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Molecular structure and motion determine properties including spectroscopy and reactivity. We study problems of fundamental chemical interest,^{1,2,3,4,5} including those with applications in biological enzyme catalysis^{6,7,8}, atmospheric chemistry⁹, and nano-science using theoretical and computational chemistry. We specialize in the development of new theoretical and computational methods^{10,11,12,13,14} to facilitate efficient and accurate study of chemical dynamics in large systems. This puts our research efforts on the interface of chemistry, computational physics and applied mathematics.

In our group, students are exposed to many different aspects of theoretical chemistry, including quantum mechanics, classical mechanics, molecular dynamics, applied mathematics and computational algorithm development. Many of the projects that are described here surmount traditional boundaries of chemistry, physics and applied mathematics, and will expose the student to important concepts in theoretical/computational physics. As you will note, many of the computational methods we develop, have lead to important new chemical insights^{1,2,3,4,5,7}. Below, following introductory remarks, a mixed set of fundamental and applied projects are provided.

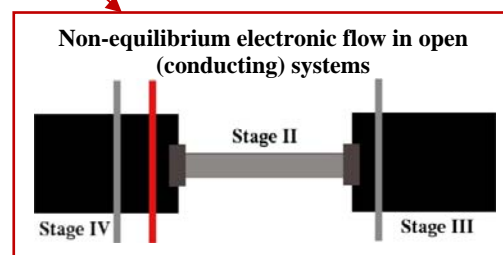
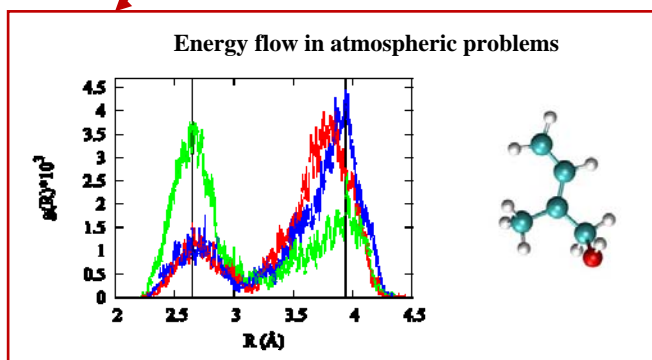
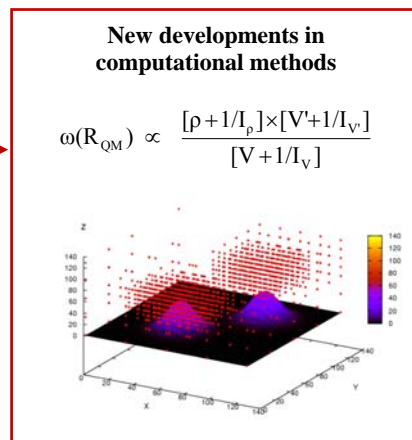
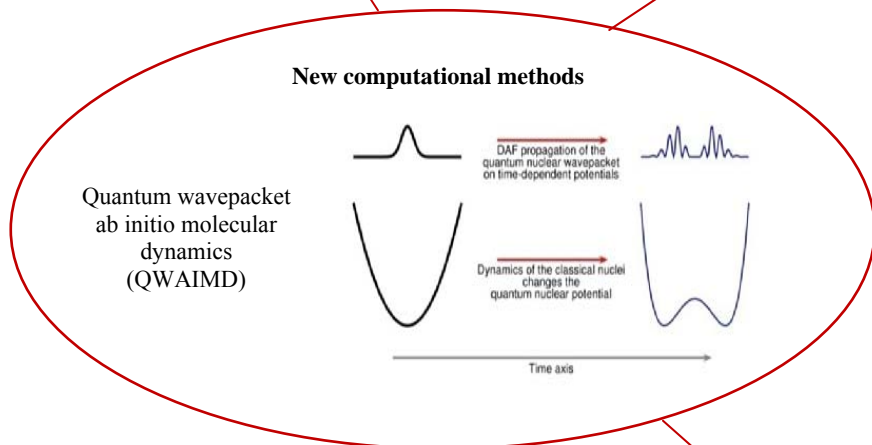
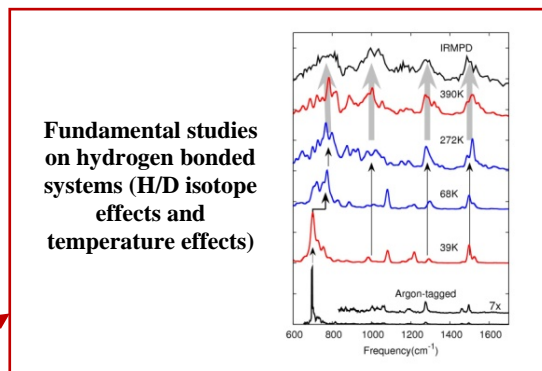
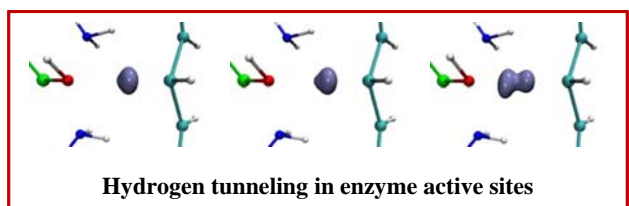
Introductory Remarks:

