# Program

**Thursday June 23**

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<th>Session</th>
<th>Speaker</th>
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<tr>
<td>12:00-13:00</td>
<td>Registration &amp; Welcome coffee</td>
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<tr>
<td>13:00-13:10</td>
<td>Welcome</td>
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<tr>
<td>13:10-13:40</td>
<td>Session 1: Recent Methodological Developments</td>
<td>Johan Åqvist</td>
<td>TBA</td>
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<tr>
<td>13:40-14:20</td>
<td>Markus Meuwly</td>
<td>Multi-surface adiabatic reactive MD for reactions in the gas- and condensed-phase</td>
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<tr>
<td>14:20-14:50</td>
<td>Andrei Tchougreveff</td>
<td>Deductive molecular mechanics and new concept of semi-empirism: Rational path to efficient models of complex molecules and processes</td>
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<td>14:50-15:20</td>
<td>Coffee Break</td>
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**Session 2: Reaction Dynamics**

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<tr>
<td>15:20-16:00</td>
<td>David Glowacki</td>
<td>A parallel multi-state EVB framework for investigation non-equilibrium reaction dynamics</td>
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<tr>
<td>16:00-16:30</td>
<td>Julian Garrec</td>
<td>Proposing innovative ways to teach and learn molecular modeling</td>
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<tr>
<td>16:30-17:00</td>
<td>Carine Clavaguera</td>
<td>Empirical valence-bond models based on polarizable force fields for infrared spectroscopy</td>
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<tr>
<td>17:00-17:30</td>
<td>Stefan Knippenberg</td>
<td>Probing membrane phases with fluorescent dyes</td>
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**Friday June 24**

**Session 3: Enzyme Catalysis I**

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<tr>
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<tr>
<td>09:00-09:40</td>
<td>Avital Shurki</td>
<td>Valence bond and enzyme catalysis: A time to breakdown and a time to buildup</td>
</tr>
<tr>
<td>09:40-10:20</td>
<td>Bjorn Olav Brandsdal</td>
<td>Evolutionary tuning of protein surface rigidity optimizes the activation enthalpy-entropy balance</td>
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<tr>
<td>10:20-10:40</td>
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<td>Break</td>
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**Session 4: Enzyme Catalysis II**

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<tr>
<th>Time</th>
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<tbody>
<tr>
<td>10:40-11:20</td>
<td>Robert Vianello</td>
<td>The selectivity and catalytic mechanism of monoamine oxidase enzymes from multiscale computational simulations</td>
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<tr>
<td>11:20-12:00</td>
<td>Janez Mavri</td>
<td>EVB simulation of monoamine oxidases catalyzed decomposition of biogenic amines</td>
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<tr>
<td>12:00-12:30</td>
<td>Anna Pabis</td>
<td>Probing the metal ion-dependent specificity patterns in methyl parathion hydrolase</td>
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<tr>
<td>12:30-13:40</td>
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<td>Lunch</td>
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**Session 5: Valence Bond and QM/MM Studies**

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<tr>
<th>Time</th>
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<tr>
<td>13:40-14:20</td>
<td>Sason Shaik</td>
<td>Valence bond - What an insightful theory it is!</td>
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<tr>
<td>14:20-15:00</td>
<td>Benoit Braida</td>
<td>A classical valence bond model for electron-rich hypervalent species</td>
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<tr>
<td>15:00-15:30</td>
<td>Etienne Derat</td>
<td>Some insights on three examples of photoredox catalysis</td>
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<td>15:30-16:00</td>
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<td>Break</td>
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**Session 6: Biological Processes I**

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<tr>
<th>Time</th>
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<tr>
<td>16:00-16:30</td>
<td>Fernanda Duarte</td>
<td>Exploring (bio)chemical systems using the EVB approach and other chemical tools</td>
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<tr>
<td>16:30-17:00</td>
<td>Ferran Feixas</td>
<td>Enhancing conformational sampling with accelerated molecular dynamics</td>
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<td>17:00-17:30</td>
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<td>Poster Pitches</td>
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<td>17:30-19:00</td>
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<td>Poster Presentation &amp; Mingle</td>
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**Saturday June 25**

### Session 7: Molecular System

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<tr>
<td>09:00-09:30</td>
<td>Marcel Swart</td>
<td>The role of spin states in the catalytic mechanism of intra- and extradiol cleavage of catechols</td>
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<tr>
<td>09:30-10:10</td>
<td>Collin Wick</td>
<td>Polarizable empirical valence bond models for acids and bases at interfaces</td>
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<td>10:10-10:30</td>
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<td>Break</td>
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### Session 8: Biological Processes II

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<tr>
<th>Time</th>
<th>Speaker</th>
<th>Title</th>
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<tr>
<td>10:30-11:10</td>
<td>Sharon Hammes-Schiffer</td>
<td>Theory of proton-coupled electron transfer</td>
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<td>11:10-11:40</td>
<td>Hanwool Yoon</td>
<td>The control of the discrimination between dNTP and rNTP in DNA and RNA polymerase</td>
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<tr>
<td>11:40-12:10</td>
<td>Nicholas Bhattacharjee</td>
<td>Hybrid potential simulation of the acylation of <em>enterococcus faecium</em> L,D-transpeptidase by carbapenems</td>
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<tr>
<td>12:10-12:30</td>
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<td>Closing Remarks</td>
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<td>12:30-14:00</td>
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<td>Lunch</td>
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*Each invited (I) talk is schedule for 40minutes; contributed (C) talks are scheduled for 30nmins including Q &A.*
Oral Presentations
I1. Entropy and Enzyme Catalysis

Johan Äqvist

Department of Cell and Molecular Biology, Uppsala University

The speed of chemical reactions in water and in enzymes varies with temperature, depending on how the free energy of activation is partitioned into enthalpy and entropy. In enzymes, this partitioning is also optimized as a consequence of the organism's adaptation to the environment. We will show how the temperature dependence of chemical reaction rates can be obtained from brute force computer simulations. Such calculations shed new light on how protein structures have evolved in differently adapted species.
I2. Multi-Surface Adiabatic Reactive MD for Reactions in the Gas- and Condensed-Phase

Markus Meuwly

\(^1\)University of Basel

Following chemical reactions at atomic resolution is one of the formidable challenges in physical chemistry. Realistic computer modeling of such events requires means to follow bond-breaking and bond-formation based on high-quality representations of the reaction energetics. In my talk I will discuss our approach to address this problem. Examples ranging from three-atom reactions at high temperatures to ligand binding reactions in proteins will be presented and the insights into atomistic details of the reactions will be discussed.

References


C1. Deductive Molecular Mechanics and New Concept of Semi-Empirism: Rational Path to Efficient Models of Complex Molecules and Processes

Andrei Tchougréeff

1 IAC RWTH Aachen Germany/Chem. Dept., MSU Russia

Contemporary quantum chemistry is obsessed by «monistic machinism» - the idea that all molecules and chemical events has to be calculated by one big program in a single approximation valid for all times and nations. No other idea is more uncongenial for chemistry than this due to enormous diversity of physical conditions occurring in different molecules or in different parts of one molecule. It is not even clear how such an immature idea could come to the clever heads of the leaders of the scientific public opinion. Even in those cases when the differences between the parts of a molecular system is recognized they are totally irrelevantly formulated as "interesting" and "uninteresting". By contrast our vision of segmentation of a molecular system is based on analysis of physical conditions as manifested through the localization of spectral and chemical events: transitions between electronic states occur in chromophores; respectively, only one or two bonds are broken or formed at once. This chemical picture has no counterpart in contemporary quantum chemistry paradigm reducing to a sequential addition of corrections to Hartree-Fock approximation having by itself quite a limited chemical relevance. Pushing off from this we in last years developed a new concept of semi-empirism in quantum chemistry based on the idea of chromophores formalized by McWeeny's group functions and the Löwdin partition technique employed to treat the boundary conditions between the groups. The efficiency of the numerical tools based on this concept is reached by targeting each method to a specific class of problems or objects in contrast with “universal” and thus inefficient methods. Each targeted code is based on singling out chromophores characteristic for a target class of molecules and applying methods of problem solving relevant for each chromophore. Methods developed along these lines include:

- ECF - effective crystal field method for analysis of electronic structure and spectra of transition metal complexes;
- SLG - linear growth group of methods for analysis of electronic structure, heats of formation, geometry, and ionization potentials of organic molecules;
- CATALYST - implementation of the effective Hamiltonian method for analysis of electronic structure of catalytic transition metal complexes;
- ECFMM - hybrid QM/MM method for analysis of PES of transition metal complexes;
- DMM - sequential derivation of classical model of PES for organic molecules and QM/MM interfaces.

