MSc in Biochemistry for Health

Dissertation Project – 2nd Cycle

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Lab/Institution: Multiscale Modeling Lab, Dynamic Structural Biology Lab / MOSTMICRO — ITQB NOVA
TITLE: Combining experiment and simulation to characterize intrinsically disordered proteins

BACKGROUND

Intrinsically disordered proteins (IDPs) are now known to make up a significant part of our proteome. These proteins — which have structural propensities that are very weak, very transient, or only over a fraction of their sequence — have been implied in many aspects of metabolism, mainly related to regulation and signaling.

Malfunction of IDPs, via misfolding and/or aggregation events, has been linked to disease. Examples include the aggregation of alpha-synuclein or of amiloid-beta proteins in Parkinson's and Alzheimer's diseases, and the misrecognition of p53's or BRCA-1's intrinsically disordered regions in the growth of several tumors.

Several techniques and methodologies can be used to characterize IDPs — namely for this project NMR and SAXS. State-of-the-art approaches now also include molecular dynamics (MD) simulation of IDPs, as simulation techniques can explicitly capture the dynamic nature of protein disorder. By coupling the simulation process to experimental information even more accurate descriptions of IDP behavior can be attained. From this comprehensive structural and dynamic characterization, one can confidently infer structure–dynamic–function relationships, and their link to disease.

OBJECTIVES

The goals of this project are to characterize IDPs at different levels by different simulation approaches and together with experimental data input. This consists of several sub-goals:

– To assess the quality of MD, namely of atomistic and coarse-grain models, when simulating IDPs;

– To compare the outcomes in the previous point to simulations where SAXS, NMR and other experimental sources of information are coupled to the simulation procedure;

– To assemble the previous approach into an optimal method combining coarse-grain simulations with SAXS and NMR data. This combination will be truly innovative in the field of IDP characterization.

PROJECT DESCRIPTION

The project is divided into five tasks, roughly divisible along the sub-goal lines described above.

Task 1 – Set up atomistic and coarse-grain simulations of IDPs for which experimental information is available. Analyze resulting structure dynamics and assess qualitative reproduction of the experimental behavior. This step will be performed using the GROMACS simulation package and the AMBER and Martini models (respectively, an atomistic and a coarse-grained one);

Task 2 – NMR and SAXS are compatible with structural investigations of IDPS in solution and provide truly complementary data. If no suitable set of experimental data is available, or to expand its scope, the collection of further experiments, namely high-field NMR and Synchrotron SAXS, can be planned. This will involve measurements at the highest field NMR-facilities in Portugal (CERMAX, hosted by ITQB). Synchrotron SAXS will be performed at Large European Facilities. The DSB lab is a regular user of such international facilities with a strong track record for obtaining the required beam-time.

Task 3 – Using the PLUMED wrapper software for GROMACS simulate the same systems as in Task 1 but with a reverse strategy: introducing biasing restraints that keep the protein in conformations compatible with the experimentally observed data.

Task 4 – Evaluate the convergence of results in Tasks 1 and 3 with known protein behavior. In Task 3 restrained simulations can be performed with different combinations of experimental input, providing different outcomes that can be used to judge consistency;

Task 5 – Compare the atomistic and coarse-grain outcomes regarding result quality and convergence. If possible, identify optimizations to the coarse-grain model and set up an automated method for use with future experimental data.

The student will be trained in an array of computing techniques with wide applicability beyond the scope of the project and even outside academia. These include the use of simulation software, structural/dynamic data analysis methods, back-calculation of NMR/SAXS observables, and overall experience with open-source operating systems.

TIMELINE (use fill tool for the cells)

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10
Task 1										
Task 2										
Task 3										
Task 4										
Task 5										
Thesis										