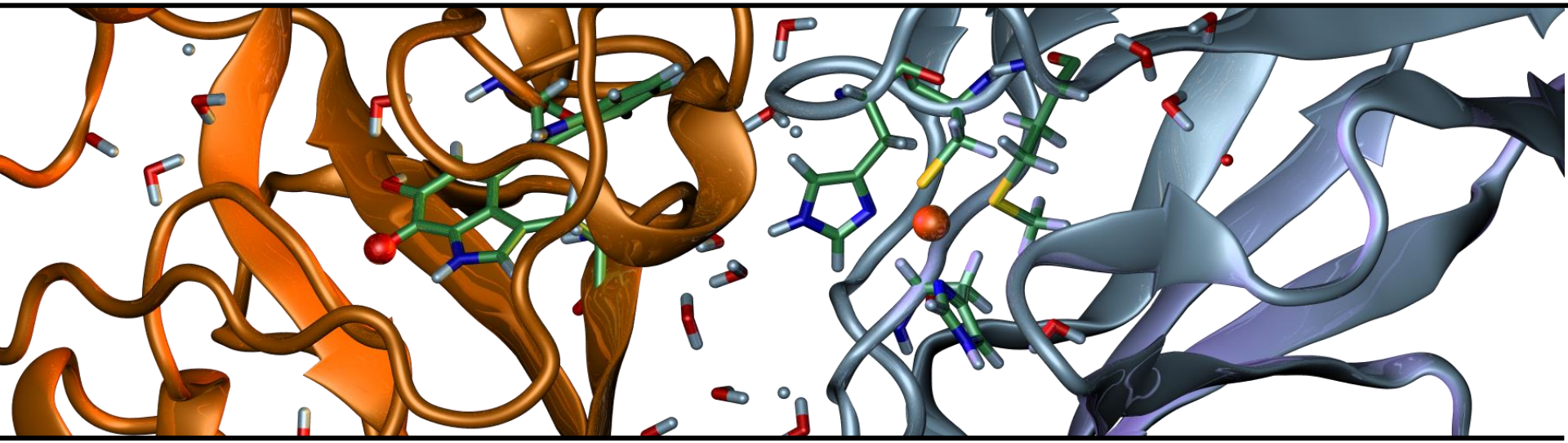
Physicochemical models to rationalize charge transfers between electron donors and acceptor?

From attosecond to microsecond time scales

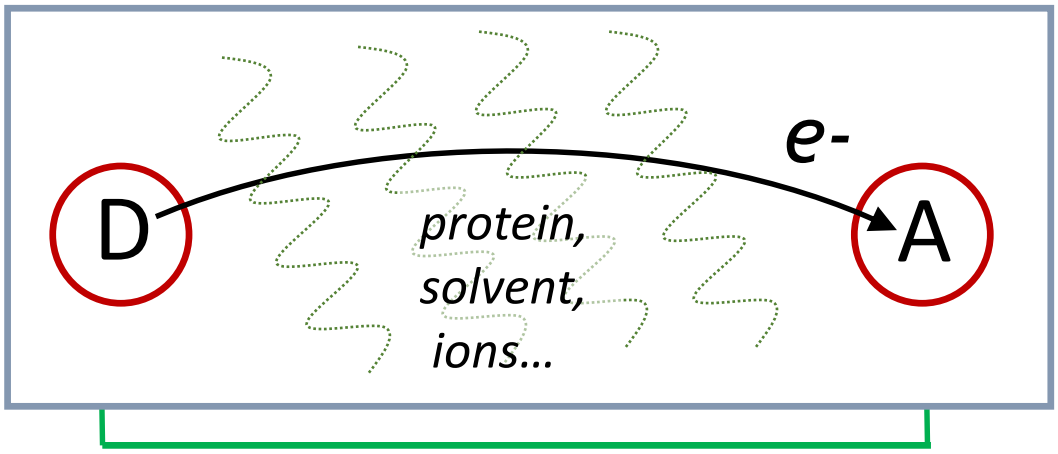


Aurélien de la Lande,

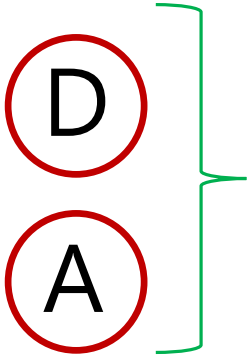
Université Paris Sud - CNRS - Université Paris Saclay

WHY GETTING INTERESTED BY ET IN BIOLOGY ?

- Respiratory chain (bacteria, mitochondria)
- Photosynthesis (photoreactive centers)
- Enzymatic catalysis (oxidoreductases)
- Bio-electrochemical system and bioinspired articifial systems
- Damages to biomolecules (e.g. DNA) by ionizing radiations



R_{DA} = 5 - 20 Å



organic cofactors:
- *quinones*
- *flavins*
- *amino acid residues*

inorganic cofactors
- *hemes*
- *chlorophyls*
- *blue copper centers*
- *iron-sulfur clusters*

A very few papers from the incommensurable electron transfers literature

Marcus Theory:

- R. A. Marcus, N. S. Sutin, *Biochim. Biophy. Acta,* **1984**, *811*, 265.
- N. R. Kestner, J. Logan and J. Jortner, *J Phys Chem*, 1974, **78**, 2148
- G. King and A. Warshel, Investigation of the free energy functions for electron transfer reactions JCP, 1990, 93, 8682,
- A. de la Lande, F. Cailliez, D.R. Salahub, *Seven Things that Might Break Down in Vanilla Marcus Theory and How to Fix them if they Do ?* in *Simulating Enzymatic Reactions*, Ed. V. Moliner, I. Tunon, RSC, 2017.

ET in biology:

- H. B. Gray, J. R. Winkler *Quat. Rev. Biophys*. **2003**, *36*, 3
- J. R. Winkler, H. B. Gray, *Biochimica et Biophysica Acta* **2010**, *1797*, 1563 (advanced)
- A. Warshel, W. W. Parson Dynamics of biochemical and biophysical reactions : insight from computer simulations. *Quat. Rev. Biophys,* **2001***, 34,* 563*.*

Tunneling in proteins:

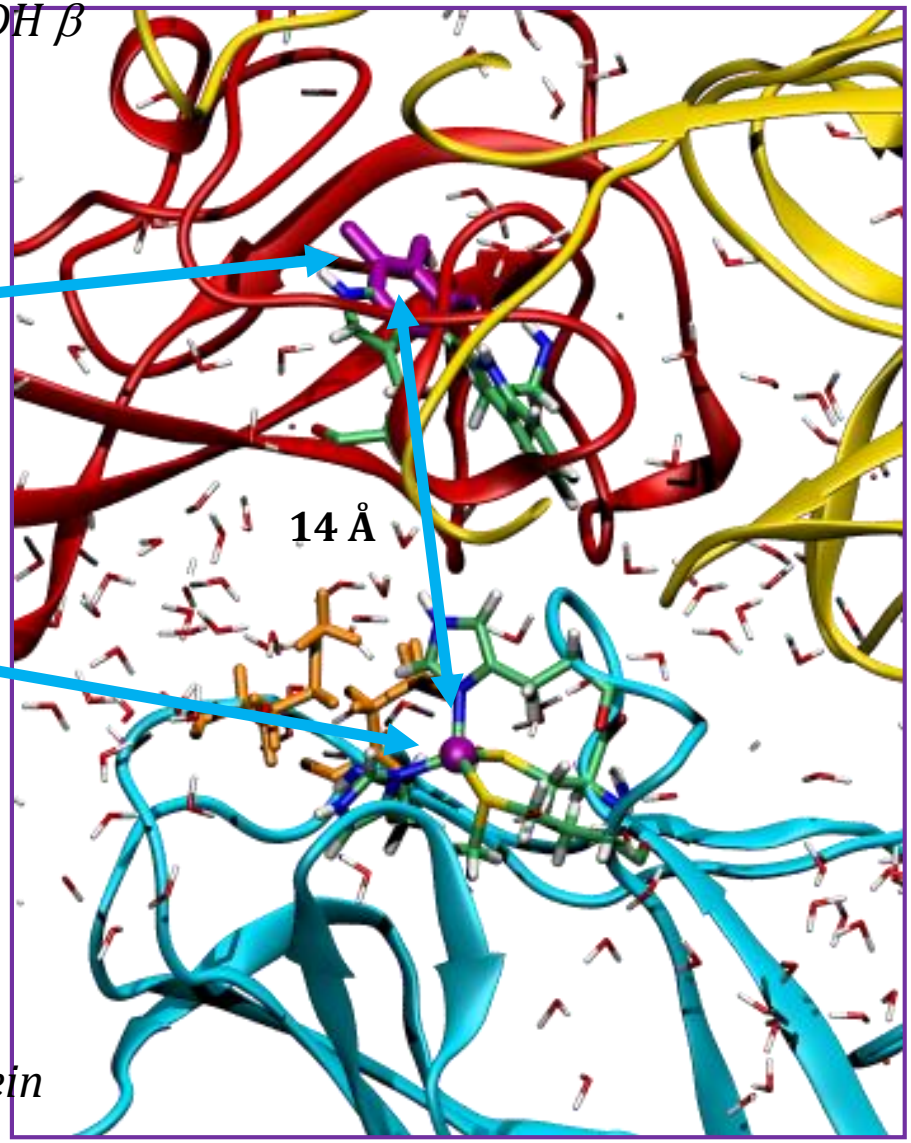
- D. N. Beratan, et al. , *Acc. Chem. Res.*, **2015**, 48, 474-481
- Literature from the groups of David N Beratan and Spiro Skourtis !

Computational approaches

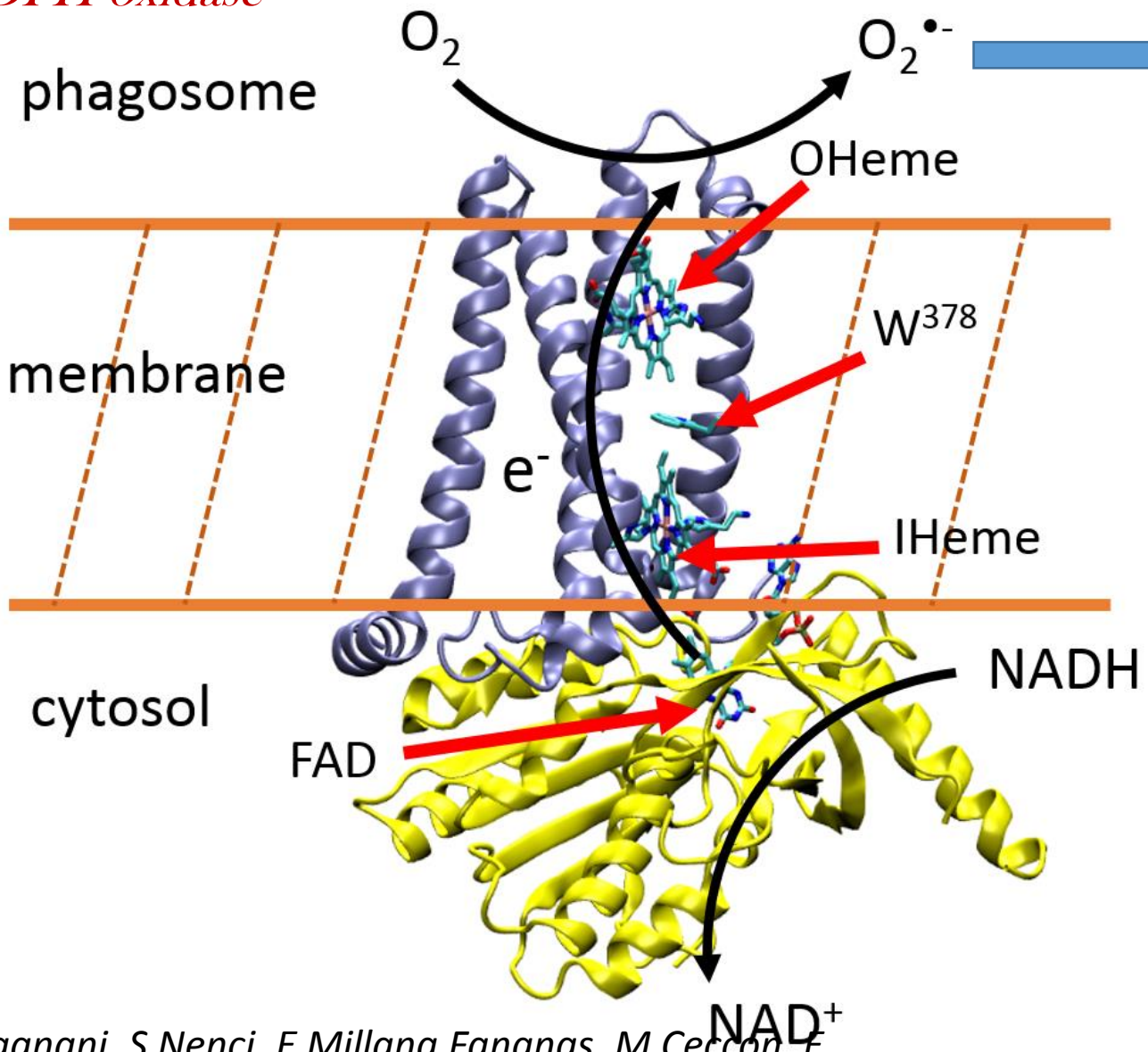
- J Blumberger Recent Advances in the Theory and Molecular Simulation of Biological Electron Transfer Reactions, *Chem. Rev.* **2015**, 115.
- J Blumberger. Free energies for biological electron transfer from QM/MM calculation:
- method, application and critical assessment. *PCCP*, **2008**, 10, 5651
- A de la Lande, S. Chen, DR. Salahub. Progress and challenges in simulating and understanding electron transfer in proteins. *Arch. Biochem. Biophys*. **2015**, 582, 28–41

Respiratory chain
Methylamine Dehydrogenase – Amicyanine
Paracoccus denitrificans

(PDB : 2MTA)
Chen *et al. Science* 1994, **264**, 86



NADPH oxidase

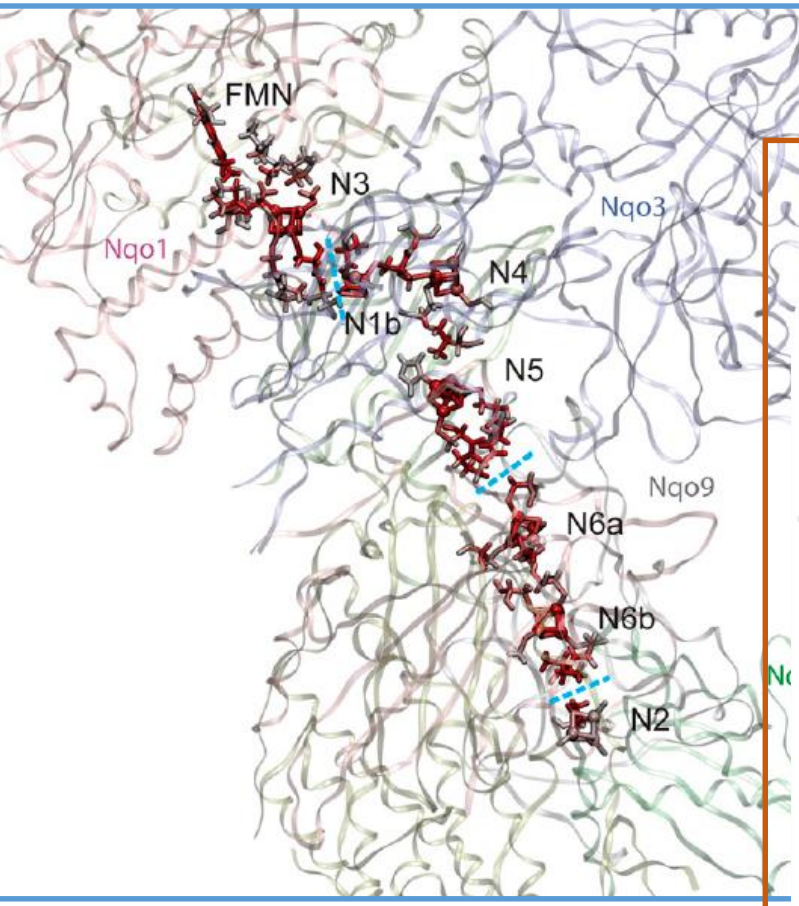


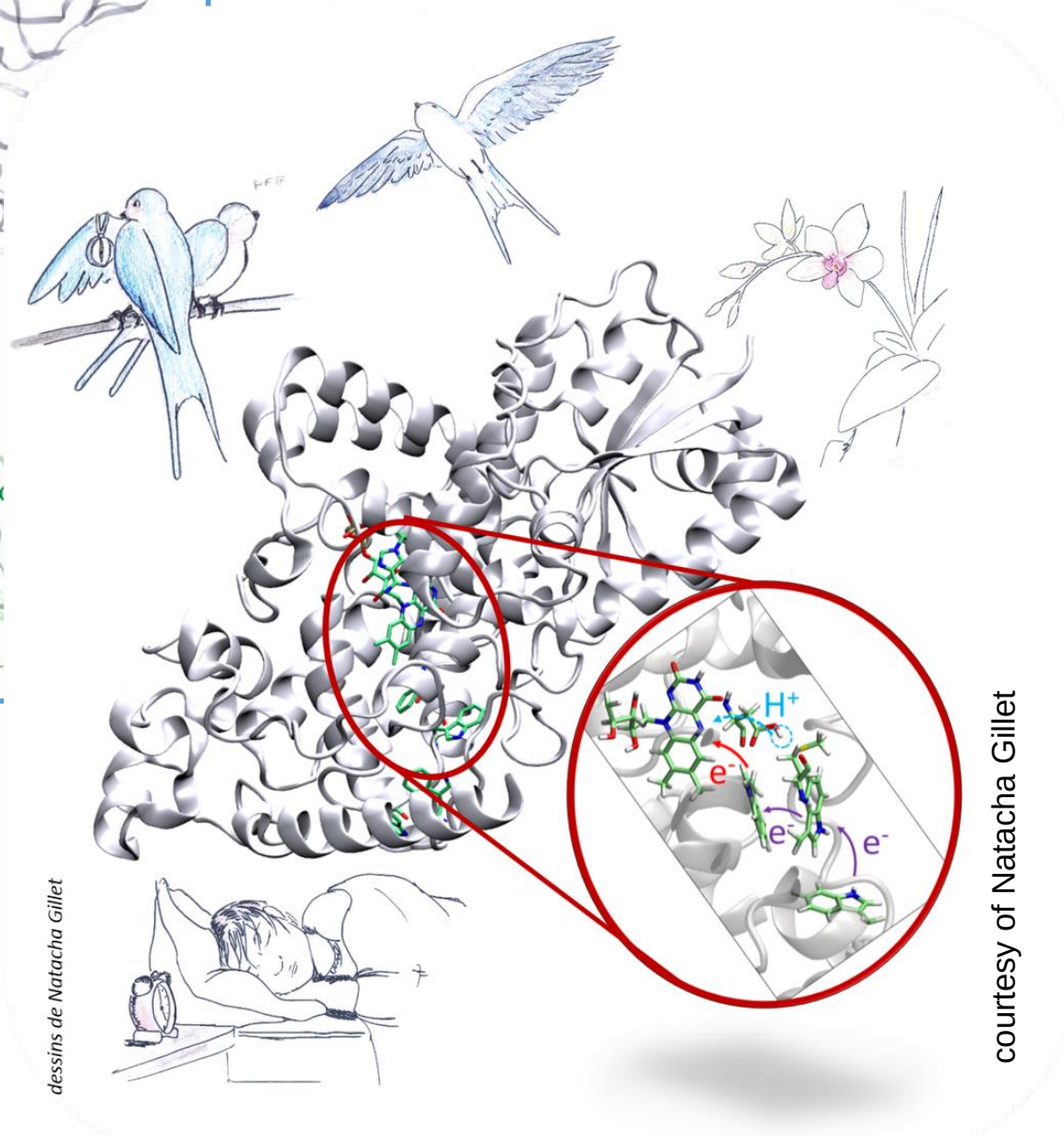
Attack entrapped pathogens

F Magnani, S Nenci, E Millana Fananas, M Ceccon, E Romero, M W. Fraaije, A Mattevi, PNAS 2017

Complex I of respiratory cain

Hayashi, Stuchebrukhov;
Proc. Nat. Acad. Soc. **2010**, *107*, 19157



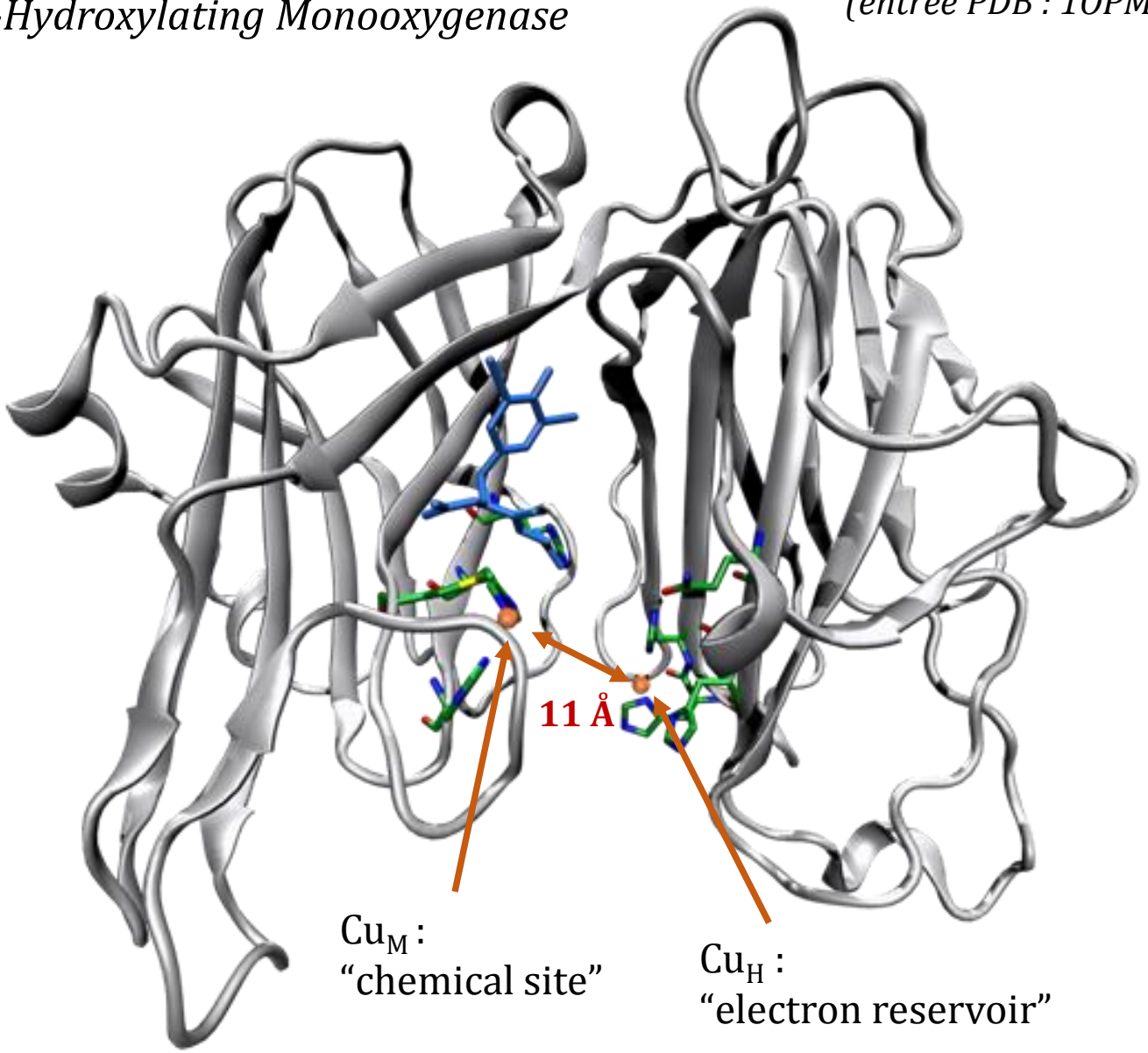


K. Brettel and coll., Nature 2000
Chaves et al. Annu. Rev. Plant Biol. **2011**, 62, 335-364.
Hore et al. Annu. Rev. Biophys. **2016**. 45, 299–344

