0.1 Report on Summer School on Simulation Approaches to Problems in Molecular and Cellular Biology

Miramar Palace, San Sebastián (Spain)

31 August-4 September 2009

School directors:

Paolo Carloni (SISSA, Trieste, Italy)

Michele Parrinello (ETH Zürich and Appl. Biosciences Lugano, Switzerland)

Ursula Röthlisberger (EPFL, Lausanne, Switzerland)

Local organizers:

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Sponsors: Psi$_k$, CECAM, ESF and DIPC

Web sites:

http://www.sissa.it/sbp/SSSAPMCB/index.htm

http://www.cecam.org/workshop-0-340.html

http://dipc.ehu.es/ws_presentacion.php?id=46

The Summer School on *Simulation Approaches to Problems in Molecular and Cellular Biology* was held in the Miramar Palace, San Sebastián, Spain from August 31 to September 4, 2009. The main goal of the School was to present the latest developments and applications of biomolecular simulation approaches aimed at predicting structure, dynamics and energetics of biomolecules. Aspects of bioinformatics-based structural prediction algorithms were also discussed.

The topics treated included:

- Simulation of rare events
- Prediction from first principles of spectroscopic and redox
- Protein and nucleic acid structure prediction
- Critical analysis of the force fields used for biomolecular simulation
- Molecular simulation of cellular events
- Simulation in molecular medicine

During the Summer School some of the most important experts in the field presented the latest developments in the theory, methodology and applications of molecular dynamics simulations applied to the biological problems described in more detail below.

There was a total of 92 assistants:

- 72 students (25 females and 47 males)
- 20 invited speakers and organizers (4 females and 16 males)

The students of the School came from 23 different countries (see Table **??** and the List of Participants below) working in Institutions from 16 different countries. The invited speakers and the organizers work in 8 different countries (see the List of Participants below).

40 of the students (55%) have received support for traveling (the average amount of this financial aid has been 478.70 euros).

Table 1: Nationalities of the students attending the Summer School

Country	Number of Students
Australia	1
Belgium	2
Bulgaria	1
China	2
Egypt	1
France	6
Germany	4
Greece	2
India	3
Island	1
Italy	14
Korea	2
Luxembourg	1
Malaysia	1
Mexico	1
Poland	2
Russia	5
Spain	15
Switzerland	3
Thailand	1
Turkey	1
USA	1
Vietnam	2

Scope of the School

Cellular functions - like growth, (programmed) cell death, metabolism, etc. - ultimately depend of interactions between macromolecules encoded by DNA. Proteins and RNA directly control the cell and regulate its functions through the reactions they perform, by allosteric changes driven by endogeneous and exogeneous factors and by their mutual interactions.

All of these processes involve molecular recognition, i.e. the process by which two or more biological molecules interact to form a specific complex. Molecular recognition is dominated by short-range, often transient, interactions at the contact surface of the interacting molecules. Even conformational changes and assembly of very large macromolecular aggregates, which can be propagated through long distances (tens of Angstroms), are the sum of local interactions between small molecules (like messengers) or macromolecules with their cellular targets.

Ultimately, therefore, even the understanding of the integration of biological complexes into cellular pathways (the so called 'systems biology') requires mechanistic understanding of the physical basis of molecular recognition. A quantitative description of cellular pathways in molecular terms is still mostly missing, although it would strongly impact on pharmaceutical sciences, as drugs target (and mutations affect) pathways, rather than single biomolecules. Such information is also crucial in nanobiotechnology, e.g. to design artificial sensing devices, which in Nature involve entire cascades of events and not only a single protein.

Molecular simulation constitute a key field to contribute to this issue. It can predict structure, dynamics, energetics, reactivity and spectroscopic properties of the cellular components (i.e. large macromolecular aggregates) involved in these pathways.

Tremendous challenges have to be taken before this ambitious goal can be reached. First, the systems are very complex and so are the interactions involved. In addition, ligand-protein processes involve small changes of free energies (less than 1 eV for non-covalent protein-protein interactions), and they are often entropy-driven. Next, the environment is very complex: cell membranes are far from being a simple lipid bilayer whilst the cytoplasm is far from being a simple aqueous solution. Finally, most often experimental structural information is partially or totally lacking. These issues and challenges have been discussed in detail in the Summer School on *Simulation Approaches to Problems in Molecular and Cellular Biology*.

Programme of the School

Monday, 31st August 2009

Chairperson: Gregory A. Voth

09:00 - 09:40 J. Hutter/ University of Zurich, Switzerland
Progress in large scale density functional calculations

09:40 - 10:20 J. Hutter/ University of Zurich, Switzerland
Calculation of NMR and EPR parameters for proteins in solution

10:20 - 10:50 — Coffee Break —

10:50 - 11:30 F. Alber/ UCLA, Los Angeles, USA
Determining the structures of macromolecular assemblies - Part 1

11:30 - 12:10 F. Alber/ UCLA, Los Angeles, USA
Determining the structures of macromolecular assemblies - Part 2

12:10 - 14:00 — Lunch Break —

Chairperson: Angel Rubio

14:00 - 14:40 G. A. Voth/ University of Utah, Salt Lake City, USA
Rigorous coarse-graining of condensed phase and biomolecular systems

14:40 - 15:20 G. A. Voth/ University of Utah, Salt Lake City, USA
Multiscale modeling of proteins and membranes: from the molecular to the mesoscale

15:20 - 16:00 — Coffee Break —

16:00 - 16:40 M. Cascella/ UNIBE, Bern, Switzerland
Development of unbiased coarse grained potentials for simulations of proteins

16:40 - 17:20 M. Dal Peraro/ EPFL Lausanne, Switzerland
Coarse-grained electrostatics in multiscale simulations of proteins

Tuesday, 1st September 2009

Chairperson: Michele Parrinello

09:00 - 09:40 R. Lavery/ Institut de Biologie et Chimie des Proteines, Lyon, France
DNA dynamics and recognition

09:40 - 10:20 R. Lavery/ Institut de Biologie et Chimie des Proteines, Lyon, France
Coarse-grain models of protein mechanics

10:20 - 10:50 — Coffee Break —

10:50 - 11:30 M. Orozco/ Institute for Research in Biomedicine, Barcelona, Spain
Pushing the boundary of MD simulations. Proteome scale atomistic simulations

11:30 - 12:10 M. Orozco/ Institute for Research in Biomedicine, Barcelona, Spain
Coarse grained dynamics simulations of proteins and nucleic acids

12:10 - 14:00 — Lunch Break —

Chairperson: Mike Klein

14:00 - 14:40 M. Sulpizi/ University of Cambridge, Cambridge, UK
Redox properties in metalloproteins

14:40 - 15:20 M. Sulpizi/ University of Cambridge, Cambridge, UK
Pka calculations from DFT-based MD simulations

15:20 - 16:00 — Coffee Break —

16:00 - 16:40 M. Dal Peraro/ EPFL Lausanne, Switzerland
Proton conduction and drug binding in the M2 channel from Influenza A virus

16:40 - 17:20 M. Cascella/ UNIBE, Bern, Switzerland
Electronic structure/function relationship in copper-bound redox proteins

Wednesday, 2nd September 2009

Chairperson: Ursula Rothlisberger

09:00 - 09:40 F. Gervasio/ Fundacion CNIO - Carlos III, Madrid, Spain
Quantitative structure-activity relationship with Metadynamics and Path-collective variables: ligand binding

09:40 - 10:20 F. Gervasio/ Fundacion CNIO - Carlos III, Madrid, Spain
Quantitative structure-activity relationship with Metadynamics and Path-collective variables: conformational selection and induced fold effects

10:20 - 10:50 — Coffee Break —

10:50 - 11:30 S. Piana/ D.E. Shaw Research, New York, USA
The precision and accuracy problems in MD simulations

11:30 - 12:10 S. Piana/ D.E. Shaw Research, New York, USA
Improving force fields for MD simulations

12:10 - 14:40 — Lunch Break —

Chairperson: Juerg Hutter

14:40 - 14:40 A. Rubio/ ETSF, Donostia-San Sebastian, Spain
First principles description of the optical properties of biochromophores

15:20 - 16:00 — Coffee Break —

16:00 - 16:40 I. Tavernelli/ EPFL, Lausanne, Switzerland
TDDFT as a tool in chemistry and biology

16:40 - 17:20 I. Tavernelli/ EPFL, Lausanne, Switzerland
Light driven reactions in biological systems

Thursday, 3rd September 2009

Chairperson: Paolo Carloni

09:00 - 09:40 C. Rovira/ ICREA, Barcelona, Spain
Substrate conformational changes in glycoside hydrolase catalysis

09:40 - 10:20 C. Rovira/ ICREA, Barcelona, Spain
The reaction mechanisms of heme peroxidases by QM/MM simulations

10:20 - 10:50 — Coffee Break —

10:50 - 11:30 H. Grubmüller/ MPI, Gottingen, Germany
Conformational motions of biological macromolecules

11:30 - 12:10 H. Grubmüller/ MPI, Gottingen, Germany
Molecular dynamics simulations of biological nanomachines: may the force be with you

12:10 - 14:00 — Lunch Break —

14:00 - 18:00 Poster Session

Friday, 4th September 2009

Chairperson: Helmut Grubmüller

09:00 - 09:40 S. Raugei/ SISSA and INFM-DEMOCRITOS, Trieste, Italy
Computational vibrational spectroscopy for biomolecules: basics

09:40 - 10:20 S. Raugei/ SISSA and INFM-DEMOCRITOS, Trieste, Italy
Computational vibrational spectroscopy for biomolecules: an application to the bacterial resistance to antibiotics

10:20 - 10:50 — Coffee Break —

10:50 - 11:30 L. Guidoni/ Universit degli Studi dell'Aquila, L'Aquila, Italy
Computing vibrational spectra of biomoleculesby Quantum Mechanics / Molecular Mechanics simulations

11:30 - 12:10 L. Guidoni/ Universit degli Studi dell'Aquila, L'Aquila, Italy
First principles calculations of photoreceptors

12:10 - 16:00 Poster Session with Buffet

Chairperson: Paolo Carloni

Participant talks

16:00 - 16:20 Brunk Elizabeth / EPFL, Lausanne, Switzerland

16:20 - 16:40 Zhu Lihze / University of Amsterdam, Amsterdam, The Netherlands

16:40 - 17:00 Losasso Valeria/ SISSA, Trieste, Italy

17:00 - 17:20 — Coffee Break —

17:20 - 17:40 Tipmanee Varomyalin / University of Cambridge, Cambridge, UK

17:40 - 18:00 Deplazes Evelyne / University of Western Australia, Crawley, Australia

18:00 - 18:20 Delemotte Lucie / Universit Henri Poincar, Nancy, France

18:20 - 18:40 Concluding Remarks

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Abstracts of contributed posters

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Coupling semi-implicit solvation to non-radial coarse grained potentials for molecular simulations of proteins

We have recently introduced a non-radial potential for coarse-grained (CG) molecular simulations of proteins. Here, we couple this novel CG description to a semi-implicit solvent model based on induced dipoles to consistently account for the dielectric response of the solvent as due to the multipolar electrostatic description of the protein. We show that the stability and dynamic features of elementary structural motifs, such as alpha-helices and beta-sheets and small proteins are improved in comparison to using non-polarizable CG models for water at a negligible computational overhead.