These methods have been extensively tested on objects which due to their complexity or size could not be studied by standard QM or MM methods. Publications on the methods and application examples are available at http://www.qcc.ru/tch. The computer codes can be used through the NetLaboratory portal at http://www.qcc.ru/netlab. Examples of their applications will be given.
I3. A Parallel Multi-State EVB framework for Investigation of Non-Equilibrium Reaction Dynamics

David Glowacki\textsuperscript{1,2}

\textsuperscript{1} School of Chemistry, University of Bristol, Bristol, BS8 1TS, UK, \textsuperscript{2} Department of Computer Science, University of Bristol, BS8 1UB, UK

Over the past few years, we have been developing efficient parallel software frameworks designed to simulate non-equilibrium chemical reaction dynamics in condensed systems. Exploiting modern parallel computational architectures, these methods utilize an MPI-parallelized linear-scaling computational framework which is able to implement arbitrarily large multi-state empirical valence bond (MS-EVB) calculations within commonly used molecular dynamics packages, including both CHARMM and TINKER. Forces are obtained using the Hellmann-Feynman relationship, giving continuous gradients and good energy conservation even for systems which include very large coupling matrices. Utilizing multi-dimensional Gaussian coupling elements fit to electronic structure theory results (including explicitly correlated coupled cluster theory), we are able to construct reactive potential energy surfaces whose balanced accuracy and efficiency considerably surpass what we could achieve otherwise.

These methods have found application in atomistic studies of fundamental non-equilibrium chemical reaction dynamics occurring in liquids, and have shed light on a number of interesting chemical phenomena, including: (a) vibrational energy deposition in typical organic solvents [1-2]; (b) ultrafast energy flow and transient spectroscopy in the immediate aftermath of a chemical reaction [3], and (c) the interplay between microsolvation dynamics and chemical reaction dynamics [4-5]. In this talk, I will outline some of the applications that we have tackled using this framework, and the microscopic insight which these MS-EVB studies have been able to provide. If time allows, I will also discuss two pieces of new work, where: (1) we have begun to apply these methods to understand how conformational dynamics impact proton transfer in the aromatic amine dehydrogenase enzyme; and (2) we have implemented GPU-accelerated MS-EVB models that allow researchers to explore real-time reaction dynamics from within new classes of virtual reality frameworks.

References


C2. Proposing Innovative Ways to Teach and Learn Molecular Modeling

Julian Garrec

ENSTA PariTech

The dominating route that is traditionally taken to teach molecular modeling is a Cartesian approach (in the sense of the René Descartes philosophy) in which the intrinsically complicated molecular problem is split into several simpler parts that must be analyzed in details and independently before merging the resulting pictures into a unified one. More specifically, this conceptual splitting takes the following form in many popular textbooks [1]:

0. State that the central object of the study is the molecule "of interest" (which can be, e.g., an organic molecule) and define the corresponding molecular Hamiltonian.

1. Introduce the Born-Oppenheimer approximation and stress that the first thing that one must understand is the quantum behavior of the electron cloud in the molecule, through the molecular orbital (MO) picture.

2. Study the effect of nuclei motion with, e.g., molecular dynamics (MD) simulations.

3. Introduce the effects of the environment (which is typically the solvent in the example given in stage 0).

While this approach provides a solid overview of many aspects of molecular physics, its main disadvantage is that students must digest an avalanche of concepts, approximations and methods before being able to perform their first actual modeling with a computer program. For instance, the presentation of the Hartree-Fock theory, which is considered as the corner stone of MO-based electronic structure calculations (stage 1 above) takes > 200 pages in the book of Szabo and Ostlund [2]. Another possible problem is that it might put too much relative emphasis on electronic structure with respect to configuration sampling. It turns out, however, that the best strategy to tackle the complexity of molecular systems is to design models that include all the aspects of the problem in a simplified manner, instead of treating very accurately only a given part of the problem while neglecting the other aspects [3]. A final problem is that, nowadays, science is spreading other unprecedented number of subdisciplines. Students typically need to explore a wider spectrum of fields in a restricted timeframe. In that context, teaching must be made in the most efficient manner, in such a way that students can learn more and faster.

Interestingly, a recent study suggests that students tend to assimilate molecular physics much faster (and with much more enthusiasm!) if they have already manipulated 3D representations of molecules with dedicated visualization programs, in a hands-on style of learning [4]. In our engineering school, we have designed a new molecular modeling course at the master level that tries to take advantage of this spirit. Through the visualization of MD trajectories of various systems including organic molecules, materials and biological systems, this approach helps to stress from the very first lecture that molecular systems in general should be regarded as N-atom
subsystems embedded in much larger subsystems (that play the role of thermostats), and that this system as a whole is intrinsically dynamic in nature. The concept of a potential energy surface is introduced in an intuitive manner using the force field method (which fits more naturally with the common idea of molecules being made of bonded atoms). It is then easier, in the subsequent lectures, to suggest possible improvement of the model, e.g., by means of advanced electronic structure techniques.

References


C3. Empirical Valence-Bond Models Based on Polarizable Force Fields for Infrared Spectroscopy

Carine Clavaguera¹, Florian Thaunay¹, Florent Calvo², Gilles Ohanessian¹

¹ CNRS and Ecole Polytechnique, ² Université Grenoble I and CNRS

A two-state EVB model has been developed to assist the interpretation of infrared spectra of gas-phase biomolecules. The model has been combined with the AMOEBA polarizable force field [1,2]. Thanks to an accurate treatment of electrostatic interactions and the explicit inclusion of polarization effects, this force field provides a high sensitivity to the chemical environment. By incorporating to AMOEBA the possibility of intramolecular proton transfers through the EVB approach, we evaluate the spectroscopic signatures of such a reactive process. For this purpose, finite temperature IR spectra are obtained from molecular dynamics simulations to include anharmonicity and dynamics effects [3]. The aspartate amino acid, for which experimental measurements are available, is taken as a first example. The EVB-AMOEBA reactive force field appears capable of reproducing the experimental spectrum. The dynamical picture of the proton migration is analyzed in detail as a function of temperature. Other examples of proton sharing between carboxylate groups are also discussed.

References

C4. Probing membrane phases with fluorescent dyes

Stefan Knippenberg, G. Fabre, P. Trouillas, M. Ameloot, S. Osella, H. Ågren, N. A. Murugan

KTH Royal Institute of Technology, LCSN – EA1069, Faculté de Pharmacie, Université de Limoges, France, UMR 850 INSERM, Faculté de Pharmacie, Université de Limoges, France, Regional Centre of Advanced Technologies and Materials, Palacký University, Olomouc, Czech Republic, Biomedical Research Institute, Hasselt University, Belgium

A new BODIPY-based membrane probe (BNP) [1] is described and is compared to the commercially available DiI-C18 one. The latter one can be excited in the red spectral region, while the previous one can be pinpointed to the blue part. Molecular dynamics simulations of BNP in a model of the DOPC bilayer indicate that the average angle of the transition moments with respect to the membrane normal is ca. 70°, which is comparable with the value reported for DiI-C18. The directions of the absorption and emission transition dipole moments of BNP are calculated to be parallel, which is experimentally reflected in the high steady-state fluorescence anisotropy.

