

## Nuclear-Electronic Orbital and Nonadiabatic Dynamics Calculations on Molecular Systems and Photoreceptors

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### Executive Summary

The quantum mechanical behavior of nuclei plays an important role in a wide range of chemical and biological processes. The inclusion of nuclear quantum effects and nonadiabatic effects between nuclei and electrons in computer simulations is challenging. Our group has developed the nuclear-electronic orbital (NEO) method for treating electrons and select nuclei quantum mechanically on the same level using an orbital-based formalism. Our group has also developed mixed quantum mechanical/molecular mechanical nonadiabatic dynamics methods for simulating photoinduced proton-coupled electron transfer processes. Both types of calculations require a large number of processors and a substantial amount of memory and storage. The highly parallel computing system on Blue Waters is advantageous for these codes because it provides the capability of splitting the large number of calculations and storage requirements over many nodes with efficient inter-node communication. We request 240,000 node hours divided equally between the NEO project and the nonadiabatic dynamics project.

### 1. Description of Research Activities and Results

#### A. Key Challenges

The overall objective of our research on Blue Waters is the development and application of computational methods for investigating proton-coupled electron transfer (PCET) reactions, which are important in a variety of chemical and biological processes. The proposed research on Blue Waters will focus on two different computational approaches developed by my group: (1) the incorporation of non-Born-Oppenheimer effects between electrons and protons into electronic structure calculations using the nuclear-electronic orbital (NEO) method to elucidate the fundamental principles of PCET; and (2) the simulation of photoinduced PCET processes to guide the design of more effective solar devices for energy production and storage and to understand light-driven conformational changes in photoreceptor proteins mediated by excited state PCET.

***The first key challenge that is being addressed is the development of computational methods that include both nuclear quantum effects and nonadiabatic effects for molecular systems.*** The inclusion of nuclear quantum effects such as zero point energy and tunneling in electronic structure calculations is important for the study of a variety of chemical systems, particularly those involving hydrogen transfer or hydrogen-bonding interactions. Moreover, nonadiabatic effects, also denoted non-Born-Oppenheimer effects, between electrons and certain nuclei are significant for many of these systems. In this case, the electrons cannot be assumed to respond instantaneously to the nuclear motions, and the concept of the nuclei moving on a single electronic potential energy surface is no longer valid. This type of nonadiabaticity has been shown to play a critical role in PCET reactions. Although a large number of computational methods have been developed to study nuclear quantum dynamics, most of these methods invoke the Born-Oppenheimer approximation between electrons and nuclei and therefore neglect these

important non-Born-Oppenheimer effects. The few electronic structure methods that include non-Born-Oppenheimer effects are extremely computationally expensive and therefore cannot be applied to systems with more than only a few electrons and nuclei.

Our objective is to develop computationally tractable methods that include non-Born-Oppenheimer effects as well as nuclear quantum effects and to apply these methods to chemically and biologically important systems. Specifically, we are developing the nuclear-electronic orbital (NEO) method, which treats electrons and select nuclei quantum mechanically on the same level using an orbital-based formalism. The NEO method is ideal for studying PCET because the timescale for proton tunneling is often faster than the timescale for electronic transitions, thereby leading to a breakdown of the Born-Oppenheimer approximation. In applications of the NEO method to PCET, all electrons and one or a few protons are treated quantum mechanically, and a mixed nuclear-electronic time-independent Schrödinger equation is solved using explicitly correlated wavefunctions.

