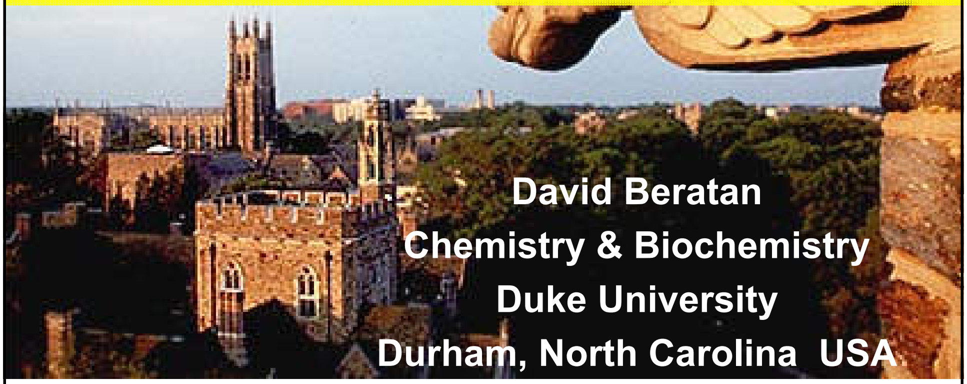
Protein Electron Transfer: When does Structure Matter, and Why?



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Problems of interest to us:

Molecular Biophysics
- Charge transfer in proteins, DNA, metal-decorated PNA
- Coarse grained models for molecular machine motion and ATP driven events

Molecular Chirality
- Spectroscopic signatures of chirality in the condensed phase (ORD, CD, ROA, RayOA); assignment of absolute stereochemistry
- Photoinduced charge transfer through chiral bridges

Nanoscience & materials science
- Inverse design of new materials
- Design of nonlinear optical materials
- C-AFM of pulled-nicked DNA
- Inelastic tunneling through molecules as a ‘double-slit’ experiment

Prologue

Nonlinear Optics

- D-(bridge)-A
- R_{da} = 5-30 Å
- Strong coupling

  π/π* bridge mediated
  eV scale ints.
- D-B-A states scrambled
- Strong CT bands

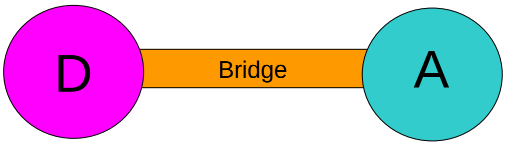
  (UV/Vis, π ł π*)

Biol. Electron transfer

- D-(protein)-A
- R_{da} = 5-30 Å
- Weak coupling

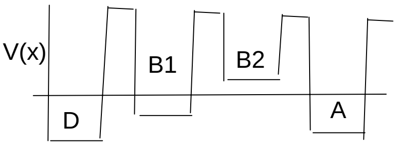
  σ/π bridge mediated
  cm^{-1} scale ints.
- D, A well localized
- Very weak CT bands

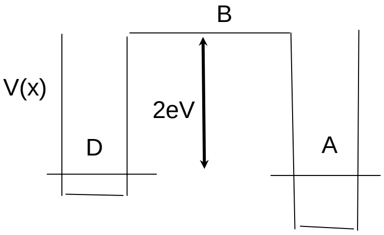
  (NIR, D ł A)



Nonlinear optics

Protein ET





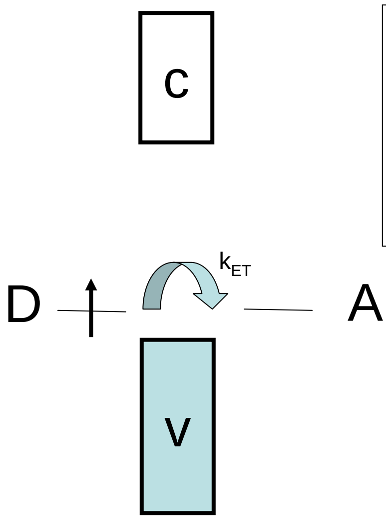
Delocalization (with some asymmetry)

Localization

pi - pi . . . pi - pi

cofactor - protein - cofactor

Electronic Energy Landscape for Electron Transfer Reactions



Analogy:

- Mid-gap dopant states (D and A) in large band-gap semi-conductor (protein)
- Hole-mediated superexchange (tunneling) mediated transport *via* filled states