Probe BNP partitions in the same lipid phase as DiI-C18(5) for lipid mixtures containing sphingomyelin and for binary mixtures of DPPC and DOPC (dipalmitoyl and dioleoyl phosphatidylcholine, respectively). In the literature however, no unambiguous answer is available about the nature of the preferred phase, which is highly determined by the chosen concentration of the various lipids [2]. To investigate it, Gibbs free energy profiles are calculated for both compounds by means of Gromacs, the 43A1-S3 force field and the Z-constrained method. The liquid disordered (Ld) phase of DOPC at room temperature is considered, as well as the gel (S0) phase and Ld phases of DPPC at 298 K and 323 K, respectively, and the liquid ordered (Lo) phase of a 2:1 mixture of Sphingomyelin and Cholesterol at room temperature.

Other fluorescent markers, which are investigated in our group, are Laurdan (6-lauroyl-2-(N,N-dimethylamino)naphthalene), and its new derivative, C-laurdan (6-dodecanoyl-2-[N-methyl-N-(carboxymethyl)amino]-naphthalene), which have been put in a DOPC lipid bilayer. The latter probe is known to have a higher sensitivity to the membrane polarity at the lipid head-group region and has higher water solubility [3]. To investigate the influence of the different phases on the (non-) linear absorption spectra of the fluorescent probes, benchmark calculations are currently performed using CC2 and higher order ADC methodologies. Comparison is made with TDDFT and diverse functionals. An elaborated set of snapshots are selected per membrane phase to perform polarizable embedding QM/MM calculations using the Dalton package of programs.

References:
I4. Valence Bond and Enzyme Catalysis: A Time to Breakdown and a Time to Buildup

Avital Shurki1, V. Rajapandian1, A. Shrir-Ivry1

1Institute for Drug Research, School of Pharmacy, The Lise Meitner-Minerva Center for Computational Quantum Chemistry, The Hebrew University of Jerusalem, Jerusalem 91120, Israel

Understanding enzyme catalysis and developing ability to control it, is one of the greatest challenges of biochemistry to date. Few successful examples of computational based enzyme design proved the fantastic potential of computational approaches in this field. Yet, relatively modest rate enhancements were reported and further development of complementary methods is still required. The significant progress of the VB methodology within 21st century enabled, in turn, great progress within the field of enzyme catalysis [1,2]. Our work offers a conceptually simple scheme to identify the specific role that each residue within the enzyme, plays in catalysis. The scheme is based on breakdown of the total catalytic effect into contributions of individual protein residues, which are further decomposed into chemically interpretable components, using valence bond theory. The scheme will be demonstrated. It will be shown to shed light on the origin of catalysis in wild-type haloalkane dehalogenase (wt-DhIA) and its mutants. Furthermore, a set of simple rules to select non-optimal sites for catalysis will be given, and choice of effective mutations to enhance the enzymatic rate will follow.

References

I5. Evolutionary Tuning of Protein Surface Rigidity Optimizes the Activation Enthalpy-Entropy Balance

Bjørn Olav Brandsdal

University of Tromsø

Faced with an exponential decrease in chemical reaction rates as the temperature is lowered, cold-adapted organisms require specialized enzymes to maintain a functional metabolism. Cold-active enzymes catalyze their reactions with lower activation enthalpies counterbalanced by more negative activation entropies, yielding higher rates at low temperatures compared to mesophilic enzymes, although the rates at room temperature are often similar. The structural mechanisms behind this universal property still remain largely unknown. We attack this problem with extensive computer simulations and high precision Arrhenius plots, showing that the protein surface rigidity outside the active site region tunes the enthalpy-entropy balance. This enables significantly higher rates at low to moderate temperatures for cold-active enzymes compared to their warm-active counterparts.
I6. The selectivity and catalytic mechanism of monoamine oxidase enzymes from multiscale computational simulations

Robert Vianello

Computational Chemistry and Biochemistry Group, Ruđer Bošković Institute, Zagreb, Croatia,

Monoamine oxidase (MAO) is an FAD-dependent flavoenzyme responsible for regulating levels of a broad range of biogenic amines in various parts of brain by metabolizing them to the corresponding imines. Insufficient levels of amine neurotransmitters, such as dopamine and serotonin, have been associated with the progression of many neurological diseases including Parkinson, Alzheimer and Huntington disease, and several forms of depression. That is why MAO has been a drug target for over 60 years, with the primary rationale of developing drugs to treat neuropsychiatric disorders.[1] Still, despite decades of extensive research, the precise molecular mechanisms of neither the catalytic activity nor the irreversible inhibition of MAO have yet been unambiguously determined.

On the basis of quantum chemical calculations within the cluster model and QM/MM simulations within the Empirical Valence Bond (EVB) formalism, we have proposed a new two-step hydride mechanism for the MAO-catalyzed oxidative deamination of amines (Scheme 1),[2] and have demonstrated that it is in agreement with all available experimental data. Calculations of the pKₐ values of three tyrosine residues[3] revealed that MAO active site is very hydrophilic, but turns hydrophobic upon the substrate entrance, which binds in the monocationic form. MAO selectivity has been investigated in the case of neurotransmitter histamine, which is not a physiological MAO substrate, but is efficiently metabolized by MAO upon the N-methylation of the imidazole ring by histamine N-methyltransferase. This fact raises a very important and intriguing question: for a promiscuous enzyme such as MAO, what is the origin of its unexpected selectivity towards two very similar compounds, yet completely identical in their reactive ethylamine chain parts? In the present work we utilized a combination of molecular dynamics simulations, MM-PBSA binding free energy calculations, and QM and EVB QM/MM simulations to address the MAO specificity with two substrates, histamine and N-methylhistamine, differing only in a single methyl group far away from the reactive centre.

Scheme 1. Two-step mechanism for the MAO catalyzed amine degradation

All these details should aid in designing novel MAO inhibitors as transition state analogues or in further optimization of current drugs that should both lead to more efficient antidepressants and antiparkinsonian drugs.
References


I7. EVB Simulation of Monoamine Oxidases Catalyzed Decomposition of Biogenic Amines

Matej Repič¹, Matic Poberžnik¹, Robert Vianello², Miha Purg³, Fernanda Duarte⁷, Paul Bauer³, S.C. Lynn Kamerlin⁵, Matic Pavlin⁴, Jernej Stare¹, Gabriel Oanca¹, Zhen T. Chu⁵, Ricardo A. Matute⁵, Jean C. Shih⁶, Janez Mavri¹

¹National Institute of Chemistry, ²Ruder Bošković Institute, Bijenička cesta 54, HR–10000 Zagreb, Croatia, ³Department of Cell and Molecular Biology, Uppsala University, Uppsala Biomedical Centre, Uppsala, Sweden, ⁴German Research School for Simulation Sciences GmbH, Jülich, Germany, ⁵Department of Chemistry, University of Southern California, Los Angeles, USA, ⁶Department of Cell and Neurobiology, Keck School of Medicine, University of Southern California, Los Angeles, USA, ⁷Department of Chemistry, University of Oxford, UK

Monoamine oxidase (MAO), which exists in two isozymic forms, MAO A and MAO B, is an important flavoenzyme responsible for the metabolism of biogenic amines such as dopamine, serotonin and norepinephrine. In this work, we present atomic details of the rate-limiting step of dopamine degradation by MAO B, which consists of the hydride transfer from the methylene group of the substrate to the flavin moiety of the enzyme. This contribution builds on our previous quantum chemical study of the same reaction using a cluster model [1], but now considering the full dimensionality of the hydrated enzyme. Well-converged activation free energies were calculated by employing the empirical valence bond (EVB) approach of Warshel and coworkers [2]. We show that the MAO B enzyme is specifically tuned to catalyze the hydride transfer step from the substrate to the FAD prosthetic group and that it lowers the activation barrier by 12.1 kcal/mol compared to the same reaction in aqueous solution, a rate enhancement of more than 8 orders of magnitude [3]. The calculated barrier in the enzyme of 16.1 kcal/mol is in excellent agreement with the experimental value of 16.5 kcal/mol. Path integral calculation of H/D kinetic isotope effect for MAO B will be discussed [4]. Preliminary results for simulation of MAO A catalyzed decomposition of noradrenaline will be given [5] and the effects of MAO A point mutations on decomposition of phenylethylamine will be presented [6]. Relevance of MAO inhibition for prevention of neurodegeneration will be discussed [7].

