Measurement and prediction of quantum coherence effects in biological processes

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In recent years experimental measurements have uncovered fine quantum effects (FQE) in biological systems. These FQE may appear as surprising given the warm soft nature of biological media, as opposed to the cold hard world where quantum effects dominate. The observation of long-lived coherences within photosynthetic antennas at room temperature for hundreds of femtoseconds is one striking example of such FQE. The basic mechanism of excitation energy transfer (EET) is described by Forster theory, but researchers have recently discovered important modifications to this theory that help explain the function of light-harvesting proteins. Recent 2D electronic spectroscopy experiments, for example, have provided evidence that long-lived quantum coherences can exist in various condensed-phase systems. Such coherences allow the possibility that quantum-mechanical effects might modify the flow of electronic excitations through light-harvesting proteins. The significance of quantum coherence to the mechanism and efficacy of energy transfer hinges on the timescale over which it survives. Up to now, it is not known whether coherent quantum dynamics is critical to make energy transfer highly efficient in large systems. Nevertheless, coherences present opportunities for controlling energy transfer in multichromophoric assemblies because of the ways they modify the random hopping mechanism assumed in the Förster model.

Other examples of FQE are given by electron tunneling (ET) between or within proteins. ET are ubiquitous in biology. Depending on the characteristics of the biosystems, ET can proceed through a myriad of competing mechanisms ranging from fully coherent to fully incoherent hopping. Electron transfers between the proteins of the cellular respiratory chains occur over ca. 10-20 Å and are usually assumed to follow the coherent super-exchange mechanism. When some molecular fragment(s) are able to host the electron (or a hole) transiently on the way to the acceptor (donor) site, multistep (incoherent) hopping is likely to be the dominant mechanism. While the Marcus Theory of electron transfer has obtained remarkable successes for rationalizing super-exchange ET, the competition between coherent and incoherent electron transfers remains difficult to handle within this framework. It is a current central subject of research within the biochemistry community to probe the occurrence of hopping in biological ET processes. Remarkable experiments have been performed for example on DNA photolyases, cryptochromes, ribonucleotide reductases or on the photosynthetic reaction center. Similarly there are currently attempts to develop ET theories that go beyond the Marcus theory. The concept of "hopping maps" or the recent modification of the standard Marcus theory to include decoherence effects are examples of these attempts. Like for biological EET, the question of the possibility for biological systems to tune the coherence time lengths for catalytic purposes is an exciting, yet unsolved, perspective.

A third example of FQE comes from the investigation of proton, hydrogen atom or hydride transfers in enzymatic reactions. Accumulating evidence from the

measurements of kinetic isotope effects on enzymatic rates tends to show that some enzyme kinetics largely exceed the semi-classical limit (i.e. the standard Transition State Theory with zero point energy corrections). Persistent deviations from empirical observation led to the incorporation of quantum mechanical nuclear tunneling in theoretical models. Many different proposals may be found in the literature like the Variational Transition State Theory or the adaptation of the Marcus Theory to hydrogen and proton tunneling. Recent models are mathematically flexible enough to cope with most experimental rates, even those involving high tunneling contributions, but they also bring important questions about their limitations (like non-equilibrium effects or the adiabatic vs. non-adiabatic kinetic character of the particle transfer) and the physics they capture. Generally speaking these models emphasize the importance of the fluctuations of the donor-acceptor distances and of the dynamics of the protein. On the other hand little attention has been paid to the importance of coherences for this type of process; at least it seems to be addressed in a different way than for EET and ET processes.

The last decades have seen a deeper and deeper exploration of biological systems up to the point of experimentally highlighting some quantum hallmarks of biological matter. The interpretation of the experimental data and the connections to FQE like coherences, decoherence, entanglement… is challenging, due to the complexity of biological systems. A more detailed understanding of quantum coherent effects in excitation energy transfer, electron or proton/hydrogen atom/hydride tunneling demands thorough and comprehensive investigations combining quantum dynamical theory with structure-based modeling based on quantum chemical calculations and molecular dynamics simulations. Computational approaches have to cope with the fact that biological systems are highly inhomogeneous and are characterized by multiscale dynamics.

This **Themed Collection** is centered on questions concerning the measurement, prediction, and consequences of coherence in biological processes. It contains fifteen contributions from leading experts on three sub-themes:

i) Excitation Energy Transfer and Excited-State Dynamics

Novoderezhkin, Romero and van Grondelle report on how exciton-vibrational coherence controls the charge separation in the photosystem II reaction center. Using 2-D electronic spectroscopy, they detect different types of coherences, vibrational, predominantly electronic and mixed exciton-vibrational, concluding that vibrational modes are in quasi-resonance with the exciton splitting. In the contribution of *Smyth, Oblinsky and Scholes* we learn that the B800-B850 coherence in the LH2 complex of photosynthetic purple bacteria correlates with the energy transfer rate, bringing out the importance of the number of chromophores that collectively contribute to the "delocalization length" of an excitation within LH2. The roots of these phenomena in bipartite and multi-partite entanglement are clarified. For their part, *Huo and Miller* use a system-bath model with two strongly coupled donor chromophores weakly coupled to a single acceptor chromophore, or *vice versa*. The dynamics are described with a real-time path integral scheme. Multi-Chromophore Förster Energy Transfer theory is used to map the original parameterization onto an alternative which allows dynamic coherence to be turned off, with the result that dynamic coherence plays only a minor role; static coherence largely

