

Beyond “Femtochemistry”

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1. Time-Resolved Mesoscale Dynamics in Biology, Chemistry, and Materials Science

The proposed seeded XFEL at Madison will open up the exploration of chemistry and biology on previous inaccessible length scales. Often, the molecular structures of reactant and product states at atomic resolution are considered to be sufficient for understanding chemical and biological phenomena. However, the pathway connecting the reactant and product states is equally important. For all but gas-phase reactions, the reaction coordinate involves highly correlated motions that occur on the nm length scale. For example, charge-transfer processes involve solvent repolarization; isomerization reactions involve displacement of solvent molecules. These motions extend out to nm distances and determine the barrier to the reaction process. Similarly, biological processes are powered by chemical reactions at atomic-scale reaction sites, but deterministic protein motions on the mesoscale (nm) direct biological function [1]. Understanding how energy in a biological system can be directed over these distances is one of the great prizes in science.

In both chemistry and biology, the key motions occur on the nm length scale and over times from 10 femtosecond to seconds [1,2]. The Madison X-Ray FEL will be unique in its abilities to explore these length and timescales. Examples of problems that this source (beamlines 3-6) will be opened up include:

1. 1 Many Body Potential of Liquid Water (“Stuff of Life”). Beamline 6

Water remains an enigma [3-5]. It is the only liquid that expands on freezing. It has the highest heat capacity and the highest degree of hydrogen bonding per mass of any substance. By all rights, water should be thicker than molasses yet it has a relatively low viscosity. The low viscosity is related to the rapid relaxation and interconversion of the different inherent structures within its spectrum of nuclear motions. The “memory” or persistence of frequency correlations live less than 50 fs under ambient conditions; Water exhibits the fastest loss of correlations and energy redistribution of any liquid [5]. Pure H₂O is actually more than an order of magnitude faster than even isotopically substituted water (HOD). It is clear that the special properties of water that breathe life into otherwise inanimate matter are related to the hydrogen-bond network. It is the hydrogen-bond network that provides the connective pathways between the various microscopic degrees of freedom. Yet again, it is the hydrogen bonds that impose spatial correlations within water and ultimately are responsible for self-assembly in biological systems.

The current picture of liquid water is that each water contains on average 3.5 hydrogen bonds per water. The local structure at each water has approximately C_{4V} symmetry, reminiscent of the ice structure. The hydrogen-bond structure is a veritable sponge with rapidly interconverting hydrogen bonds between water molecules. Currently we have no means to discern how far these correlations extend. In addition, we do not have specific information on the microscopic motions that are involved. Simultaneous measurement of

the time and length scales governing the motions of water molecules could be directly connected to the many body potential. This information would provide the most rigorous test possible for our understanding of liquid water. The WFEL is uniquely poised to finally resolve one of the fundamental problems in nature. The high time resolution is essential to capturing the full spectrum of motions. The high repetition and relatively narrow spectral bandwidth are equally important in terms of isolating the signal using spectral filtering.

The proposed experiments rely on recent advances in coherent speckle spectroscopy. This experiment is shown in Figure 1. The experiment involves a Michelson Interferometer arrangement with a variable path length to introduce a second time delay between two replica x-ray pulses that overlap within the sample. The coherent speckle pattern observed by the two arms are correlated, with slightly different viewing angles of the same water structures. By delaying the arrival time of one x-ray pulse relative to another, the time dependent speckle pattern will be recorded. The high coherence of the beams and the ability to tightly focus the beam will enable the two beams to be crossed at a very small angle to access the same waters. The coherently scattered light will be transported a sufficient distance to enable spatial separation and readout on two different detectors. There will be a small angle projection that will be different for the two beams; this difference can be corrected at $t = 0$ to give the spatial correlation between the two beams with respect to the sampled volume element. The resultant two-time coherent scatter can be inverted to the inherent lengths scales of the various water motions. In essence, this experiment will capture a two-time correlation of the water motions in k -space.

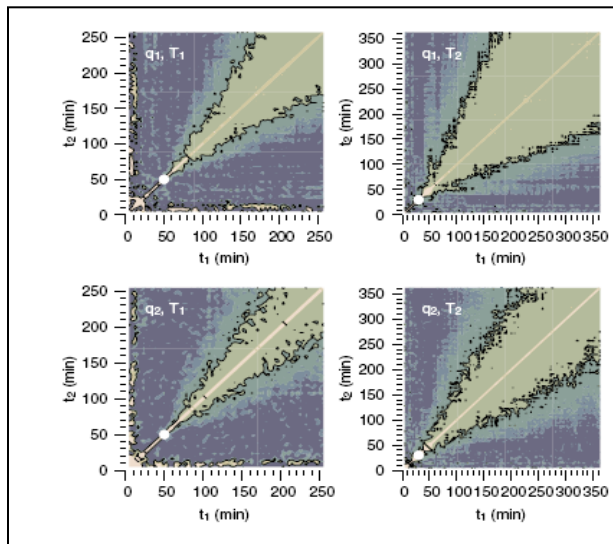


Figure 1. Data from reference 6 showing the two-time correlation for different scattering vectors. These data were collected on the minute time scale, with the time resolution provided by the detector readout. The proposed experiments will achieve 10 fs time resolution using time delays between coherently scattered beams, with separate detectors.

The information content in this experiment will be extraordinarily high. Current methods exploit two-time correlations of various vibrational bands using 2D IR spectroscopy.

High level theory is required to connect the spectrum to the intrinsic water dynamics. This comparison, to date, has been fraught with problems in treating water under the fully resonant conditions of the hydrogen bond network. All possible pathways are connected in some way and can affect the 2D spectrum. The ultimate goal in these studies is to discern the anharmonic terms in the intermolecular potential. It is really the highly anharmonic motions of molecules in the liquid state that define this state of matter. The ideal experiment would be to observe the anharmonic motions directly. The proposed experiment would do exactly this (albeit in k-space). Given the fundamental importance of water to understanding life in general, this experiment provides strong motivation for the WFEL source.