Acknowledgments: M.R. and J.M. would like to thank the Slovenian Research Agency for financial support in the framework of the program group P1–0012. R.V. gratefully acknowledges the European Commission for an individual FP7 Marie Curie Career Integration Grant (contract number PCIG12–GA–2012–334493). S.C.L.K. would like to thank the Swedish research council (VR, grant 2010–5026) for funding this work. Support from the COST action CM1103 is gratefully acknowledged.

References:
Organophosphate hydrolases are a fascinating example of how even extremely diverse enzymes can acquire the same promiscuous function, which makes them very attractive model systems for studying evolution of enzyme function. Methyl parathion hydrolase (MPH) from the metallo-β-lactamase superfamily is a particularly interesting example of an organophosphatase that has evolved to efficiently hydrolyze a wide range of toxic anthropogenic organophosphates while retaining its presumably ancestral arylesterase and lactonase activities. Moreover, MPH shows interesting metal ion-dependent selectivity patterns, the origins of which still remain unclear. Here we employ empirical valence bond (EVB) approach to study the paraoxonase and arylesterase activities of MPH complexed with five different transition metal ions. We demonstrate that the hydrolysis of both substrates proceeds via nucleophilic attack of the terminal hydroxide ion, and the origin of the metal ion-dependent specificity patterns of MPH lies mainly in the distinct electrostatic properties of the metals, which results in slight changes in the substrate and transition state geometries observed for different metal ions. Despite being very subtle, these differences can play a role in determining metal ion-dependent activity patterns observed for MPH.

Benoît Braïda¹, Philippe C. Hiberty²

¹ Université Pierre et Marie Curie, ² Université Paris Sud

Some typical hypervalent molecules, XeF₂, SF₄, PF₅, and ClF₃, as well as precursors SF (⁴S⁻ state) and SF₂ (³B₁ state), are studied by means of the breathing-orbital valence bond (BOVB) method, chosen for its capability of combining compactness with accuracy of energetics. It comes out that the bonding mode of these hypervalent species and isoelectronic ones complies to Coulson’s version of the Rundle-Pimentel model, i.e. a description in terms of 4 classical VB structures which all have significant weights, but assisted by charge-shift bonding which act as the “glue” that makes these electron-rich hypervalent molecules stable. This model directly emerges from high-level BOVB calculations, thus ensuring correctness of the interpretations. Conditions for hypervalence to take place can directly be stated from this model.
I9. Valence Bond - What An Insightful Theory It Is!

Sason Shaik\(^1\)

\(^1\)Institute of Chemistry and the Lise Meitner-Minerva Center for Computational Quantum Chemistry, The Hebrew University, Jerusalem 91904, Israel

There are a few optional topics I may cover in this talk:

The Nature of the Halogen Bond [1].

H-Abstraction: From H\(_2\) to Cytochrome P450 [2].

Charge-Shift Bonding – A New Bonding Paradigm [3].

Bonding with Parallel Spins [4].

Oriented Electric Fields and Chemical Reactivity [5].

References


C6. Some Insights on Three Examples of Photoredox Catalysis

Etienne Derat

1Université Pierre et Marie Curie, Paris VI

Since ten years, photoredox catalysis has attracted more attention, in an attempt to mimick efficiently biochemical processes. With a first example based on palladium cross-coupling chemistry, I will show by computational means that the elementary steps are not the expected ones. The second part will demonstrate how silicates can be used in photoredox catalysis to generate masked primary radicals. To finish, a biomimetic system, able to generate H₂ by photocatalysis and imitating molybdopterin-based nitrite reductase, will be introduced. In these three cases, analysis of electron transfer will emphasize the role of weak interactions in the build-up of the system.

References


C7. Understanding Functional Evolution in the Alkaline Phosphatase Superfamily

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Catalytic promiscuity has been suggested to play an important role in the evolution of function within enzyme superfamilies. However, the precise molecular basis for such promiscuous activity remains poorly understood. Here we present a detailed computational study of two evolutionarily related members of the AP superfamily. Examination of transition state geometries and contribution of individual residues to the calculated barriers suggest that the broad promiscuity of these enzymes arises from cooperative electrostatic interactions in the active site, allowing each enzyme to adapt to the electrostatic needs of different substrates.
C8. Enhancing Conformational Sampling with Accelerated Molecular Dynamics

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Some important processes such as biomolecular recognition, allostERIC regulation, protein folding, or signal transduction, usually take place on the micro- to millisecond or even longer time scales. Low-energy states relevant for these processes may be separated by high-energy barriers, which are rarely crossed over the course of conventional molecular dynamics simulations. Accelerated molecular dynamics (aMD) enhances conformational sampling through modification of the system's Hamiltonian in a relatively simple way, it does not rely on the definition of a reaction coordinate or a set of collective variables (a priori knowledge of the underlying free energy landscape is not needed), and it conserves the essential details of the free-energy landscape [1-3]. Here we focus on the potential of aMD as a tool to efficiently explore the rough free energy landscape of proteins and its applications to: 1) the study of protein folding and metal directed protein folding; 2) the study of biomolecular recognition and protein dynamics in metalloproteins.

First, folding of four fast-folding proteins, including chignolin, Trp-cage, villin headpiece, WW domain, and a Zn folding peptide is simulated via aMD. Free energy profiles calculated through improved reweighting of the aMD simulations using cumulant expansion to the 2nd order are in good agreement with those obtained from conventional MD simulations. This allows us to identify distinct conformational states (e.g. unfolded and intermediate) other than the native structure and the protein folding energy barriers [4]. Second, the potential of aMD as a tool to efficiently explore the free energy landscape of (metallo)proteins and its applications to the study of biomolecular recognition will be highlighted. In particular, we will study the role of the Fe₄S₄ cluster in cytosolic aconitase. It is said that aconitase acts as a sensor of iron through a large conformational change associated with the assembly and disassembly of the Fe₄S₄ cluster.

References

C9. The Role of Spin States in the Catalytic Mechanism of Intra- and Extradial Cleavage of Catechols

Marcel Swart¹², D. Angelone², S. Stepanovic³, M. Gruden³

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Iron-dependent enzymes and biomimetic iron complexes can catalyze the ring cleavage of very inert, aromatic compounds. The mechanism of these transformations and the factors that lead either to extradiol or intradiol cleavage are not fully understood. By using Density Functional Theory we have elucidated [1] the mechanism of the catalytic cycle for two biomimetic complexes, and explained the difference in the experimentally obtained products [2].

Scheme 1. Reaction scheme for competing extra- and intradiol pathways

It is also shown that, although the sextet state is the ground state at the beginning and at the very end of the catalytic cycle, the quartet state governs the reaction and determines the product distribution.

Part of this work was supported by COST Action CM1305 (ECOSTBio), and financial support by ICREA, MICINN, MINECO and GenCat is gratefully acknowledged.

