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The impact of experimental data quality on computational systems biology and engineering

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Abstract: The success of computational methods in systems biology and systems engineering relies on the availability of mathematical models which represent the biological system adequately. The process of model development, model analysis and model invalidation is, however, often limited by the availability of suitable experimental data leading to impaired significances of the models. Especially mathematical models build for the purpose of process control, optimization and analysis have to represent and predict the behavior of the system very well. But how to generate experimental data which is suitable for computational systems biology and engineering? In this work we demonstrate that the close connected use of experimental and theoretical methods can be the key for deriving experimental data and mathematical models of a high quality. As a first step the experimental conditions which cause the desired systems behavior have to be identified and maintained. Poor process control strategies or a general lack of control engineering are often the bottleneck, impeding a systematic experimental approach. Here we show, by applying methods from bioengineering, systems biology and control engineering, how an experimental platform can be created which allows to address systems biological questions systematically. The shown approach stabilizes the process around a chosen working point so that the reaction of the system to a defined stimulation of an input can be monitored whilst the remaining process variables are kept constant. In that way dynamic system responses can be assigned to the change of a single input and hierarchical information of complex biological systems are revealed. In this work we use our approach to study the formation of photosynthetic membranes (PM) under microaerobic conditions in *Rhodospirillum rubrum*.

Keywords: model-based control, complex biological system, experimental set up, data quality, process optimisation, model discrimination

1. INTRODUCTION

The analysis of complex biological systems is a challenge which can only be tackled by applying a combination of experimental and theoretical methods. In order to connect the work of both areas successfully special attention has to be paid on the quality of the experimental data sets, as the quality of a model can only be as good as the data sets and information which were used to derive and validate it. In this work we introduce an experimental platform which is suitable for the analysis of complex biological systems. We use this platform to study microaerobic formation of photosynthetic membranes (PM) in *R.rubrum* as an example. This process is not only complex but highly instable, as *R.rubrum* exhibits a very versatile metabolism which reacts rapidly to changes in the environmental conditions by adjusting the mode of energy conservation (aerobic, oxygen-limited (microaerobic, anaerobic, fermentative, phototrophic) (Grammel et al. (2003)). The amount of PM produced under a certain growth condition is thereby subject to the complex network of cellular redox balancing which ensures the metabolic functionality of the cell under such changing environmental conditions (cf., Figure 1). Clearly, adjusting precise and stable cultivation conditions is crucial to obtain experimental data sets which represent a process of this complexity adequately.

In this work we demonstrate how such a biotechnological challenge can be tackled by combining a close connection of experimental and theoretical methods. As a first step we show how experimental conditions which cause the systems behavior of interest can be identified and maintained in a cultivation system by quickly introducing the principle of the design process of the microaerobic process control strategy presented in Carius et al. (2013a). As a second step we give a short summary about how the obtained experimental data sets can be used to derive, analyse and validate a dynamical model of the process behaviour. As a third step, we demonstrate that models of a high quality are extremely useful for analysing the systems behavior, optimising the process performance, reconstructing inaccessible process information and predicting the process behavior. By showing so far unpublished experimental data we demonstrate that our model-based process control strategies handles various situations that would lead to a process abort under open-loop conditions. Finally we demonstrate how important it is to stabilise the system around the working point for analysing the system behavior of complex networks. For the first time

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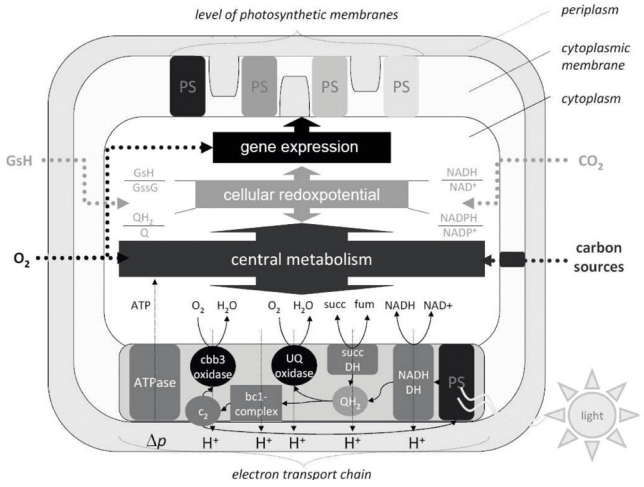

Fig. 1. Simplified map of the network of redox balancing which determines the level of PM in dependence of the prevailing growth conditions. GSH, O_2, CO_2, carbon source and light are external factors influencing cellular growth and PM synthesis in *R.rubrum*, as they interfere with cellular events (ETC, PS, central carbon metabolism, gene expression) and cellular redox potential balancing (GSH/GssG, QH_2/Q, NADH/NAD^+, NADPH/$NADP^+$). By integrating the signals from these external factors the growth mode the cells choose for energy generation and the expression level of PM associated genes is adjusted.

we show experimental data which represents the responses of the cellular network of redox balancing to changes in a single input whilst keeping all other growth influencing parameter constant.

