

## Master M2 Internship

### Molecular dynamics study of the role of water in an allosteric transition

#### Supervisor:

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Allostery is a feature of proteins where ligand binding impacts the protein properties far from this binding site. Allostery is essential to the regulation of a broad range of proteins and models, most notably by Monod-Wyman-Changeux and by Koshland have been proposed to account for allostery[1], but the mechanisms underlying allostery and especially the origin of the long-range effect, are still not fully understood. In particular, the direct or indirect implication of hydration shell rearrangements in allostery has remained elusive. Recent experimental and simulation studies have suggested that some water molecules could play an essential role during the transition[2-3]. This project aims at elucidating the role of water in allostery.

We will consider a paradigm allosteric protein together with a protein that exhibits latent allostery via hot-spot sites, and we will combine molecular dynamics simulations and analytic modelling to analyze the structural and dynamical properties of the hydration shell at locations involved in the allosteric transition.

This project will be performed in collaboration between the groups of D. Laage (ENS), O. Rivoire and C. Nizak (Collège de France), and G. Stirnemann (IBPC). The Laage group has 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]. The Rivoire group brings its recognized expertise in the description of protein sectors[6], which provide a promising approach to understand long-range correlations in proteins, and will generate experimental data to be confronted to the simulation results.

This project will involve advanced molecular dynamics simulations, theoretical modeling, development of short analysis codes and collaboration with experimentalists. This M2 internship may be continued with a PhD which is already funded. We are looking for motivated students with prior knowledge of statistical mechanics or molecular modeling or computational chemistry, and basic skills in programming/computing.

#### References

1. Changeux, J-P. Allostery and the Monod-Wyman-Changeux model after 50 years. *Annu. Rev. Biophys.* **41**, 103-133 (2012).
2. Cyphers, S. et al. A water-mediated allosteric network governs activation of Aurora kinase A. *Nat. Chem. Biol.*, **13**, 402-408 (2017).
3. Buchli, B. et al. Kinetic response of a photoperturbed allosteric protein. *Proc. Natl. Acad. Sci.*, **110**, 11725-11730 (2013).

4. Laage, D. & Hynes, J. T. A molecular jump mechanism of water reorientation. *Science* **311**, 832–835 (2006).
5. Laage, D., Elsaesser, T. & Hynes, J.T. Water dynamics in the hydration shells of biomolecules. *Chem. Rev.* **117**, 10694-10725 (2017).
6. Halabi, N., Rivoire, O., Leibler, S., & Ranganathan, R. Protein sectors: evolutionary units of three-dimensional structure. *Cell*, **138**, 774-786 (2009).