Frontiers in Multiscale Modelling of Photoreceptor Proteins

September 3-5 2019
Tel Aviv University

Organizers:

Maria-Andrea Mroginski

Technical University Berlin, Germany

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Program

Frontiers in Multiscale Modelling of Photoreceptor Proteins			
Tuesday, 3rd of September			
Start	**End**		**Title**
9:00	9:45	**Registration & refreshments**	
9:45	10:00	**Opening**	
10:00	10:05	**GFP Session,** Chairperson: Massimo Olivucci	
10:05	10:35	Anna Krylov	The Many Faces of Green Fluorescent Protein
10:35	11:05	Alexander Nemukhin	Modeling chemical reactions in photoreceptor proteins
11:05	11:10	**Phytochromes Session,** Chairperson: Maria-Andrea Mroginski	
11:10	11:40	Gerrit Groenhof	Observe while it happens: Catching photoreceptors in the act with free electron lasers and computer simulations
11:40	11:55	Christian Wiebeler	Structural Basis of the Red/Green Spectral Tuning in the Cyanobacteriochrome Slr1393
12:00	13:30	**Lunch**	
13:30	13:35	**PYP Session,** Chairperson: Nicolas Ferre	
13:35	14:05	Tatiana Domratcheva	Resonance interactions of ionic (charged) chromophores play a key role in biological photoreception
14:05	14:35	Dmitry Morozov	Probing photoreactivity of biological systems with multiscale excited-state molecular dynamics
14:35	15:05	Young Min Rhee	Simulating PYP photodynamics with IM/MM: constructing a surface model without a model
15:05	15:30	**Coffee break**	
15:30	15:35	**Flavin Protein Session,** Chairperson: Tatiana Domratcheva	
15:35	16:05	Ilia Solov'yov	Studying cryptochromes through the computational microscope
16:05	16:35	Ksenia Bravaya	Simulating photoinduced electron transfer in biomolecules: environment polarization and long-range electrostatic interactions
16:35	16:50	Alberto Pérez de Alba Ortíz	Simultaneous sampling of multiple transition channels using adaptive paths of collective variables
17:00		**Poster Session**	

Wednesday, 4th of September			
Start	**End**		
9:00	9:30	Gathering & refreshments	
9:30	9:35	**Rhodopsin Session,** Chairperson: Alexander Nemukhin	
9:35	10:05	Massimo Olivucci	On the Origin of the High Quantum Efficiency of the Light-Driven Rotary Motion of Visual Dim-Light Photoreceptors
10:05	10:35	Shigehiko Hayashi	Atomistically Deciphering Functional Processes Of Photoreceptor Proteins With Molecular Simulations
10:35	11:00	**Coffee break**	
11:00	11:30	Nicoleta Bondar	Proton binding at membrane interfaces
11:30	12:00	Nicolas Ferre	How photochemical properties of light-activated biomolecules are tuned by pH
12:00	12:30	Kazuhiro Fujimoto	Electronic coupling calculations for retinal proteins
12:30	14:00	**Lunch**	
14:00	14:15	Franzi Wolff	Spectroscopic Properties of ChR-2 and LH Complexes: QM/MM Study and Benchmark of LC-TD-DFTB
14:15	14:45	Ville Kaila	Deciphering light-capturing mechanisms in photobiology.
14:45	14:50	**Other Proteins Session,** Chairperson: Gerrit Groenhof	
14:50	15:20	Petra Imhof	Photons, Protons, and the difference they might make
15:20	15:50	**Coffee break**	
15:50	16:20	Benedetta Mennucci	Proteins and Light: What can we learn from a multiscale modeling?
16:20	16:50	Isabelle Navizet	Multiscale modelling of the light emitter system in firefly bioluminescence
17:15	17:45	Yigal Lahav	Understanding Spectral Tuning of Chlorophylls by Protein using QM/MM Calculations
Thursday, 5th of September			
Start	**End**		
9:00	9:30	Gathering & refreshments	
9:30	9:35	**Methodology Session,** Chairperson: Anna Krylov	
9:30	10:00	Tomasz Wesoloweski	Hohenberg-Kohn theorems based embedding formalism for photochemistry and photophysics
10:00	10:30	Jacob Kongsted	Polarizable Density Embedding for Proteins: Excited States in Complex Environments
10:30	10:45	Jógvan Magnus Haugaard Olsen	Polarizable Density Embedding in Protein Environments using Molecular Fractionation with Conjugate Caps
10:45	11:15	**Coffee break**	
11:15	13:00	**Final Discussion & Closing**	
13:15		**Excursion to Jerusalem**	

Invited Talks

The Many Faces of Green Fluorescent Protein

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Rich photo-physics of photoactive proteins from the GFP family continues to expand the scope of its applications. The lecture will discuss different aspects of GFP photocycle, highlighting the role of theory and methodological challenges in modeling complex photoactive systems.