References


I10. Polarizable Empirical Valence Bond Models for Acids and Bases at Interfaces

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Understanding the behavior of acid dissociation, hydronium, and hydroxide ions in aqueous environments by itself is a significant challenge that is not fully understood. When an interface is present, though, these challenges are increased to an even greater degree. Having accurate descriptions of the interaction potentials between these and water, and the ions themselves is paramount for predicting reliable interfacial properties. The empirical valence bond method allows for the description of the sharing of charge between hydronium or hydroxide ions and neighboring water molecules to be included. However, the ability for dipole polarizability can play a major role in their behavior as well. This is especially relevant when anions are present, which have been found to behave significantly different at interfaces than in bulk phases. Even with the addition of many of these aspects, parameterizing accurate models can be a significant challenge, and strategies designed to best reproduce ab initio and experimental properties are important. In the contributed work, these challenges will be outlined and strategies for overcoming them will be presented. Furthermore, successes and failures in these strategies will be shared to show their abilities and limitations.
I11. Theory of Proton-Coupled Electron Transfer

Sharon Hammes-Schiffer

University of Illinois at Urbana-Champaign

Proton-coupled electron transfer (PCET) reactions play a vital role in a wide range of chemical and biological processes. This talk will focus on recent advances in the theory of PCET. In this theory, PCET reactions are described in terms of diabatic valence bond states associated with the transferring electron(s) and proton(s) localized on their donors or acceptors. This framework enables the description of both sequential and concerted mechanisms. The quantum mechanical effects of the active electrons and transferring proton(s), as well as the motion of the proton donor-acceptor mode and the reorganization of the solvent or protein environment, are included. The derivation of analytical rate constant expressions in well-defined limits enables the calculation of rate constants and kinetic isotope effects for comparison to experiment. Applications of this theory to PCET reactions in solution, enzymes, and electrochemical systems will be presented. Studies of the enzyme soybean lipoxygenase provide a physical explanation for the experimental observation of unusually high hydrogen/deuterium kinetic isotope effects of up to 700 for C-H bond activation at room temperature. Investigations of molecular electrocatalysts for hydrogen production identify the thermodynamically and kinetically favorable mechanisms and guide the theoretical design of more effective molecular electrocatalysts. These examples illustrate the ability of the PCET theory to assist in the interpretation of experimental data and provide experimentally testable predictions.
The control of the discrimination between dNTP and rNTP in DNA and RNA polymerase

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Understanding the origin of discrimination between rNTP and dNTP by DNA/RNA polymerases is important both for gaining fundamental knowledge on the corresponding systems and for advancing the design of specific drugs. This work explores the nature of this discrimination by systematic calculations of the transition state (TS) binding energy in RB69 DNA polymerase and T7 RNA polymerase. The calculations reproduced the observed trend, in particular when they explored the water contribution obtained by the water flooding approach. Our detailed study confirms the idea that the discrimination is due to the steric interaction between the 2’OH and Tyr416 in DNA polymerase, while the electrostatic interaction is the source of the discrimination in RNA polymerase.
C11. Hybrid Potential Simulation of the Acylation of Enterococcus faecium L,D-transpeptidase by Carbapenems

Nicholus Bhattacharjee\textsuperscript{1,2}, Martin J. Field\textsuperscript{3}, Jean-Pierre Simorre\textsuperscript{3}, Michel Arthur\textsuperscript{4}, Catherine M. Bougault\textsuperscript{1}

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The L,D-transpeptidases, Ldts, catalyze peptidoglycan cross-linking in β-lactam-resistant mutant strains of several bacteria, including Enterococcus faecium and Mycobacterium tuberculosis. Although unrelated to the essential D,D-transpeptidases, which are inactivated by the β-lactam antibiotics, they are nevertheless inhibited by the carbapenem antibiotics, making them potentially useful targets in the treatment of some important diseases. In this work, we have investigated the acylation mechanism of the Ldt from \textit{E. faecium} by the carbapenem, ertapenem, using computational techniques. We have employed molecular dynamics simulations in conjunction with QC/MM hybrid potential calculations to map out possible reaction paths. We have focused on determining: (i) the protonation state of the nucleophilic cysteine of the enzyme when it attacks; (ii) whether nucleophilic attack and β-lactam ring opening are concerted or stepwise, the latter occurring via an oxyanion intermediate; and (iii) the identities of the proton acceptors at the beginning and end of the reaction. Overall, we note that there is considerable plasticity in the mechanisms, owing to the significant exibility of the enzyme, but find that the preferred pathways are ones in which nucleophilic attack of cysteine thiolate is concerted with β-lactam ring opening.
Poster Presentations
P1. Automatic calibration for the Empirical Valence Bond model with more systemic approach

Hanwool Yoon\textsuperscript{1}, Arieh Warshel\textsuperscript{1}

\textsuperscript{1}University of Southern California

The empirical valence bond (EVB) model is one of the most powerful methods to study enzymatic reactions. However, it is often difficult to produce reliable results without very careful system adjustments and analysis. Especially, the reaction geometries between the water and protein simulation easily deviate from each other generating inconsistent results with major contributions from intramolecular energies rather than electrostatics. Thus, constraining the reaction fragments is often inevitable. The learning curve for adjusting proper constraints without changing the catalysis can be steep for the new user. Moreover, there is a possibility to obtain under/overestimated results by imposing such extra constraints. In this study, a more systemic approach is proposed in which the calibration step can be automatically but more reliably calculated. This approach was applied to RB69 DNA polymerase which show that the better results can be obtained with much less efforts.
P2. Cold Adaptation: An EVB Comparison of the Mesophilic and Psychrophilic EndA from *Vibrio Cholerae* and *Vibrio Salmonicida*

Davide Michetti\(^1\), Geir Villy Isaksen\(^1\), Bjørn Olav Bransdal\(^1\)

\(^1\)UiT The Arctic University of Norway

Enzymes from organisms living in cold temperatures (psychrophiles, temperature ranging between 15\(^\circ\) and -20\(^\circ\)C) show relative (sometimes even absolute) higher catalytic properties and lower thermostability than warm adapted homologs. Furthermore reactions catalyzed by psychrophilic enzymes generally have lower activation enthalpy and more negative activation entropy than mesophilic homologs. This is claimed to be a key feature of cold-adaptation, since it can prevent the exponential damping of the reaction rate at lower temperature. From a structural point of view adaptation to cold has been proposed to originate from higher flexibility. The structural determinants are though, at the present moment not completely understood.

The overall objective of the project is to explore the activity and stability of cold-active enzymes, using the Endonuclease A from the psychrophilic *Vibrio salmonicida* and mesophilic *Vibrio cholerae*, as a model. In a first stage, Molecular Dynamics will be employed to compare the flexibility and conformational space explored by VsEndA and VcEndA. General tools of MD will be employed to analyze the trajectories (overall RMSF and PCA) and to spot regions of difference between the two homologs. In parallel EVB will be employed to compare the reaction of the two enzymes, in particular deriving the thermodynamic parameters (activation enthalpy and entropy). In a second stage, guided by the previous analysis, we will choose mutations and test them in the EVB model to assess the effect on \(\Delta H^\ddagger\) and \(\Delta S^\ddagger\).
P3. Computational Assessment of the Strength of Sulfur Center Hydrogen Bond (SCHB) in Methionine Containing Tripeptides

V. Rao Mundlapati¹, Dipak Kumar Sahu¹, Deepak Senapati¹, Dr. Himansu S. Biswal¹

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Inter and intramolecular H-bonds in the backbone and side chains of the peptides are solely responsible to give specific three dimensional structures of peptides, more so of proteins. Many such H-bonds include amide-NH•••O, amide-NH•••N, and amide-NH•••π interactions. It has also been reported that sulfur atom of methionine and cysteine side chain can take part in the hydrogen bond (H bond) formation with the backbone amide-NH, known to be sulfur center hydrogen bond (SCHB) ¹⁶. This study is aimed to comprehensively characterize the strength of the SCHBs in different tripeptides (Ac-Met-xxx-NH₂ or Ac-xxx-Met-NH₂, where “xxx” is the three letter code of the amino acid). DFT methods (B97D/aug-cc-pVDZ) were used for geometry conformational exploration, geometry optimization, vibration frequency and stabilization energy calculation. In all the peptides methionine (Met) is found to interact effectively with the backbone amide of other amino acids (xxx) through amide-NH•••S H-bonds. The strength of (SCHB) H-bonding in different conformer was analyzed by Natural Bond Order (NBO) and Quantum Theory of Atoms in Molecules (QTAIM) methods. These analyses suggest that Ac-Gln-Met-NH₂ in Ac-xxx-Met-NH₂ sequence and Ac-Met-Glu-NH₂ in Ac-Met-xxx-NH₂ sequence are capable of forming very strong N-H•••S H-bonds comparable to that of conventional N-H•••O and N-H•••N H-bonds.

