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

Proposed dates and place:

Spring 2017

Université Paris-Est Marne-la-Vallée

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Proposal

1. Introduction and motivation

Molecular recognition is the cornerstone of all cellular processes in living systems. However, the nature of the underlying molecular complexes and recognition mechanisms is still poorly understood. At the microscopic level, ligand-receptor and ligand-protein interactions represent a key step in the detection of chemical compounds. Therefore, characterizing the nature of these weak bonding interactions at an atomistic scale is crucial to elucidate the underlying mechanisms of biological function and further provides the first step toward efficient drug design. Generally, the strength of these interactions not only depends on the structure and dynamics of the proteins and the receptors, but also on the dynamics and soft-degree of freedom of the interacting ligand.

Due to the challenges associated with experimental techniques to describe and quantify activated protein-ligand complexes, structural biologists have to rely on complementary computational methods in addition to available experiments. The range of such modeling extends from *ab initio* to classical approaches and full atomistic to coarse-grained models. The applications cover an immense number of fundamental biological problems and require interdisciplinary collaborations between scientists from different experimental and theoretical fields.

2. State of the art

Molecular simulations provide outstanding possibilities to study molecular recognition principles that are extremely difficult to access using available experimental techniques. The improving capacities of high-performance computing suggest that in future, molecular simulations are bound to gain wider importance on structure-based drug design.

Nowadays, the state-of-the-art to sample the vast conformational space of proteins and protein complexes covers a wide range of different computational techniques, such as classical molecular dynamics, accelerated molecular dynamics, Monte Carlo simulations or parallel tempering methods. Depending on the problem of interest, full-atomistic or coarse-grained force fields can be used, as well as QM/MM methods, whenever quantum effects need to be addressed. It is crucial to sample the motion of the protein and receptor-proteins prior to ligand binding as molecular recognition is a highly dynamical process and free energy calculations used to determine binding affinities are usually very sensitive to a thorough conformational sampling of the protein receptor. Therefore, static structure models from NMR, X-ray crystallography, and homology modelling provide only limited insights into macromolecular structures. Upon binding, the ligand may induce a conformational change that is not necessarily sampled when the ligand is absent. To address this problem and account for protein-receptor flexibility, techniques such as the relaxed complex scheme have been developed. Such methods allow to exploit the information of protein-receptor motions that can be captured by molecular dynamics simulation.

Although X-ray crystallography remains the primary tool to experimentally determine the structure of proteins and ligand-protein complexes, methods in high resolution spectroscopy may become of interest to provide accurate parameters for the binding pocket and active center of molecular complexes. Using rotational spectroscopy in combination with *ab initio* calculations allows to accurate describe the stepwise microsolvation of ligands *via* van-der-Waals complexes with an increasing number of water molecules. Furthermore, the effect of specific binding partners on the preferred form of a biological molecule can be examined to determine interaction sites. Another way to characterize the conformational changes of a protein during activation by selected ligands can be achieved using Synchrotron radiation in the infrared range. Furthermore, the effect of specific binding partners on the preferred form of a biological molecule can be examined to determine interaction sites.

As each experimental and computational approach has its advantages and bottlenecks when it comes to practical applications, usually many approximations, assumptions, and restrictions have to be accepted. However, the importance is to keep accurate information from experimental molecular structure determinations and *ab initio* simulations in the final computational models. In practice, this goal is only partly achieved and the purpose of the present workshop is to encourage discussions between scientists from all connecting fields, as direct communication is the most promising way to understand the point of view and questions of interest of colleagues from different fields. For the present discussion meeting, we plan to tackle both theoretical and experimental approaches to describe different types of molecular recognition processes in structural biology.

3. Objectives

The aim of this meeting is to bring together experts who perform research at the interface of biology, chemistry, and physics to share their experience and interests around molecular recognition and bio-molecular interactions. For modellers, the main objective is to explore possibilities to include structural data to guide and validate their models, while experimentalists will get in contact with state-of-the-art computational methods which are useful for their specific needs. This way, the discussion meeting will stimulate future collaborations, which is required to advance the field, and may bring forward new problems which the community needs to address in near future.

Selected topics to be covered during the discussion meeting are:

- Methods to sample the conformational space of proteins
- Free energy calculations and ligand binding affinities
- QM/MM approaches in molecular recognition and ligand based drug design
- High resolution spectroscopy in protein-ligand interactions and microsolvation process
- Input from X-ray crystallography
- Computational approach to the chemical senses
- Assessing molecular interactions with biological methods

Speakers are expected to present their contributions on these topics in talks of approximately 30 minutes. The goal is to host, during 4 half days, around 15 talks with sufficient time devoted to exchanges and discussions between the participants. For this purpose a two day discussion meeting will be proposed during spring 2017 to take place at the university *Paris-Est Marne-la-Vallée*. The exact dates will be communicated as soon as possible.

4. Participant List

The discussion-meeting is organized by H. Mouhib from the Université Paris-Est Marne-La-Vallée (Multi-scale modelling), E. Ruelland from the iEEs (Biology of plants and phytohormones), and W. Stahl from the RWTH Aachen University (Microwave Spectroscopy and quantum chemistry). The preliminary list of participants comprises researchers in the fields of structural biology, computational biology and biophysics, spectroscopy, and structure determination. A few more (3-4) may still be contacted.

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Although not all potential participants have been officially contacted yet, we have mentioned to most of them the possibility that such an event will be organized in spring 2017 in Paris.

5 Financial Support

Transportation: **2500 EUR**
Accommodation: **1500 EUR**
Coffee breaks, lunch and dinner: **2000 EUR**
Total: **6000 EUR**

A **total of 6000 EUR** is requested to CECAM-FR-MOSER.

2000 EUR will be provided by the university Paris-Est Marne-La-Vallée.