Simulating the dynamics of large biological and chemical systems using computational chemistry has a long history. It is worthwhile to briefly overview this area here, before we embark into a detailed exposition of our specific research interests. We start by describing a computational tool known as molecular dynamics. Here, the molecular geometry (or conformation) is allowed to evolve in time using the inter-atomic forces between the various constituents of the system. The physical law that governs such a dynamics is given by the Schrödinger equation. However, this equation is very difficult to solve even on today's ultra-fast computers. This has lead researchers in the past to develop models to describe the inter-atomic potential energy for large systems, and these models, being easier to compute as compared to the Schrödinger equation, have been used to study the structure and dynamics of molecules and determine their properties. However, these models have a number of limitations that severely restrict their applicability to systems where chemical reactions do not occur. Since studying chemical reactions is an important aspect of understanding chemistry, the applicability of such methods is rather limited.

We specialize in using the Schrödinger equation, and more specifically the concepts of quantum mechanics, to computationally perform molecular dynamics. Such approaches that use the Schrödinger equation in their development are called *ab initio* molecular dynamics (AIMD) approaches. (The words *ab initio* are derived from Latin: *ab* stands for 'from' and *initio* means 'first-principles'; thus the term *ab initio* is used to characterize computational methods that are derived from first-principles.) And due to the rather intricate and computationally expensive methodology involved in solving the Schrödinger equation, we develop approximations and alternate approaches to facilitate the study of large systems. Specifically, our group has recently developed a new approach to *ab initio* molecular dynamics.^{10,11,12,13,14,15,7}

Our computational methodology^{10,11,12} provides an efficient framework to accurately model chemical reaction dynamics in large systems. In quantum mechanics, the "wave-function" describing the electrons and the state of the nuclear degrees of freedom, together represent the structure of the molecular system. Our approach helps propagate in time the complete state of a molecular system, in a computationally efficient fashion and hence makes the treatment of large systems^{10,11,12} possible. This approach is called ***Quantum Wavepacket Ab Initio Molecular Dynamics (QWAIMD)***, which allows the flexibility to treat a subset of the nuclei in a quantum mechanical fashion while simultaneously studying the dynamical evolution of the electrons with the majority of nuclei treated in a classical fashion. (See Refs.

10,11,12,13,14,6 for details on the theoretical aspects, or please come see us.) *The approach allows implementation over massively parallel-supercomputers.* Thus QWAIMD also presents many interesting problems from a scientific computing perspective which allows graduate students, post-docs and undergraduate researchers in our group to become familiar with state-of-the-art ideas in numerical analysis. We develop our own numerical methodologies and associated computational models. The figure below summarizes our major research initiatives.