References


P4. DFT Studies on Phospholipids Mediated Decomposition of Hydrogen Peroxide

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Hydrogen peroxide plays a significant role in controlling certain cellular functions and its excess causes significant damage to biological systems. There is experimental evidence that its decomposition is accelerated above phospholipids membranes surface. We propose a mechanism for decomposition of hydrogen peroxide on amine-phospholipid surface model based in Dmol3/DFT calculations. The model was built using periodic boundary conditions. Each unit cell contains two phospholipids molecules, two hydrogen peroxide and nine water molecules. The reaction proceeds by a polar heterolytic mechanism, amine–phospholipids lead to the polarization of the –O–O– bond in hydrogen peroxide, which allows the nucleophilic attack of an oxygen atom of a second hydrogen peroxide molecule. Overall, two hydrogen peroxide molecules react in a bimolecular reaction to yield an oxygen molecule and two water: 2 H$_2$O$_2$ → O$_2$ + 2 H$_2$O. Our results show that can be hypothesized that cell membrane surface environment could enhance this reaction by a neighboring catalyst effect.
P5. Effect of D168V Mutation in NS3/4A HCV Protease on Susceptibility of Faldaprevir: MD and 3D-RISM-KH Approaches

Thanaya Rungrotmongkol¹, Arthitaya Meeprasert¹, Jiraphorn Phanich¹, Saree Phongphanphanee², Norio Yoshida³, Fumio Hirata⁴, Supot Hannongbua¹, Nawee Kungwan⁵

¹ Chulalongkorn University, ² Kasetsart University, ³ Kyushu University, ⁴ Ritsumeikan University, ⁵ Chiang Mai University

Hepatitis C virus (HCV) is a major cause of liver inflammation and cirrhosis, which may lead to liver cancer and death. It is well known that NS3/4A protease of HCV plays an important role in a replication process by cleaving the specific scissile peptide bonds between non-structural proteins. Thus, NS3/4A becomes one of the main protein targets for drug discovery and development of new anti-HCV agents. Up to date, several HCV inhibitors have been developed e.g. faldaprevir (FDV) in clinical trials that shows high inhibition efficacy against NS3/4A. Unfortunately, a high mutation rate in HCV and lacking of proofreading have caused a resistance to some NS3/4A inhibitors. Herein, MD simulation and 3D-RISM methods were applied in order to reveal the effect of D168V mutation towards the FDV susceptibility. From the MD results, it was found that the D168V mutation disrupted the hydrogen bonds network between Q80…R155…D168…R123 close to the drug binding site. Consequently, this mutant has led to a reduction in the MM/3D-RISM-KH binding free energy of ~45 kcal/mol relative to wild type.
P6. Interplay of Directing Effect of Substituents on Aromatic Ring and Spin Crossover in Imidazole-Diazine Fe(II)

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Spin crossover in transition metal complexes (TMC) is a multiplicity change of electronic states of the metal ions under external perturbation (e.g. a variation in temperature, pressure). The majority of so-called spin-active compounds exhibiting this phenomenon are based on Fe(II) and aromatic ligands with donor nitrogen atoms.

Theoretical organic chemistry says that substituents on the aromatic ring alter the reactivity of the ring positions due to the redistribution of the electron density in the $\pi$-system. One can expect similar changes in the complexing ability manifested by the strength of the crystal field induced by the ligands. Indeed, the alternation of the diazine moiety from pyrazine to pyrimidine in the TMC pair of type FeL\textsubscript{3} (L = 2-(1H-imidazole-2-yl)diazine) leads to variation of absorption spectra and appearance of spin transition at 100 K [1]. To study the influence of the non-coordinating nitrogen position in relation to the donor nitrogen atom on the spin crossover phenomenon we applied the effective Hamiltonian crystal field method (EHCF) [2]. We calculate dependence of the splitting parameter 10Dq from the distance between the iron ion and the donor nitrogen atoms.

Moreover, we obtain a slice of the potential energy surface using a simplified scheme of a hybrid approach ECF/MM that combines EHCF and molecular mechanics approaches [3]. It turned out that the positions of the singlet and quintet profile minima for the two studied complexes lie at approximately the same interatomic distances Fe–N. However, the difference between the minima energy, which is responsible for the spin crossover ability, is significantly less in the case of the TMC with a pyrimidine fragment. This result is in agreement with experiment. Obtained dependence of splitting parameter from the relative position of nitrogen atoms in the diazine moiety is compared with $e_\sigma$ parameters of the angular overlap model [4] and the charge on the donor atoms. The detailed mechanism of transfer of the inactive nitrogen atom influence on the donor atom is determined. This process includes the charge redistribution in the $\pi$-system of diazine fragment and the energy shift of $\sigma$-molecular orbitals, which leads to the observed alternation of $e_\sigma$ and 10Dq parameters.

References:


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The quest for understanding enzyme catalysis and how to use it has been one of the main goals for biocatalysis. Even though a large number of different theories have been proposed so far, a general model on how enzymes work is still lacking.

This becomes especially true for the study of reactions involving enantio- and/or regioselective reactions, where the differences in pathway energetics can be as small as a only a few kcal/mol and thus well below the error margin of the current models. As reactions involving chiral compounds are of major importance for the production of high value chiral chemicals, a better understanding on how enzymes can be used for this task could be of great importance.

The present work focuses on our studies involving the potato (Solanum tuberosum) epoxide hydrolase 1 (StEH1) and its reactions towards chiral phenyl substituted epoxides, using the empirical valance bond model developed by Warshel and coworkers. We show that the observed enantioconvergent behavior of the enzyme is influenced by the possibility to use different substrate binding modes, and that the enzyme uses residues outside of the first shell of the binding site for modulating the active site charge.
P8. Laninamivir Susceptibility in H7N9 Neuraminidase with R292K Mutation

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The novel H7N9 influenza A virus caused the outbreak of human infection in China in 2013 with 27% of deaths. This new virus occurred by the multiple reassortment of avian influenza viruses at least four origins including hemagglutinin subtype 7 (H7), neuraminidase subtype 9 (N9) and other gene segments from two different groups of avian H9N2 viruses. Neuraminidase inhibitors (NAIs), zanamivir, oseltamivir, peramivir and laninamivir, play a role for treatment this new virus. However, some new H7N9 strains consisted of R292K substitution after patients were treated with NAIs. The R292K mutation in H7N9 neuraminidase can reduce the NAIs susceptibility (extreme resistance to oseltamivir and peramivir with >1,000 fold and mild resistance to zanamivir and laninamivir with ~ 30-50 fold). Since the study of laninamivir is less than the other drugs, we aims to explore the source of its susceptibility due to R292K mutation in H7N9 neuraminidase using molecular dynamics. As a result of the R292K substitution, although the mutated K292 residue somewhat less stabilized the laninamivir binding, the other interactions were well maintained. The water oxygen distribution showed the reduction of dehydration penalty around drug suggesting a more solvent accessibility in neuraminidase binding pocket.
P9. Molecular Dynamics and QM/MM Investigations on a 2,3-Dioxygenase Metalloenzyme

Adrian Romero¹, Silvia Osuna¹, Ulf Ryde², Marcel Swart¹

¹ University of Girona, ² University of Lund

Quercetinase is an enzyme that catalyzes the degradation of quercetin and related flavonols to phenolic carboxylic acid ester and carbon monoxide. Only a few crystal structures have been solved for this enzyme, one of which has been achieved recently from Aspergillus japonicus. Given the dynamic nature of the active site, with the involvement of a flexible loop, it is not sufficient to study just one structure of the enzyme (e.g. the average reactant structure from the MD simulations from a previous study [1]), but one should take into account the effect of the flexible lid. Moreover, there are two different conformations for the metal coordination sphere within the enzyme, which are related to the protonation state of a key glutamate residue. The communication between the flexible lid, the (de)protonated glutamate residue, the metal and substrate, and the protein environment, and how this determines the catalytic activity, is poorly understood. Moreover, the selectivity for different substrates, the preference for copper, and how this comes about is another big unknown. In this study, we investigate which is the influence of the loop on the enzyme and the importance of the copper metal center for the enzyme reaction mechanism. In particular, we compare copper with iron and nickel, which are present in other related dioxygenases. We performed 200 ns MD simulations and QM/MM calculations using Cu¹⁻⁻, the metal in the native enzyme), Fe²⁺⁻⁻ and Ni²⁺. The calculations were done in the apo state considering different coordination spheres for the metal [2] in the substrate-bound state, and at the intermediate state that leads to the rate-determining transition state as suggested by Okumura and coworkers [3].