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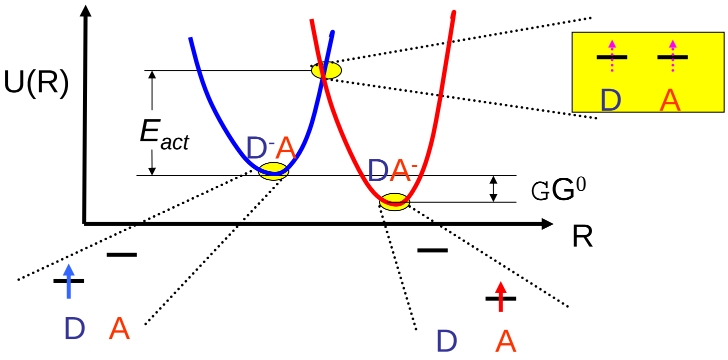
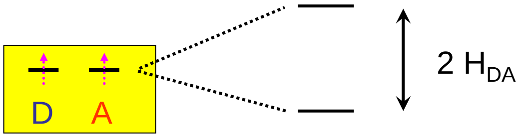
A Brief History of Protein ET

- 1956: **Marcus Theory**

$$k_{ET} = \kappa \exp[-E_{act} / kT]$$



Coupling matrix element



$$\kappa \propto \left| H_{DA} \right|^2$$

Computational methods:

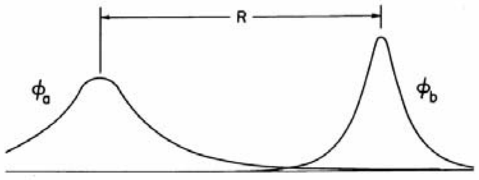
- Empiricism
- Splitting Energies (diagonalization)
- Perturbation or scattering theory methods using zero order D, A states

- 1960: Chance discovers ET between a cytochrome *c* and chlorophyll is functional at low temperature … finally at helium temps.

So electrons and nuclei are not going over the barriers – biology deals with the dual nature of matter.

- 1974: Hopfield estimates barrier to electron tunneling must be <3 eV. He guesses a 2eV **square barrier** so:

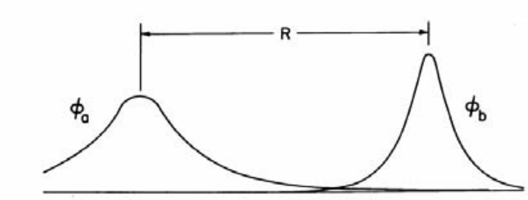
$$k_{ET} \propto \exp[-1.4R_{DA}(\mathring{A})] \times \exp[-E_{act} / kT]$$



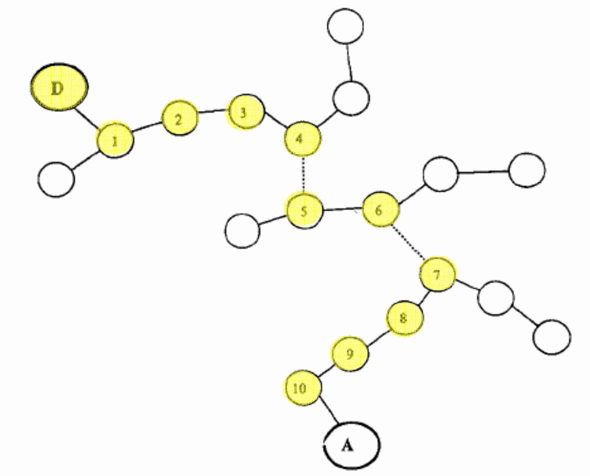
Outline

- ► Protein-Mediated ET
- ► Two Coupling Mechanisms
- ► A Proposed Unified View

Do the donor and acceptor localized states
in proteins really look like this…



…or more like this?