ENZYMATIC CATALYSIS

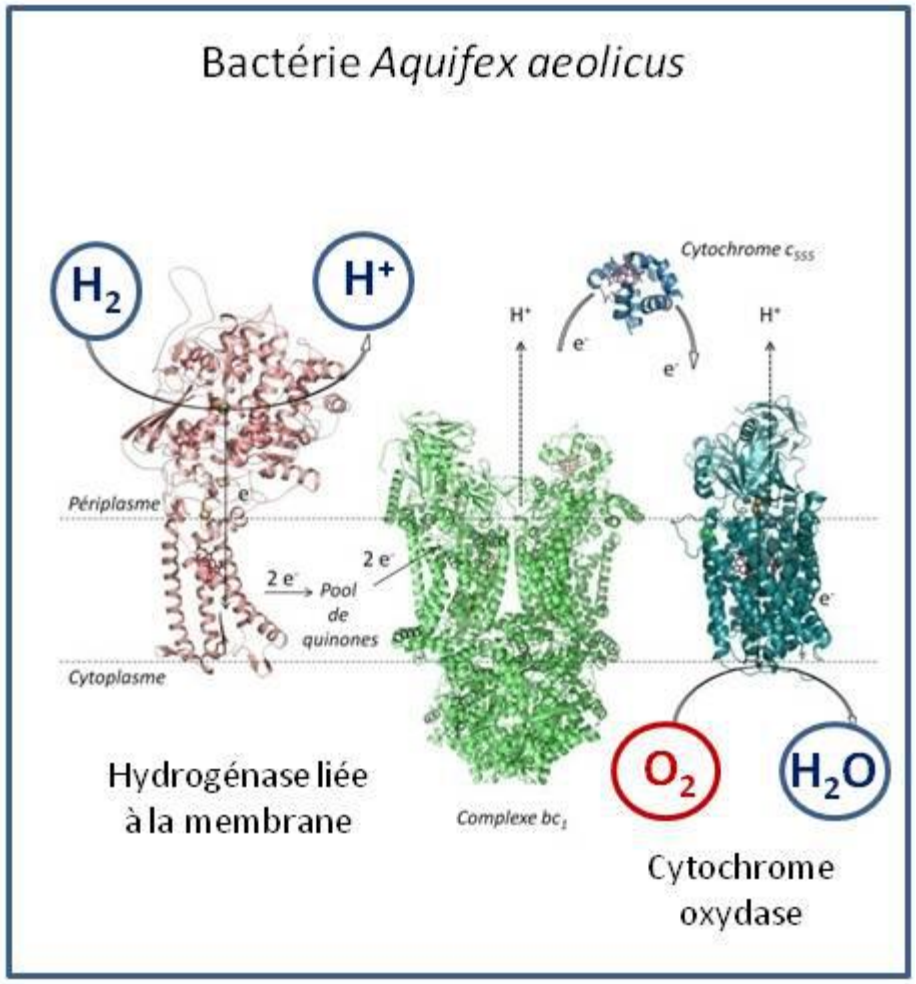
Peptidylglycine α-Hydroxylating Monooxygenase

Prigge *et al. Nat. Struct. Biol.* 1999, **6**, 976
(entrée PDB : 1OPM)

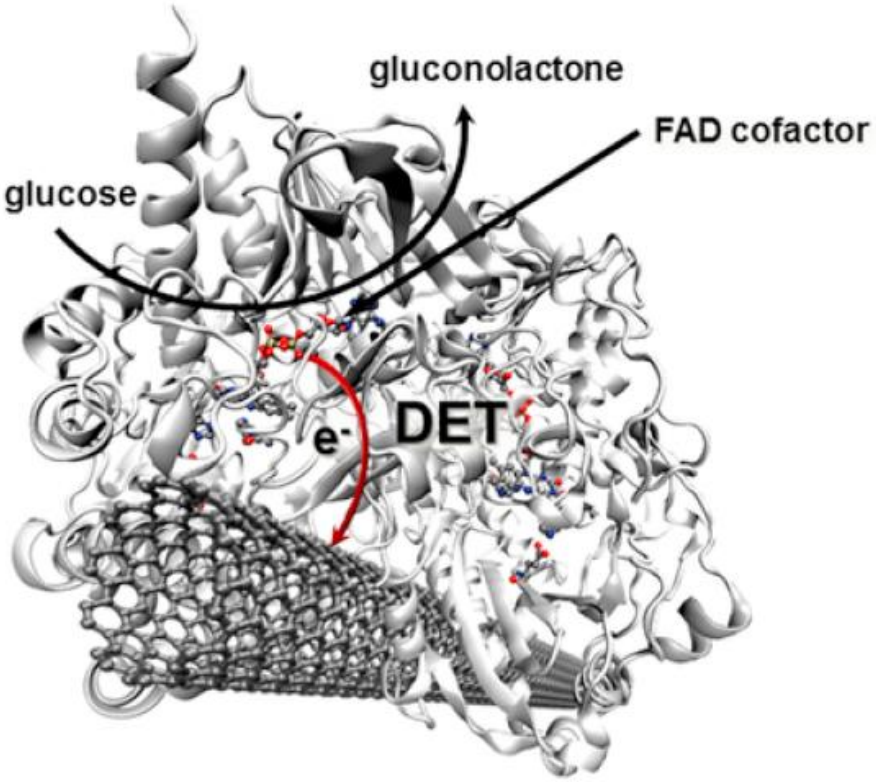


A de la Lande, O. Parisel, V. Moliner, *J. Am. Chem. Soc.* **2007**, 129, 11700
C. Melía, S. Ferrer, J. Řezáč, O. Parisel, O. Reinaud, V. Moliner, A. de la Lande
Chem. Eur. J. **2013**, *19*, 17328

biological fuel cells



From Lojou and co-workers,
Anal. Bioanal. Chem. 406 (2014) 1011.



From Cosnier and co-workers,
Journal of Power Sources. *(2016) 1011.*

- Biological systems are very complex (multiscale systems by nature)

- Interpretation of experimental data (redox potentials, rates, …) very delicate

- Theory and simulations are essential

- Marcus theory is an equilibrium theory for ET in liquids; why should it work in biology ?

- Actually stimulating to challenge MT in biology

I – The Macus theory: concepts, theory and computer simulations

I.1 Pioneer ideas from Libby, Marcus, Hush…

I.2 The Marcus theory in the era of supercomputers

I.2.a. Linear Response Approximation
I.2.b A very simple example to set ideas
I.2.c Nanosecond ET in cytochrome c oxydase

I-3. Quantum and semi-classical formulations

I.2.a. Fermi golden rule and spin-boson model
I.2.b. Mixed quantum-classical, application to inverted region
I.2.c Recent example of application in cryptochromes

II – Beyond "Vanilla Marcus theory"

II.1 Breakdown of the linear response approximation

II.1.a. High polarizability of redox cofactor
II.1.b. Non-ergodic systems

II.2 Beyond the two-state model

II.2.a. Flickering resonance model
II.2.b. Recent example of application in photolyases

III – The mystery of electron tunneling through proteins

III.1 Interpretative models for tuneling

III.1.a. Hopfield model
III.1.b. Pathway model
III.1.c Interatomic tunneling currents

I.2 Dynamical effects on tunneling

III.2.a. Inelastic tunneling
III.2.b. Recent example of application in cryptochromes
III.2.c Coherence loss in slow coupling regime

I The Marcus theory of electron transfer

Reaction	$\log K_{12}$	$k_{12,\mathrm{obsd}}$ $(M^{-1}\cdot s^{-1})$
$Ru(NH_3)_6^{2+} + Ru(NH_3)_5py^{3+}$	4.40	$1.4\cdot10^{6}$
$Ru(NH_3)_5py^{2+} + Ru(NH_3)_4(bpy)^{3+}$	3.39	$1.1\cdot10^{8}$
$Ru(NH_3)_6^{2+} + Co(phen)_3^{3+}$	5.42	$1.5\cdot10^{4}$
$Ru(NH_3)_5py^{2+} + Co(phen)_3^{3+}$	1.01	$2.0\cdot10^{3}$
$V_{aq}^{2+} + Co(en)_3^{3+}$	0.25	$5.8\cdot10^{-4}$
$V_{aq}^{2+} + Ru(NH_3)_6^{3+}$	5.19	$1.3\cdot10^{3}$
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From Marcus' Nobel lecture

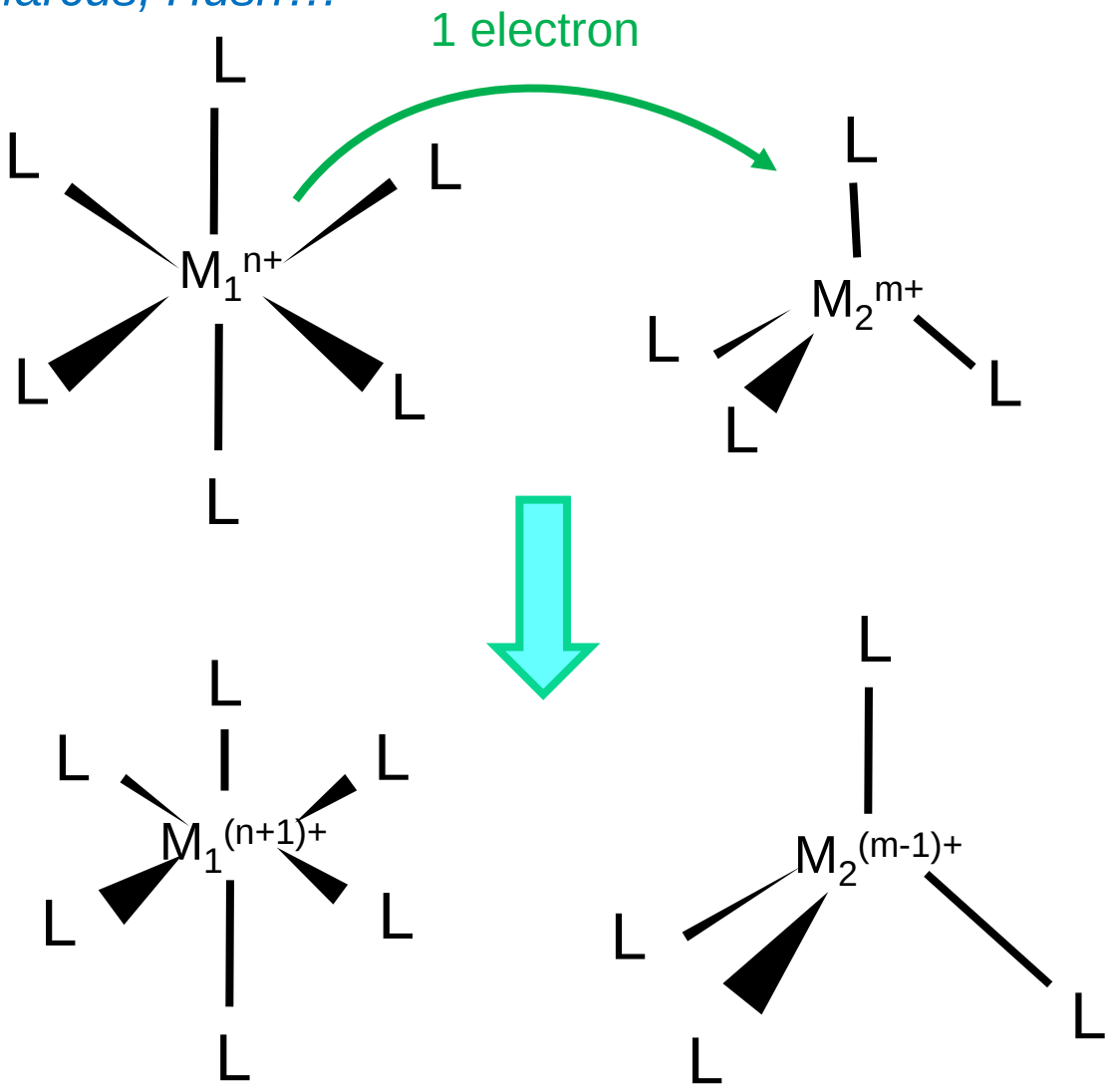
I-1. Pioneer ideas from Libby, Marcus, Hush…

Libby imports the Franck-Condon principle to chemical reactivity !!

Williard Libby

Noël Hush

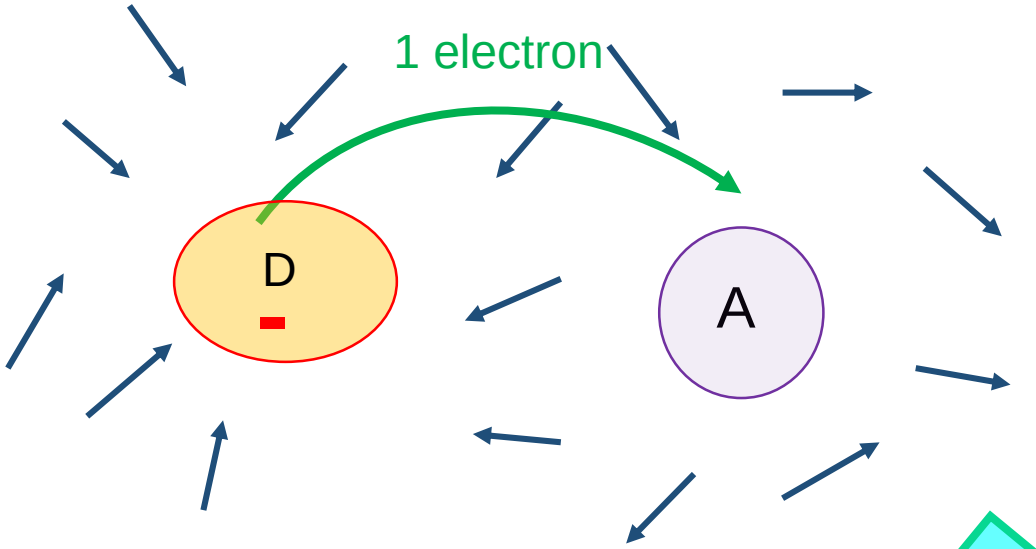
Rudy Marcus



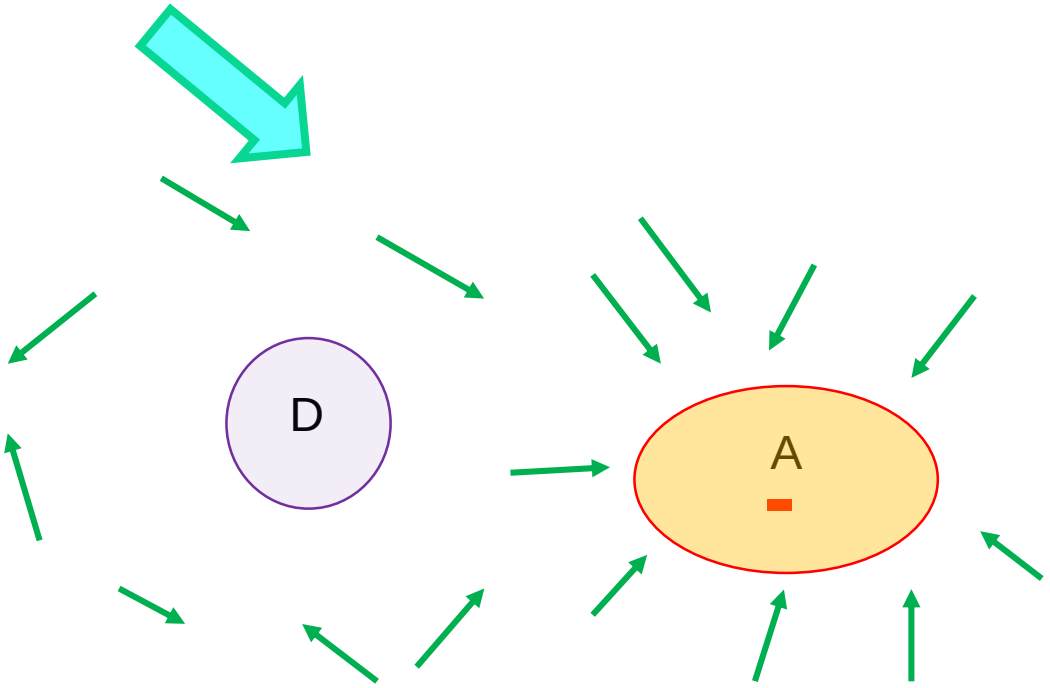
Electrons are fast, nuclei are more massive, therefore much slower

the electron "jumps" at fixed nuclear positions

I-1. Pioneer ideas from Libby, Marcus, Hush…

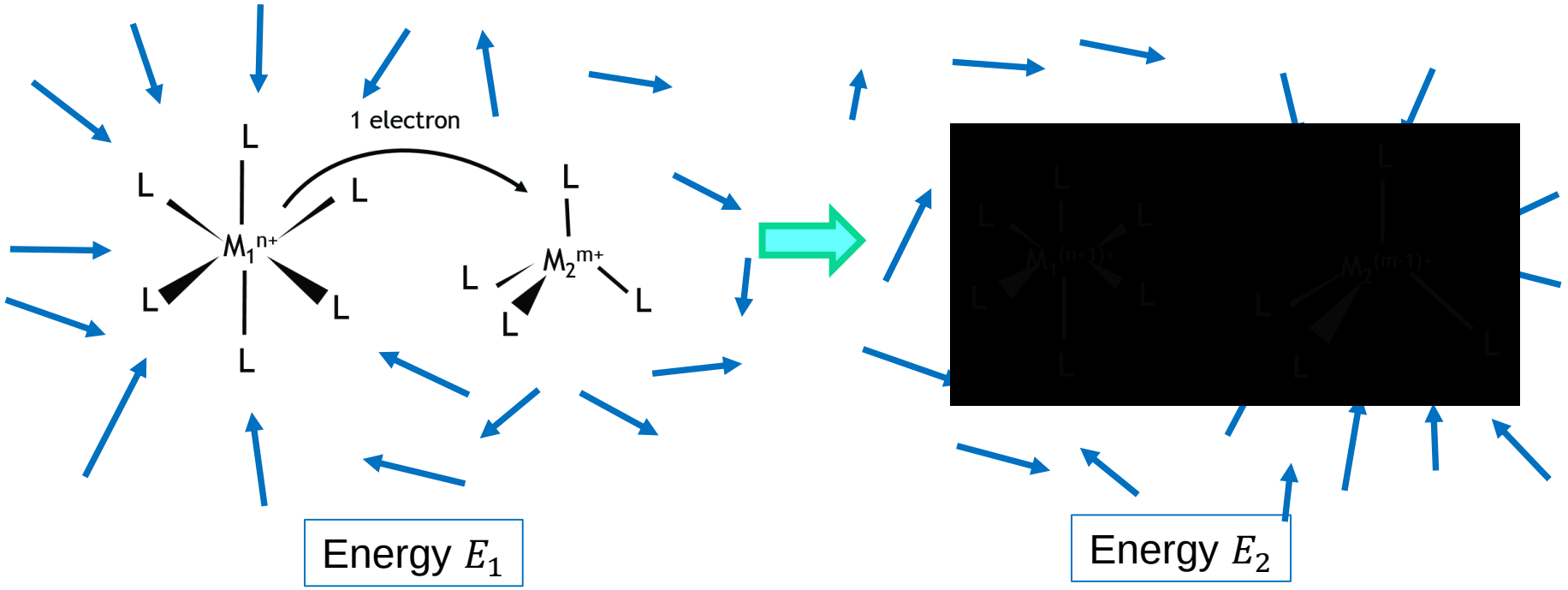


An electric charge is displaced electrostatic interactions with solvent are *different*



Molecules of the environment have to adapt to the new redox states of D and A

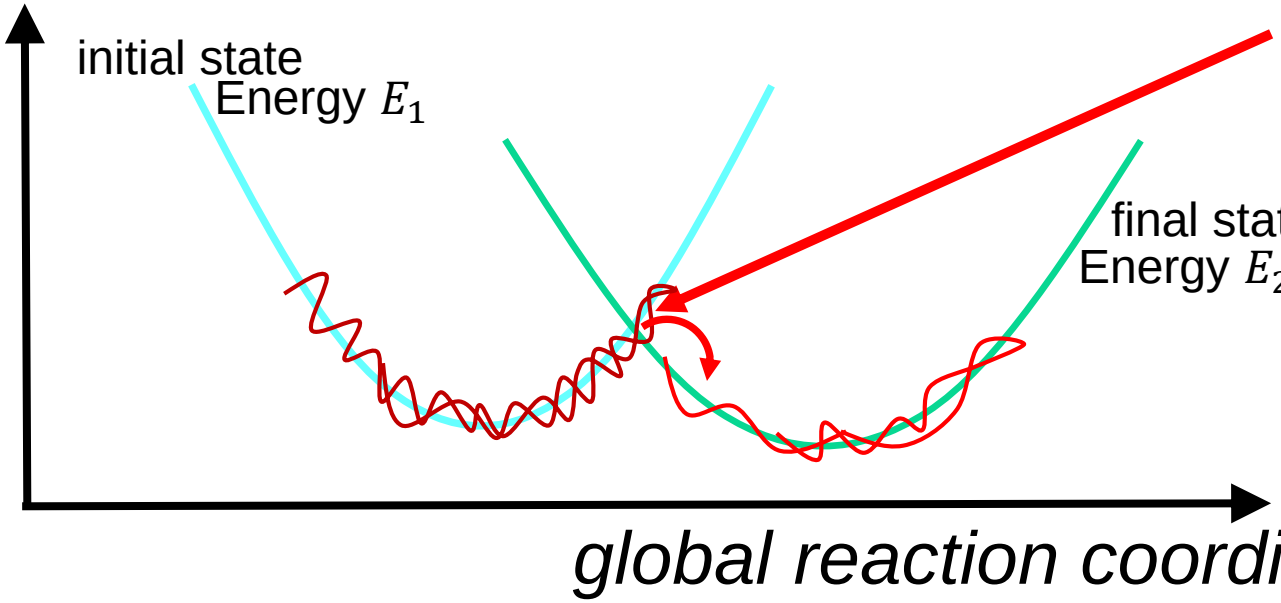
I-1. Pioneer ideas from Libby, Marcus, Hush…



Two electronic states are involved, before and after electron transfer
Each electronic state has its own potential energy
Both energies are rapidely changing because of thermal motion

To conserve the energy the electron can jump ONLY when the electronic states are degenerated

I-1. Pioneer ideas from Libby, Marcus, Hush…



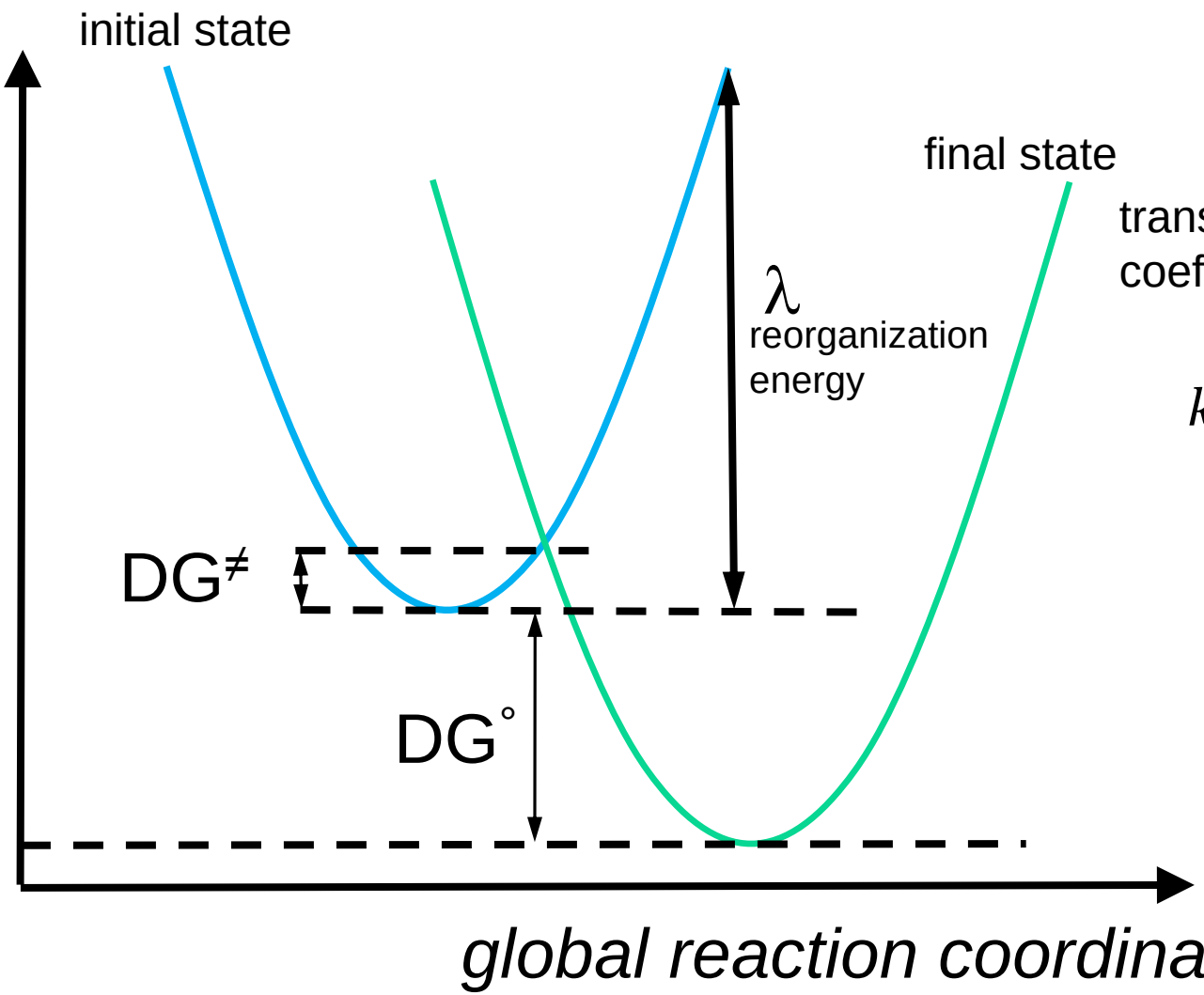
only configurationS where electron can jump