In leading up to these experiments, the theory for coherent scattering process will need to be developed. This work will be greatly augmented by recent work in lensless imaging that likely can be applied for this class of experiment. On the experimental front, the absorption of the x-rays is significant. The experiments will need to be conducted using recent advances in nanofluidics to reduce absorption problems and to also reduce the total volume of water involved in the scattering process. It is already possible to obtain flow with 100 nm channels of water and this should be pushed to even smaller path lengths. The x-ray optics need to be developed along with the detector system. This latter task can be readily handled by the WFEL core staff.

1.2 Length Scale/Time Scale of Solvent Dynamics. Beamline 6

The above described experimental station will have enormous utility in the study of other liquids including supercooled, superheated and supercritical fluids, as well as glasses. The prospect of directly observing the critical motions involved in phase transitions is an exciting prospect.

In addition to the direct observation of equilibrium fluctuations, it will be straightforward to introduce a visible excitation pulse synchronized to the x-ray pulse pair to directly observe highly nonequilibrium motions that occur during chemical reactions and biological processes. There are a number of important classes of chemical reactions that are strongly coupled to the solvent coordinate. These reactions include all electron-transfer processes (redox chemistry), acid-base reactions, isomerization reactions, basically all chemical processes occurring in solution or within polymers. This is an enormous fraction of chemistry. Over the last 60 years, pulse excitation has been used to induce a chemical process and then monitor the reaction kinetics to try to gain insight into the reaction mechanism. With the more recent advent of femtosecond lasers, the time resolution has made it possible to directly observe the primary motions driving the chemistry and a great deal of work has been done on dissecting the solvent's role in mediating the chemical process. However, the probes of the solvent coordinate are only weakly connected to the observable through solvent dependent shifts in spectral markers or the solvent response has to be subtracted from the background. The WFEL two-time x-ray correlation spectroscopy would provide a completely new window on the solvent coordinate. By exploiting nanofluidics and using high concentrations of reactants, the background problem will not be significant. Effectively, it should be possible to directly image both the time and length scales of motion of the solvent coordinate governing chemical reactions in the solution phase.

1.3 Structure-Function Correlation of Biological System. Beamline 6

This class of experiments will use both the coherent x-ray speckle spectroscopy concept and wide angle x-ray scattering to directly observe the inherent motions directing protein motion into function. Background experiments would be conducted to determine the equilibrium fluctuations of the proteins of interest. This information provides the spectral density of states. The key experiments with respect to determining the function-structure correlation will be those using pump-probe protocols to study the nonequilibrium motions that are convolved to the reaction coordinate powering the biological function. An excitation pulse will initiate the reaction and the subsequent motions of the protein followed with x-ray probes. The classic system is the bond breaking event at the heme active site in heme proteins. This system has formed the cornerstone of our understanding of allosteric regulation and the basis for the collective mode coupling model for understanding the structure-function correlation for biological systems [1,2]. These experiments will enable a direct observation of the relevant length scales to functionally relevant protein motions and should enable a direct resolution of one of the most central issues with respect to understanding biology at the molecular level of detail.

1.4 Applications to Molecular Biology. Beamlines 3-6

Proteins in cells are actively transported along the cytoskeleton; they scan along DNA to find their target sequence (Fig. 2);[7,8] they diffuse through membranes to form functional assemblies. Both muscles and cell movement require active movement of one protein along another. This motion can be imaged using different x-ray wavelengths to enhance image contrast. This work has strong overlap with the lensless imaging program for studying cells.

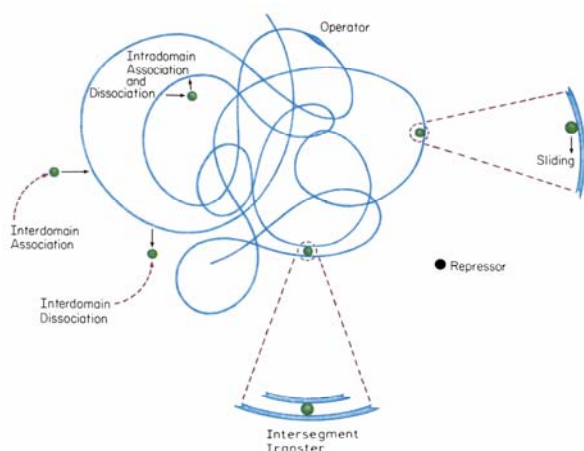
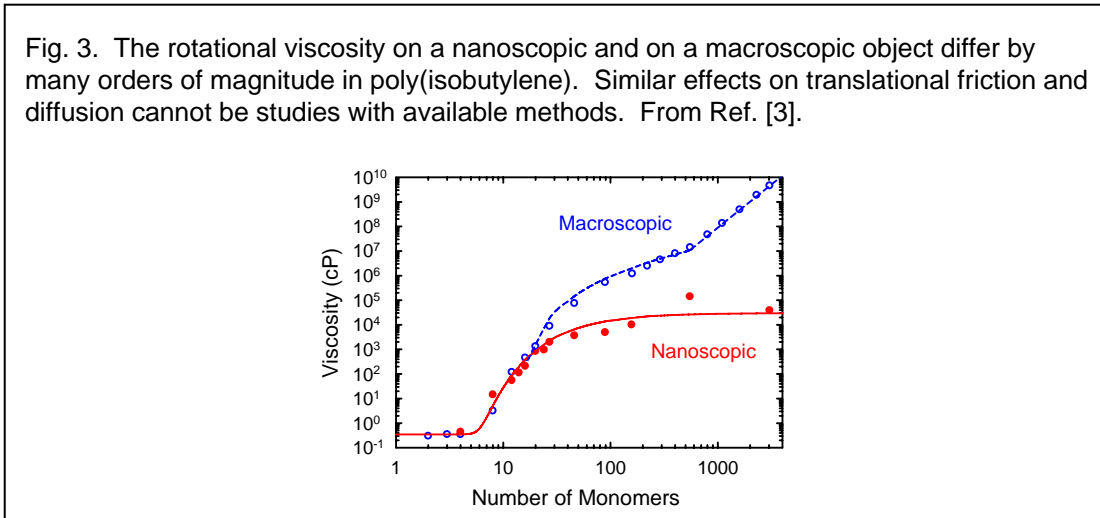


Fig. 2. The search by a protein (repressor, dots) for its target (operator) on DNA may involve many processes over mesoscopic distances. From Ref. [7].