Ansorg Kay

New warheads against tropical diseases

Proteases form one of the largest and most important groups of enzymes. They are involved in numerous important physiological processes including protein turnover, digestion, blood coagulation and wound healing, fertilization, cell differentiation and growth, cell signaling, the immune response, and apoptosis. Uncontrolled, unregulated or undesired proteolysis can lead to many disease states including emphysema, stroke, viral infections, cancer, Alzheimer's disease, inammation and arthritis. According to the investigations of the world health organization (WHO), each year 50 million people die worldwide from parasitic infectious diseases alone. A large part of these deaths is caused by so called tropical diseases, especially malaria, sleeping sickness, leishmaniasis, amoebiasis, etc., for which no vaccines exist. All of these diseases involve cysteine proteases. So latter are important targets in medicinal chemistry. Warheads for irreversible inhibitors are three-membered rings like epoxides and aziridines, Michael systems and as novel class vinyl sulfones. To increase the reactivity and selectivity of vinyl sulfones it will be necessary to study the mechanism of the inhibition on a higher level of theory. Since insights into the mechanism and its kinetics and thermodynamics are important for the design of new inhibitors, the influence of the substitution pattern on reaction mechanism and reaction energies are modelled. As a first step of our investigation we performed QM calculations for smaller model systems to gain the knowledge necessary for more extended calculations which will take the protein surrounding into account.

Archambault Fabien

Development of accurate polarizable intermolecular potentials

Most of the potential energy functions used for the simulation of biological systems only handle electronic polarization implicitly. Although these intermolecular potentials are incomplete, they have proven to be particularly effective for a large variety of systems. They, however, rapidly reach their limits when strong polarization effects are involved. The explicit treatment of polarization requires an appropriate parametrization of all the classical contributions to the interaction energy, e.g. electrostatics and van der Waals. Here, a strategy to derive a complete polarizable intermolecular potential is presented. Models of atomic charges and distributed polarizabilities are derived for isolated molecules. The intermolecular potentials are then calibrated based on a physically meaningful expansion of the total energy provided by symmetry adapted perturbation theory. As a proof of concept, the methodology is illustrated through a series of test cases that include the interaction of water and benzene with halide and metal ions.

Baday Sefer

Ammonium Transport Mechanism in Amt/Rh Family

Bacteria under low ammonium concentrations express TM proteins from the Amt/MEP family. These proteins have a high affinity for ammonium and facilitate its transport across the membrane. AmtB crystallizes as a trimer. Each of the three subunits contains a permeation pore. Based on X-ray diffraction data, it was concluded that AmtB works as an ammonia (NH3) channel. Our calculations do not support this hypothesis. We performed PMF (Potential of Mean Force) simulations to observe the stability of water molecules in the pore. We made FEP (Free Energy Perturbation) calculations of the process of successively replacing each water in the pore by ammonia dissolved in the bulk solution. Result of these calculations are used to determine the probability of water and ammonia molecules in the pore. Moreover, we performed MD simulations and we saw that water molecules can form a stable chain in the pore. As a summary, water molecules compete with ammonia for the occupancy of the pore and wins. Our calculations suggest that pore is more likely to be filled by water rather than ammonia.

Berteotti Anna

Protein conformational transitions: the closure mechanism of a kinase explored by atomistic simulations

Kinase large-scale conformational rearrangement is an issue of enormous biological and pharmacological relevance. Atomistic simulations able to capture the dynamics and the energetics of kinase largescale motions are still in their infancy. Here, we present a computational study in which the atomistic dynamics of the "open-toclosed" movement of the cyclin-dependent kinase 5 (CDK5) have been simulated. Simulations were carried out using a new sampling method that is able to find the lowest free-energy channel between an initial state and a final state. This large-scale movement has a two-step mechanism: first, the alphaC-helix rotates by approximately 45 degrees , allowing the interaction between Glu51 and Arg149; then the CDK5 activation loop refolds to assume the closed conformation. We have also estimated the free-energy profile associated with the global motion and identified a CDK5 intermediate, which could be exploited for drug-design purposes. Our new sampling method turned out to be well-suited for investigating at an atomistic level the energetics and dynamics of kinase large-scale conformational motions.

A. Berteotti et al. J.Am.Chem.Soc. 131, 244 (2009)

Bozdaganyan Marine

Molecular dynamics simulation of fullerene C60 interaction with biological membrane

One of the most important phases of the development of nanotechnology was the discovery of fullerenes and nanotubes in the second half of the 80-ies. This new allotrope form of carbon is a closed surface structure, which has specific properties as physical object and as chemical system. With its high electronegativity, fullerenes act as strong oxidants in chemical reactions, which allow to synthesize new materials based on them. The fullerene derivatives can act as antioxidants and antiallergic substances, they have cytoprotective and antibacterial activities, fullerenes may cause lipid peroxidation and also they can interact with different proteins, changing their activities.

Recent toxicological studies have shown that fullerenes and nanotubes can penetrate through the membrane into cells and influence on their functions. Inhalable ultrafine carbon particles deposit in the lungs and translocate into the brain, especially into the olfactory bulb, by means of the olfactory nerves and the blood, breaking blood-brain barrier. Toxicity of carbon nanoparticles depends on their solubility, for example, cytotoxicity of pristine fullerene 7 times higher than its derivatives with high solubility in water. However, the mechanisms by which nanoparticles can penetrate through the membrane are still poorly understood. In this paper, the method of molecular dynamics was used to study the detailed mechanisms of interaction between the nanoparticles in the aqueous phase and with biomembranes. The objects of our research were: DPPC bilayer membrane (128 lipids in 3556 water molecules) and the fullerene C60. All simulations were performed in GROMACS package. Initially, the properties of the fullerene were studied in order to check model applicability. The potential of mean force was calculated for two fullerenes in vacuum and water. The graphs show that the model of the fullerene was correct. For the membrane thickness, the area per lipid head, and density profile were calculated. All results of calculations correspond to experimental data. The study of the fullerene penetration through the membrane were performed in GROMOS force field. The dynamics of adsorption and penetration of nanoparticle were studied, the energy profiles were calculated (PMF for fullerene and membrane). Also, graphs were constructed according to the distance from the center of the membrane to the center of mass of the fullerene and changes in the lipids of the membrane (gidrophobic profiles) during and after penetration of the fullerene were calculated.

Brunk Elizabeth

An approach to direct the novel biosynthesis of target molecules

Recent efforts in metabolic engineering offer sustainable alternatives for the production and degradation of industrial feed-stocks. Considering microbial production of organic compounds provides an efficient frame- work to access renewable energy resources. Moreover, the formulation of novel biosynthetic routes could further enhance the production of biofuels. Employing the Biochemical Network Integrated Computational Explorer (BNICE) framework, novel enzymatic routes emerge from a set of generalized reaction rules that can determine possible reaction pathways, given a set of starting compounds. A successful implementation of a novel reaction pathway requires an extensive analysis of the novel substrate-enzyme complex to evaluate the feasibility and catalytic efficiency of the desired reaction. In addition, the design of enzyme functions to act efficiently on novel or existing metabolites could improve binding affinities and turn-over rates. An approach has been developed to propose a method for the biosynthesis of 3-hydroxypropanoate (3HP) from pyruvate. Further examination of this pathway considers modeling the novel step of the reaction in which Malonyl-CoA Mutase (MCM) catalyzes a 1,2 rearrangement on a novel substrate, lactoyl-CoA, to produce 3HP. Applying classical molecular dynamics methods, the structures are examined over multi-nanosecond trajectories. An assessment of the electrostatics and binding free energies allows for the comparison of novel versus wild-type substrate-MCM complexes. In addition, several mutant variants of MCM have been analyzed, applying alchemical free energy perturbation (FEP) techniques to optimize the affinity of the MCM to the novel substrate.

Campomanes Pablo

Novel anticancer drugs and their Interaction with non-classical targets

The field of anticancer metallodrugs has been traditionally dominated by the so-called classical drugs like cisplatin [Pt(Cl)2(NH3)2] and the "DNA paradigm", which presumes that the mode of action of these compounds relies on direct DNA damage. However, non-classical chemotherapeutic strategies based on DNA independent cytotoxicity are gaining significant prominence [1]. The main drawback of the classical chemotherapeutic strategies is that blocking the metabolism of the rapidly dividing cancer cells by means of drug-DNA binding inadvertently also inflicts damage on healthy cells that divide frequently as well, therefore causing undesirable side-effects. In contrast, non-classical drugs focus on specific cellular pathways by interacting with targets different from DNA and are therefore much more selective [2]. One of these targets is the Glutathione S-Transferase (GST) P1-1 enzyme. Its main function is the detoxification of toxic compounds, including anticancer drugs, in the cytoplasm. In addition, GST P1-1 regulates the mitogen-activated protein (MAP) pathway, involved in cellular survival and death signaling. Several organometallic GST inhibitors showing antitumoral properties have been recently synthesized and the corresponding GST-drug adducts have been also characterized. The atomistic knowledge of the GST-drug binding modes and the possible chemical transformations that occur upon binding is important to guide further experimental investigations and assist the rational development of more effective and targeted anticancer drugs. This knowledge can be gained by combining classical and QM/MM MD simulations. In this contribution, we will discuss the main results obtained by applying this mixed approach.

