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Review article

Progress and challenges in simulating and understanding electron transfer in proteins

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ABSTRACT

This Review presents an overview of the most common numerical simulation approaches for the investigation of electron transfer (ET) in proteins. We try to highlight the merits of the different approaches but also the current limitations and challenges. The article is organized into three sections. Section 2 deals with direct simulation algorithms of charge migration in proteins. Section 3 summarizes the methods for testing the applicability of the Marcus theory for ET in proteins and for evaluating key thermodynamic quantities entering the reaction rates (reorganization energies and driving force). Recent studies interrogating the validity of the theory due to the presence of non-ergodic effects or of non-linear responses are also described. Section 4 focuses on the tunneling aspects of electron transfer. How can the electronic coupling between charge transfer states be evaluated by quantum chemistry approaches and rationalized? What interesting physics regarding the impact of protein dynamics on tunneling can be addressed? We will illustrate the different sections with examples taken from the literature to show what types of system are currently manageable with current methodologies. We also take care to recall what has been learned on the biophysics of ET within proteins thanks to the advent of atomistic simulations.

1. Introduction

Electron transfer (ET) reactions are key events in the energy transduction pathways in living organisms, where they play a central role in a variety of fundamental biological processes, such as photosynthesis and the respiratory chain [1–3], light-harvesting [4,5], substrate oxidation [6–8], reduction of enzymes [9,10], and defense strategies against oxidative stress [11,12]. The rates of ET that occur in various proteins span a large range (from picoseconds to seconds). The rate constant of initial electron transfer in the *Rhodobacter sphaeroides* reaction center is a few picoseconds [13]. The first electron transfer in the Cytochrome bc_1 complex is in the millisecond range, while the rates of subsequent electron transfer steps increase up to the nanosecond range [14]. The electron tunneling in Ru-modified cytochromes and blue copper proteins can occur on the microsecond timescale both in solution and in crystals [1].

Many experimental and theoretical studies have been conducted to understand biological electron transfer. In proteins, productive long-range biological ET can occur either between different protein partners or between multiple redox cofactors located within the same protein. The variety of such reactions (i.e. ET) requires the experimental generation of intermediate species and the use of various time-resolved methods. Transient-state spectroscopy such as stopped flow techniques is currently used to access slow ET steps (>ms) since they imply sample-mixing limitations [15,16]. Laser photoexcitation methods to rapidly inject electrons into redox proteins represent a powerful tool for studying fast ET reactions in multisite redox enzymes bringing information on the electron transfer between protein redox centers in solution or in protein crystals [13,17]. The majority of intramolecular electron transfer rate constant data has been obtained using the spectroscopic flash-quench method which employs an exogenous ET reagent to form the precursor compound for a subsequent intramolecular ET reaction. A number of different photoexcitable electron donors have been developed and successfully applied to study catalysis in various redox enzyme systems [18–20]. Another approach to measure ET rates within proteins is pulsed radiolysis which uses a rapid pulse of electrons to generate radicals to initiate subsequent intramolecular ET [21]. Additional methodologies are also useful tools for determining ET rates such as electrochemical techniques [22] and NMR [23]. There are many factors

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that could control the rates of nonadiabatic electron-transfer reactions, including the driving force, the reorganization energy, the donor–acceptor distance, and the nature of the medium separating the donor and the acceptor [24,25]. In experiments, the electronic coupling and the reorganization free energy can be determined by measuring the rate as a function of distance and driving force, respectively, then fitting the data to the rate expression of Marcus theory (MT) [24]. In practice, however, it is difficult to modify the protein and measure the rate over a large enough range of driving forces or distances. Therefore experiments can give precise values for the driving force, while it is usually difficult to obtain quantitative estimates for the reorganization energy. In addition, most experimental techniques yield the sum of overall contributions, rather than giving atomistic insight. In this regard, computer simulations are a valuable alternative for quantitative estimation of the mechanism of the ET process.

In the early 1980s Warshel pioneered the use of microscopic simulations in the modeling of electron transfer in condensed phases [26] and more particularly, in proteins [27]. He showed, for example, how and under which conditions the Marcus theory of electron transfer could be connected to microscopic simulations and how key parameters of the theory (the driving force or the reorganization energy) could be understood at the molecular level. Other researchers contributed to the field in its early days and we may cite among others: Chandler, Sprik, Klein, Fleming, Tachiya or Hynes [28–32]. The fundamental ideas developed in these early studies remain at the roots of current modeling strategies even though the development of quantum chemistry approaches and the progress of computer power now permit more accurate modeling.

