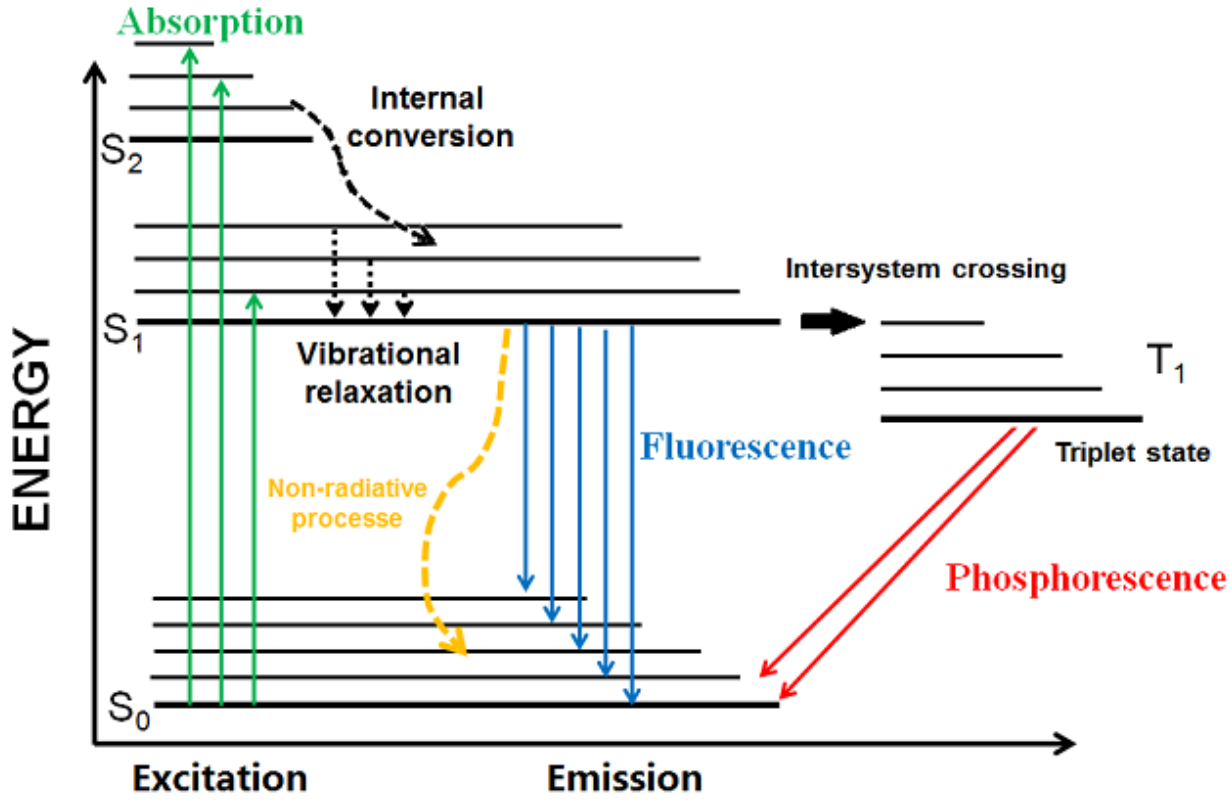
Ringvorlesung Biophysik 3
Theoretische Aspekte der Photobiologie

AK Burghardt (Institut für Physikalische & Theoretische Chemie)



Theoretical Chemistry of Complex Systems

AK Burghardt

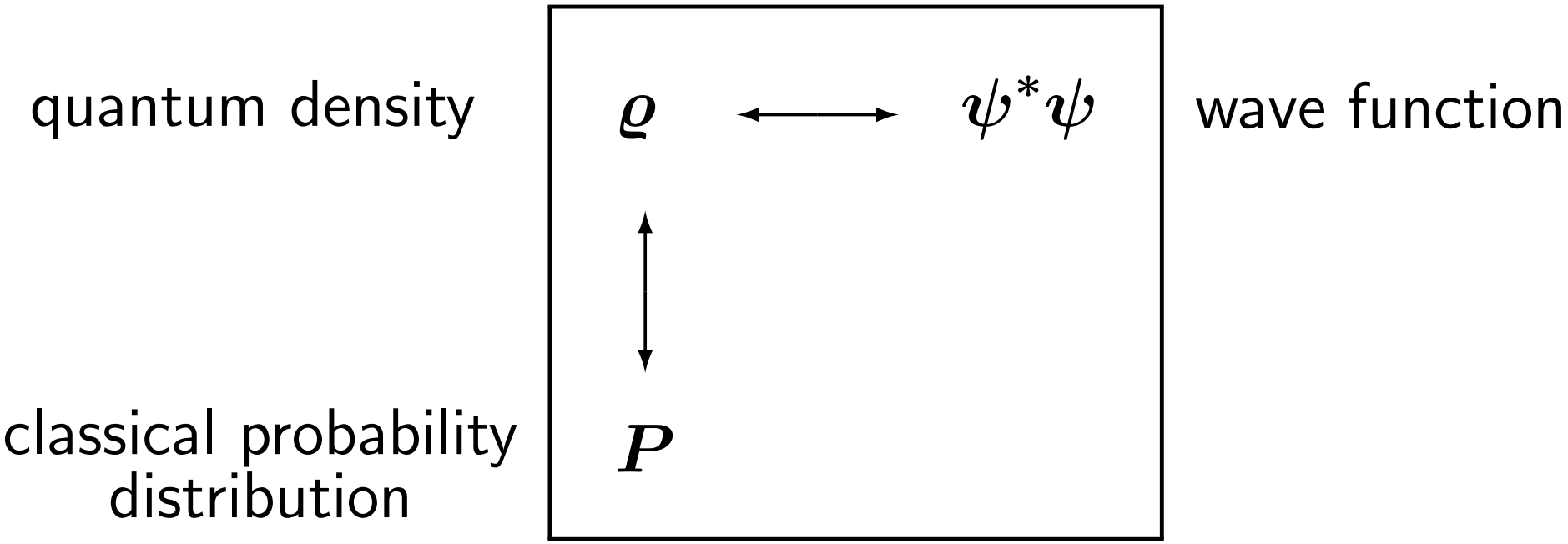
chemical + biological + material processes

chemistry
"bottom-up":

electrons + nuclei

Theoretical Chemistry of Complex Systems

AK Burghardt



Theoretical Chemistry
of Complex Systems

AK Burghardt

Teaching:

Theoretische Chemie I (Bachelor) – Burghardt
Theoretische Chemie II + Praktikum (Bachelor/Master) – Burghardt
Theoretical Photochemistry (Master) – Burghardt

Mathematische Methoden I (Bachelor) – Hegger
Mathematische Methoden II (Bachelor) – Hegger
Mathematische Methoden III (Bachelor, Master) – Hegger
+ MD-QC Praktikum (Bachelor[1]) – Burghardt, Hegger

[1] Wahlpflichtmodul "Computational Chemistry"

Topics

1. Photochemistry
   - Quantum Effects in Biological Systems
   - Photochemistry: Quantum Mechanics at Work
   - Quantum (QM) or Quantum/Classical (QM/MM-MD)?

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   - Can Theory Predict the Best Uncaging Strategies?
   - Spectroscopy: What's the Best Way to Prepare your System?
   - Selective Uncaging: Optical & VIPER Spectroscopy

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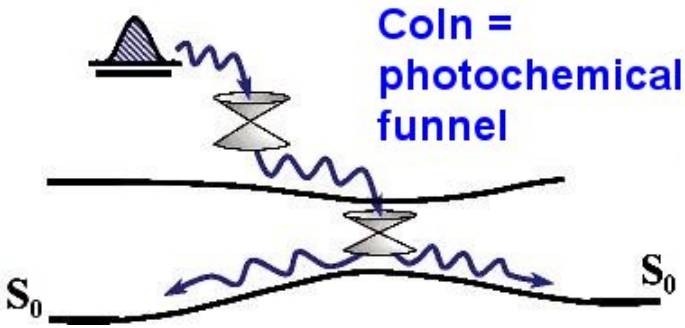
3. Photoregulation of DNA & RNA
   - Conformational Control using Covalently Attached Photoswitches
   - QM/MM Simulations
   - MM-MD Simulations

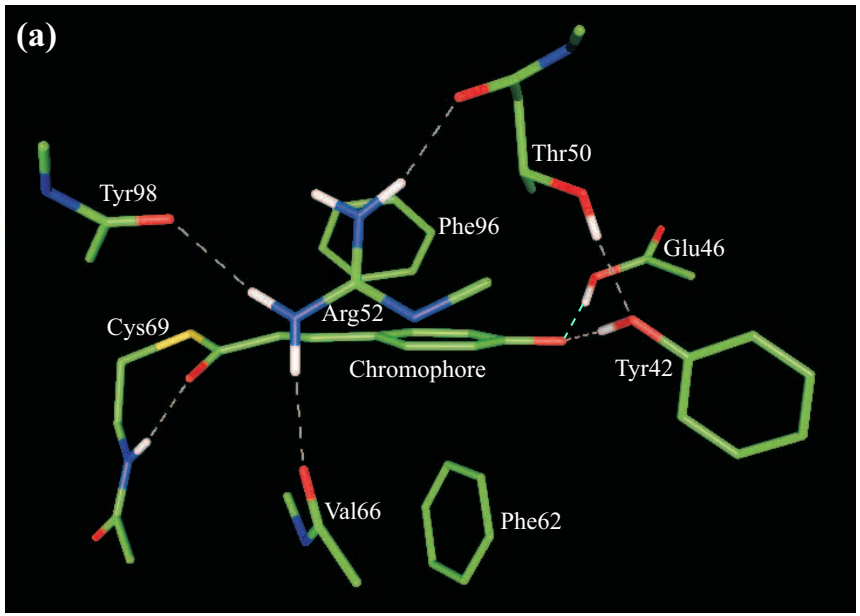
Why Worry about Quantum Effects?

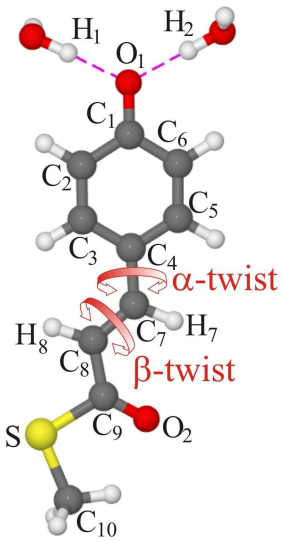
- Most properties/processes in biological & material systems can be taken to belong to the classical limit ($\lambda_{\mathrm{dB}} \ll L$, classical Wigner limit, ...)
- Hence, MD (= Molecular Dynamics) simulations are extensively used: classical-mechanical evolution of all nuclear degrees of freedom on the lowest (electronic ground state) Born-Oppenheimer (BO) surface
- However, some quantum effects are important:
  - tunneling (proton transfer, electron transfer)
  - light-induced processes: coherent superpositions
  - nonadiabatic ("non-BO") dynamics
- Methods are needed for quantum dynamics in many dimensions
  - approximate wavefunction and density operator methods
  - semiclassical approaches
  - mixed quantum-classical hybrid approaches

Photoactive Proteins: Bio-Photochemistry

Example PYP = Photoactive Yellow Protein



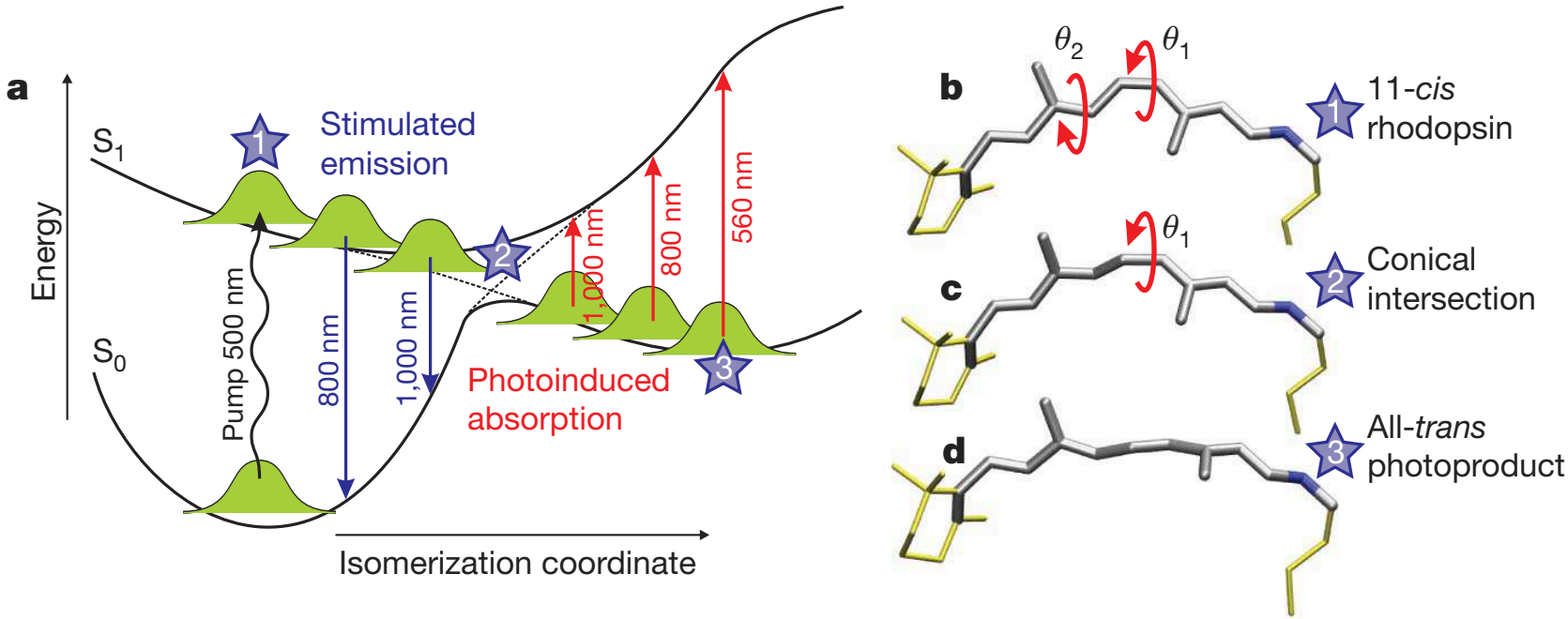




Gromov, Burghardt, Köppel, Cederbaum, J. Phys. Chem. A **115**, 9237 (2011), JACS **129**, 6798 (2007)

- photochemistry determined by conical intersection (CoIn) topology
- local environment significantly influences α vs. β twist
- interplay of steric effects / electrostatics / H-bonds / fluctuations
- excited-state lifetime: $\sim$ 700 fs (in solution: $\sim$ 10 ps)

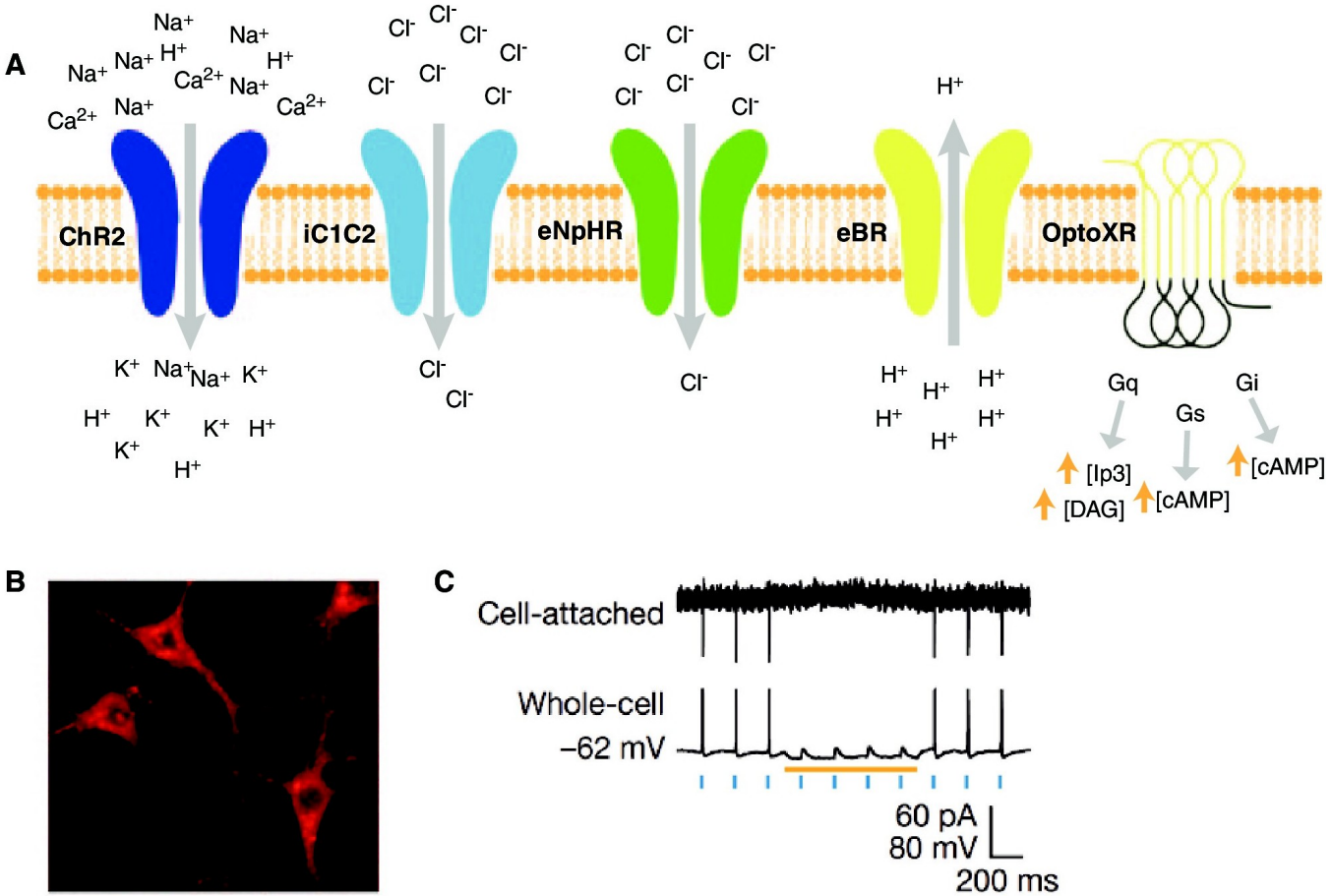
Bio-Photochemistry: Retinal/Rhodopsin



Polli et al., Nature 467, 440 (2010)

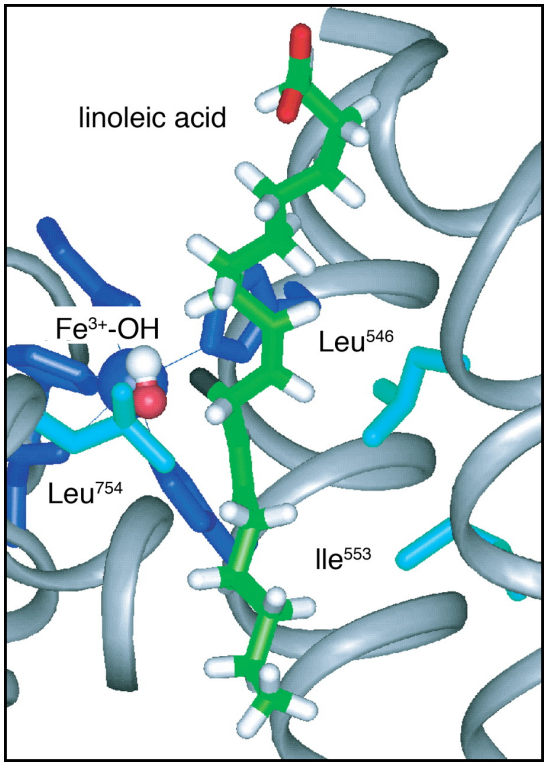
- isomerisation within ∼200 femtoseconds (but 5 picoseconds in solution)
- isomerisation happens in a volume conserving fashion

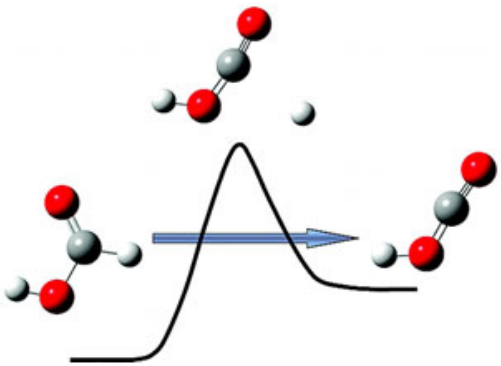
From Bio-Photochemistry to Optogenetics



Guru et al., Int. J. Neuropsychopharmacology 1-8 (2015)

