MSc in Biochemistry for Health

Dissertation Project – 2nd Cycle

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TITLE: Simulating the power stroke of the ATP synthase rotor

BACKGROUND

ATP synthase action, central to aerobic life, has been postulated and validated over the past 50 years. Molecular-level insight into this process has been recently boosted by advances in cryo-EM technology that allowed the solving of high resolution ATP synthase structures. Such structures open the door to a number of methods to infer mechanistic characteristics of ATP synthase function, and this project focuses on the function of the membrane-embedded part of ATP synthase — the F_o region — wherein the *c*-ring is the proton-actuated rotor.

The F_o region is the site of multiple disease-causing mutations. Some can be clearly ascribed to proton-flux interruption, but an intriguing case — the I192T mutation in humans — occurs in a highly variable loop region, and to threonine, which is present at that position in other mammals' ATP synthases. The current understanding of ATP synthase function cannot explain the impact of this mutation in humans.

Coarse-grain molecular dynamics (CG MD) is a powerful tool for simulations of biomolecular processes. In particular, it has been successfully employed in several studies of respiratory chain protein–membrane–ligand interactions, including some aspects of ATP synthase interaction with lipids. The study of F_o function is therefore a timely and promising application of CG MD.

OBJECTIVES

The goals of this project are:

– To simulate ATP synthase F_o rotation;

– To identify protonation states responsible for the power stroke;

– To describe the energetic landscape of the rotation under the different protonation states;

– To clarify the role of isoleucine 192 in this process.

PROJECT DESCRIPTION

The project is divided into four tasks:

Task 1 – To create a CG model of F_o and embed it in a mitochondrial membrane environment. As electrostatics are foreseen to play a fundamental role in the process, a CG model optimized for electrostatic behavior will be used;

Task 2 – To create derived models corresponding to possible intermediate protonation states;

Task 3 – To simulate the free rotation of the F_o rotor from each of the protonation states, calculating rates and evaluating lipid influence.

Task 4 – Should rotation be too slow to be observed under tractable simulation times, to employ biasing potentials to probe the system. Additionally, these will allow the mapping of the energy barriers encountered by the system as it rotates.

Task 5 – From the full description afforded by the results of the previous tasks, the relevance of the I192 site can be inferred, either as establishing intra-protein interactions, as a membrane anchor, or as a lipid–specific binding site. This can be validated by performing simulations with the I192T mutation.

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, 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										