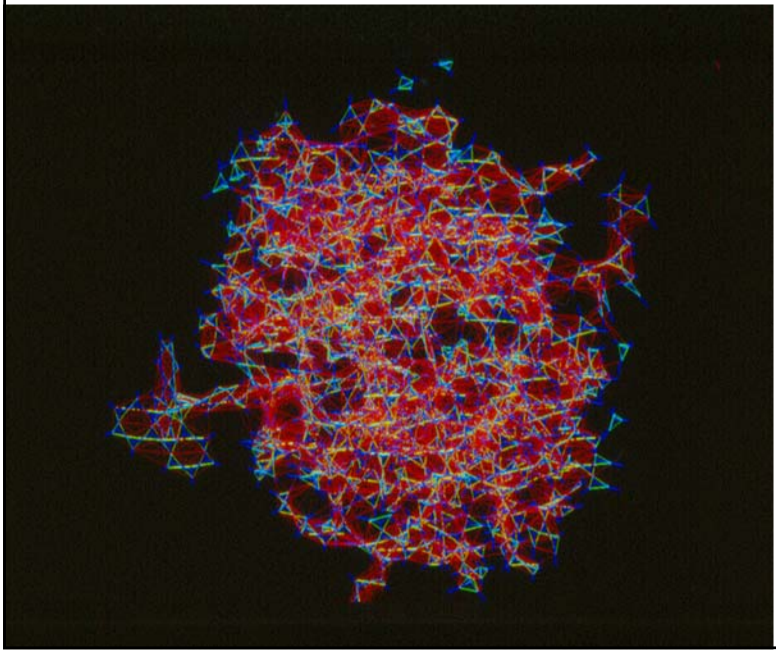


guided by the protein backbone, side chains, H-bonds etc.

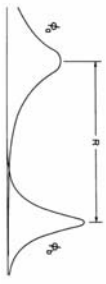
…because TB interactions >> TS interactions

…because ΔE to bridge orbitals << ΔE to ionization

► Protein-Mediated ET



OR:



Zero-order picture

- Protein is a set of local chemical bonds

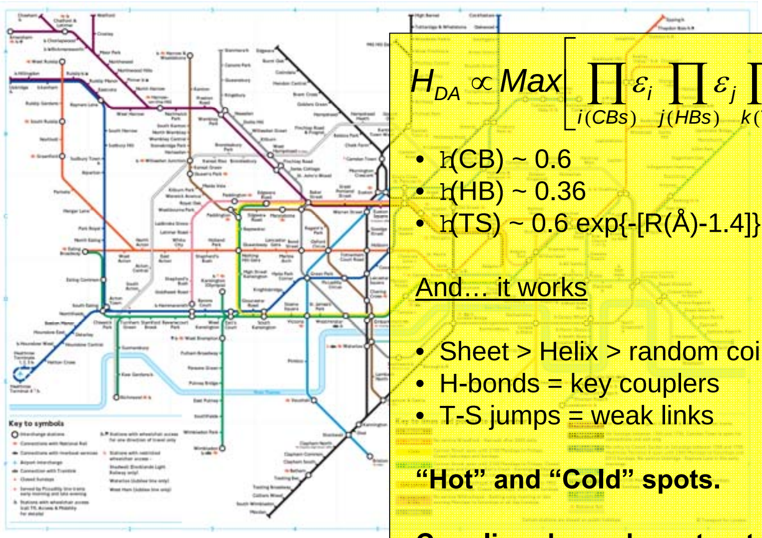
First-order picture

- Nearby bonds interact

Where does such a "chemical" picture lead?

Pathway Model:

Find the 'shortest' route from D to A



$$H_{DA} \propto Max\left[\prod_{i(CBs)}\varepsilon_i \prod_{j(HBs)}\varepsilon_j \prod_{k(TS)}\varepsilon_k\right]$$

- ε(CB) ~ 0.6
- ε(HB) ~ 0.36
- ε(TS) ~ 0.6 exp{-[R(Å)-1.4]}

And… it works

- Sheet > Helix > random coil
- H-bonds = key couplers
- T-S jumps = weak links

"Hot" and "Cold" spots.

Coupling depend on structure!

Ref: Beratan, Betts, Onuchic, 1991.

