UNIVERSITÉ PARIS-EST MARNE-LA-VALLÉE

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Book of Abstracts

Bio-molecular interactions: Experimental input from chemical crystallography

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Diffraction experiments provide a large quantity of potentially useful case studies for bio-molecular interactions. Hydrogen bonds represent the classical example: in terms of quality, single crystal neutron diffraction affords atomic coordinates and displacement parameters of unmatched accuracy.[1] The results thus obtained may be transferred to more routine studies in structural chemistry and biology. X-ray diffraction with sub-atomic resolution down to 0.4 Angstroem requires high-quality crystals and offers direct experimental access to the electron density: halogen bonds can be visualized based on the electron distribution of the partaking atoms.[2] Temperature-dependent diffraction experiments go beyond static geometry: they reliably deconvolute electron density and thermal motion and allow to validate statements concerning displacement parameters from different levels of theory.[3]

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Predicting Ligand Protein Interactions with Alchemical Free Energy Methods on Blinded Datasets

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Computer aided drug design has gained momentum in recent years, with the aim to reduce the overall cost of the development of a new drug. Therefore, the reliable prediction of binding poses and affinities of small/drug-like molecules to target proteins, with or without available crystal structures, is essential. However, despite the increase in available computational power and vast algorithmic improvements, this still remains a challenge. In particular, while there is a vast array of methods available for predicting protein-ligand interactions, until recently there has not been a systematic approach to compare different methods and assess their reliability on a set of blinded experimental data (IC50 values from FRET assays or similar). The drug design data resource (D3R) grand challenge tries to address this in form of a competition. Two rounds of the grand challenges were run in 2015 and 2016. Each challenge consisted of a blinded dataset of small molecules that serve as potential binders to a target protein. Participants were then given five months to predict the biding affinities of the small molecules to the protein as accurately as possible using any method of their choice. The accuracy of each of the predictions was then assessed after the release of the blinded data once the competition period was concluded.

Here I will present alchemical molecular dynamics (MD) simulation- and state-of-the-art analysis techniques to compute free energies of binding between ligands and proteins in the context of the D3R challenges. For this purpose, the semi-automated workflow used for ligand parameterization, simulation set, production runs, and automated analysis will be introduced based on various freely available software packages, such as FESetup [1] and Sire [2]. The two D3R grand challenge datasets will serve as a basis to illustrate the workflow and highlight the successes and failures in the presented techniques used for predicting binding affinities [3]. The D3R datasets consist of compounds that serve as inhibitors to heat shock protein 90 (HSP90) and farsenoid receptor X (FSR X). Lastly, I will discuss how well the presented alchemical MD based workflow fares in comparison to other approaches such as biased MD simulations or quantum mechanical methods used by other participants of the challenge.

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Multiscale simulations in molecular medicine: recent advances from Juelich

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Biological systems at times may be conveniently be described at different levels of granularity (QM, all-atoms force field, coarse grain). One way to address this issue is by combining different descriptions. Here we will review recent multi-scale simulations from our lab to systems of pharmacological relevance. We will close the talk with a perspective of simulating signaling cascades by combining multi-scale simulation with systems biology approaches.

Learn about learning, from a computational neuroscientific perspective

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Abstract: Across spatial and temporal scales, functional and structural brain modifications induced by normal experience (learning) or exposure to intrinsic pathogenic conditions in genetic disease, can only be understood by taking a network perspective, according to which function emerges from structured interactions among brain elements. We aim to achieve new insights into the processes of normal and abnormal experience-induced modifications in brain and genetic networks, using mathematical tools and modeling approaches to bridge research domains and spatial scales of inquiry. Using computational models (from single-neuron based to Kuramoto -models), insights from genetic modifications acting at a molecular level (resulting from the molecular genetics research line) are linked to non-invasive observations of changes in the human brain acting at neuronal population level (resulting from fMRI, MEG, EEG, and behavioral measures).

Tau protein and heparan sulfates interaction in Alzheimer's disease

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Protein misfolding is a central event in the pathogenesis of several neurodegenerative diseases including Alzheimer's disease, the most important form of neurodegeneration. One of the main hallmarks of this disease is the accumulation of neurofibrillary tangles (NFTs) in neural cells. NFTs are made of the microtubule associated protein tau in an abnormally phosphorylated and aggregated form. Although the abnormal phosphorylation and aggregation of tau have been related to the misfolding of the protein, the cause driving this misfolding are still unclear. Therefore, molecular chaperons associated with disease and able to induce conformational changes in tau are under research. Recently, we showed that HS, a family of highly anionic polysaccharides classically present at the extracellular matrix and at the cell surface of most mammal cells, colocalize with tau in cell models of Alzheimer's disease-related tauopathy. We showed that inhibiting the expression of a HS sulfotransferase in animal models of tauopathy results in disease arrest and animal recovery. We hypothesized that upon interaction with tau HS chains can induce conformational changes in the protein, allowing abnormal phosphorylation and aggregation of tau. Investigations on the capacity of HS to induce conformational changes in tau and supporting the involvement of HS in disease are under research.

