BioISI Junior

Folding equilibrium of cyclic decapeptides mediated by odd noncovalent interactions

Place of work/: Computational Chemistry & Molecular Interactions Lab (https://ccmi.rd.ciencias.ulisboa.pt/), BioISI

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The mechanism of protein folding/unfolding is one of the most fundamental questions in structural biology, as this process is paramount for regulating biological activity and targeting proteins in different cellular locations [1]. When folded, the main secondary structure motifs in proteins, most commonly α–helices and β–sheets, are characterized by the existence of noncovalent interactions, namely, hydrogen bonds (HBs), between the N–H and C=O groups of the main chain, thus, the understanding of these interactions is paramount. Cyclic peptides (CPs) are a class of potent and selective target-binding molecules with attractive features in drug design such as the ability to bind to protein targets, tunable permeability, resistance to proteolytic enzymes, and fewer conformational degrees of freedom than linear peptides. CP-based drugs have been developed in the past two decades [2], and fine-tuning their folding/unfolding equilibrium is required to modulate their target-binding properties and also for tunning their remarkable membrane permeability. Indeed, the stabilization and modulation CP conformations can be achieved not only by the usage of the ubiquitous hydrogen bond but also by using odd noncovalent interactions such as halogen bonds [3]. Our Lab has been focused on the study of halogen bonding with biomolecular applications [4] using molecular modeling techniques such as molecular dynamics simulations. In this project, we will study the conformational space and folding/unfolding equilibria of a series of CPs [3] whose stabilization of a β–hairpin structure can be achieved by both hydrogen or halogen bonds. This study aims at testing the limits of force field parametrization but also to provide insights into the potential membrane permeability and drug potential of such entities. The usage of the extensive experimental NMR structural data available allows for the validation and tuning of the parameters that describe the noncovalent interactions responsible for the stability of the β–hairpin structures, thus allowing an experimental validation of our results. This project requires someone motivated to study biochemical systems using computational methods. The results will be used not only for the Master Thesis but also to be published in a peer-review journal. Students selected for this project, after thesis registration, are eligible to apply to the BioISI Junior Programme (supporting 8 students with a 6-month Scholarship(BII), being the selection criterium, the academic merit of the candidates.

[1] C. M. Dobson, Nature, 2003, 426, 884–890.
[2] H. Zhang, S. Chen, RSC Chem. Biol., 2022, 3, 18-31.
[3] E. Danelius, H. Andersson, P. Jarvoll, K. Lood, J. Gräfenstein, M. Erdélyi, Biochemistry 2017, 56, 3265–3272
[4] R. S. Nunes, D. Vila-Viçosa, P. J. Costa, J. Am. Chem. Soc. 2021, 143, 4253−4267