1.5 Materials Science.

Diffusion of small molecules through polymers is essential in many applications: delivery of drugs encapsulated in polymers, chemical separations by differential diffusion through polymer membranes, polymer degradation by reactions with oxygen and loss of plasticizers, ion diffusion through polymer electrolytes in batteries and fuel cells [10,11]. Polymers and polymer nanocomposites [9-13] have structure on many length scales: the radius of gyration of the chain, the entanglement length, the persistence length, the size and separation of compositing particles. Understanding movement through these structures requires measurements over the corresponding mesoscopic lengths (Fig. 3).



1.6. Chemical Physics of Complex Systems. Beamlines 3-6

If a liquid is cooled rapidly, its viscosity increases dramatically, culminating in the formation of a glass. This process is still poorly understood [14-17], but it underlies the processing of many amorphous materials, including inorganic glasses, polymers and amorphous metals. Current theory is focused on the formation of nanoscopic regions of high mobility within the liquid (Fig. 4) [14,15].

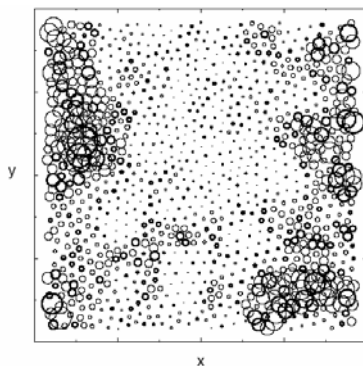


Fig. 4. Simulation of a supercooled liquid showing the range of motion of each molecule as the diameter of a circle. High mobility molecules are predicted to form nanoscopic clusters. From Ref. [17].

One approach to using x-rays to measure dynamics is to make a crystallographic movie, that is a complete atomic structure determination at every point in time [18]. Although this approach is necessary and very powerful for some problems, it is neither required nor desirable for the problems outlined above. First, much of the structure of the system is not changing and can be determined in static experiments. We only need to follow the relative motions of a few well chosen points. In the example of a protein scanning on DNA, the protein and DNA structures do not need to be measured at every time point, only the position of the protein relative to the end of the helix needs to be measured. Second, in disordered systems, there is no single trajectory that correctly represents the dynamics. In the example, a literal movie of a protein doing a random walk along DNA is not the right approach. Only a statistical average of many trajectories is meaningful.

A new and different approach to x-ray dynamics will be developed by combining advances in chemical synthesis and biochemical modification with the high performance of the proposed x-ray FEL. Bright x-ray labels will be introduced into the system to mark the points whose motion is to be followed. These labels can be based on either high local electron density, e.g., heavy metals in organic systems (Fig.5), or on the anomalous scattering of an element not normally present in the sample (Fig. 6) [19]. In addition to the labeling, the moving components must be fixed in an initial position by a chemical link that can be cleaved by an ultrafast optical pulse.

These ideas are illustrated by two examples: one in biology (Fig.5) and one in materials (Fig.6). In Fig. 5, a protein naturally binds to DNA and is held at a specific position by a photocleavable link. The DNA and the protein have each been labeled at a specific position by a cluster of eleven gold atoms (which is commercially available [20]). The link is broken by an optical pulse. At a specific time afterwards, an x-ray pulse measures the radial distribution function of the gold particles. This function is isolated by a difference measurement between labeled and unlabeled samples. Questions to be answered include: Does the protein find the target on its first encounter? Or is a rare conformation that exposes the target bases needed?[21] Are the non-target regions scanned at a uniform rate? Are there subpopulations of protein conformers that scan at different rates?

In Fig.6, a scheme for measuring small-molecule diffusion through a polymer is shown. In this case, the labeling is based on anomalous scattering from chlorine atoms.

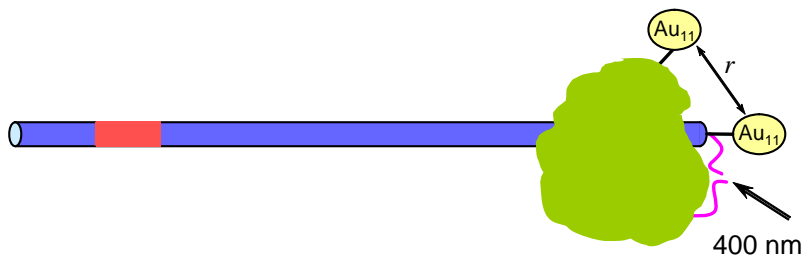


Fig. 5. A protein (green) and DNA (blue) are both labeled with gold clusters (yellow). After breaking the photocleavable link (purple), the radial distribution of the gold-gold distance (r) is measured as the protein scans for its target sequence (red).

Differences are taken between measurements with the x-ray wavelength on and off the peak in scattering at the absorption edge. Questions to be answered include: Is diffusion spatially uniform, or does it follow regions of high mobility in the polymer? Are the regions connected, or are there rate limiting jumps between regions? Are these regions compact, elongated or sheet-like? All these questions could be answered from the time-dependent radial distribution function of the labeled molecules.

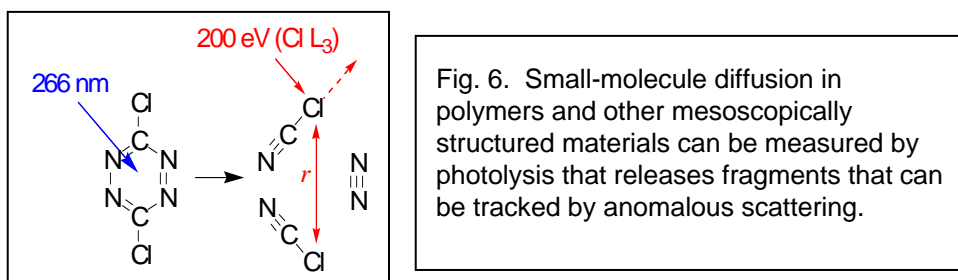


Fig. 6. Small-molecule diffusion in polymers and other mesoscopically structured materials can be measured by photolysis that releases fragments that can be tracked by anomalous scattering.