C500 Projects:

1. Quantum Dynamical Effects in Biological Enzymes:

General chemistry tells us that there exists an exponential relation between temperature and the reaction rate constant: the so-called Arrhenius rate expression. In some enzymes, such as the one in Figure 1, it is experimentally^{15,16,17} noted that *the rate constant does not depend on temperature*. The enzyme in Figure 1 represents a class of enzymes which either catalyze or involve a hydrogen-transfer reaction as their primary step. It is also noted^{18,19,20} in this particular enzyme that when the transferring hydrogen-atom is replaced by a heavier isotope, such as deuterium, the rate constant reduces by nearly a factor of 100. *Why would a car that is half the*

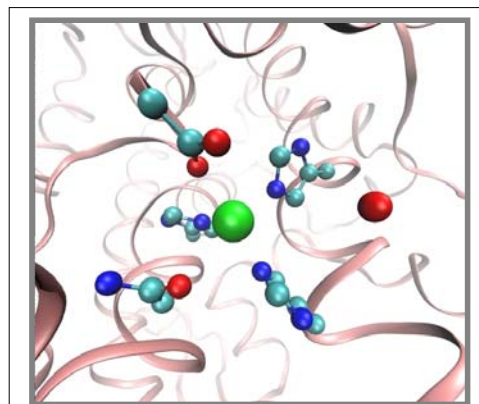


Figure 1: Active site of lipoxygenase

by a factor 100? This quandary has lead people to believe that the hydrogen atom being an extremely light atom shows the propensity to display quantum behavior such as *hydrogen tunneling*, more so than

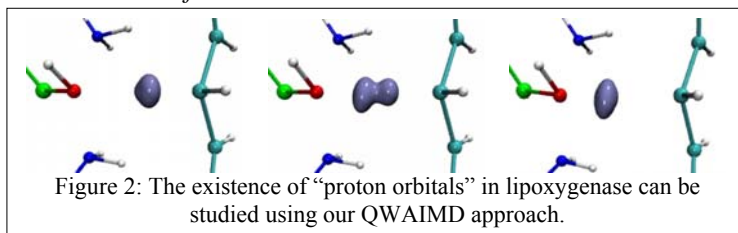


Figure 2: The existence of "proton orbitals" in lipoxygenase can be studied using our QWAIMD approach.

any other atoms, and it is believed that this might be the reason for this experimental result. However, the sheer size of enzyme systems makes time-dependent quantum dynamical studies impossible. Hence, approximate methods to examine such critical problems are essential. Our group has conducted the first fully quantum-mechanical study on this system. Our QWAIMD results⁷ indicate that indeed quantum mechanical nature of the hydrogen atom can contribute to this result and we find that "proton orbitals" such as the one in Figure 2 do exist. These orbitals facilitate "hydrogen tunneling" thus leading to the unexpected experimental results. The C500 student will have the opportunity to study such problems, using QWAIMD and its variations^{10,11,12,13,14}.

2. Vibrational spectroscopy of hydrogen bonded systems: Quantum dynamical effects and temperature dependent effects

Effects such as those described in Project 1 above are also found in many **atmospheric problems, and fundamental hydrogen bonded systems**. As it turns out, hydrogen-bonded systems, which are fundamental from a chemical standpoint, and have important biological, atmospheric and materials-chemistry implications, have a great propensity to display such effects. Hence, an active area of research in our group involves the use of quantum-mechanical dynamics (with and without nuclear quantum effects) to study the spectroscopic properties of hydrogen-bonded molecular clusters. These systems present many challenges to theory and computation. *Our group has developed new insights that explain the temperature dependent vibrational properties of a variety of hydrogen bonded systems*^{1,2,3,4,5,6}. We are one of the first groups to point out that such

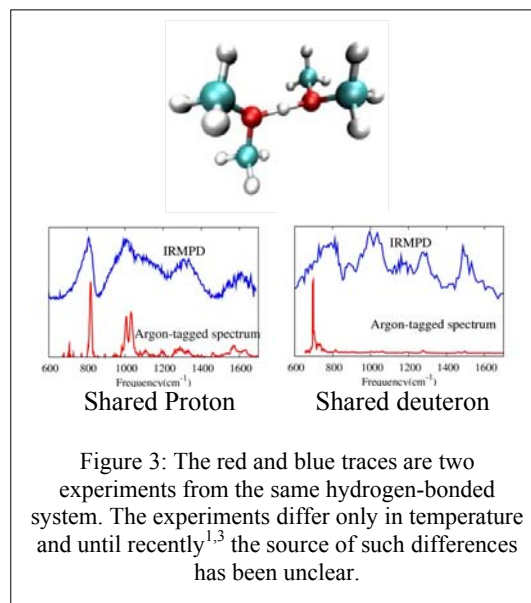


Figure 3: The red and blue traces are two experiments from the same hydrogen-bonded system. The experiments differ only in temperature and until recently^{1,3} the source of such differences has been unclear.

hydrogen bonded systems have unique, temperature dependent spectroscopic properties^{1,2,3,9(a),13} that are responsible for non-intuitive effects (Figure 3).

