Electron transport in fluctuating biological media

Spiros S. Skourtis

Department of Physics, University of Cyprus
Nicosia Cyprus

Adventures in Theory Series

Duke Univ.

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Molecular Electron Transfer (ET) reactions

Ubiquitous in physical-chemical & biological processes

all oxidation/reduction reactions,
bioenergetics,
disease,
molecular-electronic devices (nano-bio)

Theoretically interesting

electron transport through
dynamic & responsive (floppy)
molecular media

Transport mechanisms of biological ET reactions

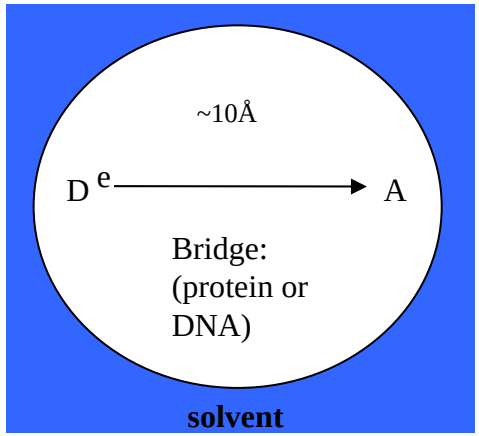
Coherent tunneling & resonant tunneling to thermally activated hopping

Main focus of talk is on tunneling ET reactions in proteins

Biological electron transfer (ET) reactions mediated by tunneling

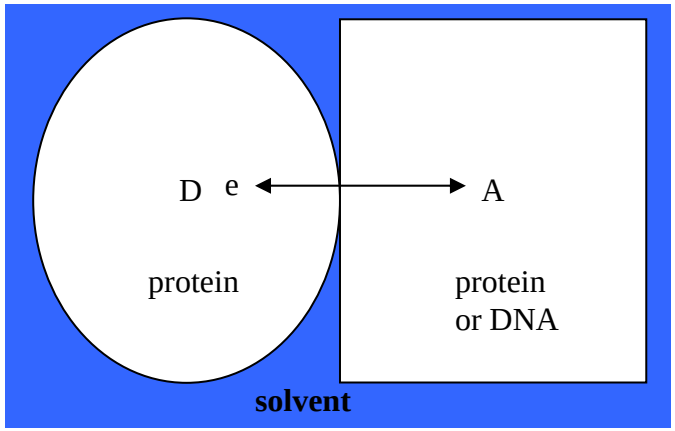
- Often long distance ET:

  The electron transfers from an initial localized (donor) state to a final localized (acceptor) state through intervening molecular matrix (bridge). Distance can be ~10Å



- Bridge:

  Protein and/or DNA,
  hundreds of atoms between donor/acceptor



- Donor (acceptor):

  metals atoms, small organic molecules, aminoacids, DNA bases

MAIN EXP. OBSERVABLE: <u>ET rate</u>
biological rates: $(psec)^{-1}$ or slower

Qualitative picture of molecular ET reactions mediated by tunneling

- Thermal fluctuations of molecule+solvent induce D-A resonance

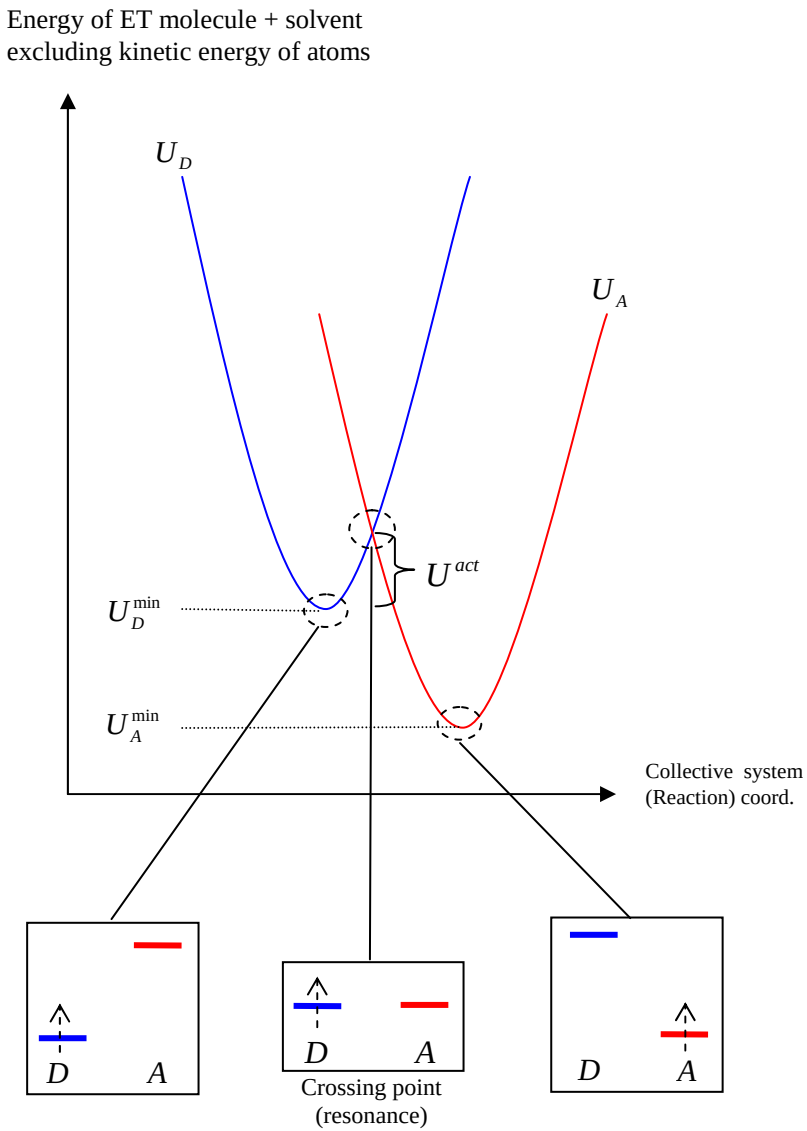
- ET by tunneling takes place at D-A resonance

- ET RATE:

$$k_{ET} \propto T_{DA}^{\ 2}\ e^{-U^{act}/K_B T}$$

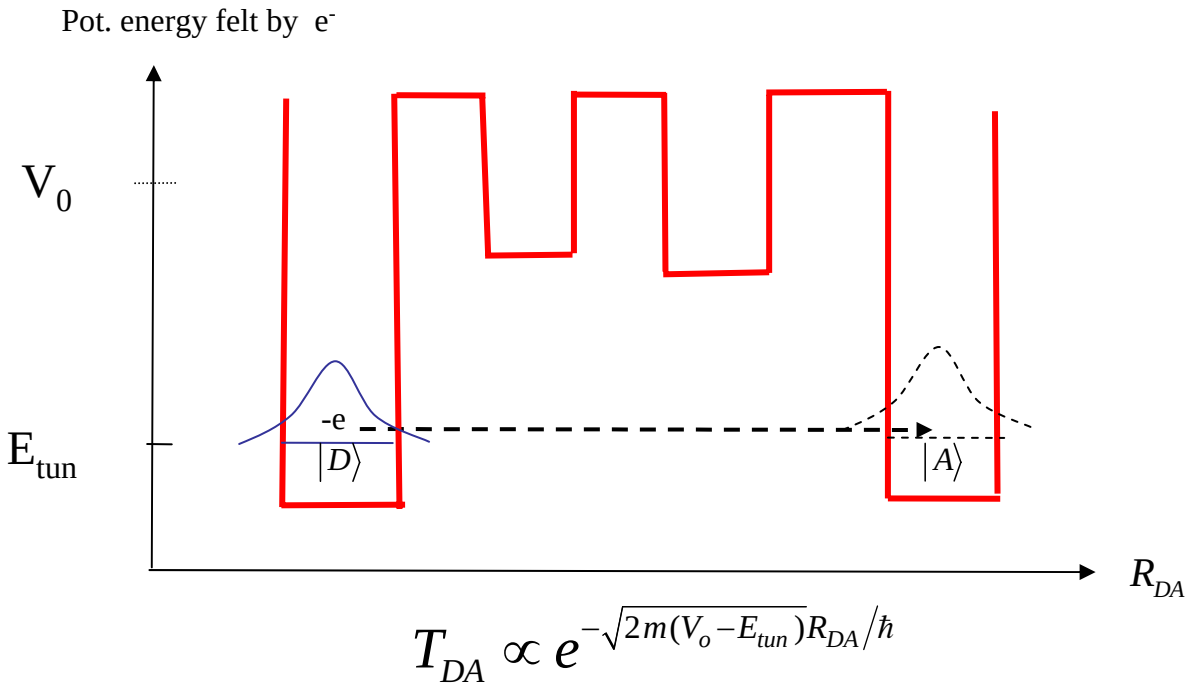
Tunneling matrix element (coupling) between D and A