Modeling chemical reactions in photoreceptor proteins

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Studies of chemical reactions occurring with chromophores or molecular groups in chromophore-containing pockets in the ground and excited electronic states, constitute an important field of the photoreceptor protein research. In this contribution, we consider chemical reactions in selected light-responsive proteins using the quantum mechanics/molecular mechanics and molecular dynamics approaches. First, we describe a full cycle of chemical transformations in the chromophore maturation in the wild-type green fluorescent protein (GFP), as well as reactions of the photo-induced decomposition of the GFP chromophore upon photobleaching of the protein. Second, we characterize the fluorescent (ON) and non-fluorescent (OFF) states of the photoswitchable GFP-like Dreiklang and simulate the thermal recovery reaction OFF → ON. The unique properties of Dreiklang are due to a reversible hydration/dehydration reaction at the imidazolinone ring of the chromophore. Recovery of the fluorescent state, which is associated with a chemical reaction of chromophore dehydration, is an important part of the photocycle of this protein. Third, we describe the competing reactions of covalent binding of the biliverdin chromophore to cysteine residues in the bacterial phytochrome domains upon assembly a prospective variant of the near-infrared fluorescent protein miRFP670.

Observe while it happens: Catching photoreceptors in the act with free electron lasers and computer simulations

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Photochemistry is at the core of technologies for harvesting, converting and storing solar energy, but there are no good catalysts available that can steer the excited-state dynamics toward the desired product state while suppressing side reactions. So far, only Nature has evolved efficient ways to control the outcome of photochemical reactions, with vision and photosynthesis as prominent examples. Exploiting the principles of photobiology, however, requires a complete understanding of the underlying molecular dynamics. Before free electron lasers became available, the relevant time and spatial resolutions were notoriously difficult to access experimentally and much of our current understanding of the ultra-fast photo-dynamics in biological systems has been obtained with computer simulations. While serial femto-second time-resolved X-ray crystallography at free electron lasers has now opened up an experimental window into this regime, the current limitations of this technique still call for results from computer simulations to complement the experiments sometimes. In the talk, we will focus on recent applications in which we combined time-resolved X-ray diffraction with computational modeling to acquire atomistic insights into the activation mechanism of biological photoreceptors.

Structural Basis of the Red/Green Spectral Tuning in the Cyanobacteriochrome Slr1393

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Cyanobacteriochromes (CBCRs) are promising candidates for use in biotechnological applications, owing to their photochromism, compactness and spectral diversity. In case of the CBCR Slr1393, one isomer absorbs red light (Pr) and the other one green (Pg) [1]. These two forms can be interconverted into each other by light illumination. Slr1393 binds phycocyanobilin

(PCB) as chromophore and the crystal structures of both forms have been obtained recently [2]. Comparing PCB from both structures shows that one double bond isomerization occurs during the photoconversion. In this contribution, results of hybrid quantum mechanics/molecular mechanics (QM/MM) calculations for the Pr and Pg forms of Slr1393 will be presented [3].

Our QM/MM studies started from the crystal structures. First, the structures were optimized in several stages, followed by classical molecular dynamics (MD) for thermalization and backbone relaxation. During these steps, it was checked that the non-covalent interactions of PCB with the protein remained intact. The snapshots for excited state calculations were then generated via QM/MM MD. The final spectrum is an average of the spectra from the different geometries of each form and the results are complemented with wave function analysis.

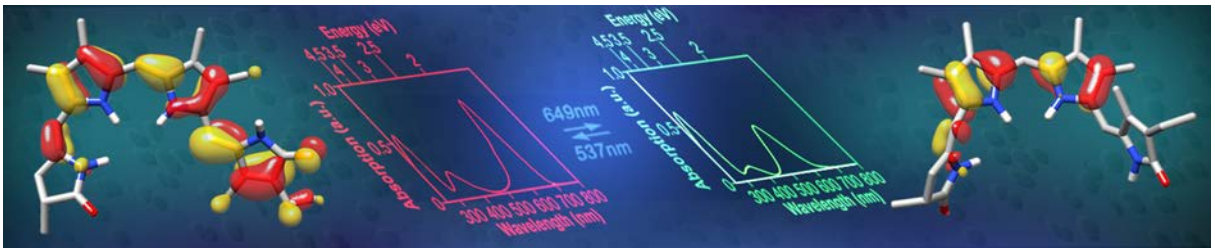

Figure 1: The difference in absorption between the red light-absorbing dark state and the green light-absorbing photoproduct of Slr1393 could be traced back to changes in the effective conjugation lengths of the chromophore in the two conformations [3].

In addition, also results from a benchmark study for this protein will be presented [4]. Its focus is on the choice of an appropriate semiempirical method for QM/MM MD, on methods for excited state calculations and on the importance of sampling.

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Resonance interactions of ionic (charged) chromophores play a key role in biological photoreception

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Ionic chromophores bound to a photoreceptor protein trigger biological photoresponses such as animal vision or bacterial phototaxis. Extensive studies have been dedicated to rationalizing the underlying molecular mechanism, yet one of the central questions how the photochemical yield of a specific photoproduct is maximized by the protein-chromophore interactions remained only partially answered. Photoactive yellow protein (PYP) is one of the best characterized model systems that allows studying how hydrogen bonds (H-bonds) facilitate double-bond isomerization. Upon light signaling, the anionic chromophore of PYP derived from the p-coumaric acid (pCA) undergoes photochemical trans-cis isomerization that eventually alters hydrogen bonding at the protein active site. The chemical structure of pCA, however, also permits excited-state single-bond rotation, which in combination with double-bond isomerization results in several possible photoproducts which overall, may reduce photoactivation efficiency. Previous extensive experimental and computational studies provided evidence that specific H-bonds of the chromophore with the protein modulate the topology of the excited-state potential energy surface favoring double-bond isomerization and at the same time disfavoring single-bond rotation. Using a high-level ab initio XMCQDPT2 calculations of the pCA containing molecular clusters we demonstrated that the effect of H-bonds is related to contributions of four resonance structures describing the chromophore charge translocation in the closed-shell and biradicaloid electronic configurations. It is the relative energy of these four resonance structures, defined by the chromophore chemical structure and its intermolecular interactions e.g. H-bonds, that governs rotation via either a single- or double-bond. We further discuss possibilities to generalize our resonance-structure model to other photoreceptor proteins that employ ionic chromophores, such as rhodopsins and phytochromes.