The C500 student will have the opportunity to understand such fundamental chemical systems through dynamical studies. An interesting side problem is whether quantum nuclear effects and dynamical effects play a critical role in NMR coupling constants? As part of the C500 project, the interested student will conduct similar studies on NMR coupling constants. NMR is an extremely fundamental tool in chemistry and in biochemistry. Specific systems that will be considered are **DNA base pairs and protein anti-parallel beta sheets**. In addition, the student will also have the opportunity to compare and contrast vibrational properties and their influence on the NMR properties, leading to new insights.

a. **Hydrophobicity of hydronium and hydroxide ions:**

We have recently noted^{3,4,5} that the hydrated proton in a water cluster has an amphiphilic (hydrophobic+hydrophilic) character. These results were obtained originally from *ab initio* dynamics^{4,5} and later confirmed by experiment²¹. The protonated species in water (that is, the hydronium ion) has “hydrophobic” and “hydrophilic” sites. The hydrophobic end of the hydronium is close to its lone pairs. Due to this reason, we have found that a hydronium ion tends to reside on the surface of a cluster of water molecules and the surface of a water/vacuum interface. This is in contrast to conventional chemical wisdom where the protonated species is expected to be solvated at the center of a cluster of water molecules. As one can imagine, this is an extremely fundamental observation and has important implications that has led to many experiments designed to test this phenomenon. These projects represent examples of how new frontiers in science may be developed through the use of novel theoretical techniques.

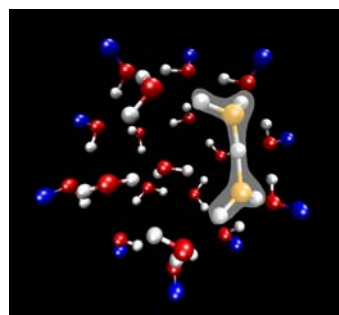


Figure 4: Amphiphilicity of the hydrated proton

However, recently fundamental questions have been raised in reference to the hydroxide ion. People have wondered if the hydroxide ion has a propensity to be hydrophobic as well. *If this is case, it could have fundamental implications towards problems such as water-oxidation* that have an effect on the energy crisis problem. We have recently found that the **hydroxide ion can display non-standard bond arrangements** when surrounded by water molecules. *The central oxygen atom displays an anomalous propensity to be pentavalent*. However, we also find that properties such as the vibrational frequencies which can be determined experimentally, are susceptible to the fact that there exists many other geometries (with similar energetics) that support a central tetrahedral oxygen; hence the measurable spectrum is an average of all these “similar” geometries. Dynamics plays an important role in this spectral averaging process.

The C500 student will have an opportunity to investigate these problems further using *ab initio* dynamics. Obviously, the implications of these studies cannot be over-stated.

3. **Quantum dynamics in open systems: applications to molecular and nano-electronics:**

The possibility of silicon based electronic chip technology coming close to its inherent physical limitations has given rise to the new area of molecular electronics. Here single molecules are connected across electrodes and treated as potential transistors, capacitors and molecular switches, that is potential components of a novel, futuristic *quantum computer*. We are also currently modifying and generalizing the *Quantum Wavepacket Ab Initio Molecular Dynamics* (QWAIMD) approach described above to treat the transport

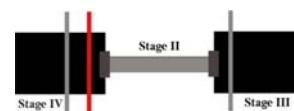
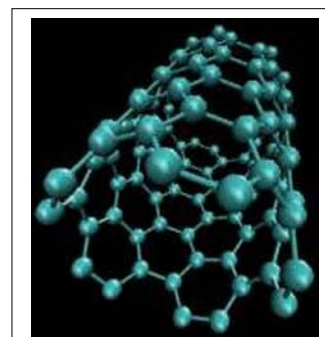


Figure 4: A carbon nanotube molecular wire (top) sandwiched by electrodes (bottom)

of excess electrons and flux of electron densities through **molecular wires and other nano-scale devices**. *Key theoretical challenges remain here which we are currently in the process of surmounting*. Some of the important issues that we are currently focusing our attention on include the accurate description of an electronic flux through a molecular wire subjected to “open system boundary conditions”.