This 2D representation is an OVERSIMPLIFICATION

There are tons of nuclear configurations associated to degeneracy

One needs to know the probability to reach each of them

I-1. Pioneer ideas from Libby, Marcus, Hush…



transmission coefficient

collision frequency

$$k = \kappa . A\sigma^2 . \exp\left(-\frac{\Delta G^{\ddagger}}{k_B T}\right)$$

$$\Delta G^{\ddagger} = \frac{(\Delta G^0 + \lambda)^2}{4\lambda}$$

assume the two free energy curves are parabolas with the same curvature

I-1. Pioneer ideas from Libby, Marcus, Hush…

$$\Delta G° = -nFE_{redox}$$

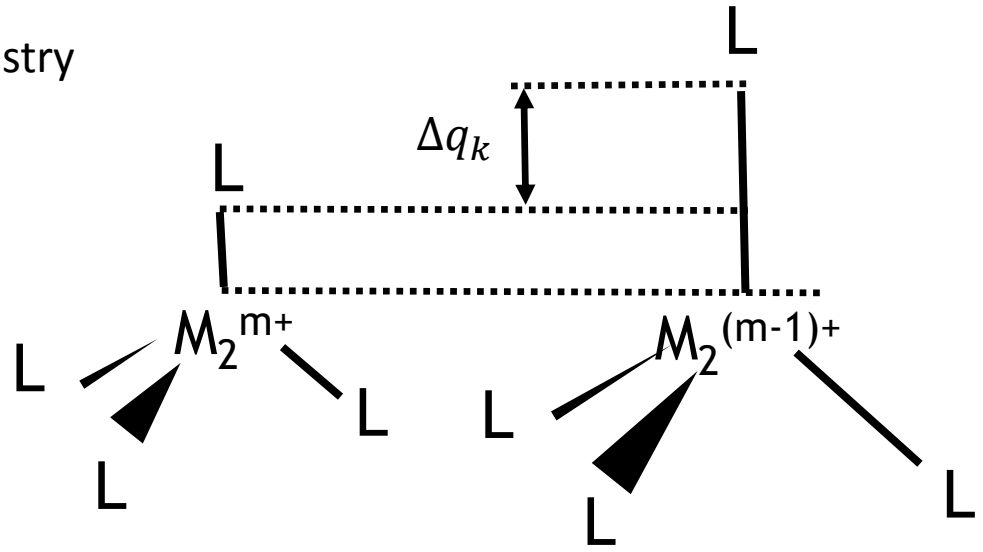
from electrochemistry

$$E_k^1(q) = \frac{1}{2} f_k^1 \left(q - q_{eq}\right)^2$$

$$\lambda = \lambda_i + \lambda_o$$

inner-sphere

outer-sphere



$$\lambda_i = \sum_{\substack{nuclear \\ vibrations\ k}} \frac{f_k^1 f_k^2}{f_k^1 + f_k^2} (\Delta q_k)^2$$

$$\lambda = \lambda_i + \lambda_o$$

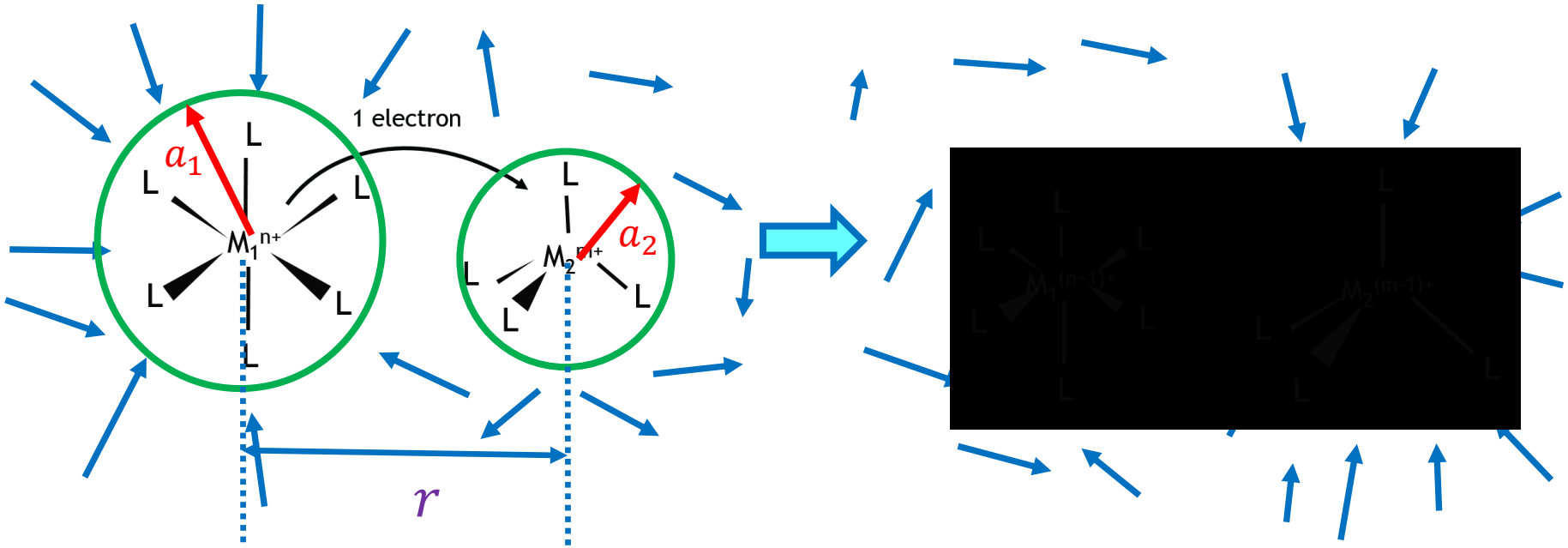
inner-sphere

outer-sphere

optical dielectric constant
square of refractive index

static dielectric constant

$$\lambda_o = \left(\frac{1}{2a_1} + \frac{1}{2a_2} - \frac{1}{r}\right)\left(\frac{1}{D_{op}} - \frac{1}{D_s}\right)$$



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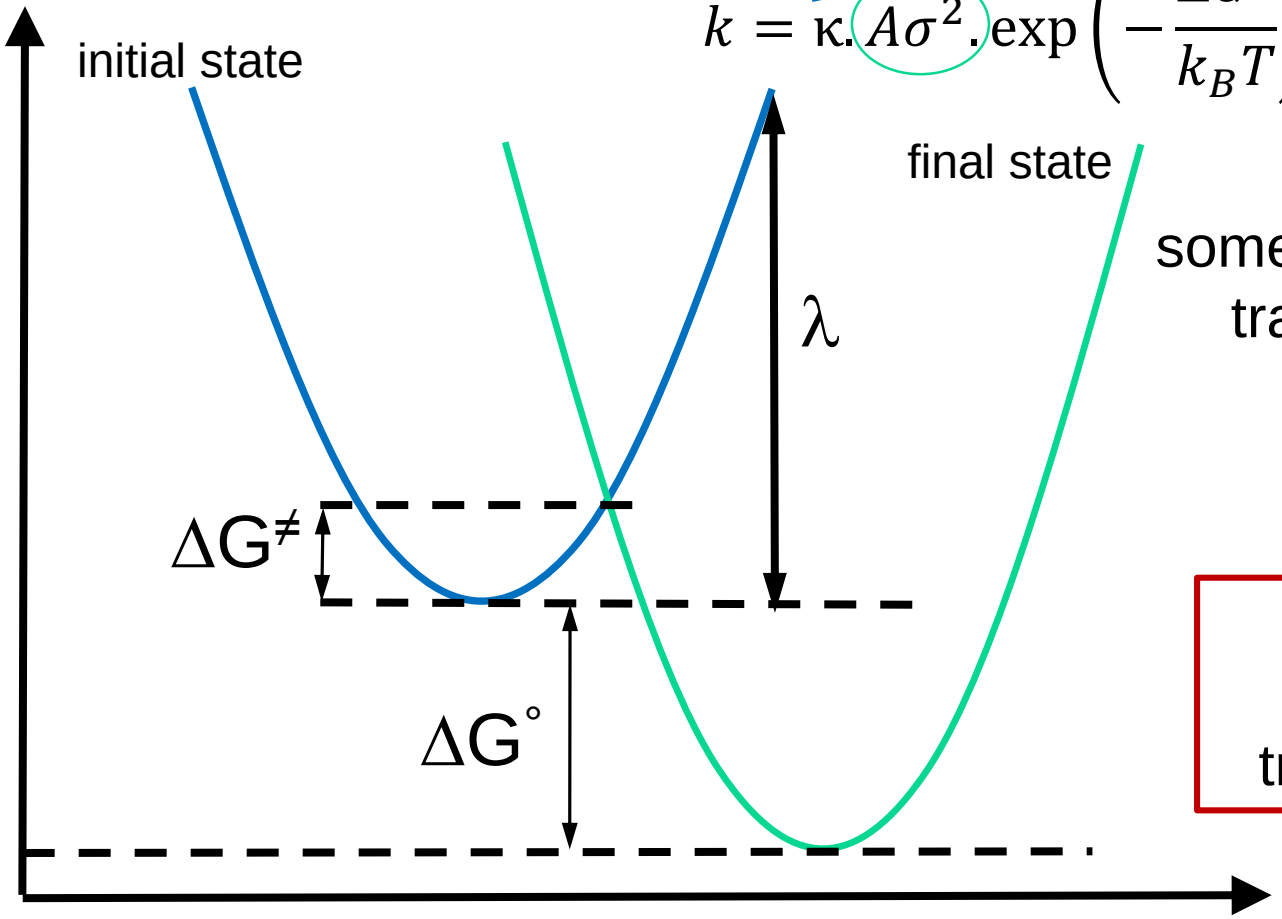

some formal analogies with transition state theory

the Marcus theory
≠
transition state theory

AND IT WORKED !!

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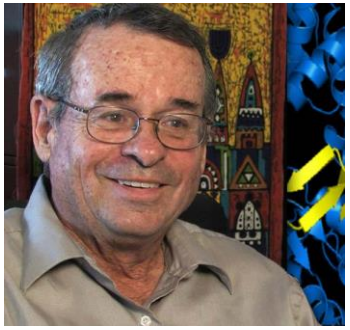
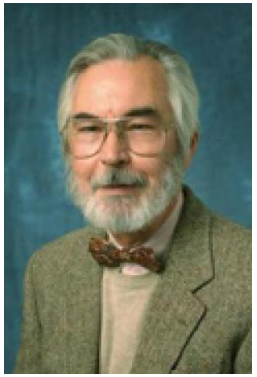
I.2 The Marcus theory in the era of supercomputers

- Microcopic (atomistic/molecular scale)
- Test hypotheses of MT
- Provide atomistic details inaccessible to experiments

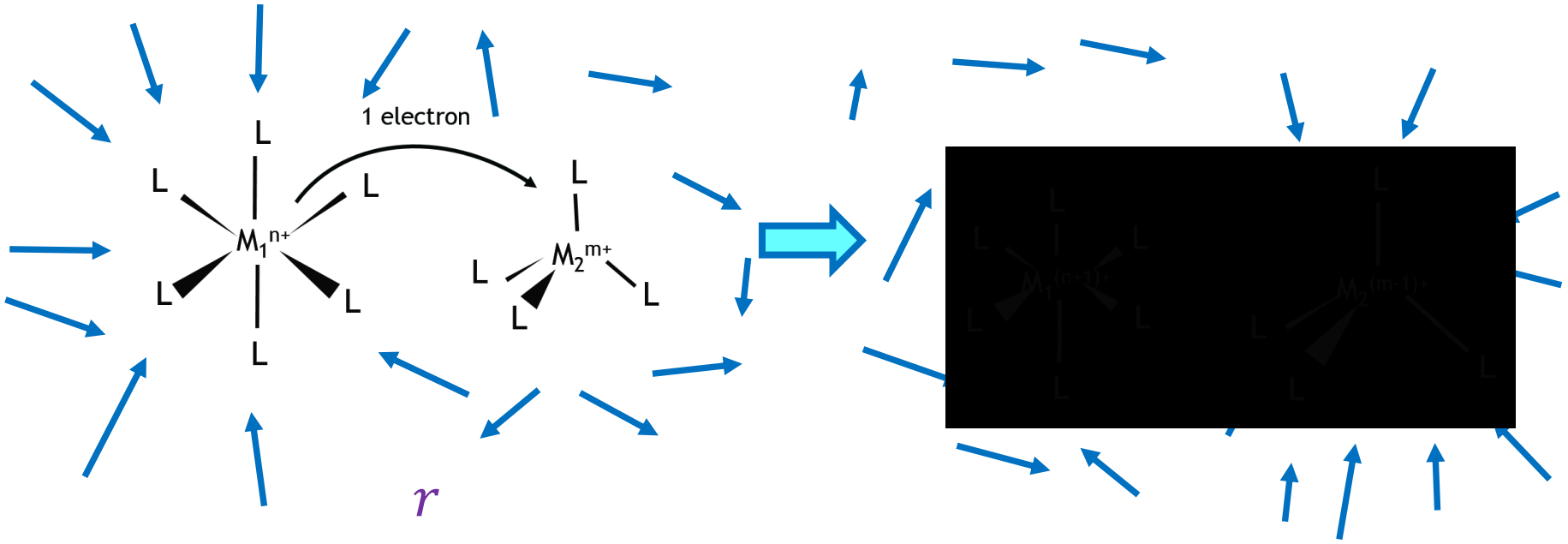


Arieh Warshel



Casey Hynes

see also Tachiya, Schulten, Chandler and many others



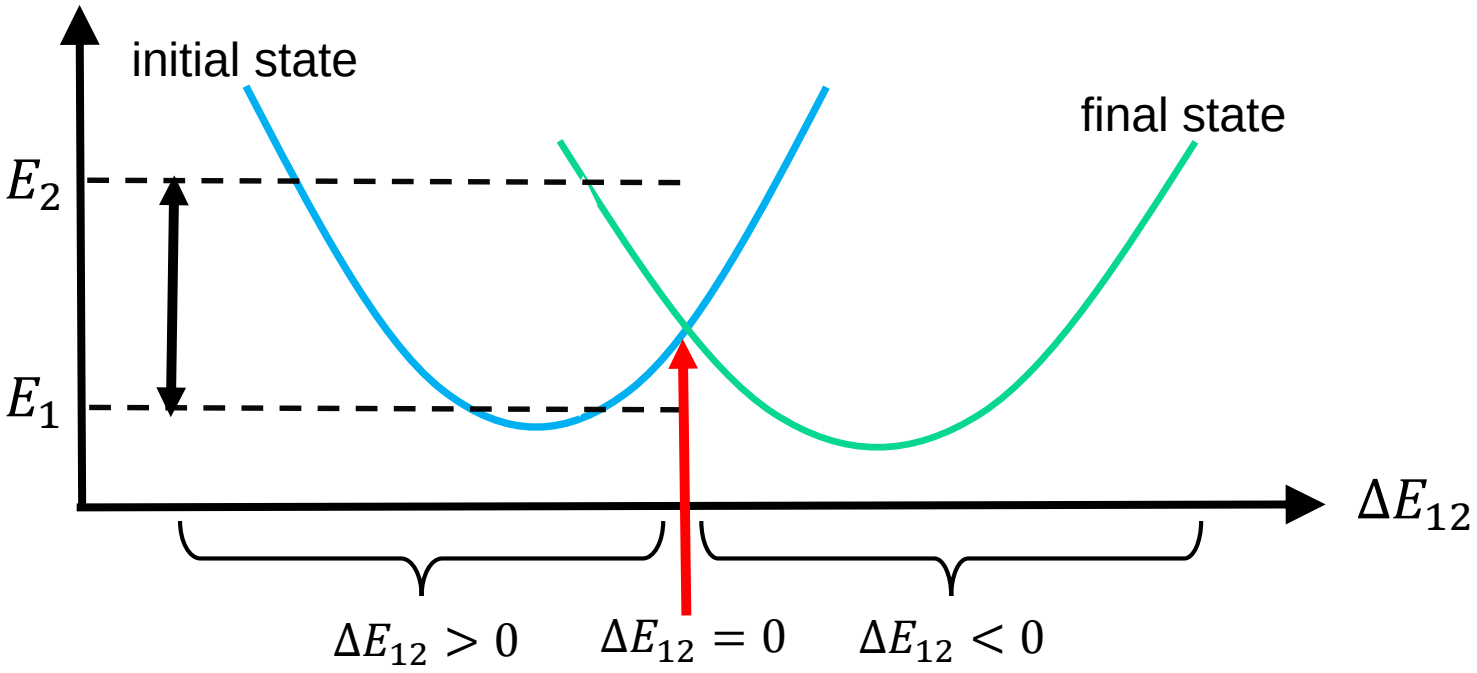
I.2 The Marcus theory in the era of supercomputers

initial state ⇒ Energy E_1

final state ⇒ Energy E_2

Vertical energy gap

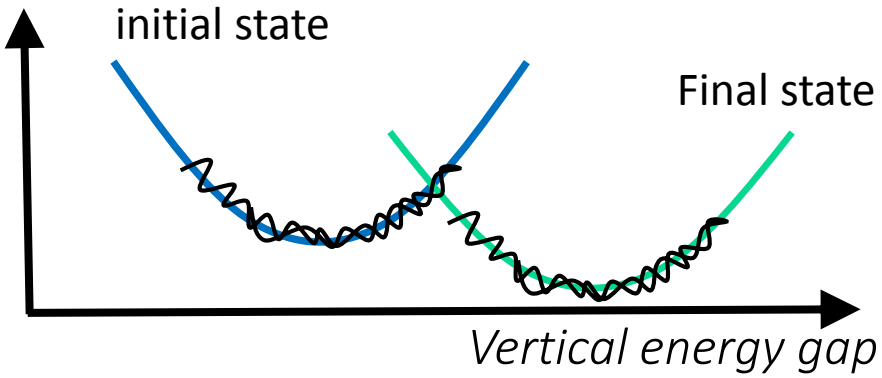
$$\Delta E_{12} = E_2 - E_1$$



The vertical energy gap is a good reaction coordinates
1) it collects all nuclear motion affecting the energies of the two states
2) it reflects how the reaction progresses

FREE ENERGIES

$$G_x(\varepsilon) = -\beta ln\big(p_x(\varepsilon)\big) + G_x^0 \qquad \beta = 1/k_B T$$



$$G_x^0 = -k_B T \ln Z_x = -k_B T \ln\left(\int \exp(-\beta E_x)\, d\Gamma\right)$$

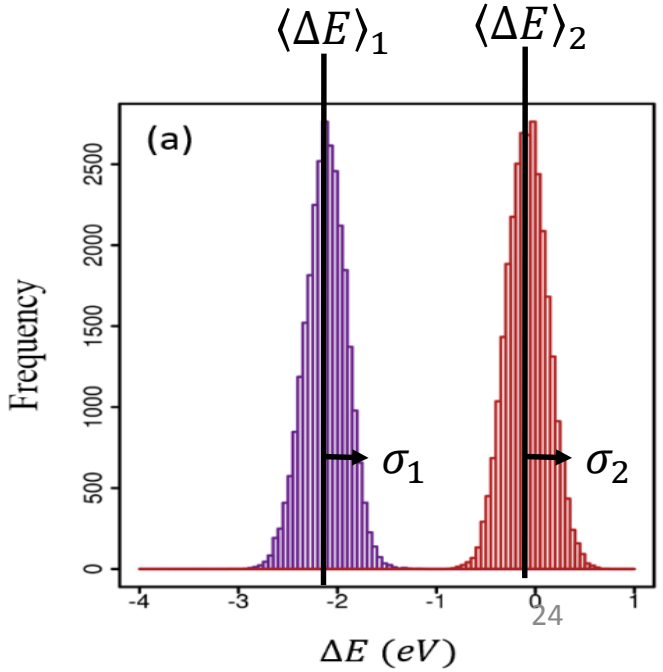
$$p_x(\varepsilon) = \frac{\int \exp(-\beta E_x)\, \delta(\Delta E - \varepsilon) d\Gamma}{\int \exp(-\beta E_x) d\Gamma} = \frac{\int \exp(-\beta E_x)\, \delta(\Delta E - \varepsilon) d\Gamma}{Z_x}$$

probability to have $\varepsilon = \Delta E_{12}$

If assume normal distribution of p_x

$$p_x(\varepsilon) = \frac{1}{\sigma_x \sqrt{2\pi}} \exp\left(-\frac{(\varepsilon - \langle \Delta E \rangle_x)^2}{2\sigma_x^2}\right)$$

LINEAR RESPONSE APPROXIMATION



Gibbs free energy curves

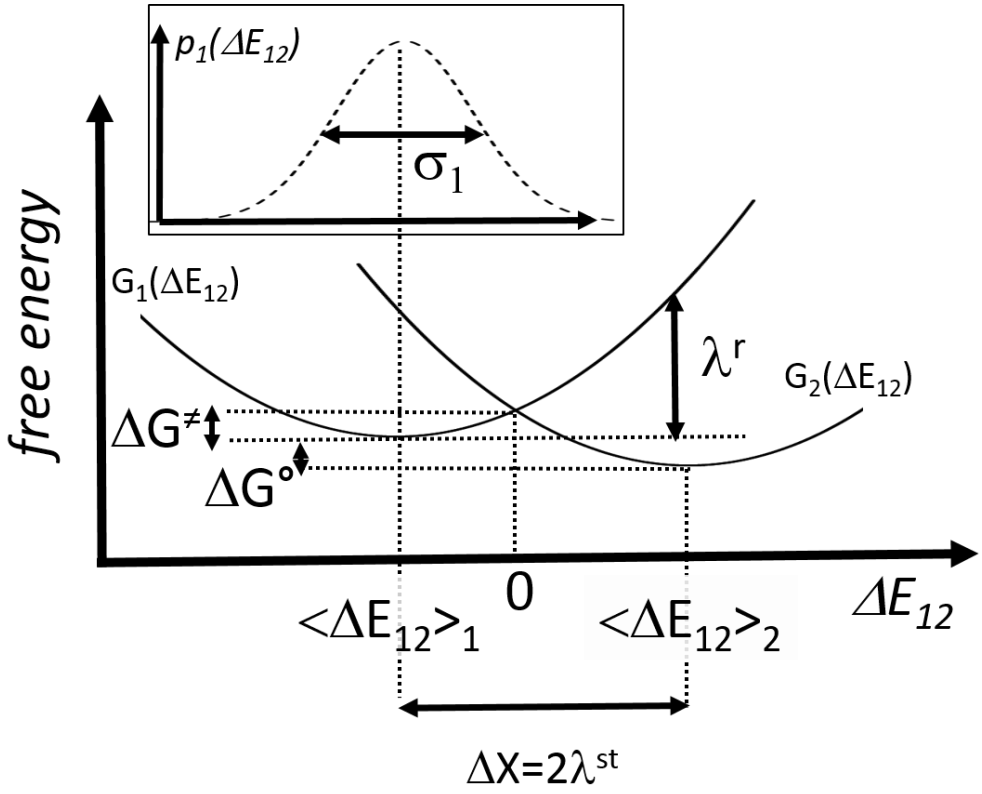
$$G_x(\varepsilon) = G_x^0 + \frac{(\varepsilon - \langle \Delta E \rangle_x)^2}{4\lambda_x^{var}} + \frac{k_B T}{2} \ln(4\pi k_B T \lambda_x^{var})$$

$$\lambda_x^{var} = \beta \sigma_x^2 / 2$$

$$\Delta G^0 = G_2^0 - G_1^0 = \frac{\langle \Delta E \rangle_1 + \langle \Delta E \rangle_2}{2}$$

$$\lambda = \frac{\langle \Delta E \rangle_1 - \langle \Delta E \rangle_2}{2} = \lambda^{St}$$

$$\lambda^{St} = \lambda_1^{var} = \lambda_2^{var} = \lambda^r$$



At the microscopic level, the Marcus theory is equivalent to the Linear Response Approximation

