Universitat Pompeu Fabra Barcelona

Master in Bioinformatics for Health Sciences

Master project 2021-2022

Personal Information

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Project

Structural bioinformatics

Project Title:

Molecular Basis of Cooperativity in Protein-Ligand-Protein complexes

Keywords:

PPI glues, cooperativity, molecular dynamics

Summary:

Multicomponent systems are extremely common in biochemistry: from allosteric modulation to organelle assembly, the underlying principle is the simultaneous interaction of more than two partners. While there are examples in which the affinity between partners is purely additive, it is often the case that these affinities are extremely affected by the presence of the remaining members of the multicomponent complex. This phenomenon is known as cooperativity and albeit been widespread and impacting many biological processes, its molecular determinants remain poorly understood. [1.2] A particularly relevant case of cooperative effects is the ability of some small molecules to stabilize the interaction between macromolecules, acting as so-called molecular glues. The stabilization effect is often orders of magnitude higher than what one may infer from the affinity of the molecular glue for any of the macromolecular partners and this mechanism is often exploited by nature to modulate biological responses. In particular, stabilizers of protein-protein interactions (PPIs) are commonly used by different organisms to control their cellular functions and regulate signaling pathways. Additionally, molecular glues are also powerful chemical probes to help us better understand the function of macromolecular complexes, and even a few noteworthy examples (e.g: cyclosporin A, Paclitaxel or Rapamycin) have been developed into drugs. However, our lack of understanding of the cooperativity phenomenon has to date prevented the purposeful and reliable development of molecular glues. In fact, the discovery, optimization and development of most of these compounds have vastly relied in serendipity and/or trial and error assays. We propose to push a paradigm shift into the development of molecular glues, moving away from trial an error and into rational design. A critical step is to understand the molecular events that underpin PPI stabilization. Employing enhanced sampling techniques and data analysis tools[3,4], the student will seek to characterize the mechanism at play during ternary complex formation in selected examples from the literature and attempt to provide a general framework to describe cooperativity in biomolecular systems.

References:

[1] de Vink, P. J. et al. Cooperativity basis for small-molecule stabilization of protein-protein interactions. Chem Sci 10, 2869-2874, doi:10.1039/c8sc05242e (2019). [2] Andrei, S. A. et al. Stabilization of protein-protein interactions in drug discovery. Expert Opin Drug Discov 12, 925-940, doi:10.1080/17460441.2017.1346608 (2017). [3] Juárez-Jiménez, J. et al. Dynamic design: manipulation of millisecond timescale motions on the energy landscape of cyclophilin A. Chemical Science 11, 2670-2680, doi:10.1039/C9SC04696H (2020). [4] De Simone, A. et al. A computationally designed binding mode flip leads to a novel class of potent tri-vector cyclophilin inhibitors. Chem Sci 10, 542-547, doi:10.1039/c8sc03831g (2019)

Expected skills::

Familiarity with the AMBER software package will be an advantage

Possibility of funding::

Yes

Possible continuity with PhD: :

To be discussed

Comments:

We are willing to consider other projects in the field of Structure Based Drug Design that match your interests and skills. Do not hesitate to get in contact.