In this Review we shall present the main approaches used in the field, taking recent examples from leading research groups to illustrate the successes of numerical simulations. We will mainly focus on ET in proteins, but we may occasionally borrow some examples of ET in nucleic acid structures since both types of process share important analogies. We will also try to highlight some limitations of the current approaches and some challenges for the coming years. While our Review is extensive it is not exhaustive; we have attempted only to identify and illustrate the main lines of investigation. We apologize at the outset to the authors of the many meritorious papers that have not been included. The first section describes recent progress in the modeling of ET by direct simulation techniques that do not rely on specific kinetic models. In the second section we focus on the calculation of the quantities characterizing the thermodynamics and kinetics of ET in proteins. Finally, the third section is devoted to the tunneling aspects of bio-ET and in particular to the question of how protein dynamics affect the propensity of protein structure and dynamics to mediate tunneling.

2. Direct simulation of electron transfers

In principle, if one were not limited by computer or algorithm performance, a recommendable strategy for simulating electron transfers in proteins would be to carry out mixed Quantum–Classical molecular dynamics (MD) simulations that include electronic state switches. Rates of ET could then be obtained from the time-evolution of the donor and acceptor charges over large numbers of trajectories. In addition a careful analysis of the MD trajectories would bring information on the role played by amino acid residues or solvent molecules in the process. Such direct simulation techniques (DST) would require (i) a method (as accurate as possible) to calculate the energies of the redox states and of the couplings between them, (ii) an algorithm for propagating the nuclear motion in time and (iii) a prescription to couple the electronic and nuclear motion, for example to decide how and when electronic state switches should take place.

A pioneering application of these ideas was reported by Warshel as early as 1982 for an ET in solution [26]. The methodology employed the Empirical Valence Bond (EVB) method developed by the author and a Landau–Zener model to deal with state switches along the MD trajectories. In 1988 Warshel and co-workers further simulated the primary charge separation process in the Photosynthetic Reaction Center (PRC) of *R. sphaeroides* the structure of which had been resolved a few years before [33]. They showed that the redox intermediates were stabilized by the protein, while keeping a small reorganization energy to facilitate ET in the range of a few picoseconds.

Other studies of the PRC were reported in the early 1990s. Chandler and co-workers analyzed the fluctuation of the energy gap along MD simulations in combination with a Landau–Zener model to estimate the survival probability for the system to remain in the initial excited state [34,35]. They showed the existence of long correlations (ps) in the energy gap that could account for vibrational coherences recorded experimentally [36].

Almost 20 years later, the range of applicability of DST has been extended to bio-systems where the charge migration take place in hundreds of picoseconds. Steinbrecher et al. reported direct simulations of charge migration in DNA radical cations [37]. They used a hybrid Quantum Chemistry/Molecular Mechanics (QM/MM) energy in which the π electrons of the purines were treated with a tight binding Hamiltonian, including a screened Coulomb potential to account for the effect of the environment (other DNA atoms and water). Because the electronic coupling between adjacent bases is high (0.1 eV) the motions of the nuclei were propagated on the lowest adiabatic potential energy surface. This study faithfully reproduced several key predictions about charge migration in DNA radical cations: the preferred localization of holes on guanine or the fact that pyrimidines only marginally participate in charge migration because of their high ionization potentials. Computed charge migration in stacked guanine–adenine was found to be within one order of magnitude of experimental values.

Elstner and co-workers devised a protocol based on a combination of classical MD simulations and Fragment-Based Density Functional Tight-Binding theory (FB-DFTB) [38]. At every MD time step FB-DFTB calculations are carried out to calculate the energies of the different states and to estimate the electronic coupling from the frontier orbitals. Atomic charges for the redox cofactors are updated at every MD step to account for the polarization of the redox cofactors by the environment. The time-dependent Schrödinger equation is solved for the electronic part and Ehrenfest (mean field) algorithms are then applied to propagate the electronic-nuclear dynamics. This algorithm has been applied to investigate multiple-site charge migrations in DNA [39], in DNA photolyases [40,41] and more recently in a plant cryptochrome [42]. In photolyase and in plant cryptochromes, the protein encapsulates a flavin cofactor which can be reduced, after electronic excitation, by a nearby tryptophan residue (Fig. 1). This initial step triggers a cascade of electron transfers through a triad of tryptophan residues. As seen from the graph on Fig. 1, showing the time-dependent populations of the different redox states, the overall charge migration takes place within a few hundreds of picoseconds, in qualitative agreement with experimental data. The strengths of this approach are (i) the absence of bias regarding the adiabatic or non-adiabatic nature of the electronic transitions, (ii) the absence of pre-assumed forms of the fluctuations of the environment polarization, (iii) the natural inclusion of non-equilibrium effects that can be encountered when charge migration is faster than the relaxation of the protein.

There is no doubt that the use of DST will continue to expand in the coming years with applications to a broader variety of