Master « Sciences, Technologie, Santé »
Mention « In Silico Drug Design »
2ème année

PROPOSITION DE STAGE
Année Universitaire 2012 – 2013

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Ecole doctorale de rattachement : iViv

Spécialité du stage : Recherche X Professionnel ☐

Indiquez par quelques mots clés, l'orientation scientifique du sujet :

Structural bioinformatics, drug research, protein-protein interactions, peptide inhibitors, closed loops, tightened end fragments, TEF

Titre du stage : Tightened End Fragments (TEF) as inhibitors of protein-protein interactions

Ce sujet constitue-t-il un premier pas vers un travail de thèse : Oui (mais pas de financement propre du labo ou contrat ANR, …)

Description du sujet (quelques lignes):

The inhibition of protein-protein interactions plays an increasingly important role in modern medicine and efficient novel strategies have to be developed to identify novel inhibitors [1]. Cyclized stable peptides are quite promising [2], as they can mimic the spatial arrangement of the important part of the binding site of the protein-protein complex [3]. The decomposition of a protein into "closed loops"[4], also named "tightened end fragments (TEF)"[5], may help to identify a candidate peptide that is already stabilized by tight van der Waals interactions at its ends and whose free-form can adopt a conformation similar to its bound-form. The two ends of a TEF are structurally nearby, typically less than 10 Å between Cα-atoms. The typical TEF length is about 10-50 residues, with the majority in the 10-20 residues range. Globular proteins can therefore be considered as an assembly of these subdomain structural fragments.

The TEF decomposition of a protein is not unique and can be optimized for the conformational stability and/or binding affinity [6]. In the first part of the internship an accurate and fast prediction method of the conformational stability of a TEF has to be developed using molecular dynamics (5ns) and protein modeling software like ROSETTA. In the second part of the internship the binding affinity of TEF-peptides will be estimated and optimized with docking based programs, like *PepCrawler* [7]. Protein-peptide docking tools (ex. *Rosetta FlexPepDock* [8]) will also be used to obtain a structural model of the protein-TEF complex. The PEP-FOLD server [9] will be used to generate an ensemble of free-form TEF structures used for the docking.

Both parts of the internship will be performed first on a small representative set of protein structures and complexes and, if the time allows it, also on a larger data set.

References

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