Biomolecular interactions *in situation:* The example of phytohormones

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Plants are all the time submitted to changes of the environment. These changes can concern physical parameters, such a light intensity, light quality, temperature (abiotic stresses). They can also be attacks by bacteria, insects, fungi (biotic stresses). To respond to these environmental stresses, plants are going to synthesize little molecules, the so-called phytohormones. For instance, abscisic acid is synthesized during drought stress or cold stress; salicylic acid during attach by bacteria; jasmonic acid during wounding. Then, these little molecules will trigger signalling pathways leading to major remodelling of gene expression that will allow plant to acclimate to the new conditions. Besides, some phytohormones, such as auxins, cytokinins or gibberellins, are synthesized during developmental processes. These developmental phytohormones trigger signalling pathways that will lead to developmental responses such as cell division, cell elongation, or cell differentiation. Phytohormones can trigger signalling pathways because they are recognized by proteins. The binding to proteins alter the protein conformation which induce changes of activity, location, protein/protein interaction….

For most phytohormones, there is only limited numbers of proteins they can bind. These proteins are the receptors for the phytohormones. Salicylic acid differs from other phytohormones because no clear receptor for it has been identified. Or, to be more precise, many proteins (up to 100) have been identified in large scale salicylic acid-binding proteomic studies. Quite surprisingly, amongst these proteins are enzymes of the primary metabolism, such as enzyme of the Calvin cycle. This leads to several questions: do all these proteins bind salicylic acid? What are the structural determinants allowing the binding of salicylic acid to these proteins? Is it possible to identify a consensus sequence for salicylic binding? We believe ab initio molecular dynamics can provide answers to some of these questions.

Molecular dynamics simulations of GPCR-ligand interactions and GPCR activation

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G protein-coupled receptors (GPCRs) are the most heavily investigated drug targets. This large family of transmembrane proteins accounts for the molecular targets of over 30% of FDA-approved drugs. Recent breakthroughs in GPCR X-ray crystallography have opened a new era of structure-based ligand design, in which atomistic-level understanding of GPCRligand interactions and GPCR activation is essential. We use microsecond-scale all-atom molecular dynamics (MD) simulations to investigate these issues. Here presented is our recent work on the μ-opioid receptor–the target of opioid analgesics such as morphine. Our MD simulations with enhanced sampling captured back-and-forth transitions between the receptor's inactive and active conformations [1]. The ligand binding affinities calculated with free energy perturbation achieved ~1 kcal/mol accuracy [2].

It is highly challenging, however, to apply such approaches on GPCRs for which no high-resolution structure is yet available. This is the case for olfactory receptors–the largest GPCR family that accounts for half of all human GPCRs and can recognize over a trillion different odors. Homology modeling enables the application of MD simulations on these receptors. The progress the perspectives in this aspect will be also discussed here.

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On the role of small S-nitrosothiols (RSNOs) as light-sensitive NO-donors for delivery in biological media

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Recent *in vivo* studies of the formation of nitric oxide through the hydrogen sulfide H_2S-assisted heme (Fe^{3+}-porphyrin) catalyzed reduction of nitrites [1] stressed out the implication of S-nitrosothiols (RSNOs) and of several small sulfur bearing species (e.g. HS^-, HSNO) in such processes. S-nitrosothiols are also used as alternative NO-releasing drugs and as potential NO-storage and transport. [2] The medical implications of such sulfur containing molecules are important (see Ref. [1] for more details), where nitrites are involved in the metabolism of H_2S in physiological, intracellular and biological media. They are used as antidotes for H_2S poisoning. Nevertheless, the implication of RSNOs remains unclear and / or non-identified because of the lack of information or characterization of the involved sulfur species, their spectroscopy or reactivity. Obviously, this is mandatory for the control and the regulation of biological and therapeutic processes. [3]

Since 2013, we performed systematic studies of small S-nitrosothiols in order to characterise them spectroscopically in their electronic ground and excited states, where we treated their neutral, positively charged and negatively charged species. Let's cite for instance, our work on HSNO, $(HSN/HNS)^q$ (q=0,-1,+1), $(SNO/NOS)^q$ (q=0,-1,+1), $[S_2NO]^q$ (q=0,-1,+1). [4] For that purposes, we use different *ab initio* methods (both standard and explicitly correlated versions) to compute multi-dimensional potential energy surfaces (PESs) of these molecular species. All electronic computations are performed using Gaussian 09 [5] or MOLPRO [16] packages. Afterwards, these PESs are incorporated into perturbative and variational treatments of nuclear motions where the couplings between all angular momenta (electronic, rotational and spin-orbit) are considered. Several examples will be presented with emphasis on the potential role of S-nitrosothiols as light sensitive NO donor in biological media.