***The second key challenge that is being addressed is the development of computational methods for simulating the nonadiabatic dynamics of photoinduced PCET processes in molecules in solution and photoreceptors.*** These approaches differ from the NEO method in that they probe the time-dependent, nonequilibrium dynamics following photoexcitation of PCET systems in solution. Although many computational methods have been developed to study photoinduced electron transfer (ET) processes, typically these methods treat all nuclei classically. In PCET processes, however, the quantum mechanical behavior of the transferring proton has been shown to be critical. Thus, our objective is to develop computationally tractable methods for simulating the nonadiabatic dynamics of condensed phase systems while including the essential nuclear quantum mechanical effects. In our approach, the transferring proton is treated quantum mechanically with Fourier grid-based methods, the solvation effects are included with explicit solvent molecules, the potential energy surfaces are generated on-the-fly with multiconfigurational electronic structure methods, and the nonadiabatic dynamics is described with a surface hopping algorithm. This methodology enables simulations that will elucidate the roles of solute and solvent dynamics, vibrational relaxation, proton delocalization, and electron-proton coupling, as well as identify the physical properties of PCET systems that determine the relaxation timescales.

## **B. Why it Matters**

Proton-coupled electron transfer (PCET) reactions play a vital role in a broad range of chemical and biological processes. The coupling between electrons and protons is central to photosynthesis, respiration, and enzyme reactions, as well as solar cells and other energy conversion devices. Understanding the fundamental physical principles underlying PCET reactions will have broad implications ranging from drug design to the design of more effective catalysts for solar energy devices.

The NEO method will have applications beyond PCET systems. It will be useful for studying hydrogen-bonding interactions, hydrogen tunneling, and geometric isotope effects in a variety of chemical and biological systems. The NEO method may also have applications in the calculation and interpretation of nuclear magnetic resonance (NMR) spectra. It will also be useful for studying positronic systems, where the electrons and positrons are treated quantum mechanically. Positron emission tomography is an imaging technique that plays an important role in medical treatments. Understanding the fundamental behavior of positrons could lead to technological advances in this technique.

Nonadiabatic dynamics methods that include the nuclear quantum effects of the transferring proton will help guide the design of more effective catalysts for energy production and storage. Such methods will also have applications to biological systems that

undergo photoinduced PCET, such as the blue light using flavin adenine dinucleotide (BLUF) photoreceptor protein and photosystems I and II.

### **C. Why Blue Waters**

The extraordinary capabilities of Blue Waters will advance both of these projects because of the highly parallelizable nature of our computer codes. The NEO code that will be used for the first project has been written in-house and has been extensively tested on several different computer architectures. Currently the computational bottleneck for the NEO method is the calculation of the multi-particle integrals and the contraction of the integrals with the density matrix to form the Fock matrix. Because these integrals can be calculated and contracted completely independently from one another, this part of the calculation is easily parallelizable using static load balancing. Thus, we applied the MPI protocol, which obviates the need for all integrals to be stored simultaneously and allows the division of the calculation over different nodes. This version of the code also demonstrates very good scalability with respect to the number of MPI processes. A supercomputer such as Blue Waters maximizes scalability. As our code has demonstrated excellent scaling, we directly benefit from using a large number of nodes on Blue Waters simultaneously with very little overhead.

The code that will be used for the photoinduced PCET simulations in the second project is an in-house modified MOPAC code and is also highly parallelizable. For each system, 100–1000 molecular dynamics trajectories must be propagated. These trajectories are computationally expensive because the excited state potential energy surfaces are generated on-the-fly with multiconfigurational electronic structure methods. Within each trajectory, the computational bottleneck is the calculation of the electronic potential energies, forces, and nonadiabatic couplings on a grid along the transferring proton coordinate at each molecular dynamics time step. However, each of these grid point calculations can be carried out independently. At the end of these independent calculations, all processors can relay the necessary information to the master processor for inexpensive computation of the proton vibrational wavefunction. The code for these simulations has been parallelized and applied to the study of a hydrogen-bonded *p*-nitrophenylphenol-*t*-butylamine complex solvated in 1,2-dichloroethane. The extraordinary capabilities of Blue Waters were necessary to provide a sufficient number of nodes with efficient inter-node communication and storage to allow these types of simulations. Current efforts are directed toward implementation of the above methodology in the framework of dielectric continuum boundary conditions to enable a more accurate description of the solvent environment, especially in protein simulations. Blue Waters will continue to be essential for studying photoinduced PCET in systems relevant to solar energy conversion and biological signaling.