Probing photoreactivity of biological systems with multiscale excited-state molecular dynamics

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The key step in activation of many photoreceptor proteins is photoisomerization of a conjugated chromophore. High efficiency of the photoreactions in many biological systems suggests that the outcome can be controlled by the interactions between chromophore molecule and the environment. In our study we have used multiscale excited-state molecular dynamics simulations (QM/MD) to predict photoreactivity of a model photoactive yellow protein chromophore (pCK). Simulations were performed in various conditions including gas-phase, solvents and protein. By choosing systems that are accessible with the state-of-the-art experimental techniques we were also able to directly validate predictivity of models. This combination of simulations and experiments provide a detailed understanding of how interactions between chromophore and environment could control the isomerization process, as well as how chemical modifications of the molecule itself could affect epy photodynamics.

Simulating PYP photodynamics with IM/MM: constructing a surface model without a model

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Dynamics in both electronically excited and ground states decides the behaviors of photoreceptor proteins. Computationally simulating the dynamics involves somehow building the potential energy surfaces (PES's) of multiple electronic states and their coupling, but modeling the PES characteristics is never a trivial task. QM/MM is often the method of choice as it can avoid the headaches of modeling. Practically, however, reaching a statistical certainty with QM/MM is out of reach with a large protein complex. The interpolation mechanics / molecular mechanics (IM/MM) has been designed as a remedy, toward reaching this certainty without compromising the reliabity of QM/MM. Here, we will discuss how

the IM/MM surface construction is attained with the photoactive yellow protein (PYP) complex, especially on the aspect of fine-tuning the interface area between the IM and the MM regions. Because IM/MM targets to reproduce QM/MM as closely as possible in terms of the PES characteristics, the same consideration of tuning the interface area should also be applicable to a QM/MM style approach. In addition, with actual simulations, we will demonstrate that the constructed PES can be utilized for simulating thousands of nonadiabatic surface hopping trajectories over a nanosecond of duration. We will attempt to explain the peculiarities of PYP dynamics based on the simulated trajectories.

Studying cryptochromes through the computational microscope

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Clearly, the laws of physics hold and are exploited in living organisms. Speaking as a physicist, most biological characteristics stem from the laws of classical physics that students learn in their first year. However, crucial characteristics in organisms are governed by quantum physics. The latter characteristics are those in which biological processes involve the jumps of electrons from one state to another. The quantum behavior of electrons covers all chemical transformations, for example it arises in optical transitions induced through light absorption by biomolecules.

The mechanism by which night-migratory songbirds sense the direction of the Earth's magnetic field appears to possibly rely on the quantum spin dynamics of light-induced radical pairs in cryptochrome proteins located in the retina. Cryptochrome binds internally the flavin cofactor, which governs it signaling through light-induced electron transfer involving a chain of four tryptophan residues, WA, WB, WC, WD.

I will discuss the state-of-the-art computational tools available for studying cryptochrome-based magnetoreception, and that are qualified to be named as the computational microscope. In particular, I will introduce VIKING (Scandinavian Online Kit For Nanoscale Modeling) – a web-based service for automating computational modeling of biophysical systems. I will discuss the essentials of VIKING, and will then demonstrate how it can be used to study structure and dynamics of avian cryptochromes in silico.

Simulating photoinduced electron transfer in biomolecules: environment polarization and long-range electrostatic interactions

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In this talk I will discuss simulating photoinduced electron transfer in biological molecules within QM/MM framework with the focus on the role of the environment polarization and of the long-range electrostatic interactions. I will show that the two factors play key role for accurate description of the energetics of electron transfer. Cryptochrome protein will be used as a model system.

Finding multiple pathways and free energies of complex biomolecular transitions via enhanced simulation

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Molecular dynamics simulations, boosted by enhanced sampling methods, are nowadays exploited in a variety of biosystems. In particular, so-called biasing methods deliver insight in the form of free energy landscapes—with interpretable stable states, transition paths and barriers—projected onto key molecular descriptors, or collective variables (CVs). Challenges remain when studying complex systems, as the computational cost of rendering the free energy grows exponentially with the number of CVs. We show that path-metadynamics (PMD) is able to find a transition path and the free energy along it with a sublinear rise in cost; and that the extended multi-PMD can simultaneously resolve multiple competing mechanisms, yielding results agreeing with experiment. The framework is demonstrated by exhaustively testing the sequence-dependence of an intricate DNA base-pairing transition. The span of such and further studies is greatly enabled by the adeptness of schemes like PMD. We envision the use of PMD to cost-effectively simulate the complex photoactivation dynamics of BLUF wild types and mutants.