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Ceres Nicoletta

Mechanical properties in thermal adaptation of proteins - A coarse grained approach

Psychrophilic, thermophilic and hyperthermophilic organisms grow and live at respectively very low, high or very high temperature. Thermal adaptation of their enzymes is the object of great scientific, biotechnological and industrial interest. These biological machines display good catalytic activity and structural stability at their extreme environmental temperatures, without loosing the fold common to their enzymatic class. This suggests a subtle relationship between activity, structure and mechanical properties in thermal adaptation of enzymes, and indeed an adapted flexibility/resilience is often cited as a key element in thermal adaptation. To try to go deeper in the understanding of the unknown physical link existing between the mechanics of protein structures and thermal adaptation, a coarse-grained model of proteins is coupled to brownian dynamic simulations. Unlike existing experimental parameters like the B-factor, which is a measure of local flexibility, this fast computational approach allows to calculate a global residue-based parameter of flexibility, 'the force constant'. Differences emerge between structurally homologous extremophilic and mesophilic enzymes, showing that a simplified model of the proteins can be applied to the study of their mechanical properties, and encourage improvements of the model needed to really clarify the relationship between structure, activity and flexibility in

Chioccioli Matteo

Modelling investigation and thermodynamic analysis of DNA-acridine complexes

In the treatment of many diseases, such as malaria and cancer, DNA-intercalators are used. Over the years a great effort has so been devoted to the design and the synthesis of new molecules able to bind and react with DNA and biomolecular simulation methods have been increasingly applied to give insight into nucleic acid structure, dynamics and interaction1. Recently, our particular interest has been focused on human DNA-telomeres, concentrated at the end of chromosomes and whose shortening leads to natural cell apoptosis. In cancer cells these telomeres maintain their length because of the activity of an overexpressed reverse transcriptase telomerase enzyme; the direct as well as the indirect inhibition of this enzyme has been proven to be attractive in antitumor strategies. An interesting feature of the 3'-end human telomeres, comprising repeats of the sequence d(TTAGGG), is the ability of folding into intra- and intermolecular G-quadruplex, a DNA secondary structure consisting of stacked coplanar cyclic arrays of guanines (G-quartet or G-tetra), which inhibits the optimal telomerase activity2. Therefore, compounds able to bind and stabilize G-quadruplex structures may interfere with telomere maintenance process. In this view, the setting up of a computational procedure for the reliable prediction of the binding free energy of ligand target complexes, involving both G-quadruplex and double-helix macromolecular structures, could help in better understanding the structure activity relationships and provide us an insight at molecular level about compounds for further developments. Preliminarily we have focused our attention on a series of molecules containing an acridine moiety, tested for their biological properties and submitted to computational investigations complemented by thermodynamic analysis. The sets of structures of ligand-DNA complexes, obtained by docking experiments3, have been collected with 10ns molecular dynamics simulations carried out with AMBER-10.4 The MM-PBSA (Molecular Mechanics Poisson-Boltzmann Surface Area) methodology, which combines the molecular mechanical energies with the continuum solvent approach, will be applied to evaluate the free energy of binding. The numerical solutions for the Poisson-Boltzmann equation will be computed by means of both pbsa5 routine and APBS6 program. Finally, estimates of conformational entropies will be made with the nmode module from AMBER-10.

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Collu Francesca

A non-radial coarse-grained potential for proteins produces naturally stable secondary structure elements

We introduce a non-radial potential term for coarse-grained molecular simulations of proteins. This term mimics the backbone dipole-dipole interactions and accounts for the needed directionality to form stable folded secondary structure elements. We show that β-sheet and α-helical peptide chains are correctly described in dynamics without the need of introducing any a priori bias potentials or ad hoc parameterizations, which typically affect CG simulations for proteins. Moreover, our model is able to catch formation of supersecondary structural motifs, like transitions from long single α-helices to helix-coil-helix assemblies. This novel scheme requires the structural information of Cα beads only, it does not introduce any additional degree of freedom to the system, and has a general formulation, which allows it to be used in synergy with various CG protocols, leading to an improved description of the structural and dynamic properties of protein assemblies and networks.

Daskalakis Evangelos

Direct evidence for multiple vibrational resonances in the His-(porphyrin)FeIV=O intermediate of Cytochrome c oxidase/O2 reaction: a Quantum Mechanics/Molecular Mechanics and Dynamics approach

Cytochrome c Oxidase (CcO), found in the inner mitochondrial membranes or in many bacteria, catalyzes the four electron reduction of molecular oxygen to water. Four protons are pumped across the inner mitochondrial membrane through CcO. In this study, Quantum Mechanics/ Molecular Mechanics and Molecular Dynamics calculations are used to probe the spectroscopic characteristics of the ferryl intermediates in the aa3 CcO/ O2 reaction. We link proton pumping activity in CcO enzyme to a multiple (1:1:2) resonance among the frequencies of FeIV=O bond stretching, the breathing mode of Histidine 411 and a bending mode of the His411-FeIV=O species (aa3 from Paracoccus denitrificans numbering). We find that the vibrations of the His411-FeIV=O unit become highly coupled depending on the protonation state of the heme a3 ring A propionate / Asp399 pair and we propose a mechanism for the resonance Raman enhancement of the bending mode δ(His411-FeIV=O). Calculations on model systems demonstrate that the position of CuB in relation to heme a3 iron-oxo plays a crucial role in regulating that resonance. We also discuss the origin of the coupling between bending, δ(His411-FeIV=O), and δ(Fe=O) stretching modes.

Delemotte Lucie

Molecular insight into the effect of mutations of voltage-gated ion channels involved in genetic diseases

Mutations of genes encoding voltage gated ion channels are associated with a variety of severe neurologic, muscle or heart diseases. Recent evidence suggests that specific mutations of positively charged residues (gating charges) of the S4 segment of voltage-gated sodium and potassium channels may lead to an abnormal behavior of the voltage sensor (VS) transmembrane domain, manifested by a leak current not observed for the wild type channels. In this study, we investigate the molecular level effect of such mutations on the structural and functional properties of the mammalian voltage-gated potassium channel Kv1.2. We present recent results from large-scale Molecular Dynamics simulations of the wild type channel and selective mutant channels in their membrane environment.

Deplazes Evelyne

Can FRET be simulated? A simple case study

Fluorescence Resonance Energy Transfer (FRET) spectroscopy is a technique that is widely used to obtain co-localisation and structural information of proteins in their native environment. The technique is based on the mechanism of energy transfer by dipole-dipole induced, non-radiative interaction between a fluorescent donor and a suitable acceptor. While the rate of energy transfer depends on the distance between the donor and acceptor, the use of FRET as a "spectroscopic ruler" is complicated by it also being dependent on the relative orientations of the fluorescent probes. In general these orientations are difficult to determine experimentally making the technique uncertain for measuring absolute distances. Simulations may offer an alternative means of understanding the behaviour of the fluorophores at the molecular level, thus enabling distances between specific sites in the sample to be determined more accurately. To examine this possibility, we attempt to simulate FRET in a simple model system consisting of single donor and acceptor molecules in an aqueous solution. The small system size makes all atom simulations in the 10's of ns feasible. Preliminary results from standard MD simulations suggest that a 25 ns simulation is enough to sufficiently sample the mobility and conformations of the individual donor and acceptor molecules as well as their relative orientations. The data shows rapidly changing values of FRET efficiency with large deviations from the average, most likely caused by large fluctuations of the relative orientations. By simulating FRET in a simple system we hope to gain insight into the process of the energy transfer and the factors affecting its behaviour. This might help to better understand and analyse data from FRET experiments. The results of this study might also be useful as indications of when simulation may help to understand and analyse data from more complicated FRET experiments.

Desai Tanay M.

Tuning protein folding cooperativity through solvent structure engineering

The term protein folding cooperativity is used to describe the coupling between the different segments of a protein during its folding-unfolding process. Studying cooperativity experimentally has proven to be a major challenge because classical folding experiments in single-domain proteins suggest an all or none process (i.e. two-state folding). However, recent experiments in downhill folding demonstrate a direct connection between folding cooperativity and the broadness of the overall unfolding curve. Taking advantage of this connection we have explored the possibility of tuning the marginal folding cooperativity of the globally downhill-folding protein BBL by changing the structural-chemical properties of the surrounding solvent. Our experimental setup is as follows: we start with BBL at pH 3, where it is fully denatured and expanded at all temperatures due to charge-charge repulsions. We then add increasing amounts of salts with different ionic radii, and accordingly, with different abilities to induce structural reordering in water (the kosmotropic effect). Finally, we perform equilibrium thermal unfolding experiments in each condition, to monitor the effects of engineering the solvent structure on the folding stability and cooperativity of BBL. We find that the three salts employed (i.e. LiCl, NaCl, CsCl) refold BBL by a combination of electrostatic screening and solvent kosmotropic effects. However, in conditions that match the thermal stability of BBL at pH 7 (i.e. 2M salt) we find that the unfolding process is much broader, signaling a significant decrease in the already marginal cooperativity of this protein. Therefore, favorable electrostatic interactions at pH 7 are a critical source of cooperativity in BBL that cannot be mimicked by stabilizing the protein through solvent restructuring. Interestingly, the degree of cooperativity induced by the three salts in matching conditions is different, being directly proportional to the solubility in water of the particular salt. Our results unravel the interplay between protein and solvent during folding. Moreover, engineering the solvent structure emerges as a powerful mechanism to modulate the conformational properties of proteins.