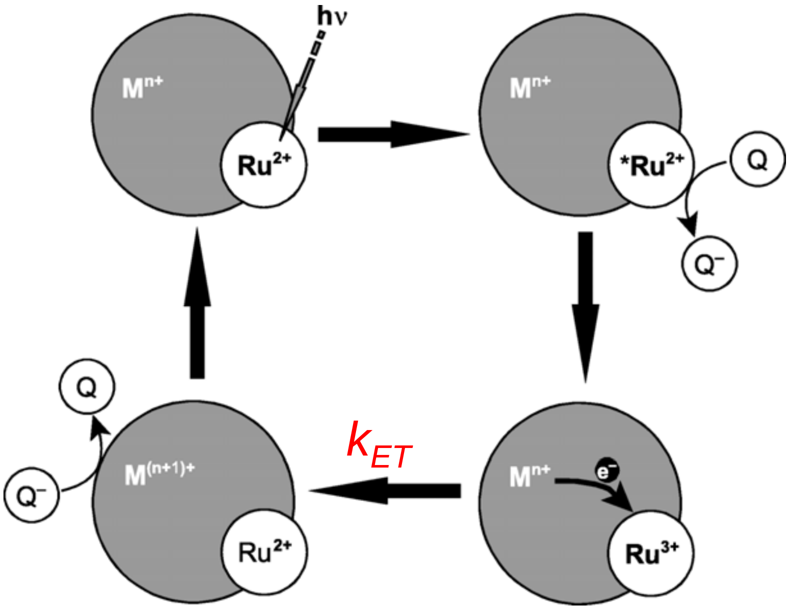
e-ology:

$$k_{ET} \propto |H_{DA}|^2 \propto \exp[-\beta R_{DA}]$$

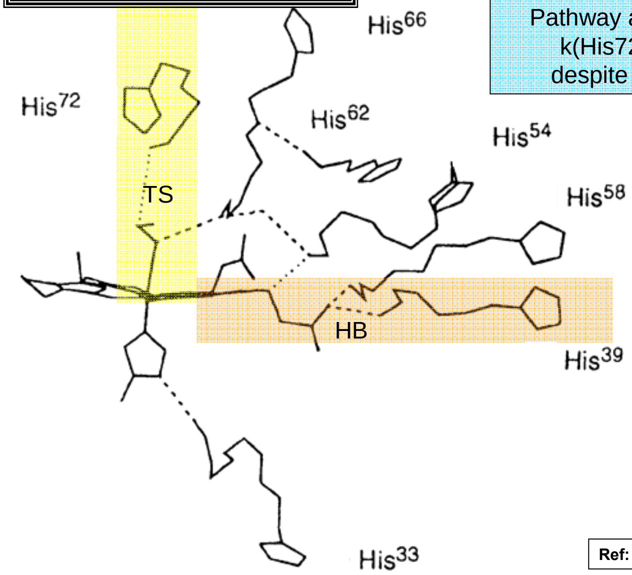
e-sheet[a]	e ~ 1.1 Å^{-1}
d-helix[a]	e ~ 1.4 Å^{-1}
Water (bulk)[b]	e ~ 1.6 Å^{-1}
Vacuum[c]	e ~ 2.4 Å^{-1}

a: pathway predictions of 1991 consistent with Gray's data from azurin and cytochrome b_{562}
b: measured by Gray (*Science,* 2005)
c: estimated from Gamov square barrier tunneling model

Flash-Quench Experiment: Winkler & Gray



The Gray-Winkler Experiment



Pathway analysis explains why
k(His72) = (1/3) k(His39),
despite 4Å closer distance.

Ref: Onuchic, Beratan,Winkler, Gray, 1992.

Pathway Model Success…

- Anomalously fast/slow rates predicted successfully
- Protein 2° structure effects $(\beta^{helix} > \beta^{sheet})$
- Predictive

Yet, we are troubled …

- Why are most (22 of 26) heme and Cu-proteins just “average” barriers – well described by the 1974 theory?

Beyond Pathways:

- Electrons are waves: need to add multi-path values together with correct signs
- Need explicit quantum models
- Should be general enough to describe pathway or average medium regime

