Abstract submission for oral presentation

Model based analysis of regulatory networks in bacteria

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Biomedical background and experimental platform. The bacterium *E. coli* is one of the most important organisms in biotechnology. For a better understanding of the regulation of nutrient uptake, a number of isogenic mutant strains were characterized in batch and continuous culture. We focused our attention on the main glucose uptake system, the PEP dependent: glucose phosphotransferase system (PTS). In addition to transport of glucose, the PTS is involved in the regulation of a number of metabolic processes like inducer exclusion, i.e. the inhibition of uptake of non PTS sugars and in the regulation of chemotaxis. To characterize the behavior of the wild type and the mutant strains, a number of measurement techniques to measure intracellular metabolite/protein concentration were developed.

Computational/mathematical modeling concept and modeling platform. The modeling concept used in this project is based on the definition of submodels [3]. The submodels are described by the type and the number of terminals representing interfaces (structural coordinate) and by assigning one or more mathematical equations (behavioral coordinate). Examples for submodels are simple enzymatic reactions or entire pathways. In order to set up a complex model, submodels are chosen from the modeling object library, are parameterized and finally are connected with other submodels. To find a suitable structure for the models, a new method to decompose a network in a hierarchical manner was introduced [2]. This will be achieved by assigning each regulatory protein to one level in the hierarchy. Signals are then transduced from the top level to the lower level, but not vice versa. All submodels are implemented in our modeling tool ProMoT [6] which was designed to support the setup of complex models by providing a number of submodels in a model library. Submodels can be connected by a graphical user interface. In the long run, the realization of a "virtual biological laboratory" [5] is planed which will allow "in silico" experiments similar to those in the real laboratory. Tools to analyze complex models should be provided by systems theory. Possible application are described in [4].

Modeling results. Using all tools and methods described above a mathematical model for carbohydrate transport for *E. coli* was set up and verified with a number of experiments [1]. In the experiments, substrate composition of the pre-culture and of the experimental culture are varied in order to stimulate the system in different ways. A part of the parameter vector could be fitted to the data, and therefore the experiments could be sufficiently described with a single set of parameters. Based on our results we conclude that using mathematical models in combination with a quantitative experimental strategy leads to a better understanding, i.e. prediction and control of cellular systems.

References

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