INSTITUT DES SCIENCES ANALYTIQUES

Modelisation & Computational Biology

Workshop – June 9, 2017

at the Institute for Analytical Sciences

Organised by the axis «Numerical and theoretical approaches for chemical analysis» at ISA

Program and Abstracts

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SOMMAIRE

INTRODUCTION

As a part of the scientific animation at ISA, the axis "numerical and theoretical aspects of chemical analysis" organised a short workshop on Friday 9 June 2017, gathering 5 guest speakers in the research community in the field.

The real technological revolution of the « numerical » affords to the "theoretical" a tremendous computing power. This power was unimaginable only ten years ago both in the flow of number of arithmetic operations per second as well as in the "miniaturization" of the compationnal units at almost derisory financial and energy costs (GPU technology).

This new power, which is still difficult to tame as we shall see, is a source of unprecedented scientific creativity, opening a gate to the analysis at the microscopic level (ie at the level of the molecules) of phenomena measured macroscopically (ie at the mole level). This link between the microscopic and the macroscopic is an ultimate dream of statistical physics that may arrive gradually at the level of chemical analysis and all its implications in chemistry, biochemistry and biology.

We hope that this 1st workshop of the ISA research axis "Numerical and theoretical aspects of chemical analysis" will give a vision of the scientific revolution in which we are.

Prof. Jean-Marc Lancelin

Scientific Animator of the Axis Numerical & Theoretical Approaches to Chemical Analysis

At the Institute of Analytical Sciences

PROGRAM

08h15 - 08h30	Welcome of the participants
08h30 - 08h40	Opening by Prof. J-M. LANCELIN Institut des Sciences Analytiques
08h45 - 09h25	**A multi-scale computational approach to cancer biology: from -omics signature to biomolecular structures** by **Dr. E. PAPALEO** Computational Biology Lab. - Danish Cancer Society Research Center
09h30 - 10h10	**Molecular dynamics investigation of DNA tandem lesions formation and repair** by **Dr. E. DUMONT** Laboratoire de Chimie - ENS Lyon
10h15 - 10h55	**Towards computerized drug discovery** by **Dr. F. CHEVALIER** Acellera, Barcelona
10h55 - 11h10	Coffee Break
11h15 - 11h55	**From multicores to Myrialus, disruptive technologies viewed by a physicist** by Dr. **E. QUEMENER** Centre Blaise Pascal - ENS Lyon
12h00 - 13h00	**Estimating Ligand/Protein and Protein/Protein Binding Free Energy and Kinetics** by **Prof. V. LIMONGELLI** Institute of Computational Science - University of Lugano

ABSTRACTS

A multi-scale computational approach to cancer biology: from -omics signature to biomolecular structures

Elena Papaleo - Computational Biology Lab., Danish Cancer Society Research Center, Copenhagen (DK)

The Computational Biology Laboratory (CBL) at the Danish Cancer Society Research Center (DCRC, Denmark) provides a highly multi-disciplinary environment where we cover research in different fields of computational biology and chemistry. The two main areas of research are: i) the use of high-throughput Next Generation Sequencing and -omics data to identify bimolecular signatures in specific cancer types, ii) computational structural biology using either high-throughput and more accurate simulation approaches to unravel the effects of cancer-related mutations and modifications at the atom level, with emphasis to their impact on stability and function. In all the projects, we tightly collaborate with experimentalists at DCRC or in other research institutes and universities in Denmark and abroad. I will introduce some key examples with focus on transcription factors, intrinsically disordered proteins and enzymes involved in key cellular pathways such as ubiquitination, autophagy and apoptosis.

Molecular dynamics investigation of DNA tandem lesions formation and repair

Elise Dumont

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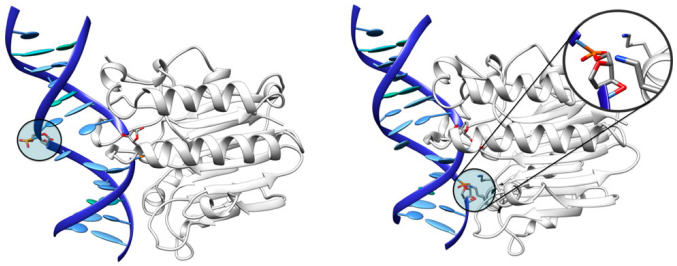
DNA integrity is constantly threatened by radicals and sunlight, leading to chemical modifications of nucleobases. For two neighboring simple DNA defects, the repair turns out to be dramatically lowered [1]. However the field suffers from X-ray or NMR structure to interpret the repair rate measurements of such tandem lesions (10% of the total 8-oxoguanines).

Relying on all-atom explicit-solvent molecular dynamics, we explore the structure of oligonucleotides and DNA-enzyme systems featuring two oxidized guanine sites. Our simulations recover sequence effects [2] and provide atomic-scale structural insights into the lack of non-covalent interactions that induce a low repair of 8-oxoguanine and abasic sites with Nfo[2], APE1[3] and Fpg.



Cartoon representation of two DNA sequences showing contrasted recognition by the endonuclease APE1, leading to a lower repair rate for seq+3.

