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

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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.


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

- 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

\[ \text{O}_2 + 4\text{H}^+ + 4\text{e}^- \rightarrow 2\text{H}_2\text{O} \]
Electron transfer and thermodynamic reversibility in complex I are illustrated. The figure shows the potential energy profile for the transfer of a single electron across the FeS cluster chain in complex I. The experimental profile, with measured potentials for the remaining three clusters, is compared to the estimated potentials for the remaining three clusters. The figure highlights the importance of thermodynamically reversible processes, analogous to the rate-limiting step in cytochrome oxidase and other oxidoreductases. The energy profile for the transfer of four protons across the NADH:fumarate oxidoreduction is also discussed, showing how a single electron moves along the chain, a problem immediately evident from 2D crystallography. The time required to traverse the chain becomes apparent because the rate required, a problem immediately evident from 2D crystallography, is irreversible in the simulation and so the reaction is thermodynamically reversible, analogous to the rate-limiting step in cytochrome oxidase.
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?
Constitutive relation:

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

\[ P = \chi E, \quad D = \epsilon \quad \text{transverse} \quad E \quad \text{longitudinal} \]

\[ \nabla \cdot D = 0 \]

\[ \nabla \times E = 0 \]

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

(a) Maxwell scenario:

\[
\frac{E_c}{E_{ext}} = \frac{3}{2\epsilon + 1}
\]

(b) Lorentz scenario:

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

Kihara solute:

\[
\phi_0(s(r)) = 4\epsilon_0s \left[ \left( \frac{\sigma_0s}{r - R_{HS}} \right)^{12} - \left( \frac{\sigma_0s}{r - R_{HS}} \right)^{6} \right]
\]
“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

Parameter quantifying the deviation from the Maxwell scenario

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

\[ \alpha = \frac{M_{0}^{\text{int}}}{M_{0}^{\text{M}}} \]
High-frequency (THz) absorption

\[ \alpha_{\text{abs}}(\omega) = \frac{4\pi \omega}{c} \frac{\chi''(\omega)}{\sqrt{1 + 4\pi \chi'(\omega)}} \]

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

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
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

\[
\frac{\epsilon_s(\omega)}{\epsilon_{\text{mix}}(\omega)} = 1 - 3\eta_0 + 3\eta_0 \epsilon_s(\omega) \chi_c(\omega) (1 - y_0(\omega))
\]

Cavity field response

Experimental input

Volume fraction

Response of the lysozyme dipole, taken from MD

\[
\chi_M = \frac{3}{2\epsilon_s + 1}
\]

Maxwell scenario

Cametti et al., JPCB 115 (2011) 7144

Vinh et al, JACS 133 (2011) 8942

DVM, JPCM 24 (2012) 325105
**Range of protein-water correlations**

\[ \chi_0(r) \propto \left(1 - \exp\left[-\frac{(r - r_0)}{\Lambda}\right]\right) \]

\[ \lambda_{\text{repressor}} = 24 \text{\ Å} \]

\[ \lambda_{\text{cytochrome c}} = 44 \text{\ Å} \]
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.
Proteins:

Large-scale electrostatic fluctuations (lots of surface charges)

Slow modes

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

\[ P \propto e^{-\beta H(p,q)}, \quad \beta = 1/(k_B T) \]

Mathematical abstraction: \( \tau_{\text{obs}} \to \infty \)
Canonical ensemble: “All the ‘fast’ things have happened and all the ‘slow’ things have not”

- R. Feynman
Biology: continuous ergodicity breaking

\[ g(\omega) \]

- biology
- rate constant \( \omega_{\text{obs}} \)
- slow
- fast

\( \omega \)
Dynamically **restricted** ensemble

Canonical (Gibbs) average over motions *faster than the rate*

$k < \omega$

\[ \omega > k \]
Nonergodic kinetics

Activation barrier depends on the rate

\[ k \propto \exp[-\beta F_a(k)] \]

self-consistent solution for \( k \)
Electron tunneling (hopping conductivity)

\[ F(X) = -k_B T \ln P(X) = \frac{(X - X_0)^2}{4\lambda} \]

Reorganization energy (extent of medium deformation)
Dynamics vs thermodynamics

Stokes-shift time correlation function:

\[ C_i(t) = \langle \delta X(t) \delta X(0) \rangle_i \]

\[ \chi''_i(\omega) = (\beta \omega/2) C_i(\omega) \]

\[ \lambda_s(k) \propto \int_{k=\omega_{\text{obs}}}^{\infty} \chi''(\omega) \frac{d\omega}{\omega} \]

\[ X = \Delta E \]

\[ \lambda \sim 1 \text{ eV} \]
Reaction free energy & activation barrier

\[ \Delta G = -\lambda \]

\[ \Delta G = -\frac{\lambda}{\kappa_G} \]

\[ \kappa_G \sim 3 - 20 \quad \text{from MD of redox proteins} \]
Bacterial photosynthesis: Energetics

\[
\begin{align*}
\lambda_{12} &\approx 0.77 \text{ eV}, \quad \lambda_{23} = 0.71 \text{ eV} \\
-\Delta G_{13} &= \lambda_{12} + \lambda_{23} = 1.48 \text{ eV}
\end{align*}
\]

Charge-transfer state according to traditional theories!