On the Origin of the High Quantum Efficiency of the Light-Driven Rotary Motion of Visual Dim-Light Photoreceptors

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The light-induced unidirectional double-bond isomerization of the dim-light visual pigment rhodopsin, operates a molecular-level opto-mechanical transduction which resemble the ones seen in synthetic molecular motors. On the other hand, the rhodopsin isomerization achieves a ca. 65% quantum yield: an efficiency largely unmatched by C=C double-bond isomerizations occurring in synthetic systems. We therefore employed QM/MM models and semi-classical trajectories to perform a mechanistic investigation of the origin of such high quantum yield with the hope to derive useful engineering principles.

Atomistically Deciphering Functional Processes Of Photoreceptor Proteins With Molecular Simulations

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Functional processes of photoreceptor proteins are often fulfilled by dynamic and global molecular conformational changes of complex protein systems which correlate with local chemical events at reaction centers. Hence the multi-scale functional coupling of chemical local events with protein global molecular dynamics need to be revealed for understanding of molecular nature of protein functions. In this talk, I will present our recent studies on photo-activation processes of a channelrhodopsin (ChR) photo-sensitive ion transporter and photo-induced redox processes of photosystem II (PSII) by a hybrid QM/MM free energy geometry optimization technique, which allows one to optimize electronic wave function and molecular geometry of a reaction center at the ab initio quantum chemistry level of theory on a free energy surface constructed with statistically extensive conformational ensemble of the protein environment obtained by long-time MD simulations.

I will first present an atomic structural model of a chimeric ChR, in a precursor state of the channel opening. The photo-activated structure features extensive tilt of the chromophore accompanied by redistribution of water molecules in its binding pocket which is absent in previously known photo-activated structures of analogous proteins, and widely agrees with experimental evidences of ChRs. The atomistic model manifests a photo-activated ion conduction pathway which is markedly different from a previously proposed one and successfully explains experimentally observed mutagenic effects on key channel properties. I will also present theoretical investigations of redox processes of PSII which includes a transition metal complex as the reaction center. Through ab initio QM/MM free energy geometry optimizations for many combinations of redox and protonation states of the reaction centers free from difficult force field determination for the electronically complex reaction centers, we successfully revealed significant structural differences of the redox centers with the different redox and protonation states.

Proton binding at membrane interfaces

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Bio-membranes host transportes, receptors and enzymes whose functioning relies on proton binding and proton transfers. Proton binding can alter the dynamics and bio-membrane interactions of bio-molecules, and it can be exploited in the design of therapeutics targeted to bio-membrane interfaces with low pH, such as in inflammation and cancer. We seek to understand general physical-chemical principles of the coupling between protonation dynamics, bio-molecule and water dynamics. We develop graph-based algorithms to describe dynamic hydrogen-bond networks that could serve as proton wires or ensure long-distance allosteric coupling between remote sites of a protein. In my talk I will use as examples bio-molecules and molecular complexes whose functioning is triggered by the absorption of light.

How photochemical properties of light-activated biomolecules are tuned by pH **Nicolas Ferre**

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Many biomolecular systems exhibit pH-dependent photochemical properties (rhodopsins, luciferases, etc...) The change of protonation state of titratable residues being the main responsible for such a pH-dependent behavior, we have chosen to study the interplay between the significantly populated protonation microstates and the investigated properties. Different models, ranging from a

crude electrostatic one to the much more involved constant-pH MD-then-QM/MM workflow, have been designed, optimized and applied to understand the molecular origin of the pH-dependent absorption spectrum in a polypeptide dyad, in Anabaena Sensory Rhodopsin (ASR) and in firefly luciferase. The main outcome of these studies is the identification of the principal amino-acids responsible for such a pH-based tuning of photophysics. Exploratory investigations of ASR excited state lifetime are also discussed.

Electronic coupling calculations for retinal proteins

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Excitation-energy transfer (EET) is a well-known phenomenon observed in pair or aggregates of molecules, and its feature is widely used in biological systems, such as green plant photosynthesis. To investigate the rate of EET, we need to estimate the value of electronic coupling. A dipole-dipole (DD) approximation was often used for this purpose. However, the utility of this approximation is limited to the case where the intermolecular separation between two interacting molecules is larger than their molecular sizes. To overcome this limitation, we developed the TDFI method using electronic transition densities [1] and the TrESP-CDQ method using transition multipoles [2]. These methods realized accurate electronic coupling calculations for systems where the DD approximation breaks down, which led to the clarification of the underlying mechanisms of the EET in xanthorhodopsin (XR) [1] and of the exciton-coupled circular dichroism (ECCD) spectra observed in a retinal dimer [3]. The TDFI method was further combined with transfer integral (TI) so as to describe charge-transfer (CT) interaction. This extension, named TDFI-TI, succeeded in analyzing the mechanism of EET via CT states [4] and calculating the excitation energies for molecular crystals [5]. Moreover, a vibronic exciton model combined with TDFI was developed [6], and it was applied to the calculation of CD spectra of XR. The absorption and CD

calculations successfully reproduced the main features of the experimental spectra. Based on these results, we investigated the mechanism of biphasic CD spectrum observed in XR. The calculations indicated that vibronic coupling between carotenoid and retinal plays a significant role in the shape of the CD spectrum.