References


P10. Predictive Computational Studies of Structure and Catalytic Affinity in NADH-cytochrome b5 Reductase with Congenital Methemoglobinemia Associated Mutations

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1Chulalongkorn University, 2Prince of Songkla University

Cytochrome b5 reductase (b5R) catalyzes the transfer of reducing equivalents from NADH, via an FAD domain to the small protein of cytochrome b5 (b5). This process is involved in many oxidation and reduction reactions, such as the reduction of methemoglobin. The deficiency of b5R leads to an accumulation of methemoglobin concentration in blood, and is known as a rare blood disorder so-called recessive congenital methemoglobinemia (RCM). In fact, RCM disorder remains a challenge for molecular research due to its two distinct clinical types; RCM-type I and RCM-type II. To better understand and give a molecular visualization in the effect of missense mutation which render to two types of RCM, the MD simulations of eight b5R-b5 complexes; wild-type, RCM-type I (M176T, C203Y, V252M), RCM-type II (K110M S127P C203R R240G) were performed under the working condition (150 mM NaCl solution at 37 °C). With regard to prediction of the binding free energy for NADH-binding, all RCM-type I systems remain a consistence with that of wild-type, ranging from -59 to -70 kcal/mol. In RCM-type II mutants, the binding affinities for NADH have a significant drop, except S127P system as shown a gradual decreased in binding free energy. Moreover, the further distances between pair atom occurring a hydride transfer reaction were found in S127P, C203R and R241G, ranging from 7.12 to 7.47 Å, than one of the other systems, ranging from 3.28 to 3.43 Å. This seems to suggest that the enzyme activity was affected significantly due to these mutations. For structure similarity analysis, the further distances between pair atom occurring hydride transfer reaction in as a consequence of the rearrangement of the NADH-binding domain, which eventually render the nicotinamide ring moved away from FAD. Meanwhile, the position of isoallozazine ring was quite maintained during the simulation time. Taking into account, the obtained information may assist provide to deeply understand in the effect of point mutation which render to the methemoglobinemia.
P11. Proposing Innovative Ways to Teach and Learn Molecular Modeling

Julian Garrec

ENSTA Paritech

The dominating route that is traditionally taken to teach molecular modeling is a Cartesian approach (in the sense of the René Descartes philosophy) in which the intrinsically complicated molecular problem is split into several simpler parts that must be analyzed in details and independently before merging the resulting pictures into a unified one. More specifically, this conceptual splitting takes the following form in many popular textbooks [1]:

0. State that the central object of the study is the molecule "of interest" (which can be, e.g., an organic molecule) and define the corresponding molecular Hamiltonian.

1. Introduce the Born-Oppenheimer approximation and stress that the first thing that one must understand is the quantum behavior of the electron cloud in the molecule, through the molecular orbital (MO) picture.

2. Study the effect of nuclei motion with, e.g., molecular dynamics (MD) simulations.

3. Introduce the effects of the environment (which is typically the solvent in the example given in stage 0).

While this approach provides a solid overview of many aspects of molecular physics, its main disadvantage is that students must digest an avalanche of concepts, approximations and methods before being able to perform their first actual modeling with a computer program. For instance, the presentation of the Hartree-Fock theory, which is considered as the cornerstone of MO-based electronic structure calculations (stage 1 above) takes > 200 pages in the book of Szabo and Ostlund [2]. Another possible problem is that it might put too much relative emphasis on electronic structure with respect to configuration sampling. It turns out, however, that the best strategy to tackle the complexity of molecular systems is to design models that include all the aspects of the problem in a simplified manner, instead of treating very accurately only a given part of the problem while neglecting the other aspects [3]. A final problem is that, nowadays, science is spreading other unprecedented number of subdisciplines. Students typically need to explore a wider spectrum of fields in a restricted timeframe. In that context, teaching must be made in the most efficient manner, in such a way that students can learn more and faster.

Interestingly, a recent study suggests that students tend to assimilate molecular physics much faster (and with much more enthusiasm!) if they have already manipulated 3D representations of molecules with dedicated visualization programs, in a hands-on style of learning [4]. In our engineering school, we have designed a new molecular modeling course at the master level that tries to take advantage of this spirit. Through the visualization of MD trajectories of various systems including organic molecules, materials and biological systems, this approach helps to
stress from the very first lecture that molecular systems in general should be regarded as N-atom subsystems embedded in much larger subsystems (that play the role of thermostats), and that this system as a whole is intrinsically dynamic in nature. The concept of potential energy surface is introduced in an intuitive manner using the force field method (which fits more naturally with the common idea of molecules being made of bonded atoms). It is then easier, in the subsequent lectures, to suggest possible improvement of the model, e.g., by means of advanced electronic structure techniques.

References


P12. Proton Translocation in Cytochrome cbb3 Oxidase

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Cytochrome c oxidases (CcOs) are large membrane protein complexes found in bacteria and the mitochondria of eukaryotes. They catalyze the final step of aerobic respiration, namely the reduction of oxygen to water, in a biochemical process called oxidative phosphorylation. CcOs couple the redox energy generated during catalysis to the “uphill” proton pumping across the membrane, thus contributing to the establishment of an electrochemical gradient that is used for ATP synthesis. Our work focuses on the distinctive C-type CcOs, which are mostly present in Bacteria and exhibit a number of unique features such as high catalytic activities at low oxygen concentrations, and nitric oxide reduction activity under anaerobic conditions. It has been shown that such characteristics are essential for the colonization of anoxic tissues by some human pathogens (e.g. Campylobacter jejuni and Helicobacter pylori). At the moment, the functioning mechanism of C-type CcOs is still poorly understood.

In this work we performed EVB calculations to study the proton translocation pathways for both the “chemical” and “pumped” protons in a C-type CcO – cbb3 from Pseudomonas stutzeri [1]. Our results contribute to a better understanding of cbb3 mechanism and provide basis for future experimental and computational studies.

References

P13. Sulfur Bonds: Exploration of a Novel Non-Covalent Intermolecular Bond and Its Role in Drug Development

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According to recent drug development studies, unconventional non-covalent interactions utilizing a σ-hole have gained increased attention in medicinal chemistry. Sulfur, one of the most prominent atoms in pharmaceuticals and biologically active molecules, possesses these σ-hole formations which lead to non-covalent interactions similar to hydrogen bonding. Specifically, divalent sulfur atoms contain low lying sulfur σ* (antibonding) orbitals which are the foundation for the localized partial positive (i.e. σ-hole) regions that can interact with electron donating Lewis bases, such as oxygen and nitrogen, contained in the protein. The use of sulfur bonding and halogen bonding interactions are becoming key components in the lead optimization of top hits in the drug discovery process.
P14. The Role of Spin States in the Catalytic Mechanism of Intra- and Extradiol Cleavage of Catechols

Marcel Swart$^{1,2}$, D. Angelone$^2$, S. Stepanovic$^3$, M. Gruden$^3$

$^1$ICREA, $^2$Universitat de Girona, $^3$University of Belgrade

Iron-dependent enzymes and biomimetic iron complexes can catalyze the ring cleavage of very inert, aromatic compounds. The mechanism of these transformations and the factors that lead either to extradiol or intradiol cleavage are not fully understood. By using Density Functional Theory we have elucidated [1] the mechanism of the catalytic cycle for two biomimetic complexes, and explained the difference in the experimentally obtained products [2].

![Scheme 1](image)

**Scheme 1.** Reaction scheme for competing extra- and intradiol pathways

It is also shown that, although the sextet state is the ground state at the beginning and at the very end of the catalytic cycle, the quartet state governs the reaction and determines the product distribution.

Part of this work was supported by COST Action CM1305 (ECOSTBio), and financial support by ICREA, MICINN, MINECO and GenCat is gratefully acknowledged.