THE REVOLUTION OF NUMERICAL SIMULATIONS

- Possibility to assess validity of Marcus theory and its underlying hypothesis

- Bring insights not achievable by experimental approaches

- Numerical approaches are not constrained by MT hypothesis

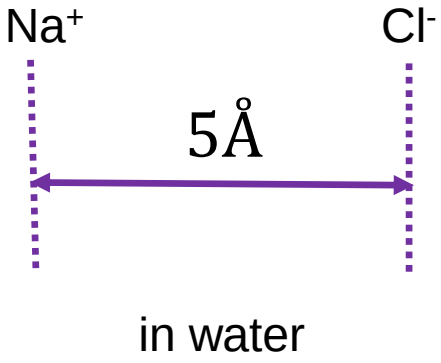
--> applicable to biological systems

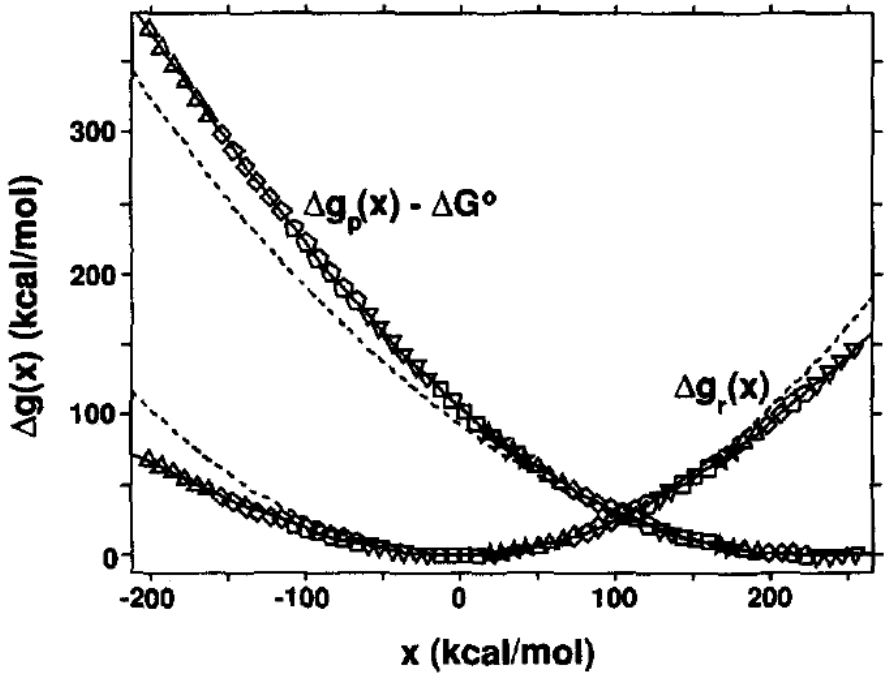
A very simple example to set ideas

King and Warshel, JCP, 1990, 93, 8682

Investigation of the free energy functions for electron transfer reactions

- Evaluate E_1 and E_2 (QM; QM/MM; MM...), then ΔE_{12}
- Sample **as extensively as possible** nuclear configurations for the two redox states to access $\langle \Delta E \rangle_1$ and $\langle \Delta E \rangle_2$, then ΔG^0, λ and the free energies of activations (rates)

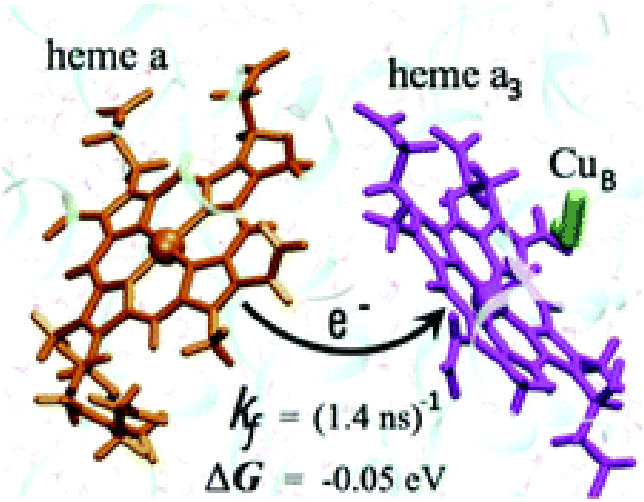


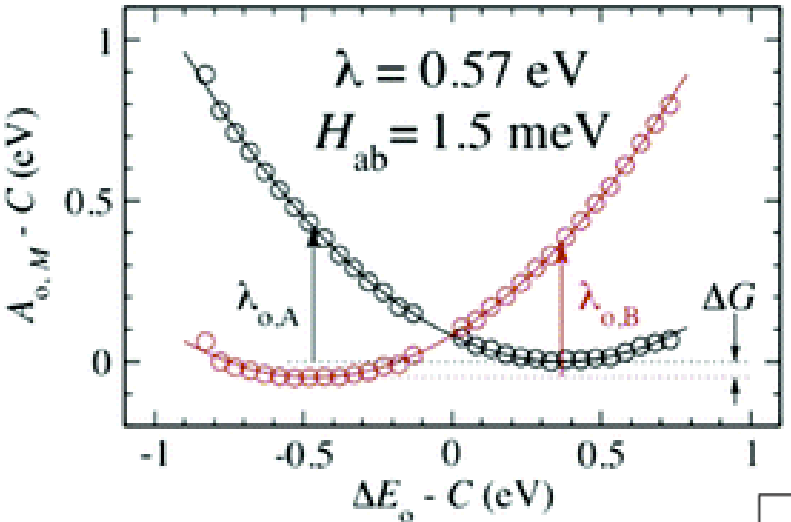


$\lambda = 105.6\ kcal/mol$ with non-polarizable Force field

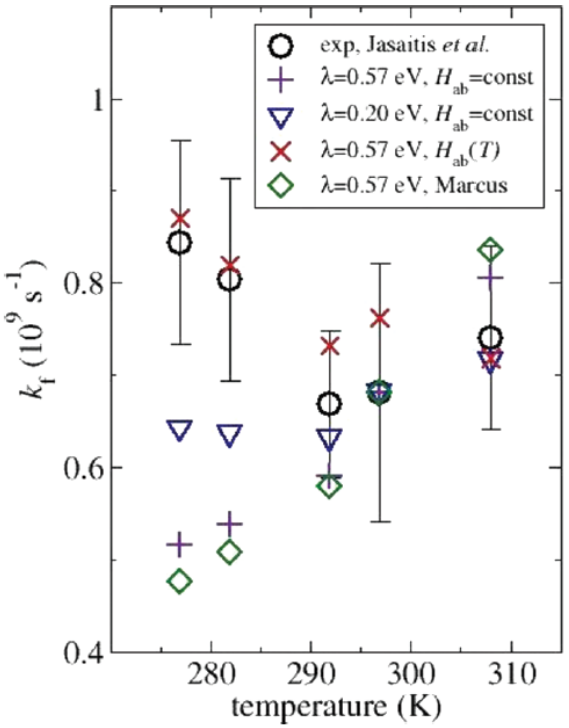
$\lambda = 70\ kcal/mol$ with polarizable Force field

Kinetics of the Terminal Electron Transfer Step in Cytochrome c Oxidase





V. Tipmanee, J. Blumberger, J. Phys. Chem. B, 2012, 1166, 1876-18



Redox cofactors: DFT (IP and EA)
Environement : Molecular Mechanics Force Fields

QM+MM approaches
J Blumberger, *Chem. Rev*. 2015, 115.
J Blumberger, PCCP 2008, 10, 5651

I – The Macus theory: concepts, theory and computer simulations

I.1 Pioneer ideas from Libby, Marcus, Hush…

I.2 The Marcus theory in the era of supercomputers

I.2.a. Linear Response Approximation

I.2.b A very simple example to set ideas

I.2.c Nanosecond ET in cytochrome c oxydase

I-3. Quantum and semi-classical formulations

I.2.a. Fermi golden rule and spin-boson model

I.2.b. Mixed quantum-classical, application to inverted region

I.2.c Recent example of application in cryptochromes

I-3. Quantum and semi-classical formulations

Levich and co-workers, 1960'
Kubo, *Prog Theor Phys*, 1955, **13**, 160-182.
Lax, *J Chem Phys*, 1952, **20**, 1752-1760.

transition probability for vibronic state $1v$ to $2w$

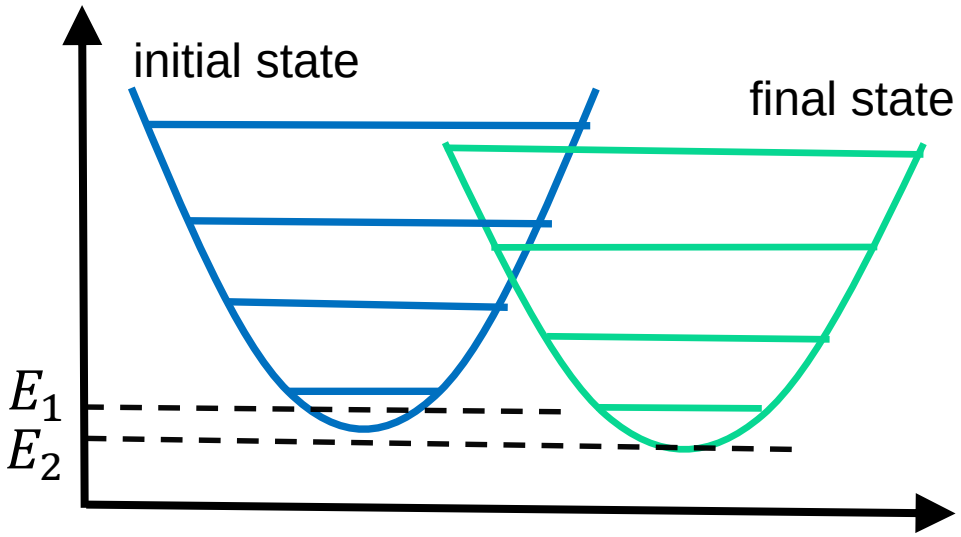
$$W_{1v} = \frac{2\pi}{\hbar}\sum_{w}\left|H_{1v,2w}\right|^2\delta(E_1 + \varepsilon_v - E_2 - \varepsilon_w)$$

coupling between vibronic states

$$H_{1v,2w} = \langle v|\langle 1|H|2\rangle|w\rangle$$

$$|\langle 1|H|2\rangle||\langle v|w\rangle| \equiv |H_{DA}||\langle v|w\rangle|$$

Condon approximation



Sum over all possible vibronic states

$$k_{ET} = \frac{2\pi}{\hbar}|H_{DA}|^2\sum_{v}\sum_{w}P(\varepsilon_v)|\langle v|w\rangle|^2\delta(E_1 + \varepsilon_v - E_2 - \varepsilon_w)$$

Frank Condon Weighted Density of States (FCWD)

$$k_{ET} = \frac{2\pi}{\hbar}|H_{DA}|^2 FCWD$$

$$FCWD \approx \frac{1}{\sqrt{4\pi\lambda k_B T}} \exp\left(-\frac{(\Delta G° + \lambda)^2}{4\lambda k_B T}\right)$$

valid in the high temperature limit

$$\boxed{k_{ET} = \frac{2\pi}{\hbar}|H_{DA}|^2 \frac{1}{\sqrt{4\pi\lambda k_B T}} \exp\left(-\frac{(\Delta G° + \lambda)^2}{4\lambda k_B T}\right)}$$

Marcus Theory non-adiabatic rate expression

Mixed quantum-classical model

S. Efrima and M. Bixon, *Chem Phys*, 1976, **13**, 447
J. Ulstrup and J. Jortner, J Chem Phys, 1975, 63,

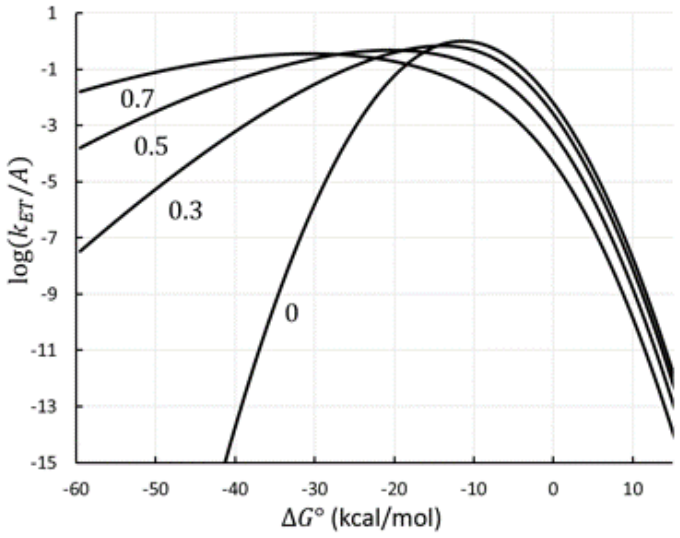
inner-sphere: Vibrational modes above 500 cm^{-1} should be quantized

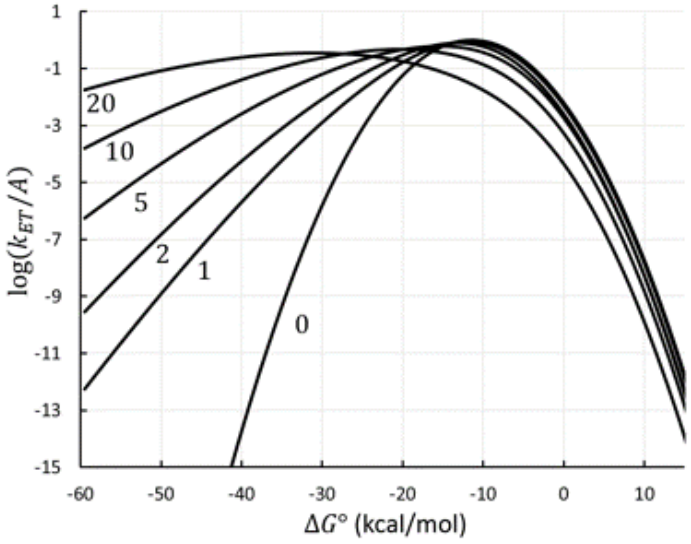
outer-sphere : Slow reorganization upon ET, no quantum effects, standard Marcus OK

Inner and outer-spheres are decoupled (hypothesis)

$$k_{ET} = \frac{2\pi}{\hbar}\frac{1}{\sqrt{4\pi\lambda_o k_B T}} {H_{DA}}^2 \sum_{v,w} |\langle v|w\rangle|^2 \exp\left(-\frac{(\Delta E + \Delta E_{vib} + \lambda_o)^2}{4\lambda_o k_B T}\right)$$

$$k_{ET} = \frac{2\pi}{\hbar}\frac{1}{\sqrt{4\pi\lambda_o k_B T}} {H_{DA}}^2 \exp(-2\mathrm{NS}) \sum_{k=0}^{\infty} \frac{N^k}{k!} S^k \exp\left(-\frac{(\Delta E + \hbar\omega k + \lambda_o)^2}{4\lambda_o k_B T}\right)$$





. Spin-boson and dispersed polaron model

$$k_{ET} = \frac{2\pi}{\hbar}|H_{DA}|^2 FCWD$$

Warshel, Schulten, Chandler … 1980’

Assume a set of harmonic oscillators to describe protein and solvent vibrational modes

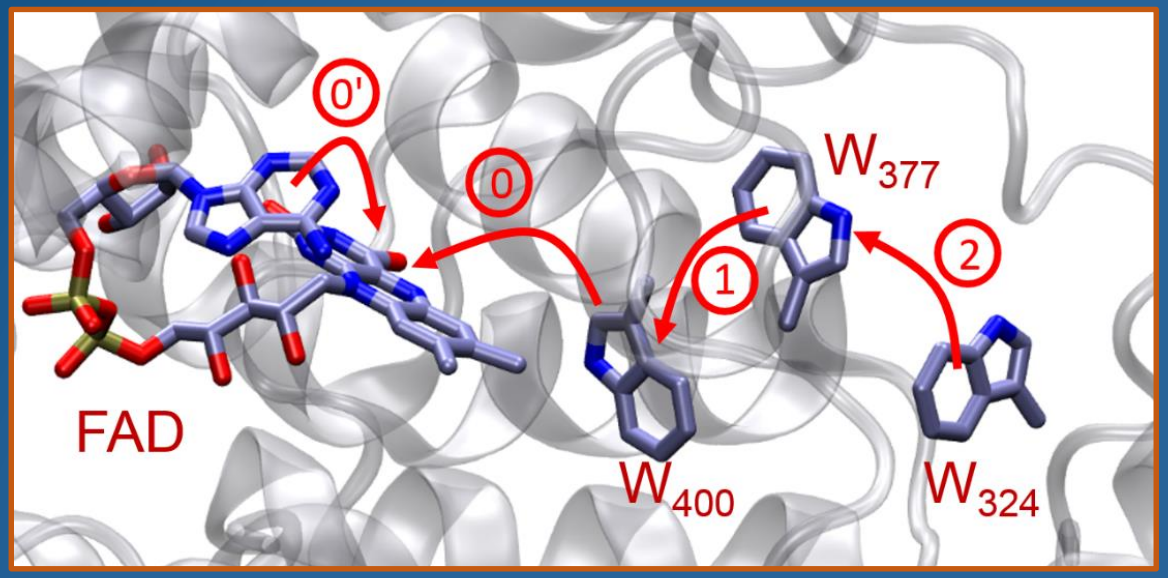
$$k_{ET} = \frac{H_{DA}^2}{\hbar}\int_{-\infty}^{+\infty} dR \exp\left\{-[1/2k_BT + iR/k_BT]\Delta G^\circ\right.$$

$$J(\omega) = \left|\int_{-\infty}^{+\infty}\langle\delta\Delta E(0)\delta\Delta E(t)\rangle \exp i\omega t\, dt\right|$$

Spectral density (can be evaluated from classical MD simulations)

Applied in ultrafast charge separation in photoreactive center, in DNA, hemeproteins …

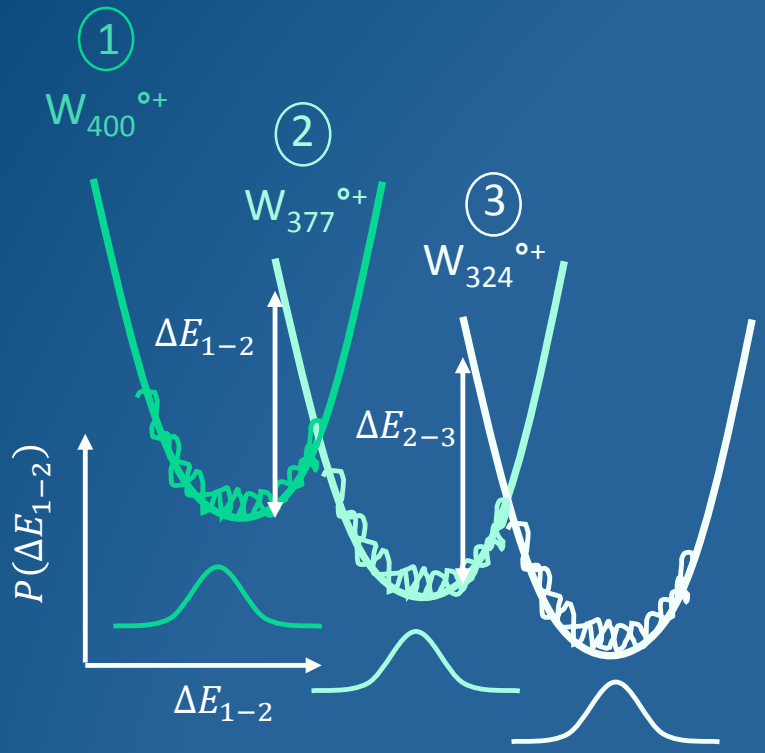
A recent example off numerical simulations of ET
Successive ET in cryptochromes

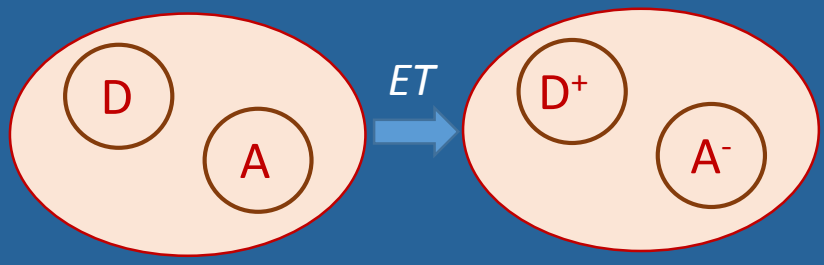


Steps 1-2: Th. Firmino, E. Mangaud, F. Cailliez, A. Devolver, D. Mendive-Tapia, F. Gatti, C. Meier, M. Desouter-Lecomte, A. de la Lande, *Phys. Chem. Chem. Phys*. 2016, *18*, 21442

Steps 0/0': F Cailliez, P Müller, M Gallois, A de la Lande, *J. Am. Chem. Soc*. **2014**, *136*, 12974-12986.

THE DIABATIC DESCRIPTION OF ET





initial electronic state

final electronic state

LINEAR RESPONSE APPROXIMATON

G. King, A. Warshel *J. Chem. Phys.* **1990**, *93*, 8682

free reaction energy

$$\Delta G^{\circ}_{i\to j} = \frac{1}{2}\left(\langle \Delta E_{j-i}\rangle_i + \langle \Delta E_{j-i}\rangle_j\right)$$

Stokes reorganization energy

$$\lambda^{St}_{i\to j} = \frac{1}{2}\left(\langle \Delta E_{j-i}\rangle_i - \langle \Delta E_{j-i}\rangle_j\right)$$

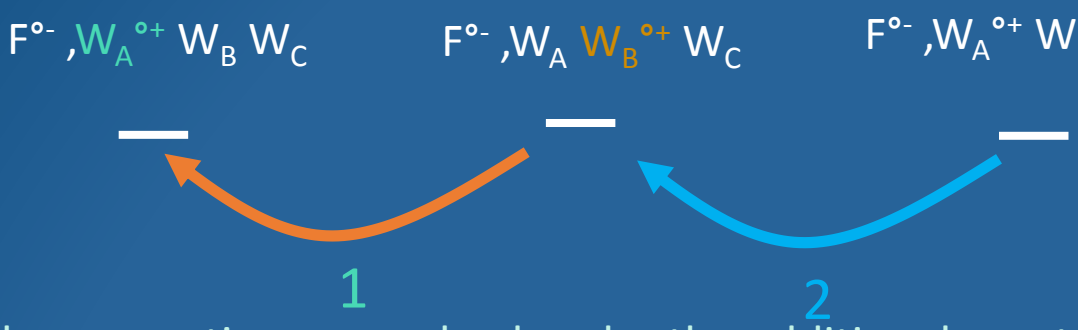
Variance reorganization energy

$$\lambda^{var}_{i\to j} = \frac{1}{4k_BT}\left(\sigma^2(\Delta E_{j-i})_i + \sigma^2(\Delta E_{j-i})_j\right)$$

The vertical energy gap ΔE is a key quantity

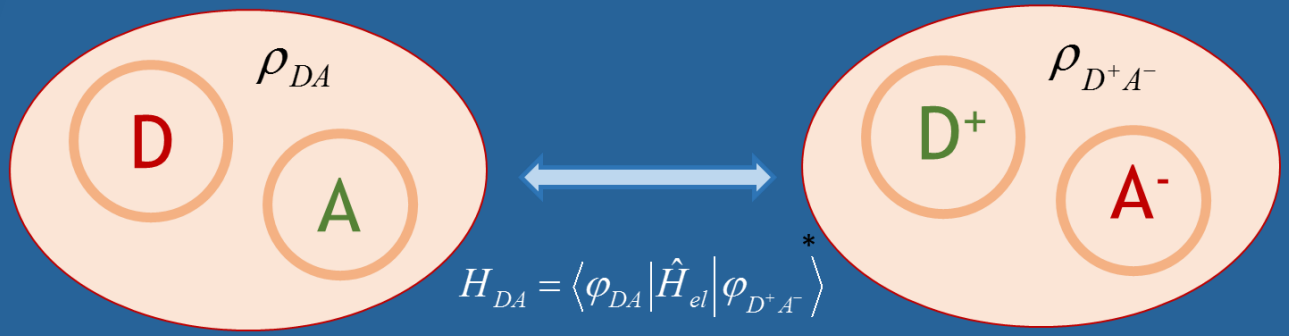
DEFINING DIABATIC STATES AT DFT LEVEL

Dederichs *et al*. *Phys. Rev. Lett*. **1984**, *53*, 2512
Q Wu, T Van Voorhis, *Phys. Rev. A*. **2005**, *72*, 024502



The Kohn-Sham equations are solved under the additional constraint(s) that the integrated density on specific groups of atoms equals Nc

$$E_{cDFT}[\rho] = \min_{\rho} \max_{\lambda_C} \left[E_{DFT}[\rho] + \lambda_C \left(\int \rho(r) w(r) dr - N_c \right) \right]$$