Boltzmann factor for activation to resonance conformation



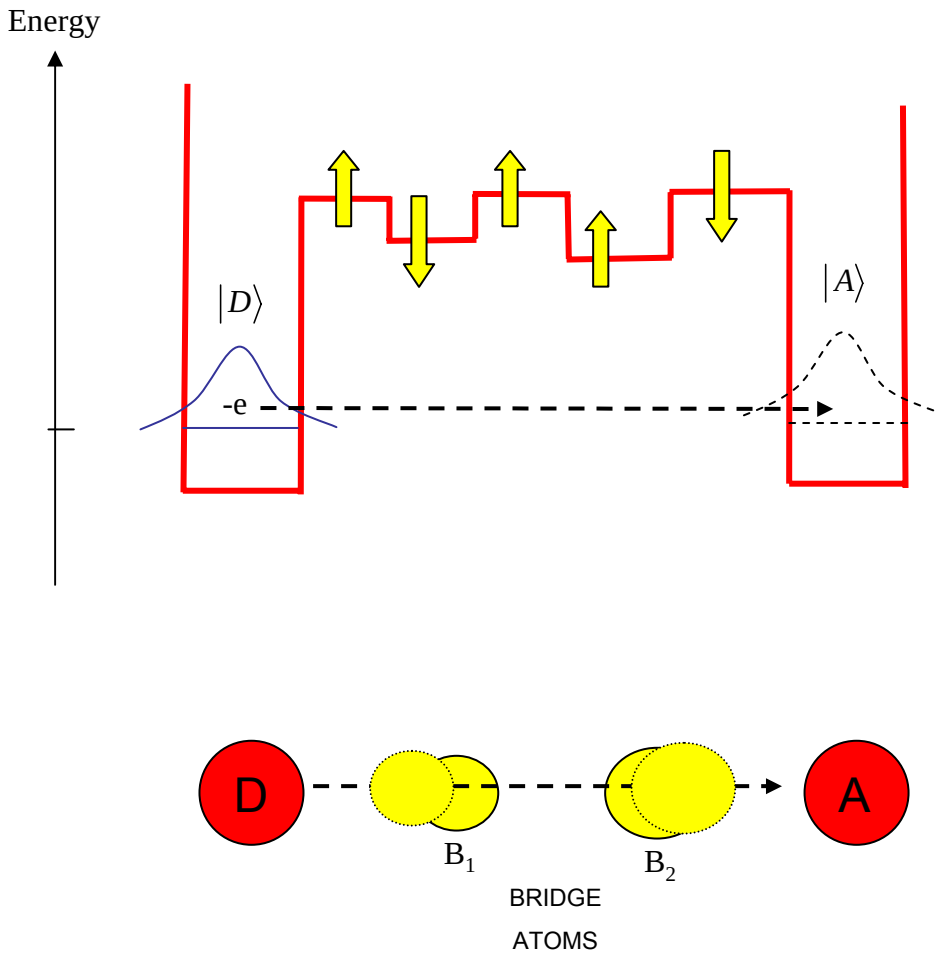
T_{DA}: Donor-Acceptor coupling (tunneling matrix element)

Bridge atoms lower tunneling barrier and enhance the Donor-Acceptor coupling



Biomolecules are **very floppy**: Fluctuating barrier tunneling

Bridge thermal motion → Fluctuating tunneling matrix element: $T_{DA}(t)$

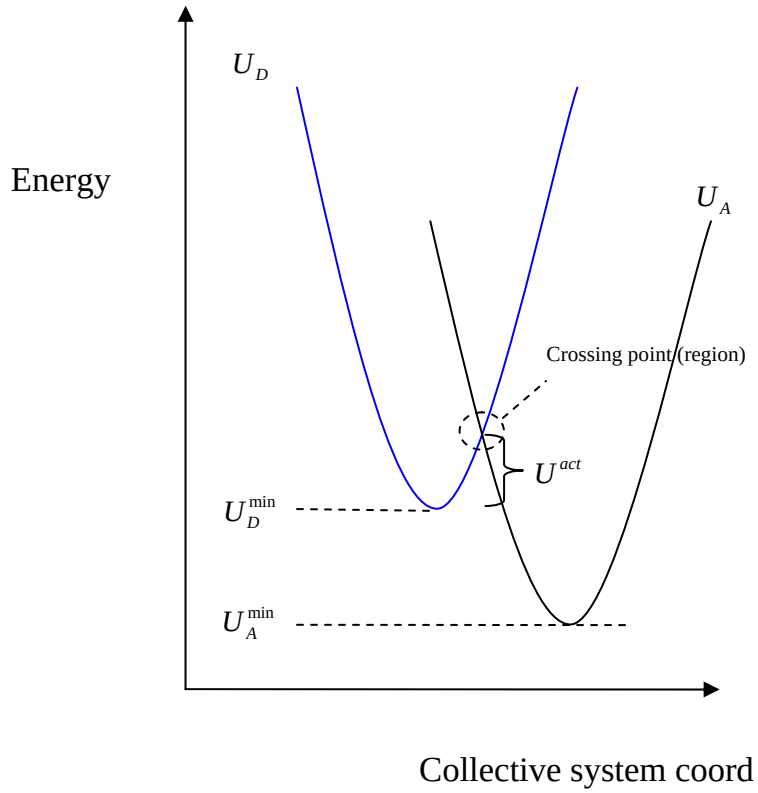


ET rate for a fluctuating tunneling matrix element

In high-temp limit:

$$k_{ET} = \frac{2\pi}{\hbar}\left\langle T_{DA}{}^{2}\right\rangle \rho_{FC}$$

Average of $T_{DA}{}^{2}$ over diff. molecular conformations



FC factor

$$\rho_{FC} = \frac{1}{\sqrt{2\pi\ \sigma_{\Delta U}{}^{2}}} \exp\left[-U^{act}/\mathrm{K}_B T\right]$$

rms fluctuation in the D-A energy gap: U_D-U_A

Some central questions
of interest to theory and experiment
(addressed in this talk)

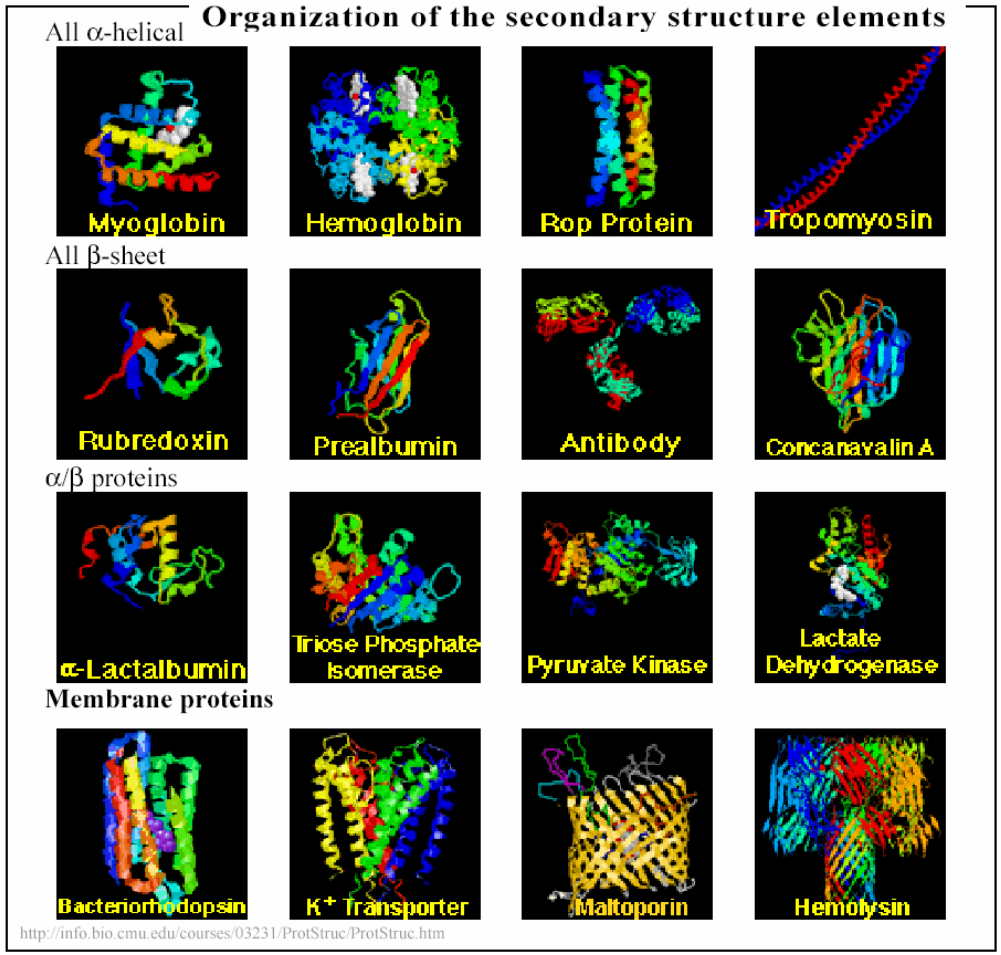
How does electron tunneling ($\langle T_{DA}^2 \rangle$) depend on:

- The structure of the ET biomolecule
- The dynamics of the ET biomolecule
- The nature of the D and A states

Dependence of electron tunneling on biomolecular structure

Different proteins have different structures (folds)

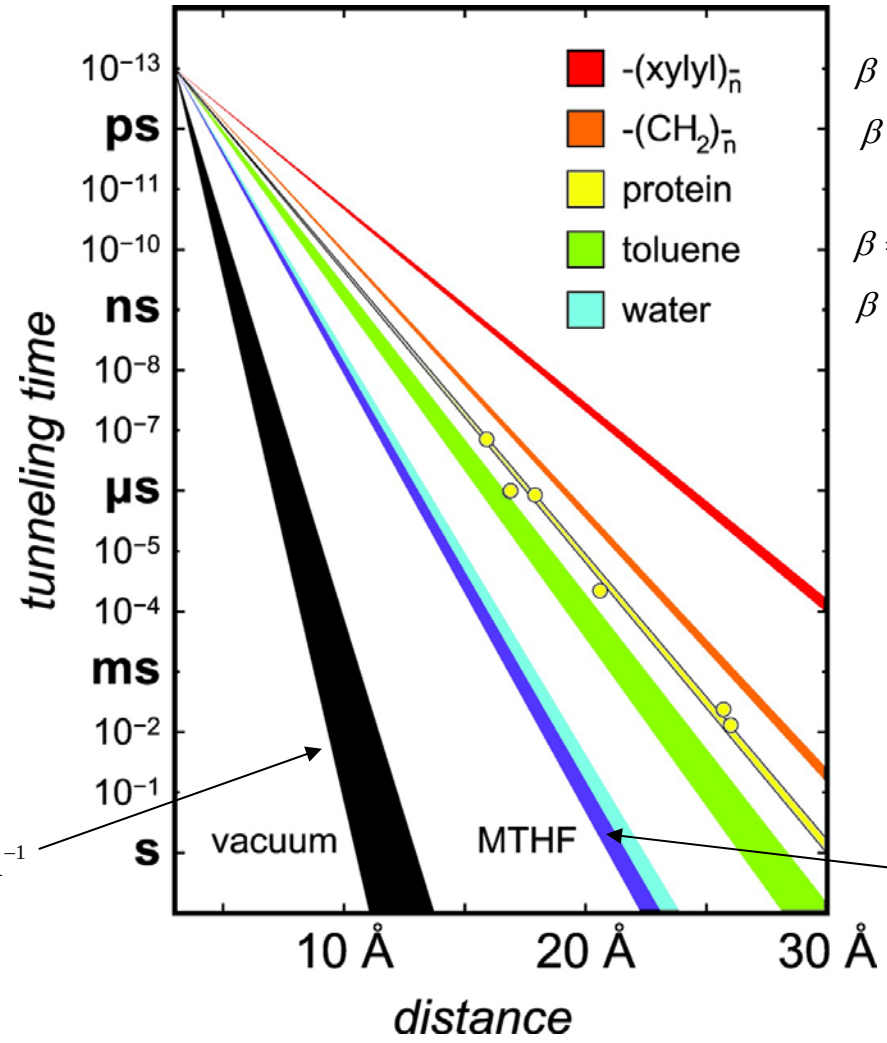
Protein Data Bank @ http://www.pdb.org/



Proteins vs other media

$$k_{ET} \propto T_{DA}^{\ 2}$$
$$T_{DA}^{\ 2} \propto e^{-2\beta R_{DA}}$$

activationless $\longrightarrow \frac{1}{k_{ET}}$



$\beta = 0.76 Å^{-1}$ (covalent, π)

$\beta = 1.0 Å^{-1}$ (covalent, σ)

$\beta = 1.18 - 1.28 Å^{-1}$ (glass, VdW, π)

$\beta = 1.55 - 1.65 Å^{-1}$ (glass H-bond, σ)

$\beta = 2.9 - 4.0 Å^{-1}$

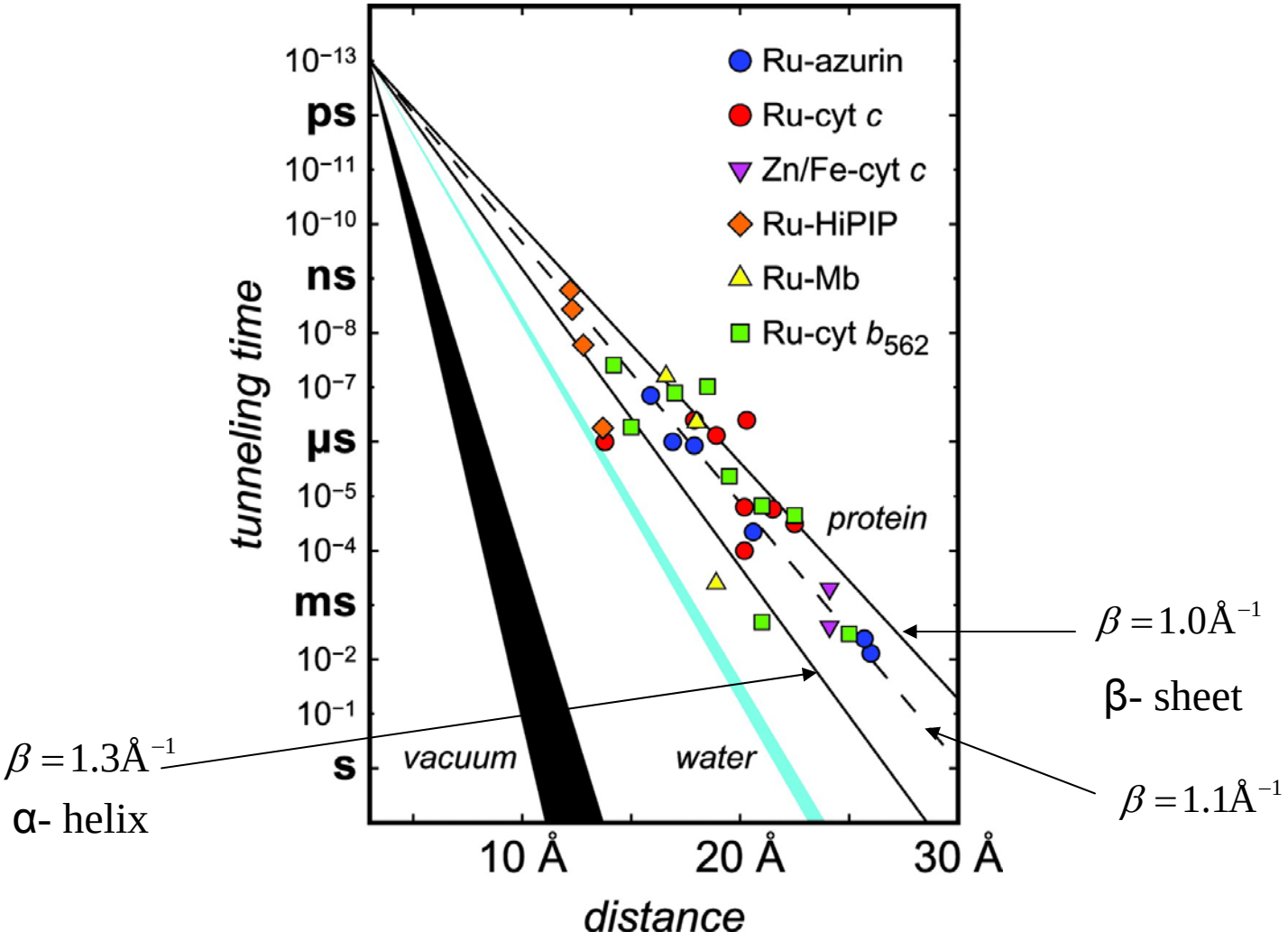
$\beta = 1.57 - 1.67 Å^{-1}$ (glass, VdW, σ)

Gray H. B., Winkler J. R. PNAS 2005;102:3534-3539

PNAS

Protein ET systems

(large rate scatter)