### **D. Accomplishments**

#### **i. NEO calculations**

In the NEO approach, typically all electrons and one or a few protons are treated quantum mechanically, and a mixed nuclear-electronic time-independent Schrödinger equation is solved. The nuclear and electronic molecular orbitals in the nuclear-electronic wavefunction are expanded in terms of nuclear and electronic Gaussian basis sets, respectively, and application of the variational method leads to equations that must be solved iteratively to self-consistency using standard techniques. To include the essential electron-proton correlation, we developed an explicitly correlated method, denoted NEO-XCHF, which incorporates explicit electron-proton correlation with Gaussian-type geminal functions that depend on the electron-proton distance in the ansatz for the total nuclear-electronic wavefunction. To improve the computational tractability, we developed a reduced version of NEO-XCHF, denoted NEO-RXCHF. In this approach, only select electronic

orbitals are explicitly correlated to the nuclear orbital(s). In addition to the wavefunction based NEO-XCHF and NEO-RXCHF approaches, we have developed a multicomponent density functional theory method, denoted NEO-DFT, which incorporates explicit electron-proton correlation by explicitly correlating the electron and proton densities.

Over the past year, we have extended the NEO-DFT method by introducing a reduced version of NEO-DFT, denoted NEO-RDFT, which only includes explicit electron-proton correlation between a subset of the electron density and the proton density. Test calculations demonstrated that relative to NEO-DFT, the NEO-RDFT approach offers improved computational tractability with essentially no loss of accuracy. The extension of the NEO-DFT method to NEO-RDFT also led to a general embedding theory for multicomponent systems that may prove more generally useful beyond the NEO approaches. These results were published in the *Journal of Chemical Physics*. We have also continued to benchmark the NEO-RDFT method by parameterization of the Gaussian-type geminal functions.

We have used the NEO-RXCHF method to study positron binding to neutral atoms. The NEO-RXCHF results compare well with the highly accurate stochastic variational method (SVM) for both the positron binding energy and the two-photon electron-positron annihilation rates. Additional calculations performed using NEO approaches that do not include any explicit electron-positron correlation do not predict positron binding, demonstrating the importance of explicit electron-positron correlation for positronic atom systems. The SVM method, while highly accurate, is computationally demanding and has not been used on a system with more than five quantum particles. Due to the better scaling characteristics of the NEO-RXCHF method compared to the SVM, NEO-RXCHF is a promising method to study positron binding to molecules. The results from this study have been accepted for publication in the *Journal of Physical Chemistry A*.

While parameterizing the Gaussian-type geminal functions for NEO-RXCHF calculations, we discovered that the NEO-RXCHF wavefunction ansatz may not be sufficiently flexible to describe electronically adiabatic systems. Our calculations on adiabatic systems elucidate the reason for this lack of flexibility, and these results are currently in preparation for future publication. This discovery has also led to the proposal of the new NEO-ADFT method in which the electronic basis functions are allowed to follow the proton position. This NEO-ADFT method includes explicit electron-proton correlation in a different manner than NEO-RXCHF, but it still requires the computation of multi-particle integrals for which the use of Blue Waters is essential.

## ii. QM/MM nonadiabatic dynamics simulations

In the previous allocation period, we developed the methodology for the quantum mechanical treatment of the transferring proton in nonadiabatic dynamics simulations of photoinduced PCET processes and applied this methodology to the hydrogen-bonded *p*-nitrophenylphenol-*t*-butylamine complex in solution, resulting in a publication in the *Journal of Physical Chemistry B*. Over the past year, we have studied other systems relevant to solar energy conversion and biological signaling for which photoinduced PCET is a crucial step in the overall function.

Based on the fundamental mechanistic insights obtained from our studies on the *p*-nitrophenylphenol-*t*-butylamine complex, we have investigated the effects of changing the nature, number, and position of the electron-withdrawing group, the number of bridging phenyl rings, the nature of the proton acceptor, and the solvent properties to formulate design strategies for tuning photoinduced charge transfer. The results have been submitted for publication as part of an invited Perspective in *ACS Energy Letters*.