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Spectroscopic Properties of ChR-2 and LH Complexes: QM/MM Study and Benchmark of LC-TD-DFTB

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Rhodopsins are light-sensitive receptor proteins, which respond to light and enable the signal pathways of the cells. The discovery of the Channelrhodopsins in the last decade paved the way for a new technology in the field of neuroscience. These light-gated ion channels enable neuroscientists to selectively activate nerve cells in tissues with short laser pulses. This technique is the basis for the field of Optogenetics and thus a milestone for the investigation of neural networks. The tool development in this field is an ongoing challenge and requires the molecular understanding of the dependency between structure and colour tuning and the function mechanism of the rhodopsins. However, the description of such complex system, like e.g. the correct description of the hydrogen bonding pattern, and their absorption properties represent a challenge for MM methods. Therefore, combined QM/MM methods need to be applied.

We analysed two rhodopsins, Channelrhodopsin-2 (ChR2) and the bimodal switchable Histidin Kinase Rhodopsin (HKR), with QM methods (DFTB, CASSCF, OM2/MRCI) and molecular dynamics. We identified the origin of the multipeak absorption spectrum of ChR2, the pre-gating mechanism and verified the model by the X-Ray structure. We modelled and validated a homology model on HKR and compared the spectroscopic characteristics with experimental data. On the received structures, calculations in the excited state (CASSCF) are performed and give an insight into the photochemical process. Proton transfer calculations give a hint about the origin of the bimodal switch character in HKR.

Calculations in the excited state of retinal are still challenging for DFT based methods, thus we tested the new LC-TD-DFTB method on several retinal models and rhodopsins.

Deciphering light-capturing mechanisms in photobiology

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Photons, Protons, and the difference they might make

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Proteins and Light:

What can we learn from a multiscale modeling?

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Organisms of all domains of life are capable of sensing, using and responding to light. The molecular mechanisms used are diverse, but most commonly the starting event is an electronic excitation localized on a (multi)chromophoric unit bound to the protein matrix. The initial excitation rapidly "travels" across space to be converted in other forms of energy and finally used to complete the biological function. The whole machinery is largely determined by the coupling between the electronic process and the nuclear motions of the involved chromophores and the dynamics of the protein. Here we present a computational strategy aimed at describing such a complexity of interactions and dynamics; the strategy integrates quantum chemistry and classical models in a mutually polarizable way. Some examples of application to light-driven bioactivity will be presented and discussed.

Multiscale modelling of the light emitter system in firefly bioluminescence

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The emitting light in fireflies arises from the electronic relaxation of oxyluciferin, an organic compound resulting from the oxidation of the D-luciferin substrate inside an enzyme called luciferase.

As the fireflies' bioluminescent system is already used as a marker in biology, man needs to understand what are the chemical and physical important factors responsible for the emitted light's color. In order to have insight of the mechanism of the light emission, both experimental and theoretical joint studies have been performed.

I will present here how theoretical tools can give insight to the colour modulation in the fireflies' bioluminescence. In order to theoretically study such systems, the use of quantum mechanical/molecular mechanical (QM/MM) methods is required. Taking into account the surrounding protein at the MM level is essential in order to understand the colour modulation and influence of the enzyme.

The presentation will present briefly the methods used and will discuss examples of how theoretical studies can give complementary insights to the experimental results for the understanding of such complex phenomena. Fluorescence and bioluminescence phenomena will be compared. Influence of the surrounding environment or artificial modification of the wild light emitter will be presented.

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Understanding Spectral Tuning of Chlorophylls by Protein using QM/MM Calculations

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Tuning of chlorophyll light-absorption spectra by the protein environment is a major factor in determining the efficiency and robustness of photosynthetic light harvesting systems. Type II Water Soluble Chlorophyll-binding Proteins (WSCP) are useful for studying spectral tuning mechanisms in chlorophyll-proteins due to their relatively simple and symmetric structure, and the ability to rigorously modify the protein by recombinant DNA techniques. These were recently used to demonstrate how the protein environment can significantly shift the chlorophyll absorption spectra by inducing deformation of the macrocycle ring. Here, we show that hybrid Quantum Mechanics and Molecular Mechanics calculations can accurately predict protein-induced chlorophyll spectral shifts, and thereby be used to quantify the relative contributions of steric and electrostatics factors to these shifts. We find that when considering conformational dynamics, ring deformation accounts for about a third of the spectral shift whereas protein electrostatics accounts for the rest of the shift. Since protein electrostatics is easier to control and manipulate than chlorophyll conformations, it may be more readily implemented in the design of artificial protein-chlorophyll complexes. This may provide an important tool for designing and constructing protein-based building blocks for solar energy conversion systems.

Frozen-Density Embedding Theory based multi-level simulations: the formalism, approximations, and setting up practical simulation protocol

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Compared to most of QM/MM methods, which are founded on theory of intermolecular interactions, Frozen-Density Embedding Theory (FDET) [1-3] follows a different paradigm. The embedded wavefunction is obtained from constrained minimization of the total energy. In the original formulation, the embedded wavefunction corresponded to the non-interacting reference system [1]. This formulation was extended for interacting embedded wavefunctions obtained from variational [2] and non-variational [3] methods of quantum chemistry. For excited states, Linearized FDET [4] provides a formal framework also based on constrained minimization of the total energy guaranteeing orthogonality of the embedded wavefunctions at different states. In the first part, we focus on relation between energy contributions obtained from FDET and intermolecular interaction theory (especially induction and dispersion) and overview general performance of simple approximations in FDET in describing systems non-covalently bound to the environment [3,5]. In the final part, we provide an illustrative example of setting a FDET based simulation for studies of chromophores embedded in a biomolecular environment.

