Mini-symposium JOBIM – 7 Juin 2022

Caractérisation structurale de macro-assemblages par des méthodes intégratives

La bioinformatique structurale vise à déterminer *in silico* les structures 3D de systèmes moléculaires, étudier leur dynamique et comprendre/prédire/modifier leur fonction biologique. En particulier, la modélisation structurale intégrative associe des données expérimentales de plusieurs natures (biophysique, biochimie, structures 3D à des résolutions variées) pour la modélisation de larges macro-assemblages.

Les bouleversements récents de la bioinformatique structurale, en particulier avec l'avènement d'AlphaFold pour modéliser les protéines ou leurs complexes, permettent de rediriger ses enjeux sur des problèmes jusqu'ici difficilement abordables. Le mini-symposium permettra d'aborder certaines de ces questions, comme la modélisation des assemblages macromoléculaires de grande taille ou l'étude de la dynamique de ces larges machineries dans leur contexte cellulaire, par l'intégration de données complémentaires, notamment expérimentales.

PROGRAMME

15h **Introduction**

15h05 **Pablo Chacon** *Rocasolano Institute of Physical Chemistry (IQFR-CSIC) , Madrid.*

Contradictory tips for integrative modeling of Cryo-Electron Microscopy Maps

We have witnessed considerable advancements over the past few years in both prediction structures using machine learning and structure determination using Cryo-Electron Microscopy (Cryo-EM). Commenting on my recent experience as a modeler, I briefly introduce the impact of such advances in the integrative modeling of Cryo-EM electron density maps. In this context I discuss two systems 1) tyrosine hydroxylase inhibition by dopamine and reactivation by Ser40 phosphorylation and 2) and continuous flexibility analysis of SARS-CoV-2 Spike prefusion structures.

15h40 **Guillaume Bouvier** *Institut Pasteur, Université de Paris, CNRS.*

Integrative structural biology through the lens of structural bioinformatics

Structural bioinformatics is a field of research at the interface of multiple areas. To create structural models of biological macromolecules, ones often need to integrate heterogeneous data coming from multiple experiments; e.g., Nuclear Magnetic Resonance (NMR), X-ray crystallography, Small Angle X-ray Scattering (SAXS), Cryo-Electron Microscopy (Cryo-EM), Chemical cross-linking in combination with mass spectrometry (XL-MS)… The combination of such heterogeneous data into a structural model requires

the development of modeling methods to process them and extract meaningful information from them. Furthermore, the recent breakthrough in deep-learning approaches applied in the field of structural biology has remodeled the way of thinking about problem-solving strategies. I will expose the new methodological developments we made for the structural characterization of large biomolecular assemblies. I will start from the traditional approaches then turn out into the recent development we made in the field of machine-learning and especially deep-learning.

16h15 Pause café

16h45 **Pierre Legrand** *Synchrotron SOLEIL - Institut Pasteur.*

Crystallographer Adventures in Wonderland

Last summer, as AlphaFold2 hurried by, some crystallographers burning with curiosity ran after it across a new field and, eventually, jumped into a large AI-Hole. Down, down, down, they felt as if the fall would never come to an end. We will share the journey of one of them in this wonderful new deep field and hear what he discovered. Although he half believed the wonders he saw, in the after-time he pictured to himself how this could help him fertilize his own experimental garden.

17h20 **Stéphanie Baud** *CNRS, URCA, Reims*.

Simulating and understanding the Extracellular Matrix. From isolated elements to reconstructed pictures: key role of the in silico approach.

The extracellular matrix (ECM) is a three-dimensional network of macromolecules that is the architectural support for cells and allows tissue cohesion. This dynamic structure regulates many biological functions such as adhesion, migration, proliferation, differentiation and cell survival. Four main families of macromolecules constitute this interstitial medium: collagens, structural glycoproteins, proteoglycans and elastins.

From the modeling point of view, the ECM remains a challenging object: indeed its study can be approached according to different aspects and scales (quantum, atomic, molecular or even mesoscopic) which nevertheless remain complementary. According to the framework of investigation, the diversity of size, function and nature of the ECM molecules imposes to choose a given scale of description. Indeed, there are still few methods available in physics that can describe/model a complex system using a unified approach combining physico-chemical properties linked to different descriptive scales.

Using simulation and modeling from the atomistic scale up to mesoscopic scale, our team is aiming at understanding and deciphering the structural and dynamic behavior of the ECM. In particular, the recent research projects we have been developing focus on a better description of the ECM, the interactions with its microenvironment as well as the impact of its modifications (natural such as the phenomenon of aging, or pathological such as diabetic or cancerous contexts). In particular, the detailed description of the interactions between the various constituent elements of the ECM and the finalization of a modeling tool adapted to the mesoscopic scale have been investigated.

17h55 **Conclusion**

COMITE D'ORGANISATION

Isaure Chauvot de Beauchene (CNRS, LORIA, Nancy)

Jessica Andreani (CEA, I2BC, Gif-sur-Yvette)

Anne Lopes (Univ. Paris-Saclay, I2BC, Gif-sur-Yvette)

Matthieu Montes (GBCM, CNAM, Paris)

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