The Bacell-SysMO project

The SySMO project is a European transnational funding and research initiative on "Systems Biology of Microorganisms". The goal pursued by SySMO is to record and describe the dynamic molecular processes going on in unicellular microorganisms in a comprehensive way and to present these processes in the form of computerized mathematical models.

The objective of this project is an integrated understanding of the metabolic and genetic network that controls the transition from growth to glucose starvation, as shown in Fig. 7. This transition is a fundamental ecophysiological response that serves as a scientific model for environmental signal integration and is pivotal for industrial fermentations of Bacillus that occur predominantly under nutrient starvation.

The σB regulon (Fig. 2) confers B. subtilis with the ability to respond to stress stimuli and adapts it for future stress incidents.

- Anti-sigma factor W binds B thereby precluding formation of RNA-polymerase holoenzyme. (React. 1)
- The affinity of V towards W (React. 2) is reduced by phosphorylation of V by W (React. 3).
- Following Glc-starvation VP dephosphorylation rate is increased resulting in V increase. (React. 4)
- V associates with W thereby reducing free W level. (React. 5)
- Reduced W level stimulates dissociation of WB complex. (React. 1)
- Increased levels of B (σB) associates with RNA-polymerase to induce expression of genes. (React. 5)
- Proteins and complexes are degraded with a first order mechanism (React. 6)

The fitness of parameter combinations shows high robustness of the system against changes in 

Parameter Fitness Correlations

Goal: determining parameter ranges that satisfy pre-defined observations for the fitness of stress response.

Fitness: low level of free B, high level of WB complex.

Procedure:
1. select two parameters & corresponding boundaries
2. randomly combine the two parameter values
3. evaluate the model fitness for each combination

Results:
- phosphorylation and dephosphorylation: Antagonistic reactions, only a narrow parameter region is physiological feasible. (Fig. 5)
- protein expression and degradation: Antagonistic reactions, but fitness is very sensitive on the balance of both reactions. (Fig. 5)

Conclusions and Perspectives

A model was developed that reproduces the available experimental data. However, the models are non-identifiable meaning that non-unique parameter sets can reproduce the data. To render the model identifiable, model reduction processes will be conducted to lump parameters and combine components. Additionally, we will gather more diverse data including concentrations of components in the regulation upstream of B-activation.

The fitness of parameter combinations shows high robustness of the system against changes in WB association rate. Considering pre-stress steady state fitness conditions will help to determine missing parameter values. Similar investigations will be conducted for possible steady state conditions during long lasting stress conditions.

Transcriptome results show that gene-specific sigma factor competition needs to be implemented in the models and that unknown post-transcriptional events modulate protein concentrations.

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Transcriptome:
- activation of expression of the σB regulon during entry into starvation (Fig. 7).
- expression of the operon fails to increase (Fig. 7) despite the positive transcriptional feedback loop of σB on its operon.
- Possible reason: sigma factor competition on the operon.