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Polarizable Density Embedding for Proteins: Excited States in Complex Environments

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We review recent progress within the polarizable embedding (PE) and polarizable density embedding (PDE) methods highlighting the general flexibility and accuracy of these computational models designed

for calculation of general response properties of composite systems. Finally, we will show how the PDE model recently has been extended to the case of covalently bonded environments, e.g. proteins. molecular sizes. To overcome this limitation, we developed the TDFI method using electronic transition densities [1] and the TrESP-CDQ method using transition multipoles

Polarizable Density Embedding in Protein Environments using Molecular Fractionation with Conjugate Caps

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Polarizable density embedding (PDE) is a fragment-based QM/QM/MM-type model aimed at efficient and accurate calculations of spectroscopic properties of large and complex molecular systems. In PDE, as with other embedding models, a central core of a molecular system is described by an electronic-structure model and embedded in an environment that is treated at a different level or resolution. However, in contrast to most other embedding models, the molecular environment is subdivided into computationally manageable fragments from which the properties that are used to model the effects from the environment on the core part are derived. The distinguishing features of the PDE model is that a) the permanent charge distribution of the fragments is modeled using the electronic density and point nuclear charges, b) the induced charge distribution of the fragments is modeled using atom-centered polarizabilities, and c) non-electrostatic repulsion is modeled using a projection operator. This combination results in a highly accurate, efficient, and robust environment model that performs well also in cases where other models fail due to electron spill-out. The PDE model was initially formulated for environments consisting of small molecules, e.g., solute–solvent systems. Here I will present a recently developed extension in which the PDE model is combined with the molecular fractionation with conjugate caps (MFCC) approach. This allows use of the PDE model for environments consisting of large molecules such as proteins. I will show preliminary calculations of excitation energies and associated one-, two, and three-photon absorption strengths that highlight the robustness and accuracy of the model.

Posters

Structural Factors Determining the Absorption Spectrum of the Channelrhodopsin Chimaera C1C2

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Channelrhodopsins (ChR) are light-activated ion channels with a retinal chromophore covalently attached to a lysine amino acid residue via a protonated Schiff base.1 After absorbing a photon the retinal isomerises, which starts a photocycle that leads to cations entering the cell, thereby causing a depolarization of the plasma membrane.2 ChRs have found application in optogenetics, where cells or whole organisms are controlled by light-sensitive ion channels.2-3

We have investigated factors that determine the absorption maximum of the retinal chromophore inside the ChR chimaera C1C2.4 Our aim is to derive an understanding at the molecular level in order to be able to tailor the absorption wavelength by mutations. We have sampled the geometries of membrane-embedded C1C2 and computed absorption spectra for 3000 snapshots. Our calculated absorption maximum of 524 nm is within 0.3 eV of the experimental value of 470 nm.4 Dissection of our spectra according to different structural and electronic determinants reveals that protonation of the counterion E162 causes a red shift of ~20 nm. Moreover, the absorption maximum is strongly correlated with the bond order alternation of the retinal ($r = 0.8$). Lastly, we conclude that differences in the hydrogen-bonding networks involving the retinal Schiff base have a negligible effect on the absorption spectrum.

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Hybrid QM/MM Study of the Photochemistry in the Cyanobacteriochrome all2699g1

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Phytochromes (Phys) are photosensors found in plants, bacteria, and fungi, first discovered in plants. They possess a three-domain structure, with one of them covalently binding an open-chain tetrapyrrole as a chromophore for light absorption. Canonical Phys exhibit reversible photoconversion between red (Pr) and far-red absorbing (Pfr) forms1. Recently, a sub-group of Phys was discovered called cyanobateriochromes (CBCRs). CBCR requires the chromophore binding GAF domain for complete photochemistry. CBCRs can be classified in at least four categories based on the typical absorption of dark state and photoproduct: red/green, green/red, blue/orange (insert-Cys), and blue/green (DXCF). Recently, a new subfamily of CBCRs was found that switches from a red absorbing dark state (Pr) to a far-red absorbing photoproduct (Pfr), like Phys.2 Thus, in the all2699g1 CBCR a complete red/far-red photocycle is achieved with just one instead of three domains.

In this contribution we have studied all2699g1 using hybrid quantum mechanics/molecular mechanics in combination with an ab initio wave function method to unravel the factors governing its unique photochemistry. Such an approach has already proven to be successful to obtain a molecular understanding of the photoproduct tuning in Slr1393g3.3 Hence, we have performed sampling in the ground state to explore the conformational flexibility of all2699g1 and then compare the results obtained for Slr1393g3. Subsequently, we have computed UV/Vis and CD spectra to analyze how the different conformations can be analyzed spectroscopically.

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Correlated motions in Deinococcus Radiodurans bacteriophytochrome photosensory domain

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Phytochromes are biological photoreceptors found in all kingdoms of life. Numerous physical chemical and spectroscopic studies of phytochromes have been carried out for many decades, both experimentally and computationally, with main focus on the photoconversion mechanism involving the tetrapyrrole chromophore. In this computational work we concentrate on large scale dynamic motion of the photosensory domain of Deinococcus Radiodurans by means of classical all-atoms molecular dynamic (MD) simulations. Conventional- and accelerated- MD methods in combination with two different force fields, CHARMM27 and AMBER ff14SB were tested on long simulations to confront the dynamic of monomer- and dimer forms. These calculations highlight dissimilar equilibrium conformations in aqueous solutions and, in turn, different large scale dynamic behaviour of monomer form vs dimer. While phytochrome monomer tends to close the cavity entailed between GAF- and PHY- domains, the opposite trend is predicted for phytochrome dimer which opens up as consequence of the formation of strong salt bridges between PHY-domains of two molecules in water.