CONSTRAINED DFT IN deMon2k

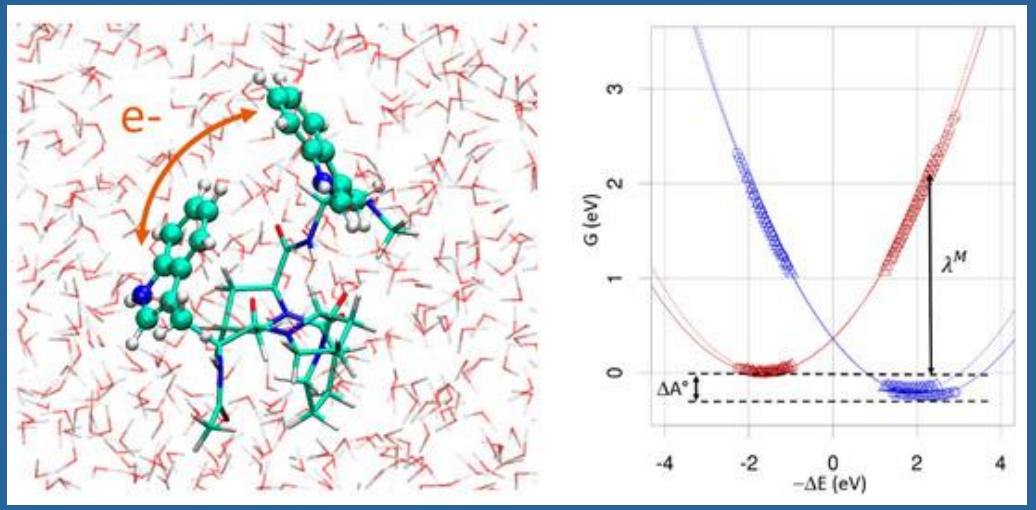
deMon2k
density of Montréal

Robust and efficient implementation

Compatible with QM/MM schemes
--> extented systems

Energy gradients available
--> Ab initio MD simulations

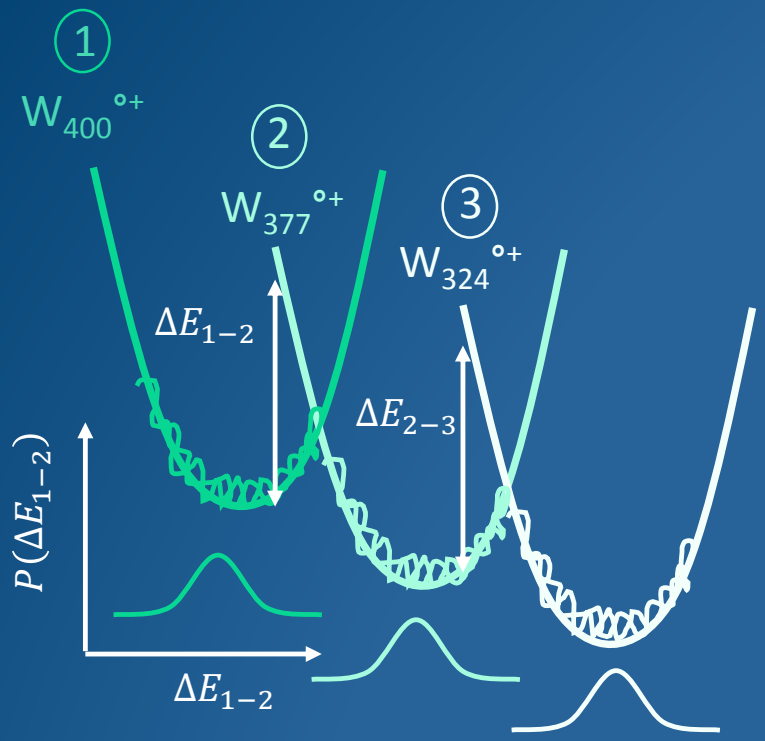
Electronic coupling

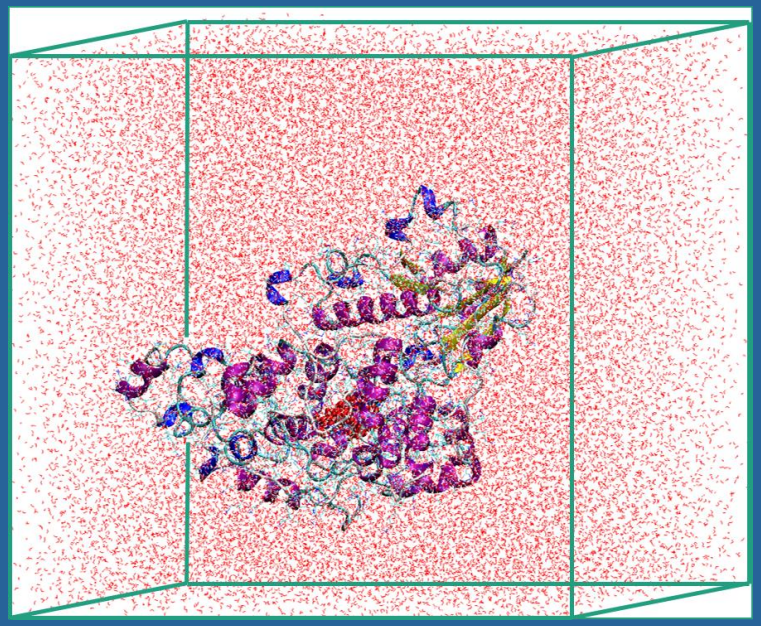


Molecules **2019**, 24, 1653

- A de la Lande, DR Salahub *J. Mol. Struct. THEOCHEM*, **2010**, 943, 115
J Řezáč, B Lévy, I Demachy, A de la Lande, *J. Chem. Theor. Comput*. **2012**, 8, 418.
- A de la Lande, D Salahub, A Köster **2013**. Ed. CRC Press. **2013**
"*Extending the domain of application of constrained density functional theory to large molecular systems*"
- N Gillet, L Berstis, X Wu, F Gajdos, A Heck, A de la Lande, Blumberger, Elstner, *J. Chem. Theor. Comput*. **2016**, 12, 4793
- de la Lande, A.; Alvarez-Ibarra, A.; Hasnaoui, K.; Cailliez, F.; Wu, X.; Mineva, T.; Cuny, J.; Calaminici, P.; López-Sosa, L.; Geudtner, G.; Navizet, I.; Garcia Iriepa, C.; Salahub, D.R.; Köster, A.M. *Molecules* **2019**, 24, 1653

COMPUTATIONAL DETAILS





600 ps of cDFT/MM MD simulation in total

QM: deMon2k (Constrained DFT)
PBE functional
DZVP-GGA basis set
GEN-A2 auxiliary basis set

QM/MM: ONIOMM scheme
MM: CHARMM Force field
electrostatic embedding

MD simulations on PES of states (1) , (2) *and* (3)

$\Delta E(t) = E_f(t) - E_i(t)$
$H_{DA}(t)$

recorded every fs

ENERGETICS OF ET STEPS

$$\Delta G^{\circ}_{i\to j} = \frac{1}{2}\left(\langle \Delta E\rangle_i + \langle \Delta E\rangle_f\right)$$

$inner - sphere$ = tryptophans

$outer - sphere$ = protein, water, FAD, ions....

ET STEP	1	2
$\Delta G^0_{inner-sphere}$	-0.02	0.107
$\Delta G^0_{outer-sphere}$	-0.50	-0.55
ΔG^0_{total}	-0.51	-0.44

values in eV

$$\lambda^{var}_{i\to j} = \frac{1}{4k_BT}\left(\sigma^2\left(\Delta E_{j-i}\right)_i + \sigma^2\left(\Delta E_{j-i}\right)_j\right)$$

ET STEP	1	2
$\lambda^{var}_{inner-sphere}$	0.26	0.29
$\lambda^{var}_{outer-sphere}$	0.90	1.40
λ^{var}_{cross}	< 0.01	< 0.01
λ^{var}_{total}	1.17	1.68

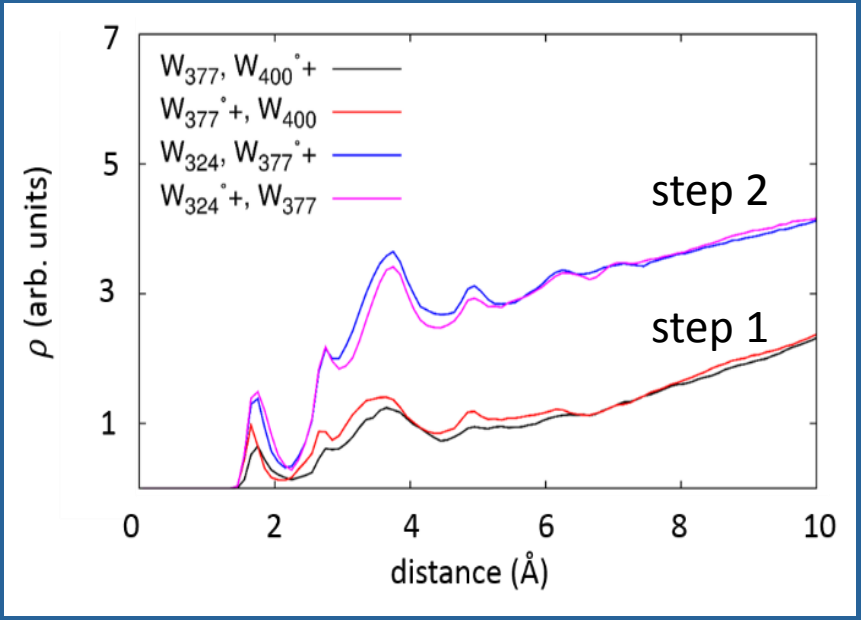
values in eV

REORGANIZATION ENERGIES

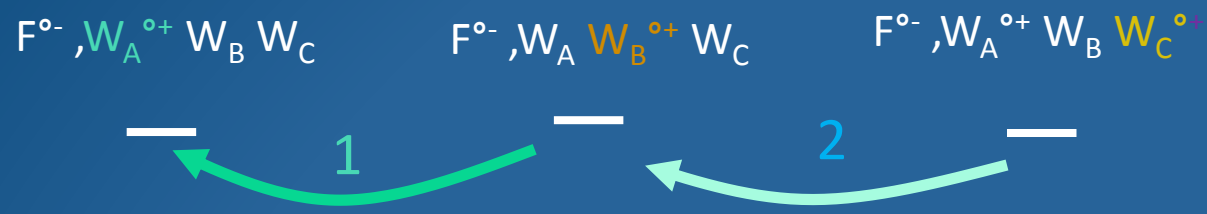
values in eV

ET STEPS	1	2
λ_{FAD}^{var}	0.08	0.02
λ_{water}^{var}	0.76	2.37
$\lambda_{protein}^{var}$	0.76	0.86
λ_{ATP}^{var}	0.03	0.03
λ_{ions}^{var}	0.04	0.05
λ_{cross}^{var}	-0.56	-1.57

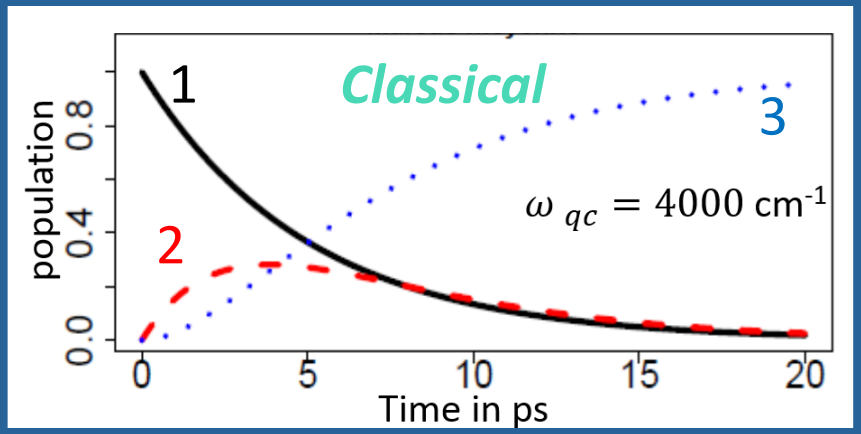
Radial distribution functions of water molecules from the distance of the Trp pair



KINETICS



$$k_{ET} = \frac{2\pi}{\hbar} \frac{1}{\sqrt{4\pi\lambda k_B T}} \langle {H_{DA}}^2 \rangle \exp\left(-\frac{(\Delta G° + \lambda)^2}{4\lambda k_B T}\right)$$



NUCLEAR QUANTUM EFFECTS - KINETIC FORMALISM

ω_{qc} : quantum-classical cutting frequency

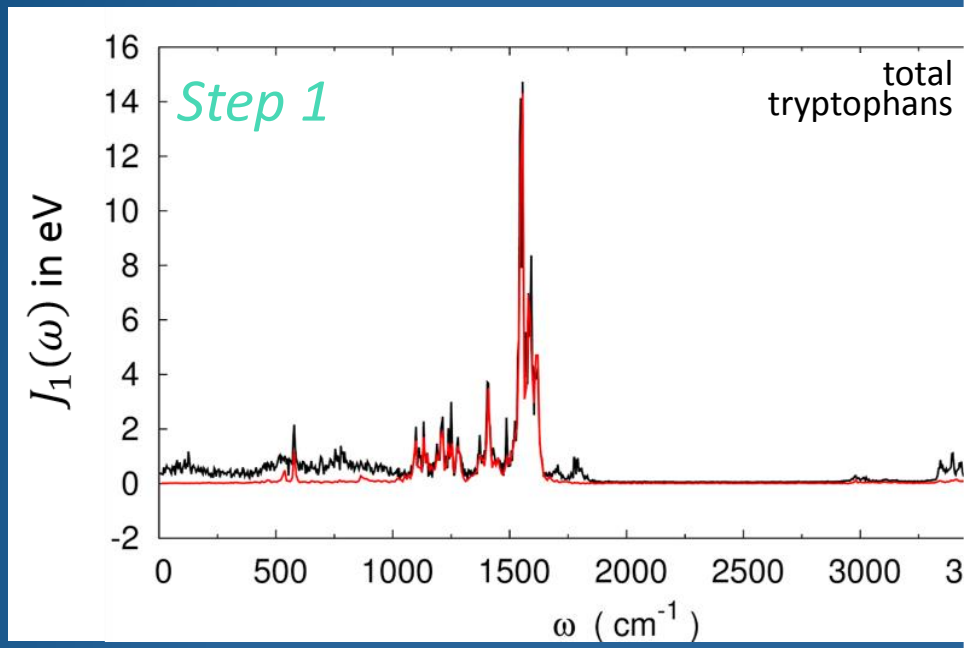
X. Song and A. A. Stuchebrukhov,
J. Chem. Phys., **1993**, 99, 969-978.

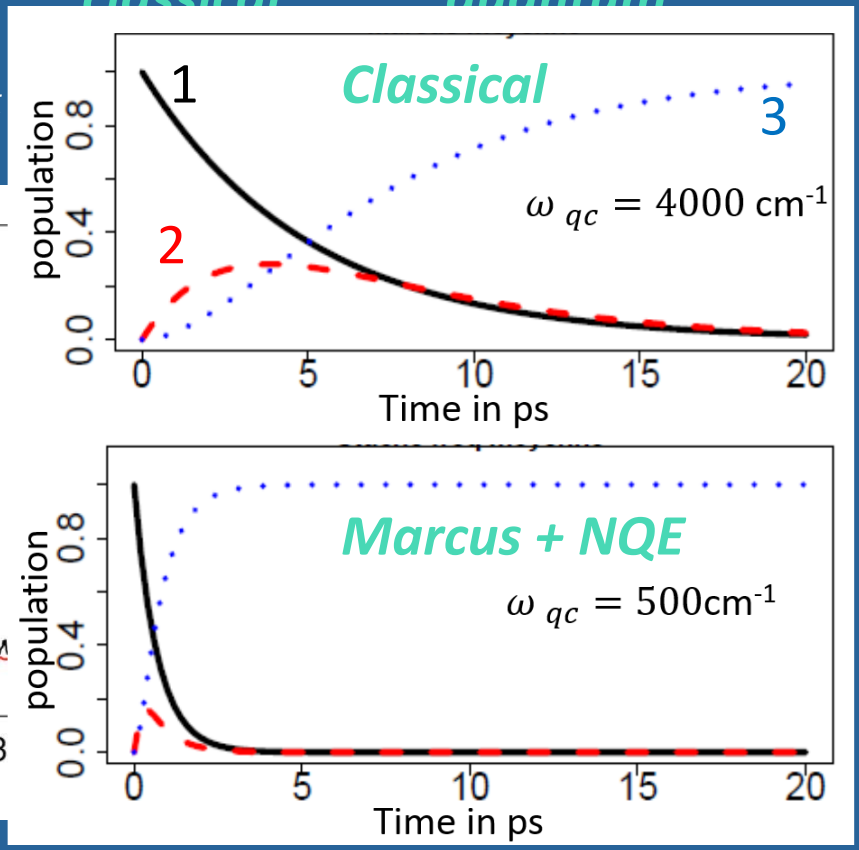
$$k = \frac{2\pi}{\hbar}\langle H_{DA}^2\rangle \frac{1}{\sqrt{4\pi\lambda^J(\omega_{qc})k_B T}} exp\left(\frac{-(\Delta G^\circ + \lambda^{St})^2}{4\lambda^J(\omega_{qc})k_B T} - \frac{1}{\pi\hbar}\int_{\omega_{qc}}^{\infty}\frac{J(\omega)}{\omega^2}d\omega\right)$$

$\omega < \omega_{qc}$ classical

$\omega > \omega_{qc}$ quantum

$$J(\omega) = \frac{\beta\omega}{2}\int_{-\infty}^{+\infty}\langle\delta\Delta E(0)\delta\Delta E(t)\rangle \exp i\omega t\, dt$$





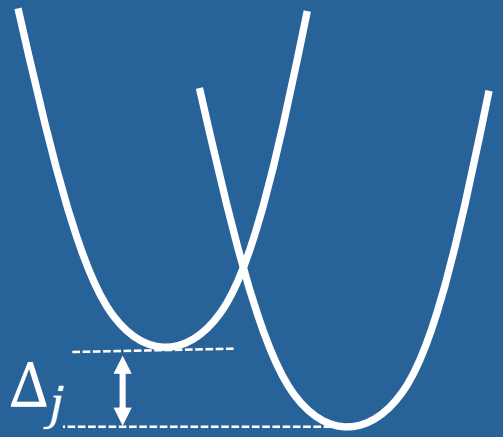
AN ALTERNATIVE METHODOLOGY
DISSIPATIVE QUANTUM DYNAMICS

Etienne Mangaud (PhD 2015)
Chris Meier (Toulouse, Fr.)
Michèle Desouter Lecomte (Orsay, Fr.)

system-bath coupling

$$H_j = \underbrace{\begin{pmatrix} 0 & H_{DA,j} \\ H_{DA,j} & \Delta_j \end{pmatrix}}_{H_{S,j}} + \underbrace{\begin{pmatrix} 1 & 0 \\ 0 & -1 \end{pmatrix}}_{S_j} \underbrace{\sum_{i=1}^{M} \frac{c_{i,j}}{2} q_{i,j}}_{B_j} + H_{B,j} \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}$$

Electronic coupling



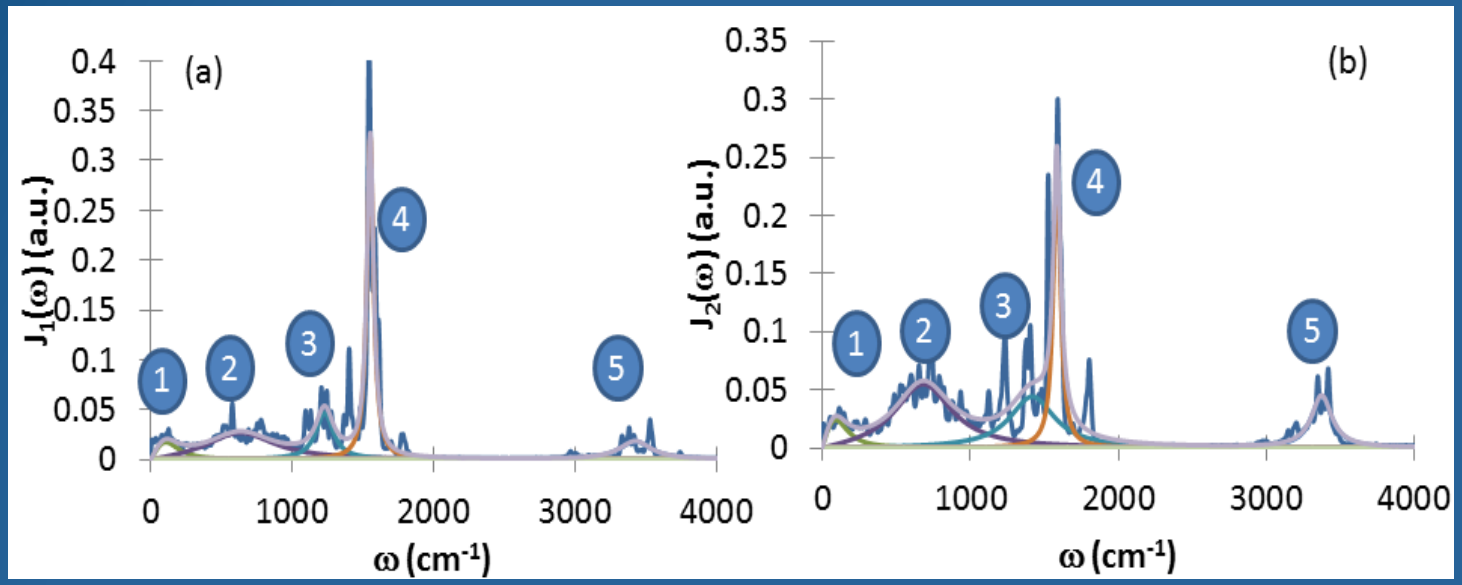
Extension to three electronic states
Strong (system-bath) coupling regime

algorithms based on the Hierarchical Equations of Motion

MAPPING THE SD WITH LORENTZIAN FUNCTIONS

Step 1

Step 2

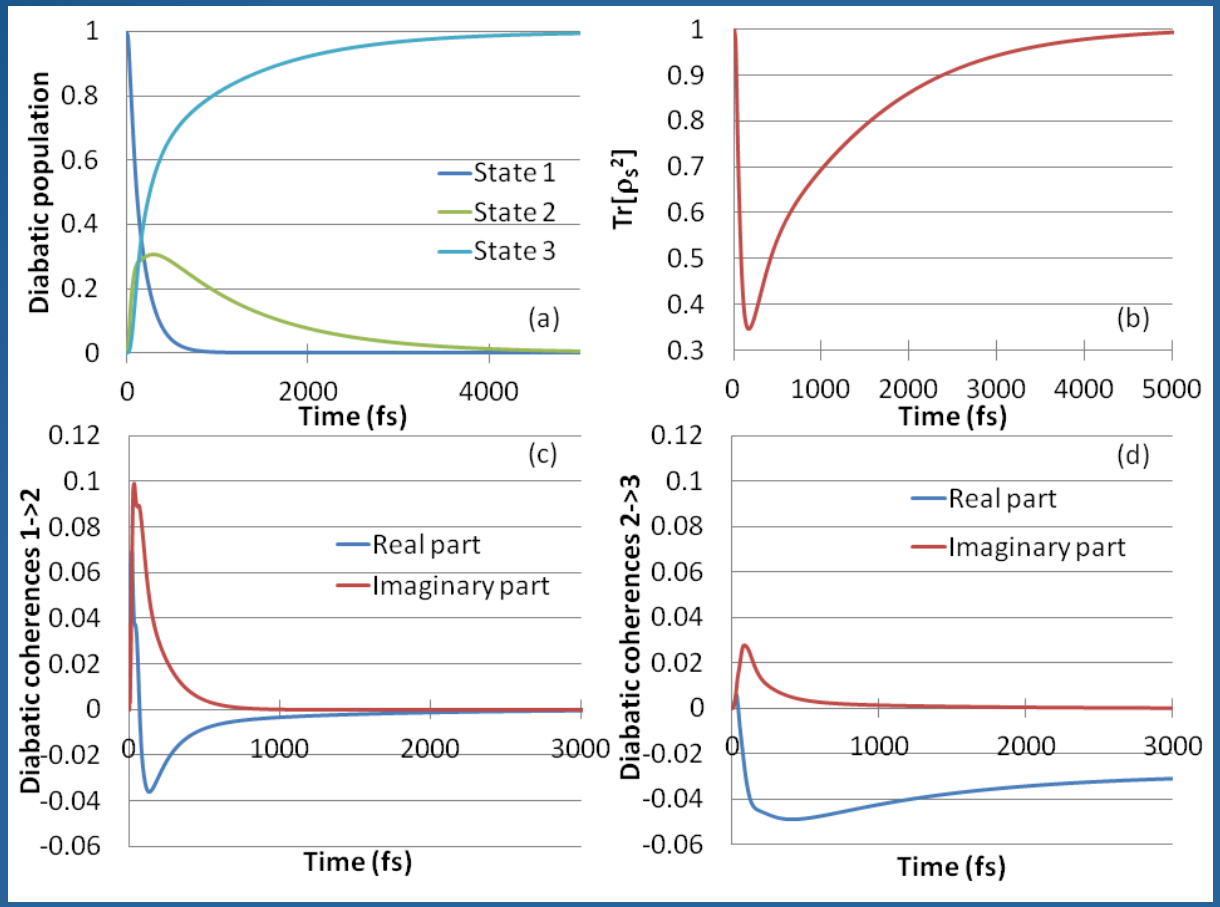


DISSIPATIVE QUANTUM DYNAMICS

Etienne Mangaud

Electronic coherences are lost in few fs

Times scales similar to those given by kinetic theories



Th. Firmino, E. Mangaud, F. Cailliez, A. Devolver, D. Mendive-Tapia, F. Gatti, C. Meier, M. Desouter-Lecomte, A. de la Lande, *Phys. Chem. Chem. Phys*. **2016**, *18*, 21442

D. Mendive-Tapia, E. Mangaud, Th. Firmino, A. de la Lande, M. Desouter-Lecomte, H. Dieter-Meyer, F. Gatti, *J. Phys. Chem. B.* **2018**.*122*, 126 (Treatment with ML-MCTDH)