As part of a C500 project the student will have the opportunity to make important, fundamental contributions and participate in critical steps required to calculate the conductivity of electrons across molecular wires, connected across electrodes using generalizations of our QWAIMD approach. For example, it is unclear how the variational principle in quantum mechanics changes when a system is exposed to an external flux and does not conserve the number of electrons. The interested C500 student will have a pivotal role on the addressing such critical problems, that are currently being examined in our group.

4. **The role of energy redistribution in hydrogen-bonded systems of implication in atmospheric and biological chemistry:** Closely related to projects 1 and 2 is the subject of energy flow. Let me go ahead and state three fundamental questions that are related to energy flow. These questions will all benefit from the computational developments here on energy flow. (a) In hydrogen-bonded systems and in hydrogen transfer reactions, recent experiments have found a rather intriguing result where isotope substitution at secondary locations, that is at locations distal to the hydrogen transfer site, greatly influence reaction rate. (b) In fundamental protonated complexes involving water, again, isotope substitution distal to the hydrogen bonding site causes non-trivial changes in the spectroscopy. Both of these problems are related to how the vibrations in the back-bone of a hydrogen bonded system are coupled to the hydrogen-bond network; the fact that such a phenomenon can have interesting consequences is already seen in Figure 3 above. *This C500 project deals with the development of techniques to study energy flow and two-dimensional spectroscopy*. Apart from direct application to the projects of secondary isotope effects in enzymes and the study of hydrogen bonded systems in water, the C500 student will also have the opportunity to participate in atmospheric chemical research as part of the application of the computational tools developed in this project. I outline the atmospheric chemistry problem below.
 - a. The project is related to ozone production and photochemical smog^{6(b)} and is part of a collaborative project **with the Philip Stevens Group**. The problem of photochemical air pollution remains a serious threat to human health and welfare. Ozone, the primary component of photochemical smog, forms from chemical reactions involving nitrogen oxides (NO_x) and volatile organic compounds (VOCs) emitted from transportation, energy production, and industrial activities. Despite years of control legislation, many areas in the United States have consistently exceeded the National Ambient Air Quality Standard for ozone. Hence, recent strategies on ozone control are focusing on regional ozone production. The dominant natural emission of isoprene from trees can contribute significantly to the production of ozone through its high reactivity with the hydroxyl radical (OH), the main oxidant in the atmosphere. Ozone reduction strategies depend on an accurate understanding of isoprene chemistry under a variety of conditions.

As part of the C500 project, the students will have the opportunity to study these fundamental atmospheric chemistry problems using state-of-the-art theoretical methods. Specifically, we have developed a new approach which allows us to probe energy flow in quantum systems^{1,9(b)} Energy flow pertains to stability of products in chemical reactions and hence is of fundamental consequence. The C500 student will have the opportunity to: (a) utilize our new methods to understand energy flow, (b) develop the methods further to study more complicated problems.
5. **Fundamental theoretical and computational methods development:** Apart from the projects described above, there are several projects in our group that deal with fundamental computational

methods development. The interested student should certainly come see us. Below, I describe a few of these problems.

a. **Generalization of ab initio quantum dynamics to rigorous electronic structure treatments.**

