Electron transport in fluctuating biological media

Spiros S. Skourtis

Department of Physics, University of Cyprus
Nicosia Cyprus

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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: ET rate 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:

\[ k_{ET} \propto T_{DA}^2 e^{-U_{act}/K_BT} \]

\[ D \quad A \]

Tunneling matrix element (coupling) between D and A

Boltzmann factor for activation to resonance conformation

Energy of ET molecule + solvent excluding kinetic energy of atoms

Collective system (Reaction) coord.

Crossing point (resonance)
**$T_{DA}$**: Donor-Acceptor coupling
(tunneling matrix element)

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

\[ T_{DA} \propto e^{-\frac{\sqrt{2m(V_0 - E_{tun})R_{DA}}}{\hbar}} \]

Pot. energy felt by $e^{-}$

\[ V_0 \]

\[ E_{tun} \]

\[ R_{DA} \]

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**Diagram:**

- Donor (D)
- Acceptor (A)
- Bridge atoms (B₁, B₂)
- Tunneling barrier
- Potential energy levels $V_0$
- Tunneling energy $E_{tun}$
- Distance $R_{DA}$

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**Equation:**

\[ T_{DA} \propto e^{-\frac{\sqrt{2m(V_0 - E_{tun})R_{DA}}}{\hbar}} \]
Biomolecules are very floppy: Fluctuating barrier tunneling

Bridge thermal motion $\rightarrow$ 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

\[ \rho_{FC} = \frac{1}{\sqrt{2\pi \sigma_{\Delta U}^2}} \exp\left[-\frac{U^{act}}{K_B T}\right] \]

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 ($<T_{DA}^2>$) 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/](http://www.pdb.org/)
Proteins vs other media

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

activationless \[ \frac{1}{k_{ET}} \]

\[ \beta = 2.9 - 4.0 \text{Å}^{-1} \]
\[ \beta = 0.76 \text{Å}^{-1} \] (covalent, \(\pi\))
\[ \beta = 1.0 \text{Å}^{-1} \] (covalent, \(\sigma\))
\[ \beta = 1.18 - 1.28 \text{Å}^{-1} \] (glass, VdW, \(\pi\))
\[ \beta = 1.55 - 1.65 \text{Å}^{-1} \] (glass H-bond, \(\sigma\))

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Protein ET systems
(large rate scatter)

\[ \beta = 1.3 \text{Å}^{-1} \]
\[ \beta = 1.0 \text{Å}^{-1} \]
\[ \beta = 1.1 \text{Å}^{-1} \]

\( \alpha \)-helix
Structure-function analysis of $T_{DA}$

Input: experimental protein structure \( \rightarrow \)

Hamiltonian/Fock matrix \( \rightarrow \)

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


Tunneling pathway decomposition of $T_{DA}$

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

where

$\hat{T} = \hat{\mathcal{V}} \; \hat{G}^{(B)}(E_{tun}) \; \hat{\mathcal{V}}$

and

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

Very useful for the interpretation of tunneling in terms of bridge structure
\[ \hat{G}^{(B)}(E_{\text{tun}}) = \left[ E_{\text{tun}} \hat{I} - \hat{H}^{(B)} \right]^{-1} \]

\[ \langle D | \hat{T} | A \rangle = \langle D | \hat{V} \ \hat{G}^{(B)}(E_{\text{tun}}) \ \hat{V} | A \rangle \]
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,
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)

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

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

$\sigma_{T_{DA}}^2 \ll \langle T_{DA} \rangle^2$

**SMALL** $T_{DA}$ fluctuations

EQUILIBRIUM MOLECULAR STRUCTURE DETERMINES STRONG ET PATHWAYS

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

Static calculation of $T_{DA}$ is OK
(e.g., for minimum energy conformation)

$\sigma_{T_{DA}}^2 \gg \langle T_{DA} \rangle^2$

**LARGE** $T_{DA}$ fluctuations

NON-EQUILIBRIUM MOLECULAR STRUCTURES DETERMINE STRONG ET PATHWAYS

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

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


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

$R_{DA} \approx 17 \text{ A}$
$T_{DA}^{rms} \approx 10^{-5} \text{ eV}$
$k_{D \rightarrow A}^{-1} \approx 10^{-6} \text{ sec}$

$R_{DA} \approx 26 \text{ A}$
$T_{DA}^{rms} \approx 10^{-8} \text{ eV}$
$k_{D \rightarrow A}^{-1} \approx 10^{-2} \text{ sec}$
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 $\rightarrow$ 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

![Diagram of pyrimidine dimers](image)


• A pyrimidine dimer distorts DNA & interferes with DNA replication

![Diagram of DNA photolyase binding](image)


• 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)

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

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

Examination of ET mechanism

T. Prytkova, D.N. Beratan and S.S. Skourtis  

- 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 \(<T_{DA}^2>\)

- Structure-function analysis of \(<T_{DA}^2>\)
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)
S1
S2
S3
ET to dimer (200 psec)
Rapid relaxation

Distal side of flavin (furthest from the dimer)
Proximal side of flavin (closest to the dimer)

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

$T_{DA}^{rms} \approx 5 \times 10^{-4} \text{ eV}$

Dimer – FADH$^-$ (no adenine)

$T_{DA}^{rms} \approx 5 \times 10^{-4} \text{ eV}$

Dimer – FADH$^-$ (no CH$_3$)

$T_{DA}^{rms} \approx 1 \times 10^{-3} \text{ eV}$
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 \(\sim(200)^{-1}\) psec\(^{-1}\)
Some open and interesting theoretical & computational problems
DNA electron transfer

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

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


ET control / ET molecular devices
Molecular double-slit paradigm:

Manipulate ET pathways by IR excitation of pathway-specific vibration


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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