Quantum Tunneling in Enzymes



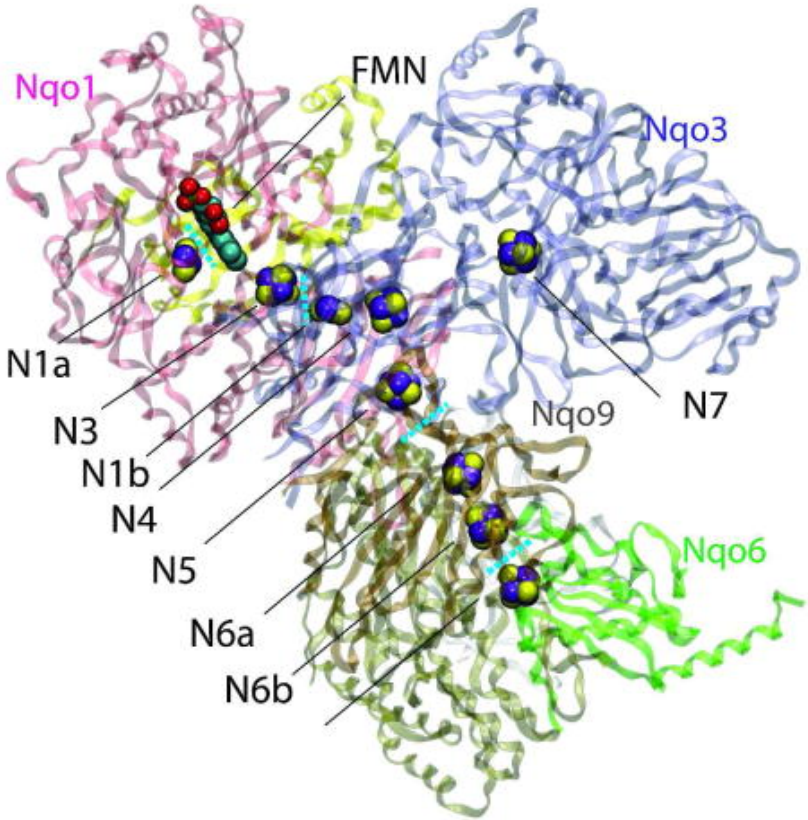


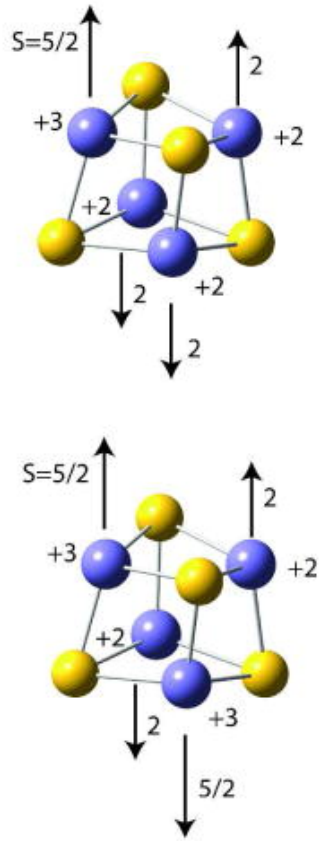
- "Did enzymes evolve to capitalize on quantum tunneling?" The Scientist, 2005
- "Our present findings on hydrogen transfer under physiological conditions cannot be explained without invoking both quantum mechanics and enzyme dynamics" Klinman, Nature 1999
- "Taking Ockham's razor to enzyme dynamics and catalysis": no need to go beyond Transition State Theory (TST) + tunneling corrections

  Glowacki et al., Nature Chem. 2012

Meyer, PNAS 105, 1146 (2008)
"Enzyme structure and dynamics affect hydrogen tunneling:
The impact of a remote side chain (I553) in soybean lipoxygenase-1"

Electron Tunneling: Respiratory Chains

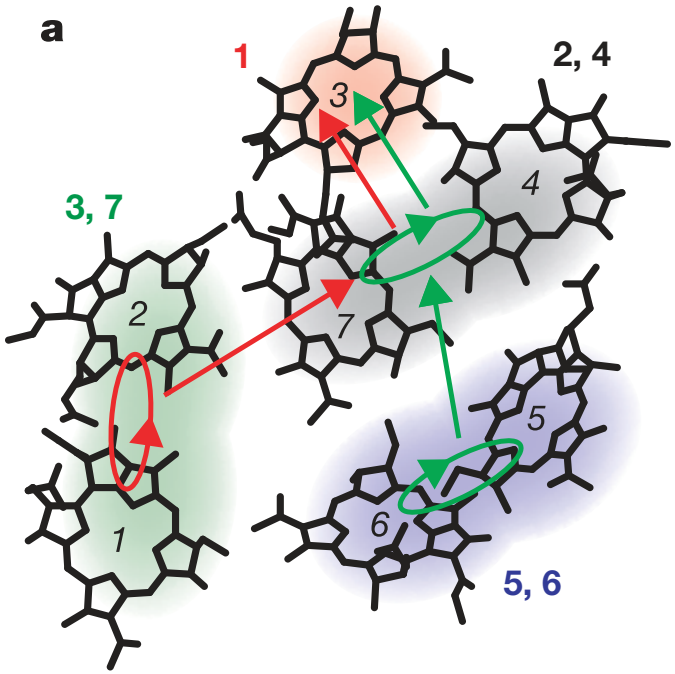




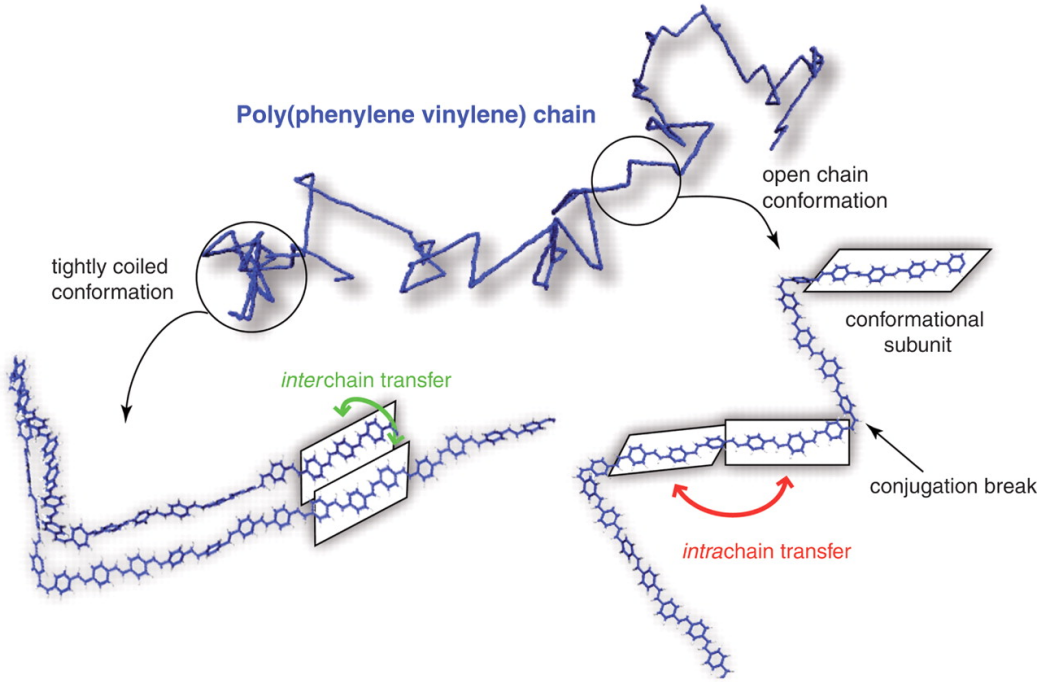
"Quantum Electron Tunneling in Respiratory Complex I1", Hayashi, Stuchebrukhov, J. Phys. Chem. B 115, 5354 (2011)

- "electronically wired" iron-sulfide (FeS) clusters
- quantum interference resulting from multiple tunneling pathways

Coherent Photoinduced Energy and Charge Transport in Biological and Material Light-Harvesting Systems



Lee, Cheng, Fleming, Science 316, 1462 (2007)



Collini, Scholes, Science 323, 369 (2009)

- one would expect an extremely rapid dephasing (decoherence): $\tau_{\mathrm{dec}} < 50$ fs
- but observed coherence lifetimes are $\sim$ 300 fs to 1-2 ps (or more)

Fluorescence Resonance Energy Transfer (FRET)

E.g., Fluorescence Resonance Energy Transfer (FRET) between fluorescent proteins: calculate FRET rates $\propto r_{DA}^{-6}$

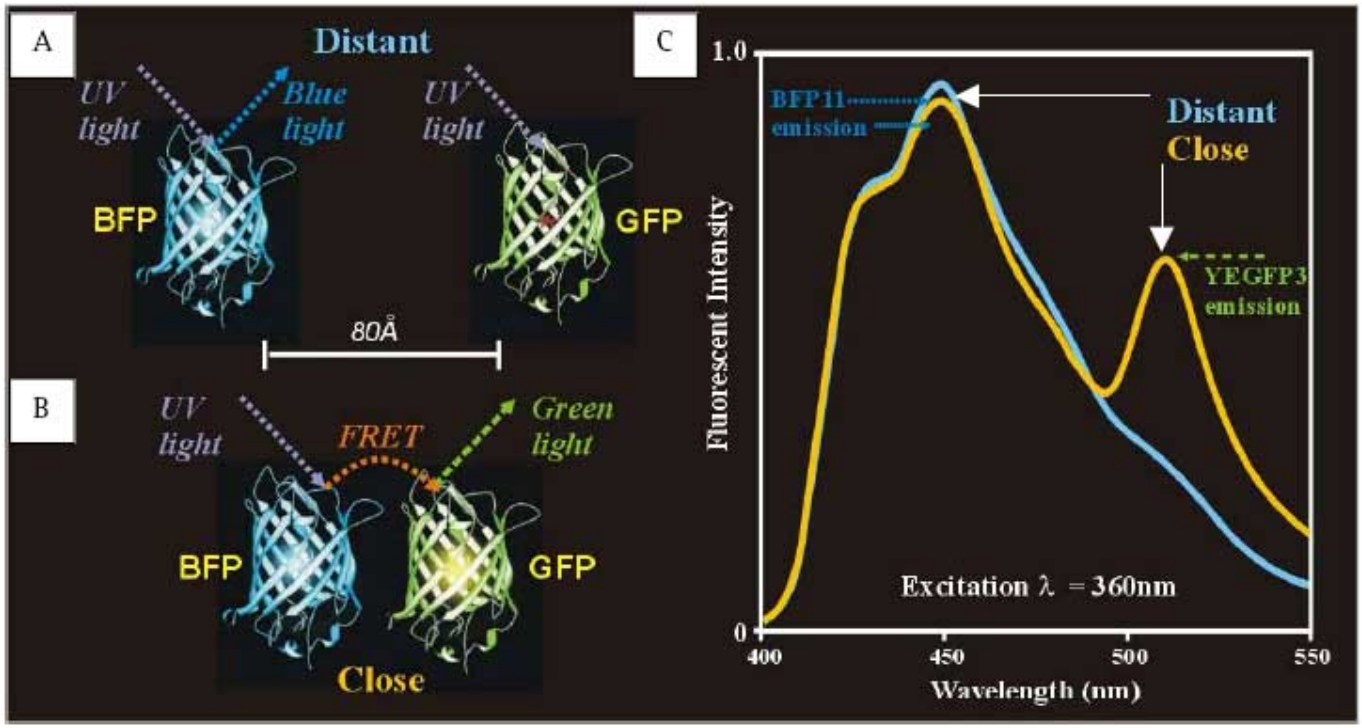
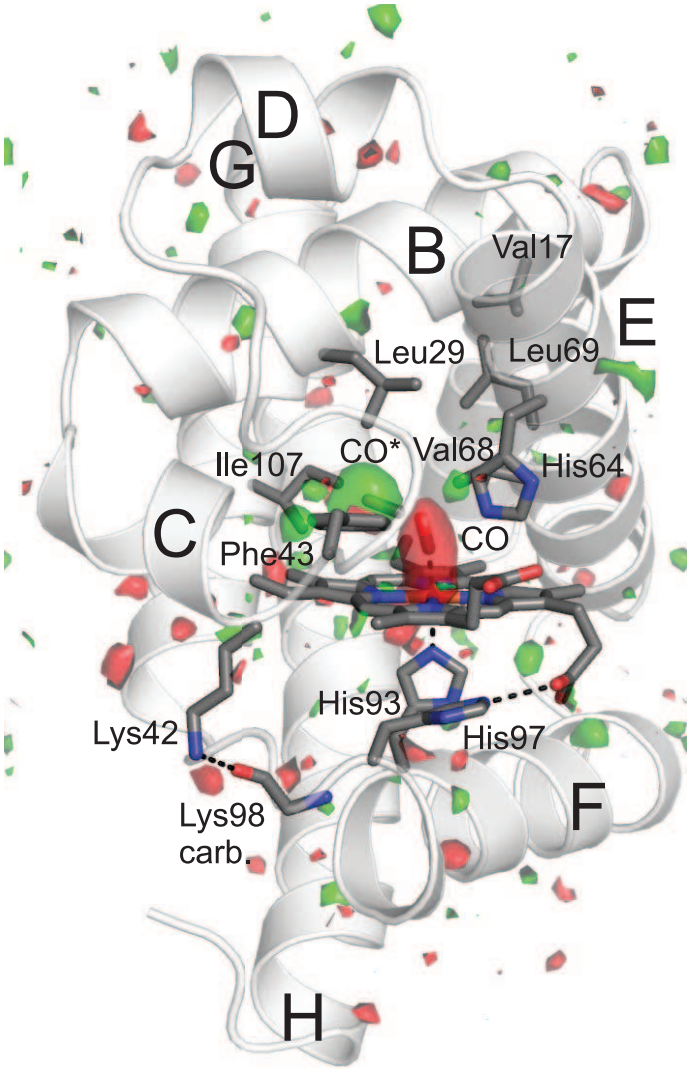


Figure 1. *The use of GFP variants to produce FRET. In A, Distant; UV light excites BFP (donor fluorophore) to emit blue light (peak emission = 450nm), but GFP (acceptor) is not close enough to draw energy from the excited donor. In B, Close; proximity of GFP to BFP allows non-radiative energy transfer, the stimulated BFP exciting GFP to fluoresce green (peak emission = 510nm). Figure 1C shows the expected emission spectra when the GFP fluorophores are either close or distant.*

Photoinduced CO Ligand Dissociation from Myoglobin



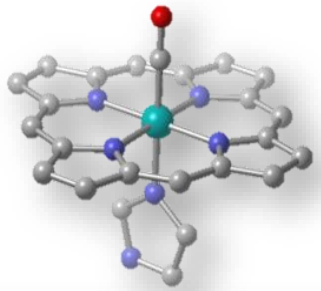
Direct observation of ultrafast collective motions in CO myoglobin upon ligand dissociation

Thomas R. M. Barends,[1*] Lutz Foucar,[1] Albert Ardevol,[2] Karol Nass,[1] Andrew Aquila,[3] Sabine Botha,[1] R. Bruce Doak,[1] Konstantin Falahati,[4] Elisabeth Hartmann,[1] Mario Hilpert,[1] Marcel Heinz,[2,4] Matthias C. Hoffmann,[5] Jürgen Köfinger,[2] Jason E. Koglin,[5] Gabriela Kovacsova,[1] Mengning Liang,[5] Despina Milathianaki,[5] Henrik T. Lemke,[5] Jochen Reinstein,[1] Christopher M. Roome,[1] Robert L. Shoeman,[1] Garth J. Williams,[5] Irene Burghardt,[4] Gerhard Hummer,[2] Sébastien Boutet,[5] Ilme Schlichting[1*]

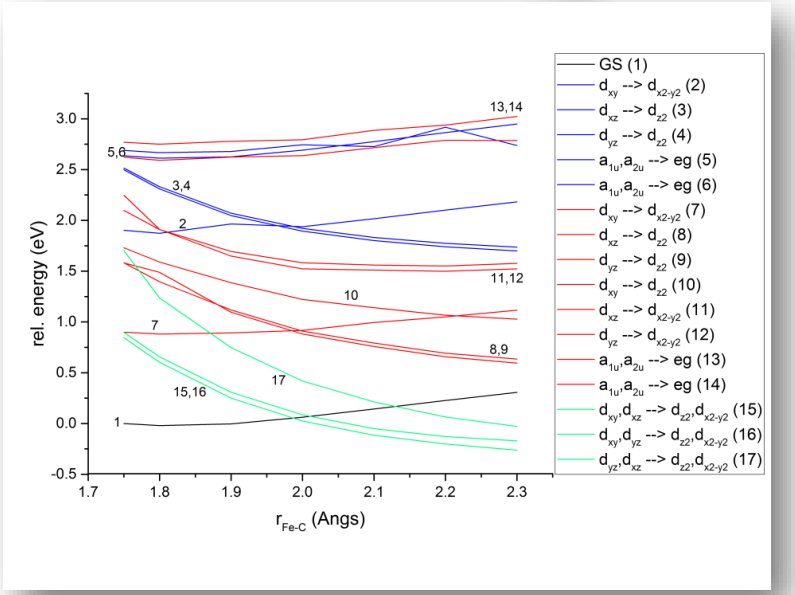
Science, 350, 445 (2015)

PHOTODISSOCIATION OF MYOGLOBIN

carboxy-hemoproteins are among the most studied systems to evaluate (collective) protein dynamics that determine structure and reactivity



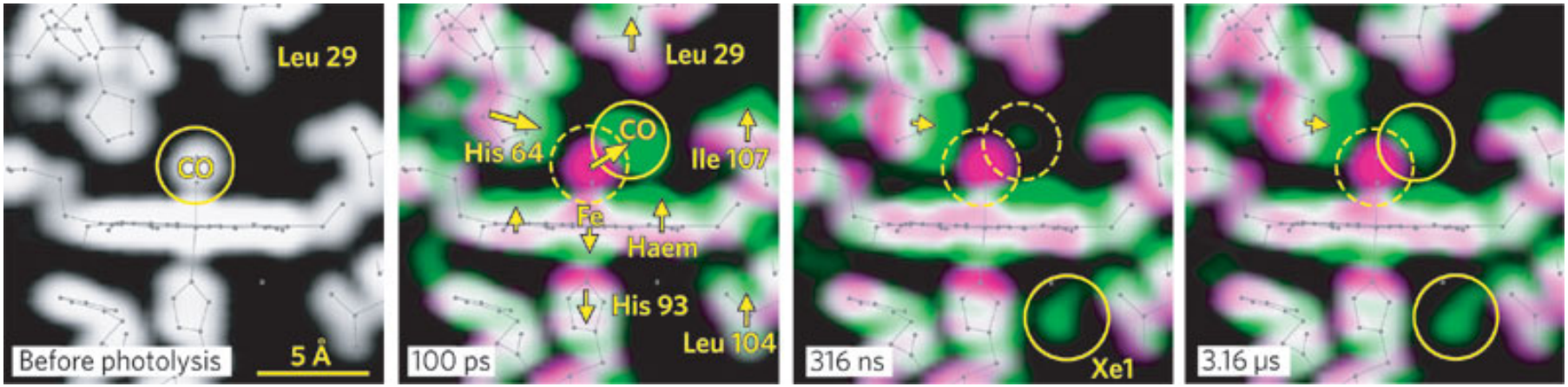
quantum mechanical *ab initio* calculations at TD-DFT and CASSCF/CASPT2 level reveal complex setting of excited states

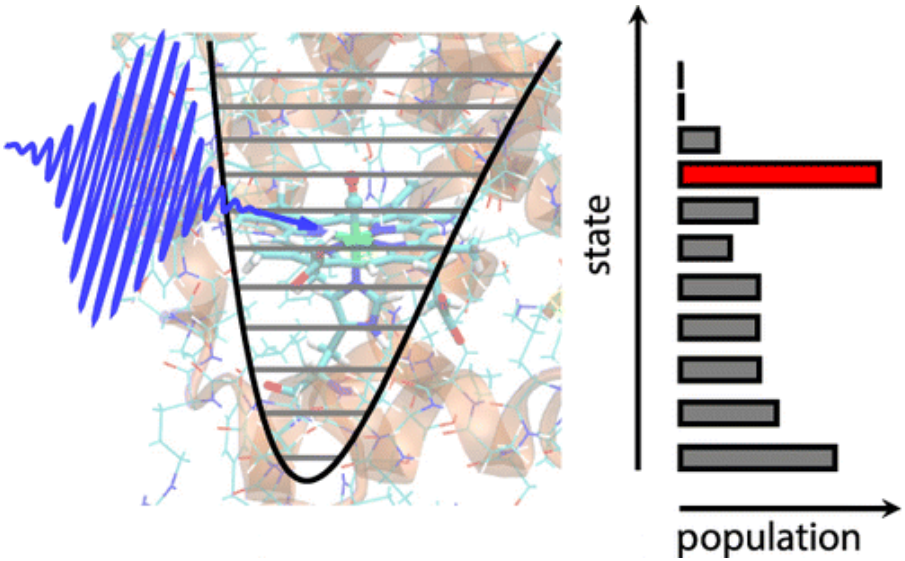


large manifolds of singlet, triplet and quintet states within range of experimental excitation

interaction based on vibronic coupling and/or spin-orbit coupling may cause overall ultrafast dissociation within < 100 fs