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OH1 from Orf virus: a new tyrosine phosphatase that displays distinct structural features and triple substrate specificity

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Protein tyrosine phosphatases (PTPs) from bacteria and virus are recognized as important effectors of host-pathogen interactions. For instance, the VH1 protein is essential for the pathogenesis of Vaccinia virus contributing to elude the immune response. The structural characterization of VACV VH1 revealed a homo-dimeric quaternary structure involving an extensive domain swapping of the N-terminal α-helices stabilized by non-covalent interactions[1]. Proteins sharing sequence identity to VH1 have been identified from other viruses, even though a complete study of these phosphatases is not currently available. In this work, homology modeling of the VH1 homologue in the Orf virus, named OH1, revealed both gap insertion and a Ser to Cys substitution that could impede the quaternary dimeric organization, so we determined the crystal structure of OH1. This virus, the causative agent of contagious Ecthyma, belongs to the *Poxviridae* family as Variola and Vaccinia but it is a representative member of a different genus, the Parapoxvirus genus. Correspondingly to Variola and Vaccinia VH1, OH1 is a dimer. Nevertheless, instead of dimerization involving domain swapping of the two N-terminal helices α1, OH1 homodimer is remarkably stabilized by a covalent disulfide bond engaging both N-terminal cysteine 15 residues of helices α1in the two monomers. Residue Cys15 is only conserved within the Parapoxvirus genus (Segovia et al, submitted in Structure). The *in vitro* functional characterization confirms that OH1 is a dual specificity phosphatase, and unexpectedly reveals its ability to dephosphorylate phosphatidylinositol 3,5 biphosphate. Docking analysis of several phosphatidylinositol phosphates confirm that they can be accommodated in the active site of OH1. This new activity could be relevant in phosphoinositide recycling during virion maturation. By analogy with VH1, where the homodimer has been proposed to be a structural and mechanistic feature to regulate the activity and the recognition of its putative physiological substrate STAT1[2], we are now undergoing pull-down experiments of OH1 with STAT1, while exploring *in silico* this possibility of interaction for OH1 complexed to STAT1.

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Photoswitching mechanism of the Fluorescent protein Padron

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Fluorescent proteins of the GFP family are widely used in cellular imaging technics. Among them, activatable proteins are essential players in nanoscopy approaches based ont the super-localization of single molecules. These fluorescent proteins are fascinating systems since very few mutations, even only one, may strongly affect fluorescent properties, quenching processes, bleaching and blinking phenomena.
Fluorescent proteins are then interesting objects to study and analyze the interplay between the protein dynamics, the chromophore-surrounding interactions and the different processes occurring in the singlet excited state. We will describe particularly the photo-isomerization process and the protonation change in the photoswitchable protein Padron.
The simulation of these rare events is based on molecular dynamics at nanosecond timescale and must be done without prior choice of the environment reaction coordinates.

Free energy of solvation of molecules of any size in few minutes by molecular density functional theory

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Understanding and predicting solvation of molecules and macromolecules or protein-drug affinity for example requires an explicit description of the solvent molecules at the same atomic level as the solute itself. As an alternative to the precise but very time consuming explicit solvent numerical simulations, we propose a liquid-state physics approach called the molecular density functional theory in three dimensions (MDFT). It is based on the molecular Ornstein-Zernike equations and on the minimization of a classical functional of the molecular density of the solvent density. The functional at its minimum is built to be the solvation free energy and the density that minimizes the functional is the solvent density at equilibrium. While we lose some dynamical information in the process, MDFT allows to compute accurately the solvent position and orientation distribution around a given solute or between two solutes and the associated free energy of solvation or binding *in few minutes only*.

I will first derive the method and show why and how one can trade reasonable precision against a speedup by four orders of magnitude, which results in computations of solvation free energies and solvation profiles in few minutes only. Then, I will benchmark the method by showing systematic comparisons of free energies of solvation as calculated by reference molecular dynamic simulations and with MDFT. Finally, I will illustrate the calculation of protein-ligand binding free energies and of the preferential positions and orientations of water molecules around these molecules or complexes.

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A multiscale computational approach to explore the complex dynamics of an ion channel voltage sensor domain

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Voltage-gated ion channels are ubiquitous proteins that orchestrate electrical signaling across excitable membranes. Key to their function is activation of the voltage sensor domain (VSD), a transmembrane four alpha-helix bundle that triggers channel opening. Modeling of currents from electrophysiology experiments yields a set of kinetic parameters for a given channel, but no direct molecular insight. Here we use molecular dynamics (MD) simulations to determine the free energy landscape of VSD activation and to, ultimately, predict the time evolution of the resulting gating currents. Our study attempts at providing the long-sought-for bridge between electrophysiology and microscopic molecular dynamics and confirms, as already suggested on the basis of experiments, that rate-limiting barriers play a critical role in activation kinetics.

CECAM Discussion-Meeting

"Modelling bio-molecular interactions: A multi-scale approach joining theory and experiment"

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