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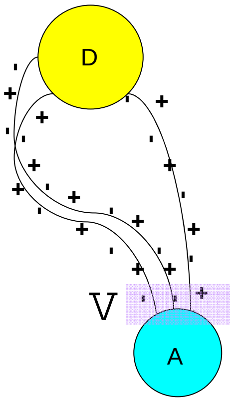
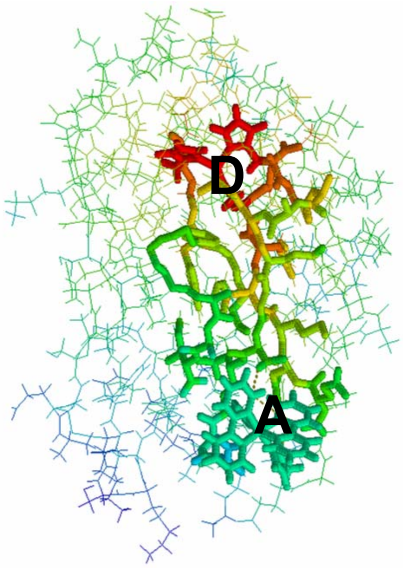
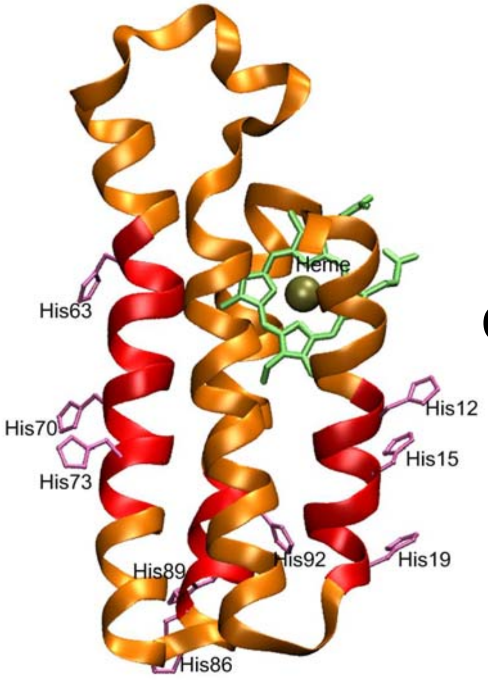
Multi-pathway methods



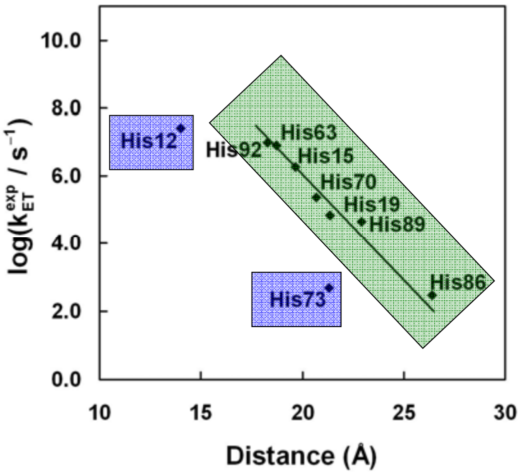


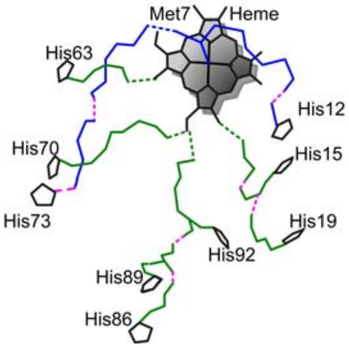
Ref: Skourtis & Beratan, *Adv. Chem. Phys.*, 1999.