Quantum Oscillators in Highly Specific Environments

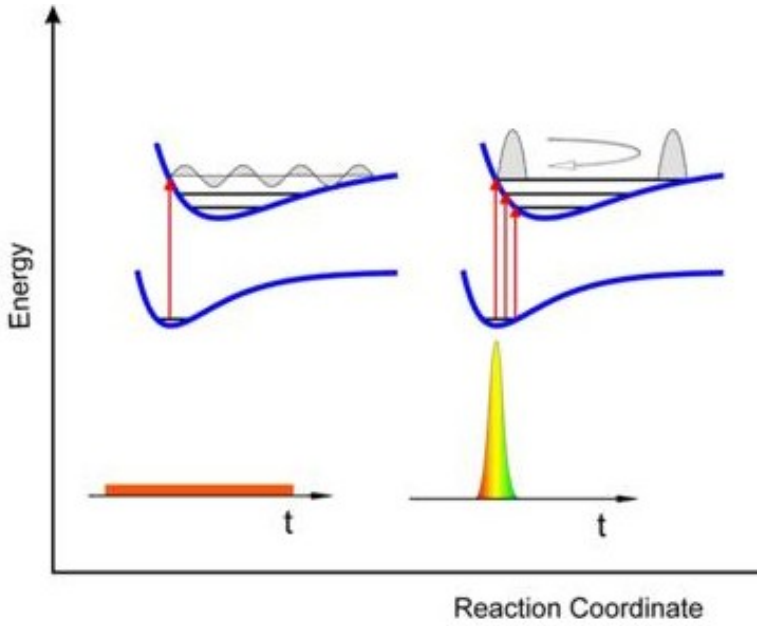




- CO-myoglobin complex
- photoinduced CO dissociation from myoglobin
- state-specific excitation feasible
- relaxation/decoherence depend critically on local environment

Debnath, Falvo, Meier, J. Phys. Chem. A, 117, 12884 (2013)

Light Pulses Create Excited-State Wavepackets



left: CW excitation,
right: pulsed excitation

http://www.uni-heidelberg.de/fakultaeten
/chemgeo/pci/motzkus/research/wavepackets.html

- wavepacket = superposition of eigenstates

$$\psi(x,t) = \sum_n c_n \varphi_n(x) e^{-iE_n t/\hbar}$$

non-stationary state (in contrast to a single eigenstate)

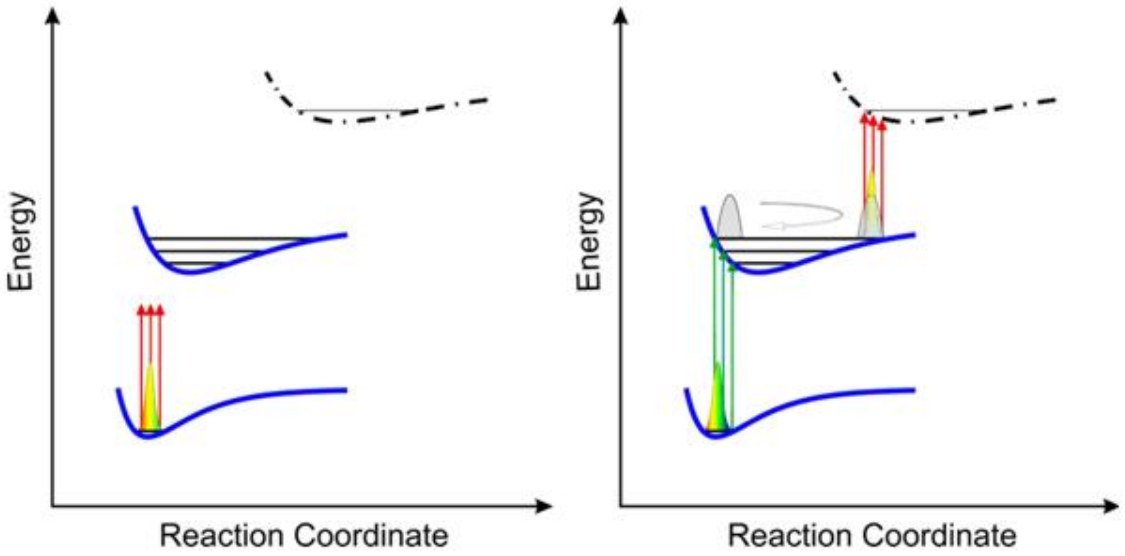
- solve the time-dependent Schrödinger Equation:

$$i\hbar \frac{\partial \psi}{\partial t} = \left(\hat{H}_{\mathrm{mol}} - E(r,t)\hat{\mu} \right) \psi$$

where $\hat{H}_{\mathrm{mol}}$ is the molecular Hamiltonian and $\hat{\mu}$ is the dipole operator

Femtochemistry: Watching Wavepackets in Real Time

Nobel Prize Ahmed Zewail 1999



http://www.uni-heidelberg.de/fakultaeten/chemgeo/pci/motzkus/research/wavepackets.html

- nonlinear optical spectroscopy
- wavepacket dynamics in electronically excited states: quantum coherence
- theoretical interpretation: explicit simulation needed!

Pump-Probe Spectroscopy

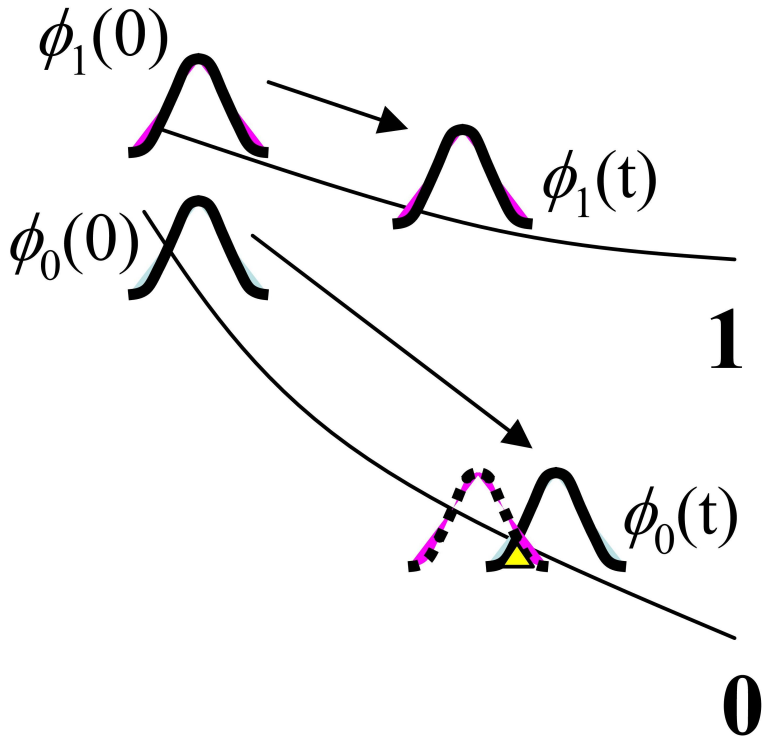
Theory: electronic structure ($\longrightarrow$ potential surfaces) + quantum dynamics

Quantum Coherence – and Decoherence

$$|\psi(t)\rangle = c_0(t)|0\rangle|\phi_0(t)\rangle + c_1(t)|1\rangle|\phi_1(t)\rangle$$

electronic coherence:

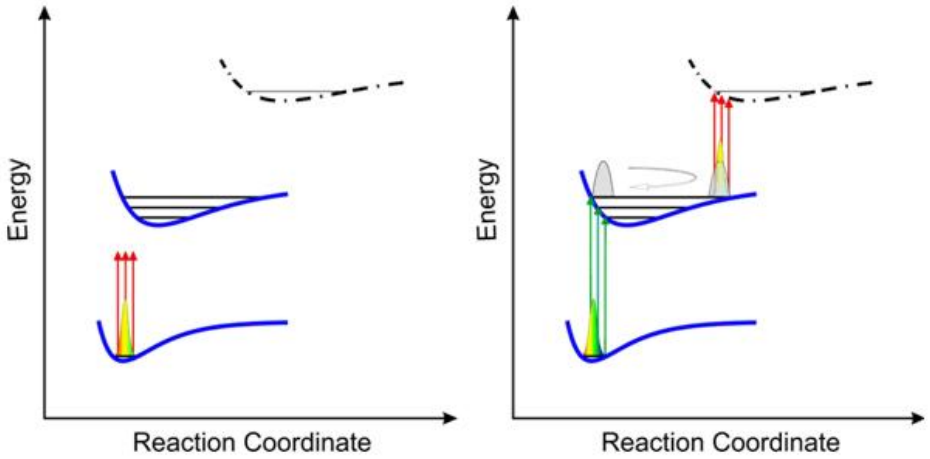
$$\rho_{01}(t) = \mathrm{Tr}[|0\rangle\langle 1|\hat{\rho}(t)]$$
$$= \langle 1|\hat{\rho}(t)|0\rangle = c_1^*(t)c_0(t)\langle\phi_1(t)|\phi_0(t)\rangle$$

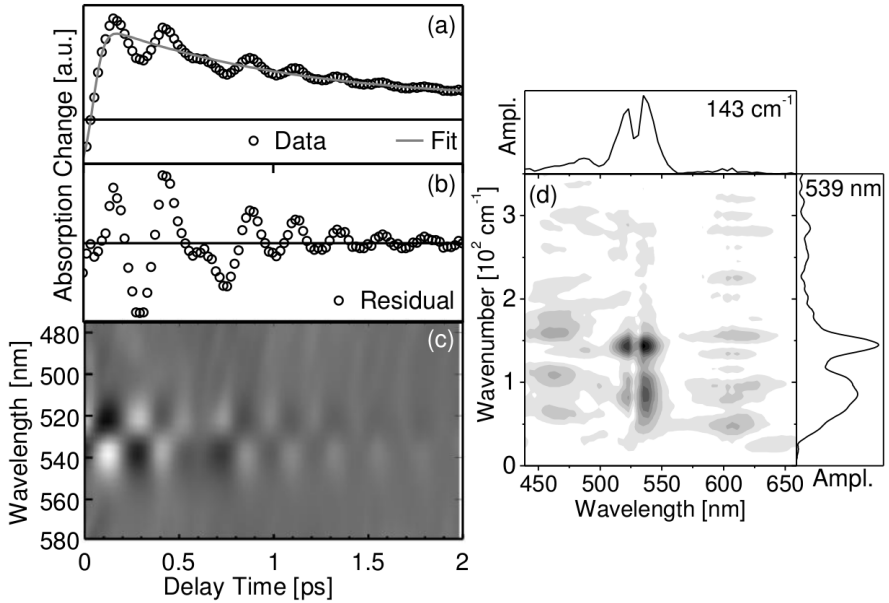


picture: P. Rossky et al.

- coherence $\propto$ overlap of nuclear wavefunctions
- typical decoherence times: ~ 30 fs
- loss of coherence cannot be captured by a classical trajectory picture

Vibrational Coherence & Coherence Transfer





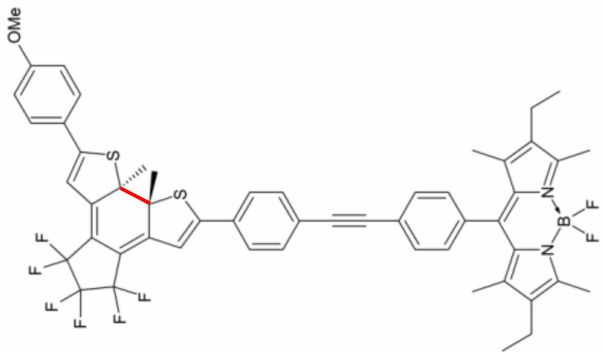
Pump-Probe spectroscopy

http://www.uni-heidelberg.de/fakultaeten
/chemgeo/pci/motzkus/research/wavepackets.html

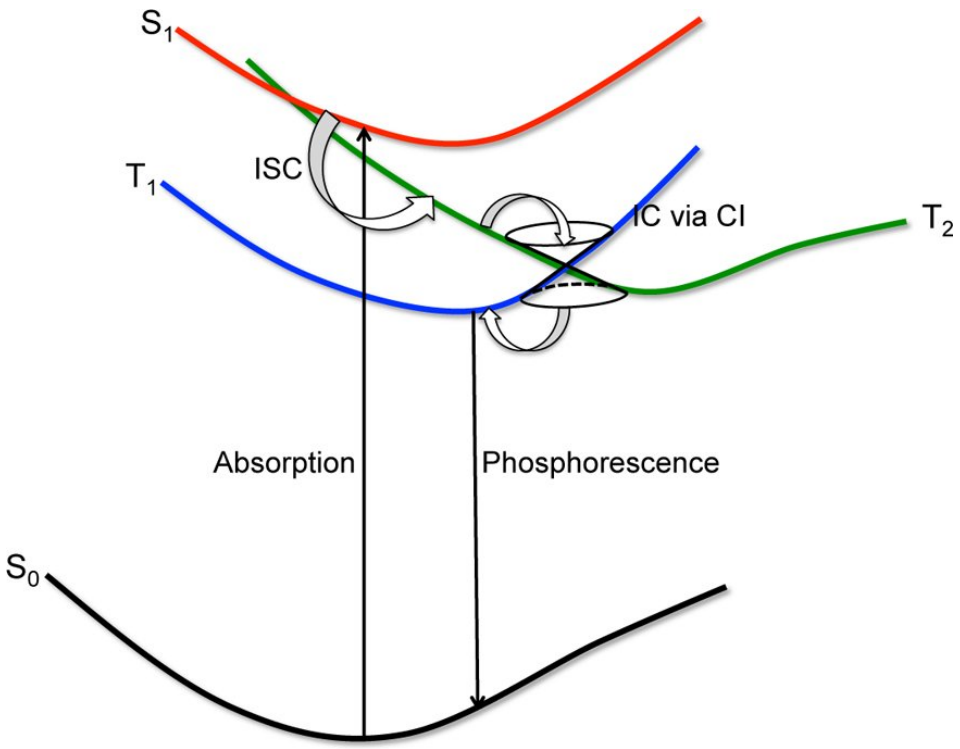
- vibrational coherence
  ⟷ wavepacket motion
- coherence transfer due to coupled vibrations

Vibrational coherence transfer in an electronically decoupled molecular dyad

Schweighöfer et al., Scientific Reports (2015)

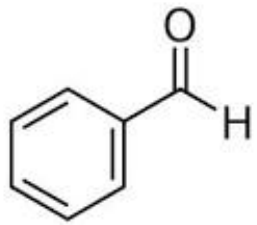


Even in Small Systems, Excited-State Dynamics is Complex



Ou, Subotnik, J. Phys. Chem. C. 117, 19839 (2013)

- Example: benzaldehyde



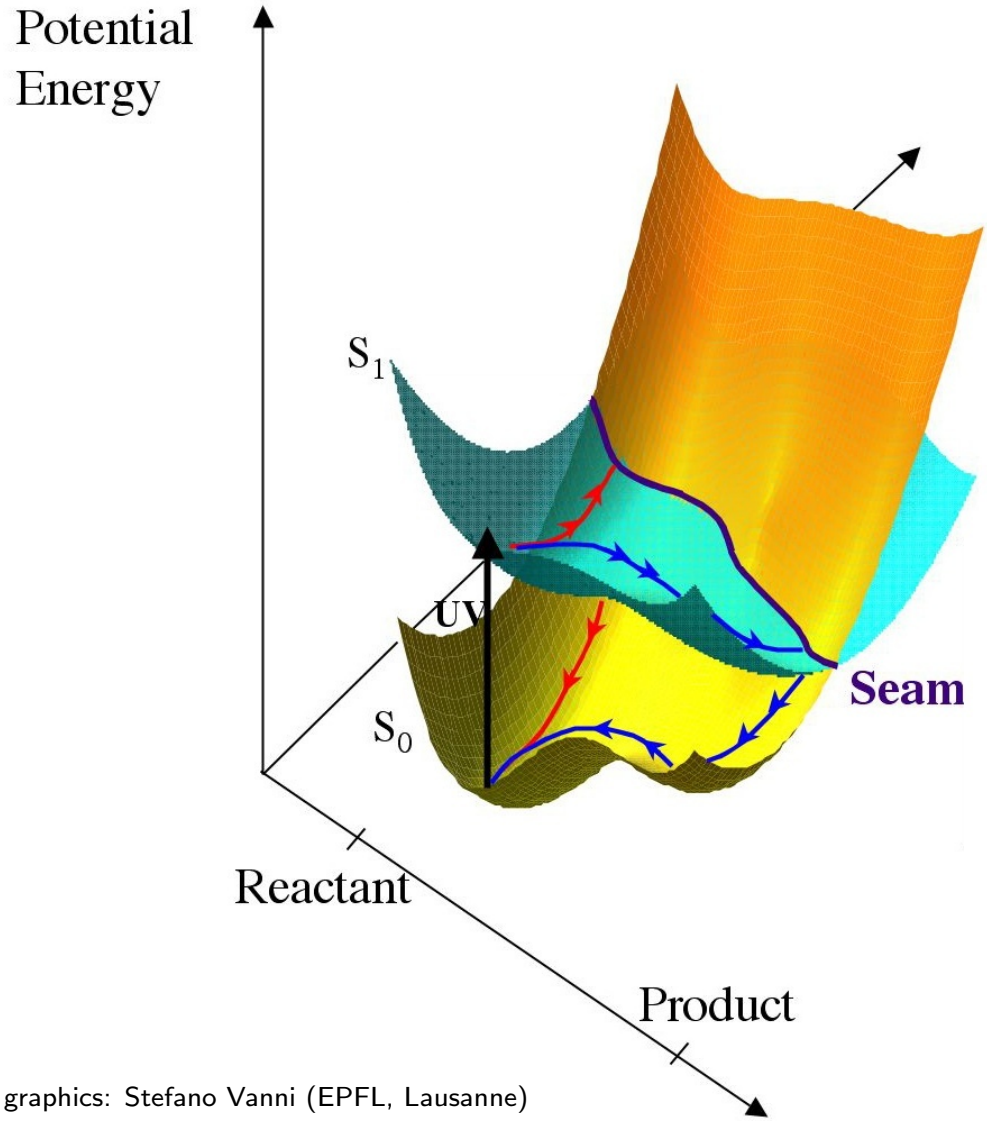
- ISC = intersystem crossing
- IC = internal conversion
- CI = conical intersection

- ISC time scale:
  $\sim 10^{-9}$ s – "untypically" fast!
- phosphoresence lifetime
  $\sim 2 \times 10^{-3}$ s

- state-to-state couplings needed
- characterize special topologies: conical intersections
- identify most relevant coordinates

Beyond Born-Oppenheimer

- "non-adiabatic" dynamics
- quantum dynamical description required
- mean-field (Ehrenfest) and surface-hopping approaches often insufficient



graphics: Stefano Vanni (EPFL, Lausanne)

What Do We Need To Calculate?

electronic structure : $$H_{\mathrm{el}}\psi_n^{\mathrm{el}}(r,R) = \varepsilon_n(R)\psi_n^{\mathrm{el}}(r,R)$$

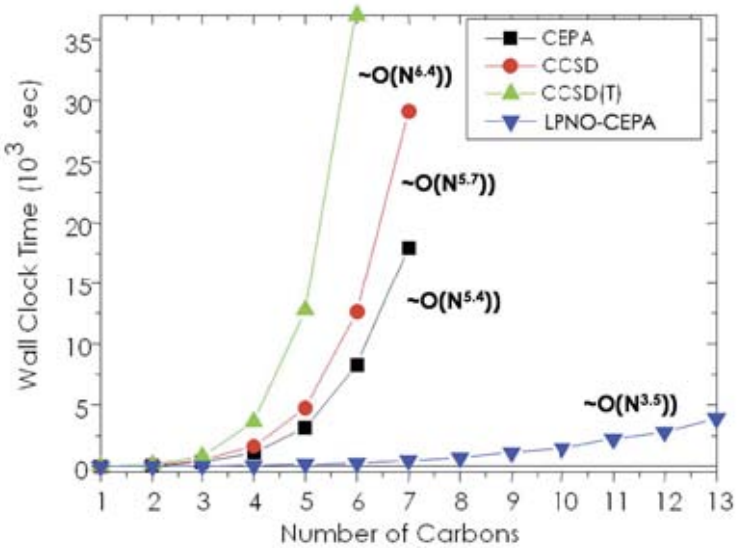
- high-level methods (CC2, ADC(2),CASSCF/CASPT2,MRCI)
- density functional methods (DFT, TDDFT)
- quantum mechanics / molecular mechanics (QM/MM) hybrid methods
- linear scaling methods

quantum dynamics : $$i\hbar\dot{\psi}_n^{\mathrm{nuc}}(R) = (T_{\mathrm{nuc}} + \varepsilon_n(R))\psi_n^{\mathrm{nuc}}(R)$$

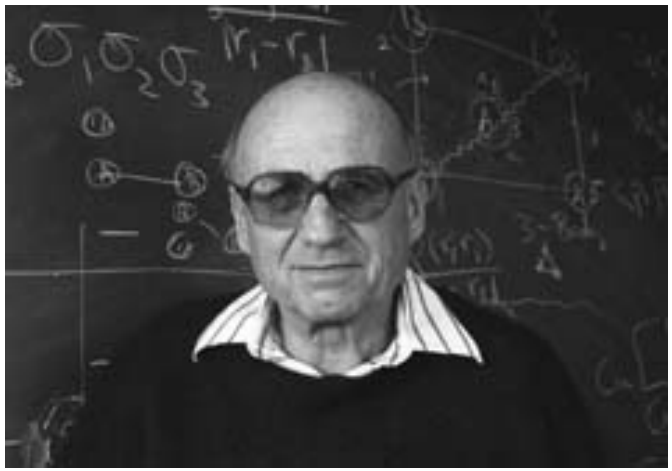
- multiconfigurational methods (MCTDH)
- mixed quantum-classical methods
- reduced-dimensional descriptions (effective modes, mesoscopic descriptions)
- Markovian and non-Markovian master equations

  ⟶ method development!

