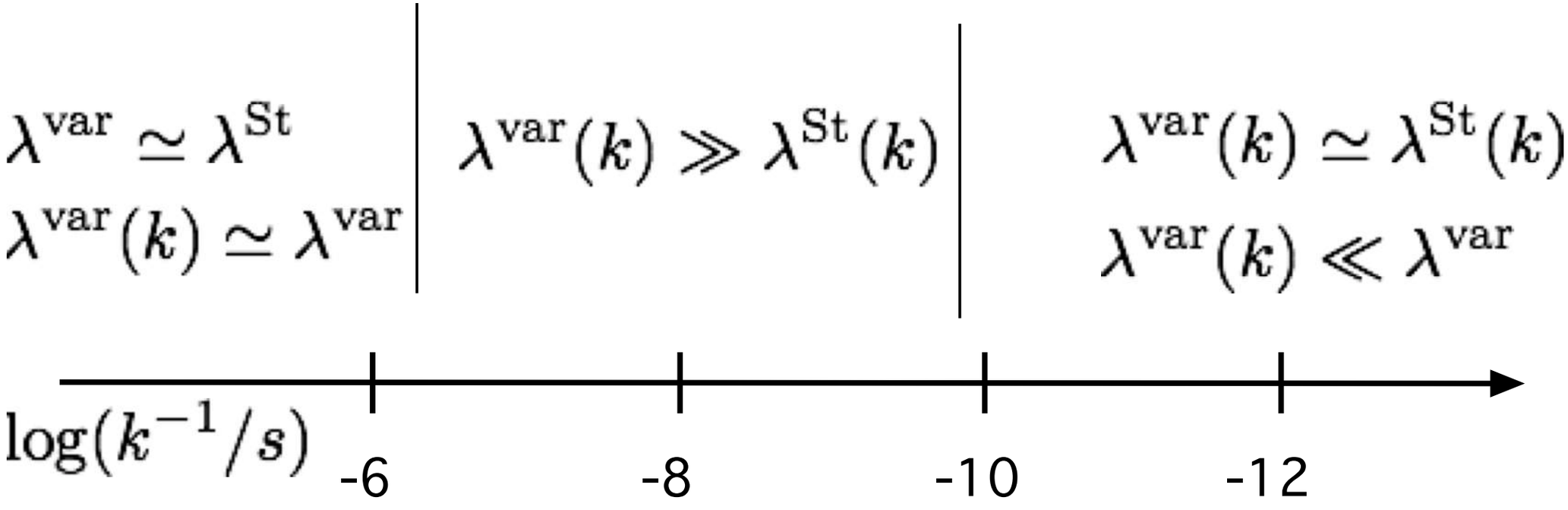
Canonical ensemble: $\lambda^{\rm St} = \lambda^{\rm var}$