Gray H. B., Winkler J. R. PNAS 2005;102:3534-3539

Structure-function analysis of T_{DA}

Input: experimental protein structure →

Hamiltonian/Fock matrix →

Quantum electronic structure calculations

- **Computation of T_{DA}**
  - Effective Hamiltonian & Green's function methods
  - Energy-splitting methods
  - Mulliken-Hush methods (excited state calcs)
- **Analysis of T_{DA}**
  - Green's function tunneling pathways
  - Tunneling currents
  - Substitutions & pruning

Reviews

- *S.S. Skourtis and D.N. Beratan Adv. Chem. Phys. 106, 377 (1999)*

- *M.D. Newton, in: Electron Transfer in Chemistry, Vol I, Ed. V. Balzani, Wiley-VCH Verlag GmbH: Weinheim, Germany p. 3. (2001)*

- *A.A. Stuchebrukhov Adv. Chem. Phys. 118, 1 (2001)*

- *N. Roch & A.A. Voityuk, in: Long-Range Electron Transfer in DNA Vol II, ed. G. Schuster Top. Curr. Chem. P. 37 (2004)*

Tunneling pathway decomposition of T_{DA}

$$T_{DA} = \langle D | \hat{T} | A \rangle$$

where

$$\hat{T} = \hat{V}\ \hat{G}^{(B)}\left(E_{tun}\right)\ \hat{V}$$

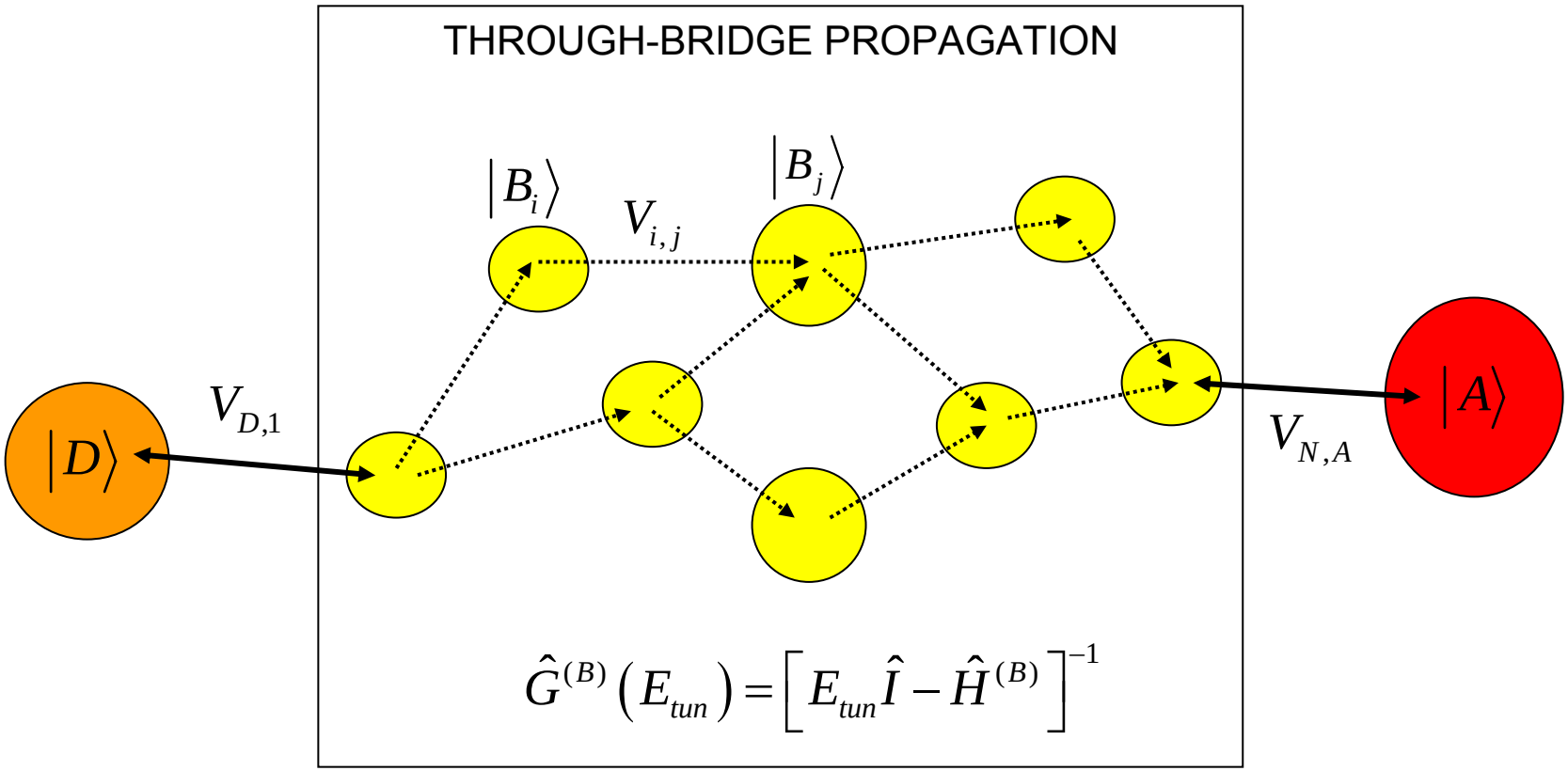
and

$$\hat{G}^{(B)}\left(E_{tun}\right) = \left[E_{tun}\hat{I} - \hat{H}^{(B)} \right]^{-1}$$

Bridge Green's function operator

Tunneling energy

Very useful for the interpretation of tunneling in terms of bridge structure



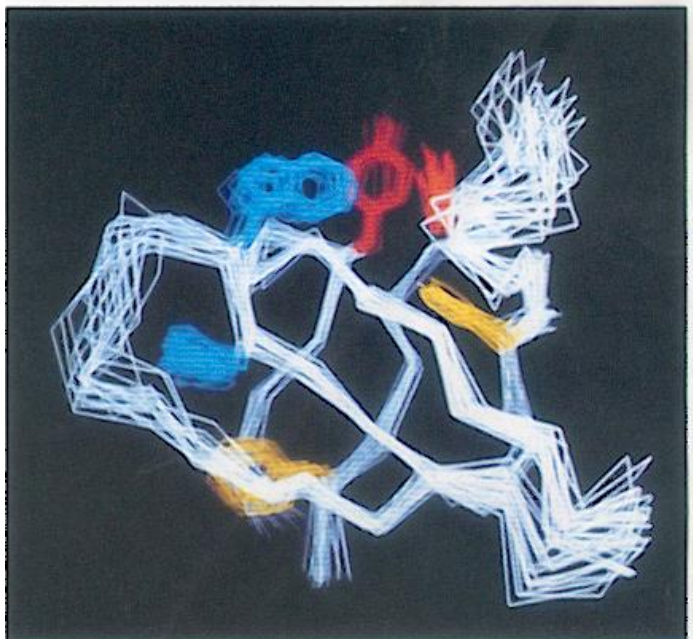
$$\langle D|\hat{T}|A\rangle = \langle D|\hat{V}\ \hat{G}^{(B)}(E_{tun})\ \hat{V}|A\rangle$$

Dependence of tunneling on molecular dynamics

Review

S.S. Skourtis, J. Lin, and D. N. Beratan
The effects of bridge motion on electron transfer reactions mediated by tunneling
Modern methods for Theoretical Physical Chemistry of Biopolymers,
E. B. Starikov, S. Tanaka, and J. P. Lewis, editors, Elsevier, pp. 357-379 (2006)

A protein fluctuates around its structure



Time scales of structural fluctuations: tens of fsec to μsec/msec

Size of structural fluctuations: a few to tens of Angstroms

Are static methods transferable to time dep. systems?

When and how do they become bad approximations?

How does one compute time dep. pathways?