Exponential Scaling Problem



Standard methods: exponential scaling ⟶ limit reached already for 6 carbon atoms

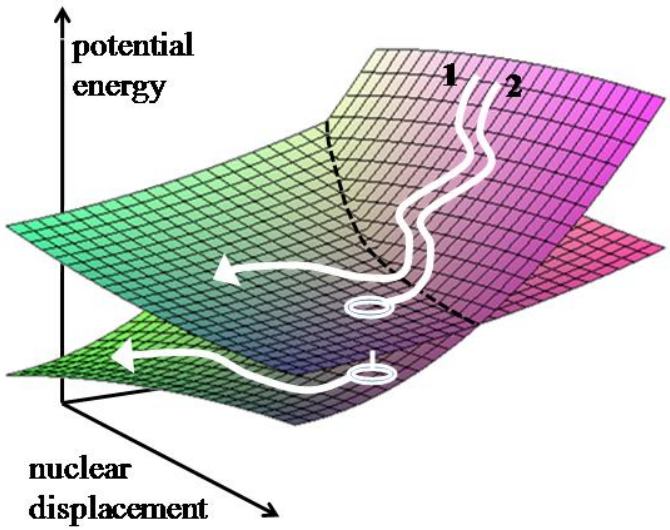


"I cannot foresee any technological progress which should make such calculations feasible."
Walter Kohn, Nobel Lecture 1998

- here, electronic structure example – but same problem for quantum dynamics!
- development of approximate methods is of key importance

Various Approximate Approaches

1. *On-the-fly* Quantum-Mechanics/Molecular Mechanics (QM/MM) + Surface Hopping (SH) – Example: Photocontrol of DNA and RNA
2. Parametrized Hamiltonians + Quantum Dynamics (QD) – Example: Elementary Events in Organic Photovoltaics

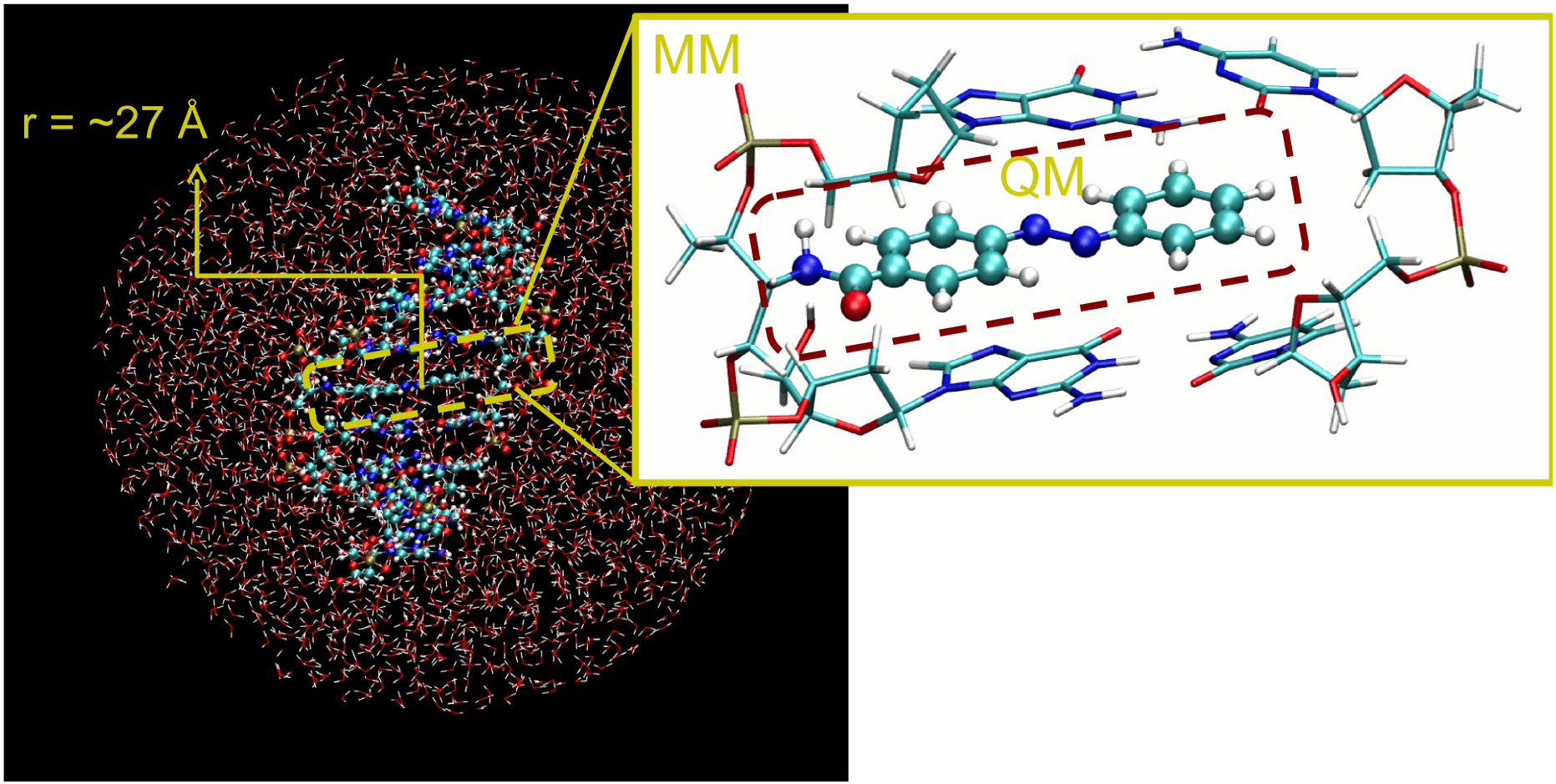


M. Barbatti, http://www.newtonx.org/

Surface Hopping (SH):
stochastic trajectories mimic wavepacket motion on coupled potential surfaces

QM/MM simulations

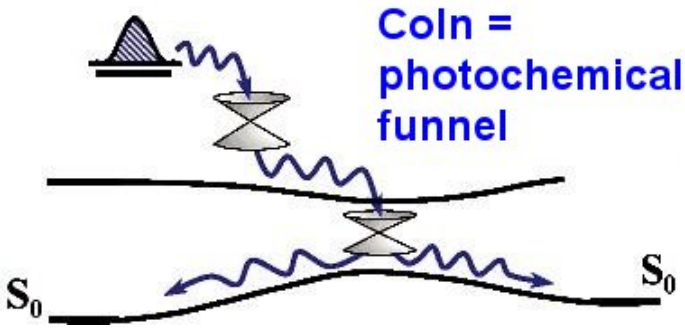
2013 Nobel Prize for Martin Karplus/Michael Levitt/Arieh Warshel

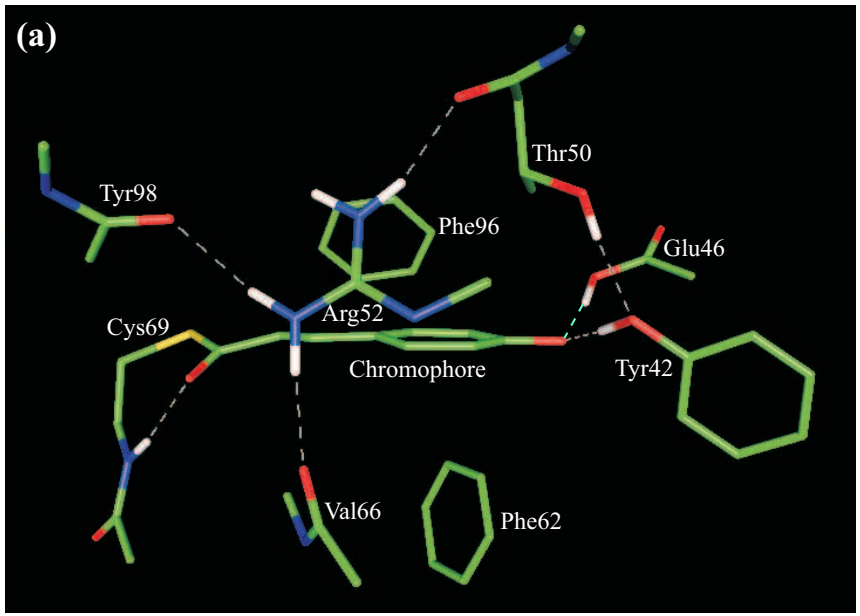


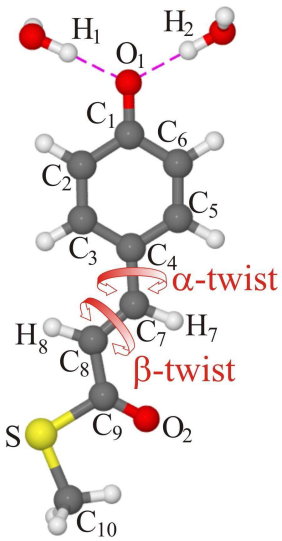
various approaches: NEWTON-X, MNDO/Chemshell, MOPAC (Pisa version), ...

Photoactive Proteins: Bio-Photochemistry

Example PYP = Photoactive Yellow Protein







Gromov, Burghardt, Köppel, Cederbaum, J. Phys. Chem. A **115**, 9237 (2011), JACS **129**, 6798 (2007)

- photochemistry determined by conical intersection (CoIn) topology
- local environment significantly influences α vs. β twist
- interplay of steric effects / electrostatics / H-bonds / fluctuations
- excited-state lifetime: $\sim$ 700 fs (in solution: $\sim$ 10 ps)

Sometimes Rate Theories are Sufficient . . .

E.g., Fluorescence Resonance Energy Transfer (FRET) between fluorescent proteins: calculate FRET rates $\propto r_{DA}^{-6}$

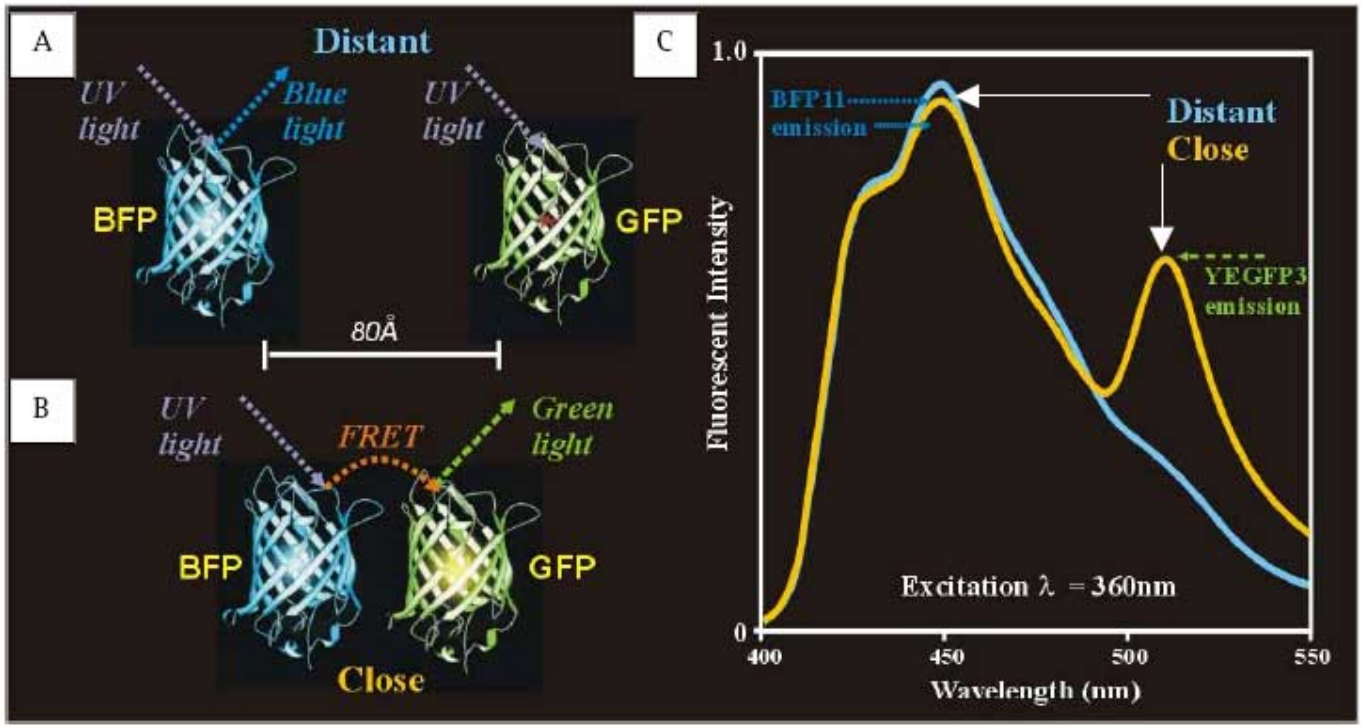
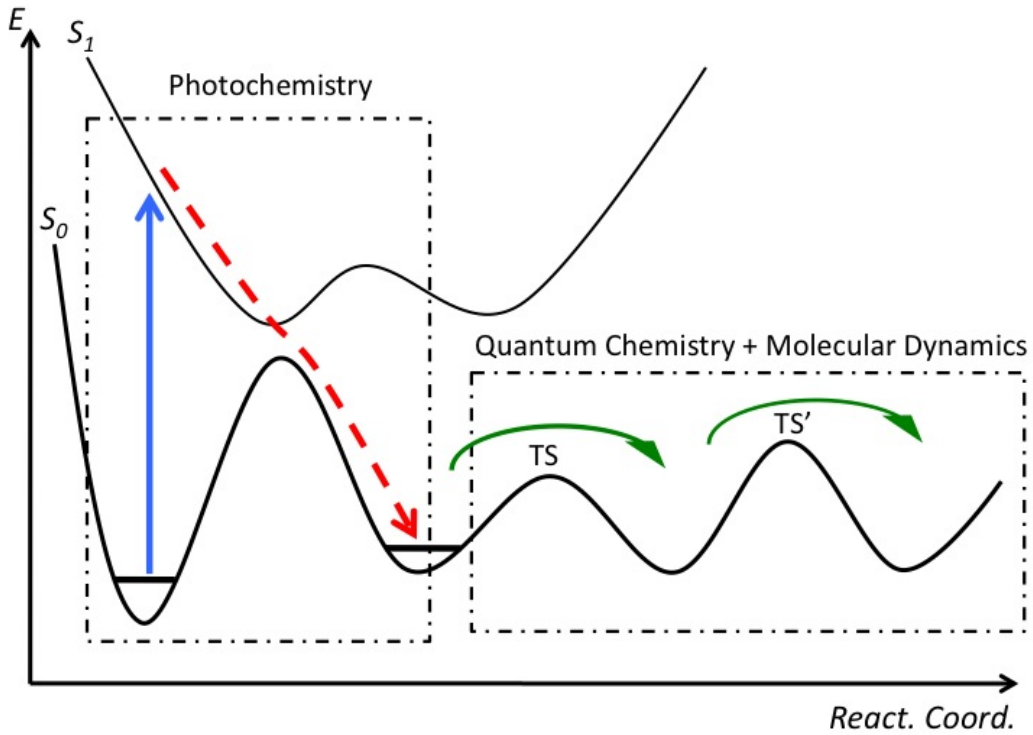


Figure 1. *The use of GFP variants to produce FRET. In A, Distant; UV light excites BFP (donor fluorophore) to emit blue light (peak emission = 450nm), but GFP (acceptor) is not close enough to draw energy from the excited donor. In B, Close; proximity of GFP to BFP allows non-radiative energy transfer, the stimulated BFP exciting GFP to fluoresce green (peak emission = 510nm). Figure 1C shows the expected emission spectra when the GFP fluorophores are either close or distant.*

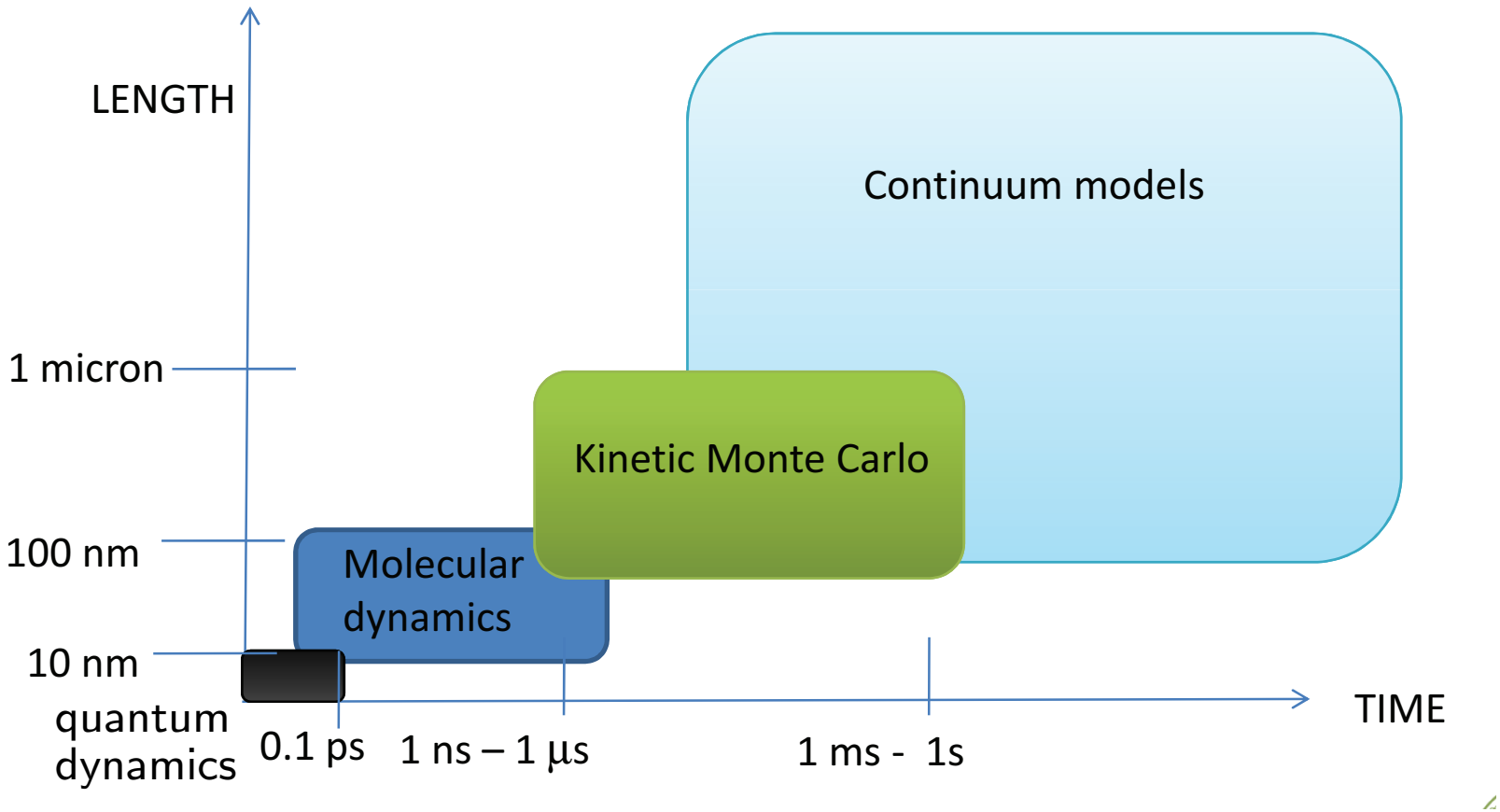
How to Tackle Multiple Time Scales?