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I.2.c Recent example of application in cryptochromes

II – Beyond "Vanilla Marcus theory"

II.1 Breakdown of the linear response approximation

II.1.a. High polarizability of redox cofactor
II.1.b. Non-ergodic systems

II.2 Beyond the two-state model

II.2.a. Flickering resonance model
II.2.b. Recent example of application in photolyases

III – The mystery of electron tunneling through proteins

III.1 Interpretative models for tuneling

III.1.a. Hopfield model
III.1.b. Pathway model
III.1.c Interatomic tunneling currents

I.2 Dynamical effects on tunneling

III.2.a. Inelastic tunneling
III.2.b. Recent example of application in cryptochromes
III.2.c Coherence loss in slow coupling regime

II.1 Breakdown of the linear response approximation

II.1.a. High polarizability of redox cofactor

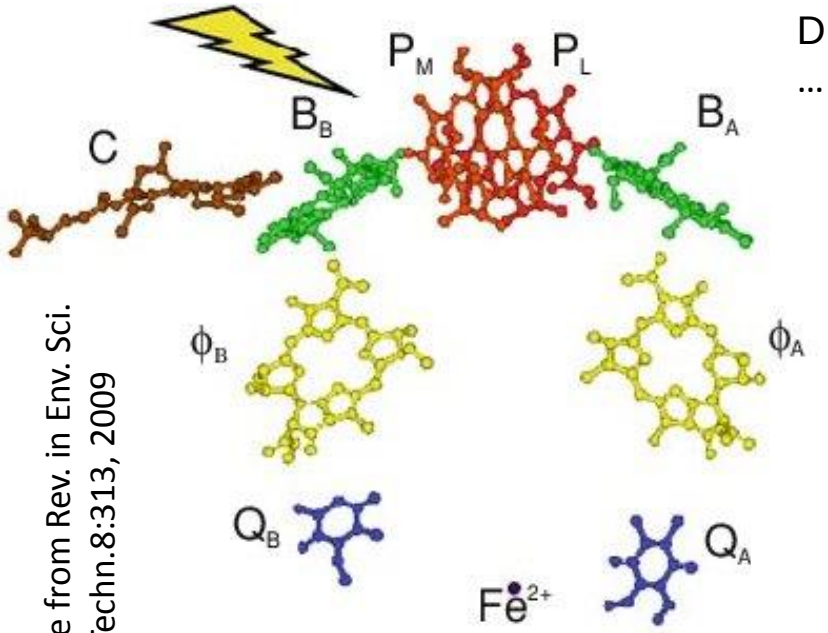


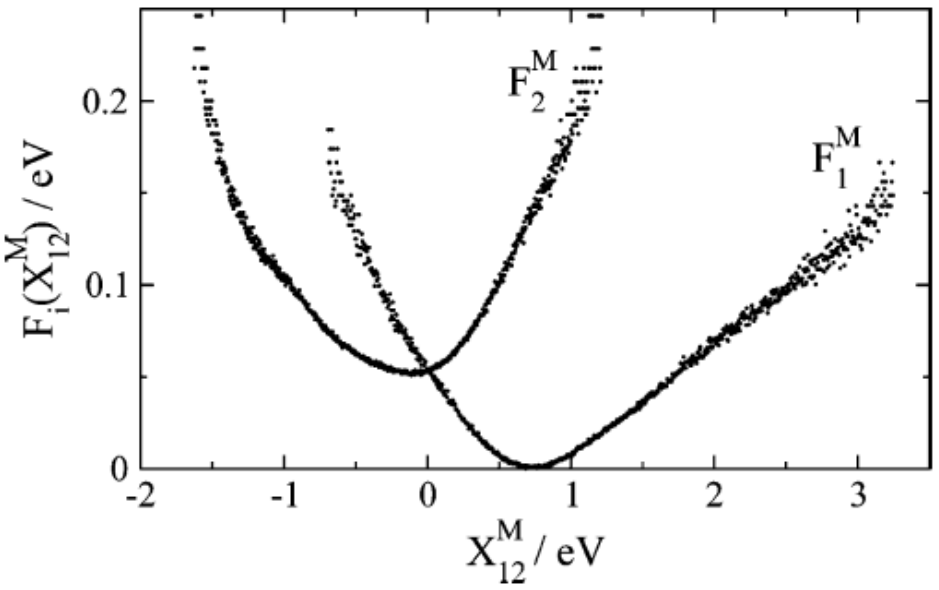
Image from Rev. in Env. Sci. Bio/Techn.8:313, 2009

D. V. Matyushov and G. A. Voth, *J Chem Phys*, 2000, **113**, 5413
D. Matyushov, Acc. Chem. Res. **2007,** 40, 294-301
DN LeBards, D. Matyushov *J. Phys. Chem. B* **2009,** *113,* 12424
…

Q-model

$$E_x(\mathrm{q}) = E_x^0 - C_x q + \frac{1}{2}\zeta_x q^2$$

$[P^*,B_A]\rightarrow[P^+,B_A^-]$



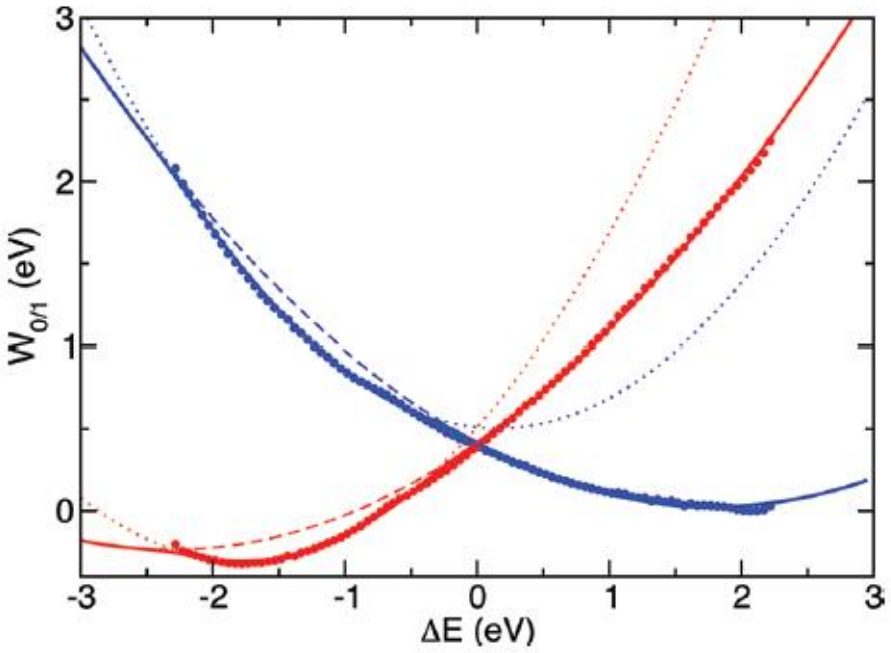
II.1 Breakdown of the linear response approximation

II.1.a. Non-ergodic effects

R. Vuilleumier, K. A. Tay, G. Jeanmairet, D. Borgis A. Boutin, *J Am Chem Soc*, 2012, **134**, 2067-2074

Solvation state change drastically between two redox states

But… the linear response approximation remains valid within each solvation states



$Cu_{aq}^{+} \rightarrow Cu_{aq}^{2+}$ in water

See also Matyushov (Univ. Arizona) for dedicated framework to treat redox and spectroscopic properties in non-ergodic biological systems

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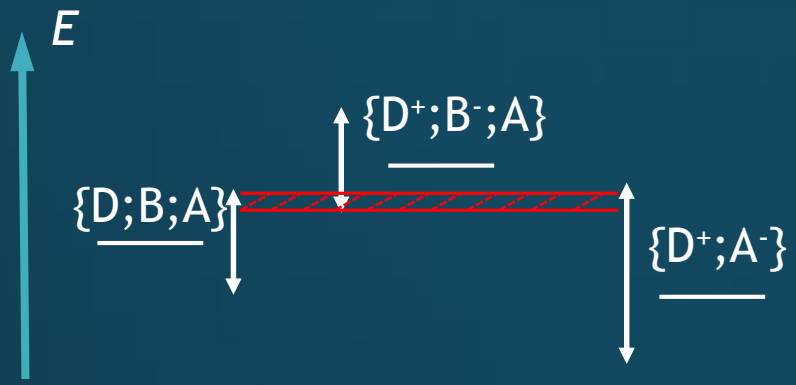
II.1 Breakdown of the linear response approximation

II.1.a. High polarizability of redox cofactor
II.1.b. Non-ergodic systems

I.2 Beyond the two-state model

II.2.a. Flickering resonance model
I.2.b.

SITES ENERGY FLUCTUATIONS, COUPLING FLUCTUATIONS …

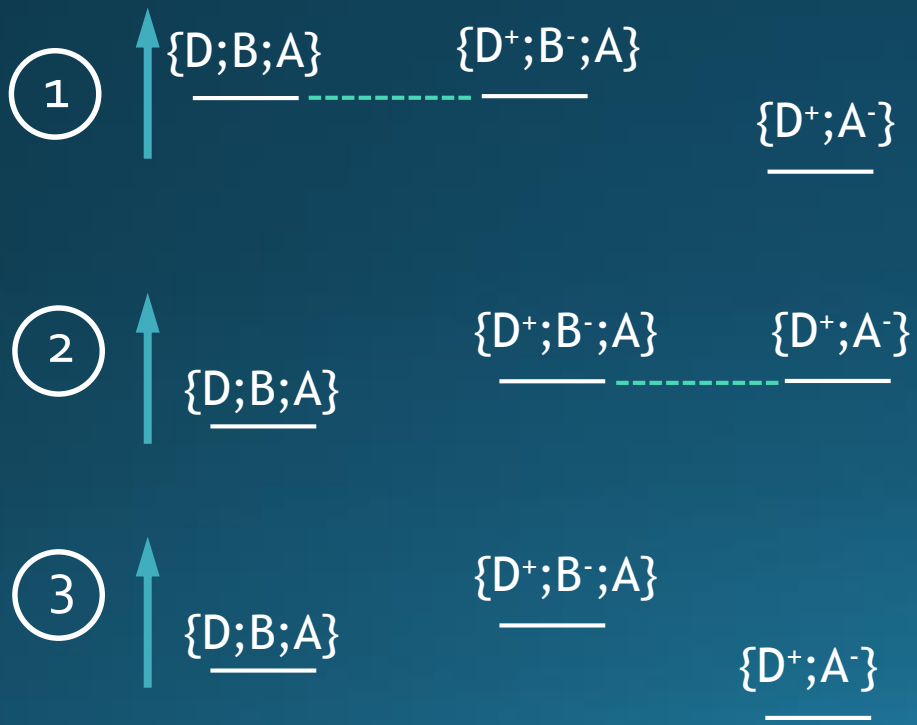


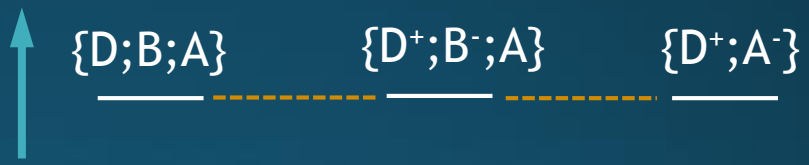
Condition of resonance:

$$\Delta E \leq H_{DA}$$

Incoherent mechanism

Coherent mechanism





A KINETIC MODEL: THE FLICKERING RESONANCE MECHANISM

Generalization of the Hopfield theory* of ET to multiple sites **

$$W_1^{\circ +} W_{i=2,N-2}\ W_N \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} (W_1^{\circ +}\ W_{i=2,N-2}\ W_N)^* \xrightarrow{k_{trans}} (W_1\ W_{i=2,N-2}\ W_N^{\circ +})^* \xrightarrow{k_{trap}} (W_1\ W_{i=2,N-2}\ W_N^{\circ +})$$

$$k_{FR}(\mathrm{N}) = \frac{1}{\tau} \times P_{match}(N)$$

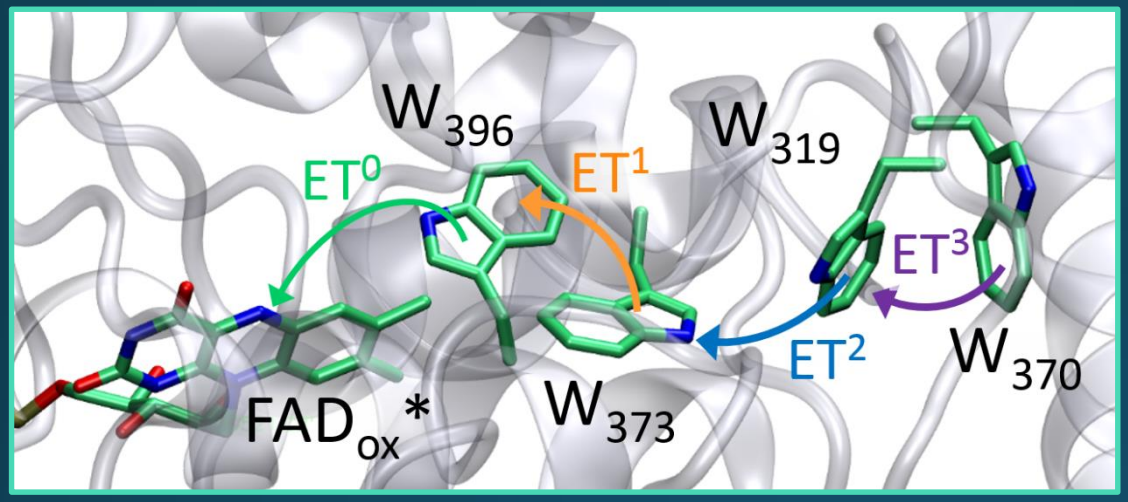
$$P_{match}(N) = \int_{-\infty}^{-\infty} dH_{DA}\, \rho_H(H_{DA}) \int_{-\infty}^{-\infty} dE_1 \rho_1(E_1) \int_{E_1 - H_{DA}}^{E_1 + H_{DA}} dE_2 \rho_2(E_2) \ldots \int_{max\{E_1,\ldots,E_{N-1}\}\mathrm{c} - H_{DA}}^{min\{E_1,\ldots,E_{N-1}\} + H_{DA}} dE_N \rho_N(E_N)$$

$$\rho_{D/D+}^{o,a_x}(\Delta E_D^{ox}) = \frac{1}{\sqrt{2\pi}\sigma_D} exp\left(\frac{-\left(\Delta E_D^{ox} - \overline{\Delta E_D^{ox}}\right)^2}{2\sigma_D^2}\right)$$

* J. J. Hopfield, *Proc Natl Acad Sci*, 1974, **71**, 3640

Zhang, Y.; Liu, C.; Balaeff, A.; Skourtis, S. S.; Beratan, D. N. *Proc. Natl. Acad. Soc.* **2014, *111*, 10049

An example in the case of photolyaes
Competition between incoherent and coherent mechanisms



Xenopus laevis (frog)
(6-4) photolyase

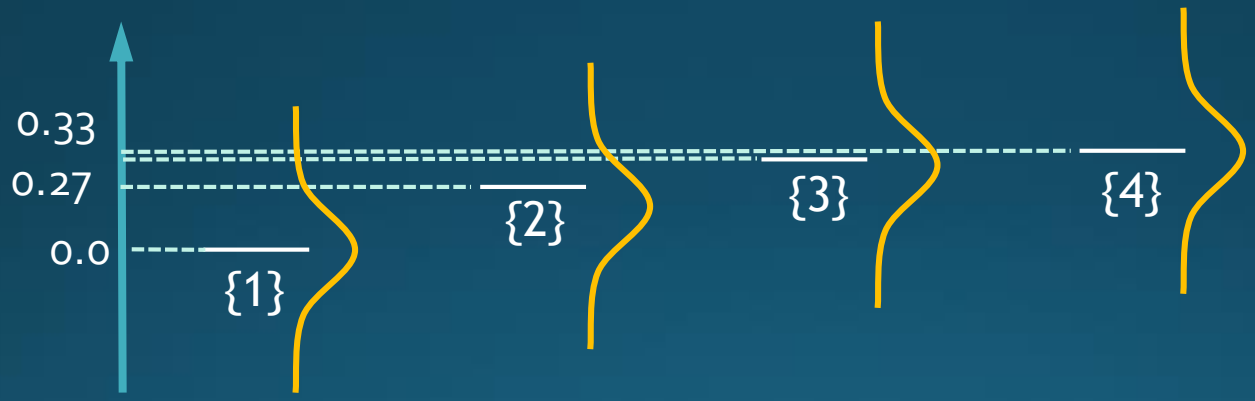
Müller, P.; Yamamoto, J.; Martin, R.; Iwai, S.; Brettel, K. *Chem. Commun.* **2015**, *51*, 15502

F. Cailliez, P. Muller, Th. Firmino, P. Pernot, A. de la Lande, *JACS*, **2016**, *138*, 1904

ENERGY LEVEL ALIGNMENT

based on DFT + polarizable MD

N	2	3	4
$\overline{\Delta E_D^{ox}}$ (eV)	0.27 (0.04)	0.33 (0.11)	0.33 (0.09)
σ_D (eV)	0.18 (<0.01)	0.20 (<0.01)	0.21 (<0.01)
$P_{match}(N)$	5.75 10-3 (1.23 10-3)	1.23 10-4 (5.64 10-5)	3.11 10-6 (1.83 10-6)

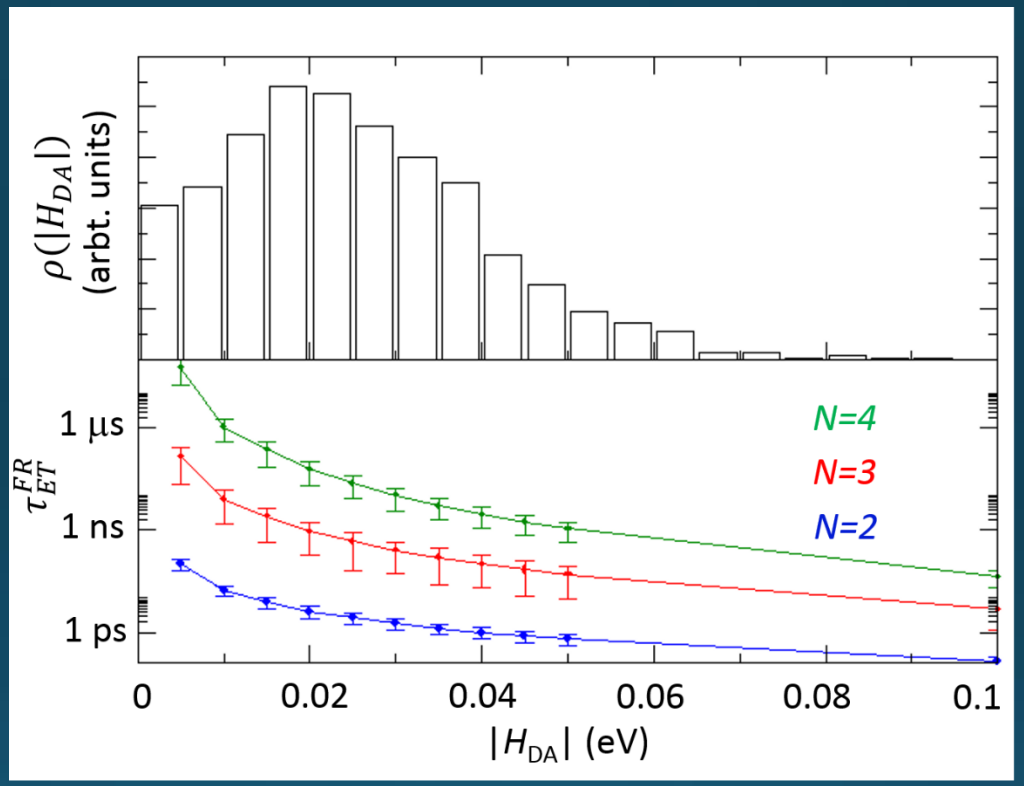


The probability to align the first three energy levels is substantial.
But strong dependence on the initial nuclear configuration

F. Cailliez, P. Muller, Th. Firmino, P. Pernot, A. de la Lande, *JACS*, **2016**, *138*, 1904

FLICKERING RESONANCE TIME SCALES

$$k_{FR}(\mathrm{N}) = \frac{1}{\tau} \times P_{match}(N)$$



FR over three sites can be envisionned
Again, strong dependence on the initial nuclear configuration

F. Cailliez, P. Muller, Th. Firmino, P. Pernot, A. de la Lande, *JACS*, **2016**, *138*, 1904

I – The Macus theory: concepts, theory and computer simulations

I.1 Pioneer ideas from Libby, Marcus, Hush…

I.2 The Marcus theory in the era of supercomputers

I.2.a. Linear Response Approximation
I.2.b A very simple example to set ideas
I.2.c Nanosecond ET in cytochrome c oxydase

I-3. Quantum and semi-classical formulations

I.2.a. Fermi golden rule and spin-boson model
I.2.b. Mixed quantum-classical, application to inverted region
I.2.c Recent example of application in cryptochromes

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III.1 Interpretative models for tuneling

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III.1.b. Pathway model
III.1.c Interatomic tunneling currents

III.2 Dynamical effects on tunneling

III.2.a. Inelastic tunneling
III.2.b. Recent example of application in cryptochromes
III.2.c Coherence loss in slow coupling regime

Tunneling in proteins why is it important ?

$$H_{DA} = \langle \varphi_1 | H_{el} | \varphi_2 \rangle$$

- Determines the probability of electronic change

example of Landau Zener theory $P_{LZ} = 1 - \exp\left(\frac{-2\pi H_{DA}^2}{\hbar \dot{\Delta E}}\right)$

- Remind that Fermi golden rule assumes weak coupling (<~ 100 cm^{-1})

- Reflects the likelyhood of tuneling from D to A

$$H_{DA} = \langle \varphi_1 | H_{el} | \varphi_2 \rangle$$

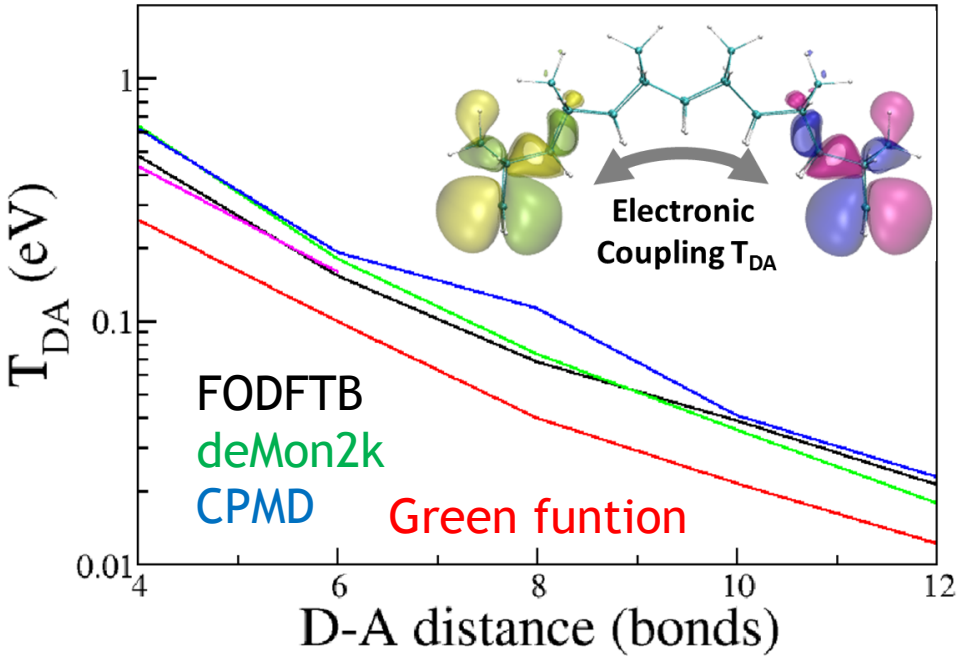
QUANTUM CHEMISTRY METHODS

M.D. Newton, *Chem. Rev*. (Washington, DC, U.S.) 91 (1991) 767–792.
A.A. Stuchebrukhov, *Theor. Chem. Acc.* 110 (2003) 291–306.
Progress and challenges in simulating and understanding electron transfer in proteins. A de la Lande, S. Chen, DR. Salahub. *Arch. Biochem. Biophys*. 582 (2015) 28–41

electronic states in a *diabatic* basis

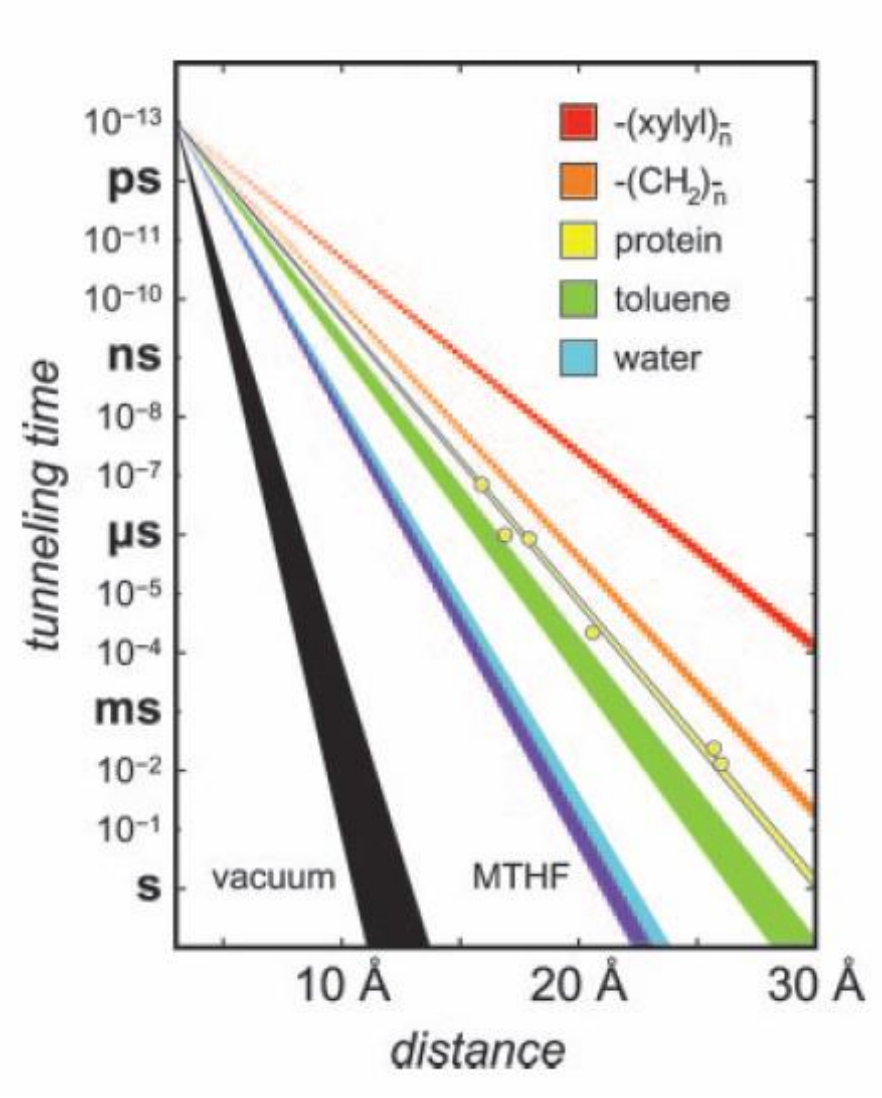
$$H_{DA} = \langle \varphi_1 | H_{el} | \varphi_2 \rangle$$