Results of long (ca. 15 ns) simulations:

From the Stokes shift

From the distribution width (parabola's curvature)

- 1.48 eV

traditional theory
HA to QA

\(v, \text{GHz}\)

\(\chi''\)

\(k_{\text{exp}}, k_{\text{CS}}\)

\(\lambda_{\text{var}}, \text{eV}\)

\(k, \text{ps}^{-1}\)

HA QA -> HA-QA

\(k_{\text{exp}}\)

\(k_{\text{CS}}\)

\(\lambda_{\text{var}}\)

\(\lambda_{\text{exp}}\)

CS

e
from chicken heart mitochondria (Zhang et al., 1998) with an inhibitor (stigmatellin) bound at the Q\textsubscript{o} site (proximal position). In this structure the His-161 of the ISP coordinating the Fe\textsubscript{2}S\textsubscript{2} cluster formed a hydrogen bond to stigmatellin. However, in the structure of the native bc\textsubscript{1} complex from chicken (Zhang et al., 1998) the soluble part of the ISP domain was rotated with respect to its position in the structure with the inhibitor, as shown in Fig. 2. In this conformation (distal position) the Fe\textsubscript{2}S\textsubscript{2} cluster was located 21.3 Å from cytochrome c\textsubscript{1}. In P6\textsubscript{5}22 crystals from bovine heart, the Fe\textsubscript{2}S\textsubscript{2} cluster was found sufficiently close to heme c\textsubscript{1} to form a hydrogen bond to the propionate side chain of the heme (Zhang et al., 1998; Iwata et al., 1998). In another structure of the bc\textsubscript{1} complex from bovine heart from P6\textsubscript{5}22 crystals (Iwata et al., 1998), the ISP was observed to assume a third, "intermediate" position, in which the Fe\textsubscript{2}S\textsubscript{2} cluster was located 27.5 Å from cytochrome c\textsubscript{1} and 13 Å from the Q\textsubscript{o} site, so that it would be impossible for His-161 to form a hydrogen bond to the quinone. The ability of the ISP soluble head to occupy different positions in the complex has been interpreted to imply that the quinol oxidation mechanism involves a substantial movement of the soluble head of the ISP between reaction domains in the cytochrome b and cytochrome c\textsubscript{1} subunits, while the transmembrane part of the ISP remains fixed, i.e., that when quinol binds to the Q\textsubscript{o} site, the mobile ISP head moves into the proximal position, bringing the Fe\textsubscript{2}S\textsubscript{2} cluster close to the Q\textsubscript{o} site. After the Fe\textsubscript{2}S\textsubscript{2} cluster is reduced by quinol, the ISP head moves into the distal position to reduce cytochrome c\textsubscript{1} (Zhang et al., 1998; Iwata et al., 1998; Kim et al., 1998; Crofts and co-workers, submitted for publication).

One can investigate the movement of the ISP through molecular dynamics simulations. However, the expected time scale of the rotation (Crofts and co-workers, submitted for publication) is beyond the reach of molecular dynamics simulations, which are presently limited to time scales of a few nanoseconds for large proteins. Steered molecular dynamics (SMD) provides a means of overcoming this limitation by inducing the movement on the time scale accessible to molecular dynamics (Izrailev et al., 1997, 1998; Balsera et al., 1997; Isralewitz et al., 1997; Gullingsrud et al., 1999). In SMD simulations, time-dependent external forces are applied to specific atoms or groups of atoms, leading to the desired motion. This approach has been used to study the dynamics of the ISP head in the bc\textsubscript{1} complex, providing insights into the mechanism of quinol oxidation.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{Catalytic mechanism of bc\textsubscript{1} complex. Two cycles of QH\textsubscript{2} oxidation at the Q\textsubscript{o} site are required to generate the two-electron reduction of Q to QH\textsubscript{2} at the Q\textsubscript{i} site. The shaded area represents the membrane.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig2.png}
\caption{Rotation of the ISP mobile head in the bc\textsubscript{1} complex upon binding of the inhibitor (stigmatellin). The cytochrome b, cytochrome c\textsubscript{1}, and ISP subunits are shown. (a) Arrangement of the bc\textsubscript{1} complex subunits when stigmatellin is bound to the Q\textsubscript{o} site. (b) Arrangement of the bc\textsubscript{1} complex subunits in the absence of the inhibitor.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig3.png}
\caption{Interaction of the ISP head with the Fe\textsubscript{2}S\textsubscript{2} cluster and the quinone.