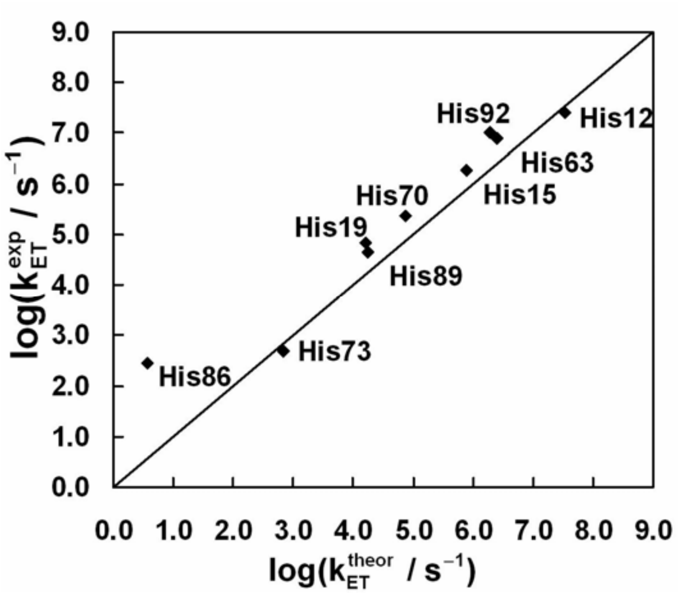


Test Case: Cytochrome b_{562}

Cytochrome b_{562}



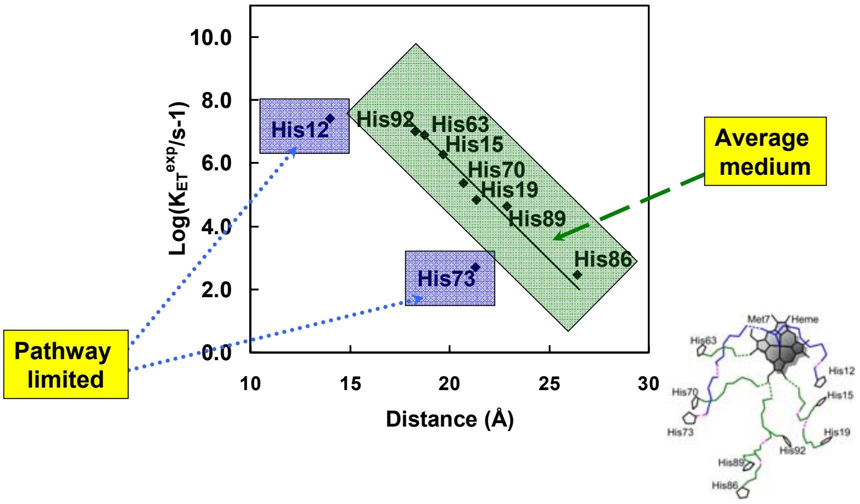




Recall Avg. Medium vs. Pathway Models:

Average Medium (1974)	**Pathway Regime**
• Only D-A distance matters • Rates drop rapidly with distance • All proteins are “the same”	• Protein structure determines rate • Rates drop rapidly with distance • The fold matters

► Are two coupling regimes possible?

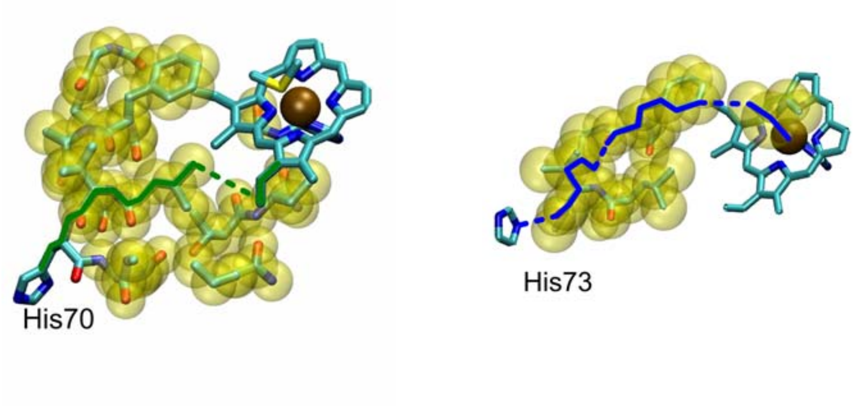


If two regimes, what aspects of structure lead:

to average medium?

to single pathway control?

Indeed, pruned structures are of two kinds:



Multi-path like (7/9)	**Single Path like (2/9)**
Fit by Avg. Medium model	**Weak Coupling for Distance**
Heme-Edge Coupled	**Axial-ligand Coupled**

Protein dynamics completes the picture…

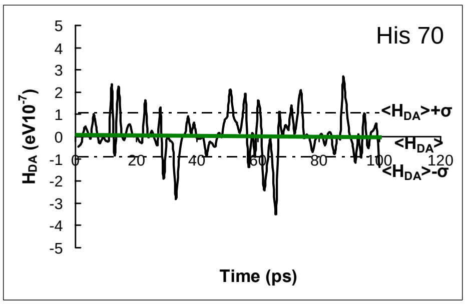
Quantifying Multi-path Effects…

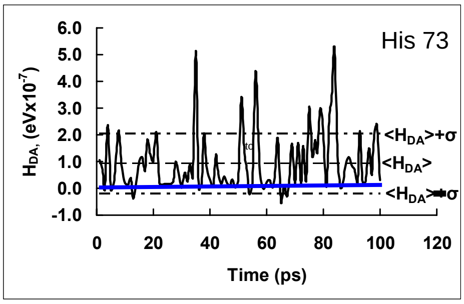
The Balabin-Onuchic parameter:

