Universitat Pompeu Fabra Barcelona | Master in Bioinformatics for Health Sciences

Master project 2020-2021

Personal Information

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Project

Structural bioinformatics

Project Title:

Deciphering the mechanism of drug action at G protein coupled receptors (GPCRs)

Keywords:

G protein-coupled receptors, molecular dynamics, data analysis, drug design

Summary:

G-protein coupled receptors (GPCRs) are the most abundant class of receptors in the human organism. They are present in almost every type of cell, and govern almost every process in the human body (i.e. cognitive and inflammatory processes or control of the cardiovascular system). Owning to their ubiquity, they are targets of more than 30% of current drugs, and every day new GPCRs are revealed to be pharmacological targets for existing diseases. GPCR drugs can either be agonist, antagonist or inverse agonists. They act by binding to the receptor and establishing transient interactions with protein residues that form the binding pocket. Those interactions alter the GPCR structure, leading to a specific downstream signalling response. However, important features responsible for a distinct drug profile (selectivity, signalling outcome, etc.) are still unclear. Uncovering those factors would provide important structural insight for further drug-design endeavours. Currently, there exist multiple GPCR structures bound to various ligands (chemicals binding to GPCRs), however a static look at ligand-receptor interactions doesn't allow to fully rationalize the signalling profile. Molecular dynamics (MD) is a novel and sophisticated technique that enables to simulate protein behaviour in a physiological environment. They offer a unique opportunity to study GPCR-ligand interactions at single atom resolution, providing insights on receptor behaviour. The development of MD techniques has been rewarded with a Nobel Prize in 2013, and the number of papers using MD is growing exponentially. In our group we have carried out a massive MD projects to unravel general principles of GPCR signalling and drug binding. With the aid of an international consortium we have simulated over 90 GPCRs crystallized with diverse ligands, amounting impressive simulation time (www.gpcrmd.org). We are looking for a motivated student that would be interested in participating in the analysis of this data. The students would be involved in analysing the generated MD data. During the project they will learn how to set up, and simulate their own biological systems. They will learn about GPCR biology, as well as about in silico drug design. To analyse the data the students will learn to write in house scripts in tcl, bash and python, as well as use several statistical methods. The student will have the opportunity to collaborate with international experts renowned in the GPCR field (members of the consortium see reference). We expect that the results of the analysis will be published in a high impact journal, and the skills acquired by the student will make him/her a valuable asset for pharma companies. The project can be extended into a PhD thesis.

References:

Rodríguez-Espigares & Torrens-Fontanals et al. GPCRmd uncovers the dynamics of the 3D-GPCRome (https://www.biorxiv.org/content/10.1101/839597v2.abstract)

Expected skills::

Experience in structural biology, python, and bash. Experience with molecular dynamics simulations is a plus. Good level of English.

Possibility of funding::

To be discussed

Possible continuity with PhD: :

Yes