A: Overview of the bc\textsubscript{1} complex subunits.
B: Close-up view of the ISP head with highlighted residues.
C: Molecular interactions with the Fe\textsubscript{2}S\textsubscript{2} cluster (red) and the quinone (blue).

Donor

Acceptor

HIS-141

HIS-161

CYS-160

CYS-144

Fe\textsubscript{2}S\textsubscript{2}

Q\textsubscript{0}

\textcopyright Martin, LeBard, DVM, JPCL 4 (2014) 3602.}
\end{figure}
$bc_1$ 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: \[ \sigma(T)^2 = 2\lambda \var T \propto T \]

Proteins: \[ 2k_B T \lambda \var \propto T - T_0 \]
Glassy kinetics

High-temperature rate constant:

\[ k_{ET} \propto P(0) \]
\[ 2k_B T \lambda^{\text{var}} \propto T - T_0 \]

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

Fogel-Fulcher-Tammann high-temperature kinetics
Bacterial charge separation (3 ps reaction time!)

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

\[ k \propto \exp[-\beta F_a(k)] \]
self-consistent solution for \( k \)

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

\[ \lambda(k \to 0) = 2.4 \text{ eV} \]
“Surface” dielectric constant

\[ E^C(r) = \sum_i q_i \Phi_s(r) \]

solvent potential

\[ \sigma_P = \frac{1}{k_BT} \left< \delta P_n \delta E^C \right> \]

JCP 140, 224506 (2014)
Dissipative Electro-Elastic Network Model (DENM)

Spring Constant

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

Hessian Matrix

\[ \delta r = r - r_0 \]

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

\[ \chi_{ij}^{\alpha\beta}(\omega) = C^{-1} \sum_m U_{m_i}^{\gamma\alpha} [\lambda_m + i\omega \zeta(\omega)]^{-1} U_{m_j}^{\gamma\beta} \]

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

JCP 137 (2012) 165101
CytB: potential response

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

\[ \lambda_s(k) \propto \int_{k=\omega_{obs}}^{\infty} \chi''(\omega) \frac{d\omega}{\omega} \]

Elastic deformations of the protein shape
Nonergodic free energy surfaces

\[ \lambda^{\text{var}} = 5 \text{ eV} \]

\[ \kappa_G = 1.0 \]

\[ \kappa_G = 2.0 \]
Spectroscopy in super-cooled liquids

\[ \omega_{\text{obs}} = \frac{1}{\tau_{\text{em}}} \]

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

DVM, Acc.Chem.Res'07
Signature of nonergodicity

\[ \phi = \phi_w + \phi_p \]

protein [Fe]
water

\[ \lambda^{\text{var}} = \beta \langle (\delta X)^2 \rangle / 2 \]

\[ 2\lambda^{\text{St}} = X_1 - X_2 \]

Canonical ensemble: \( \lambda^{\text{St}} = \lambda^{\text{var}} \)

\[ \chi_G = \frac{\lambda^{\text{var}}}{\lambda^{\text{St}}} \quad \chi_G \gg 1 \]

proteins
Time arrow of biological electron transport

\[ \lambda_{\text{var}} \sim \lambda_{\text{St}} \]
\[ \lambda_{\text{var}}(k) \sim \lambda_{\text{var}} \]
\[ \lambda_{\text{var}}(k) \gg \lambda_{\text{St}}(k) \]
\[ \lambda_{\text{var}}(k) \ll \lambda_{\text{var}} \]

\[ \log(k^{-1}/s) \]
-6 \hspace{2cm} -8 \hspace{2cm} -10 \hspace{2cm} -12

energetically inefficient transport
energetically efficient transport
energetically efficient transport

\[ \Delta G \rightarrow \Delta G / \kappa_G \]
Population dynamics

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

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

\[ P(t) = \int P(X, t) dX \]

LeBard, Kapko, DVM, JPCB 112 (2008) 10322
Does sequence matter?

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

<table>
<thead>
<tr>
<th>Protein</th>
<th>(\lambda_p), eV</th>
<th>(\lambda_w), eV</th>
<th>(\lambda_s), eV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myoglobin</td>
<td>9.9</td>
<td>7.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Cytochrome c</td>
<td>6.9</td>
<td>3.3</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Protein-water compensation depends on the **surface charge** (sequence+fitolding).
\[ \tau_{\text{obs}} \ll \tau_{\text{tr}} \]

\[ \lambda_{\text{St}} \ll \lambda_{\text{var}} \]

\[ \lambda_{\text{St}} = \lambda_{\text{var}} \]
Energy conversion machinery

INPUT: continuous light
light-harvesting complex

exciton
reaction center

electron cycle, quinone cycle, proton cycle,
driven by single exciton electron cycle, quinone cycle

QH2
Q

ATP-synthase

bc1 complex

ADP

OUTPUT

H+