$$C = \frac{< H_{DA} >^2}{< H_{DA}^2 >}$$

Large *C*: Single path

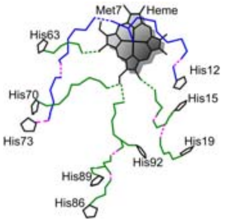
Small *C*: Multi-path





***Multi-Path* Behavior: Frequent zero crossings.**

$$\frac{< H_{DA} >^2}{< H_{DA}^2 >} = 4 \times 10^{-3}$$



$$\frac{< H_{DA} >^2}{< H_{DA}^2 >} = 0.5$$

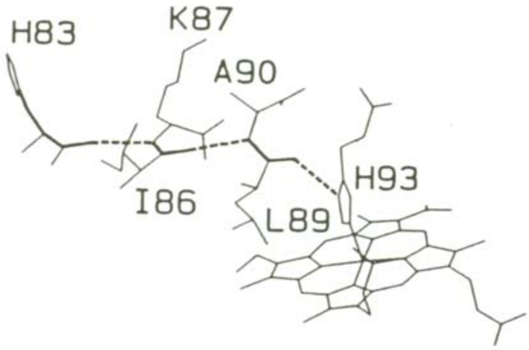
***Single Path* Behavior: Rare zero crossings.**

- **Small *C***
    - Dynamical averaging of multiple paths
    - Square barrier model works – structural details washed out
    - Macrocycle edge coupled
- **Large *C***
    - Structure matters and must be analyzed
    - Axial ligand coupled

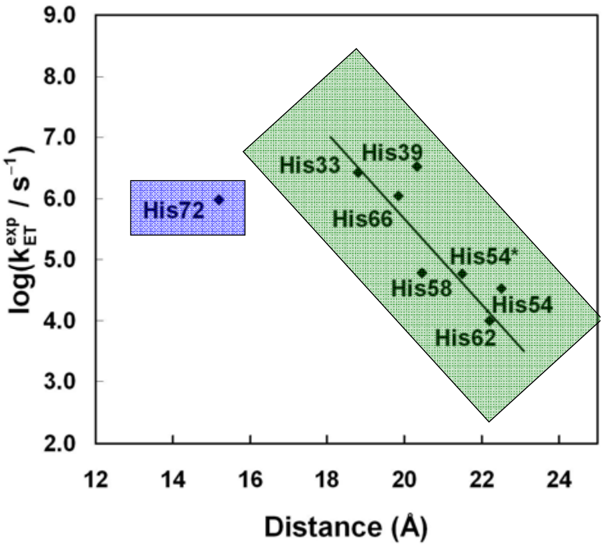
Is this view general?

Myoglobin

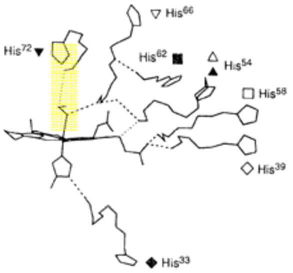
His83 is slow for its distance



Cytochrome *c*



His72 is slow for its distance

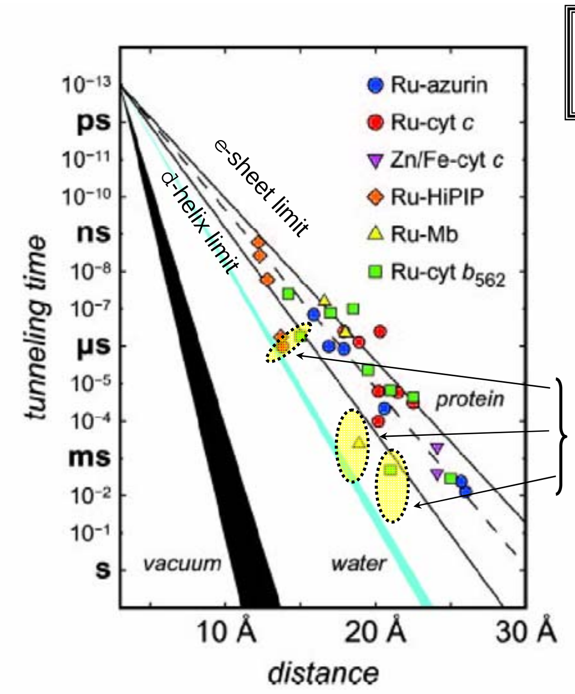


(also has edge routes)

Heme edge coupling

- All heme-**edge** coupled Winkler-Gray proteins are “**average**” (large target, multiple dynamically-averaged paths).
- All “**slow**” Winkler-Gray heme proteins are **axial**-ligand coupled (smaller target, single path).