P15. Theoretical Study of Hydrophobic-Hydrophilic Ionic Liquids

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Hydrophobic-hydrophilic ionic liquids \cite{1} (HHILs) are the water insoluble ionic liquids (ILs) with high content of water. This unusual behavior of the HHILs provides the interest in theoretical study of the system «water-ionic liquid». In the literature it is believed that the abnormal high solubility of water in HHILs is connected with nanostructural organization in liquid phase. In our work we try to obtain theoretical evidences of this hypothesis.

Previous theoretical studies of ILs have showed that electrostatic interactions play the most important role in explanation of ionic liquids' physical properties. To obtain charge distribution of the molecules QM method which based on wave function representation as the antisymmetrized product of two-electronic strictly localized geminals \cite{2,3} was used.

Van-der-Waals interactions were taken into account by using Lennard-Jones potential in its classical form.

Monte-Carlo (MC) simulations were then used for modeling «trioctylmethylammonium salicylate (TOMAS)/water» and «tetraoctylammonium lauroyl sarcosinate (TOALS)/water» binary systems.

Some physical properties (mutual solubilities, densities, enthalpies of vaporization) and radial distributions functions for these systems were obtained.

References


Understanding the Comparative Molecular Field Analysis (CoMFA) in Terms of Molecular Quantum Similarity and DFT-Based Reactivity Descriptors

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The three-dimensional quantitative structure activity relationship (3D QSAR) models have many applications, although the inherent complexity to understand the results coming from 3D-QSAR arises the necessity of new insights in the interpretation of them. Hence, the quantum similarity field as well as reactivity descriptors based on the density functional theory were used in this work as a consistent approach to better understand the 3D-QSAR studies in drug design. For this purpose, the quantification of steric and electrostatic effects on a series of bicycle [4.1.0] heptane derivatives as melanin-concentrating hormone receptor 1 antagonists were performed on the basis of molecular quantum similarity measures. The maximum similarity superposition and the topo-geometrical superposition algorithms were used as molecular alignment methods to deal with the problem of relative molecular orientation in quantum similarity. In addition, a chemical reactivity analysis using global and local descriptors such as chemical hardness, softness, electrophilicity, and Fukui functions, was developed. Overall, our results suggest that the application of this methodology in drug design can be useful when the receptor is known or even unknown.
P17. Unveiling the Details of the Phosphoryl Transfer Mechanism in Cyclin-Dependent Kinases: Insights from QM/MM Calculations

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Protein kinases have become the second most important therapeutic target after G-protein-coupled receptors [1], therefore a complete understanding of the reaction mechanisms taking place in this protein family is desired. CDKs (Cyclin-Dependent Kinases) are crucial in the regulation of the eukaryotic cell cycle, and their misregulation has been connected to cancer [2]. However, despite the extensive research done on protein kinases, many aspects of the phosphoryl transfer mechanism are still unclear. One of them is whether the chemical transformation proceeds through a substrate-assisted or a base-assisted mechanism. In particular, in CDK2, the substrate-assisted mechanism involves a proton transfer reaction from a Serine residue to one of the oxygen atoms of the γ-phosphate; while in the base-assisted route, Asp127, a well-conserved residue in all kinases, assists deprotonation. Previous computational studies had suggested that the former mechanism would be preferred over the base-assisted pathway [3], however more recent studies have endorsed the second route [4]. By means of quantum mechanics/molecular mechanics (QM/MM) calculations at the B3LYP/6-31+G*:OPLS-2005 level, we have studied in detail the phosphoryl transfer reaction catalysed by CDK2. We found an important difference in the energy barriers for both reactions positioning the base-assisted mechanism as the most favourable route. Charge and bond order analysis, over the atoms of the active site, also gave us new insights into charge transfer processes taking place in the reaction and details into why the base-assisted pathway is preferred. In summary, our results are conclusive in favour of Asp127 acting as a general base for the catalysis. The potential energy profiles are being refined by a new implementation of the string method [5] to obtain free energy barriers also considering two Mg²⁺ cofactors in the active site. This protein aspect has not been computationally addressed before.

References


P18. Computational study of the substrate specificity of monoamine oxidase B

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Histamine plays an important role in the human body and is involved in more than twenty different physiological processes. Due to histamine potent physiological activity, its degradation has to be carefully regulated to avoid adverse reactions. The major routes of histamine inactivation in mammals include monoamine oxidase B (MAO B) and diamine oxidase (DAO) enzymes. The fact that MAO B metabolizes only N-methylhistamine while DAO prefers histamine¹–², pinpoints their remarkable selectivity towards two compounds that differ only in one methyl group. The mechanism of enzyme catalysis and specificity are usually elucidated from the differences in mechanistic aspects of enzymatic reactions for each possible substrate, which provide unambiguous quantitative information about the thermodynamics and the kinetics of reaction pathways. Unfortunately, mechanistic studies are not always experimentally approachable. Therefore, we utilized a combination of molecular dynamics (MD) simulations, MM-PBSA binding free energy analysis, quantum mechanical cluster approach and empirical valence bond QM/MM calculations to address the substrate specificity and mechanism of MAO B catalysis. We have identified favourable hydrophobic interactions between methyl group of the N-methylhistamine substrate and the hydrophobic side chains of the enzyme binding site that keep substrate anchored and properly oriented for the enzymatic reaction. Since histamine is deprived of a methyl group, it cannot be properly anchored and rotates within the active site, which results in non-productive orientation for the reaction. Quantum-chemical mechanistic analysis revealed higher activation parameters for histamine relative to its N-methyl counterpart, thus aiding in rationalizing the mentioned selectivity. Inspection of the calculated free-energy profiles convincingly shows that MAO B selectivity for the N-methylhistamine over histamine is a result of two synergistic effects: lower activation barrier and more favourable reaction thermodynamics. Moreover, reaction pathway obtained from QM calculations is consistent with recently proposed hydride mechanism of MAO B mechanism of catalysis³–⁴. EVB simulations of the rate-limiting hydride transfer step, including full enzyme structure and extensive thermal sampling, gave barriers of 16.2 and 17.9 kcal/mol for N-methylhistamine and histamine, respectively, thus putting our results in a firm agreement with experiments.

References
P19. Characterization of Metal Ion Binding to the Amyloid-β Peptide in Alzheimer’s Disease

Cecilia Wallin[1], Yashraj Kulkarni[2], Axel Abelein[1,3], Jüri Jarvet[1,4], Qinghua Liao[5], Birgit Strodel[5,6], Lisa Olsson[1], Jinghui Luo[1,7], Jan Pieter Abrahams[8,9], Sabrina B. Sholts[1,10], Per M. Roos[11,12], Shina C. L. Kamerlin[2], Astrid Gräslund[1] and Sebastian K. T. S. Wärmländer[1]


There is ever increasing evidence of the involvement of metal exposure in neurodegenerative diseases. However, despite observations of abnormal amounts of metal ions in Alzheimer’s disease (AD) brains, their precise role in disease engenderment or proliferation remains unclear. The formation of amyloid-β (Aβ) peptides and their subsequent aggregation is considered to be one of the important factors in AD pathogenesis. Aβ peptides have been previously shown to display specific binding to Cu(II) and Zn(II) ions [1-4]. We have recently developed non-bonded parameters for the classical simulations of a range of metal ions including Zn(II), Mn(II) and Jahn-Teller distorted Cu(II) [5,6]. In this study [7], experimental as well as computational methods have been used to characterize the binding of different metal ions and in particular Mn(II) to the Aβ peptide. While nuclear magnetic resonance (NMR) spectroscopy experiments show that Mn(II) binds weakly to the N-terminal region of Aβ, other studies using circular dichroism (CD) spectroscopy, fluorescence spectroscopy and atomic force microscopy (AFM) suggest weak binding with no large effect on peptide aggregation. Molecular dynamics (MD) simulations carried out at the N-terminal region of Aβ complex with Zn(II), Cu(II) and Mn(II) corroborate the experimental results. That is, they show that Aβ-Mn(II) binding is weaker and non-specific compared to Aβ-Zn(II) and Aβ-Cu(II) binding (based on the stability of the different complexes formed in our simulations). Identification of an additional metal displaying Ab binding and modulating Aβ activity enriches the field of AD metal chemistry with further knowledge and intrigue.

References
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