Laboratoire de Biochimie Théorique
Institut de **B**iologie **P**hysico-**C**himique
13, rue Pierre et Marie Curie
75005 PARIS

S E M I N A I R E

Irene Maffucci

DISFARM – Universita degli studi di Milano, Italy

« OPTIMIZATION AND APPLICATION OF COMPUTATIONAL METHODS FOR THE DESIGN OF PROTEIN-PROTEIN INTERACTIONS MODULATORS «

Protein-protein interactions are involved in many biological events and the development of molecules targeting PPIs is one of the main goals of contemporary medicinal chemistry. Recently, much attention has been paid to the design of peptides containing non-natural amino acids (nnAAs) able to stabilize a certain secondary structure, often the right-handed helical one, in order to combine the high selectivity and specificity and low toxicity of well-designed peptides with the stability toward peptidases and proteases provided by the nnAAs. One of the most exploited classes of nnAAs is that of chiral Cα-tetrasubistuted amino acids (cCTAAs), which stabilize the helical secondary structure by limiting the backbone conformational freedom and induce a preferential helical screw sense in otherwise achiral peptidesthanks to their side chains. In this framework, after a protocol optimization,1the rationales behind the helical secondary structure stabilization and the helical screw sense selectivity exerted by chiral cCTAAs have been investigated through REMD simulations and QTAIM analyses. Moreover, the mechanisms responsible of the helical screw sense inversion have been studied through PNEB simulations. It has been found that two complementary mechanisms are responsible of the helical stabilization and screw senseselectivity: the first depends on the steric hindrance exerted by the cCTAA in an area parallel to the peptide helix axis, whereas the second consists in the strengthening of the helical H-bond network thanks to peculiar C-H···O=C interactions.2,3Furthermore, it has been observed that the helical screw sense inversion requires the formation of γ-turns, although a preferential screw sense inversion direction was not found.
At the same time, computational methods for the estimation of binding energies, suchas MMGBSA, usually applied for classic ligand-receptor complexes have to be tested and optimized on PPIs, because of their peculiar structural features. Therefore, an MMGBSA based method, called Nwat-MMGBSA, aimed to improve the correlation between predicted binding energies of PPI complexes and experimental data, has been developed. This approach consists in the inclusion, as part of the receptor, of hydration shells around the ligand during the MMGBSA calculations,4and it proved to be successful on classical receptor-ligand complexes.5Thus, it has been automatized, optimized and tested on PPI complexes, giving initial promising results. In details, when water plays a significant role in mediating protein-ligand interactions, the application of Nwat-MMGBSA improved the correlation between predicted and experimental data. On the other hand, if the solvent does not explicitly participate to the interaction, it did not give detrimental results compared to those obtained with the standard approach, at the same computational cost. In addition, the protocol proved to be robust and reproducible, giving equivalent results by using different setups. Finally, anon-negligible advantage of Nwat-MMGBSA is represented by the possibility to automatize it, making it applicable for drug design/discovery purposes.

(1) Maffucci, I.; Contini, A. An Updated Test of AMBER Force Fields and Implicit Solvent Models in Predicting the Secondary Structure of Helical, β-Hairpin and Intrinsically Disordered Peptides. *J. Chem. Theory Comput* **2016**, DOI: 10.1021/acs.jctc.5b01211.
(2) Maffucci, I.; Clayden, J.; Contini, A. Origin of Helical Screw Sense Selectivity Induced by Chiral Constrained Cα-Tetrasubstituted α-Amino Acids in Aib-Based Peptides. *J. Phys. Chem. B***2015**, *119*, 14003–14013.
(3) Maffucci, I.; Pellegrino, S.; Clayden, J.; Contini, A. Mechanism of Stabilization of Helix Secondary Structure by Constrained Cα-Tetrasubstituted α-Amino Acids. *J. Phys. Chem. B***2015**, *119*, 1350–1361.
(4) Maffucci, I.; Contini, A. Tuning the Solvation Term in the MM-PBSA/GBSA Binding Affinity Predictions. In *Frontiers in Computational Chemistry Volume 1*; Bentham Science, 2015; pp 82–120.
(5) Maffucci, I.; Contini, A. Explicit Ligand Hydration Shells Improve the Correlation between MM-PB/GBSA Binding Energies and Experimental Activities. *J. Chem. Theory Comput.***2013**, *9*, 2706–2717.

Mardi 23 février 2016 -11h00

BIBLIOTHEQUE