In addition to sophisticated chemical synthesis, these measurements will require the new capabilities of the proposed FEL. The labels will be dilute, making high accuracy difference measurements necessary. On the order of 100 measurements at various time points are needed in a dynamic experiment, where one measurement would suffice in a static experiment. Thus, a bright, stable x-ray source accurately synchronized to an optical source is essential. In addition, a narrow bandwidth, tunable source is needed to take advantage of the sharp peak in the anomalous scattering that occurs at the exact absorption edge [19].

Finally, new microfluidic sample handling methods are needed. Large distances are most easily measured with long wavelength x-rays, but the samples must be thin due to the high absorption at these wavelengths. Optical triggering is destructive, so the sample must be flowed rapidly. In addition, the total sample volumes will be small, due to the limited amount of highly modified molecules available. Micro- and nano-fluidic techniques allow the precise and efficient manipulation of small sample volumes and will be adapted to allow combined optical and x-ray access with appropriate flow rates.

2. Correlation of electronic and nuclear motions using ultrafast x-ray absorption. Beamlines 3-5

The coherent ultrashort soft x-ray source provided by the Wisconsin FEL (WFEL) with photon energy up to 1 keV (wavelength $>12.3 \text{ \AA}$) and pulse duration of 10 fs fwhm, as well as spectral tunability opens up new frontiers in chemical physics, especially molecular and electronic dynamics during chemical reactions. Studies described below intend to outline the research opportunities that may be enabled by the WFEL.

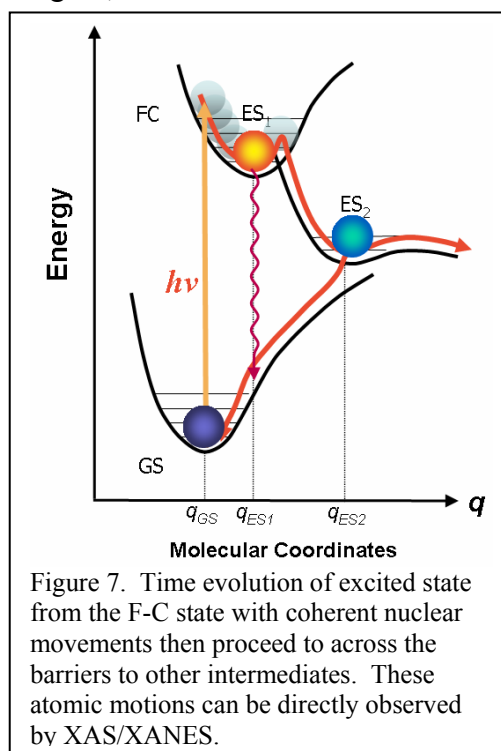
A. Correlation of electronic and nuclear motions in photochemical reactions by ultrafast x-ray absorption

Atomic rearrangements and electronic charge redistribution represent key molecular transformations occurring in chemical reactions. Ultrafast spectroscopic investigations over the last couple of decades have exploited the inherent time resolution available with optical pulses to probe these dynamics with ever increasing precision and sophistication. Yet one of the ultimate goals of chemical physics is to watch such transformation in real time (10^{-15} to 10^{-9} s) with atomic level structural resolution (10^{-8} to 10^{-10} m), atomic specificity, and the ability to map the evolution of the electronic wave function. Because the electronic and nuclear structures of molecules are intimately correlated, the complete understanding of a chemical reaction will require mapping out both configurations the electronic configuration and the nuclear positions during the course of the reaction. This is so-called 4-D imaging [22].

Photoinduced charge transfer, energy transfer, isomerization, dissociation and association reactions comprise important classes of chemical transformation. When a molecule absorbs a photon with energies in the UV to near IR region, the valence electrons are displaced, resulting in an excited state molecule [23]. Highly unstable in nature, the nuclei in this initial excited state, referred as Franck-Condon (F-C) state, retain the ground state geometry. The nuclei will subsequently adjust relative positions to accommodate the new electronic structure [24], leading to an equilibrated geometry differing from that of the ground state as illustrated in Figure 7. While these processes are the first steps in most photoreactions; they also provide important paradigms systems to investigate the fundamental reactive or transition state of a broad class of thermal reactions.

Ultrafast optical laser spectroscopy has played an important role in mapping out the energetics, dynamics and coherences of different molecular and electronic interactions, with sometimes surprising results. A recent study used two dimensional ultrafast optical laser spectroscopy to reveal that the energy transfer processes between chromophores can be a wavelike coherent processes - even in very complicated arrays imbedded within a large macromolecule such as natural photosynthetic light harvesting protein complexes [25].

However, the optical absorption spectra for condense phase systems, including most molecules in solution are broad and congested, with overlapping absorptions from different transient species. Hence, even very sophisticated optical measurements often



provide only an indirect probe of the electronic and nuclear structure. Consequently, a number of outstanding questions remain unanswered for most systems: how do the electronic and nuclear configurations interfere with each other; what active vibrational modes govern photoinduced electron transfer; how does energy flow from one vibrational mode to another; what are the precise nuclear movements in photochemical reactions; what is the pathway for transformation of the electronic state?

The highly coherent, ultrashort, and tunable pulses provided by WFEL will provide the opportunity to use x-ray absorption spectroscopy (XAS) to probe the coherent electron and nuclear motions for the first time with atomic scale resolution. The energy range of < 1keV will cover the K-edges of N, O, and C and the L-edges of the first row transition metals. With the N, O, and C K-edge XAS, chemical bonding speciation and covalency of these atoms can be monitored during the chemical reaction. On the other hand L-edge XAS measurements of the first row transition metals have the advantage over the K-edge measurements because the dipole allowed 2p to 3d transitions are more intense than the quadrupole-allowed 1s to 3d transitions measured in K-edge XAS. In addition, the L-edge XAS measurements are particularly sensitive to metal d orbital electronic configurations – whose optical transitions are often obscured by stronger (π, π^*) transitions in visible transient absorption spectroscopy. Although the spectral congestion in the L-edge region complicates EXAFS measurements, X-ray absorption near edge spectroscopy (XANES) enabled by the WFEL will enable the characterization of time-dependent changes in ligation, oxidation state, spin state, structure and electronic orbital structure of transition metal complexes following photoexcitation. Ultimately the coherence, pulse duration, and intensity of the WFEL source will also enable the development of soft x-ray coherent multidimensional absorption spectroscopy analogous to the techniques now heavily exploited in the IR regime and becoming possible in the UV and visible regimes.