$$\chi_G = \frac{\lambda^{\rm var}}{\lambda^{\rm St}}$$

$$\chi_G \gg 1$$

proteins

Time arrow of biological electron transport



energetically inefficient transport

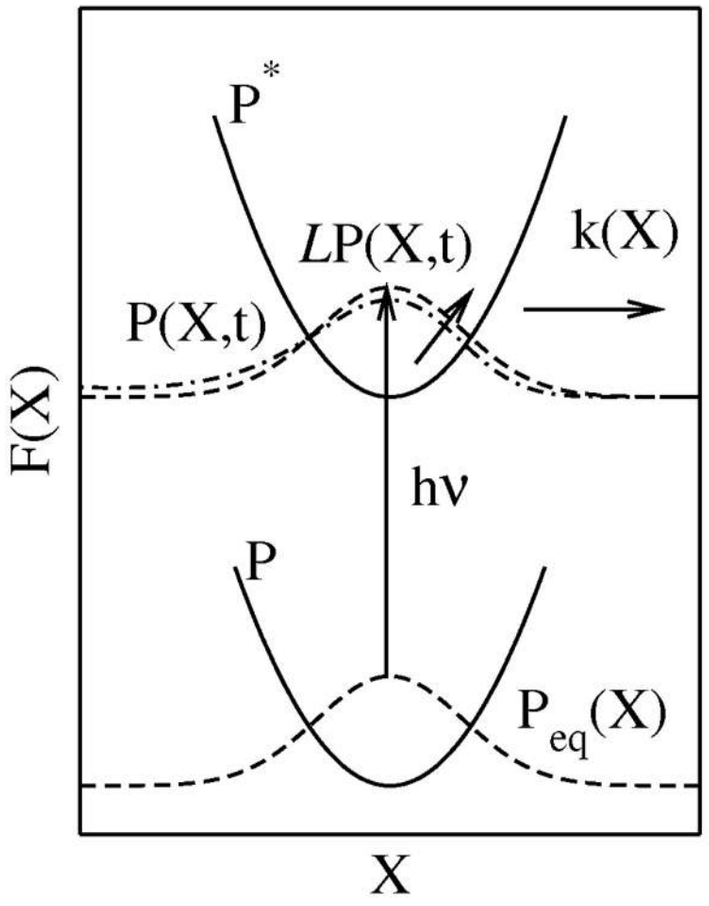
energetically efficient transport

