

Thesis topic: **“Analysis of bacterial interactome for fighting drug resistance”**

Thesis supervisors:

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There is a critical need to address the emergence of drug resistant varieties of pathogens for several infectious diseases. For example, drug-resistant tuberculosis has continued to spread internationally and is now approaching critical proportions. Approaches to counter drug resistance have so far achieved limited success. It has been proposed that this lack of success is due to a lack of understanding of how resistance emerges in bacteria upon drug treatment and that a systems-level analysis of the proteins and interactions involved is essential to gaining insights into the routes required for drug resistance.

This project aims to facilitate such a systems-level analysis of proteins and interactions in pathogens of infectious diseases. Furthermore, we plan to use tuberculosis as a test case. For example, let us assume that a comprehensive protein interactome of *Mycobacterium tuberculosis* is available. Then one could identify a minimal set of proteins (or protein interactions) whose inhibition would disconnect all essential pathways in *M. tuberculosis*. Alternatively, one could trace the interaction route of the known targets of a drug to various efflux-pump proteins and drug-modifying enzyme proteins.

The premise of such an analysis is the existence of a comprehensive protein interactome map of the relevant pathogen. The quantity and variety of protein interaction data have increased rapidly since the publication of two yeast interactome maps based on the yeast two-hybrid technology eight years ago. In particular, two-hybrid-based interactome maps have been generated for model organisms such as *C. elegans*, *Drosophila*, and human; and proteome-scale interactome maps have also been generated for yeast by TAP-MS experiments. However, very few bacterial species have been analyzed at the proteome level for protein interactions. Furthermore, the quality of interactome maps has much to be improved in general.

Thus a systems-level analysis of proteins and interactions in pathogens of infectious diseases for identifying drug resistance pathways is difficult. In particular, we have to deal with the following challenges in this project:

1. Paucity of bacterial interactome maps.

We propose to investigate techniques for inferring protein-protein interactions. We choose *M. tuberculosis* as the target bacterial species because the emergence of drug resistant tuberculosis is posing a major threat to global tuberculosis eradication programs. We shall integrate -- based on homology, synteny, and other information -- as many bacterial interactome maps as possible to form a more comprehensive interactome map for *M. tuberculosis*. Possible interactome maps that can serve as starting points include *C. jejuni*, as well as a partial *M. tuberculosis* interactome. We also propose to develop and improve techniques for de novo prediction of protein interactions.

2. Unreliability of bacterial interactome maps.

We propose to investigate techniques for improving the reliability of interactome maps. We shall use the idea of “guilt by association” -- two proteins sharing a large number of common partners are more likely to be co-located and to participate in the same cellular processes, and thus they are more likely to interact. We shall apply this idea, along with an expectation maximization process to clean the interactome map for *M. tuberculosis* in Step 1. We shall also investigate techniques for predicting protein complexes and biological functional modules from the interactome map to derive higher-level information for the interactome

map.

3. Pathways to drug resistance.

The partitioning of multiple essential pathways into disconnected pieces should effectively disrupt the survival of a bacterium even when it has multiple pathways to drug resistance. So we propose to investigate ways to find a minimal subset of proteins or interactions, from the interactome map of Step 2, such that their suppression leads to the disruption of as many essential pathways as possible. Efflux pumps, drug-modifying enzymes, horizontally transferred detoxifying genes are some known mechanisms involved in drug resistance. So we further propose to investigate ways to infer the interaction paths, based on the interactome map from Step 2, from known drug targets to proteins known to be involved in various mechanisms for drug resistance. Such an interaction path should correspond to a chain of interactions that allows the bacterium to escape the effect of the drug, e.g., by transporting the drug out of the cell through an efflux pump.

The PhD student will spend alternative academic years at University of Warsaw and the National University of Singapore, with the first year spent in Warsaw. The cost of staying in Singapore will be covered by the National University of Singapore. Polish fellowship for the period spent in Poland will be covered by University of Warsaw. This research will be a part of a larger project funded by the Singaporean side and including Medical Doctors. For this reason we expect the successful candidate to have a fluent command of English. Please contact Prof. Jerzy Tiuryn at tiuryn@mimuw.edu.pl for an appointment before the actual evaluation procedure for admittance to the MISDoMP program.