Hierarchy of methods:

- quantum dynamics: femtoseconds to picoseconds
- classical molecular dynamics (MD): picoseconds to nano-/microseconds
- kinetic models: microseconds to seconds (and longer)

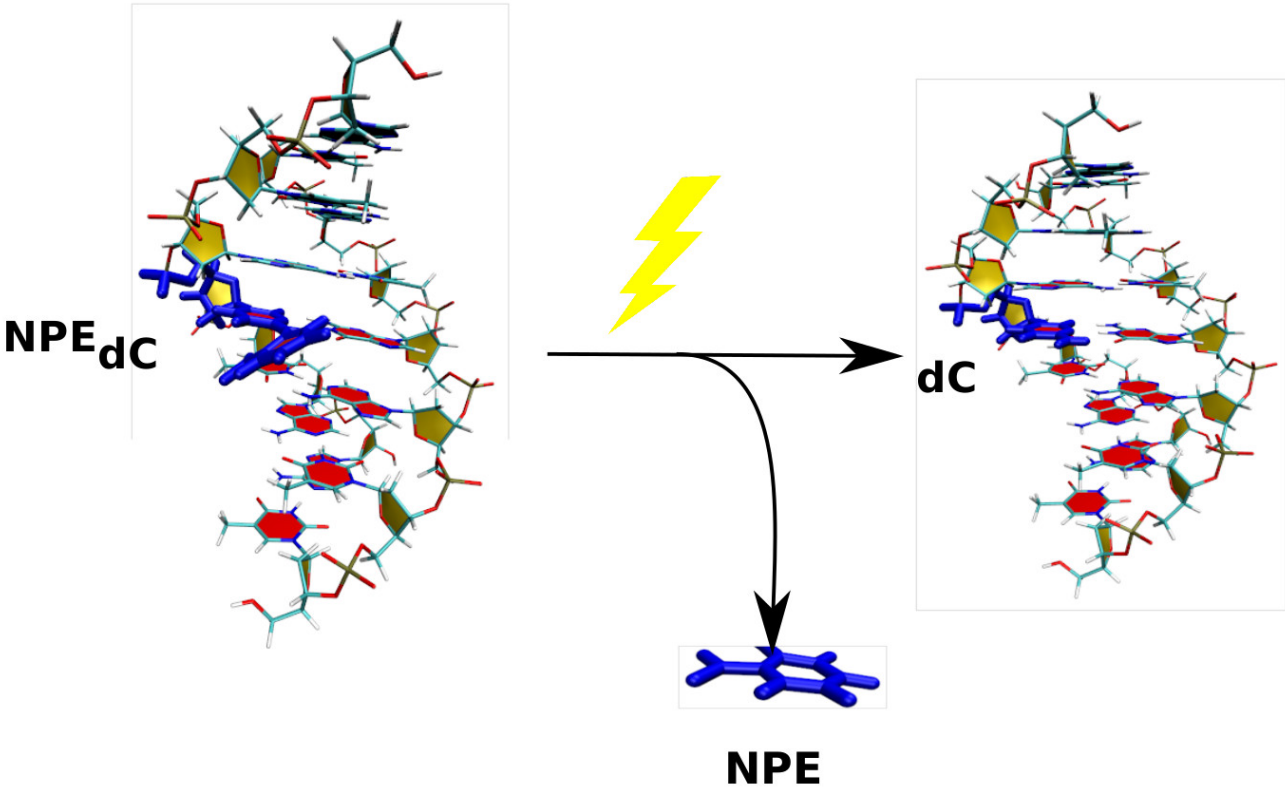
Hierarchy of Time and Length Scales



- Coarse-graining techniques can bridge length scales

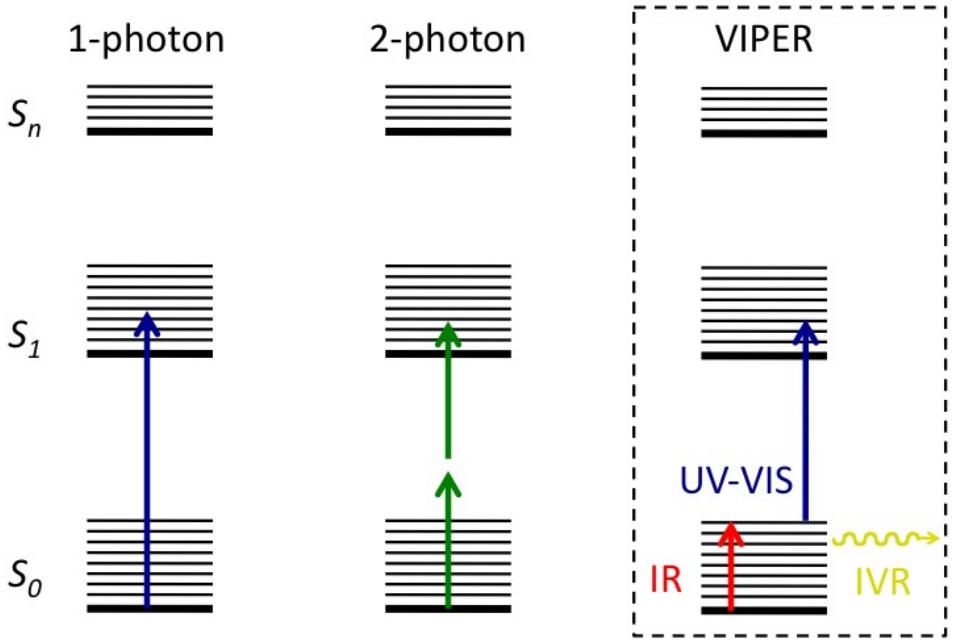
Topics

Photocontrol by Uncaging



- Graduate School CLiC = Complex scenarios of Light Control

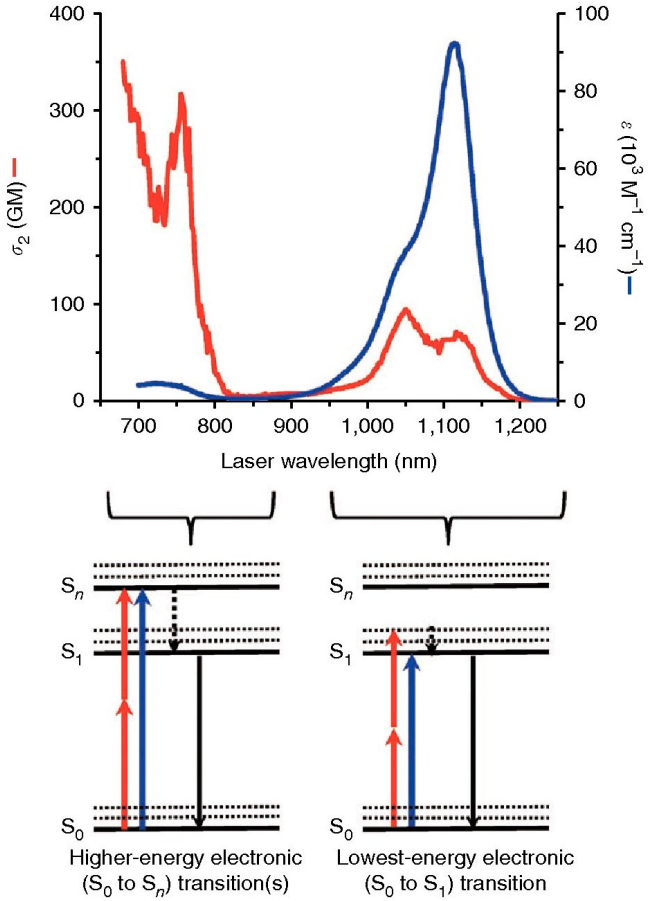
Spectroscopy: What's the Best Way to Prepare Your System?

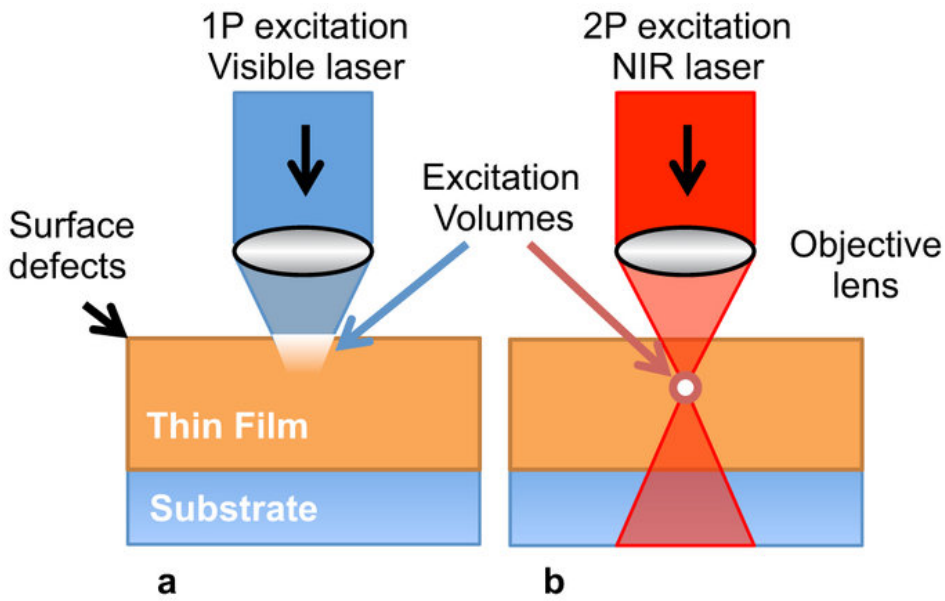


Criteria:

- absorption efficiency (e.g., single-photon vs. two-photon)
- spatial resolution: two-photon induced fluorescence decrease as the fourth power of the distance from the focal plane ("emission from a single point")
- frequency-domain selectivity: e.g., higher selectivity in the infrared domain as used in the VIPER experiment
- design of sequential (two-color) uncaging systems

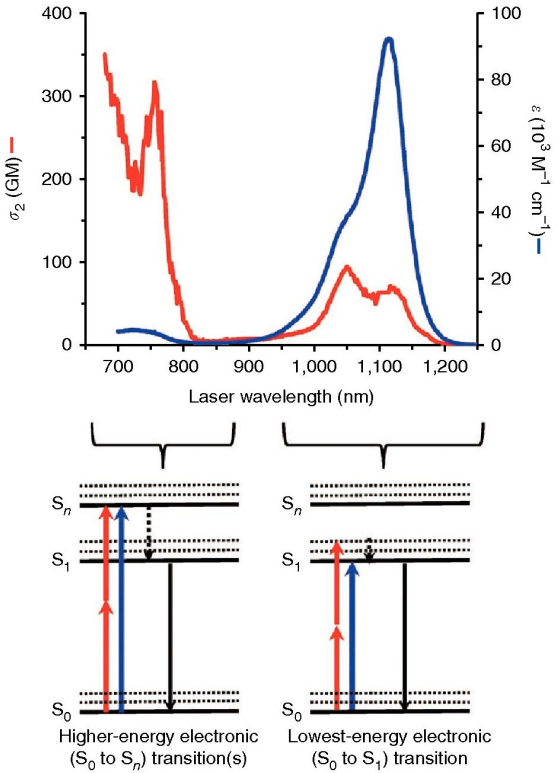
Two-Photon Absorption



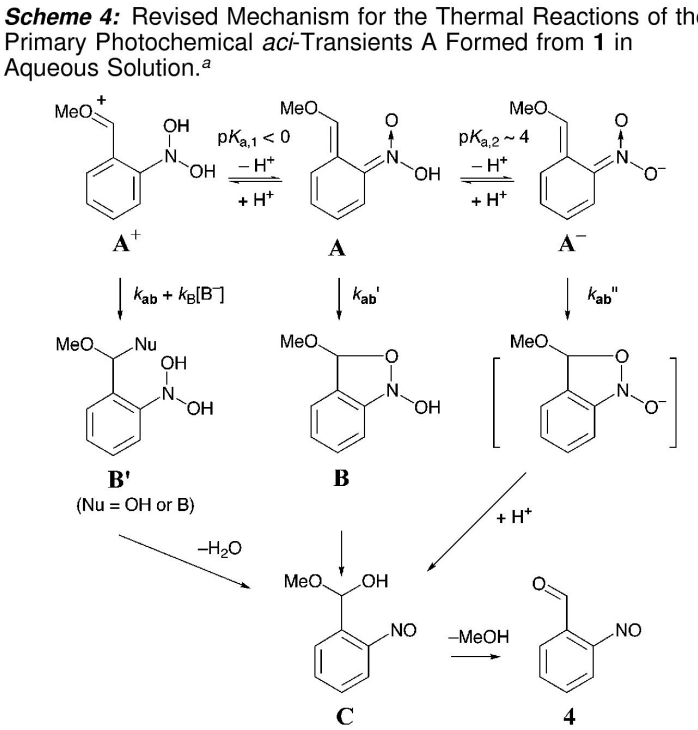


- TPA is quadratically proportional to the intensity of the incident light
- localized excitation in a small volume: useful for materials & biosystems!

Calculation/Prediction of Uncaging Efficiencies (e.g., o-Nitrobenzyl Caging Groups)



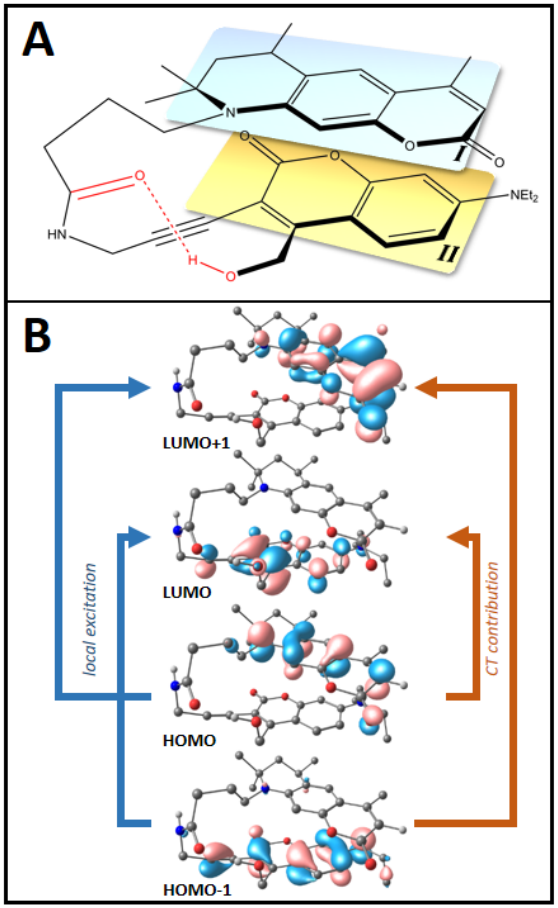
Drobizhev et al., Nat. Meth. 8, 393 (2011)

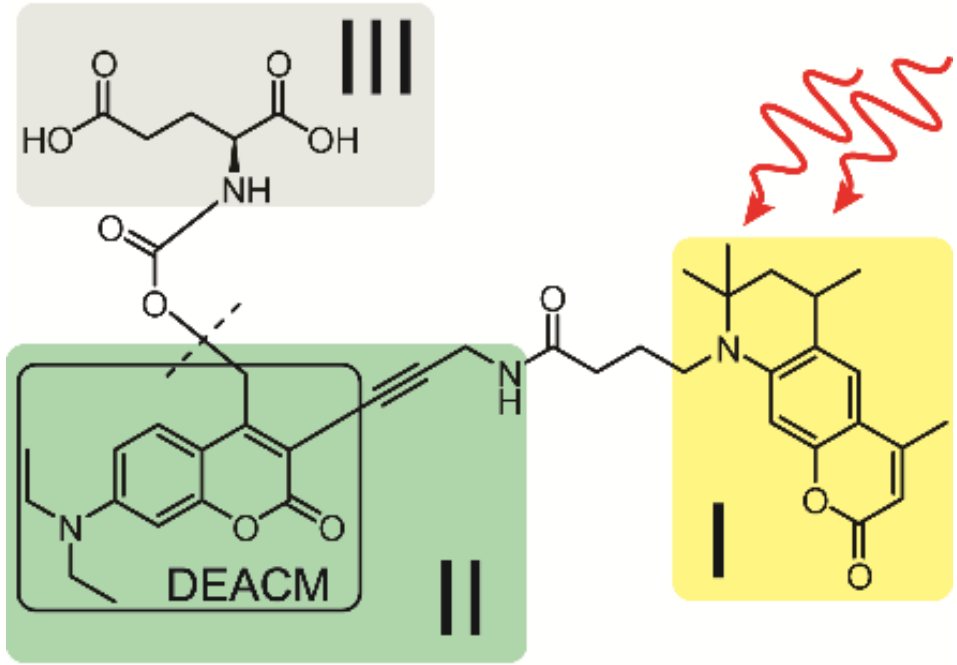


Il'ichev et al., J. Am. Chem. Soc. 126, 4581 (2004)

- efficiency = $\boxed{\varepsilon \cdot \Phi}$ (1-photon) or $\boxed{\delta \cdot \Phi}$ (2-photon)
- intrinsic quantum yields (Φ): reaction paths, intermediates required

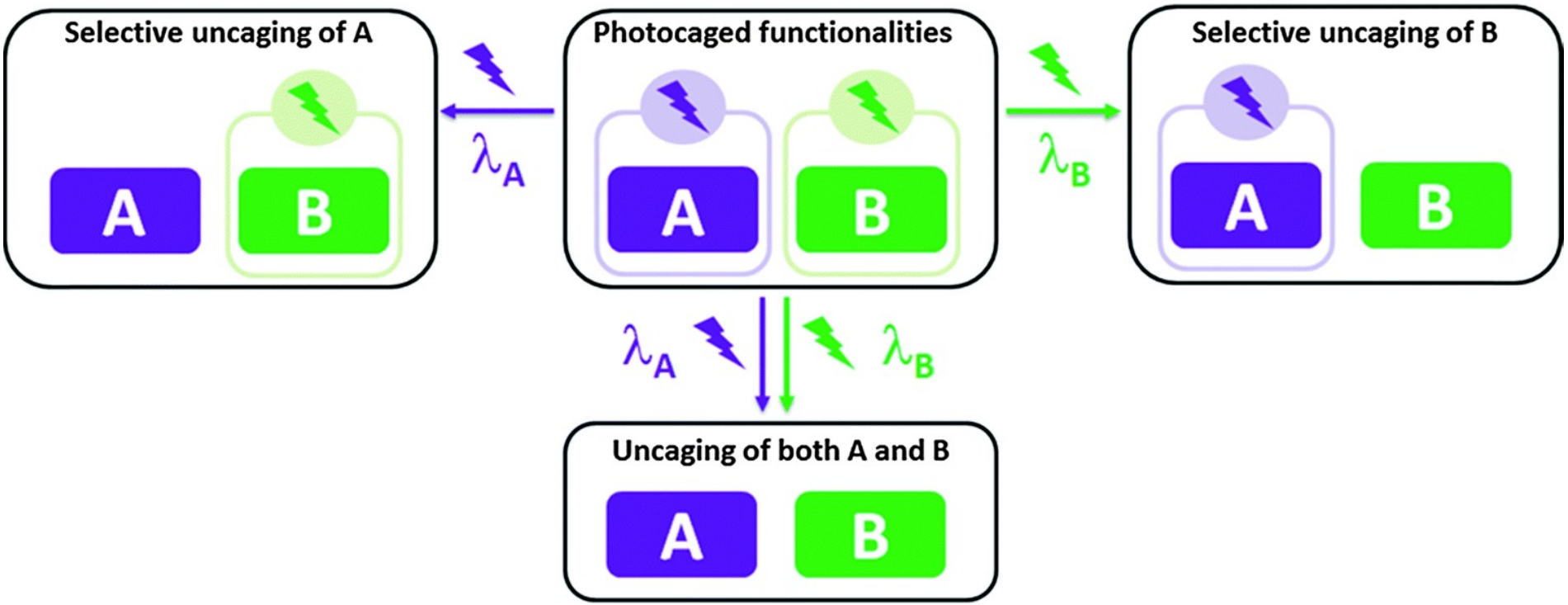
New Two-Photon Protecting Groups





- Atto 390-DEACM-cargo triad [Hammer et al., submitted (2017)]