- Analytical work
- Simulations of simple tight-binding models
- Simulations of the protein azurin (molecular dynamics+electronic structure)

- *A. Teklos and S. S. Skourtis Chem. Phys. 319, 52-68 (2005)*
- *S. S. Skourtis Chem. Phys. Lett. 372, 224-231 (2003)*
- *S. S. Skourtis, G. Archontis and Q. Xie J. Chem. Phys. 115, 9444-9462 (2001)*
- *Q. Xie, G. Archontis and S. S. Skourtis Chem. Phys. Lett. 312, 237-246 (1999)*

Molecular-dynamics (MD) simulations coupled to quantum electronic-structure calculations

- MD simulations →

  ensemble of molecular conformations

For each molecular conformation

- Electronic-structure calculations →

  Input for computation of:

-Electron donor and acceptor states

-Tunneling matrix element T_{DA}

-Tunneling pathway analysis

T_{DA} fluctuation effects

$$\left\langle T_{DA}{}^2 \right\rangle = \left\langle T_{DA} \right\rangle^2 + \sigma_{T_{DA}}{}^2$$

$\sigma_{T_{DA}}{}^2 << \left\langle T_{DA} \right\rangle^2$

SMALL T_{DA} fluctuations

EQUILIBRIUM MOLECULAR STRUCTURE DETERMINES STRONG ET PATHWAYS

$$k_{DA} \approx \frac{2\pi}{\hbar} \left\langle T_{DA} \right\rangle^2 \rho_{FC}$$

Static calculation of T_{DA} is OK

(e.g., for minimum energy conformation)

$\sigma_{T_{DA}}{}^2 >> \left\langle T_{DA} \right\rangle^2$

LARGE T_{DA} fluctuations

NON-EQUILIBRIUM MOLECULAR STRUCTURES DETERMINE STRONG ET PATHWAYS

$$k_{DA} = \frac{2\pi}{\hbar} \left\langle T_{DA}{}^2 \right\rangle \rho_{FC}$$

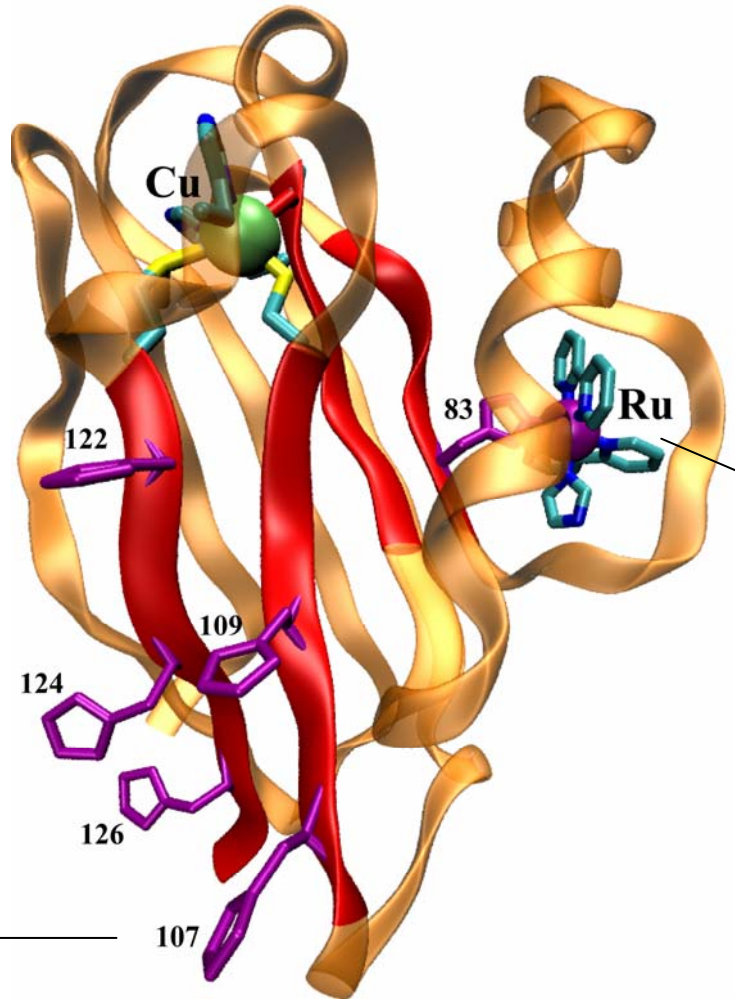
Rate is determined by non-equil. conformations with strongest T_{DA}

Extensive MD sampling is necessary

T_{DA} fluctuation effects in the ET protein azurin

S.S. Skourtis, I. Balabin, T. Kawatsu, and D.N. Beratan Proc. Natl. Acad. Sci. USA 102, 3552 (2005)

$$\frac{\sigma_{T_{DA}}^{2}}{\langle T_{DA} \rangle^{2}} > 10$$



$R_{DA} \approx 17$ A

$T_{DA}^{rms} \approx 10^{-5} eV$

$k_{D\to A}^{-1} \approx 10^{-6}$ sec

$R_{DA} \approx 26$ A

$T_{DA}^{rms} \approx 10^{-8} eV$

$k_{D\to A}^{-1} \approx 10^{-2}$ sec

Fluctuations become important for large donor-acceptor distances

Critical distance R_c

$R_{DA} < R_c$

$\sigma_{T_{DA}} < \langle T_{DA} \rangle$

$R_{DA} > R_c$

$\sigma_{T_{DA}} > \langle T_{DA} \rangle$

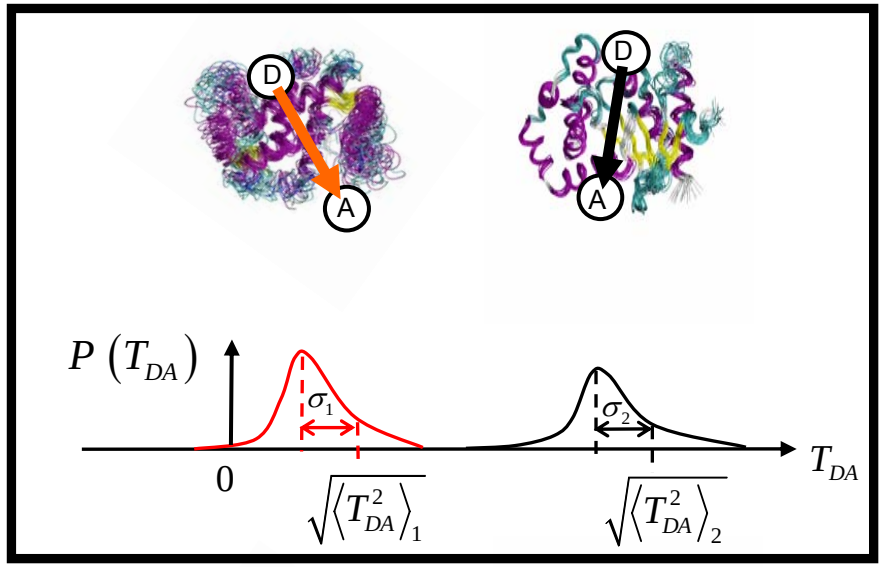
Water-mediated tunneling R_c = 2-3 Angstroms

Protein-mediated tunneling R_c = 6-7 Angstroms

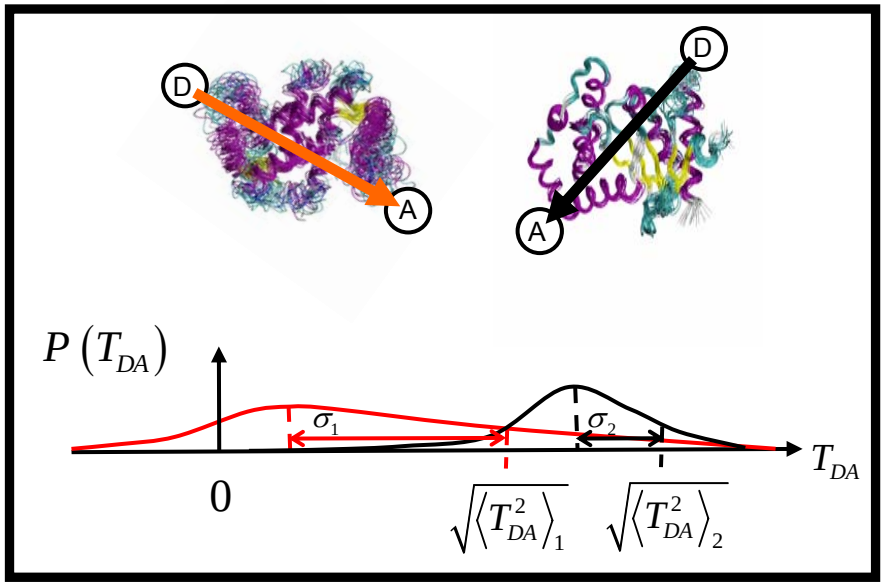
Do fluctuations wash out structural differences?