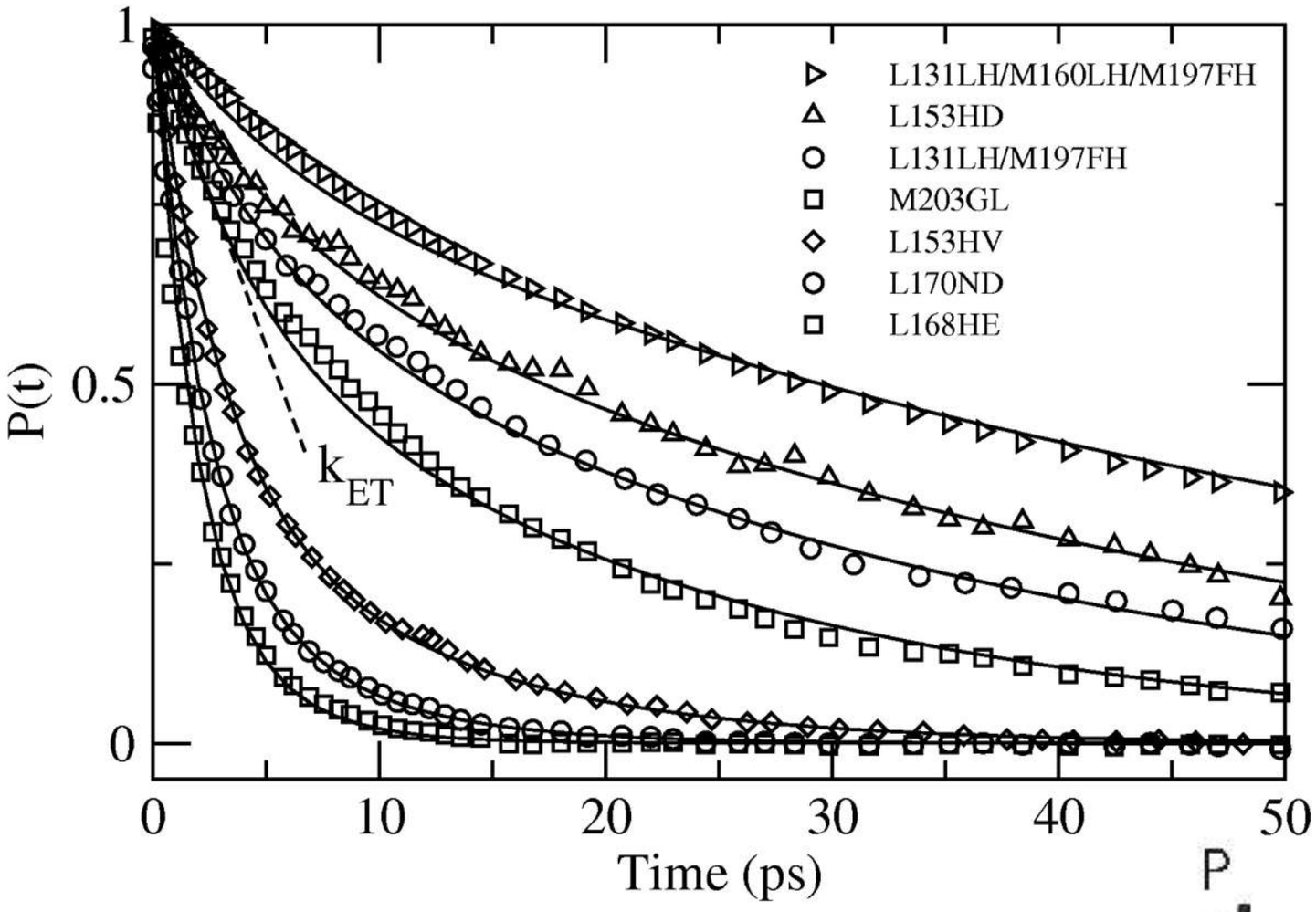
energetically efficient transport

$$\Delta G \to \Delta G/\kappa_G$$

JCP 139 (2013) 025102

Population dynamics

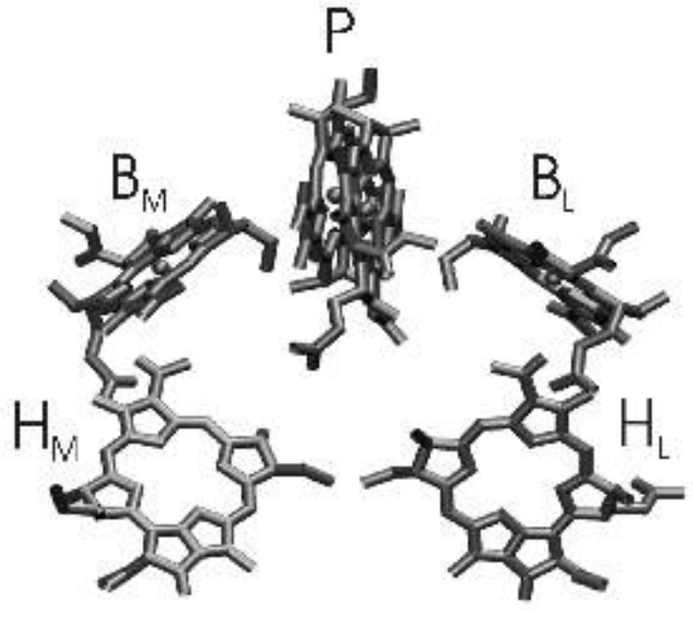