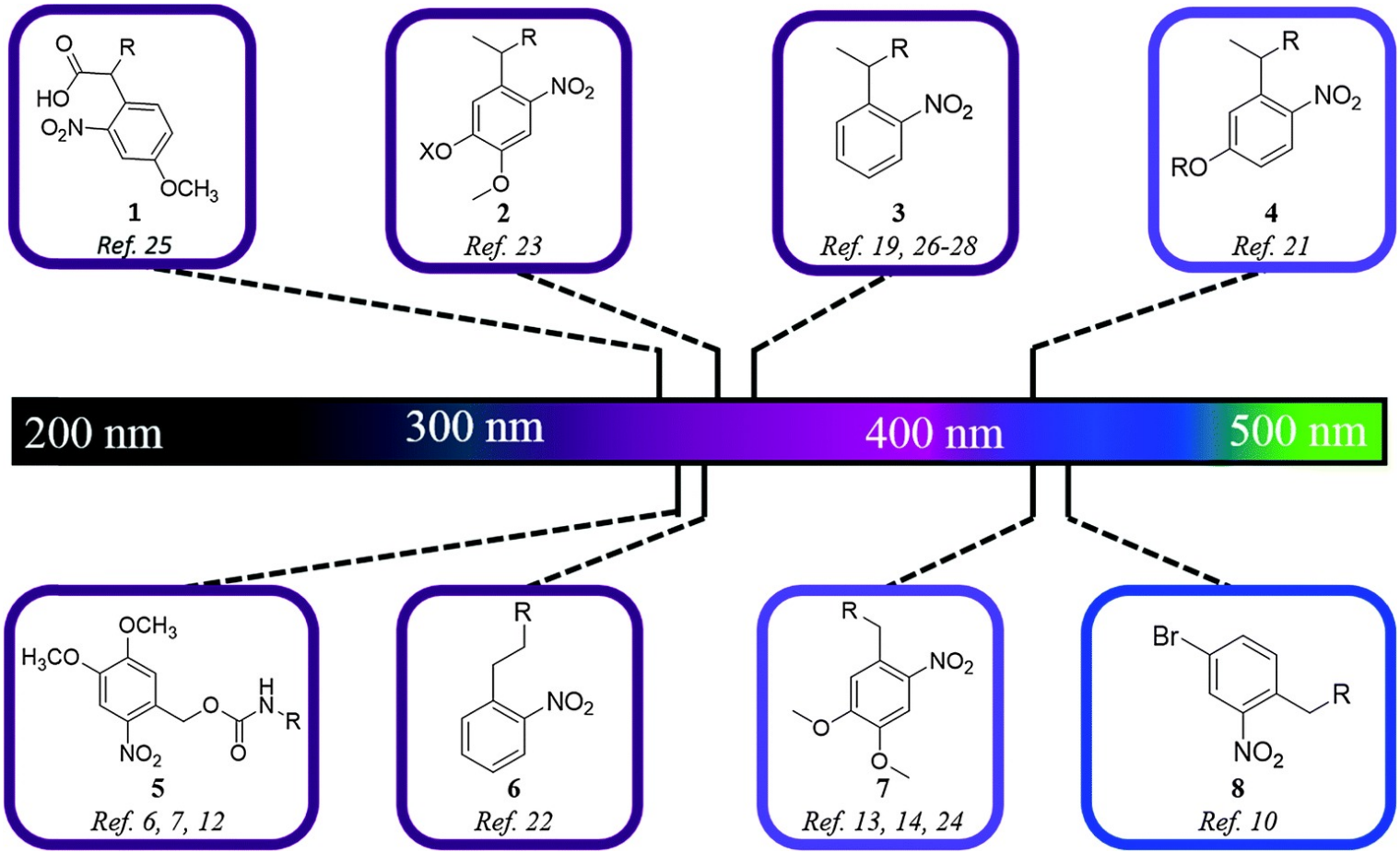
Selective Uncaging



- Concept: cages (protecting groups) that can be addressed fully selectively

[Hansen et al., Chem. Soc. Rev. 44, 3358 (2015)]

Selective Uncaging

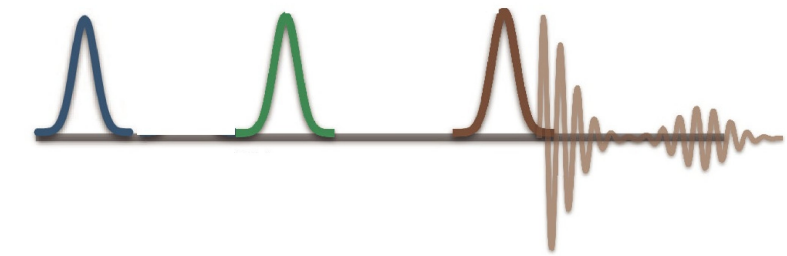


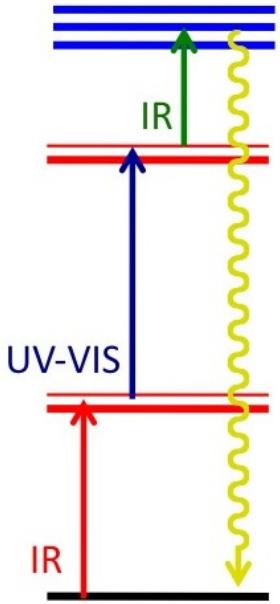
- To some extent, selectivity can be achieved in the optical domain

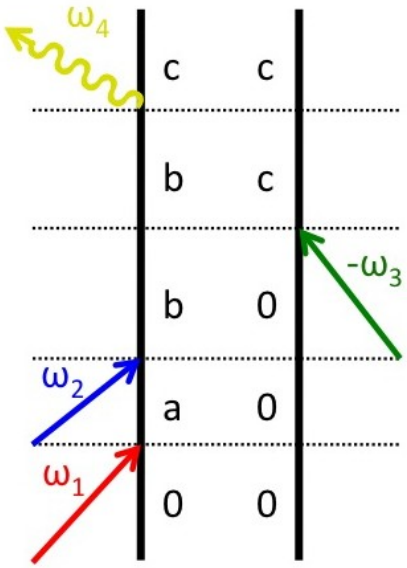
[Hansen et al., Chem. Soc. Rev. 44, 3358 (2015)]

But Better Selectivity Might be Available in the IR

A4: Vibrationally Promoted Electronic Resonance (VIPER) 2D spectroscopy







- mixed IR/UV-Vis pulse sequence [Bredenbeck & collaborators, Angew. Chem. Int. Ed. 2014, 53, 2667]
- shaped femtosecond IR pulses
- calculate optical response functions

Very High Selectivity Available in the IR

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Article
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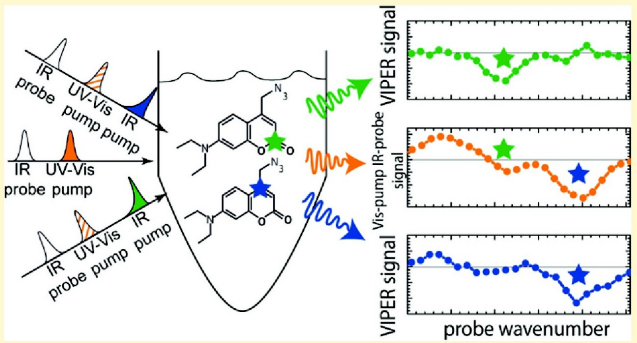
Controlling Photochemistry via Isotopomers and IR Pre-excitation

Daniela Kern-Michler,[†,⊥] Carsten Neumann,[†,⊥] Nicole Mielke,[†] Luuk J. G. W. van Wilderen,[†] Matiss Reinfelds,[‡] Jan von Cosel,[§] Fabrizio Santoro,[∥] Alexander Heckel,[‡] Irene Burghardt,[§] and Jens Bredenbeck*[,†]

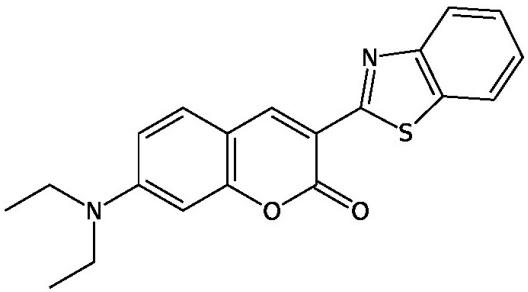
[†]Institute of Biophysics, Goethe University Frankfurt, Max-von-Laue-Str. 1, 60438 Frankfurt am Main, Germany
[‡]Institute of Organic Chemistry and Chemical Biology, Goethe University Frankfurt, Max-von-Laue-Str. 7, 60438, Frankfurt am Main, Germany
[§]Institute of Physical and Theoretical Chemistry, Goethe University Frankfurt, Max-von-Laue Str. 7, 60438 Frankfurt am Main, Germany
[∥]Consiglio Nazionale delle Ricerche (CNR), Istituto di Chimica dei Composti Organo Metallici (ICCOM-CNR), UOS di Pisa, Via G. Moruzzi 1, I-56124 Pisa, Italy

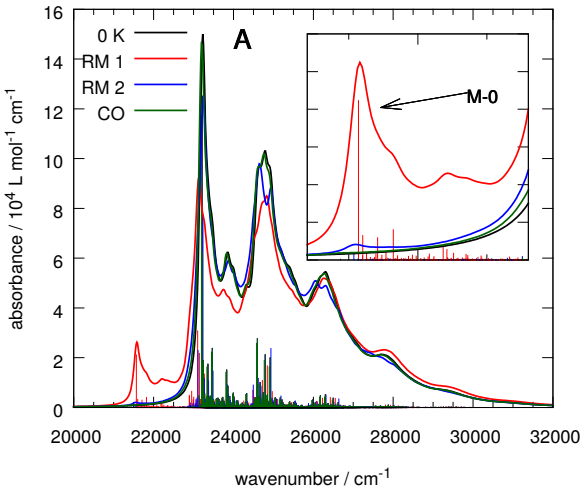
Supporting Information

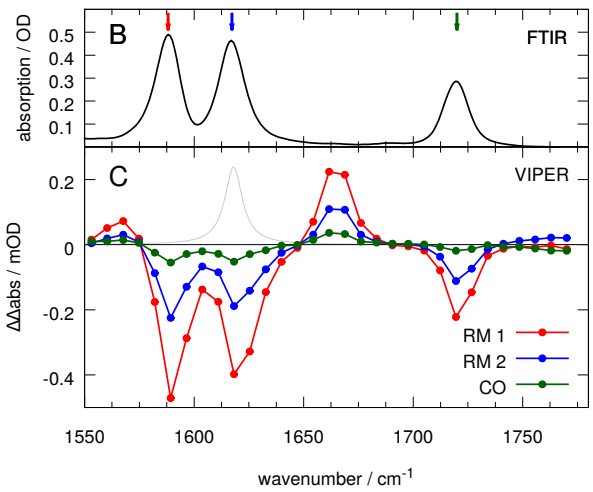
ABSTRACT: It is a photochemist's dream to be able to photoinduce a reaction of a specific molecular species in an ensemble of similar but not identical ones. The problem is that similar molecules often exhibit nearly identical UV−vis absorption spectra, making them difficult or impossible to distinguish or to select spectroscopically. The ultrafast VIPER (VIbrationally Promoted Electronic Resonance) pulse sequence allows to pick a single species for electronic excitation based on its infrared spectrum. The latter usually shows more features that allow to discriminate between species than the UV−vis spectrum. Here, we show that it is possible to induce and monitor species-selective photochemistry even for molecules with virtually identical UV−vis spectra, which is the case for isotopomers. Next to isotope-selective photochemistry in solution, applications to orthogonal photo-uncaging and species-selective spectroscopy and photochemistry in mixtures are within reach.



Simulation of VIPER experiment







- first step: calculate absorption spectrum with vibrational pre-excitation

$$\alpha(\omega) = \frac{4\pi^2\omega_I}{3\hbar c}\sum_n |\langle\psi_n^E|\hat{\mu}|\psi_0^G\rangle|^2\delta(\omega_I-\omega_n) = \frac{2\pi\omega_I}{3\hbar c}\int_{-\infty}^{\infty} dt\langle\phi_E(0)|\phi_E(t)\rangle e^{i\omega t}$$

- complementary time-independent and time-dependent approaches (full quantum approach needed, for hundreds of normal modes!)
- identify the modes that are best suited for VIPER effect

[von Cosel et al., J. Chem. Phys. 147, 164116 (2017)]

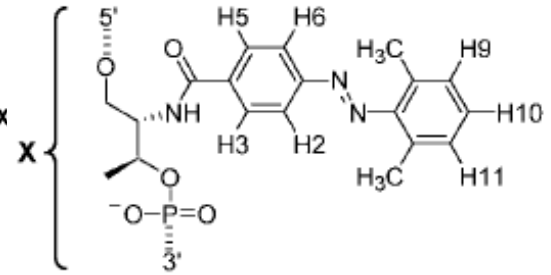
Topics

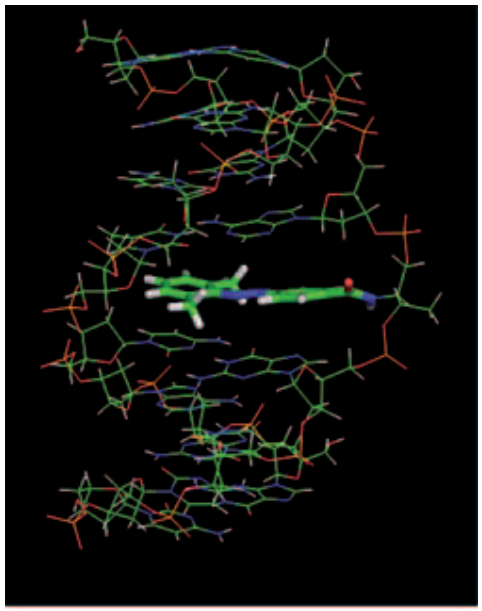
Azobenzene + DNA

- experiments by Asanuma & co: light-triggered conformational changes
- cis/trans melting temperatures are a sensitive function of substituents:
  - 2',6'-dimethyl-*trans*-azobenzene slightly stabilizing
  - 2',6'-dimethyl-*cis*-azobenzene destabilizing
  - p-^{i}Pr-*trans*-azobenzene destabilizing
  - p-^{i}Pr-*cis*-azobenzene slightly destabilizing

Duplex	Temp. [C]		ΔT
CXG/GC	Trans	Cis	
Native	47,7	47,7	
Azo	48,9	43,2	5,7
2',6'-Me-Azo	50,9	36,3	14,6

a) 5′-G^{1} C^{2} G^{3} A^{4}XG^{5} T^{6} C^{7} C^{8}-3′
3′-C^{16}G^{15}C^{14}T^{13} C^{12}A^{11}G^{10}G^{9}-5′

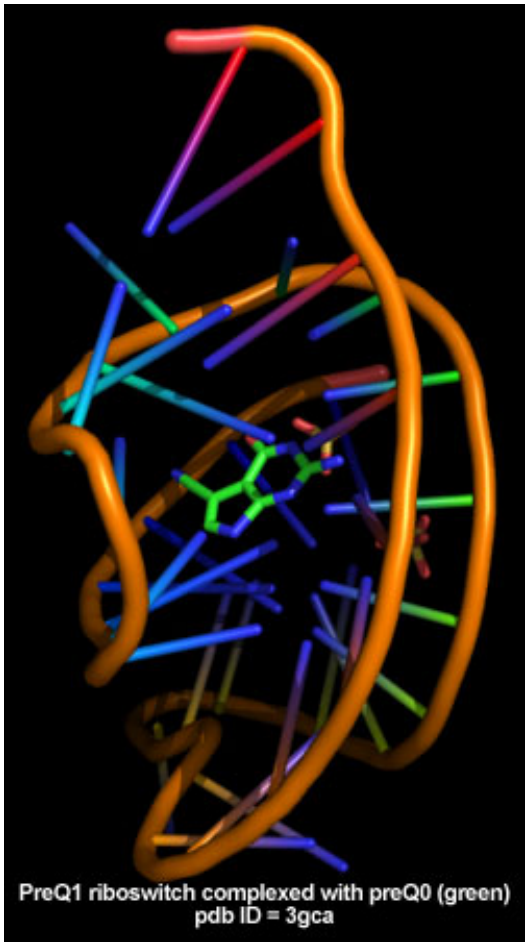




Asanuma and collaborators, Chem. Eur. J. 2009, Nucleic Acids Symposium Series 2007

RNA: e.g., Riboswitch-Ligand Complexes

- controlled riboswitch (de-)activation by small ligand species (e.g., metal ions, amino acids)
- recent works by Asanuma/Heckel: photoinduced activation by photoswitches (azobenzene, spiropyrane)
- characterization of RNA folding intermediates
- SFB 902 "Molecular mechanisms of RNA based regulation"



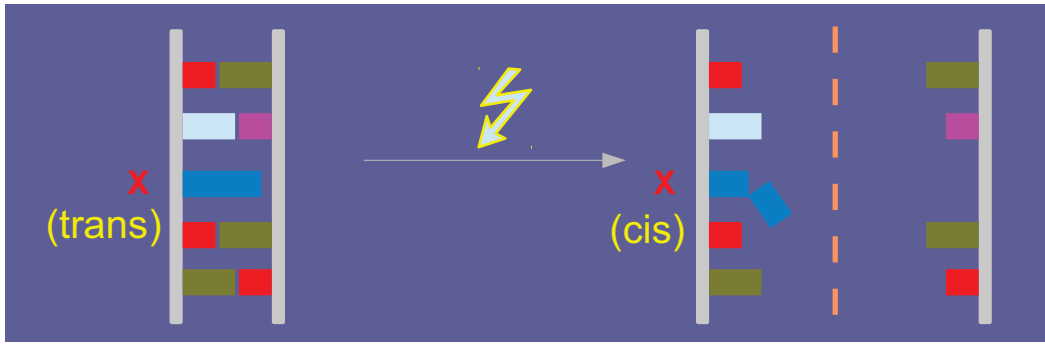
Spitale et al., J. Biol. Chem. 284, 11012 (2009)

How Does a Photoswitch Control DNA / RNA Unfolding?