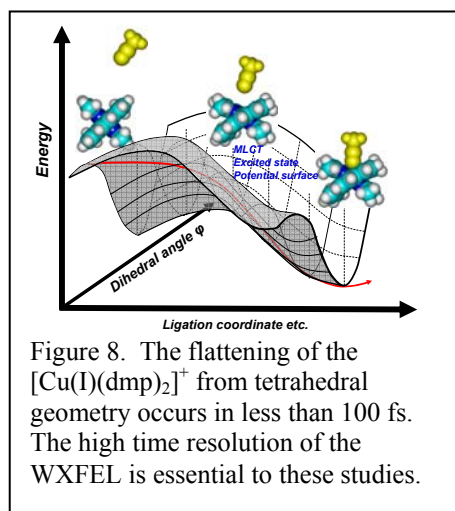
B. Specific examples using the WFEL for XAS investigations of photoinitiated reactions.

1. Structural dynamics of first row transition metal complexes

Transition metal complexes and metalloporphyrin derivatives (phthalocyanines and dipyrriis) are important chromophores for solar energy utilization and molecular electronics and photocatalysis. In particular, the excited state transition metal complexes often perform functions as photosensitizers and electron or energy donors/acceptors through metal-to-ligand-charge-transfer (MLCT) transitions, or ligand-to-metal-charge-transfer (LMCT) transitions, where electrons flow between the metal center and its coordinating ligand groups in the excited states, resulting in changes in oxidation states of the metal center. MLCT electron density shifts within molecules are the bases for the function of these complexes as chromophores for light energy conversion [26-29].

One of the most commonly used transition metal complexes for the dye sensitized solar cell (DSSC) [30] is ruthenium(II)tris-bipyridine [Ru(II)bpy complex, which absorbs light within the solar spectrum and eject one electron into titanium dioxide nanoparticles.

Although the application of DSSC has been successful, its efficiency remains relatively low around 11%, and its requirement for Ru complexes will make the device inevitably expensive. Therefore, it has been a great effort in understanding fundamental mechanisms for DSSC [31,32] as well as in replacing the Ru complexes with those of the first row transition metals [33]. Recently, one of those potential replacements complexes have been studied with both laser-initiated time-resolved XAS and the ultrafast optical absorption and emission spectroscopy [34-36]. The study revealed an ultrafast flattening (< 77 fs) of the tetrahedral geometry of the F-C state $[\text{Cu(I)dmp}_2]^+$ upon the photoexcitation and the structure dependent excited state dynamics (Figure 8).



The rate constants for intersystem crossing, fluorescence emission and internal conversion are all correlated with the dihedral angle between the two ligand planes. This ultrafast structural dynamics can be studied by the Cu L_1 -edge XAS near 932 eV [37] because the MLCT transition will convert Cu(I) ($3d^{10}$) to Cu(II) ($3d^9$), changing 3d orbital vacancy from 0 to 1, with anticipated new transition emerge as the process complete. Meanwhile, N K-edge XAS near 410 eV can be used as a complementary measurement for the covalency change in this ultrafast dynamics process. Although it is not clear currently if the flattening can be directly measured by the XAS, a complementary scattering method can also be used to measure pair distribution functions of the molecules from which the geometric change can be extracted. From these measurements, we will learn exactly how the electron transfer within the molecule is correlated with the molecular geometry change. Several other first row transition metal complexes with Fe, Cr, Ni, and Co can be studied similarly and these are all candidates for replacing Ru complexes for DSSC applications. Once we learned the correlation between the electronic and nuclear configurations, we may design the ligands to restrict the geometry of the molecules in a certain way to change the properties for the applications.

2. Structural dynamics of metalloporphyrin derivatives

Metallo-porphyrins, phthalocyanines and dipyrins are chromophores and building blocks for diverse functionalities induced by light from natural photosynthesis to molecular devices. However, the excited state behaviors of these molecules vary due to many different structural factors, such as metal electronic configuration and spin states, peripheral groups as well as metal ligation. Minor modifications in structures may alter excited state properties significantly. The diverse excited state structural dynamics can be exemplified by Ni(II)porphyrins, which has complicated excited state pathways as shown in Figure 9, including internal conversion, intramolecular energy transfer, intersystem crossing, ligand dissociation/association, and vibrational relaxation [38-43]. Despite observations of complicated excited state dynamics through ultrafast laser spectroscopy and synchrotron x-ray transient absorption, the excited state electronic

configuration and geometry are not completely clear, or mainly inferred by quantum mechanical calculations, because the excited state absorption features are broad and congested. It is still unclear how metal molecular orbitals (MO) interact with those on the ligands in terms of electronic distribution at the excited state, and how the electronic redistribution leads to the nuclear rearrangements.

Especially interesting is the correlation between the metal d orbital centered excited state and the macrocycle centered excited states, and the correlation between the change of electronic occupation and metal and the porphyrin configuration, and ligand dissociation. The latter will also serve as model system for iron-containing heme groups in myoglobin and hemoglobin. Although nuclear coordinates are not directly obtained due to the limitation of XANES, the structural information can be deduced by the absorption peak shifts due to the UV-VIS excitation which correspond to oxidation state and covalency change, complementary to what one can obtain from optical laser transient absorption spectroscopy.