The student involved in this project will have the opportunity to study electronic structure theory and dynamics, two major areas of quantum chemistry. The basic idea behind this project is as follows. In many important and practical problems, such as the search for high-energy low-density rocket fuels, theoretical treatments are required to predict properties with great accuracy. Currently, ab initio dynamics can provide accurate results in the vicinity of 1 kcal/mol, but to go beyond this a fundamentally different approach is required. We will develop first-principles dynamics approaches that will use highly accurate post-Hartree-Fock methods in our dynamics scheme. This project involves theoretical development, and the interested students participate in the development of a novel computational formalism. *Once the methods are developed they will generally be interfaced with one of the above fundamental chemical problems and hence the C500 student will also have the opportunity to eventually contribute to those chemical studies.*

b. **Non-adiabatic Reaction Dynamics of Complex Systems.**

In many biological and chemical systems, reactions can involve multiple electronic energy levels. This is particularly the case for photochemical reaction. For example, in rhodopsin (Figure 5), which is found in the mammalian eye, the cis-trans isomerization of a protonated Schiff base called retinal causes a conformational change leading to vision. This is among the fastest known chemical reactions. Detailed quantum mechanical study of such processes constitutes an unsolved problem in computational biophysical chemistry. The incoming graduate student will have the opportunity to further develop QWAIMD to treat such problems. This project is primarily a development project that will involve training in computation, mathematics and chemical-physics. Of course, one of the goals of the development is towards a problem of chemical significance.

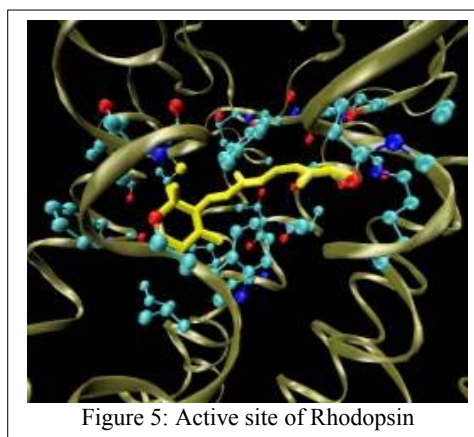


Figure 5: Active site of Rhodopsin

c. **Quantum-mechanics/molecular mechanics (QM/MM) and continuum model generalizations for Quantum Wavepacket Ab Initio Molecular Dynamics.**

In the framework described in project 1, only a portion of the full enzyme can be treated due to the computational complexity of QWAIMD. As a result, the bulk of the enzyme system will not be treated this way. The student will have an opportunity to modify this and construct more realistic models to the enzyme. This project can be coupled with project 1 above, but that is not a requirement.

d. **New paradigms to QWAIMD that interface with information theory** are currently being explored in our group. The interested C500 student will have the opportunity to participate in this development project that is designed to have impact on both the enzyme problem (project 1) as well as hydrogen bonded system problem (project 2 above).

Selected Publications:

¹ (a) X. Li, D. T. Moore and S. S. Iyengar, "Insights from first principles molecular dynamics studies towards infra-red multiple-photon and single-photon action spectroscopy: Case study of the proton-bound di-methyl ether dimer". *J. Chem. Phys.* **128**, 184308 (2008).

(b) X. Li, J. Oomens, J. R. Eyler, D. T. Moore, S. S. Iyengar, "Isotope dependent, temperature assisted, energy redistribution in hydrogen bonded systems" *Proc. Natl. Acad. Sci. USA* Submitted. [Manuscript available upon request.]

² X. Li, V. E. Teige and S. S. Iyengar "Can the four-coordinated, penta-valent oxygen in hydroxide water clusters be

detected through experimental vibrational spectroscopy?”. *J. Phys. Chem. A* **111**, 4815-4820 (2007).

³ S. S. Iyengar “Further analysis of the dynamically averaged vibrational spectrum for the 'magic' protonated 21-water cluster”. *J. Chem. Phys.* **126**, 216101 (2007).

⁴ M. K. Petersen, S. S. Iyengar, T. J. F. Day, and G. A. Voth, “The Hydrated Proton at the Water liquid/vapour interface Behavior”, *J. Phys. Chem. B* **108**, 14804 (2004).

⁵ S. S. Iyengar, T. J. F. Day, and G. A. Voth, “On the Amphiphilic Behavior of the Hydrated Proton: An Ab Initio Molecular Dynamics Study”, *Int. J. Mass Spectrometry* **241**, 197-204 (2005).

⁶ (a) S. S. Iyengar, I. Sumner and J. Jakowski "Hydrogen tunneling in an enzyme active site: a quantum wavepacket dynamical perspective". *J. Phys. Chem. B* **112**, 7601 (2008).