In addition, we have laid the groundwork for the study of nonadiabatic dynamics in the AppA BLUF photoreceptor by investigating the relative probabilities of key active site

conformations on the relevant electronic states and the relationship between the active site conformations and photocycle activation. The BLUF photoreceptor protein absorbs blue light via its flavin chromophore, followed by electron and proton transfer from a nearby Tyr residue to flavin. These excited state charge transfer processes have been postulated to lead to rearrangements of the hydrogen-bonding network in the active site that are coupled to long-range conformational changes and ultimately regulate gene expression. Our studies utilized extensive free energy calculations to answer long-standing questions regarding the orientations of the electron- and proton-donating Tyr residue, a conserved Gln that has been proposed to relay the proton from Tyr to flavin, and a Trp residue that can compete with Tyr for electron and proton transfer to flavin. In agreement with the experimentally available structures for the AppA BLUF domain, we found the conformation with Trp in the vicinity of flavin to be favored over the one with Trp away from the active site region. We also uncovered an important relationship between the orientation of the Tyr and Gln residues and the feasibility of electron transfer from Tyr to flavin: when Tyr and Gln are well-oriented for proton transfer to flavin, the feasibility of electron transfer from Tyr to flavin is higher than when Tyr and Gln are not properly oriented for proton transfer to flavin. This work highlights the role of the active site conformation in photocycle activation of the AppA BLUF domain and resulted in a manuscript accepted for publication in the *Proceedings of the National Academy of Sciences of the United States of America*.

## 2. List of Publications and Presentations Associated with this Work

### A. Publications that Featured Blue Waters Projects in 2016

- P. Goyal, C. A. Schwerdtfeger, A. V. Soudackov, and S. Hammes-Schiffer, "Proton quantization and vibrational relaxation in nonadiabatic dynamics of photoinduced proton-coupled electron transfer in a solvated phenol-amine complex," *J. Phys. Chem. B* **120**, 2407-2417 (2016). DOI: 10.1021/acs.jpccb.5b12015
- T. Culpitt, K. R. Brorsen, M. V. Pak, and S. Hammes-Schiffer, "Multicomponent density functional theory embedding formulation," *J. Chem. Phys.* **145**, 044106 (2016). DOI: 10.1063/1.4958952
- K. R. Brorsen, M. V. Pak, and S. Hammes-Schiffer, "Calculation of positron binding energies and electron-positron annihilation rates for atomic systems with the reduced explicitly correlated Hartree-Fock method within the nuclear-electronic orbital framework," *J. Phys. Chem. A* (published on-line). DOI: 10.1021/acs.jpca.6b10124
- P. Goyal and S. Hammes-Schiffer, "Role of active site conformational changes in photocycle activation of the AppA BLUF photoreceptor," *Proc. Nat. Acad. Sci. USA* (accepted).
- P. Goyal and S. Hammes-Schiffer, "Tuning the Ultrafast Dynamics of Photoinduced Proton-Coupled Electron Transfer in Energy Conversion Processes," *ACS Energy Lett.* (submitted).

### B. Presentations that Featured Blue Waters Projects in 2016

- University of California at Los Angeles, Los Angeles, California, January 13, 2016 (Distinguished Lecture): "Proton-Coupled Electron Transfer in Catalysis and Energy Conversion"

