Master « In Silico Drug Design »
2ème année

PROPOSITION DE STAGE
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Spécialité du stage : Recherche ☐ Professionnel ☒

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

docking; polypharmacology; development; fragment scoring; ligand reconstruction; chemo-proteomic;

Titre du stage :

Ligand reconstruction in binding sites at a polypharmacological level by mining PDB existing data embedded in a Chemo-proteomic programming interface.

Ce sujet constitue-t-il un premier pas vers un travail de thèse : Oui - Non

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Description du sujet (quelques lignes):

From the initial fast heuristic to compare/superpose 3D interaction surfaces within the Protein Data Bank [Jambon2003], MEDIT SA has explored for the last 10 years many new chemo-proteomic applications for (A) Functional Annotation [Jambon2005, Doppelt2007, Doppelt-Azeroual2010], (B) Binding Site Characterization to detect within a protein family very similar subpockets from more specific subpocket [Doppelt-Azeroual2009], (C) Drug repurposing & Scaffold Hopping [Moriaud2011a], (D) Fragment Based Drug Design by deconvoluting PDB ligand in Pubchem like smaller entities and then hybridising those protein-fragments having similar 3D interaction surfaces with the protein target [Moriaud2009, Oguievetskaia2009], (E) Bioisosteric Replacement by searching in 2D fragments that are having a strong overlap after a 3D binding site comparison/superposition [Moriaud2011b], and even for unpublished proof of concept such as off-target identification and epitope scaffold search. Last, a new architecture to mine in real time the chemo-proteomic diversity spaces with 2D-topological and 3D-interaction-surface metrics has been set up into the C2P prototype (Chemo Proteomic Platform).

Knowing that the PDB is hosting material that can be used to predict partial or complete ligand conformation in the protein binding site [under submission], we can consider now to validate a complete rebuilding protocol based on a new heuristic proposed by MEDIT based on a very fast convergent hybridisation. Such validation would include multiple configurations like:

(a) the rebuild of a given ligand in multiple targets ; we would first consider all PDB ligands already available in more than one protein target, and then extend the dataset of targets to more PDB structures if Pubchem data are available on inactivities toward those targets;

(b) the rebuild of a given ligand from different binding site conformation as available in the PDB;

(c) exploring various implicit scores like the propensity for a given PDB fragment (that would be used to rebuild the 2D ligand) to conserve more or less its binding site mode;

(d) exploring existing scoring functions to better score the importance of the protein-fragment PDB-observed interactions.

Depending on priorities and project advances, the subject is susceptible to slightly change.

[Jambon2003] M. Jambon et al., Proteins 2003, 52(2):137-45

[Jambon2005] M. Jambon et al., Bioinformatics 2005, 21(20):3929-30

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[Moriaud2009] F. Moriaud et al., J Chem Inf Model 2009, 49:280-94

[Oguieteskaia2009] O. Oguievetskaia et al., JCAMD 2009, 23(8): 571-82

[Doppelt-Azeroual2009a] O. Doppelt-Azeroual et al., Drug Design Development and Therapy 2009, 3:59-72

[Doppelt-Azeroual2009b] O. Doppelt-Azeroual et al.. “A review of MED-SuMo applications”, Infect Disord Drug Targets 2009; 9(3):344-57

[Doppelt-Azeroual2010] O. Doppelt-Azeroual et al., Prot. Sci.2010, 19(4): 847-67

[Moriaud2011a] F. Moriaud et al., Brief Bioinfor 2011, 2(4):336-40

[Moriaud2011b] F. Moriaud et al., ACS Symposium 2011, series1076, Chapter book 5:71-88

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