I. Balabin, D.N. Beratan and S.S. Skourtis (submitted)

Fluctuations do not wash out structural differences



Fluctuations do wash out structural differences



FLUCTUATIONS DO NOT WASH OUT STRUCTURAL DIFFERENCES IN PROTEINS

(FLUCTUATIONS DEPEND ON STRUCTURE)

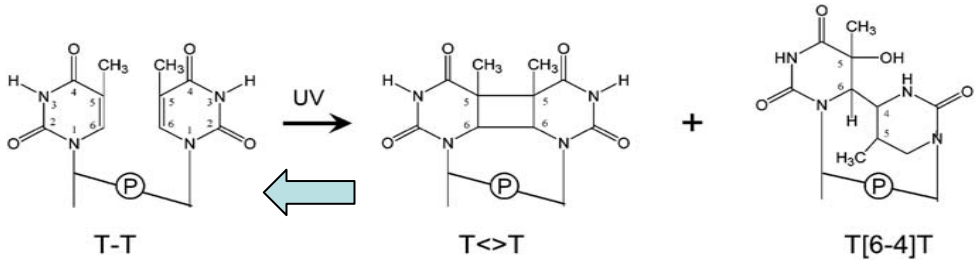
Dependence of tunneling on the electron donor and electron acceptor states

Excited-state ET → Electron donor state is photo-prepared

DNA photolyase

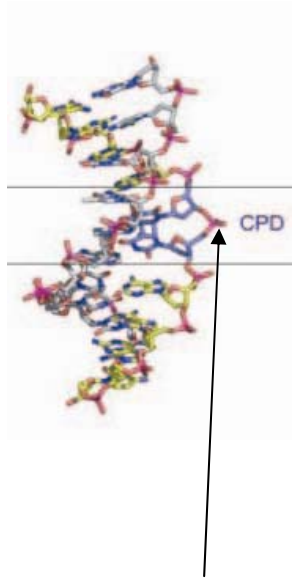
Electron transfer protein
that repairs UV-damaged DNA
upon absorption of a photon

- Absorption of UV radiation by DNA can lead to the creation of pyrimidine dimers



A. Shancar *Chem. Rev*. 103, 2203-2237 (2003)

- A pyrimidine dimer distorts DNA & interferes with DNA replication



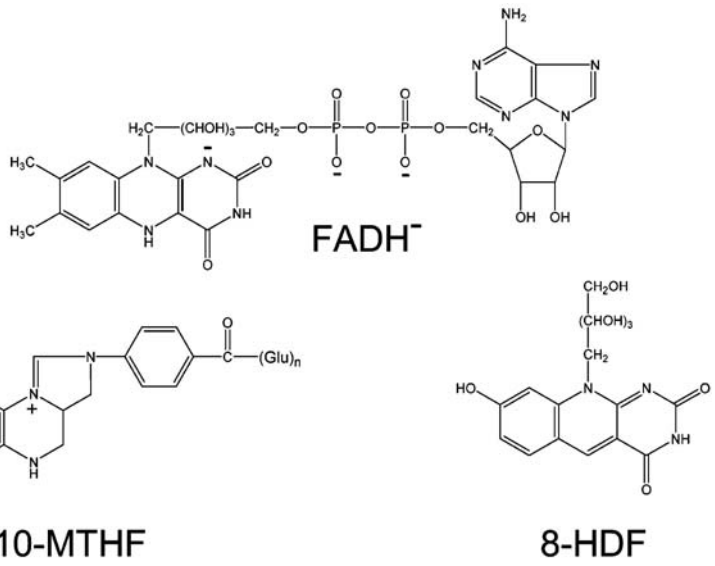
A. Mees et al. *Science* 306, 1789-1793 (2004)

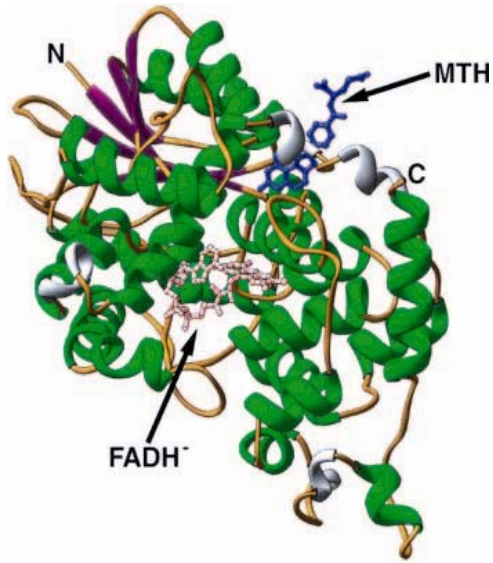
- DNA photolyase binds to DNA & repairs the damaged dimer

Protein contains:

An electron donor molecule ($FADH^-$)

An antenna molecule (5-10 MTHF or 8-HDF)



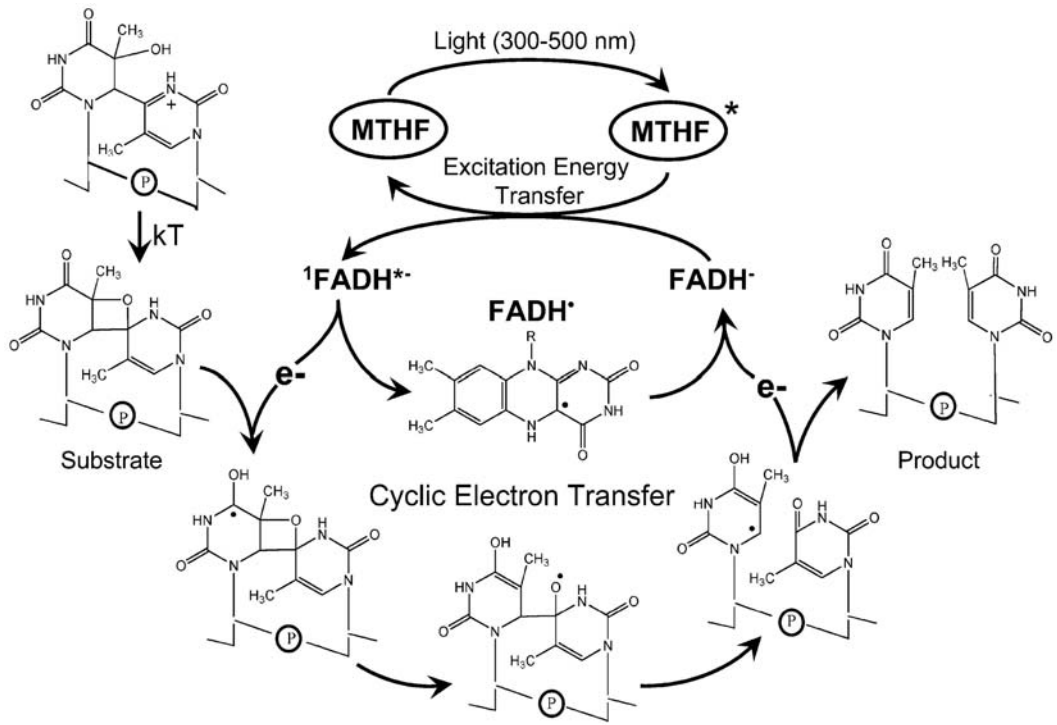


A. Shancar *Chem. Rev*. 103, 2203-2237 (2003)

Mechanism of DNA repair

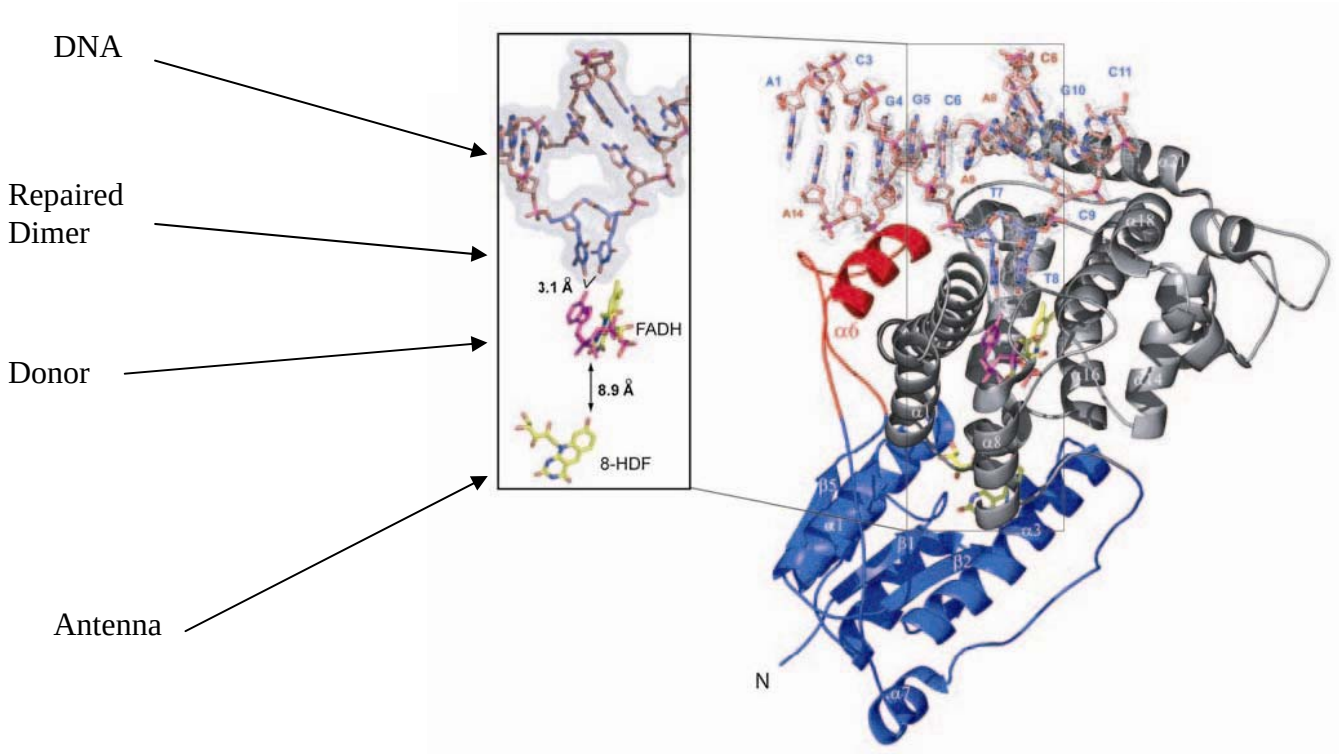
- Protein binds to DNA at the position of the dimer
- Antenna molecule absorbs a photon (350-500 nm)
- Antenna transfers energy to electron donor molecule
- Donor molecule transfers an electron to the dimer
- Injection of electron initiates dimer repair

