

2017_Proposal for six-month internship (M2)

Subject: Control of specificity and diversity in gene regulation by protein interactions: Study by computational techniques

Gene regulation is central to developmental, evolutionary and pathological processes, and largely relies on the activity of transcription factors that form large regulatory complexes with DNA. Little is known about how such regulatory complexes provide specificity and diversity in gene regulation. During the 6-months internship the student will focus on how dynamics of protein-protein and protein-DNA interactions endow such regulatory complexes with specific transcriptional properties. The project will rely on the use of a wide range of state-of-the-art computational techniques, and Hox proteins, key regulators of development and evolution, as a general paradigm for transcription factors [1,2], regarding the structure-related aspects. During this internship, the student will master essential computational techniques – structure prediction using homology modeling, molecular dynamics and free energy simulations. He (she) will simulate various Hox proteins, either free in solution or bound to DNA and/or to other protein, with the objective to shed light on possible mechanisms of allosteric regulation. Another important question that will be addressed is whether interactions between transcription factors have plasticity that has been recently suggested. To test this hypothesis, the student will use the free energy simulations techniques, including implicit solvent Poisson-Boltzmann method to probe protein-protein and protein-DNA interactions. Characterization of allosteric regulation will be performed with our original approach - MODular NETwork Analysis (MONETA) [3]. The proposed project will be done in close collaboration with the experimental group of Dr. Y. Graba (Developmental Biology Institute of Marseille, IBDM) which will first provide the structures for simulations and further perform experimental tests to validate the computational findings. The topic will be extended to the PhD thesis project.

References:

- [1] Saadaoui M, Merabet S, Litim-Mecheri I, Arbeille E, Sambrani N, Damen W, Brena C, Pradel J, Graba Y. Selection of distinct Hox-Extradenticle interaction modes fine-tunes Hox protein activity. **(2011)** *Proc Natl Acad Sci U S A*. 108(6):2276-81.
- [2] Foos N, Maurel-Zaffran C, Maté MJ, Vincentelli R, Hainaut M, Berenger H, Pradel J, Saurin AJ, Ortiz-Lombardía M, Graba Y. A flexible extension of the Drosophila ultrabithorax homeodomain defines a novel Hox/PBC interaction mode. **(2015)** *Structure*. Feb 3;23(2):270-9. doi: 10.1016/j.str.2014.12.011.
- [3] Allain A, Chauvot de Beauchêne I, Langenfeld F, Guarracino Y, Laine E, Tchertanov L. **(2014)**. Allosteric Pathway Identification through Network Analysis from Molecular Dynamics Simulations to Interactive 2D and 3D Graphs. *Faraday Disc.*, DOI: 10.1039/C4FD00024B.

Required competence: The student should possess an excellent skill in mathematics/statistics or theoretical physics and computational/structural biology or engineering/computer sciences. Previous experience with the Linux environment and basic script programming is desired, but not mandatory. Strong dedication to the project is essential and, thus, mandatory.

Supervision: The student will perform the project in the *Centre de Mathématique et de Leurs Applications* located in *ENS Cachan/Université Paris-Saclay* under the supervision of Dr. Luba Tchertanov and Dr. Alexey Aleksandrov.

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