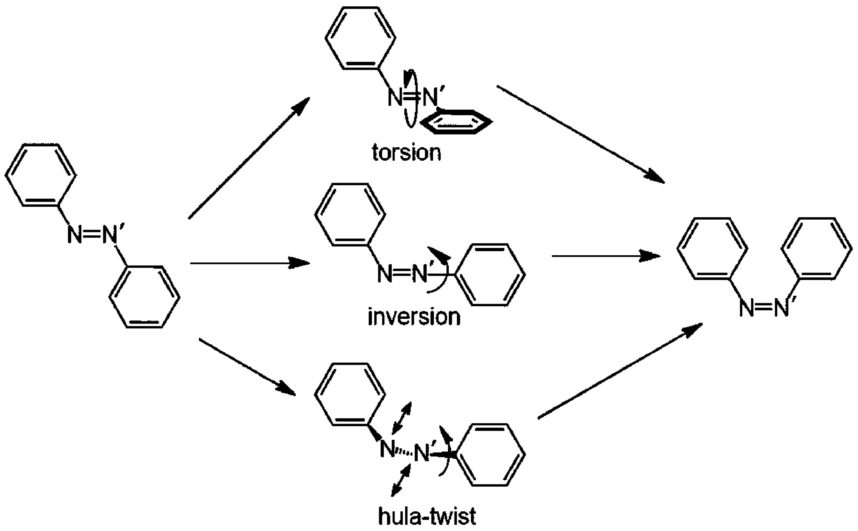
Combine four approaches:

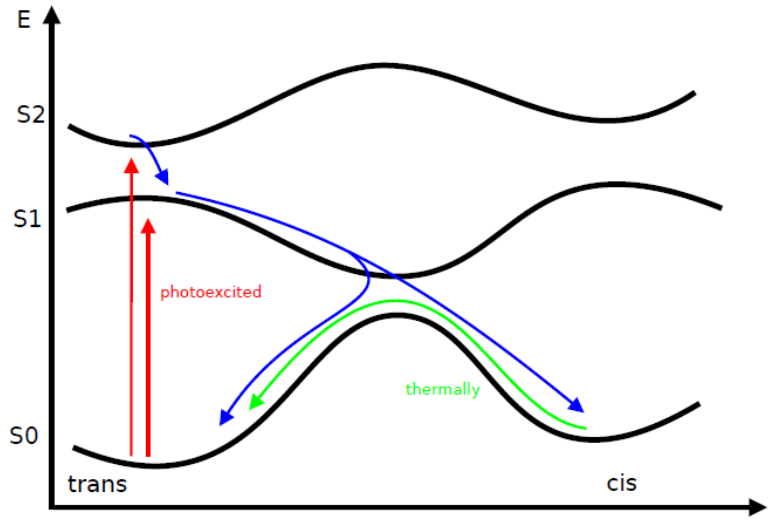
1. characterization of chromophore: QM (electronic structure)
2. ultrafast photoswitch dynamics (fs-ps scale): QM/MM + MD simulations including RNA
3. ps-ns time scale: MD
4. μs-s time scale: kinetic modeling: e.g., Markov State Models

QM = Quantum Mechanics
MM = Molecular Mechanics
MD = Molecular Dynamics



Azobenzene Switch





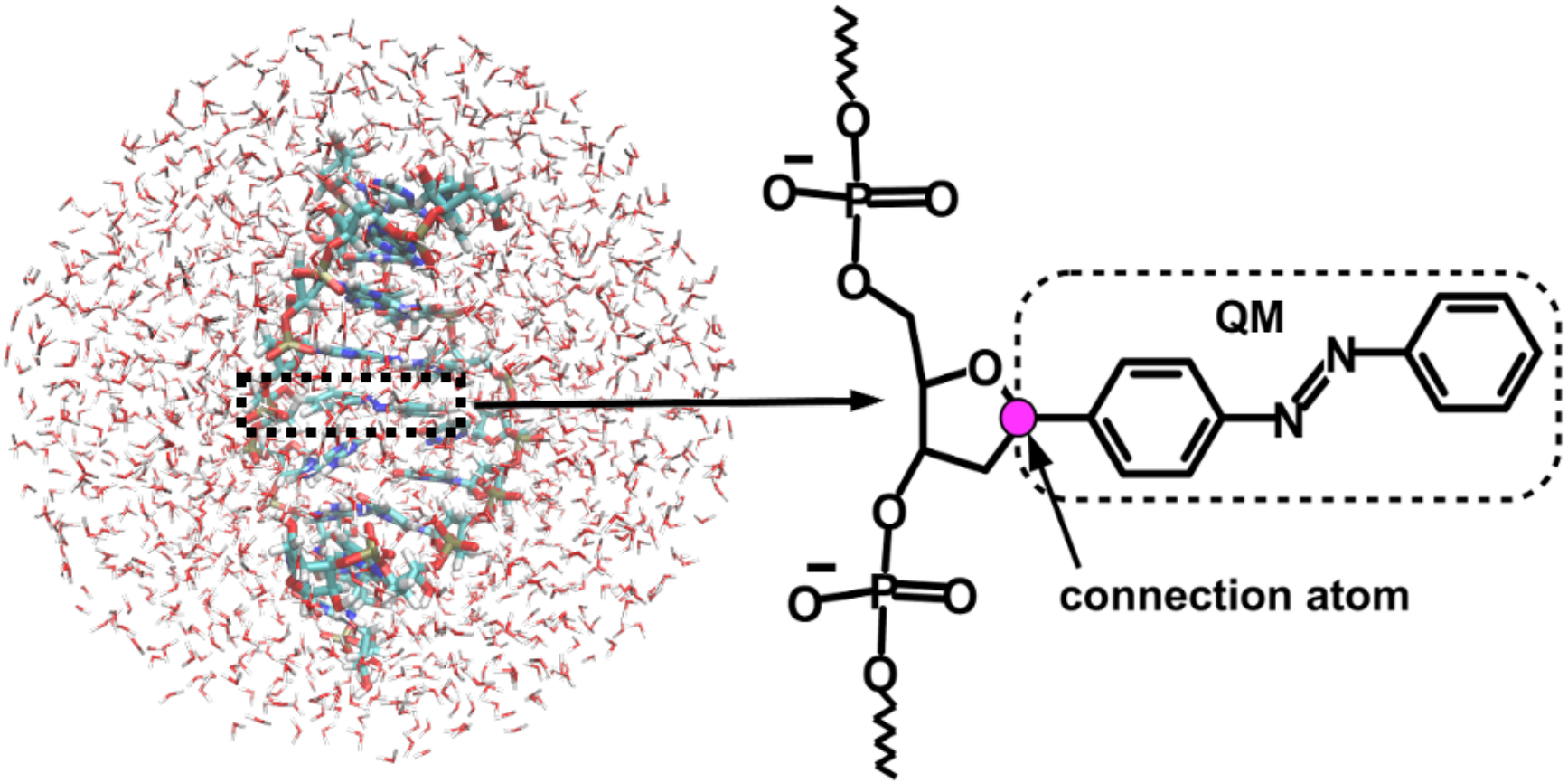
Quick et al., J. Phys. Chem. B, 2014, 118, 8756

- more precise picture: conical intersection ("photochemical funnel")
- ultrafast (fs-ps scale) decay of electronically excited states
- several competing pathways: isomerization, rotation, "hula-twist"
- picture can be modified by substituent effects, environmental constraints

"Femtosecond spectroscopy reveals huge differences in the photoisomerization dynamics between azobenzenes linked to polymers and azobenzenes in solution", Bahrenburg et al., PCCP 16, 11549 (2014)

QM/MM simulations

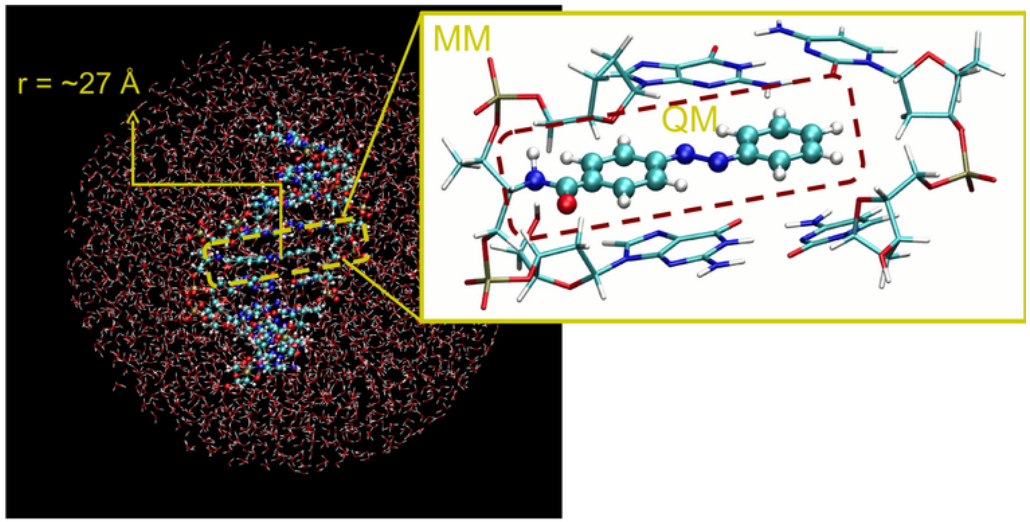
Padmabati Mondal; collaboration with M. Persico & co (Pisa)

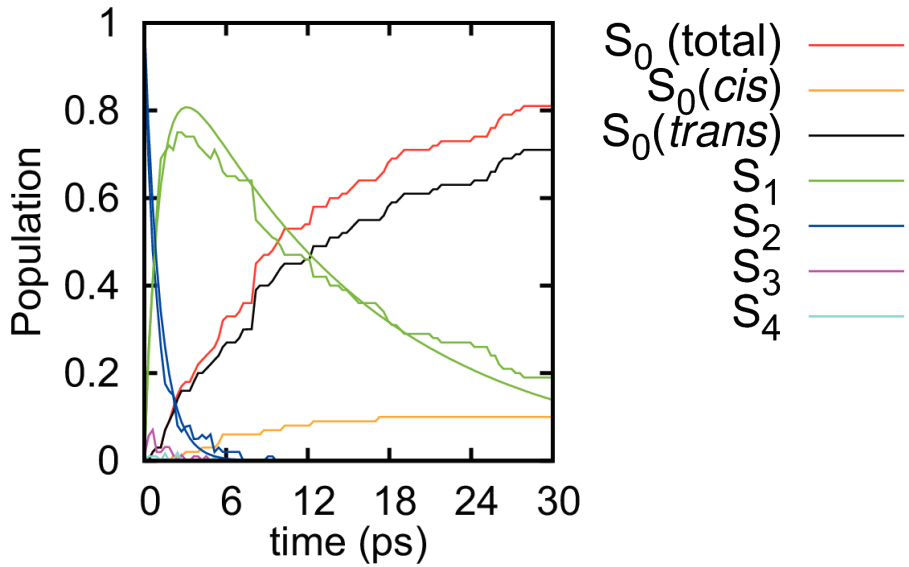


- QM part: MOPAC / MM part: TINKER for RNA + ions + water
- electrostatic embedding / link atom scheme for covalent bonding

Azobenzene & RNA: QM/MM + Surface Hopping

QM/MM = Quantum Mechanics/Molecular Mechanics

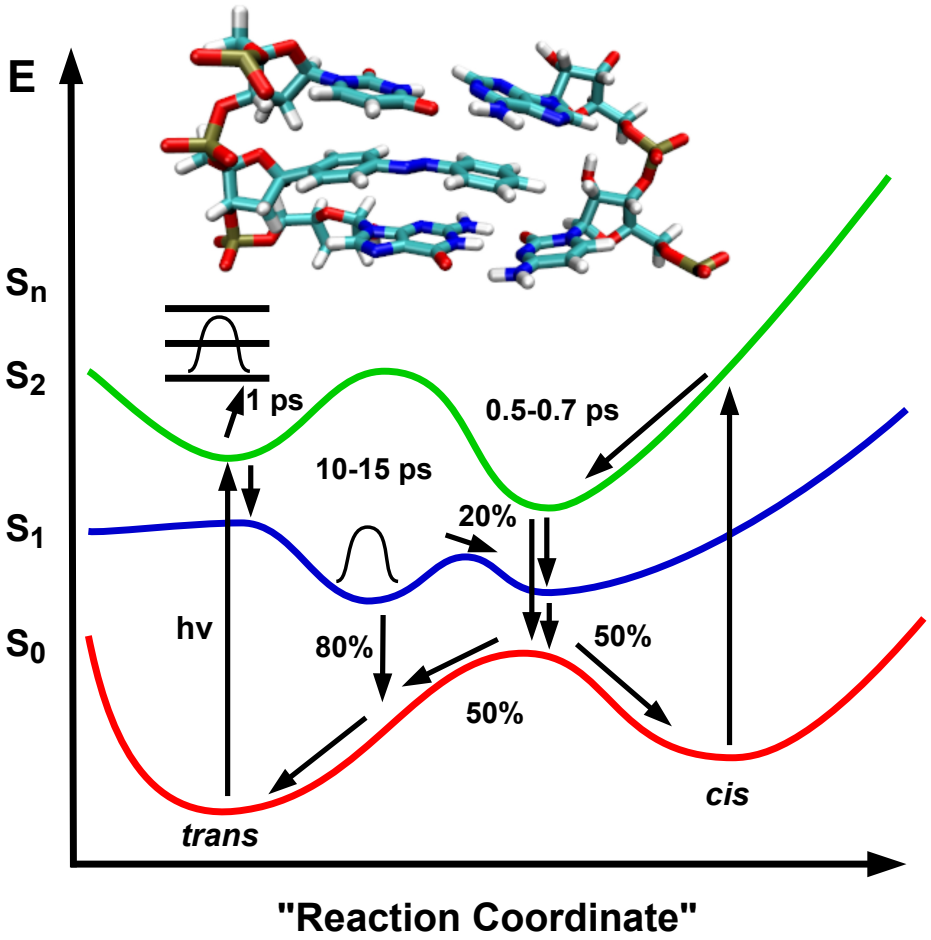




- *trans-cis* isomerization of azobenzene photoswitch triggers unfolding of RNA
- QM part: FOMO-SCF-CI (FOMO = Floating Occupation Molecular Orbital)
- MM part: TINKER (interfaced with MOPAC), Amber ff99sb force field
- QM/MM electrostatic embedding; connection atom scheme for covalent linkage
- initial excitation to $S_2(\pi - \pi^*)$
- quantum yield $\Phi_{\text{trans}-\text{cis}} = 10\%$, $\Phi_{\text{cis}-\text{trans}} = 50\%$
- comparatively slow *trans-cis* isomerization: ca. 20 ps instead of 300 fs (gas phase)

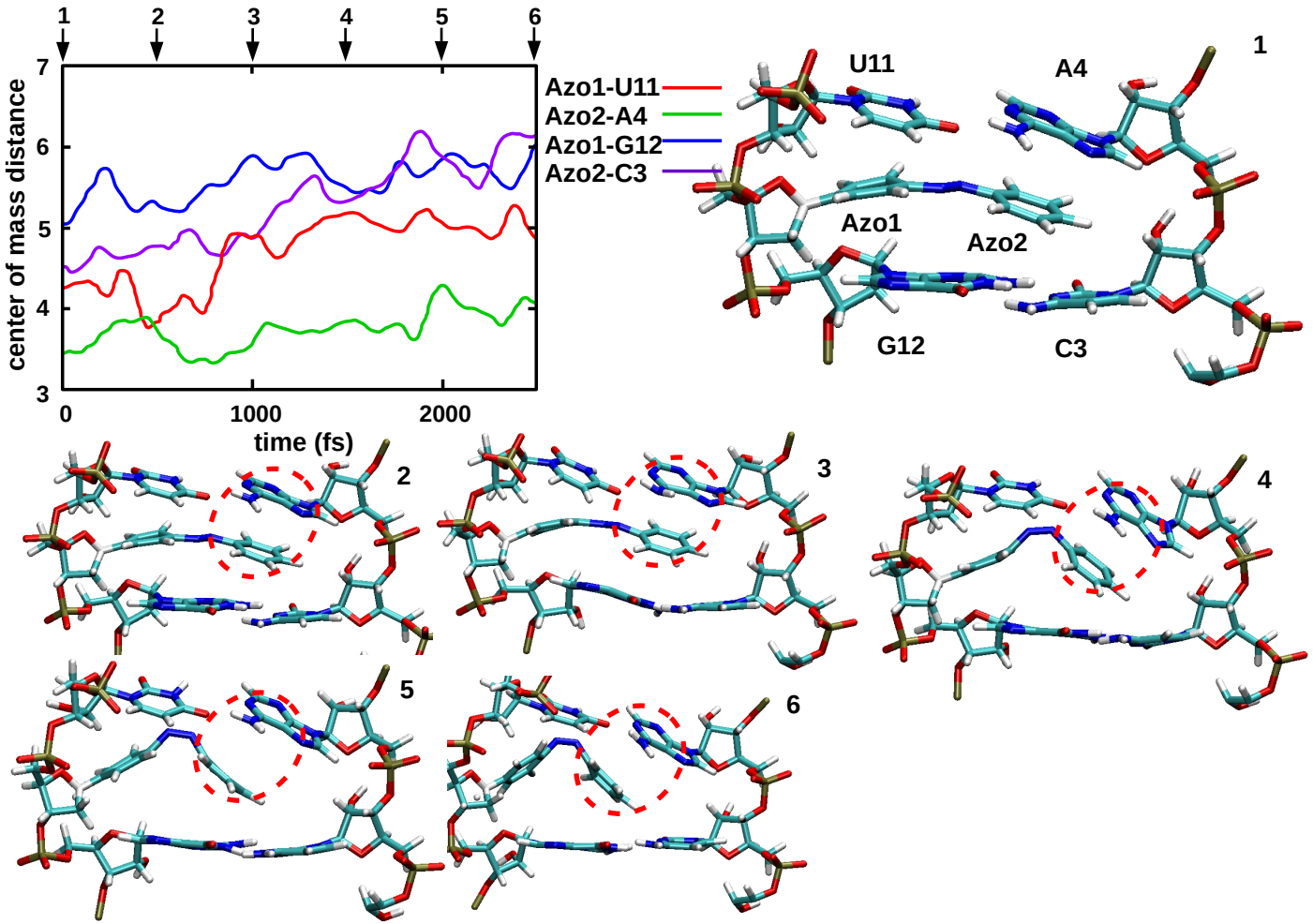
Mondal, Granucci, Ortiz-Sanchez, Persico, Burghardt, to be published

Modified dynamics in RNA environment



- rapid decay from "bright" S_2 state to S_1 state
- long S_1 lifetime, presumably due to stacking interactions

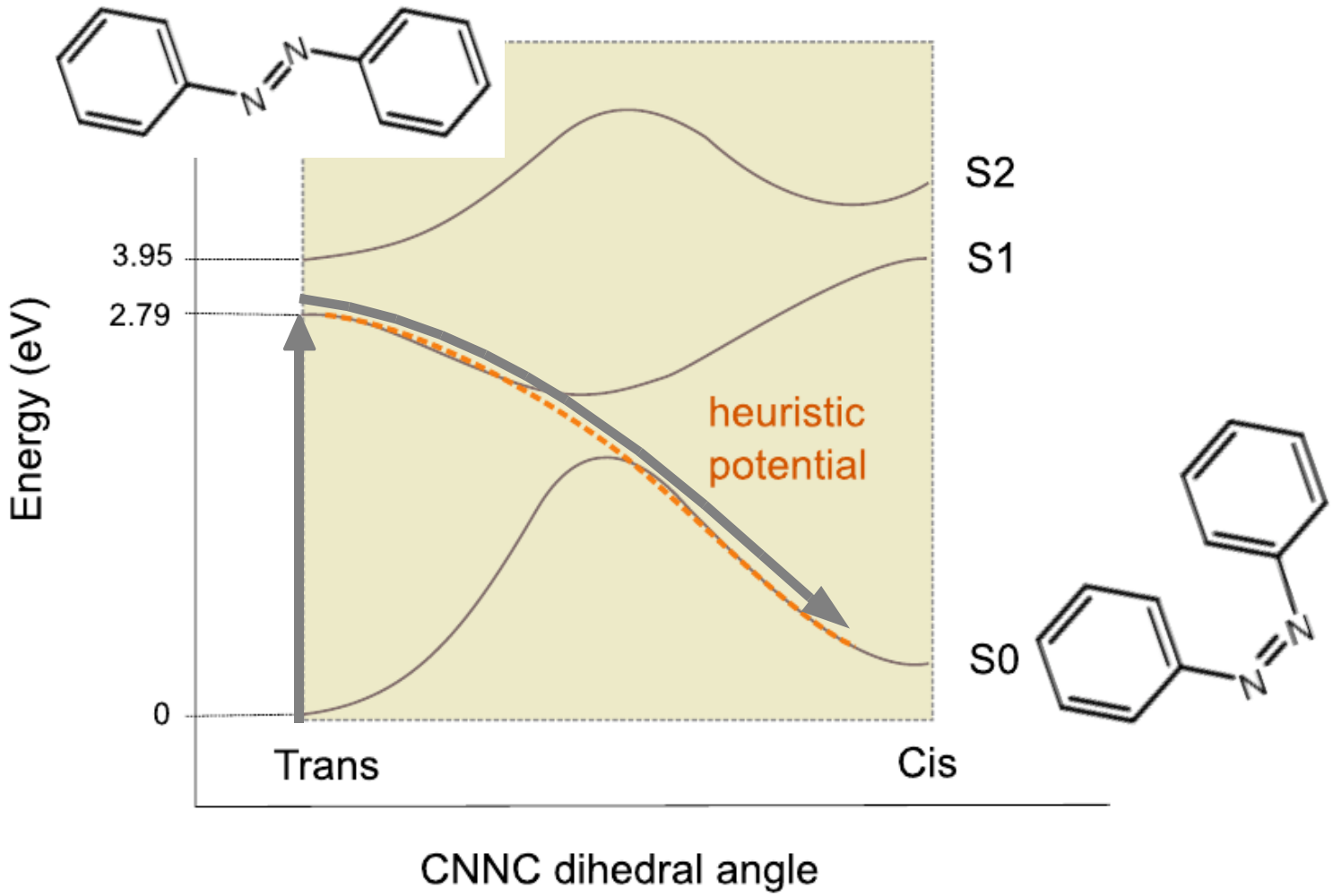
How exactly does the dynamics happen?