- Jean Dreyfus Boissevain Lectureship, University of Colorado at Denver, Denver, Colorado, March 10, 2016 (invited public lecture): “Proton-Coupled Electron Transfer in Catalysis and Energy Conversion”
- University of Colorado, Boulder, Colorado, March 11, 2016 (invited talk): “Proton-Coupled Electron Transfer in Catalysis and Energy Conversion”
- American Chemical Society National Meeting, Symposium entitled Computational Materials Chemistry, San Diego, California, March 13-17, 2016 (invited talk): “Avoiding the Born-Oppenheimer Separation between Electrons and Protons: Explicitly Correlated Wavefunctions and Multicomponent Density Functional Theory”
- Walter Kauzmann Lecturer, Princeton University, Princeton, New Jersey, April 18, 2016 (invited talk): “Proton-Coupled Electron Transfer in Catalysis and Energy Conversion”
- AFOSR Molecular Dynamics Contractor’s Meeting, Arlington, Virginia, May 24-26, 2016 (invited talk): “Nonadiabatic Dynamics of Photoinduced Proton-Coupled Electron Transfer”
- 8<sup>th</sup> Molecular Quantum Mechanics Conference, Uppsala, Sweden, June 26 -July 1, 2016 (invited talk): “Nonadiabatic Dynamics of Photoinduced Proton-Coupled Electron Transfer”
- Gordon Research Conference on Molecular Interactions and Dynamics, Stonehill, Massachusetts, July 10-15, 2016 (invited talk): “Nonadiabatic Dynamics of Photoinduced Proton-Coupled Electron Transfer Processes”
- Gordon Research Conference on Computational Chemistry, Girona, Spain, July 24-28, 2016 (invited talk): “Nonadiabatic Dynamics of Photoinduced Proton-Coupled Electron Transfer”
- American Chemical Society National Meeting, Symposium entitled Dynamics of Natural and Artificial Systems for Energy Conversion: Insights Gained from Spectroscopic Methods and Theory, Philadelphia, Pennsylvania, August 21-25, 2016 (invited talk): “Electrochemical and Photoinduced Proton-Coupled Electron Transfer in Energy Conversion Processes”
- Theory and Applications of Computational Chemistry, Seattle, Washington, August 28 – September 2, 2016 (invited plenary lecture): “Proton-Coupled Electron Transfer in Catalysis and Energy Conversion”
- Thomas-Young Centre (TYC) for Materials Modelling, London, United Kingdom, September 22, 2016 (invited talk): “Proton-Coupled Electron Transfer in Catalysis and Energy Conversion”
- University of Bristol, Bristol, United Kingdom, September 23, 2016 (invited talk): “Nonadiabatic Dynamics of Photoinduced Proton-Coupled Electron Transfer Processes”
- Brooklyn College, New York, New York, November 22, 2016 (invited talk): “Proton-Coupled Electron Transfer in Catalysis and Energy Conversion”

### C. Plan for Next Year

We request 240,000 node hours for the fourth year of the Blue Waters Professorship. The estimated usage per quarter is 60,000 node hours, corresponding to continuous, steady use over this time. We expect to require ~20 TB of storage per year. This allocation request can be justified on the basis of the projects described above. We expect to use our entire allocation this year.

With the implementation of the NEO-RDFT method and the new NEO-ADFT method, we plan to continue benchmarking as well as pursue chemical applications during the next

allocation period. The NEO-ADFT method will require many methodological improvements that must be benchmarked. Moreover, these improvements will enable calculations on larger molecular systems such as amino acids. These types of applications will provide new fundamental physical insights into electron-proton interactions and nuclear quantum effects.

The QM/MM nonadiabatic dynamics code is also parallelized and tested for small molecular systems, and we are ready for production calculations with a quantized proton on various systems relevant to solar energy conversion. Specifically, we will use the existing code to study the nonadiabatic dynamics of photoinduced PCET in a bis(imino)isoindole derivative in solution. In addition, we are currently developing an interface between the MOPAC and CHARMM codes that will allow us to carry out hybrid quantum mechanical/molecular mechanical (QM/MM) simulations with dielectric continuum boundary conditions for the study of excited state proton transfer and nonadiabatic dynamics in the BLUF photoreceptor. Because of the large system size, even calculations with a classical treatment of the transferring proton require parallelization and the extraordinary capabilities of Blue Waters. After the implementation and testing of dielectric continuum boundary conditions, the code will be used to study photoinduced PCET in the BLUF photoreceptor protein.

