MASTER « *In Silico* Drug Design »
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PROPOSITION DE STAGE
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Titre du stage : Computational docking for the identification of protein interactions perturbed by pathological mutations and characterization as potential drug targets

Description du sujet (quelques lignes):

Single amino acid variants (SAV) are commonly found in inherited diseases and have an important effect on the individual sensitivity to therapeutic drugs. Thus, their annotation and understanding at the molecular level can be an important step towards the goal of personalized medicine. Many pathological mutations are directly involved in protein-protein interactions, but they are difficult to identify due to the lack of structural data. In this context, available computational docking tools, such as pyDock, developed by Pr. Juan Fernando Recio from the BSC group in Spain, can be used to identify interface and hot-spot residues and help to interpret pathological mutations.

The general goal of this proposal is to computationally characterize protein-protein interactions involving proteins with mutations associated to diseases detected in newborn screening, so that this knowledge can be applied to increase the accuracy of pathogenicity predictions of new mutations. This is part of an ongoing collaboration of the BSC group with Prof. Xavier de la Cruz (VHIR, Barcelona), in the context of an Interreg-POCTEFA European project. In the context of this collaboration, we already have collected a list of 59 proteins with near 6000 mutations associated to diseases included in the newborn screening in North Spain and South France (POCTEFA region). Protein interaction networks have been built for 51 of these proteins, based on Interactome3D, and surface mutations have been already mapped on the available complex structures. With this information, >700 interface pathological mutations (either located at the rim or core of the interface) have been identified, which will be the starting point for the proposed project.
The detailed activities proposed during the 2-month project are:

1. Estimate, for a set of these proteins, the impact of the interface mutations on protein-protein binding affinity by characterizing the energetic contribution of each interface residue based on the complex structure, using the energy scoring function in pyDock partitioned by residue.
2. Analyze the importance of conformational flexibility in selected mutations by modeling and refining them with molecular dynamic simulations. Pathological mutations involved in protein interactions with no apparent effect on binding affinity as calculated from structure, might be explained by the introduction of conformational changes.
3. Bonus: If there is time, on the basis of this mutational mapping and energetic characterization, select protein-protein interactions with therapeutic interest. Then, identify potential cavities for ligand binding

by integrating surface analysis, molecular dynamics and docking-based hot-spot predictions, and explore their use for ligand docking and virtual screening with dedicated chemical libraries.

4. Finally, apply protein-protein docking and hot-spot predictions to extend the characterization of mutations possibly involved in interactions for which structural data is not available.

This work is in collaboration with Pr. Olivier Taboureau from the Computational Modeling of Protein Ligand Interactions (CMPLI) and you are welcome to contact him if you want more information.

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