Laboratory of Systems and Synthetic Biology: Computational Systems Biology group

Modelling metabolic changes induced by iron limitation in *Staphilococcus Aureus.*

Level: MSc
Keywords: Metabolic modelling, Genome-Scale constraint based models, COBRA toolbox (Matlab)
Requirements: none

Virtually all bacterial pathogens require iron to successfully infect their human hosts. This presents a challenge to invading bacteria because the majority of iron is tightly bound by iron-binding proteins and the host environment. In fact, one of the major host defence systems is oriented to reduce the iron available to the pathogens. The ability of pathogenic bacteria to overcome iron deprivation represents a major virulence determinant.

Bacterial pathogens have developed elaborate mechanisms to acquire nutrient iron during infection, but also they have developed mechanisms to limit their iron requirements, the iron sparing response, that acts for example to repress the expression of iron-rich proteins when iron is limited.

The goal of this thesis project is to gain insight into how the amount of available iron impacts the human pathogen *Staphylococcus aureus* and specifically, what are the metabolic changes that are induced under conditions of iron starvation. It has been observed (Friedman et al. 2006) that *S. aureus* coordinates a redirection of the central metabolic pathways causing the bacteria to produce large amounts of acidic end-products. The accumulation of these acidic end-products facilitates the release of iron from host iron-binding proteins, in effect increasing the availability of this precious nutrient source.

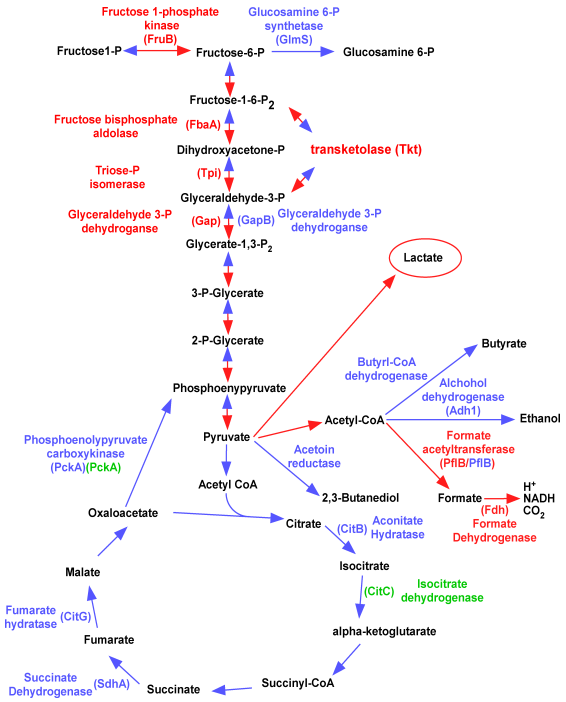

Figure 1: A subset of the predicted central metabolic reactions of S. aureus is shown. Proteins shown in red are up-regulated in the absence of iron. Proteins shown in blue are down-regulated in the absence of iron. The red arrows predict the direction of reactions upon iron starvation, while the blue arrows predict reactions that are inhibited upon iron starvation. Friedman et al. 2006

Genome scale metabolic models and their analysis using constraint based modelling techniques is an expanding field within **Systems Biology**. This type of models is a natural next step after sequencing a genome and allow to model the effect of the media and its nutrients on a chosen organism. Genome scale models for *S. aureus* have already been developed, tested and

successfully used to identify drug targets (Lee et al. 2009) . However no techniques have been developed to simulate using these models how metabolism changes under a cofactor (such as iron) limitation.

Thesis project:

1. To get familiar with this type of modelling techniques, the initial goal will be to perform initial simulations of growth of *S. aureus* on different media.
2. A re-annotation using already existing tools (VAPP) of the genome of *S. aureus* will be done, to enlarge the models with information on cofactor requirements for each reaction.
3. Implement a preliminary algorithm to simulate the adaptation to cofactor limitations.
4. Further develop this algorithm by comparing the results with experimental data from literature.
5. Explore the biological implications of the different observed patterns in the context on central metabolism.
6. Expand this analysis to other pathogens such as *Mycobacterium tuberculosis*.

Methodology: The simulations will be performed using either the COBRA tool box (Matlab or Python implementations) or the R package Sybil.

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Friedman et al 2006. "*Staphylococcus Aureus* Redirects Central Metabolism to Increase Iron Availability." *PLoS Pathog* 2 (8)

Lee, et al. . 2009. "Comparative Genome-Scale Metabolic Reconstruction and Flux Balance Analysis of Multiple *Staphylococcus Aureus* Genomes Identify Novel Antimicrobial Drug Targets." *Journal of Bacteriology* 191 (12)