The Photo-repair Cycle



A. Shancar *Chem. Rev*. 103, 2203-2237 (2003)

The structure of a DNA photolyase bound to a DNA oligomer (2004)



A. Mees et al. *Science* 306, 1789-1793 (2004)

Examination of ET mechanism

T. Prytkova, D.N. Beratan and S.S. Skourtis *Proc.Natl. Acad. Sci. USA* *104, 802 (2007)*

- MD simulations of protein with thymine dimer in the active site

  Amber 8.0

- Calculation of the excited electron donor state in $FADH^-$

- Calculation of $FADH^-$ - dimer $\langle T_{DA}^2 \rangle$

- Structure-function analysis of $\langle T_{DA}^2 \rangle$

Excited-state calculations of $FADH^{-*}$ elec. donor state

Methods:

- Intermediate Neglect of Differential Overlap/Configuration Interaction Singles (INDO/S CIS)

- Time Dependent Density Functional Theory (TDDFT)

  B3LYP, BHandHLYP 6-31+G(d)

- Time Dependent Hartree-Fock Theory (TDHF), CIS

Solvated $FADH^-$ in the protein active-site environment (represented by atomic point charges)

T_{DA} calculations

Methods:

- INDO/S

  Green's function, energy splitting, generalized Mulliken-Hush

- Rms T_{DA} computed by averaging over MD trajectories

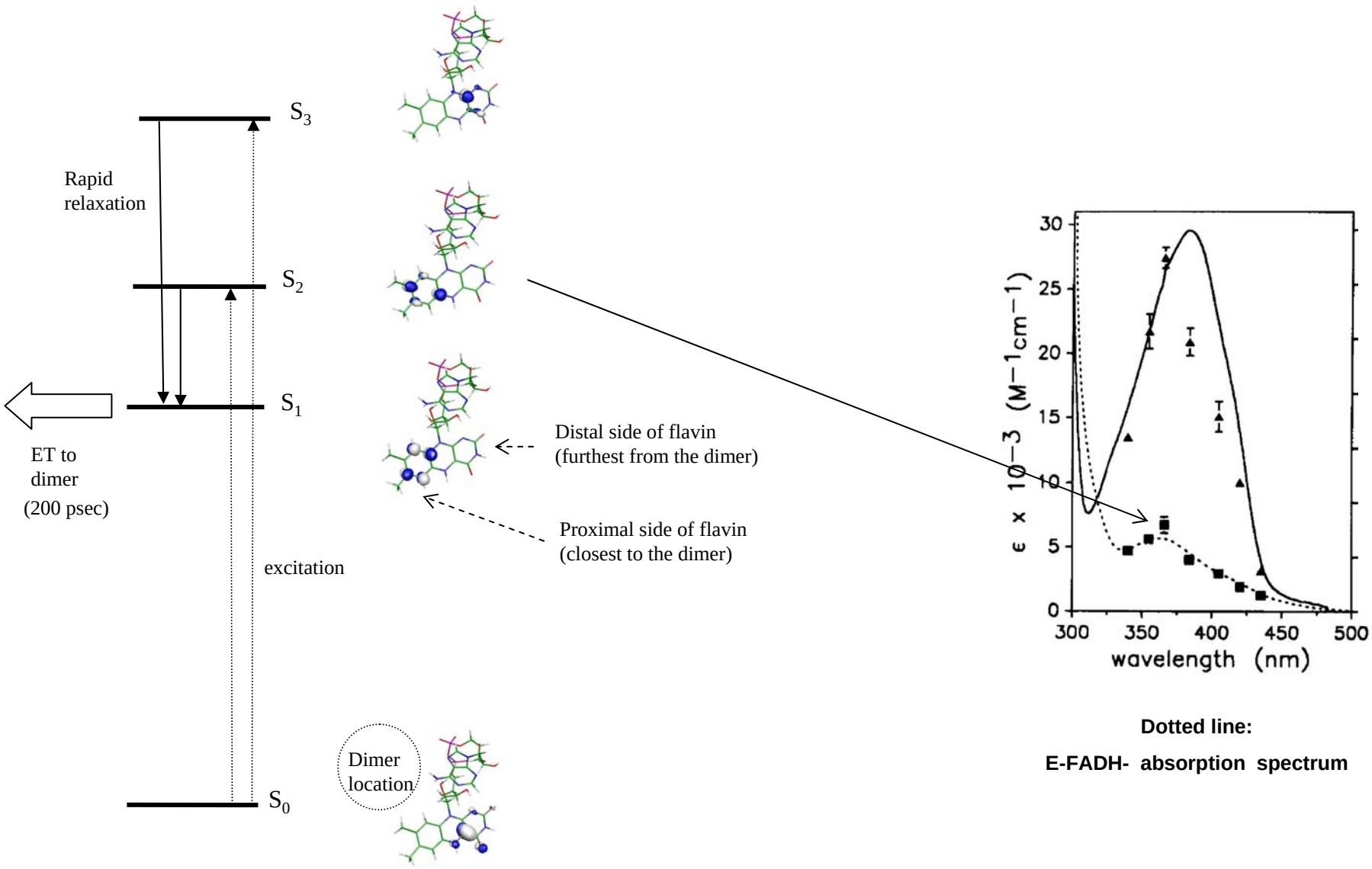
- Tunneling pathway analysis:

  Modified-donor-cofactor approach

Excited state calculation results

Photo-excitation shifts the donor electron next to the thymine dimer

($\pi \rightarrow \pi^*$ charge transfer transition of flavin ring)



Dotted line:

E-FADH- absorption spectrum

T_{DA} calculation results

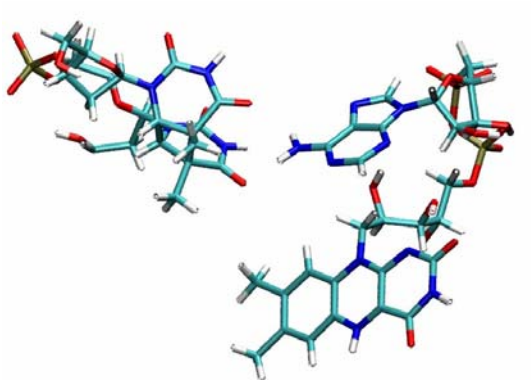
The $\pi \rightarrow \pi^*$ charge transfer transition

enhances T_{DA} & determines the ET pathways

The excited electron directly tunnels to the dimer mainly through CH_3

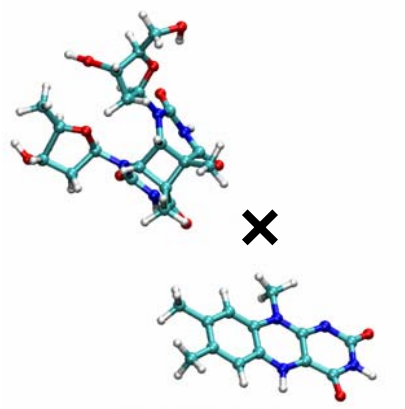
Dimer – Full $FADH^-$ system

$T_{DA}^{rms} \approx 5\times10^{-4} eV$



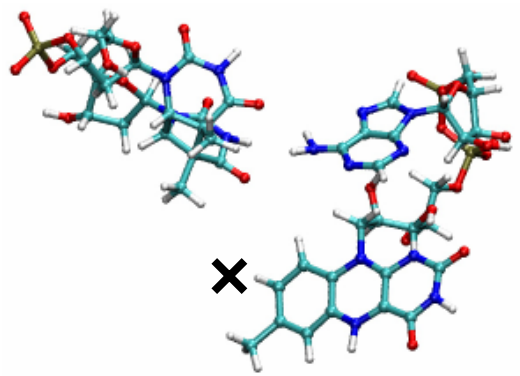
Dimer – $FADH^-$(no adenine)