References

[1] F. Bergeron, F. Auvré, J. P. Radicella, J.-L. Ravanat, *Proc. Natl. Acad. Sc.*, **107** (2010), 5528-5533

[2] E. Bignon, H. Gattuso, C. Morell, F. Dehez, A. Georgakilas, A. Monari, E. Dumont *Nucl. Acids Res*., **44** (2016), 8588-8599

[3] H. Gattuso, E. Durand, E. Bignon, C. Morell, A. Georgakilas, E. Dumont, C. Chipot, F. Dehez, A. Monari *J. Phys. Chem. Lett*., **7** (2016), 3760-3765

Towards computerized drug discovery

Dr. Franck Chevalier

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Since 1977 and the first published work in molecular dynamics, it has been shown that simulations can be drastically enhanced to reach real time molecular motions time scale, offering an atomistic view of phenoma observed by biophysics techniques. What are the Accomplishments and challenges to understanding macroscopic event at microscopic scale by molecular dynamics ? A perspective from the industry.

From multicores to Myrialus, disruptive technologies viewed by a physicist

Emmanuel QUEMENER

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The new processors (CPU), notably graphics (GPU), have largely changed scientific computing in recent years: communities of tens or even thousands of computing units, wild teraflops in chaos. However, taming them remains difficult and their behavior sometimes leaves us puzzled. Emmanuel Quemener, a research engineer at the Center Blaise Pascal (ENS-Lyon) and a GPU experimenter for about ten years, will present their power through a few illustrative tests implemented in OpenCL. Their comparison will also be an opportunity to focus on the temporal reproducibility affecting these components.

Des architectures multi-coeurs aux myri-alus, des technologies disruptives vues par un physicien

Les nouveaux processeurs (CPU), notamment graphiques (GPU), ont largement bouleversé le calcul scientifique ces dernières années : des communautés de dizaines voire de milliers d'unités de calcul, des Téraflops sauvages en pagaille. Cependant, les dompter reste difficile et leur comportement laisse parfois perplexe. Emmanuel Quemener, ingénieur de recherches au Centre Blaise Pascal (ENS-Lyon) et expérimentateur sur GPU depuis une dizaine d'années, présentera, avec son regard de physicien, leur puissance à travers quelques tests implémentés en OpenCL. Leur comparaison sera également l'occasion de s'intéresser à la reproductibilité temporelle affectant ces composants.

Estimating Ligand/Protein and Protein/Protein Binding Free Energy and Kinetics

Vittorio Limongelli - Institute of Computational Science - University of Lugano (Switzerland) - vittoriolimongelli@gmail.com

Predicting the thermodynamic and kinetic properties of the binding process of a drug to its target is of primary relevance to shed light on its mechanism of action and develop new medications [1,2,3]. In this talk I illustrate how this information can be obtained from advanced calculations. In particular, we studied the binding of benzamidine to trypsin using a new approach, called Funnel- Metadynamics (FM) [4]. This method enhances the exploration of the ligand bound poses and its solvated states leading to an accurate estimation of the absolute protein-ligand binding free energy. Furthermore, one can retrieve from metadynamics the ligand unbinding kinetic rate (koff) and identify the rate-limiting step using a recently developed protocol [5,6]. In our simulations, the x- ray conformation is found as the lowest energy pose and the computed ligand binding free energy in good agreement with experiments. We disclose further precious details of the binding process such as the presence of alternative binding modes and the solvent role. Albeit very recent, FM has proven to be successful in studies complex ligand/protein and ligand/DNA interactions [7,8].

Finally, I present a very recent protocol that combines multiscale and enhanced sampling methods (coarse-grained/metadynamics) to simulate long time-scale events in very large systems [9]. Using such approach the dimerization mechanism in membrane of the transmembrane helices of the epidermal growth factor receptor has been energetically and structurally characterised, shedding light on possible activation pathways of the receptor. Our protocol allows reaching the second time scale, opening new opportunities to study protein clusters in membrane (e.g., GPCRs, ion channels) and protein/protein interactions (e.g., antigen/antibody) in more physiological environment.

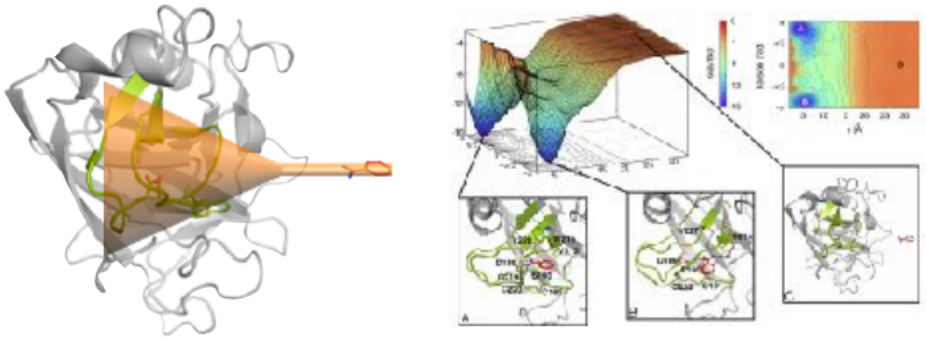

Figure. (*Left*) The funnel-potential applied to the benzamidine/trypsin system. (*Right*) The free energy surface of the benzamidine binding to trypsin with the most relevant states reported as insets (see ref. 4 for details).

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