$$\partial P(X,t)/\partial t = [L(k_{\mathrm{ET}}, X) - k(X)]\, P(X,t)$$

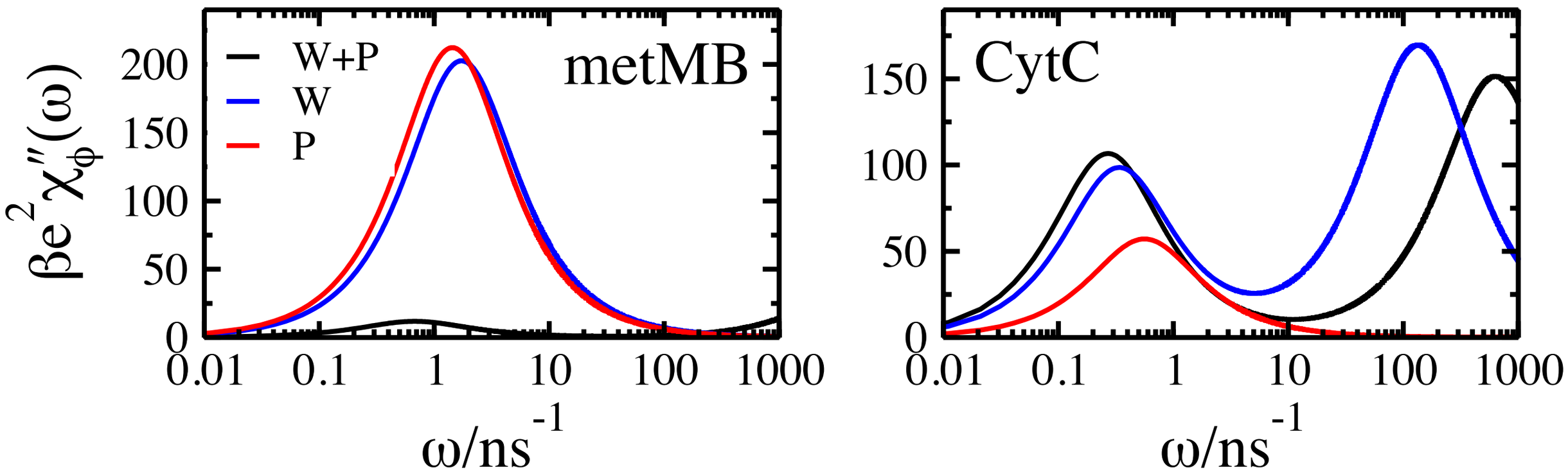
Fokker-Planck operator depending on $F(X, k_{\mathrm{ET}})$

$$P(t) = \int P(X,t) dX$$



LeBard, Kapko, DVM, JPCB 112 (2008) 10322

Does sequence matter?

