Application of Metabolomics on Fermentation at Industrial scale

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1. Introduction

Industrial scale fermentations confront microorganisms with a strongly dynamic extracellular environment. There are gradients of sugar concentrations, dissolved oxygen concentrations and shear rates, which likely disturb optimal metabolic performance. Lab-scale fermentations usually are designed to display ideal conditions, without the dynamics representative of large scale operation, as a result of which the cellular performance is biased. This is the basis of scale-up problems. As it is not practical to sample industrial bioreactors, the industrial conditions need to be simulated in the lab. Understanding of metabolism under simulated large-scale dynamics can be accomplished by design and operation of scale-down simulators, rapid sampling and quenching, followed by metabolomics analysis. Thereby, challenges related to fast metabolic cycles, i.e. in the order of less than a minute, need to be overcome.

2. Approach

Industrial fermentations of *Saccharomyces cerevisiae* and *Penicillium chrysogenum* were analysed via a computational framework integrating computational fluid dynamics (CFD) and reaction dynamics (CRD). This uses Lagrangian particle tracking, where thousands of individual microorganisms can be monitored simultaneously on their journeys in large-scale bioreactors. The observed environmental dynamics, i.e. cellular life-lines, show how fast the environmental changes are, and how strong the disturbances. This information is then used to design and operate scale-down simulators, in the lab, so that representative conditions are set.

3. Results

The computational results reveal that on average in industrial bioreactors, cycle times of 30-60 seconds are prominent. Further, the glucose concentrations can vary a factor 100 or more during the cycles. This triggers the internal metabolism, which undergoes similar rapid and vast changes. Under these feast-famine conditions, the average levels of metabolic intermediates are different than under conditions of ideal mixing. Especially glycolytic intermediates and storage metabolites (trehalose, polyols) cycle around different average levels, inducing futile cycles, drain of ATP and redox power, and branching to by-products, which puts pressure on the metabolic efficiency towards product formation.

4. Discussion

A combination of scale-down simulation and rapid metabolomics can provide metabolic insight, relevant to large-scale bioreactors. This insight can be very different from conditions of ideal mixing, usually applied in lab-scale bioreactors. Leads for metabolic adjustment, coping with such dynamics, are equally important as optimizing the product pathway under ideal conditions, which seems to be the current research preference. It might be even better to strive for metabolic robustness and tolerance towards environmental dynamics first, before optimizing the metabolic product pathway.

References

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