Universitat Pompeu Fabra Barcelona

Master in Bioinformatics for Health Sciences

Master project 2021-2022

Personal Information

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Project

Structural bioinformatics

Project Title:

Simulation meets experiment: refinement of cryo-EM GPCR structures using molecular dynamics

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). Owing 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. Recent advances in cryo-electron microscopy (cryo-EM) and image classification provide insights into ensembles of low- to high-resolution that describe differently populated conformational states of proteins. However, methods for deriving accurate atomistic models from cryo-EM density maps lag behind this resolution revolution. The increasing amount of molecular detail requires the development of new methodologies and software to accurately and timely interpret experimental densities. Molecular dynamics (MD)-based refinement methods have grown into a valuable approach to tackle this challenge. In this project, the Master student will develop an MD-based pipeline that can be applied to GPCRs. This represents an important milestone for the scientific community as it can provide novel structural insights into this important drug targeting class. For this, the student will learn how to setup simulations and how to use correlation-driven MD for the refinement of atomistic models into cryo-electron microscopy maps. We expect that the results of the analysis will be published in a high impact journal, and the expertise acquired by the student will make her/him a valuable asset for pharma companies in future. We are looking for a highly motivated and skilled student with exceptional academic records that allows pursuing a PhD afterwards.

References:

Rodríguez-Espigares & Torrens-Fontanals et al. GPCRmd uncovers the dynamics of the 3D-GPCRome, Nature Methods 2020, DOI: 10.1038/s41592-020-0884-y Igaev et al. Automated cryo-EM structure refinement using correlation-driven molecular dynamics, Elife 2019, DOI: 10.7554/eLife.43542

Expected skills::

Experience in structural biology, programming in python/bash, molecular dynamics engines (GROMACS, NAMD, etc.), analysis tools/packages (VMD, Chimera, MDtraj…) and high level of English, oral and written.

Possibility of funding::

To be discussed

Possible continuity with PhD: :

Yes