#### **i. NEO Calculations**

We plan to use 120,000 node hours for the NEO project. We have begun benchmarking the Gaussian-type geminal functions for the NEO-RDFT method and the nuclear and electronic Gaussian basis sets for the NEO-RDFT and NEO-ADFT methods. This benchmarking involves numerous calculations, as the exponents for the nuclear orbitals must be optimized variationally. Based on the current rate of benchmarking, we estimate that completion of the benchmarking will require 60,000 additional node hours. This estimate is obtained from preliminary benchmarking data, where the average calculation has taken 30 minutes on 128 nodes, and we estimate running 300 NEO-RDFT benchmark calculations for the Gaussian-type geminal functions and 300 Gaussian basis set benchmark calculations for both the NEO-RDFT and NEO-ADFT methods for a total of 900 benchmark calculations.

In the second part of the allocation period, we plan to utilize Blue Waters to study larger molecular systems such as amino acids. The amino acid systems will be computationally tractable due to several algorithmic and numerical improvements that have been implemented, but it will still require ~3,000 node hours for each system. The estimate of 60,000 node hours is obtained by assuming that on average the calculation for each of the 20 systems studied will require 256 nodes for 12 hours. Table 1 provides a more detailed breakdown of the computational requirements for the NEO calculations. The completion of the benchmarking and the NEO calculations on the amino acid systems will require approximately 119,040 node hours. We do not anticipate transferring any significant amount of data to or from Blue Waters for the NEO project.

**Table 1.** Computational requirements for the NEO calculations.

Number of benchmarking calculations	900
Node hours per benchmarking calculation	64
Node hours for benchmarking calculations	57,600
Number of amino acid calculations	20
Node hours per amino acid calculation	3,072
Node hours for amino acid calculations	61,440
<b>Total number of node hours</b>	<b>119,040</b>

## ii. QM/MM nonadiabatic dynamics simulations

We plan to use 120,000 node hours for the QM/MM nonadiabatic dynamics project. We will use the existing code to study photoinduced PCET in a bis(imino)isoindole derivative with a quantum mechanical treatment of the transferring proton and two solvents of differing polarity that exhibit different experimentally measured rates of excited state proton transfer. After implementation of the dielectric continuum boundary condition, we will study the excited state PCET process in the BLUF photoreceptor protein with two different active site conformations and a classical treatment of the transferring proton. This application will represent the first nonequilibrium quantum dynamical study of photoinduced PCET in this protein.

Our estimate of the number of node hours is based on propagating 100 trajectories for the bis(imino)isoindole derivative in each solvent and 135 trajectories for each active site conformation of the BLUF protein. The trajectories will differ in the initial coordinates and velocities. For the bis(imino)isoindole derivative, each trajectory will be 5 ps long and will require ~132 node hours. For the BLUF protein, each trajectory will be 25 ps long and will require ~347 node hours. Detailed information about the computational requirements for these QM/MM nonadiabatic dynamics simulations is provided in Table 2. The propagation of 200 and 270 nonadiabatic dynamics trajectories for the bis(imino)isoindole derivative and the BLUF protein, respectively, is estimated to require approximately 120,137 node hours. Each trajectory will require ~60 GB of memory per node. Storage of these trajectories for subsequent analysis will require ~20 TB. We do not anticipate transferring any significant amount of data to or from Blue Waters for the QM/MM nonadiabatic dynamics project.

**Table 2.** Computational requirements for the QM/MM nonadiabatic dynamics simulations.

	bis(imino)isoindole derivative	BLUF protein
Molecular dynamics time step	0.1 fs	0.1 fs
Real time per dynamics time step (using 1 node)	9.5 s	5 s
Length of each trajectory	5,000 fs	25,000 fs
Number of time steps per trajectory	50,000	250,000
Node hours per trajectory (using 1 node)	131.94	347.22
Number of trajectories	200	270
<b>Number of node hours</b>	26,388	93,749
<b>Total number of node hours</b>	<b>120,137</b>	

## iii. Estimated Blue Waters Usage Schedule

Both projects will use the allocation evenly throughout the year: Q1: 25%, Q2, 25%, Q3, 25%, Q4, 25%.