2. CONTROLLING THE EXPERIMENTAL CONDITIONS

Here we introduce a process control strategy for the systematic assessment of the microaerobic growth range of an organism. This strategy reliably reproduces different states of oxygen limitations in common stirred-tank bioreactors, so that representative experimental data sets of the microaerobic growth range can be derived.

The shown approach is inspired by methods used for the characterisation of systems in the background of control engineering and chemical process engineering (Stephanopoulos (1984)). These methods use a sudden change of an input to analyse the systems response, hence, the time evolution of its outputs. In that way the dynamics of a system can be described and control parameter can be tuned empirically. We applied the concept of these methods to develop a control strategy which allows to monitor the responses of the cultures to defined and sudden changes in the oxygen supply, so that the impact of different degrees of oxygen limitation on the growth behavior and the formation of PM can be determined.

The control strategy uses the stepwise reduction of the oxygen supply to transfer the process to oxygen limited condition. As the dissolved oxygen amount can not be measured directly, the culture redox potential (CRP) is

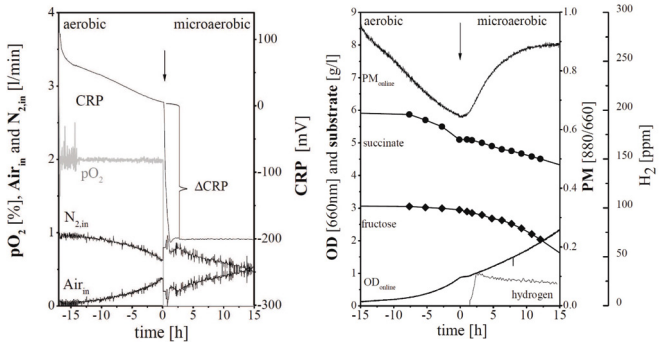

Fig. 2. Culture redox potential(CRP)-dependent control strategy. Step in the CRP transfers the culture from aerobic to microaerobic conditions (left). Cellular response to changes in the oxygen supply (right). See Carius et al. (2013b) a detailed description.

employed as a feed back signal to monitor and control the oxidative state of the culture broth. The degree of oxygen limitation is defined by the stepsize of the CRP reduction referred to as $\triangle$CRP in the following (cf., Figure2).

CRP steps ($\triangle$CRP) in the range of 0 and -400mV were performed during this work. During the time period after the CRP step, we analysed the cellular response by collecting time course data of growth determining parameter: cell growth, PM production, substrate consumption, production of organic acids and hydrogen emission (cf., Figure 2(right)). Samples were taken in triplicates. Every CRP step was performed twice. Experimental data sets describe the growth behavior for every $\triangle$CRP and indicate that the cells adapt to the new degree of oxygen limitation by changing their energy conversation mode. Reaction rates $\hat{r}_j$ of each $\triangle$CRP were calculated from these experimental data sets, representing the first 0-10 to 0-15 hours of the CRP-controlled cultivation phase. Every $\triangle$CRP resulted in one unique and reproducible growth behaviour, hence, set of $\hat{r}_j$. We therefor conclude that the applied strategy allows to systematically analyse the microaerobic growth range of an organism. The introduced strategy has been successfully applied during batch and continuous process mode (Carius et al. (2013b,a)). For a detailed description of the experimental data sets refer to Carius et al. (2013b).

3. MODELLING THE SYSTEMS BEHAVIOR

Here we quickly summarize the approach we applied for deriving a predictive model for process control based on the available experimental data sets (cf., Carius et al. (2013a)). We employed several analysis tools to derive and to validate an adequate model. Firstly, we derived the principal structures of the model. Based on different model hypotheses we determined nominal parameterization of all models by applying a least-squares approach. Secondly, we validated whether the parameter of the models are identifiable for the given conditions. Finally, we employed a set-based approach that can distinguish between models that are able to reproduce the data and those that are not.

3.1 Model Development

Only parameter relations with significance for process control and process optimisation are taken into account. The