Most quantum chemistry methods give ***adiabatic*** states



N Gillet, L Berstis, X Wu, F Gajdos, A Heck, A de la Lande, J Blumberger, M Elstner, *J. Chem. Theor. Comput*. **2016**, 12, 4793

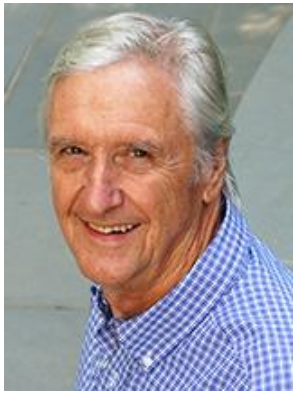
THE NEED FOR RATIONALIZATION MODELS



Harry Gray

David Beratan

John Hopfield



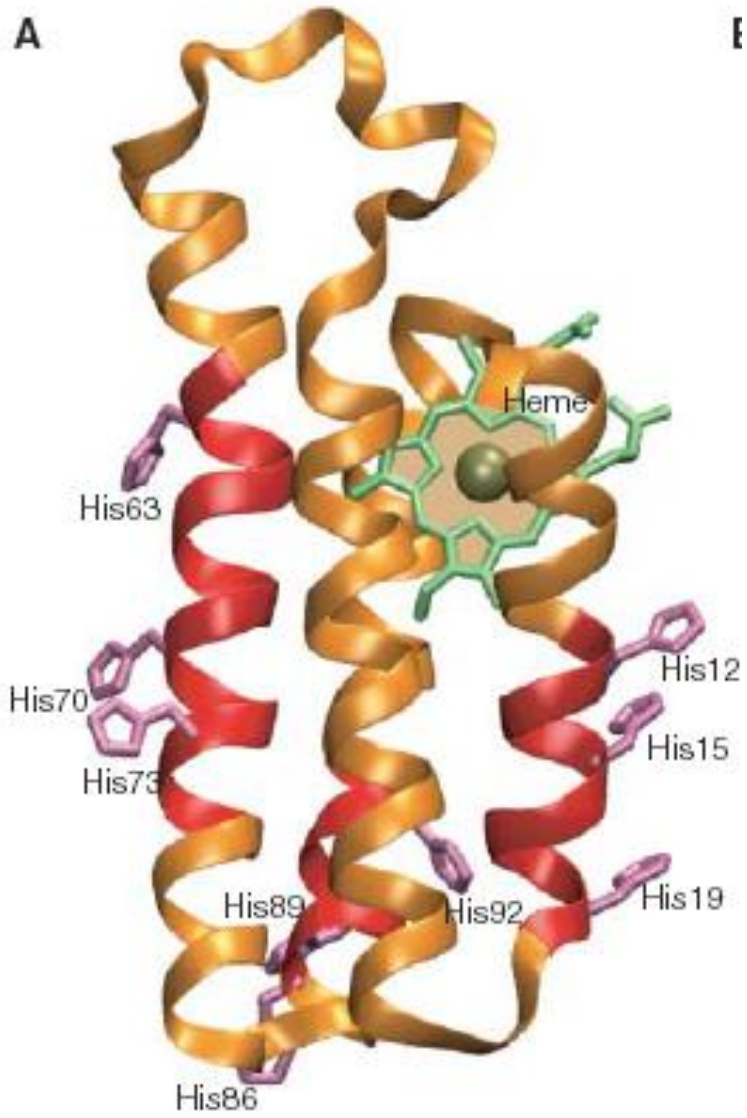
Leslie Dutton

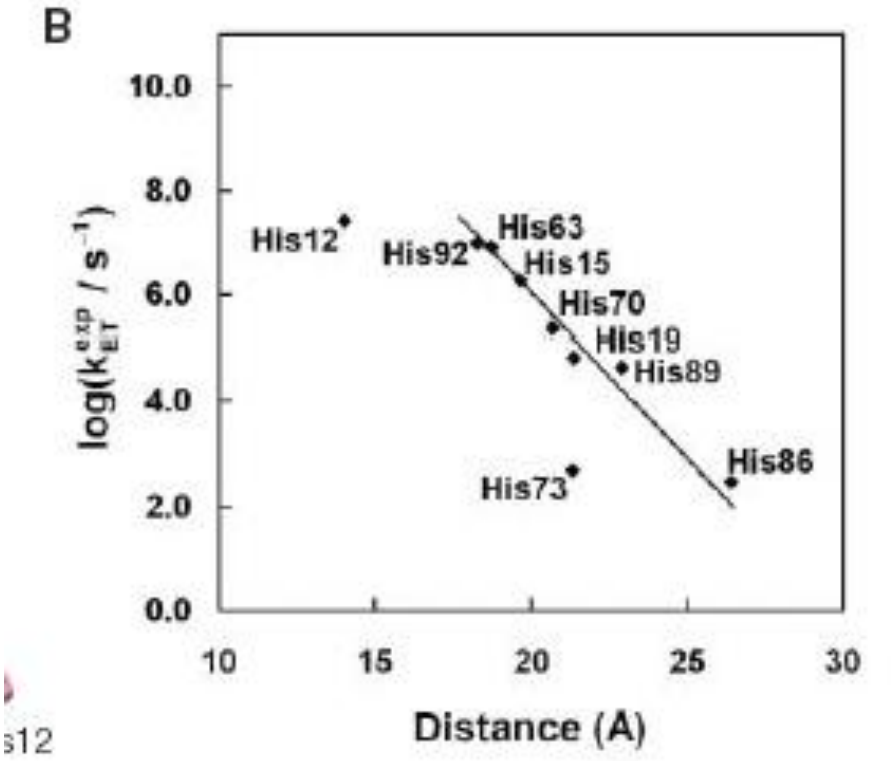
from H. B. Gray, J. R. Winkler, *PNAS*, **2005**, 102, 3534

A VERY CLEVER STRATEGY

HB Gray and co-workers

Ru-cytochromes
Ru-myoglobines
Ru-azurines

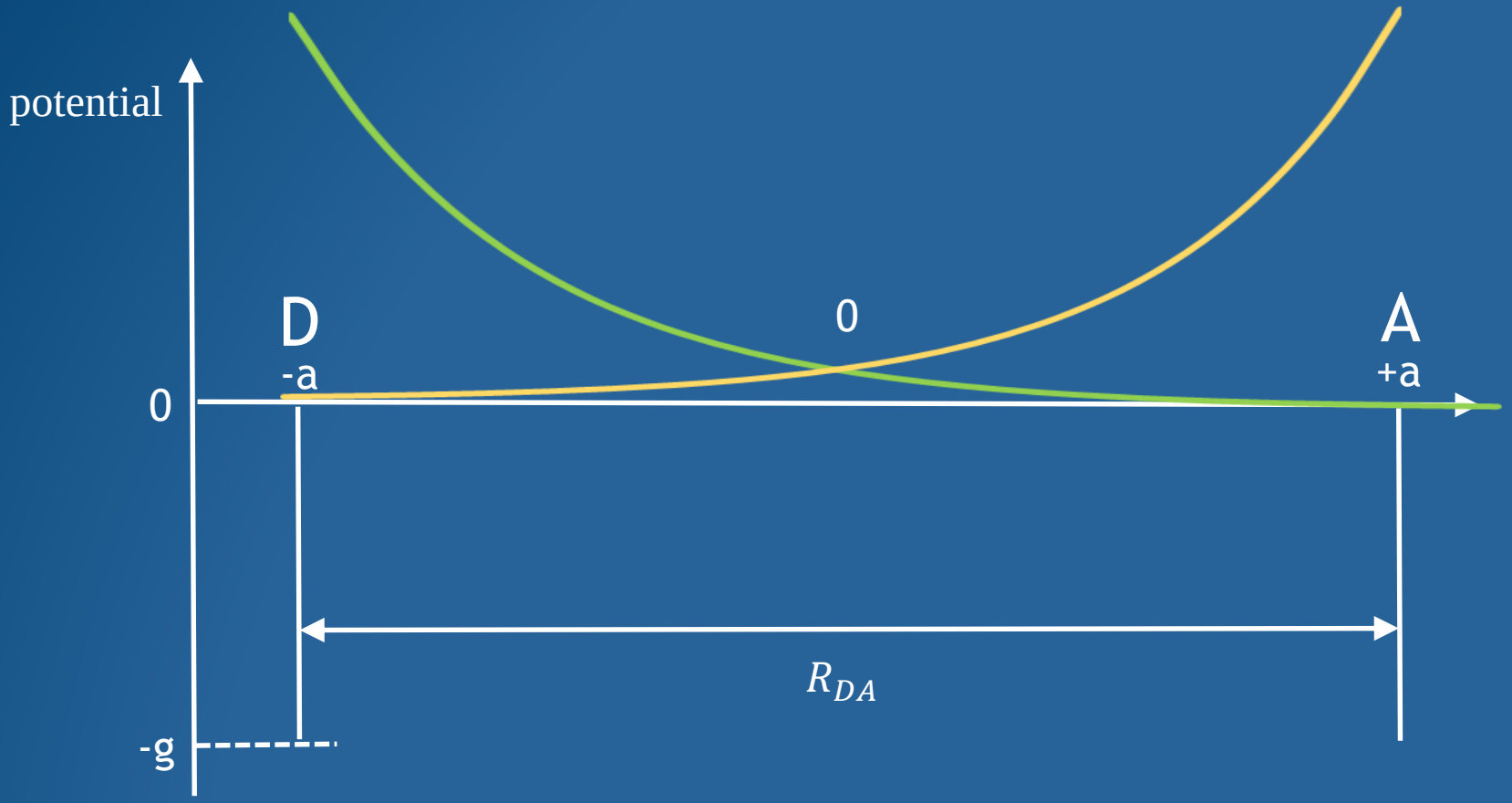




from T. R. Prytkova, I. V. Kurnikov and D. N. Beratan, *Science* **2007**, *315*, 622

$\phi_D(x) = \sqrt{\kappa}.\exp(-\kappa|x-a|)$

$\phi_A(x) = \sqrt{\kappa}.\exp(-\kappa|x+a|)$



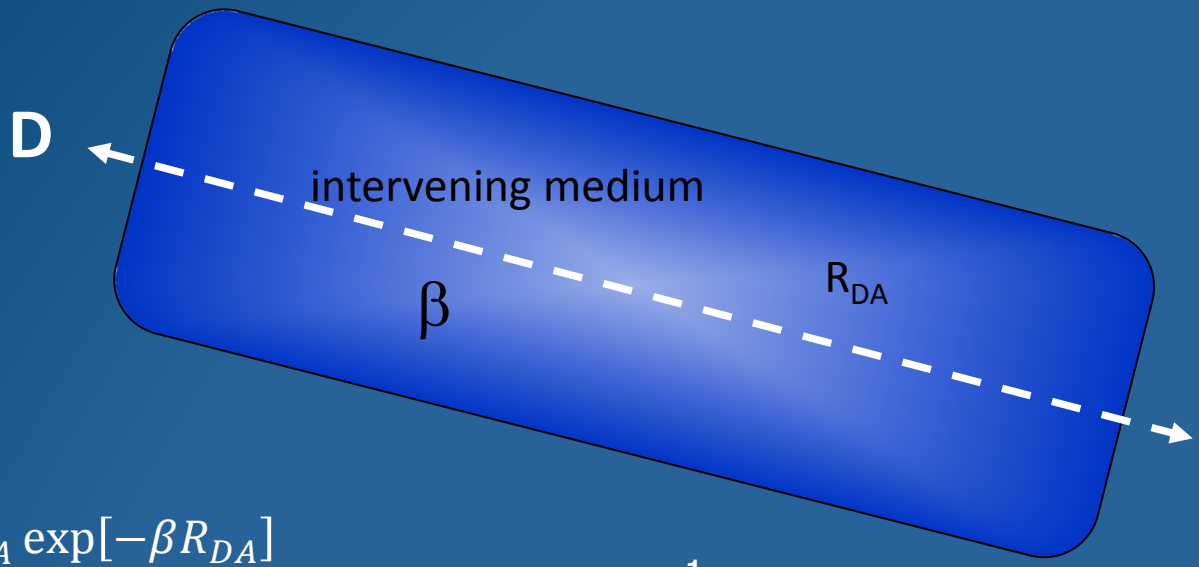
$\kappa = m_e g/\hbar^2$

$$H_{DA} = \frac{-g^2}{2\hbar^2}\exp\left[-2a\sqrt{-2m_e E_0/\hbar^2}\right] = H_{DA}^0 \exp[-\beta R_{DA}]$$

Homogeneous systems models

Hopfield (1974)

John Hopfield

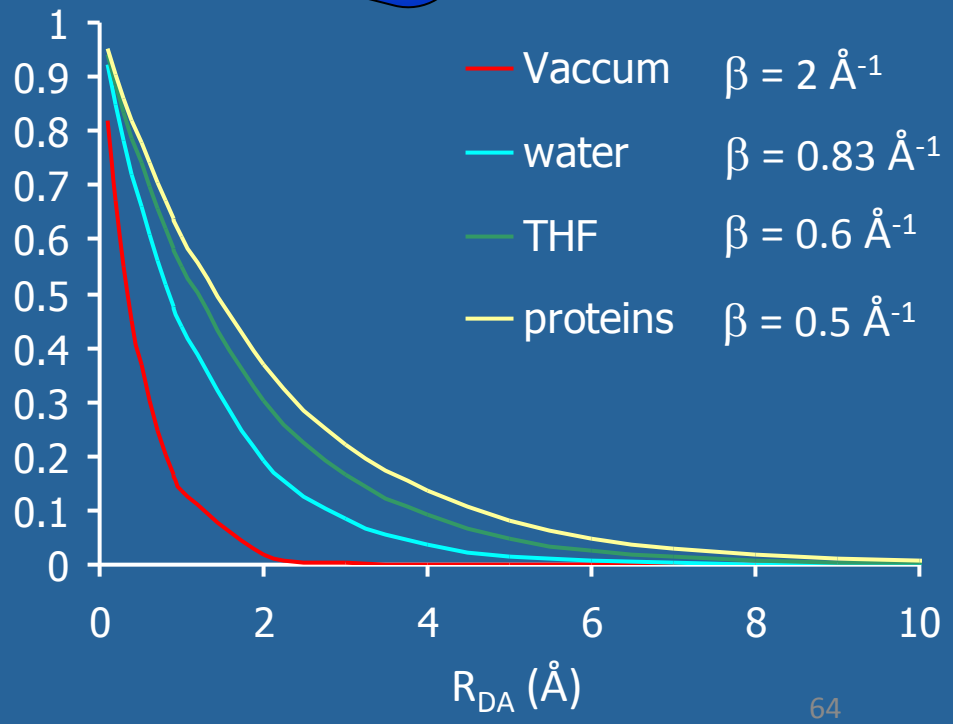


$$H_{DA} = H_{DA}^{0} \exp[-\beta R_{DA}]$$

$$\beta = \sqrt{-2m_e E_0/\hbar^2}$$

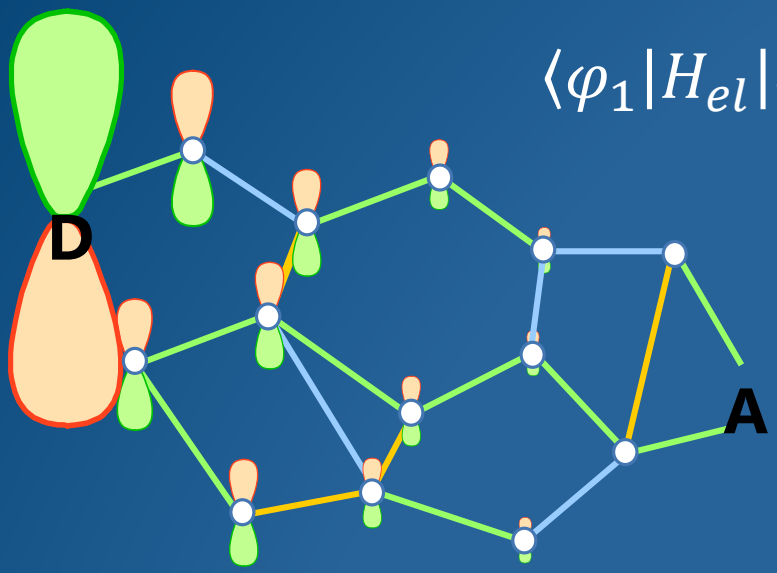
for proteins the $\sigma \rightarrow \sigma^*$ band gap of the surrounding material ($\approx$ 3eV)

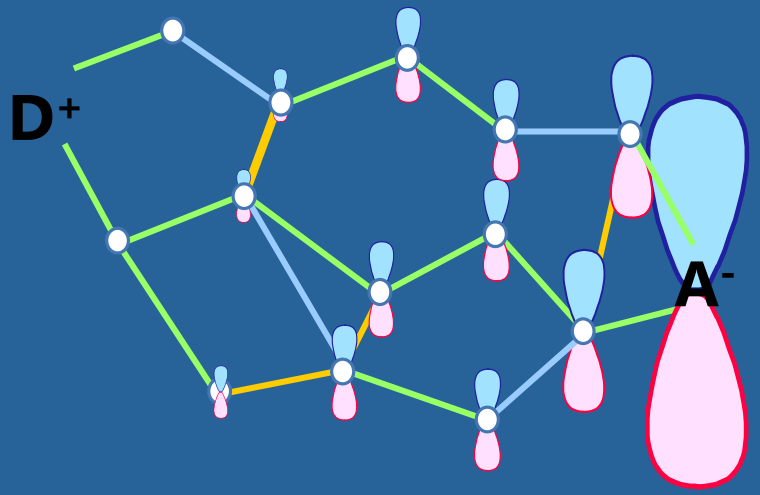
$$\beta = 0.72$$

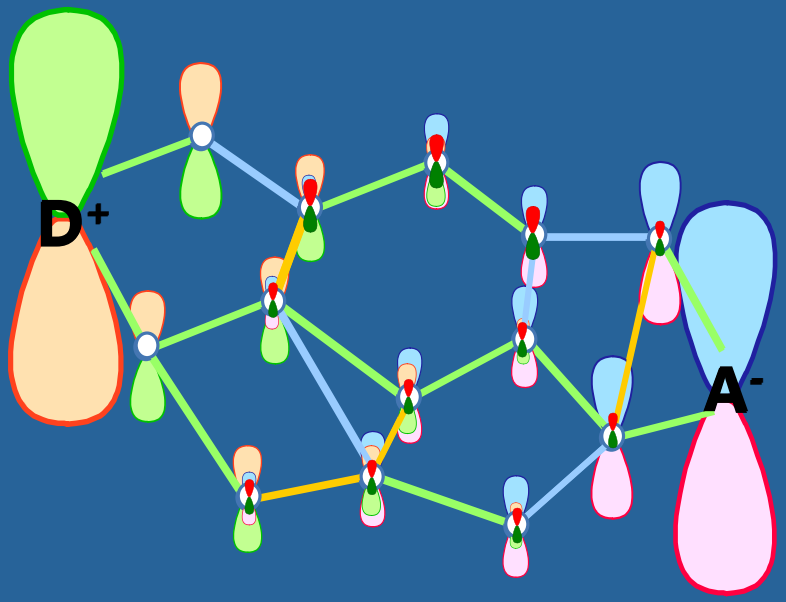


Let's just consider the pair of MOs that exchange electrons

$$\langle \varphi_1 | H_{el} | \varphi_2 \rangle \propto \langle \varphi_1 | \varphi_2 \rangle$$



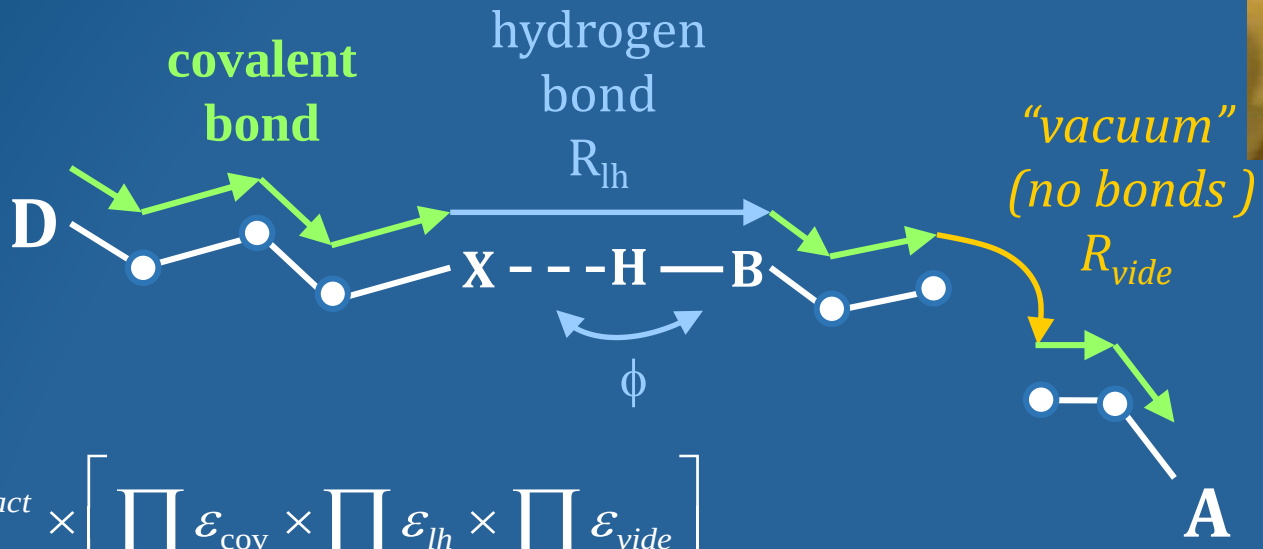




THE TUNNELING PATHWAY MODEL

D. N. Beratan *et Coll*. 1991

- atomes



$$H_{DA} = H_{DA}^{contact} \times \left[\prod_{N\,\mathrm{cov}} \varepsilon_{\mathrm{cov}} \times \prod_{Nlh} \varepsilon_{lh} \times \prod_{Nvide} \varepsilon_{vide} \right]$$

↗ $\varepsilon_B = \varepsilon_c = 0.6$

↗ $\varepsilon_H = \varepsilon_c^2 \exp[-1.7(R^H - 2.8)]$

↗ $\varepsilon_S = \varepsilon_c \exp[-1.7(R^S - 1.4)]$

} good conductivity

} bad conductivity

SEARCH FOR THE BEST PATHWAY

Dijkstra algorithm

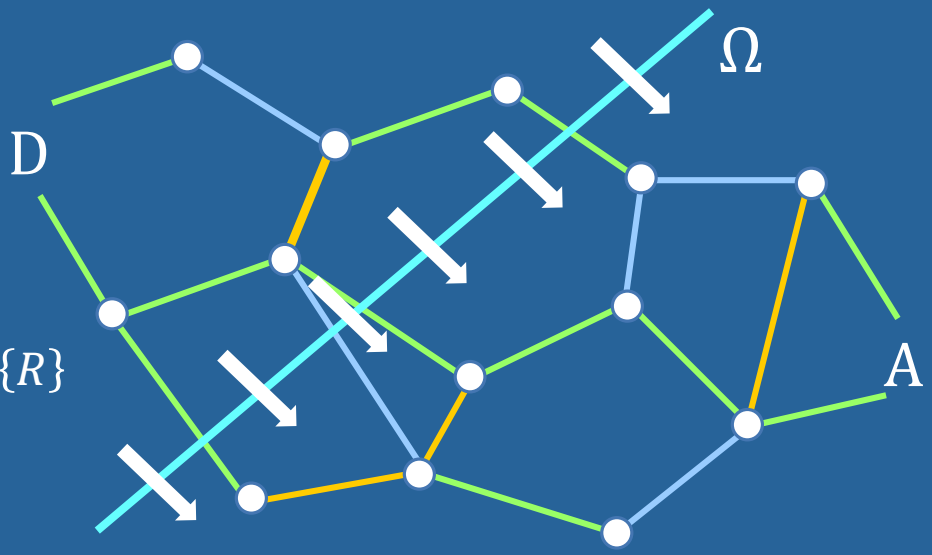
find your way on a map !

