PhD project

Molecular dynamics study of the role of water in allostery

Allostery is a key feature of proteins where a perturbation (ligand binding, mutation,. . .) at one site of a protein has an impact at another distant site. It raises both practical and fundamental problems. Practically, the ability to predict allosteric sites would have far-reaching implications in biology and biotechnology. Fundamentally, the physical mechanisms by which long-range effects propagate within proteins are not understood. Recent experimental and simulation studies have suggested that some water molecules could play a role [1-2] but whether and how the water surrounding a protein is implicated in allostery remains an open question. On the other hand, evolutionary analyses and biological experiments provide datasets that effectively map all the allosteric 'hot-spots' at the surface of proteins [3].

The project is to confront numerical molecular dynamics simulations of proteins to evolutionary and experimental datasets to identify the structural and dynamical properties involved in allostery, with a particular focus on the role of water. The two goals are: (1) to propose a computational approach to predict allosteric hot-spots; (2) to understand the physics behind allostery.

The project will be part of a collaboration between the groups of D. Laage (ENS), O. Rivoire (Collège de France), C. Nizak (Sorbonne Universit), and G. Stirnemann (IBPC). Our groups have a well-established expertise in the theoretical description of the structural and dynamical properties of biomolecular hydration shells [4-5]. This includes for example the determination of the molecular jump mechanism [4] which governs the rearrangements of the hydrogen-bond network and the elucidation of how different protein sites affect water dynamics [5]. They also have expertise in the description of protein sectors [6], which provide a promising approach to understand long-range correlations in proteins, in the development of theoretical models of allostery [7] and in the generation of experimental data.

This project will involve advanced molecular dynamics simulations, data analyses, theoretical modeling and collaborations with experimentalists. We are looking for a motivated student with prior knowledge of statistical mechanics or molecular modeling or computational chemistry, and basic skills in programming/computing.

References:

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[3] Reynolds, K. A., McLaughlin, R. N., & Ranganathan, R. Hot spots for allosteric regulation on protein surfaces. Cell, 147(7), 1564-1575 (2011).

[4] Laage, D. & Hynes, J. T. A molecular jump mechanism of water reorientation. Science 311, 832?835 (2006).

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[7] Rouviere, E., Ranganathan, R., Rivoire, O. On the emergence of single versus multi-state allostery, arXiv preprint 2111.09377 (2021)