Diaz Leines Grisell

Role of conserved residues around the Flavin chromophore during photoactivation of BLUF proteins

The biological photoreceptors have the task of regulating the response to different regions of the light spectrum participating in different cellular controlling processes. Proteins containing blue-light sensor domains using FAD (BLUF) belong to a third class of the flavin-binding blue light photoreceptors that were recently discovered in eukaryotic and prokaryotic microorganisms. Up to now, the BLUF domains have been characterized by different experimental techniques and photo-excitation has been proposed to involve hydrogen- bond rearrangement in the surroundings of the chromophore which leads to formation of a stronger C=O hydrogen-bond and a 10 nm red shifted intermediate state in the protein that slowly decays back to the ground state. This red shifted state (BLUF red) probably represents the signal state. Although a photo-cycle reaction has been proposed for some of these BLUF photoreceptors, the molecular details for the translation of light signal into a change in protein structure are largely unknown. Based on the crystal structures obtained by different experimental techniques we have characterized the behaviour of the hydrogen bond network and conserved residues in the region nearby the FAD for different BLUF structures (AppA, T110078, Blbr, Blrp1) using equilibrium molecular dynamics simulations at room temperature and elevated temperatures. Preliminary results indicate that some of the conserved residues in BLUF domains surround the flavin chromophore have dynamical properties that could give insight about their crucial role during the photoactivation process and the light signal transduction in the BLUF domains.

Do Nhu Trang

Molecular dynamics studies of HIV-1 TAR RNA and its complex with a cyclic peptidic inhibitor

Dynamical behavior of HIV-1 TAR RNA and its complex with a cyclic peptidic inhibitor in aqueous solution are simulated by means of molecular dynamics. Starting structures are taken from NMR experiments. During the simulations, water is included explicitly, periodic boundary conditions are applied, and Particle Mesh Ewald method is used for treating long-range electrostatic interaction. AMBER force field ff03 with Orozco correction is utilized. Structural and free energy analyses are performed to understand the dynamical behavior of free TAR and TAR in complex with the inhibitor. Contribution of van der Waals and electrostatic interaction to the formation of the complex is evaluated, and conformational rearrangement from free to bound state of TAR is analyzed.

Dudek Marta and Stasiewicz Juliusz

Modeling of adsorption of ethanol solutions in activated charcoal - molecular dynamics and Monte Carlo simulations

Adsorption of aqueous ethanol solutions in activated charcoal (AC) provides a promising tool for toxicological treatment of alcohol overdose. However, no intense theoretical studies have been yet performed in this area. In this work a model of AC is proposed as consisting of disordered graphene-like layers. Electrostatic and van der Waals interactions between adsorbate and carbon lattice are being considered. Methods of molecular dynamics and Monte Carlo are being employed both in optimization of AC structure and study of adsorption phenomena.

Enciso Marta

A new hydrogen bond model for studying protein aggregation

In spite of being essential for the development of life, we are far from a complete understanding of the molecular and physical basis of protein behaviour. Biomolecular simulation may shed some light on this, as it provides useful tools for describing the interactions that govern the formation of protein structures from a microscopic point of view. Proteins usually adopt a specific conformation in solution, which is called the native state. However, in pathological or high concentration environments, proteins unfold and different chains interact with one another, forming therefore aggregates. These aggregates share a ?-type structure no matter the protein itself [1] and can be explained by the formation of hydrogen bonds among the chain backbones [2], which are also responsible for the formation of the protein secondary structure. Thus, studying the role of hydrogen bonds may give some clues for the competition between protein folding (native-like structures) and aggregation in different conditions of temperature and concentration. Describing huge conformational changes by molecular simulation requires large computational efforts. One way to speed up these calculations is by using reduced models, but this frequently implies the loss of some of the characteristic features related to the strong directionality of the hydrogen bond. In spite of the amount of models that have been published recently, most of them have failed to describe the natural structures accurately. In this work, we have developed a hydrogen bond model with a very good compatibility with observed structures. Thanks to it, we have studied the influence of different parameters (concentration, temperature, chain length, etc.) on the competition among structures. We show results of short peptides in different conditions. In low concentration environments, the peptidic chains form native-like ?-helices as the most stable conformation. The increase of the system concentration implies the gradual stabilization of ?-type structures. The structures obtained and the good description of peptide behaviour makes our model an excellent tool for the study of protein aggregation.

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Garate Joseph

Electromagnetic field and distance dependent effects on carbon nanotube assisted water self-diffusion across lipid membranes

Water-self diffusion through single-walled carbon nanotubes (SWCNTs) inserted normal to a phospholipid membrane has been studied using equilibrium and nonequilibrium molecular dynamics simulations in the presence of static and electromagnetic (e/m) fields. Four different SWCNTs were investigated: (5,5), (6,6), (8,8) and (11,11) and also three arrays of four (6,6) SWCNTs separated by 15, 20 and 25 respectively. The (5,5) system shows interesting behavior, where an increase in the applied field frequency in the z direction decreases the water permeation rates, reaching values at higher frequencies similar to zero field conditions. The (6,6) arrays simulations demonstrated that there is a friction effect, when the nanotubes are closely packed, which retards the movement of the individual water files.

Ghitti Michela and Spitaleri Andrea

Combined use of NMR binding studies and computational methods to characterize novel αvβ3 interactors

Integrins, the major class of heterodimeric transmembrane glycoprotein receptors, play crucial roles in mediating tumour angiogenesis, therefore gaining increasing importance as drug targets in antiangiogenic cancer therapy. Recent biochemical studies have shown that the deamidation of the NGR sequence gives rise to isoDGR, a new αvβ3-binding motif (Curnis et al, J Biol Chem 2006, 281:36466-36476). Accordingly, a cyclo-peptide containing the isoDGR motif is a competitive antagonist of αvβ3-ligand RGD, inhibiting endothelial cell adhesion, proliferation, and tumor growth. No competition is observed with cyclo-peptides containing DGR or NGR sequences, thus implying a precise stereospecific recognition at the basis of isoDGR interaction with αvβ3 (Spitaleri et al, J Biol Chem 2008, 238:19757-19768). In order to gain additional insights into the molecular basis of the interactions, we designed and synthesized a small library of pentacyclic-peptides, including CRGDC, CisoDGRC, C(d)isoDGRC, acetyl-CisoDGRC, CDGRC, and CNGRC. Then, we characterized both their conformations and their αvβ3-binding ability by a combination of NMR and computational methods, including docking and molecular dynamics simulations. The conformational properties of the cyclopeptides were first analysed by classical solution NMR methods, and then refined by MetaDynamics (MtD) simulations using as collective variable the glycine phi/psi dihedral angle. The MtD refinement allowed to identify the most populated conformers in solution, which were next docked onto the αvβ3 crystallographic structure in its "RGD-bound" conformation using HADDOCK-2.0. Both NMR and metadynamics results show that acetyl-CisoDGRC has a reduced conformational flexibility compared to CisoDGRC. In addition, this peptide has the correct conformation to dock inside the αvβ3 binding pocket, thus reducing the unfavourable entropic binding contributions observed in the flexible non-acetylated CisoDGRC macrocycle. Moreover the acetyl group carbonyl of acetyl-CisoDGRC stabilizes its interaction with αvβ3, establishing an additional hydrogen bond with the R214 side-chain. These results are in agreement with in vitro αvβ3-binding studies showing that peptide acetylation increases the affinity for αvβ3 over CisoDGRC. Finally, we confirmed the binding of the cyclopeptides to intact living cells using NMR transfer NOE experiments. Using two human cell-lines expressing different levels of CD13 and αvβ3, we clearly show that CisoDGRC and acetyl-CisoDGRC bind to cells expressing αvβ3, whereas NGR containing ligands bind to cells expressing CD13

Giangreco Ilenia

Molecular dynamics simulations of Matrix Metalloproteinase-2 with alloxan derivatives

Matrix metalloproteinases (MMPs) are a family of structurally related zinc-containing endopeptidases involved in tissue remodelling and degradation of extracellular matrix. The design of new selective and potent MMP inhibitors is becoming an extreme challenge in the health-care area for the failure of synthetic inhibitors used in the treatment of various pathological states such as inflammation, arthritis, and cancer. Allegedly, an over-expression of MMP-2 is supposed to be responsible of many different human tumours and inflammatory processes involving the hydrolysis of the type IV collagen, the main component of the basement membrane. Campaigns of molecular virtual screening of several large chemical libraries resulted in a number of attractive hits biased towards MMP-2. Among the occurring chemical scaffolds (incorporating zinc binding groups), we focused our efforts on alloxan-like structures. Interestingly, preliminary biological experimental data awarded a number of these selected derivatives with inhibition measures in the nM range. Encouraged by these outcomes, a series of complexes of MMP-2 with alloxan inhibitors were subjected to further in-silico computations with the aim of shedding light on the tetrahedrical coordination of the alloxan core structure to the catalytic zinc and three histidine residues (i.e., His120, His124 and His130). Molecular dynamics and free energy calculations were performed to obtain quantitative differences in binding energies for a series of designed alloxan derivatives. On this basis, the more promising compounds will be first synthesized and then tested through enzymatic assays.

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Gkeka Paraskevi

Coarse-grained simulations of α-helical peptides

Peptide-membrane interactions are of great importance for various biological phenomena, such as antimicrobial defence mechanisms, membrane fusion and virus translocation. In our studies, we are mostly interested in amphipathic α-helical peptides, like the Simian Immunodeficiency Virus fusion peptide (SIV) or the LS3 pore forming synthetic peptide. One of the key factors affecting the way these peptides interact with the cell membrane is the distribution of hydrophobic and hydrophilic residues along the helical axis. Based on this distribution, one may identify several possible scenarios of peptide-membrane interaction [1]. Computer simulations are able to provide a detailed description of these processes on molecular level. The study of large-scale phenomena, like pore formation, is beyond the reach of atomistic simulations, typically limited to tens of nanometers and hundreds of nanoseconds in scale at most. Alternatively, such a description can be sought using a coarse-grained protocol (CG). In this study, we employ a recently introduced coarse-grained model, MARTINI [2,3]. We perform molecular dynamics simulations in order to test the ability of the model to predict various peptide-membrane interaction patterns [4].