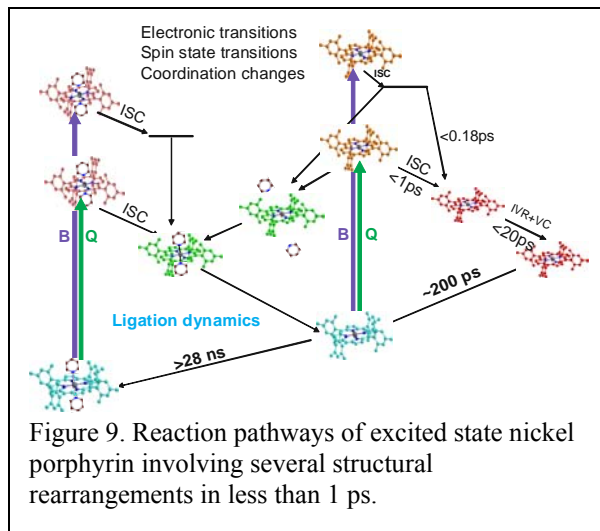


Figure 9. Reaction pathways of excited state nickel porphyrin involving several structural rearrangements in less than 1 ps.

3. Cobalamin containing systems

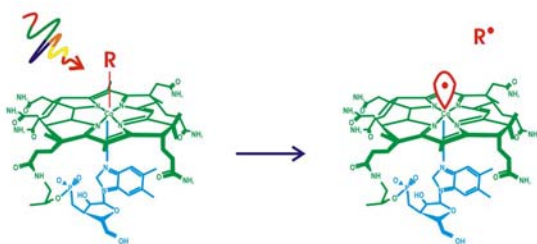


Figure 10. Optical excitation may be used to initiate bond cleavage in B₁₂ coenzymes.

Another important macrocycle, related to the porphyrin systems described above, is the cobalt containing cobalamin molecule. Vitamin B₁₂ or cyanocobalamin (CNCbl) is an important biological cofactor and an essential human nutrient (Figure 10). Two B₁₂ dependent human enzymes, methylmalonyl-CoA mutase and methionine synthase, incorporate active alkylcobalamins derived from CNCbl.

Adenosylcobalamin-dependent (AdoCbl) enzymes catalyze rearrangement reactions that proceed via mechanisms involving organic radicals generated by homolysis of the coenzyme cobalt-carbon bond to produce an adenosyl radical and cob(II)alamin [44-45]. The influence of the protein environment facilitating the homolysis of the Co-C bond remains a significant open question. Recent time-resolved spectroscopic measurements have demonstrated that the electronic structure and bond dissociation of vitamin B₁₂ coenzymes depends sensitively on the local environment of the cofactor [46-49]. In particular the data suggests that the protein environment stabilizes the lowest charge-transfer or ligand field state of these molecules. Time-resolved XAS will provide a powerful tool to probe the evolution of the Co 3d electronic structure following

photoexcitation identifying oxidation and ligation states with specificity unattainable in UV-Vis measurements.

C. Extension of time-resolved x-ray absorption spectroscopy to the investigation of general complex reactions.

Time-resolved x-ray spectroscopies have the potential to contribute to the understanding of reaction mechanism with a level of detail and specificity unattainable by other methods. However, to exploit XAS techniques in a general fashion, beyond the interesting – but limited class of fast photoreactions, it will be necessary to develop phototriggers capable of synchronizing an ensemble of complex systems. While several key paradigm systems are capable of femtosecond initiation with high quantum yield – most potential photochemical triggers occur on picosecond to nanosecond timescales, and may be complicated by competing reactions. The full utilization of the ultrafast dynamical resolution of short x-ray sources for spectroscopy or scattering measurements will require a move beyond simple pump-probe protocols relying on the “natural” dynamics of the photon trigger. Coherent control of bond breaking, molecular rearrangement, and/or electron transfer provides a means to bypass the limitations of the molecular system. Optical pulse shaping may be used to produce “sculpted” ultrafast pulses as *smart reagents* to control photodissociation and chemical reactivity. Control over physical processes in molecules via phase shaping of an ultrafast laser pulse has now been widely demonstrated [50-56]. Coherent Control pulse shaping protocols will permit synchronization with sufficient time-resolution for x-ray probes to follow the subsequent transformation in real time with atomic level structural resolution and atomic specificity. The direct participation of pulse shaping enables steering the chemical/biological pathway in a manner that enables a reconstruction of the all important reaction surface. Here the combination of high repetition rate and spectral resolution of the W FEL is essential to permit active feedback methods to construct atomically resolved potential energy surfaces. This area will constitute an entire new field that is distinct from studies that focus solely on structural dynamics --- we will have the ability to construct topological maps of reactive surfaces not highly averaged single cross sections. We will move beyond simple 1-d model surfaces such as Figure 7 to full topological details. A topological map is needed to fully understand any terrain and in chemistry and biology we would have an opportunity to make such “hiking” maps for researchers to properly find their way in controlling processes in completely new ways.

1. *Energetics and Dynamics of Deterministic Protein Motion*, R. J. D. Miller, Acc. Chem. Res. **27**, 145-150 (1994).
2. *Mother Nature and the Molecular Big Bang*, R. J. D. Miller, Can. J. Chem. **80**, 1-24 (2002).
3. *Ultrafast Vibrational Dephasing of Liquid Water*, J. Stenger et al., Phys. Rev. Lett. **87**(2), 027401/1-027401/4 (2001).
4. *Water Dynamics: Vibrational Echo Correlation Spectroscopy and Comparison to Molecular Dynamics Simulations*, J.B. Asbury et al., J. Phys. Chem. A **108**, 1107-1119 (2004).
5. *Ultrafast Memory Loss and Energy Redistribution in the Hydrogen Bond Network of Liquid H₂O*, M.L. Cowan, B. Bruner, N. Huse, E. Nibbering, T. Elsaesser, and R. J. D. Miller, Nature **434**(7030), 199–202 (2005).