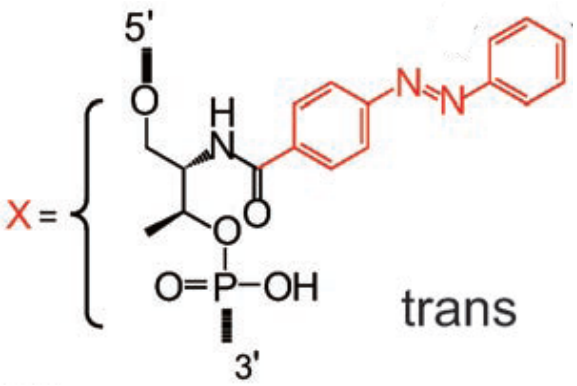
- stacking interactions remain conserved as much as possible
- trajectory switches between S_1 and S_0 around $t \sim$1.5 ps

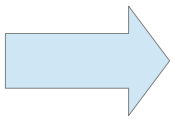
Drastic simplification: isomerisation via effective potential

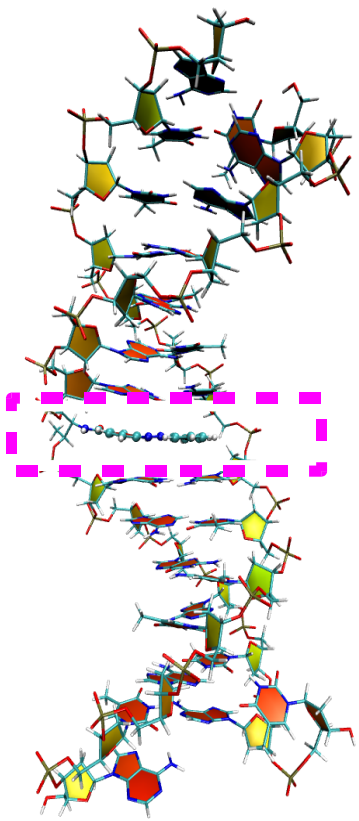
Biswas, Burghardt, Biophys. J., 107, 932 (2014)

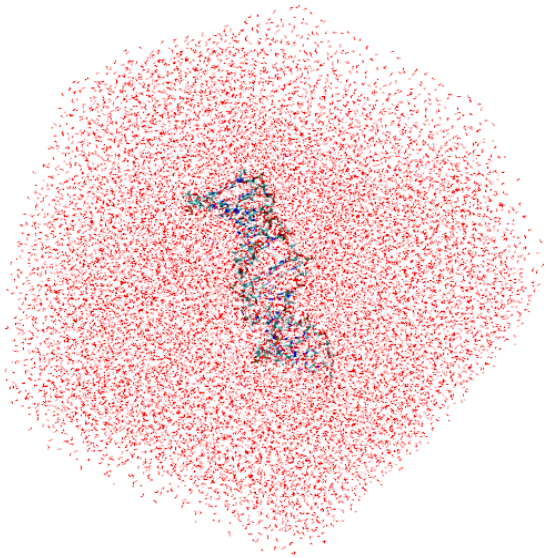


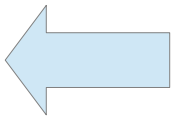
Simulation Set-Up







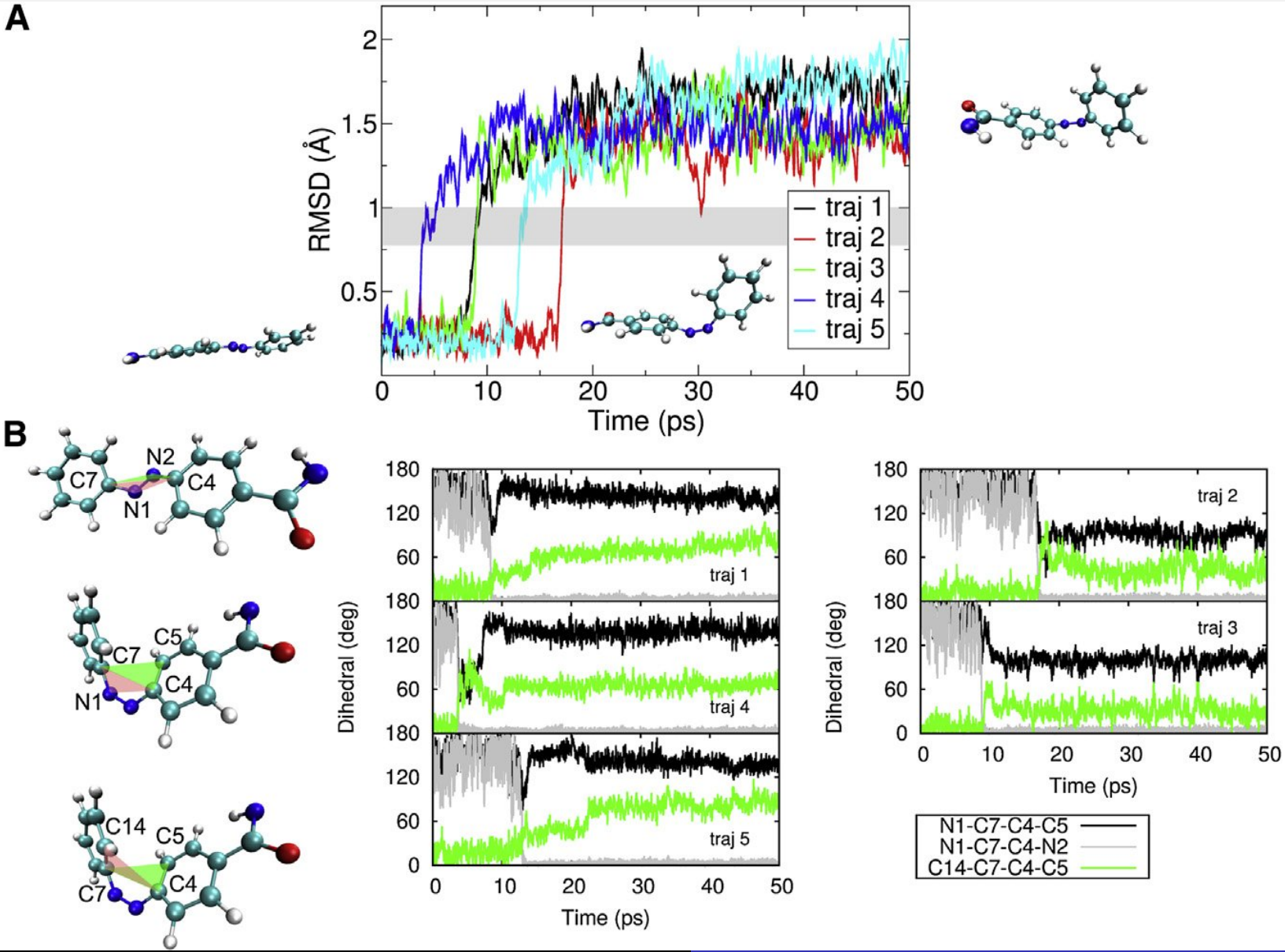




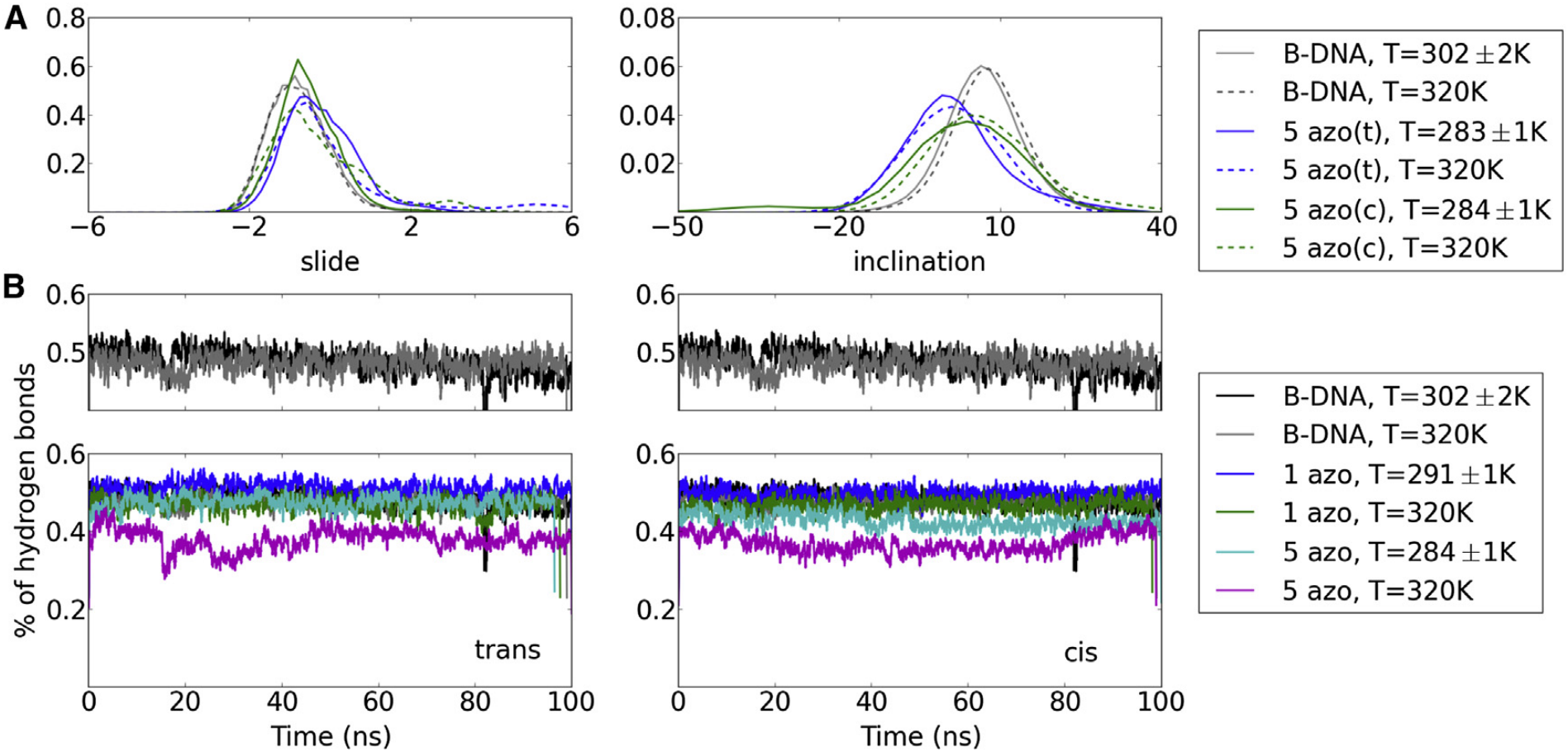
- 5'TAAGAAGXGAGATAT-3' sequence
- azobenzene + 14 mer DNA 29357 atoms
- L-threoninol linkage
- AMBER99 force field with parambsc0 correction
- NAMD program
- 26 Na+ ions
- 2 trans, 2 cis trajectories of duration 50 ns each

Trajectory dynamics

Biswas, Burghardt, Biophys. J., 107, 932 (2014)



DNA Destabilization

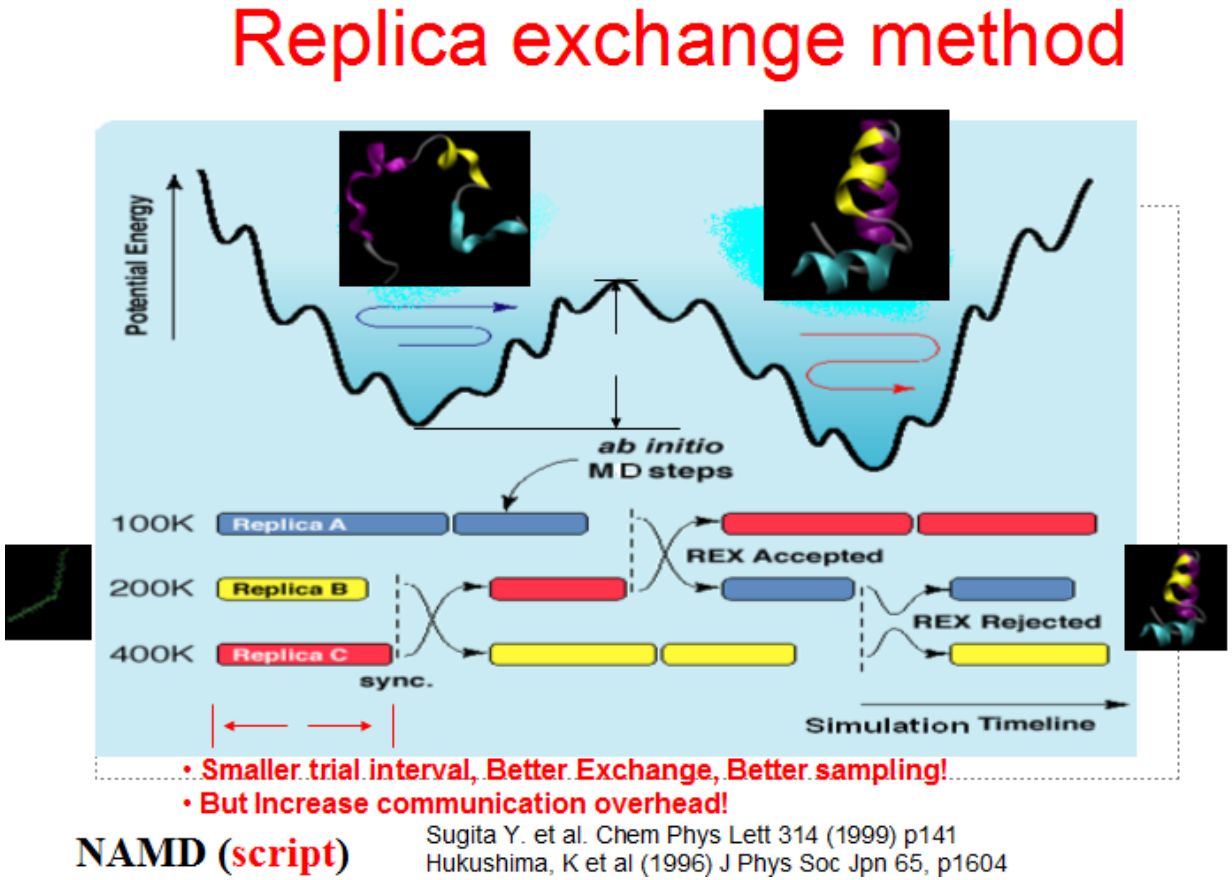


- distribution of helical parameters (slide, inclination) changes noticeably as a function of azobenzene attachment
- in this case, cis and trans forms do not show a significant difference

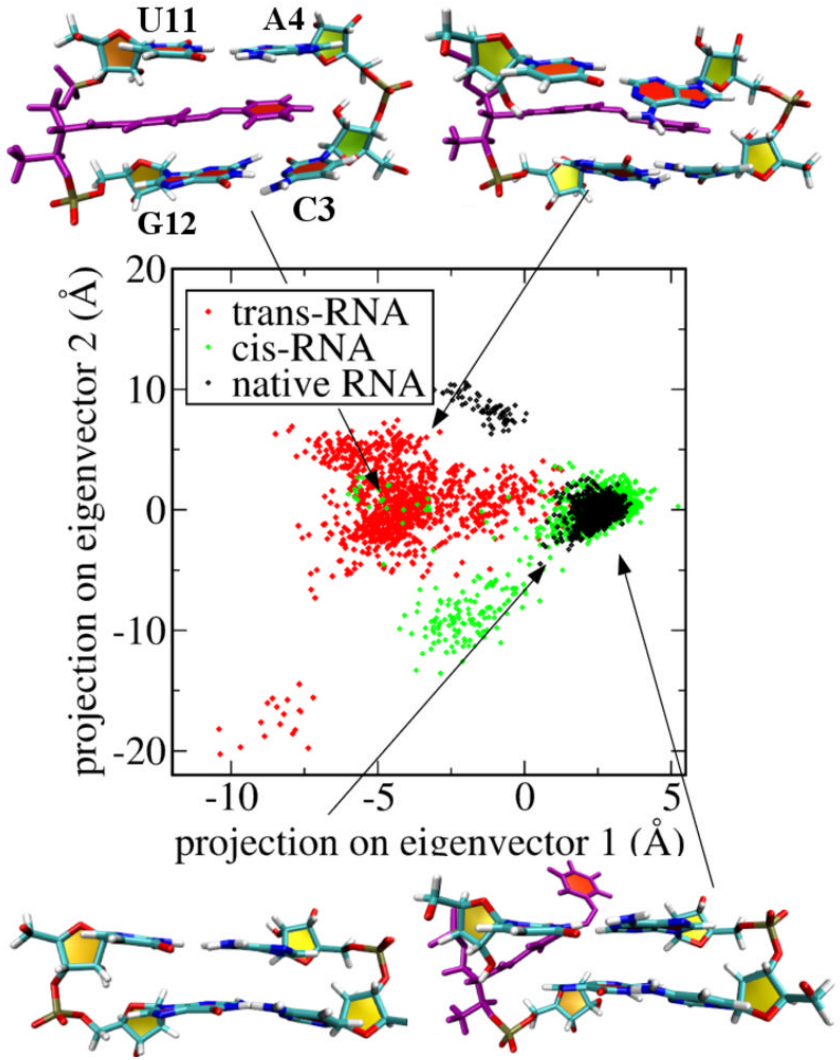
Replica Exchange MD (REMD) simulations

- enhanced sampling technique: "watch" the unfolding of the double helix!
- REMD: run multiple isothermal MD simulations in parallel at a sequence of increasing temperatures and intermittently swap between temperatures

[Sugita, Okamoto, 1999]



Destabilization of Double Strand Structure



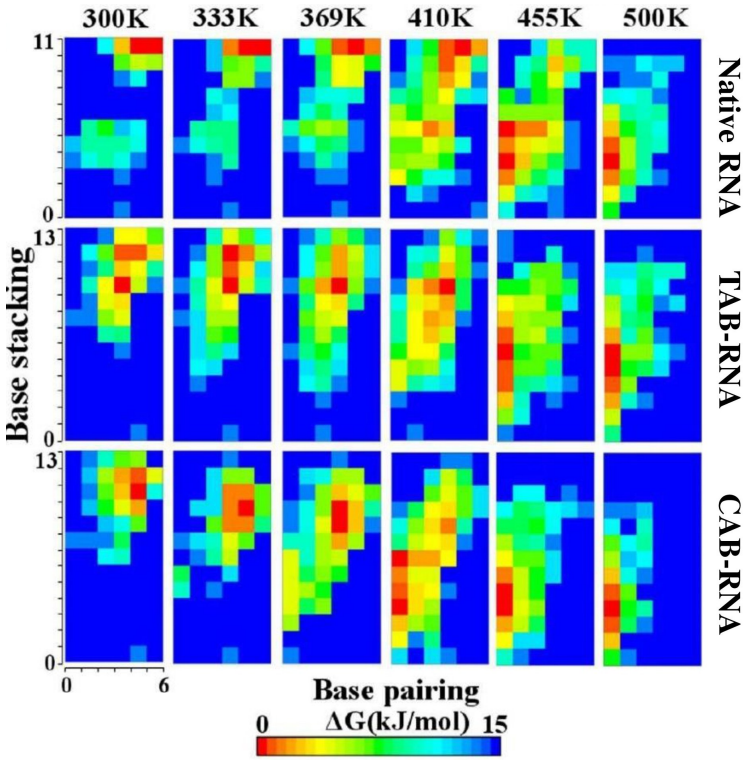
Rastaedter, Biswas, Burghardt, J. Phys. Chem. B, 118, 8478-8488 (2014)

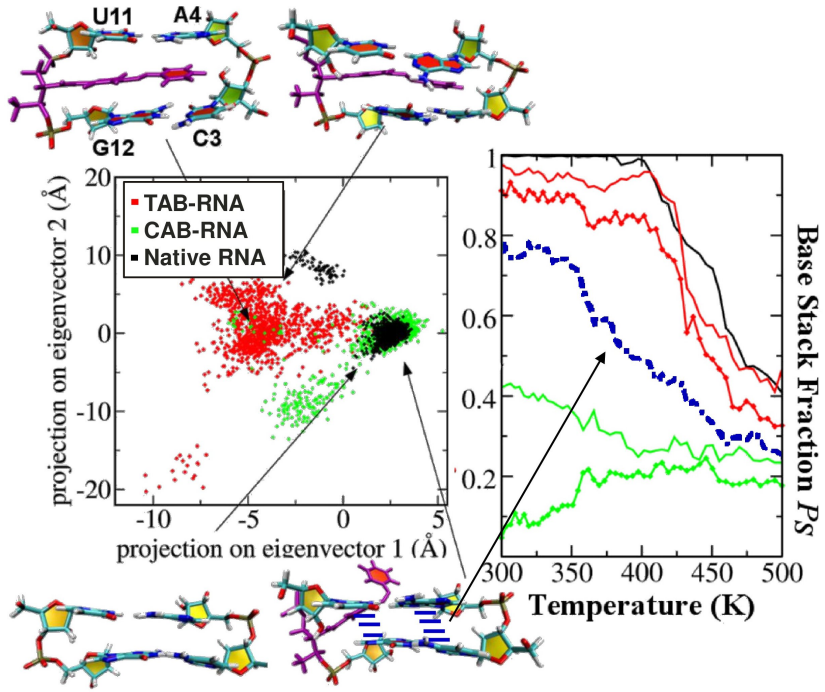
- several conformational ensembles for *trans* form (red)
- single conformational ensemble for *cis* form (black), close to native RNA ⟶ *cis* azobenzene has flipped sideways out of the double strand!

- degree of destabilization depends on several factors:
  - stacking interactions
  - hydrogen bonding
  - properties of the linker
  - presence of abasic site

Free Energy Landscape and RNA Melting

(RNA tetraloop hairpin, D-threoninol linker)





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- unfolding more rapid for the trans/cis substituted species than for native RNA
- folding parameter $Q(t) = \frac{1}{2}(P_H(T) + P_S(T))$
- estimated melting temperatures T_m: cis/trans/native: $382^\circ/418^\circ/427^\circ$
- scaled values T_m^{scaled}: cis/trans/native: $305^\circ/334^\circ/342^\circ$

Bottom line: multiscale methods needed!