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Helbling Rachel

Theoretical investigation of electrophilic trifluoromethylating hypervalent iodine compounds

Trifluoromethylating agents present a promising field of research in chemistry and chemical biology. Trifluoromethylation enhances the capability of a drug being uptaken by the body, since a trifluoromethyl group augments the lipophilicity of the drug candidate molecule. We consider specific agents, namely 1-(trifluoromethyl)-1,2-benziodoxole derivatives. These are mild electrophilic trifluoromethylating species easy to handle experimentally. They bear a hypervalent iodine atom, which makes this molecule interesting from a theoretical point of view since the treatment of iodine is difficult. We are interested in understanding the reactivity of this class of molecules, especially how the exothermic decomposition occurs. We investigate the crystal system with ab initio Molecular Dynamics calculations. Furthermore, we would like to examine the reaction mechanism of the trifluoromethylation reaction. For this purpose, DFT and semi empirical methods are used. We investigate their chemical properties and also the thermochemistry of some specific reactions, as well as their reactivity and behaviour upon nucleophilic attacks.

Khan Abid Ali

Comparative modeling of hemoglobin D of Ring Necked Pheasant

The 3D structure of the Ring Necked Pheasant HemoglobinD and its adaptation to survival at low oxygen levels is predicted through automated homology modeling. HbD crystal structure of Chicken was selected using BLAST (NCBI) for calculation of homology models. The conservation of important amino acid residues was analyzed by multiple alignment by CLUSTAL X. The calculation of homology model was achieved by MODELLER (8v1). Model evaluation and assessment was performed by PROCHECK, and superposition of Cα traces and backbone of model over template. The homology modeling studies revealed the loss of interaction between α119Pro-β55Leu in HbD model. The interaction of α34Leu- β128Ala in oxy state had also been found lost; instead interaction between α34Leu- β124Pro in oxy state had been found in HbD models. Two new hydrogen bonds were found while one was found missing in HbD model. Mutation at some of the key positions resulting either in loss of specific interactions or development of new interactions led us to hypothesize that this bird has all the ingredients that are required for survival at low oxygen levels. Chicken HbD, too, has high oxygen affinity, but neither of the Galliformes fly at high altitudes and hence the reason for this adaptation remains unknown.

Larriva-Hormigos Maria

Can a simple topology-based simulation model reproduce protein folding pathways?

The ribosomal protein S6 from Thermus thermophilus (S6T) and its circular permutants have been subjected to intense experimental and theoretical studies in recent years in order to analyze the dependence of the transition state of the protein on the topology of the native state and the effects of circular permutation on the protein folding pathway. Circular permutation experiments are designed by breaking the polypeptide chain at a certain position and connecting the original N- and C- termini by a chemical bond or peptide linker. This keeps the global interactions along the structure but changes the topology of the native state in each new permutant. The native structure of S6T consists of two helices packed against four β-strands, which are symmetrically distributed along the sequence, with a hydrophobic core. Detailed experiments have shown than wild type S6T presents a transition state in which two β-strands are coupled against a single α-helix [1]. Moreover, this "nucleation motif" is shared by the S6T permutants, and appears in different parts of the amino acid chain depending on how the secondary structure elements are connected. This two-strand-helix motif is not unique to S6T and it has been also observed in the S6 protein from the hyperthermophilic bacterium Aquifex aeolicus (S6A), which is interesting not due to its topology, almost identical to that of S6T, but for its hydrophobic core with a large proportion of Phe side-chains. In our work, we use a coarse-grained model for protein folding, whose interactions are based on the topology of the native state, to analyze the thermodynamic characteristics of the folding process and the structural features of the transition state of the ribosomal protein S6T, 4 permutants (P13-14, P35-36, P54-55, P68-69) and its homologous variant, S6A. We have tested the behaviour of our proposed model in order to describe the folding transition for each target using two complexity levels in order to represent the protein: one in which we use a single-bead representation for every amino acid, centered at the corresponding α-carbon position, and a more complex representation that includes for each residue an extra interaction center located in the amino acid sidechain. We have observed significant differences between both model and we have compared them with experimental and simulation data available in order to discuss and validate our results.

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Larrucea Julen

Ab-initio study of aromatic amino acid complexes with aluminum(III)

Different static and dynamic calculations have been performed in order to understand the behavior of the Al(III) in biological environments. The results show a charge redistribution effect on the amino acids when forming complexes with Al(III)

Lee Wook

Computational study on the mechanism of nucleophilic activation of active site cysteine in KasA

Mycobacterium tuberculosis is causative pathogen of tuberculosis which was estimated to give rise to 8 million new infections and 2 million fatalities per year. KasA (β-ketoacyl ACP synthase I) is one of the main enzymes participating in fatty acid synthesis pathway for cell wall in Mycobacterium tuberculosis. It has been reported that the depletion of KasA causes cell lysis of Mycobacterium tuberculosis and eventually leads to cell death. Therefore, KasA has been drawn attention as an attractive novel drug target. One of the key steps in reaction catalyzed by KasA is the nucleophilic activation of active site cysteine. In present study, we investigate how this catalytic cysteine is activated using molecular dynamics simulation and QM/MM calculation. By these calculations, we demonstrate that deprotonation of cysteine by catalytic histine 311 through water molecule is energetically most favourable. Additionally, our computations also reveal that ion pair state is more stable than neutral form.

Lelimousin Mickael

Photoconversion of the fluorescent protein EosFP: a hybrid potential simulation study reveals intersystem crossings

Fluorescent proteins undergoing green to red photoconversion have proved to be essential tools in cell biology, notably in super-localization nanoscopy. However, the exact mechanism governing photoconversion, which overall involves irreversible cleavage of the protein backbone and elongation of the chromophore π-conjugation, remains unclear. Here, we present a theoretical investigation of the photoconversion reaction in the fluorescent protein EosFP, using excited-state hybrid quantum chemical and molecular mechanical potentials, in conjunction with reaction-path-finding techniques. Our results reveal a mechanism in which the hydroxybenzylidene moiety of the chromophore remains protonated and involving an ESPT from the conserved His62 to Phe61. Excitation of the neutral green form of EosFP to the first singlet excited state is followed by two intersystem crossing events, first to a triplet state and then back to the ground state singlet surface. From there, a number of rearrangements occur in the ground state and lead to the red form. Analyses of the structures and energies of the intermediates along the reaction path enable us to identify the critical role of the chromophore environment in promoting photo-induced backbone cleavage. Possible ways in which photoconvertible fluorescent proteins can be engineered to facilitate photoconversion are considered.

Losasso Valeria

Structural prediction of a giant system: Enterotoxigenic Escherichia coli pseudopilus

Enterotoxigenic E. coli (ETEC) is responsible for gastroenteritis in developing countries [1]. An important strategy against its action is the inhibition of the secretion out of bacterial cells of heat-labile (HT) and heat-stable (ST) enterotoxins [2]. Toxins are secreted by 6 (Type I to Type VI) specialized secretion systems. Type II secretion system is the best characterized. It is composed of an inner membrane part, a periplasmic pseudopilus and an outer membrane complex [3]. Although the entire structure is not available, the one of 3 components of the pseudopilus complex was recently solved [4]. Pseudopilus acts as a piston that pushes the toxins out of the cell, playing a central role in the ETEC pathogenicity. We used multiscale computational methods to provide the full atomic structure of pseudopilus, since the size of the system makes necessary the use of simplified descriptions. In particular: 1) we built an initial model of the complex based on known experimental data [4,5,6]; 2) we ran 1 μs molecular dynamics simulation using a full coarse-grained (full CG) approach [7]; 3) we refined protein-protein interfaces using a hybrid MM (molecular mechanical) / CG treatment [8]; 4) we reconstructed the full-atom complex. An exhaustive understanding of the pseudopilus structural biology may help designing drugs affecting the interaction among the subunits.

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Lupieri Paola

Predicting the optical properties of fluorescence probes in a protein matrix: a 2-rhodamines-labeled biosensor for inorganic phosphate