A combined computational and crystallographic study of the early photochemical events in bacteriorhodopsin

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Bacteriorhodopsin (bR) is a trans-membrane protein, which was found in Halobacteria salinarum. It serves as a light-activated proton pump from the cell. It contains retinal chromophore covalently bound to Lys216 via Schiff base, which absorbs the photon of 2.17 eV (570 nm) energy and undergoes all-trans to 13-cis isomerization. After the primary event there is a series of conformational changes coupled with proton transfer reactions along different amino acids.

In present work we are focused on the first events of the photocycle which take place within 1 ps after photoexcitation. The time-resolved serial femtosecond crystallography (TR-SFX) was utilized to study the ultrafast structural changes of a protein and a series of structural snapshots was collected. Nevertheless, the TR-SFX technique measures the electron density, so the structural refinement is necessary but even the use of the excited state geometry parameters might significantly deviate from the real one.

To overcome the limitation of the experiment we employed the high level computational chemistry techniques. Using the XMS-CASPT2 method we have obtained the early I, J, and K intermediates and each of them was characterized by computing the vertical absorption, fluorescence (for I intermediate) and excited-to-ground state electron density difference. The obtained results are in a good agreement with the experimental data and thus show a close interplay between theory and experiment.

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Involvment Of Triplet State In Retinal Isomerization

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The aim of this work is to study the involvement of a triplet state in the photoisomerization process of the retinal and its derivatives using quantum chemical calculations. This reaction is the initial step in the photocycle of rhodopsin. Three groups of analogous molecules that are related to the retinal were studied: protonated Schiff base (PSB), Schiff Base (i.e. non-protonated SB), and aldehydes. For each group, three models were investigated. These models had three, four and five double bonds, respectively.

First, the GS geometry and the excitation energies were computed to establish the relative order of the excited states. A broad range of ab initio quantum chemical methods (e.g. B3LYP, CAM-B3LYP, CC2, and XMS-CASPT2) were used for benchmarking. Subsequently, interpolated geometries between the Franck-Condon (FC) point and the point of minimum energy conical intersection (MECI) were obtained. The calculation of the energies was performed at the XMS-CASPT2 level of theory between the FC point and the MECI.

We concluded that the MECI¬ of S1/S0 (MECI¬1) of PSB models shift to higher energies when increasing the number of double bonds. The SB3 (i.e. SB with three double bonds) model showed that the S¬1 and T2 are nearly degenerated along the interpolation from MECI of S2/S1 (MECI2) to MECI1. The S0 and T¬1 state are also nearly degenerated along the latter interpolation. Moreover, for the SB3 model the S0, S1, T1, and T2 states are degenerated at MECI1. For the aldehyde with three double bonds (i.e. ALDE3) the interpolation from MECI2 to MECI1 revealed that the S1 and T2 evolve in parallel until the T1/T2 crossing after which the S1 follows T1 until the MECI1. At the MECI1 of ALDE3 the S1 and T1 have different character which makes the transition to the triplet state most probable compared to all models we've studied. Hence, we conclude that the involvement of the triplet state in the photochemistry of PSB is negligible, while it is much higher for SB and ALDE by higher probability to facilitate a singlet-triplet crossing.

Chromophore-protein Interactions in Phytochromes: A Fragment Molecular Orbital Study

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The identification of key residues involved in chromophore-protein interactions provide valuable information for rationalizing the sequence of steps during complex biological reactions, such photoinduced reaction cycles responsible for activating the photocycle of biological photoreceptors1. Since electrostatic calculations based on molecular mechanics force field has been the most common approach for the identifying pair interactions within biological molecules, a significant number of molecular interactions cannot be explained because of their high complexity. An excellent alternative to overcome this issue is the Fragment Molecular Orbital (FMO) method2,3, which is one of the most efficient approaches for studying intermolecular interactions in large biomolecular systems. Herein, we have applied the FMO method to the Deinococcus radiodurans DrBphP phytochrome in the Pr state. Pair interaction energy decomposition analysis (PIEDA) was used to identify the nature and quantify the strength of the non-covalent interactions between chromophore and protein of the DrBphP phytochrome. FMO detected the pyrrole water, Asp207 and Glu27 as key residues for the stabilization of the pyrrole rings A, B, C and D of the BV-chromophore, by forming six H-bonds. Furthermore, the conserved Arg254 and His260 were also identified as key residues in the conformational stability of both propionic side chains B and C. Interestingly, new interactions were identified in the chromophore binding pocket, two non-classical H-bonds (CH/O interactions) between Asp207 and Tyr263 and a OH/π interaction between the hydroxyl of Tyr263 and ring D of the BV-chromophore, which might have photochemical relevance.