- Assume on pathway dominate over the others (in practice an excellent approximation)

- No explicit interferences among pathways

EVEN HIGHER RESOLUTION: INTER-ATOMIC TUNNELING CURRENTS

A. A. Stuchebrukhov, *Theor. Chem. Acc.* **2003**, *110*, 291



- The electronic wave function is a linear combination of the two diabatic states

$$\psi_{el}(t) = \cos\left(\frac{H_{DA}}{\hbar}t\right)\phi_1\{R\} - \sin\left(\frac{H_{DA}}{\hbar}t\right)\phi_2\{R\}$$

- The density current operator reads

$$\boldsymbol{j}(\boldsymbol{r},t) = \frac{\hbar}{2m_e i}(\psi_{el}^*\nabla\psi_{el} - \psi_{el}\nabla\psi_{el}^*)$$

Only one pair of MOs are important

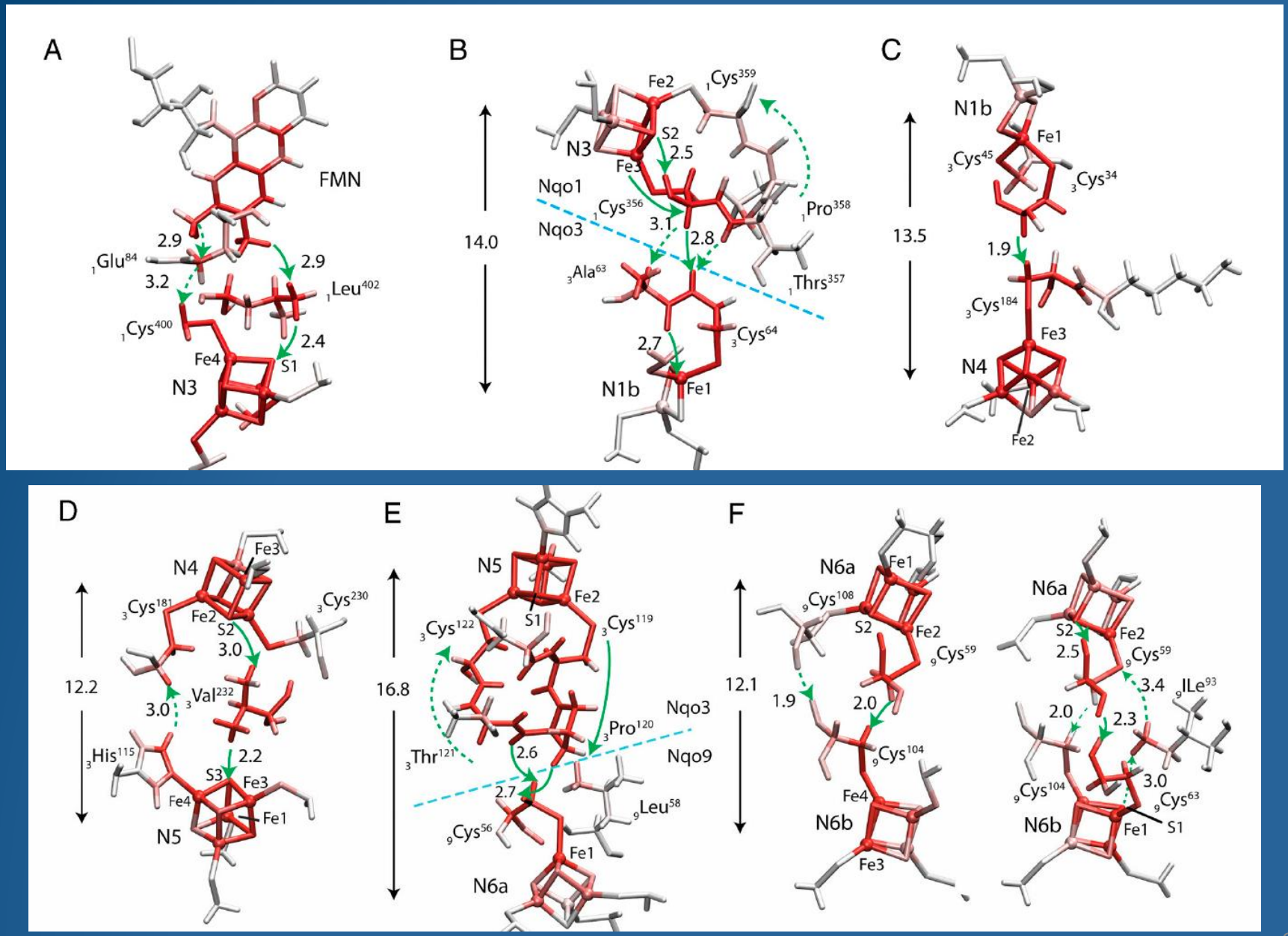
$$\boldsymbol{J}(\boldsymbol{r}) = \langle\phi_1|\boldsymbol{j}|\phi_2\rangle = \frac{\hbar}{2m_e}(\phi_1^*\nabla\phi_2 - \phi_2\nabla\phi_1^*)$$

$$H_{DA} = -\hbar\int_\Omega \boldsymbol{J}(\boldsymbol{r})d\Omega$$

interatomic decomposition

$$H_{DA} = \sum_{a\in\Omega}\sum_{b\notin\Omega} J_{ab}$$

EVEN HIGHER RESOLUTION: INTER-ATOMIC TUNNELING CURRENTS



Hayashi, Stuchebrukhov; *Proc. Nat. Acad. Soc*. **2010**, *107*, 19157

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WHAT ABOUT THERMAL MOTION ?

WHAT ABOUT THERMAL MOTION ?

$$k_{ET} = \frac{2\pi}{\hbar}\frac{1}{\sqrt{4\pi\lambda k_B T}}|H_{DA}|^2 \exp\left(-\frac{(\Delta G° + \lambda)^2}{4\lambda k_B T}\right)$$

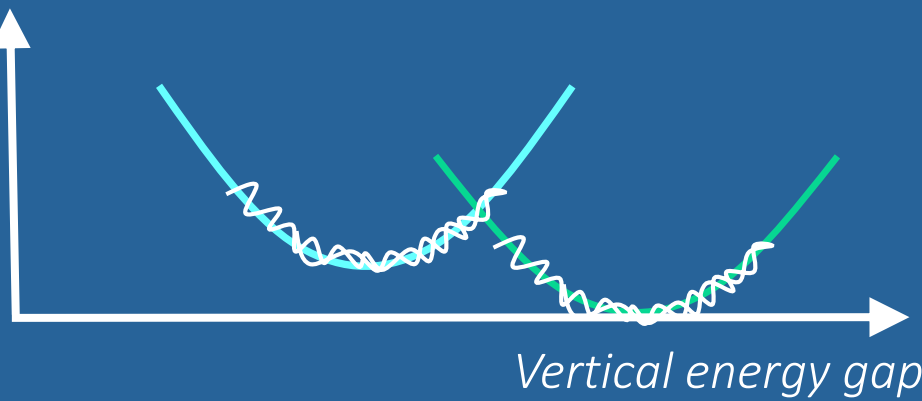
THIS IS NOT A CONSTANT !!!

$$k_{ET} = \frac{2\pi}{\hbar}\frac{1}{\sqrt{4\pi\lambda k_B T}}\langle|H_{DA}|^2\rangle \exp\left(-\frac{(\Delta G° + \lambda)^2}{4\lambda k_B T}\right)$$

TWO IMPORTANT TIMESCALES

τ_{FC} How fast the diabatic energy gap changes in time

τ_{coh} How fast the electronic coupling changes in time



$\tau_{coh} \ll \tau_{FC}$ FAST coupling regime

$$k_{ET} = \frac{2\pi}{\hbar} \frac{1}{\sqrt{4\pi\lambda k_B T}} \langle |H_{DA}|^2 \rangle \exp\left(-\frac{(\Delta G^\circ + \lambda)^2}{4\lambda k_B T}\right)$$

breakdown of Condon approximation

Theories of inelastic tunneling

A. Troisi, A. Nitzan and M. A. Ratner, J Chem Phys, 2003, 119, 5782-5788.

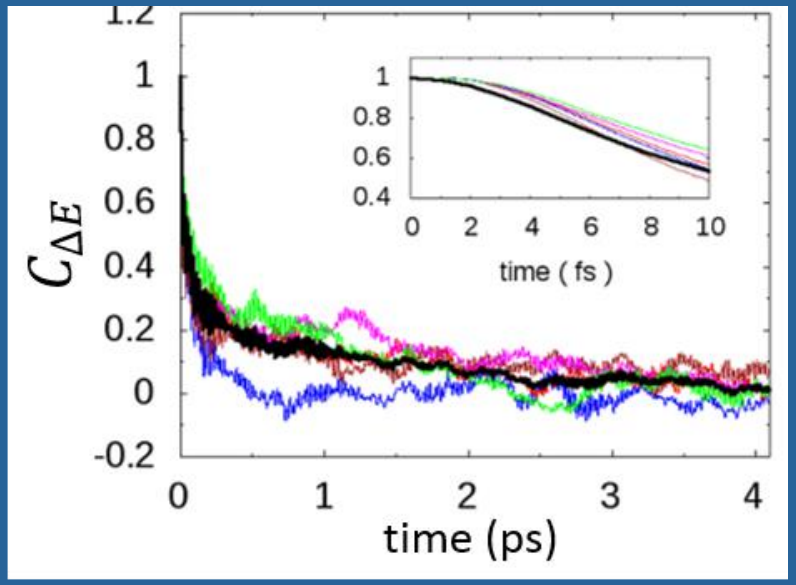
E. S. Medvedev and A. A. Stuchebrukhov, J Chem Phys, 1997, 107, 3821-3831

$\tau_{coh} \gg \tau_{FC}$ SLOW coupling regime

$$k_{ET} = \frac{2\pi}{\hbar} \frac{1}{\sqrt{4\pi\lambda k_B T}} \langle |H_{DA}|^2 \rangle \exp\left(-\frac{(\Delta G^\circ + \lambda)^2}{4\lambda k_B T}\right)$$

HOW TO OBTAIN τ_{coh} AND τ_{FC} ?

I. A. Balabin, J. N. Onuchic, *Science*, **2000**, 290, 114-117
D. N. Beratan, et al. , *Acc. Chem. Res.*, **2015**, 48, 474-481.



$$C_{H_{DA}}(t) = \langle H_{DA}(t) H_{DA}(0) \rangle / \langle H_{DA}(0)^2 \rangle$$

$\Rightarrow \tau_{coh}$

$$C_{\Delta E}(t) = \langle \Delta E(t) \Delta E(0) \rangle / \langle \Delta E(0)^2 \rangle$$

$\Rightarrow \tau_{FC}$

$$\tau_{FC} = \hbar / \sqrt{2\lambda k_B T}.$$

COMPUTATIONALLY RATHER INVOLVED

THE CASE OF CRYPTOCHROME

$R_{coh} = \langle H_{DA} \rangle^2 / \langle H_{DA}^2 \rangle$

cDFT corrected H_{DA}

ET STEP	1	2
$\langle H_{DA} \rangle$ in meV	15	11
$\langle H_{DA}^2 \rangle$ in meV²	386	1300
R_{coh}	0.59	0.55
τ_{coh} in fs	54	36
τ_{FC} in fs	39	62

characterizes how fast ΔE fluctuates

characterizes how fast H_{DA} fluctuates

Non-Condon effects are negligible in most of our simulations

factorization of the electronic factor in rate expressions

DYNAMICAL EFFECTS ON ET RATES

D. N. Beratan, et al. , *Acc. Chem. Res.*, **2015**, 48, 474-481

$$\langle H_{DA}^2 \rangle = \langle H_{DA} \rangle^2 + \sigma^2 \qquad \sigma^2 = \langle (H_{DA} - \langle H_{DA} \rangle)^2 \rangle$$

$\langle H_{DA} \rangle^2 \gg \sigma^2$

SINGLE PATHWAY REGIME

$\langle H_{DA} \rangle^2 \ll \sigma^2$

MULTIPLE PATHWAY REGIME

$$C = \langle H_{DA} \rangle^2 / \langle H_{DA}^2 \rangle$$

$C \to 1$

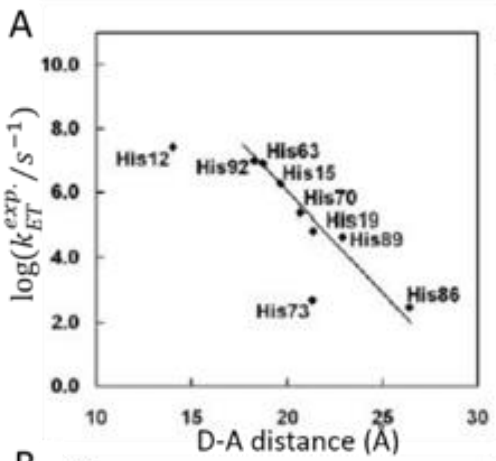
$C \to 0$

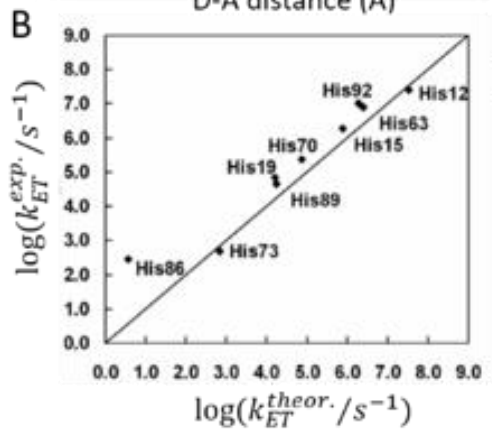
WHAT ABOUT THERMAL MOTION

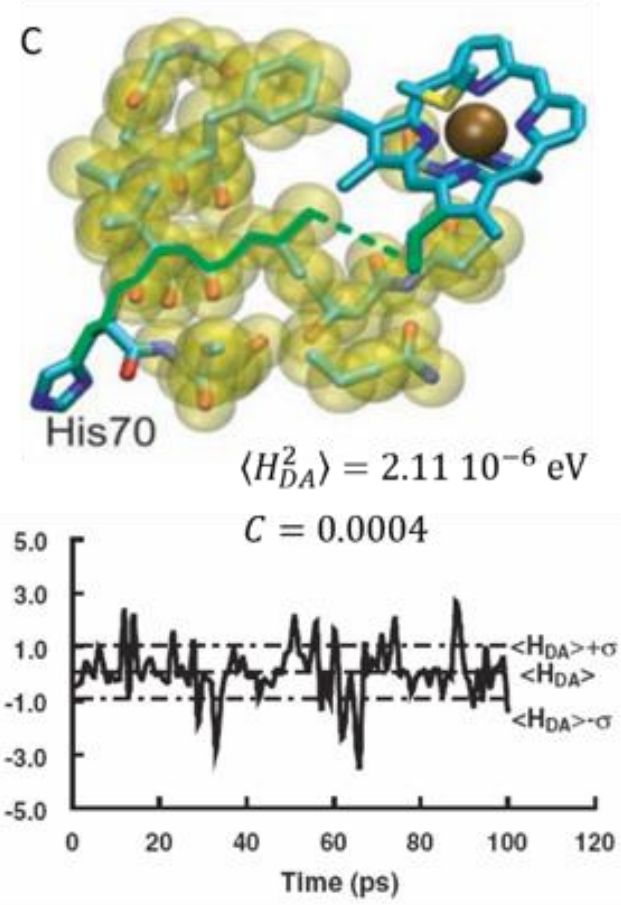
T. R. Prytkova, I. V. Kurnikov and D. N. Beratan, *Science* **2007**, *315*, 622

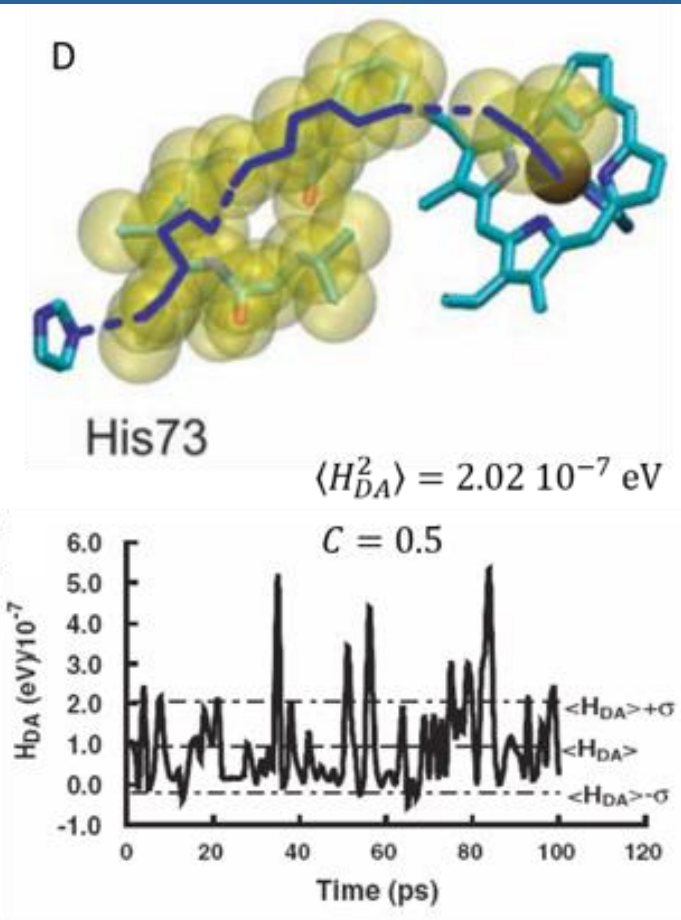
$$(\Delta G^\circ + \lambda)^2/4\lambda \approx 0$$

$$k_{ET} \approx \frac{2\pi}{\hbar}\frac{1}{\sqrt{4\pi\lambda k_B T}}\langle|H_{DA}|^2\rangle$$





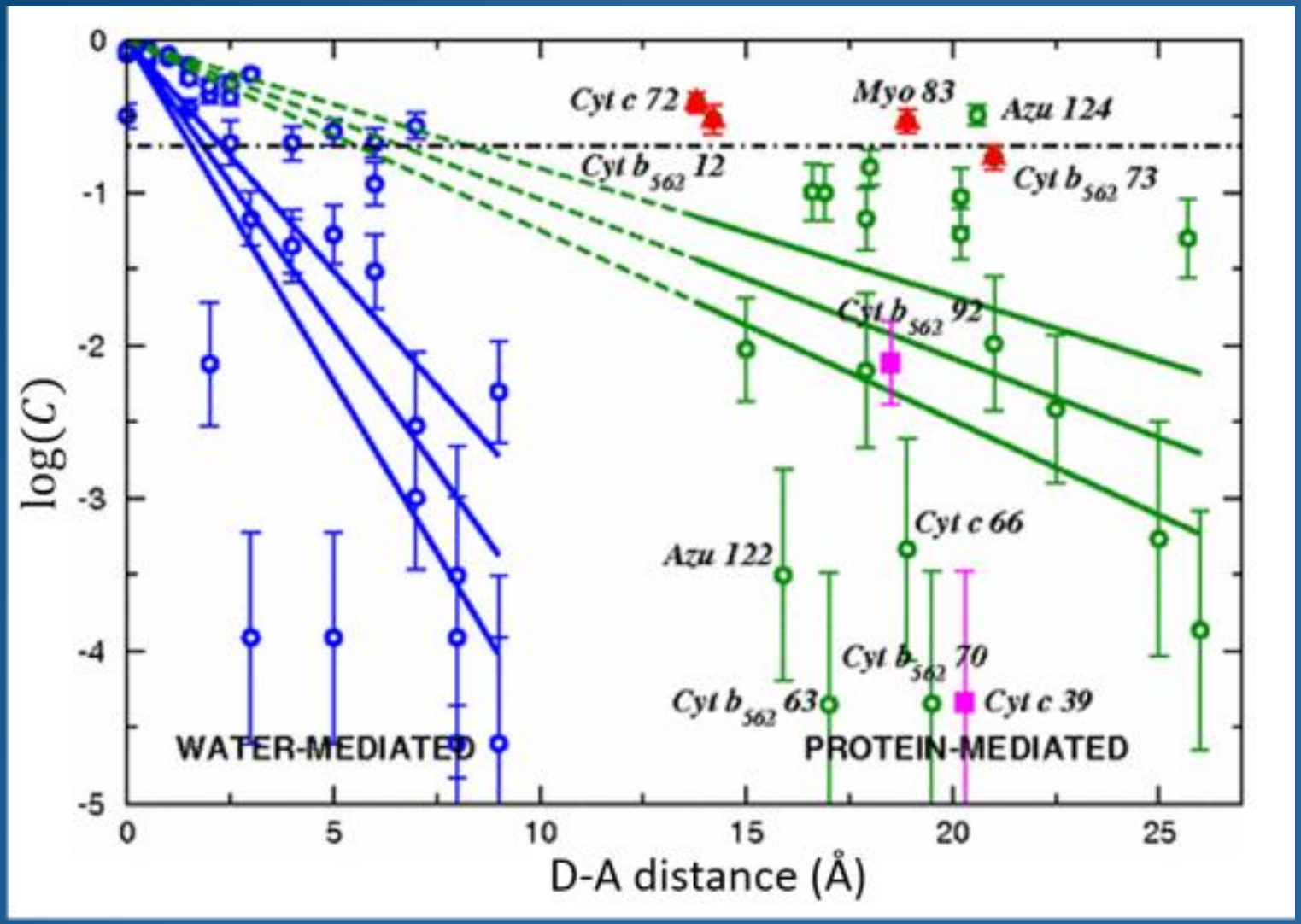




MULTIPLE PATHWAY REGIME

SINGLE PATHWAY REGIME

EVEN FOR VERY LONG RANGE ET, THE UNDERLYING PROTEIN STRUCTURE MATTERS



I. A. Balabin, D. N. Beratan and S. S. Skourtis, *Phys Rev Lett*, 2008, **101**

http://demon-software.com

Dennis Salahub

deMon2k

density of Montréal

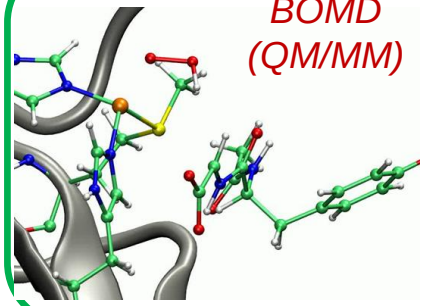
Tzonka Mineva

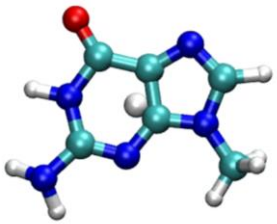
- Highly efficient Auxiliary DFT code, **free for academics**
- Several magnetic and optical properties available
- QM/MM (Amber ff99, polarizable ff02, CHARMM, OPLS)
  (additive scheme, link atom, capping potential)
- User friendly tutorials for QM/MM simulations
- **Born-Oppenheimer** MD, **Ehrenfest** MD, **Electronic** Dynamics
- Interface with PLUMED 2.0 (metadynamics, path integral)
- **Constrained DFT** to simulate electron tranfers

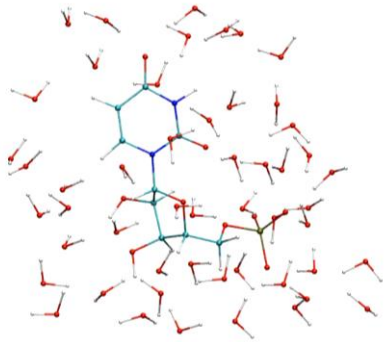
Andreas Köster

Daniel Mejia Rodriguez

Patrizia Calaminici







Mark Casida, Roberto Flores, Jérome Cuny, Aurelio Alvarez-Ibarra

…

And many other