Measuring optical properties of fluorescence probes is routinely used to monitor a myriad of in vivo and in vitro biological processes. Despite its importance, it is not yet clear how the environment tunes such properties. Understanding the molecular details of the probe-target interactions by computational methods may be of tremendous impact on our knowledge of molecular processes such as drug binding, signaling and metabolitic pathways. The processes involving the inorganic phosphate (Pi) enzymatic release in the cell are among the most relevant ones. They include ATP and GTP enzymatic hydrolysis and phosphatase-based signaling processes, such as the ion channels regulation in the nervous transmission. Monitoring Pi concentration is used to describe many activities in healthy cells as well as for pharmacological applications [Webb (2003) in Kinetic analysis: a practical approach, Johnson K. A. Ed., pp 131-152, Oxford University Press, Oxford, U.K.]. Changes in Pi concentration can be followed with fluorescent biosensors [Luecke and Quiocho (1990), Nature 347, 402; Okoh et al. (2006) Biochemistry 45, 14764], such as rhodamines, in combination with the phosphate binding protein from E. coli (PBP). The structure of PBP has been solved by X-ray diffraction, both in the apo form and with the Pi bound [Luecke and Quiocho (1990) Nature 347, 402; Brune et al., (1998) Biochemistry 37, 10370]. PBP has two domains, hinged so they close around the Pi that binds in the cleft between them. This conformation change is an essential component of the binding process and provides a basis for the development of sensors. In the approach of Martin Webb's group, two 6-IATR rhodamines are covalently attached to the sulfur atoms of an Ala to Cys double mutant of PBP (A17C, A197C) [Okoh et al. (2006) Biochemistry 45, 14764]. The mutated residues are selected on the surface of the protein in order to have a large change in the relative positions of the two fluorophores upon Pi binding to the PBP, in turn to exploit a property of rhodamines: two rhodamines can stack to produce an essentially non-fluorescent complex [Kasha (1963) Radiat. Res. 20, 55]. On Pi binding and its associated conformational change, the fluorescence emission increases about 18-fold [Okoh et al. (2006) Biochemistry 45, 14764]. Based on absorbance changes, it has been suggested that the changes on Pi binding relate to disruption of the intramolecular rhodamine interactions ("stacking"). In fact, rhodamines in solution undergo concentration-dependent dimerization. The dimer has a different absorption spectrum to the monomer, while dimer fluorescence is very much weaker than that of the monomer [Selwyn and Steinfeld (1972) J. Phys. Chem. 76, 762; Chamber et al. (1974) J. Phys. Chem. 78, 380]. The dimer, in absence of external constraints, has a face-to-face interaction of the xanthene rings [Edmundson et al. (1984) Mol. Immunol. 21, 561; Blackman et al. (2002) Biochemistry 41, 12244]. In constrast, the rhodamine-labeled PBP provides a rigid scaffold, switchable between two states by binding of Pi. Despite the large fluorescence enhancement when Pi binds, the absorption spectrum remains similar to that of the dimer. In this sense, the rhodamine-labeled PBP appears to be an experimentally unique situation. Based on the experimental information available, we are here using classical molecular dynamics simulations [Fiorin et al. (2006) Biophys J 91, 2768] along with QM/MM simulations [Dal Peraro et al. (2007) Curr Opin Struct Biol 17, 149] to build structural models of the PBP/2-rhodamines adducts. Preliminary results suggest that the mode of stacking of the two rhodamines bound to the PBP is different than

the one assumed when they are free in solution (Figures (a) and (b)). In order to validate the structural model obtained, several techniques will be applied to calculate the optical properties of the double mutants, to be compared with the experimentally derived ones: TDDFT [Sulpizi et al. (2003). Phys. Chem. Chem. Phys 5, 4798], GW/BSE [Onida et al. (2002) Rev Mod Phys 74, 601], as well as CASPT2 [Garavelli (2006) Theoretical Chemistry Accounts, 116, 87] will be the main approaches followed. Our calculations will provide the physical basis of the optical properties' changes. The approach proposed may be used to predict structural facets of biochemical events monitored with fluorescence biosensors and may help establish a computational protocol to study fluorescent probes interacting with proteins.

Meher K. Prakash

Large scale pH-induced conformational changes in dengue virus envelope protein during cell infection

One of the key steps in the infection of the cell by dengue virus is a pH induced conformational change of the viral envelope proteins. These envelope proteins undergo a rearrangement from a dimer to a trimer, with large conformational changes in the monomeric unit. We use metadynamics simulations to capture the key aspects of these large scale pH induced changes. The stability of the protein structure is studied at low and high pH using all atom, explicit solvent simulations of the monomeric structures. These simulations suggest a mechanism with an intermediate detached state between the two crystallographic structures. Free energy profiles obtained along appropriate collective coordinates demonstrate the domain interfacial destabilization with pH. Using further analysis, the key residue level interactions responsible for the instability and the pH sensors in the envelope protein were identified. The insights gained from the present study and methodology can be extended for studying similar mechanisms in the E proteins of the other members of class II flavivirus family.

Michielssens Servaas

Hydrolysis of aspartic acid phosphoramidate nucleotides: a comparative quantum chemical study

L-Aspartic acid has recently been found to be a good leaving group during HIV reverse transcriptase catalyzed incorporation of deoxyadenosine monophosphate (dAMP) in DNA. This showed that L-Asp is a good mimic for the pyrophosphate moiety of deoxyadenosine triphosphate. The present work explores the thermochem- istry and mechanism for hydrolysis of several models for L-Aspartic-dAMP using B3LYP/DGDZVP, MP2/6-311++G** and G3MP2 level of theory. The effect of the new compound is gradually investigated: starting from a simple methyl amine leaving group up to the aspartic acid leaving group. The enzymatic environment was mimicked by involving two Mg2+ ions and some important active site residues in the reaction. All reactions are compared to the corresponding O-coupled leaving group, which is methanol for methyl amine and malic acid for aspartic acid. With methyl amine as a leaving group a tautomeric associative or tautomeric dissociative mechanism is preferred and the barrier is lower than the comparable mechanism with methanol as a leaving group. The calculations on the aspartic acid in the enzymatic environment show that qualitatively the mechanism is the same as for triphosphate but the barrier for hydrolysis by the associative mechanism is higher for L-Aspartic-dAMP than for L-Malic-dAMP and pyrophosphate.

Nerl Hannah

Interactions between nanoparticles and cells

Nanoparticles are currently investigated for usage in medical applications such as drug delivery and DNA/RNA therapeutics. However, little is known about the uptake mechanism and the toxicity of nanoparticles. The aim of this project is to investigate the interactions and toxicity of nanoparticles in cells.

Nguyen Chuong Ha Hung

Application of homology modeling and molecular dynamics in predicting 3D structure of G-Protein-Coupled Receptors

G-Protein-Coupled Receptors (GPCRs) are the largest class of human receptors responsible for the majority of signal transduction across the cell membrane. Almost 30% of all marketed drugs act on GPCRs. Despite their importance as drug targets, few experimental structural information is available since the difficulties in obtaining their X-ray structures. Therefore, homology modeling and molecular dynamics are key approaches in probing the 3D structural information of GPCRs. Here we propose the combination of homology modeling (HM) with molecular mechanics/coarse-grained (MM/CG) model to build the 3D structure of GPCRs. In this approach, the model obtained by HM is used as initial structure for MM/CG simulation. MM/CG allows a fast and efficient description of the mechanical coupling between the active site with the enzymatic substrate. Therefore, this method could help to improve the quality of GPCR models for studying ligand binding. Our approach is tested by modeling human beta2-adrenergic receptor based on crystal structure of bovine rhodopsin (PDB code: 1F88).

Nuansing Wiwat

Spectroscopy and diffraction study of short aromatic peptides

The short aromatic peptides Phe-Phe, Fmoc-Phe-Gly-OH and N-protecting reagent 9-Fluorenmethanol were crystallized from a highly polar solvent (hexafluoro-2-propanol) and characterized by confocal Raman spectroscopy and X-ray diffraction in order to study crystal structures of the interactions between aromatic rings in fluorenyl and phenyl.

Ozerov Ivan

Structural aspects of peptide-receptor recognition

There are many low-molecular peptides with known physiological effects. Besides that, more and more novel artificial peptides are discovered. Their biological activity is investigated for the purpose of making new drugs. For better understanding of the peptide's role in nature it is necessary to inquire into interactions of such ligands with their receptors and to determine intermolecular contacts specific for the certain functional groups. Such study would be useful for the design of new peptides with predefined pharmacological and kinetic properties. During this research the interactions of peptide ligands with their receptors have been analysed. 3D structures of ligand-receptor complex were taken from PDBBind database. The database consists of more than 3000 receptor-ligand complexes and includes more than 150 structures with peptides possessing two or more peptide bonds. A number of modern quantitative approaches such as the concept of MHP (Molecular Hydrophobicity Potential) for the numerical estimation of nonpolar interactions were used. Also the other types of intermolecular contacts were analyzed including hydrogen bonds and stacking. The aim of this work was to determine structural features typical for the peptide-binding receptors responsible for specific recognition of peptides in the active site. The results of this research will be used for the efficient design of novel peptides with modified biological activity.

Porrini Massimiliano

Heme cavity dynamics of photodissociated CO from ba3-cytochrome c oxidase: the role of Ring-D Propionate

Intracavity molecular dynamics studies of photodissociated carbon monoxide from ba3-cytochrome c oxidase have been performed by sampling the phase space with several hundreds of trajectories each integrated up to 100 ps time interval. It is shown that the cis conformation of protonated ring-D propionate of heme a3 and its trans conformation for the deprotonated species control the CO location by creating two distinct equilibrium states for CO confined in a cavity internal to the distal heme pocket. Thus, these cis (closed gate) and trans (open gate) conformations of heme a3 propionate D play the role of a switch, opening or closing a gate for confining CO in a cavity internal to the heme pocket or releasing it to a bigger outer cavity. The geometry of the inner cavity and the validity of the potential function employed are further investigated by Density Functional Theory calculations for the active site, potential of mean force curves along the copper-CO bond as well as with Quantum Mechanics/Molecular Mechanics calculations. In the light of the present study trajectory scenarios for the dissociation of CO previously suggested from time-resolved infrared spectroscopy are reexamined.

Pouillon Yann

Structural and optical transitions of biliverdin

Calculated IR, Raman, and optical spectra of a phytochrome.

Pyrkov Timothy V.

PLATINUM: Web-site for analysis and visualization of hydrophobic organisation of biomolecular complexes

Molecular docking approach has become an integral part of biomolecular studies aimed at understanding the mechanism of enzyme functioning and drug discovery programmes. Improvement of methods to place and score a ligand in the receptor binding site used in docking is now an area of active research. The major problems arise from inaccuracy of energy scoring functions and limited flexibility of the receptor structure in the docking procedure. One of the promising approaches is re-scoring of the docking poses with more efficient ranking criteria. Many popular scoring functions do not explicitly account for ligand-protein hydrophobic and stacking contacts. In our studies (Pyrkov et al., 2007, PROTEINS 66, 388-398; Pyrkov et al., 2008, SAR QSAR Environ Res 19, 91-99) we have demonstrated that taking these interactions into account can greatly improve the efficiency of scoring functions. To make this approach available to a broader community, we have designed web-server PLATINUM (Protein-Ligand ATtractions Investigation NUMerically). It provides an easy-to-use and customizable tool to estimate the hydrophobic/hydrophilic match or mismatch on the interface of two interacting molecules, given their 3D-coordinates. To calculate molecular hydrophobic/hydrophilic properties we use the concept of Molecular Hydrophobicity Potential (MHP) which is based on empirical atomic constants derived from the water-octanol partition coefficients for organic compounds. Besides, hydrogen bonds, stacking, and cation-pi contacts are assessed in a quantitative manner. The efficiency of using explicit hydrophobic term in a scoring function is demonstrated by development of ATP-specific scoring function and its application to modeling 3D-structure of the complex of ATP with Ca- and Na/K-ATPase.