6. *X-Ray Intensity Fluctuation Spectroscopy of Phase Ordering Systems*, A. Fluerasu, M. Sutton, and E. M. Dufresne, *Phys. Rev. Lett.* **94**, 055501 (2005).
7. *Facilitated Target Location in Biological Systems*, P. H. von Hippel and O. G. Berg, *J. Biol. Chem.* **264**, 675-678 (1989).
8. *Diffusion-Driven Mechanisms of Protein Translocation on Nucleic Acids. 1. Models and Theory*, O. G. Berg, R. B. Winter, and P. H. Von Hippel, *Biochemistry* **20**, 6929-6948 (1981) <http://dx.doi.org/10.1021/bi00527a028>.
9. *Torsional Relaxation and Friction on the Nanometer Length Scale: Comparison of Small-Molecule Rotation in Poly(dimethylsiloxane) and Poly(isobutylene)*, M. M. Somoza, M. I. Sluch, and M. A. Berg, *Macromolecules* **118**, 2721-2732 (2003) <http://dx.doi.org/10.1021/ma021181n>.
10. *Diffusion in and through Polymers*, W. R. Vieth (Hanser Publishers, Munich, 1991).
11. *Diffusion in Polymers*, edited by J. Crank and G. S. Park (Academic Press, London, 1968).
12. *Nanocomposite Science and Technology*, P. M. Ajayan, L. S. Schadler, and P. V. Braun (Wiley-VCH, Weinheim, 2003).
13. *Polymer/Layered Silicate Nanocomposites: A Review from Preparation to Processing*, S. S. Ray and M. Okamoto, *Prog. Polym. Sci.* **28**, 1539-1641 (2003).
14. *Supercooled Liquids and the Glass Transition*, P. G. Debendetti and F. H. Stillinger, *Nature* **410**, 259-267 (2001).
15. *Spatially Heterogeneous Dynamics in Supercooled Liquids*, M. D. Ediger, *Annu. Rev. Phys. Chem.* **51**, 99-128 (2000).
16. *Molecular Dynamics Studies of Heterogeneous Dynamics and Dynamic Crossover in Supercooled Atomic Liquids*, H. C. Andersen, *Proc. Natl. Acad. Sci. U.S.A.* **102**, 6686-6691 (2005) <http://dx.doi.org/10.1073/pnas.0500946102>.
17. *How Reproducible Are Dynamic Heterogeneities in a Supercooled Liquid? A.* Widmer-Cooper, P. Harrowell, and H. Fynewever, *Phys. Rev. Lett.* **93**, 135701 (2004) <http://dx.doi.org/10.1103/PhysRevLett.93.135701>.
18. *Extended Subnanosecond Structural Dynamics of Myoglobin Revealed by Laue Crystallography*, D. Bourgeois, B. Vallone, A. Arcovito, G. Sciara, F. Schotte, P. A. Anfirud, and M. Brunori, *Proc. Natl. Acad. Sci. U.S.A.* **103**, 4924-4929 (2006) <http://dx.doi.org/10.1073/pnas.0508880103>.
19. *Anomalous X-Ray Scattering for Materials Characterization: Atomic-Scale Structure Determination*, Y. Waseda, Springer Tracts in Modern Physics Vol. 179 (Springer, Berlin, 2002).
20. Nanoprobes, Inc., <http://www.nanoprobes.com>
21. *Enzymatic Capture of an Extrahelical Thymine in the Search for Uracil in DNA*, J. B. Parker, M. A. Bianchet, D. J. Kroskey, J. I. Friedman, L. M. Amzel, and J. T. Tivers, *Nature* **449**, 433-437 (2007) <http://dx.doi.org/10.1038/nature06131>.
22. Zewail Ahmed, H. "4D Ultrafast Electron Diffraction, Crystallography and Microscopy", *Ann. Rev. Phys. Chem.* 2006, **57**, 65-103.
23. Lever, A. B. P. Excited States and Reactive Intermediates, ACS Symposium Series, 1985; Vol. 307.
24. Zewail, A. H. "Femtochemistry: Atomic-Scale Dynamics of the Chemical Bond", *J. Phys. Chem. A* 2000, **104**, 5660-5694.

25. Engel, G. S.; Calhoun, T. R.; Read, E. L.; Ahn, T.-K.; Mancal, T.; Cheng, Y.-C.; Blankenship, R. E.; R., F. G. "Evidence for wavelike energy transfer through quantum coherence in photosynthetic systems", *Nature* 2007, 446, 782-786.
26. Meyer, T. J. "Chemical Approaches to Artificial Photosynthesis", *Acc. Chem. Res.* 1989, 22, 163-170.
27. Vlcek, A., Jr. "Mechanistic roles of metal-to-ligand charge-transfer excited states in organometallic photochemistry", *Coordination Chemistry Reviews* 1998, 177, 219-256.
28. Balzani, V.; Credi, A.; Venturi, M. "Photochemistry and photophysics of coordination compounds. An extended view", *Coord. Chem. Rev.* 1998, 171, 3-16.
29. Durr, H.; Bossmann, S. "Ruthenium Polypyridine Complexes. On the Route to Biomimetic Assemblies as Models for the Photosynthetic Reaction Center", *Acc. Chem. Res.* 2001, 34, 905-917.
30. O'Regan, B.; Graetzel, M. "A low-cost, high-efficiency solar cell based on dye-sensitized colloidal titanium dioxide films", *Nature (London)* 1991, 353, 737-40.
31. Damrauer, N. H.; Cerullo, G.; Yeh, A.; Boussie, T. R.; Shank, C. V.; McCusker, J. K. "Femtosecond Dynamics of Excited-State Evolution in $[\text{Ru}(\text{bpy})_3]^{2+}$ ", *Science* 1997, 275, 54-57.
32. Yeh, A.; Shank, C. V.; McCusker, J. K. "Ultrafast Electron Localization Dynamics Following Photo-Induced Charge Transfer", *Science* 2000, 289, 935-938.
33. Gregg, B. A.; Pichot, F.; Ferrere, S.; Fields, C. L. "Interfacial recombination processes in dye-sensitized solar cells and methods to passivate the interfaces", *Journal of Physical Chemistry B* 2001, 105, 1422-1429.
34. Chen, L. X.; Jennings, G.; Liu, T.; Gosztola, D. J.; Hessler, J. P.; Scaltrito, D. V.; Meyer, G. J. "Rapid excited-state structural reorganization captured by pulsed x-rays", *Journal of the American Chemical Society* 2002, 124, 10861-10867.
35. Chen, L. X.; Shaw, G. B.; Novozhilova, I.; Liu, T.; Jennings, G.; Attenkofer, K.; Meyer, G. J.; Coppens, P. "The MLCT State Structure and Dynamics of a Cu(I) Diimine Complex Characterized by Pump-probe X-ray and Laser Spectroscopies and DFT Calculations", *J. Am. Chem. Soc.* 2003, 125, 7022-7034.
36. Shaw, G. B.; Grant, C. D.; Castner, E. W.; Meyer, G. J.; Chen, L. X. "Ultrafast Structural Rearrangements in the MLCT Excited State for Copper(I) bis-Phenanthrolines in Solution", *J. Am. Chem. Soc.* 2007, 129, 2147-2160.
37. Sarangi, R.; DeBeer George, S.; Jackson Rudd, D.; Szilagyi, R. K.; Ribas, X.; Rovira, C.; Almeida, M.; Hodgson, K. O.; Hedman, B.; Solomon, E. I. "Sulfur K-Edge X-ray Absorption Spectroscopy as a Probe of Ligand-Metal Bond Covalency: Metal vs Ligand Oxidation in Copper and Nickel Dithiolene Complexes", *J. Am. Chem. Soc.* 2007, 129, 2316-2326.
38. Kim, D.; Kirmaier, C.; Holten, D. "Nickel porphyrin photophysics and photochemistry. A picosecond investigation of ligand binding and release in the excited state", *Chem. Phys.* 1983, 75, 305-22.
39. Rodriguez, J.; Holten, D. "Ultrafast Vibrational Dynamics of a Photoexcited Metalloporphyrin", *Journal of Chemical Physics* 1989, 91, 3525-3531.
40. Eom, H. S.; Jeoung, S. C.; Kim, D.; Ha, J.-H.; Kim, Y.-R. "Ultrafast Vibrational Relaxation and Ligand Photodissociation/Photoassociation Processes of Nickel(II) Porphyrins in the Condensed Phase", *J. Phys. Chem. A* 1997, 101, 3661-3669.

