Drug Design Pipeline Development for Proteinopathies

Place of work/: BioISI Ed. C8 – piso 5 Workspace

Supervisors: Nuno Galamba (njgalamba@fc.ul.pt); Hugo Martiniano (hugo.martiniano@insa.min-saude.pt)

Protein aggregation is implicated in several human pathologies, ranging from sickle cell disease (SCD), a red blood cell disorder, to type 2 diabetes mellitus, and various neurodegenerative diseases (NDs), such as Alzheimer's (AD), Huntington's (HD), or Parkinson's disease (PD), commonly known as proteinopathies. A major challenge regarding *in silico* drug design studies concerns the assessment of the aggregation inhibitory activity of drugs found to bind to the proteins involved in these diseases. Thus, the fact that a drug binds to a specific pocket or region of the protein of interest does not necessarily imply its ability to interfere with the aggregation process. The reason for this difficulty is associated with the large size of these systems and the fact that protein aggregation and dissociation may occur on time scales not available through typical all-atom molecular simulation methods. To address this problem we propose to develop a pipeline which integrates a set of coarse grained and all-atom molecular simulations and develop a set of structural descriptors that can predict the aggregation inhibitory activity of drugs already studied *in vitro* for simple model proteins and peptides. These will then be used to evaluate the performance of a series of potential drug candidates for one or more proteins involved in proteinopathies such as sickle cell anemia, Parkinson's disease or Alzheimer's disease.

The candidate is expected to have an interest in learning about molecular simulations as well as in the development of python-based molecular and statistical analysis tools. A simple pipeline encompassing molecular simulations, performed with the program GROMACS, and analysis tools, that allows probing the effect of any drug on protein aggregation,is expected to be developed.

The project will be developed at BioISI-FCUL under the supervision of the researchers Nuno Galamba and Hugo Martiniano. Students selected for this project, after thesis registration, are eligible to apply to the BioISI Junior Programme (supporting 8 students with a 6-month Scholarship BII), being the selection criterium the academic merit of the candidates.