governs the kinetics. *Tscherbul and Brumer* address the contentious issue of whether excitation with natural, incoherent, light can still invoke coherent EET. They find, surprisingly, at least to some, that a sudden turn-on of incoherent pumping can generate substantial Fano coherences among the excited states of retinal. *Nenov, Giussani, Fingerhut, Rivalta, Dumont, Mukamel and Garavelli* present an efficient way to incorporate nuclear dynamics in nonlinear electronic spectroscopy within the framework of a single-trajectory mixed quantum-classical dynamics. Their scheme incorporates *ab initio* (CASSCF, CASPT2, RASSCF, RASPT2) calculations of the excitation energies and it accounts for the electronic energy fluctuations due to nuclear degrees of freedom, explicitly incorporating the fluctuations of higher excited states. Computed 2-D spectra for pyrene yield realistic lineshapes and allow the unambiguous assignment of the excited-state absorption features. Finally, in an insightful Perspective, *Jurinovich, Viani, Curutchet and Mennucci* review the limitations and potentials of quantum chemical methods in the modeling of photosynthetic antennae. They focus on three main aspects: i) the quantum-mechanical calculation of excitonic parameters (site energies and couplings), ii) the incorporation of environmental effects through hybrid quantum/classical approaches and iii) modeling the dynamical coupling among the excitonic parameters and the vibrations of the pigment-protein complex.

ii) Electron Transfer

In the area of bridge-mediated electron transfer, *Bertsis and Baldrige* have developed a new localized molecular orbital Green's function pathway method that enables an intuitive understanding of electron tunneling in terms of through-bond and through-space interactions. An accuracy of 0.1 eV is claimed for the electronic couplings. Amongst other applications, the tunneling pathways in a Gly_5 model peptide are elucidated. *Borrelli, Capobianco, Landi and Peluso* break new ground in the theory and computation of ET for bridged systems with three or more electronic states by adapting techniques from molecular spectroscopy. They partition the Hilbert space for time-independent basis functions in such a way that the convergence of the time-dependent dynamics can be checked and use a Duschinsky analysis, with equilibrium structures and vibrations from DFT, to calculate the coupling, yielding an insightful analysis of ET in single-stranded DNA oligomers. *Antoniou, Ma, Zhang, Beratan and Skourtis* have accepted the challenge of elucidating the process by which infrared pulses may be used to control ET reactions. Vibrational excitation of a bridge joining donor and acceptor modulates the electronic couplings within a scheme using simple models and *ab initio* computations. The nature of the vibrational spectra, the strengths of the electron-vibrational coupling and the interactions between molecular vibrations and infrared radiation conspire to provide vibrational control for fast coherent ET reactions. *Mangaud, de la Lande, Meier and Desouter-Lecompte* show us how constrained-DFT can be used effectively to provide the spectral density for a Redfield-based theory of dissipative dynamics using the examples of mixed-valence organic compounds. They provide a perspective roadmap for future QM/MM simulations for larger systems encountered in the life sciences.

iii) Proton, Hydrogen Atom and Hydride Transfer

Two contributions deal with the reactions catalyzed by thymidylate synthase (TSase). In the first, *Ghosh, Islam, Krueger, Abeysinghe and Kohen* addressed the question of the

nature of the general base for the proton abstraction step. They measured the temperature dependence of the kinetic isotope effect (KIE) for a mutant, Y94F, and concluded that Y94 is involved in the transition state, but as part of a hydrogen-bonded network involving several active site residues and several water molecules. The general base is a network! In the second TSase contribution *Świderek, Kohen and Moliner* look at the rate-limiting hydride-transfer step. QM/MM molecular dynamics simulations are employed, using two different crystal structures as starting configurations to explore different conformational spaces, showing the existence of chemical paths with not only different reactivities but also different reaction mechanisms. The calculations reproduce and rationalize the observed normal H/T secondary kinetic isotope effect. *Nadal-Ferret, Gelabert, Moreno and Lluch* report on the feasibility of spontaneous proton transfer in a green fluorescent protein (GFP). They use a combination of QM/MM with time-dependent DFT and the Heidelberg multi-configurational time-dependent Hartree model to reveal details of the triple proton transfer, including the existence of a non-stationary, transient low-barrier hydrogen bond. In their contribution "Protein motions and dynamic effects in enzyme catalysis" *Luk, Loveridge and Allemann* focus on the hydride transfer catalyzed by dihydrofolate reductases (DHFRs) from a wide variety of sources. Isotopically substituted enzymes have been used to characterize the biophysical properties both experimentally and computationally. The most general conclusion is that "The full catalytic power of Nature's catalysts appears to depend on finely tuning protein motions in each step of the catalytic cycle.". Finally, *Johannissen, Hay and Scrutton* provide a Perspective on nuclear quantum tunneling from an enzymologist's point of view. Tunneling and (compressive) dynamics are the main players. While there is no direct experimental evidence that the temperature-dependence of KIEs arises from vibrational modes coupled to tunneling, they argue that a combination of experiment and computation make a compelling case.

We think that this **Themed Collection** represents an interesting snapshot of some of the important directions that are being taken towards the elucidation of the effects of quantum coherences in a variety of biological processes. We hope that the Collection will be of interest to established researchers and that it will also entice newcomers to enter this exciting new field.

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