$T_{DA}^{rms} \approx 5\times10^{-4} eV$



Dimer – $FADH^-$(no CH_3)

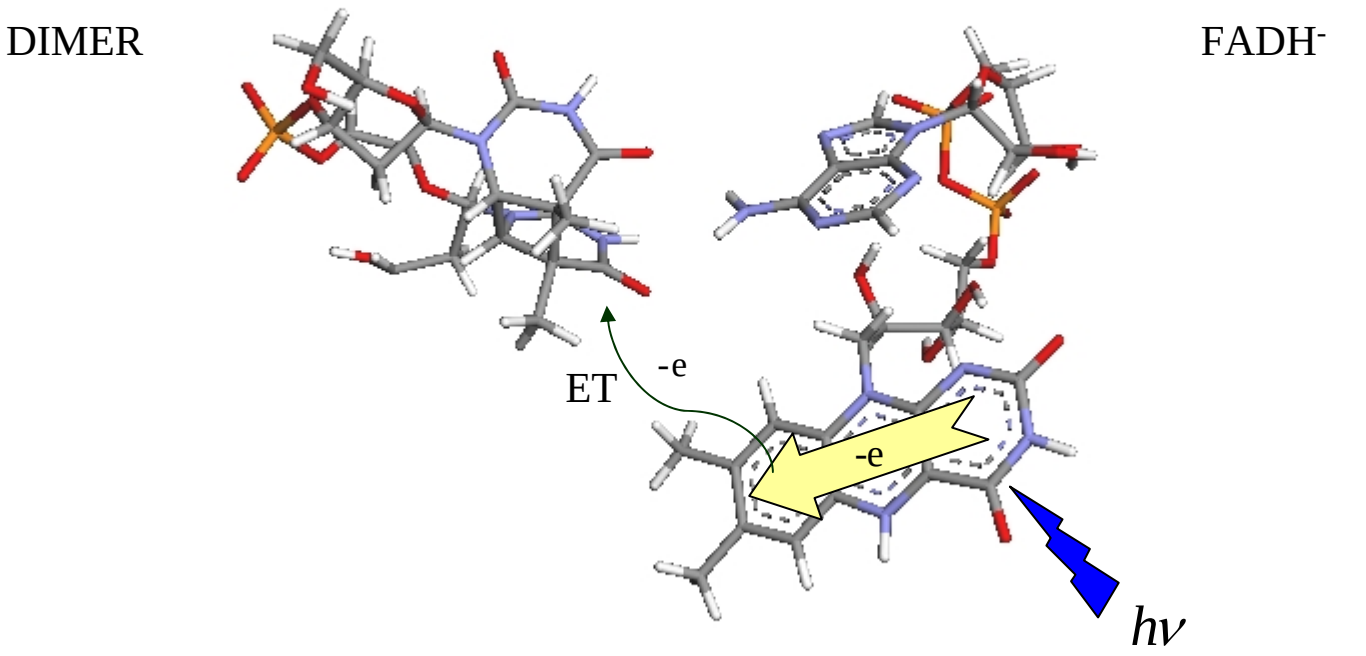
$T_{DA}^{rms} \approx 1\times10^{-4} eV$



Conclusion

Photo-selected tunneling pathways

In DNA Photolyase the photo-excitation itself enhances the electronic coupling between $FADH^-$ and the thymine dimer

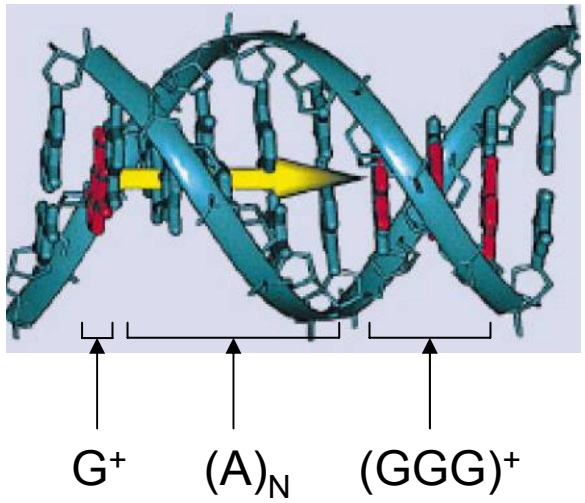


Experimental rate = $(230)^{-1}$ $psec^{-1}$

Max Predicted rate ~$(200)^{-1}$ $psec^{-1}$

Some open and interesting theoretical & computational problems

DNA electron transfer



B.Giese et al. (Nature 412, 318-320 (2001))

$G^+ (A)_N (GGG) \rightarrow G (A)_N (GGG)^+$

Different ET mechanisms working in parallel

tunneling

resonant tunneling

thermally activated hopping

E. Hatcher, A. Balaeff, S. Keinan, R. Venkatarami, and D.N. Beratan (JACS) In press

How does one calculate the ET rate?

Important for understanding the dependence of DNA ET rate on:

- donor-acceptor distance
- donor-acceptor energetics
- sequence
- structural motions
- temperature

Reviews::

R.G. Enders, D.L. Cox, and R.P. Singh Rev. Mod. Phys. 76, 195-214 (2004)

Long-Range Electron Transfer in DNA Vols I-II, ed. G. Schuster Top. Curr. Chem. (2004)

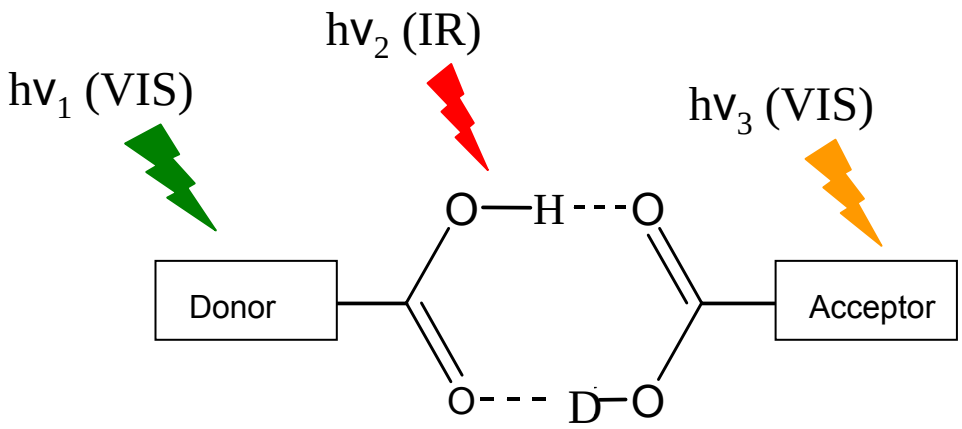
ET control / ET molecular devices

Molecular double-slit paradigm:

Manipulate ET pathways by
IR excitation of pathway-specific vibration

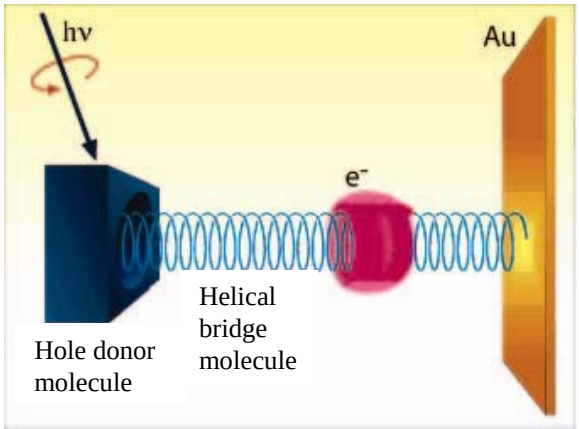
S.S. Skourtis, D.H. Waldeck and D.N. Beratan JPC B 108, 15511-15518 (2004)

D. Xiao, D.N. Beratan, S.S. Skourtis (to be submitted)



Chiral control of electron transmission through molecules

The transmission through helical bridges of electrons carrying angular momentum depends on the bridge handedness



S.S. Skourtis, D.N. Beratan , R. Naaman, A. Nitzan D.H. Waldeck (to be submitted)

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Dr. B. Desinghu

D. Xiao

H. Carias

Cyprus

Prof. G. Archontis

Dr Q. Xie

A. Teklos

C. Aristi

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