Pyrkova Daria V.

Molecular dynamics of binary phospholipid bilayers: a case study of DOPC/DPPC system

Biological membranes are complex molecular mixtures. Their properties are to a large extent governed by the composition of the bilayer that comprises lipids of various types and different membrane proteins. Many experimental studies are bases on simplified model systems. Theoretical methods play an important role in studying the atomic-scale picture of the structure and kinetics of membrane assembly. One of the most informative computational techniques to do that is molecular dynamics simulations (MD). Until now most computer simulations have been focused on bilayers of pure lipids and lipid/cholesterol mixtures (studying of formation of ordered lipid domains, etc.). Only recently, a number of studies on binary phospholipid systems have appeared in scientific literature. In this study we present results of detailed simulations of a bilayer composed of a mixture of dipalmytoylphosphatidylcholine (DPPC) and dioleoylphosphatidylcholine (DOPC) phospholipids. Five systems were generated: two of them comprised only one type of lipid molecule, and three composed of mixtures of DOPC and DPPC with 70%, 50% and 20% fraction of DOPC. For these five systems we carried out molecular dynamic simulations of 15 ns length. Several important macroscopic average characteristics were estimated for the equilibrium parts (during last 5 ns) of the trajectories: the area per lipid molecule (AL), the order parameter of acyl chains (Scd), the distance between the planes determined by phosphorus atoms of lipids in different monolayers (DP-P), the distribution of molecular hydrophobicity potential (MHP) on the membrane surface. Analysis of average macroscopic characteristics (AL, DP-P) of single-component systems showed that they are in good agreement with those observed experimentally. It was shown that Scd and distribution of MHP steadily changes with the increase of concentration of DOPC. Hydrophobic clusters in mixed systems have the same character as those in the systems containing only DPPC. Physically reliable model for the zwitterion two-component phospholipid bilayers with different concentration of unsaturated lipids in the liquid crystalline phase was elaborated and validated in our computational experiments.

Rangaswamy Geethalakshmi

Structural investigation of the active sites of vanadium containing enzymes with QM/MM computed 51V NMR spectra

51V NMR spectroscopy can be a sensitive tool to elucidate the structural details of the active sites of vanadiumdependant haloperoxidases. Using a protocol based on X-ray structures and a popular hybrid QM/MM optimizations, 51V NMR tensor parameters can be computed for the native and peroxo form of the entire vanadium enzyme, where the special attention is called to the protonation state and protonation sites of the vanadates cofactor. In particular, anisotropic chemical shifts and the nuclear quadrupole tensors appear to be sensitive to changes in the proton environment of the vanadium nuclei. For the vanadium containing haloperoxidase [1], QM/MM approach turned out to be a valuable complement to experimental 51V solid state NMR spectroscopy and X-ray crystallography to identify possible structural candidates. For the native bromoperoxidase [2] and the peroxo variants [3], the predicted 51V NMR data should certainly allow for similar structural assignments, once the accurate solid-state NMR spectra become available experimentally. Based on the predicted NMR spectra, the distinction between different protonated states in the active site of these enzymes should be readily possible. Thus, the combination of protein Xray crystallography, QM/MM modeling, and solid state NMR spectroscopy makes an eminent structural tool for the active site of metalloenzymes.

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Ruiz Serrano Alvaro

Towards an approach for variable spatial accuracy in linear-scaling Density Functional Theory calculations with the ONETEP program

Density Functional Theory (DFT) [1] has proved to be one of the most successful methods for quantum mechanical simulations of matter. It is used in many fields of chemistry, physics and biology to determine several properties of molecules and materials, such as binding energies, structures and spectra. Conventional DFT calculations scale with the third power of the number of atoms N, O(N3), therefore only molecules with no more than few hundreds of atoms can be simulated. onetep [2] is a program for DFT calculations in parallel computers in which the computational effort scales linearly with the number of atoms, O(N), so molecules with thousands of atoms like those encountered in biochemistry [3] or nanoscience [4] can be simulated. ONETEP is based on the single-particle density matrix, $\rho(\mathbf{r},\mathbf{r}')$, which for systems with a non-zero band gap decays exponentially as a function of the distance between $\mathbf{r}$ and $\mathbf{r}'$. In conventional DFT, this matrix can be written in terms of the molecular orbitals $\psi_i(\mathbf{r})$ like:

$$\rho(\mathbf{r},\mathbf{r}') = \sum_i f_i \psi_i(\mathbf{r}) \psi_i^\star(\mathbf{r}'), \tag{1}$$

where f_i are the occupancies. The density matrix can be truncated to a sparse-band matrix $\rho(\mathbf{r},\mathbf{r}')$. In practice the way to do that is by expressing it in terms of a set of spatially localised, non-orthogonal functions, $\{\phi_\alpha(\mathbf{r})\}$:

$$\rho(\mathbf{r},\mathbf{r}') = \sum_\alpha \phi_\alpha(\mathbf{r}) K^{\alpha\beta} \phi_\beta^\star(\mathbf{r}'), \tag{2}$$

where $K^{\alpha\beta}$ is called the density kernel, defined by the above equation. In ONETEP the set of functions $\{\phi_\alpha(\mathbf{r})\}$ is optimised during the calculation, along with the density kernel, in order to minimise the energy of the system. The functions $\{\phi_\alpha(\mathbf{r})\}$ are called Nonorthogonal Generalised Wannier Functions (NGWFs) [5], and they are constrained within an atomic centred region. The NGWFs can be represented as a linear combination of psinc functions [6]. Alternatively they could be represented as a linear combination of spherical waves [7], a systematic basis set that naturally allows for imposing localisation. The aim of this project is to implement a multiple-accuracy method in ONETEP that will allow to perform plane-wave accuracy DFT on a particular region of a molecule while treating the rest at a lower level of accuracy. At the high-accuracy region a full DFT calculation will be performed, and both the density kernel and the NGWFs will be optimised according to normal ONETEP procedure. In the low accuracy region an approach similar to the self-consistent ab-initio tight-binding method (SC-AITB) [8] will be used. This method requires NGWFs that do not vary during the calculation, and only the density kernel $K^{\alpha\beta}$ will be modified. Therefore it is important to choose the NGWFs suitable for the particular chemical environment. Accordingly, the different contributions to the forces on the atoms have to be implemented as they will be needed in structure optimisation and molecular dynamics simulations. This method can be implemented to scale linearly with the number of atoms. As a result it will allow even larger simulations with ONETEP where the "high accuracy" region could consist of thousands of atoms and the "low" accuracy of tens of thousands. Such simulations are useful in many fields. For example in biophysics they could allow the simulation of an entire ion channel in a lipid membrane while describing naturally the charge transfer and polarisation [9], which are very difficult to achieve by force field approaches.

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Schmidt Thomas

Do molecule crystal environments indeed approximate protein surroundings?

The success of rational drug design strongly depends on an intimate knowledge of the interactions between the target enzyme and the active compound. These interactions are determined by the electron density (ED), which is, in principle, experimentally available by high-resolution X-ray measurements. Although high-resolution X-ray experiments become more common for small- to medium-sized molecules, biologically active compounds and macromolecules, the corresponding experiments for proteins or protein-ligand complexes are still extremely demanding. Hence, most approaches use experimental EDs of inhibitors obtained from crystals of the pure compound to approximate the EDs in biological environments, for example, in a given enzyme-inhibitor complex. Such investigations are based on the assumption that the environment inside of a crystal of the pure compound influences the ED, and thus all the properties, of the inhibitor in a similar way as the enzyme surrounding. This supposition was tested using quantum mechanical (QM) and combined quantum mechanical/molecular mechanical (QM/MM) calculations for two inhibitors, the reversible trans-4-(amminomethyl) cyclohexan-1-carboxylic acid (AMCHA) and the irreversible E64c[1]. Four different environments were tested within these calculations (the gas phase, a continuum solvent model, crystals of the pure compound and the enzyme-inhibitor complexes). To investigate the reason for the differences in the EDs, the source function was applied to water clusters as models systems.

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Schneider Julian

A classical potential to model protein adsorption on natively oxidised titanium surfaces

In order to investigate the surface properties of metals in a realistic fashion it is crucial to take into account the thin oxide layer that forms spontaneously when the surface is exposed to an oxidizing environment. Starting from reference oxide layer structures obtained in extensive first-principles molecular dynamics simulations, we have developed a novel classical potential which is able to reproduce the topological binding features of the amorphous oxide network on Ti as well as the interfacial behavior of the TiOx/water interface. The analytic form of the potential has been chosen so that it can be easily combined with well-established biomolecular force fields. This allowed us to perform classical simulations of small organic molecules on the oxide surface and compare the results with those of density functional theory calculations. Ongoing work is focusing on the application of our force field to simulate the adsorption of amino acids, small peptides and larger protein fragments on oxidized Ti surfaces.

Schulz Robert

Simulating E.coli's major efflux pump: the extrusion mechanism for substrates

Bacteria, such as E. coli, use multidrug efflux pumps to export toxic substrates through their cell membranes. The RND transporter of the AcrAB-TolC efflux pump is able to export structurally and chemically different substrates. This is one reason of the increasing antibiotic resistance of bacteria. The energy is converted in the transmembrane domain and transduced towards the periplasmic part and used there to initiate a three-cyclic peristaltic pumping [1]. The effects of conformational changes on the extrusion of drugs, which have been located into one of the proposed binding pockets, are assessed using different computational methods like targeted molecular dynamics (TMD). The mechanism of pumping is investigated in greater detail than ever before [2]. Within TMD, a linear transition between two conformations is described. To investigate the effect of the conformational changes a feasible substrate, doxorubicin, has been placed into one of the binding pockets. Previously, the conformational changes of TolC which lead to an opening of the aperture have been investigated [3].