(b) I. Sumner and S. S. Iyengar, “Analysis of hydrogen tunneling in an enzyme active site using von Neumann measurements”, In preparation. [Available upon request.]

⁷ **A Molecular Dynamics and Ab Initio Molecular Dynamics Study of Ligand Binding in Ancestral hemoglobins in Archaea**, James S. Newhouse, Tracey Allen K. Freitas, Maqsudul Alam, and Srinivasan S. Iyengar, *Proc. Natl. Acad. Sci.*, In Preparation.

⁸ **Hybrid Ab-Initio/Empirical Molecular Dynamics: Combining the ONIOM Scheme with the Atom-centered Density Matrix Propagation (ADMP) Approach**, N. Rega, S. S. Iyengar, G. A. Voth, H. B. Schlegel, T. Vreven and M. J. Frisch, *J. Phys. Chem. B* **108** 4210-4220 (2004).

⁹ (a) **Dynamical effects on vibrational and electronic spectra of hydroperoxyl water clusters**, S. S. Iyengar, *J. Chem. Phys.* **123**, 084310 (2005).

(b) D. Vimal, A. B. Pacheco, S. S. Iyengar and P. S. Stevens, "Experimental and theoretical study of the kinetics of the OH + 1,3-butadiene reaction between 263 and 423 K at low pressure". *J. Phys. Chem. A* In Press.

URL: <http://www.indiana.edu/%7Essiweb/papers/butadiene-isoprene.pdf>

¹⁰ **Quantum Wavepacket Ab Initio Molecular Dynamics: An approach to study quantum dynamics in large systems**, S. S. Iyengar and J. Jakowski, *J. Chem. Phys.* **122** 114105 (2005).

¹¹ **Ab Initio Dynamics with wave-packets and density matrices**, S. S. Iyengar, *Theo. Chem. Accts. Special issue on "New Perspectives in Theoretical Chemistry"* **116**, 326-337 (2006)

¹² **Computational Improvements to Quantum Wavepacket Ab Initio Molecular Dynamics using a potential-adapted, time-dependent deterministic sampling technique**, J. Jakowski, I. Sumner and S. S. Iyengar, *Journal of Chemical Theory and Computation* **2**, 1203-1219 (2006).

¹³ I. Sumner and S. S. Iyengar "Quantum Wavepacket Ab Initio Molecular Dynamics: An approach for computing dynamically averaged vibrational spectra including critical nuclear quantum effects". *J. Phys. Chem. A*, **111**, 10313-10324 (2007).

¹⁴ I. Sumner and S. S. Iyengar, "Combining quantum wavepacket ab initio molecular dynamics (QWAIMD) with QM/MM and QM/QM techniques: Implementation blending ONIOM and empirical valence bond theory" *J. Chem. Phys.* **129**, 054109 (2008).

¹⁵ **Enzyme dynamics and hydrogen tunnelling in a thermophilic alcohol dehydrogenase**, A. Kohen, R. Cannio, S. Bartolucci, and J. P. Klinman, *Nature* **399**, 496 (1999).

¹⁶ **A link between protein structure and enzyme catalyzed hydrogen tunneling**, B. J. Bahnson, T. D. Colby, J. K. Chin, B. M. Goldstein, and J. P. Klinman, *Proc. Natl. Acad. Sci. U.S.A.* **94**, 12797 (1997).

¹⁷ **Hydrogen Tunneling in Enzyme Reactions**, Y. Cha, C. J. Murray, and J. P. Klinman, *Science* **243**, 1325 (1989).

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¹⁹ **A link between protein structure and enzyme catalyzed hydrogen tunneling**, B. J. Bahnson, T. D. Colby, J. K. Chin, B. M. Goldstein, and J. P. Klinman, *Proc. Natl. Acad. Sci. U.S.A.* **94**, 12797 (1997).

²⁰ **Hydrogen Tunneling in Enzyme Reactions**, Y. Cha, C. J. Murray, and J. P. Klinman, *Science* **243**, 1325 (1989).

²¹ Petersen, P.; Saykally, R. J.; "Evidence for an Enhanced Hydronium Concentration at the Liquid Water Surface," *J. Phys. Chem. B.* **109**, 7976-7980 (2005).