41. Drain, C. M.; Gentemann, S.; Roberts, J. A.; Nelson, N. Y.; Medforth, C. J.; Jia, S.; Simpson, M. C.; Smith, K. M.; Fajer, J.; Shelnut, J. A.; Holten, D. In *J. Am. Chem. Soc.*, 1998; Vol. 120; pp 3781-3791.
42. Chen, L. X.; Jager, W. J. H.; Jennings, G.; Gosztola, D. J.; Munkholm, A.; Hessler, J. P. "Capturing a photoexcited molecular structure through time-domain x-ray absorption fine structure", *Science* 2001, 292, 262-264.
43. Chen, L. X.; Zhang, X.; Wasinger, E. C.; Attenkofer, K.; Jennings, G.; Muresan, A.; Lindsey Jonathan, S. "Tracking Electrons and Atoms in a Photoexcited Metalloporphyrin by X-ray Transient Absorption Spectroscopy", *J. Am. Chem. Soc* 2007, 129, 9616-9618.
44. Ludwig, M.; Matthews R. "Structure-Based Perspectives On B₁₂-Dependent Enzymes" *Annual Rev. Biochem.* 1997, 66, 269-313.
45. Marsh, E. N. G. "Coenzyme B12 (cobalamin)-dependent enzymes" *Essays Biochem.* 1999, 34, 139-154.
46. Sension, R. J.; Cole, A. G.; Harris, A. D.; Fox, C. C.; Woodbury, N. W.; Lin, S; Marsh, E. N. G. "Photolysis and Recombination of Adenosylcobalamin Bound to Glutamate Mutase" *J. Am. Chem. Society*, 2004, 126, 1598-1599.
46. Sension, R. J.; Harris, D. A.; Stickrath, A.; Cole, A. G.; Fox, C. C.; and Marsh, E. N. G. "Time Resolved Measurements of the Photolysis and Recombination of Adenosyl-cobalamin Bound to Glutamate Mutase" *J. Phys. Chem. B*, 2005, 109, 18146-18152.
48. Shiang, J. J.; Cole, A. G.; Sension, R. J.; Hang, K.; Weng, Y.; Trommel, J. S.; Marzilli, L. G.; Lian, T. "Ultrafast Excited State Dynamics in Vitamin B12 and Related Cob(III)alamins" *J. Am. Chem. Society*, 2006, 128, 801-808.
49. Harris, D. A.; Stickrath, A. B.; Carroll, E. C.; Sension, R. J. "The Influence of Environment on the Electronic Structure of Cobalamins: Time-Resolved Absorption Studies of the S1 State Spectrum and Dynamics" *J. Am. Chem. Society*, 2007, 129, 7578-7585.
50. Damrauer, N. H.; Dietl, C.; Krampert, G.; Lee, S. H.; Jung, K. H.; and Gerber, G. "Control of bond-selective photochemistry in CH₂BrCl using adaptive femtosecond pulse shaping" *Europ. Phys. J. D*, 2002, 20, 71-76.
51. Cardoza, D; Baertschy, M; Weinacht, T. "Understanding learning control of molecular fragmentation" *Chem. Phys. Lett.*, 2005, 411, 311-315.
52. Cardoza, D.; Pearson, B. J.; Baertschy, M.; Weinacht, T. "Charge-transfer as a mechanism for controlling molecular fragmentation" *J. Photochem. Photobiol. A*, 2006, 180, 277-281.
53. Herek, J. L.; Wohlleben, W.; Cogdell, R. J.; Zeidler, D.; Motzkus, M. "Quantum control of energy flow in light harvesting" *Nature*, 2002, 417, 533-535.
54. Prokhorenko, V. I.; Nagy, A. M.; Waschuk, S. A.; Brown, L. S.; Birge, R. R.; Miller, R. J. D. "Coherent Control of Retinal Isomerization in Bacteriorhodopsin" *Science*, 2006, 313, 1257-1261.
55. Carroll, E. C.; Pearson, B. J.; Florean, A. C.; Bucksbaum, P. H.; Sension, R. J. "Spectral phase effects on nonlinear resonant photochemistry of 1,3-cyclohexadiene in solution" *J. Chem. Phys.*, 2006, 124, 114506.
56. Vogt, G.; Krampert, G.; Niklaus, P.; Nuernberger, P.; Gerber, G. "Optimal Control of Photoisomerization" *Physical Review Letters*, 2005, 94, 068305.