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Seydou Mahamadou

Molecular mechanics and ab-initio investigations of carbon nanotube and graphene sheet interaction

The size, structure, low reactivity and hydrophobic nature of carbon nanotubes make them ideal candidates to probe local force in AFM. To determine the mechanical properties of these nanotubes, measures of thermal noise, modulation of frequency or contact are experimentally realized in our team. These measurements are made by interacting probes on a surface of graphene witch is known to be perfectly flat and smooth. To interpret the results, we have made analytical calculations, molecular mechanics and quantum chemistry. In this paper we present calculations of molecular mechanics and ab-initio interaction of a nanotube with structure given on a graphene. We show the effect of the interaction length and diameter on the accession of the tube. The general idea is to understand what governs the adhesive energy of nanotube on the surface, its elastic response, the friction and get an understanding of the mechanical behaviour of nanotube when interacting with a surface. The results will be compared to experimental data obtained by dynamic AFM

Sgrignani Jacopo

NMR chemical shifts and molecular simulations: a multidisciplinary approach to study metalloproteins

Nuclear magnetic resonance (NMR) chemical shifts are experimental observables available in the first stage of the protein structure determination process. Recently some methodologies has been implemented to build structural model of proteins using only this experimental data [1, 2]. All these methodologies use the chemical shifts information both to select the protein secondary structural elements and to evaluate the structures obtained. The secondary structure of the different regions of a protein is usually selected comparing the actual data with databases of protein fragments whose nuclei have been assigned; after this selection process the chosen fragments are assembled using computational techniques. Finally, the produced structures are ranked using both molecular mechanics energy and a chemical shifts based score, calculated using the differences between the experimental and the simulated NMR spectrum [3]. The data available in literature highlight that the structures built using chemical shifts can have a quality comparable to those produced using classic NMR protocol [4]. However, none of the structures investigated contains metal ions. Thus we decided to try to extend these methods also to metalloproteins identifying a computational approach to model the metal in the chemical shifts derived structures. Computational methods such as Replica Exchange Molecular Dynamics (REMD) and Montecarlo based Simulated Annealing (MCSA) have been combined with the experimental information given by the chemical shifts using recently released software that are able to perform very fast NMR spectra prediction, allowing the use of chemical shits as an experimental constrain in molecular simulations. The method has been preliminary tested using two small metalloproteins, i.e. the yeast copper chaperone Atx1 and the copper(I)-binding domain of the Ccc2 ATPase, to validate the computational protocol and to explore the performances of the different software and then applied to challenging systems such as human Cu, Zn superoxide dismutase and the soluble CuA domain of Thermus thermophilus cytochrome c oxidase.

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Spiga Enrico

A novel coarse-grained force field for proteins which accounts for chirality and electric dipoles of aminoacid side-chain

We have recently introduced a novel non-radial potential for coarse?grained (CG) molecular dynamics (MD) simulations of proteins. Here, we present the ongoing development of a CG force field, which is consistent with this new Hamiltonian form, and takes into account the chirality of L-aminoacids and their side-chain electrostatic dipolar contribution. For each aminoacid we impose the chirality of CG sidechain beads on the basis of the statistical analysis of a non?redundant set of structures extracted from the Protein Data Bank. Whereas for aminoacid side?chains that naturally possess a permanent dipole we describe its discrete orientation in space as extracted from all-atom MD simulations. Both the chirality and dipoles of side?chains are consistently coupled with a non-radial CG representation of the backbone scaffold, and contribute to describe the intrinsic anisotropy of protein structures. These ingredients would likely lead to an improved description of the structural and dynamic properties of large protein assemblies and networks at CG resolution as shown by preliminary results obtained for a set of significant test cases.

Tipmanee Varomyalin

Electron transfer in heme-containing protein: prediction of reorganisation free energies, comparing Ru-modified cytochrome c, and cytochrome b5 and four helix bundle protein

Most biological electron transfer(ET) reactions are usually described by semiclassical Marcus theory. In this theory rate of reaction, k_{et}, is determined by three factors: electronic coupling between donor and acceptor (H_{12}), driving force (ΔG), and an exponential term containing reorganisation free energy (λ).

Reorganisation free energy is difficult to measure in the experiment. Here we present a theoretical technique that allows us to estimate reorganisation energy quantitatively. Using density functional calculation and molecular dynamics simulation with an electronically polarizable force field, we calculate reorganisation free energies for three heme containing ET proteins that differ in their protein fold and in the hydrophilicity, and solvent accessibility of the electron accepting cofactor. As a validation of our approach we calculate the reorganisation free energy for intraprotein ET from heme c to a solvent exposed $Ru(am)_5$ complex (am= ammine ligand) docked to His33 of cytochrome c, and obtain a value of 1.28 eV in good agreement with the experimental estimate of 1.15-1.24 eV. Furthermore, we report the reorganisation free energies from the intraprotein ET from heme c, and heme b5, to a $Ru(bpy)_2(im)$((bpy=2,2'-bipyridine, im = imidazole), obtaining reorganisation free energies, equal to 1.26 eV for heme c and 1.17 eV for heme b_5, respectively. The major components of reorganisation are the protein and the solvent, whereas the contributions from the redox active cofactors are in all cases small but not negligible. In three ET proteins protein reorganisation free energy is a collective effect including many residues, each of which contributing a small fraction. In such a case reorganisation free energy may not be effectively controlled by single point mutations but by the degree of solvent exposure of the ionizable cofactors.

Valsson Omar

Ab-initio study of the photoisomerization of retinal chromophore models

We investigate the gas-phase Franck-Condon relaxation of several protonated Schiff base (PSB) models of the 11-cis retinal chromophore, using the quantum Monte Carlo (QMC), complete-active-space second-order perturbation theory (CASPT2), and coupled cluster (CC) approaches. In the last decade, most studies of the isomerization mechanisms of the retinal chromophore in vacuo and in the protein have employed the complete-active-space self-consistent-theory (CASSCF) approach, and predicted a relaxation proceeding via a CC-bond stretching and bond inversion, followed by a rotation around a bond which was double in the ground state [1]. This picture has been recently challenged by CC calculations by Send and Sundholm [2]. To settle this controversy, it is important to employ techniques such as QMC and CASPT2, which allow a balance description of both dynamical and static electronic correlation since CASSCF calculations lack dynamical correlation while CC may fail in describing excitations with a strong multi-reference character.

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Vanni Stefano

Insights into structure and function of adrenergic receptors from all-atom molecular dynamics simulations

G protein coupled receptors (GPCRs) are a large family of integral membrane proteins involved in signal transduction pathways, making them appealing drug targets for a wide spectrum of diseases. The recently crystallized structures of two engineered adrenergic receptors have opened new avenues for the understanding of the molecular mechanisms of action of GPCRs, but they also generated some controversy on the proposed mechanism of GPCR activation[1,2]. Taking the two crystal structures as a starting point, we carried out submicrosecond molecular dynamics simulations of wild type β1 and β2 adrenergic receptors in a lipid bilayer under physiological conditions. We identified highly conserved Asp(2.50) as a crucial residue in the activation mechanism and a direct correlation between its protonation state and the cytoplasmatic conformation of the receptors. In particular, protonation of Asp(2.50) leads to recovery of all the previously suggested features of inactive GPCRs including formation of a salt bridge between the cytoplasmatic moieties of helices III and VI ("ionic lock") that is absent in the crystal structures[3], while deprotonation of Asp(2.50) keeps the "ionic lock" open and drives the receptors in an active-like conformation. Evolutionary conserved differences between opsins and non-opsins GPCRs in the surrounding of Asp(2.50), that influence the acidity of this residue, can be rationalized with respect to the constitutive activity of many class A GPCRs.

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Yong-Hyun Kim

Melting of nanoclusters and its implication to protein dynamics

We calculated a first-principles heat capacity of Al nanoclusters. Constant-temperature molecular dynamics (MD) with first-principles force fields were used to sample potential energy ensembles of the Al clusters at various temperatures from 130 to 1200K. The total simulation time was about 10 ns. Using the multiple-histogram method, we can reproduce all characteristic features of nanocluster melting, including the location, height, and broadening of the melting transition peak, consistent with experiment. The sampled first-principles trajectories of the Al clusters near the melting temperature represent various, intrinsic dynamic states of the Al clusters. We will also discuss implications of our findings to understanding of protein dynamics.

Zhang Chao

Assessment of biomolecular force fields for non-ideal NaCl and KCl aqueous solutions

Ionic strength plays a fundamental role in signal transduction and molecular recognition. Standard biomolecular force fields for ions such as Na+, K+, Cl- are developed under infinite dilute condition[1]. Here we evaluate the accuracy of such models for NaCl and KCl in aqueous solution at finite concentrations. The Kirkwood coupling parameter method [2] was used. The finite size correction for ion solvation in Particle Mesh Ewald method, which is strongly dependent on the dielectric constant of the solution [3], was included. The following properties were calculated as a function of concentration and compared with experimental data [4-6] (i)The excess chemical potentials (activity coefficients), which indicate the no-ideality of solutions; (ii) The dielectric constants of the solutions. (iii) The structural factors.

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Zhu Lihze

Replica Exchange MD study of HAMP domain

The HAMP domain is a linker domain in prokaryotic sensor proteins which function in two-component signal transduction pathways. This four-helices-parallel-coiled-coil domain has been proposed for signal conversion between the receptor domain and transmitter domain. We present Replica Exchange MD simulations of HAMP (from A.fulgidus) in both the active(wild type) and the inactive state(mutant). Our simulations show that subtle changes in the hydrophobic core of HAMP lead to larger rearrangements. The implications of these results for other HAMP containing signal transduction pathways are discussed