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The origin of heterogeneity in the red/green cyanobacteriochrome AnPixJg2

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Cyanobacteriochromes (CBCRs) are a recently discovered member of the phytochrome superfamily1. Like phytochromes they bind a linear tetrapyrrole as a chromophore but in contrast, CBCRs require only the GAF domain for their function. CBCRs also have a more diverse spectral tuning that covers the entire visible spectrum. There are at least four different sub-families known in CBCRs out of which the red/green CBCRs have a red-absorbing reactant and a green-absorbing photoproduct. We have carried out classical molecular dynamics (MD) simulations of AnPixJg2 in the red-absorbing form. In the simulations we have considered a histidine residue (H322), that is conserved among red/green CBCRs and is critical for the chromophore binding2, in two different protonation states. These are the neutral, singly protonated state (SPH model) and the charged, doubly protonated state (DPH model)3. In the DPH model, PCB is found to be structurally heterogeneous exhibiting two distinct sub-states in contrast to the SPH model where PCB is homogeneous. We carried out umbrella sampling MD simulations to explore the origin of this different behavior. These simulations have revealed that the energy barrier between the two sub-states in the DPH model is lower compared to the SPH model. The symmetry-adapted perturbation theory (SAPT0) calculations show that three important structural factors are critical for the transition between the two sub-states: histidine-water, tryptophan flexibility and tyrosine hydrogen bonding. Based on hybrid quantum mechanics/molecular mechanics (QM/MM) calculations of spectroscopic properties4, we have shown that the two sub-states cannot be distinguished based on UV/Vis absorption spectra but exhibit distinct features in CD spectra.

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Understanding Spectral Tuning of Chlorophylls by Protein using QM/MM Calculations

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The spectroscopic changes between the inactive and active forms of a Bacteriophytochrome: An integrated MD and QM/MMPol study

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Phytochromes are multidomain photoreceptors that reversibly interconvert between a biologically active and inactive form of a photosensory module by absorbing far-red/red light. In this work we focus on the changes seen in the absorption spectra of the two forms of the Deinococcus radiodurans phytochrome assembled with its tetrapyrrole chromophore biliverdin. The computational strategy integrates classical molecular dynamics with a polarizable quantum/molecular mechanics (QM/MMPol) description. This strategy allows us to investigate the correlation of the torsional degrees of freedom of the chromophore with position and shape of the absorption bands and to quantify the role of the several H-bonds connecting the chromophore within the protein pocket in stabilizing its different conformations in the active and inactive form.

Understanding the Red-Shifted Variants of Green-Light-Absorbing Proteorhodopsin

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Engineering red-shifted rhodopsins is a major focus of a research line to improve their utilization as tools in optogenetics. Red light has the advantage of reducing the absorption by the tissue. Recently, a strategy of combining site-specific mutagenesis and analogs of retinal has resulted in a strongly shifted absorption maximum at 740 〖nm〗^([1]) in a green-absorbing Proteorhodopsin. Green-absorbing Proteorhodopsin is a light sensitive transmembrane protein that acts as a proton pump and is a member the rhodopsin

protein family. It carries a retinal as its chromophore, that can be activated by absorbing light of the green wavelength. To understand these effects, we performed quantum calculations of the excitation energies of the gas phase of retinal and its four analogs A2 (all-trans-3,4-dehydroretinal), MOA2 (all-trans-3-methoxy-3,4-dehydroretinal), DMAR (all-trans-3-dimethylamino-16-nor-1,2,3,4-didehydroretinal) and MMAR (all-trans-3-methylamino-16-nor-1,2,3,4-didehydroretinal) that are mainly modified in the beta ionone ring. The obtained results were correlated with experimental absorption spectra. Further, we have analyzed the ground and excited state wave function to rationalize the origin of the large red shift.

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Finding multiple pathways and free energies of complex biomolecular transitions via enhanced simulation

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On the role of protein environment in the excited state dynamics of the green absorbing proteorhodopsin

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The primary photochemical reaction of the green absorbing Proteorhodopsin is investigated by means of a hybrid quantum mechanics/molecular mechanics (QM/MM) approach. The homology model for the green absorbing Proteorhodopsin was derived from the crystal structure of blue-absorbing variant.1

The nonadiabatic molecular dynamics was initiated from sampling 100 initial conditions from the ground state trajectories. We have analyzed the resulting nonadiabatic trajectories within 1 ps of simulation time. The photoisomerization of the GPR occurs through a highly specific path in which the S1 to S0 population transfer is achieved by the torsion around C13=C14 bond. The photoisomerization quantum yield from trans to cis isomer is found to be 0.59 which is in very good agreement with the experimental

yield of 0.65 at the alkaline medium. The excited state population shows a time constant of 239 fs (for the trajectories that hopped to the S0 state) compared to the experimental value of 300 fs.

All these calculations were carried out by keeping the binding pocket relaxed around 5 Å from the retinal chromophore. We have tested the effect of constrained protein environment by fixing the amino acids of the binding pocket in space. In this case the C13=C14 rotation leads the retinal out of the FC region until the S1-S0 transition occurs within 200 fs.2 An "aborted bicycle pedal" mechanism of isomerization was observed involving a concerted rotation about C13=C14 and C15=N, with the latter being highly twisted but not isomerized. Further, the simulation showed an increased steric interaction between the hydrogen at the C14 of the isomerizing bond and the hydroxyl group at the neighbouring tyrosine Y200. Our simulations indicate that the retinal-Y200 interaction plays an important role in the overall outcome of the photoisomerization.

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Spectroscopic Properties of ChR-2 and LH Complexes: QM/MM Study and Benchmark of LC-TD-DFTB

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