MSc in Biochemistry for Health

Dissertation Project – 2nd Cycle

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TITLE: Characterizing the quinone binding sites in *S. aureus* respiratory oxireductases by coarse-grained simulations

BACKGROUND

Even though the bacterial respiratory chain is closely analogous to the eukaryotic one, differences do exist and make for plausible targets for antimicrobial therapies. To that end, it becomes useful to understand the catalysis mechanism. Coarse-grain (CG) simulations have recently emerged as a powerful technique to study such enzyme–substrate interactions in a respiratory context, providing unrivaled structural and dynamic detail.

Several oxidoreductases specific to *Staphylococcus aureus* have been identified and demonstrated to interact with quinone/quinol molecules. *S. aureus* is an opportunistic pathogen and one of the most frequent causes for community acquired and nosocomial infections. It has become a major public health threat due to the increased incidence of its drug resistance. Preliminary CG simulations in a representative bacterial membrane have been able to identify putative binding sites for some of these oxidoreductases. This opens the door to a number of simulations to characterize the catalysis and to devise modifications that can affect efficiency.

OBJECTIVES

The goals of this project are to characterize quinone reductase catalysis from CG simulations:

– To identify and characterize further quinone/quinol binding sites;

– To quantify quinone binding rates;

– To compare the behavior of the quinol products;

– To identify and test mutation targets to modulate activity.

PROJECT DESCRIPTION

The project is divided into five tasks.

Task 1 – To set up multiple simulations of quinone–enzyme binding, for different oxireductases. This includes simulations in aqueous environment, for soluble oxireductases, and in a membrane environment, for membrane-bound oxireductases;

Task 2 – Starting from states of bound quinones obtained in Task 1, to modify them to quinols and follow their unbinding dynamics;

Task 3 – For both Task 1 and Task 2 analyze times to binding/unbinding and identify binding site access/egress pathways;

Task 4 – From the information in Task 3 infer common properties of quinone/quinol binding proteins. These hypothetical determinants of quinone/quinol binding can then be tested by simulating the impact of their mutation in activity, as data for future experimental validation.

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										
Thesis										