MASTER « *In Silico* Drug Design »

1ère année

PROPOSITION DE STAGE
Année Universitaire -- /--

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Titre du stage : Test a new artificial intelligence model to guide receptor conformation selection in ensemble docking

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Description du sujet (quelques lignes):

The pivotal role of protein-protein interactions (PPI) in key biological functions and the development of diseases is widely recognized. Despite this, small molecules disrupting the interaction between two proteins are relatively rare in comparison to other drug classes. PPIs are viewed as challenging targets, and in some cases as undruggable. To overcome these difficulties, specific computational tools have been developed to assist the drug discovery process of PPI inhibitors.

As a relevant contribution to the field, the host lab has recently developed a new deep learning model, called InDeep, enabling to predict on a 3D protein structure where a protein partner can interact (intractability model) and where a ligand could bind (ligandability model). It is, therefore, possible to predict unknown PPI interfaces and potential binding sites where PPI inhibitors could bind.

In addition to the InDeep ability to detect ligandable patches on the whole surface of a given static protein structure, the ligandability model has been tested on an ensemble of known ligand binding site conformations generated by molecular dynamics (MD). InDeep can potentially distinguish binding site conformations with higher ligandability propensity. This information has a direct application on structured-based drug design, where the identification of ligandable binding site conformations could be used to perform molecular docking in virtual screening campaigns.

This internship aims to assess whether InDeep tool can improve virtual screening performance and boost the discovery of new PPI inhibitors.

To do so, a set of well-known PPI targets will be selected as a testing case. Enough small molecule experimental activity data and binding site structural information should be available for the protein systems. The conformational space of the protein target will be sampled by MD. Resulting binding site conformations will be profiled in terms of ligandability using InDeep model and clustered based on their structure. A set of conformations having high ligandability propensity and being thermodynamically accessible will be selected to perform ensemble docking. The enrichment capacity of these receptor conformations will be computed in order to assess the utility of InDeep to assist PPI inhibitors drug design.

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