The Gray-Winkler Ru-Proteins



ALL SLOW RATES ARE:

- **Axial Pathway Coupled**
- **Single Path Regime**
- **Have large *C* parameters (confirmed for b_{562})**

► A Unified View

- Single pathway regime ($C \sim 1$) is axial-ligand coupled and **requires structure-specific analysis to predict rates**. **Sparse pathways**.

- Multi-path coupling ($C << 1$) includes all heme-edge coupled derivatives and average decay models work. **Highly degenerate dynamically avg'd. paths.**

  The photosynthetic reaction center falls in this same regime.

  All azurin derivatives have small C too (degenerate routes through e-barrel?).

Summary: for 26 Ru-Proteins: 25 years worth of data!

- **4** slow Ru-heme proteins are *all* axial coupled (2 ◦ b_{562}; 1 ◦ myo; 1 ◦ cyt c). *C*'s are large. Single pathway regime.

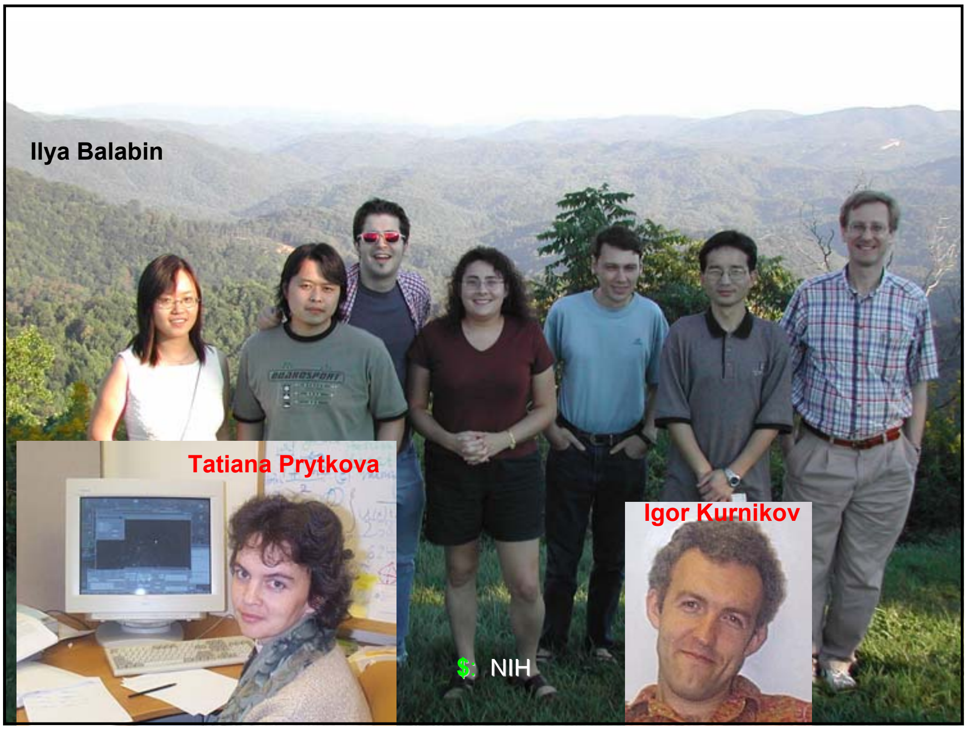
- **22** derivatives are single exponential with β characteristic of average protein fold. C's are small.

- Dynamical pathway averaging generates single-exponential decay with distance in **22** of 26 cases.

- Decay exponents predicted by pathway model –from 2° structure ($\Delta\beta \sim 0.3$ Å^{-1} for helix vs sheet)

- This is the physical framework. **Does evolution have a wiring preference?**

Prytkova, Kurnikov, Beratan, Science, Feb 2, 2007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