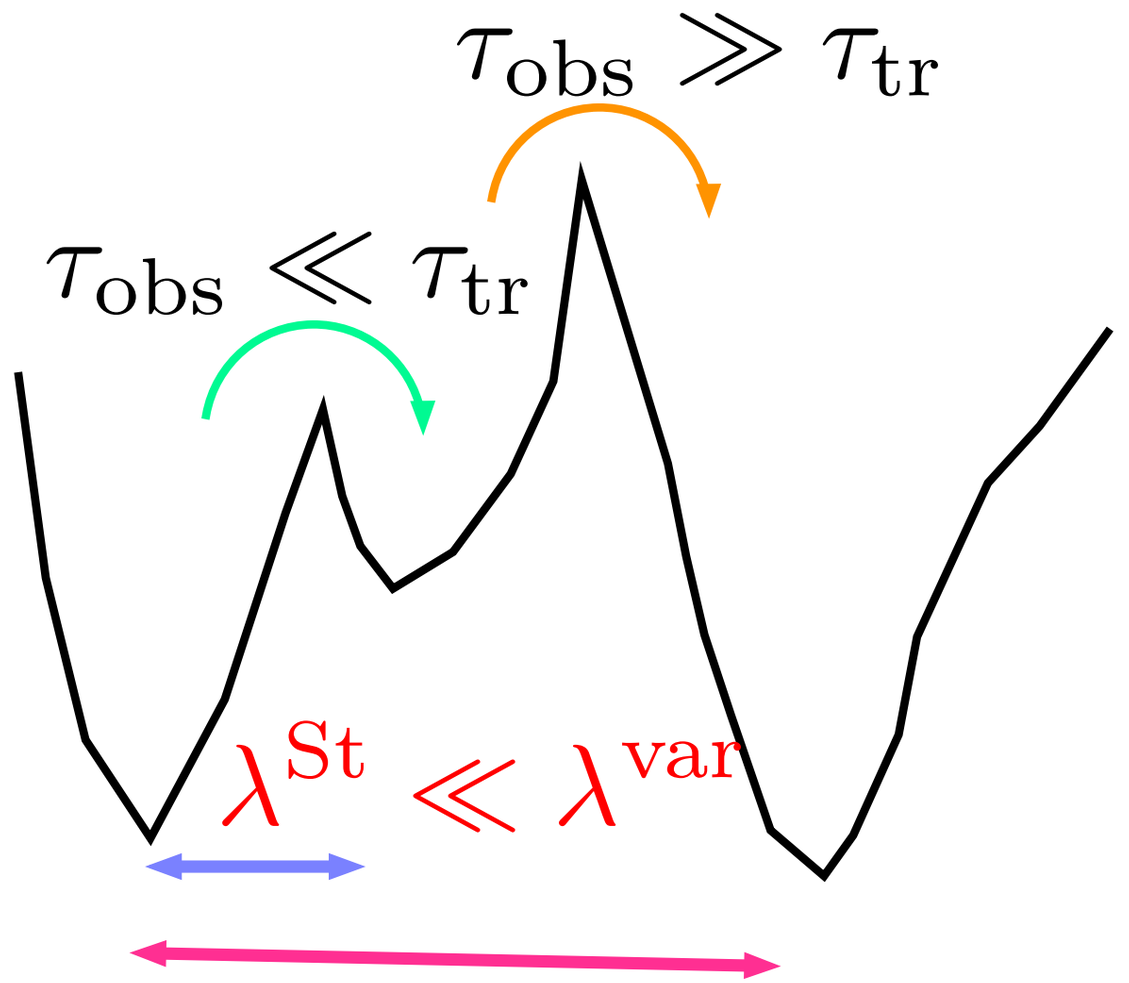


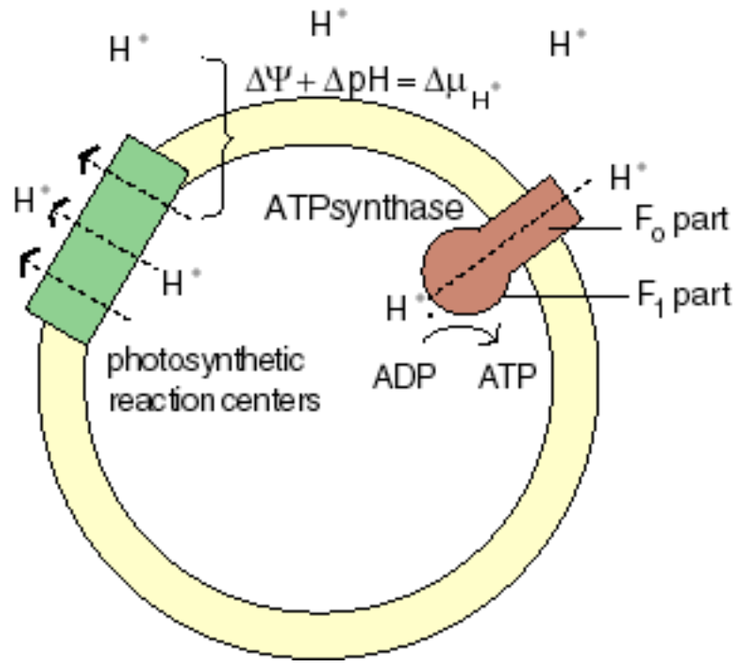
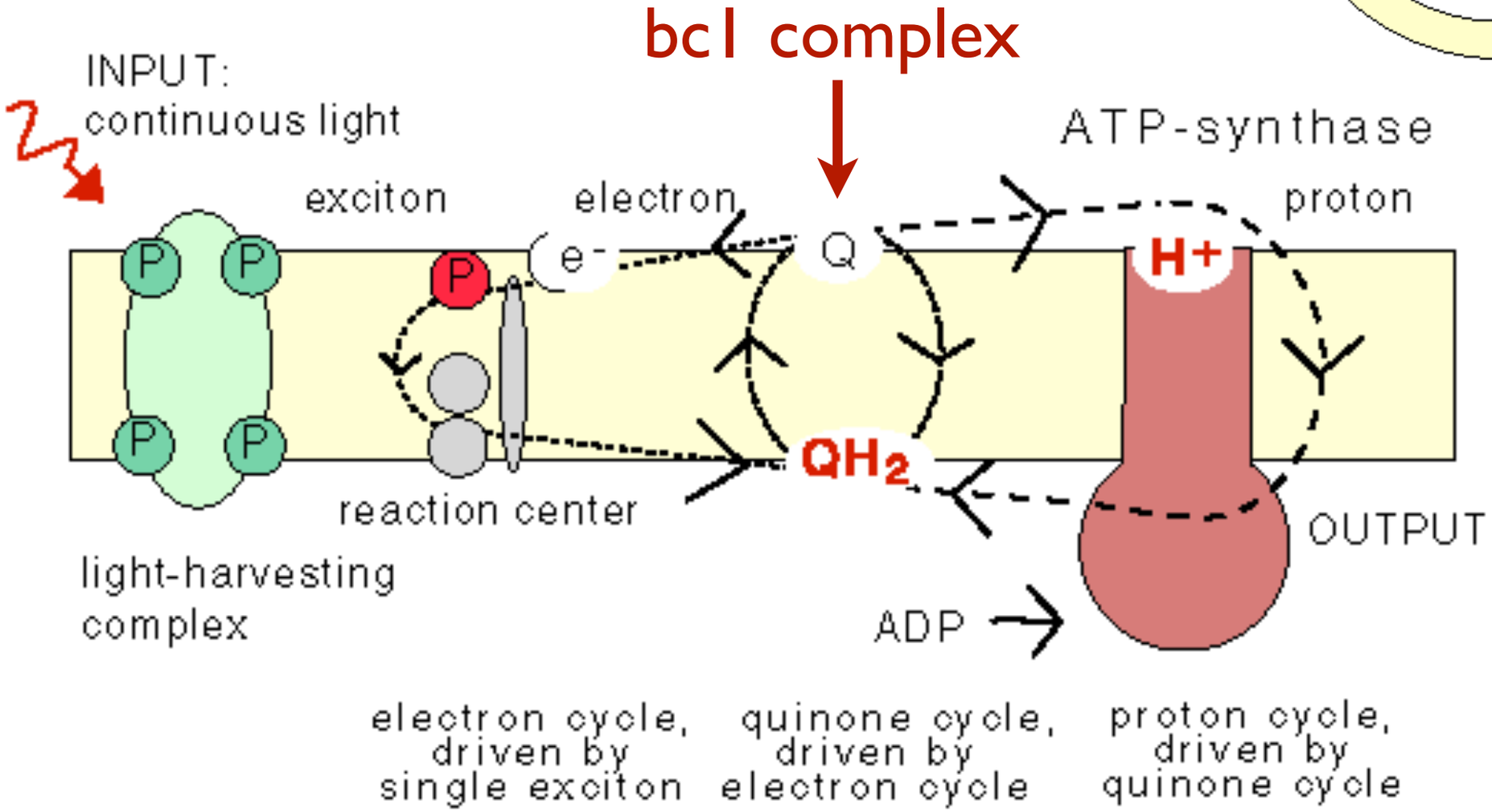
$$\lambda_s = \lambda_w + \lambda_p + \lambda_{pw} \propto \langle (\delta X_w + \delta X_p)^2 \rangle$$

Protein	λ_p, eV	λ_w, eV	λ_s, eV
Myoglobin	9.9	7.9	1.8
Cytochrome c	6.9	3.3	6.7

critical term

Protein-water compensation depends on the **surface charge** (sequence+folding).



$$\lambda^{\mathrm{St}} = \lambda^{\mathrm{var}}$$

Energy conversion machinery