Kluyver CENTRE | Kluyver Centre for Genomics of Industrial Fermentation

TU Delft

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The Bioprocess Technology section

The section has broad experience in cultivation and modelling both bioreactor systems and metabolic networks. Experimental and theoretical tools for the in vivo analysis of metabolite dynamics are developed. The tools are applied to study the metabolic reaction network and control structures in Saccharomyces cerevisiae and Penicillium chrysogenum. The focus is central carbon metabolism but also product pathways and biomass pools are monitored.

Tracking currency metabolites in yeast

Yeast is an important eukaryotic organism that is used as production host for biofuels, beverage and many other compounds. As it is well studied it is an important organism for system biological studies on genetic, transcriptomic and metabolic regulation.
Within the proposed project the metabolic level is focused. In eukaryotic cells the metabolic activity is distributed over different subcellular compartments with certain functions. Catabolism generates reduction equivalents and energy in form of NAD(P)H and ATP. These co-factors (conserved moieties) cannot pass the intracellular membranes and it is known that the concentrations (ratios) differ significantly in the single compartments. In the project two approaches for the measurement of the subcellular concentrations should be elaborated:
1) sensor reactions that mirror the ratio in sensor metabolites (Canelas et al., 2008),
2) a sampling and measurement protocol based on subcellular fractionation (Soboll et al., 1978).
The methods should be evaluated and compared based on chemostat experiments. When these methods are established, the response to different environmental conditions will be studied in batch and chemostat cultivations and pulse experiments. These measurements are important for a better understanding of the central carbon metabolism especially its driving forces (e.g. thermodynamic) and kinetic properties.

Applicants should have a strong background in chemical/biochemical engineering and microbial physiology. Candidates need to hold a MSc degree in biotechnology resp. life science oriented disciplines (with engineering). Furthermore the candidate should have a vivid interest in experimental research in the field of industrial fermentation in connection with theoretical developments especially mathematical modeling. Candidates are expected to have good communicative skills and team spirit. Furthermore fluency in English is a requirement for this position.

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Canelas, A.B., Van Gulik, W.M., Heijnen, J.J., *Determination of the cytosolic free NAD/NADH ratio in Saccharomyces cerevisiae under steady-state and highly dynamic conditions*. Biotechnology and Bioengineering, **2008**, 100, 734-743.

Soboll, S., Scholz, R., Heldt, H. W. *Subcellular metabolite concentrations. Dependence of mitochondrial and cytosolic ATP systems on the metabolic state of perfused rat liver.* Eur J Biochem, **1978**, *87*, 377-390

Analysis of yeast metabolism under fluctuating substrate conditions

Yeast is an important eukaryotic organism that is used as production host for biofuels, beverage and many other compounds and an important organism for system biological studies on genetic, transcriptomic and metabolic regulation.
Within the project the interactions of storage carbohydrates and central carbon metabolism as well the environmental conditions are studied. Saccharomyces cerevisiae accumulates carbohydrates in the form of glycogen and trehalose. The total intracellular amounts of these carbohydrates strongly depend on the growth conditions and can reach up to 25% of the biomass dry weight.
Various physiological studies have been performed showing the variability of the storage compound amounts. Nevertheless, there is only few quantitative knowledge about the kinetics of storage. The synthesis and degradation of these compounds is closely connected to central carbon metabolism but its regulation is only partially understood. Because of its strong interactions the dynamics of storage fluxes are highly relevant in metabolic perturbation experiments for the identification of (unbiased) in-vivo kinetics.
In the project mobilization/accumulation of storage pools under steady state conditions as well as its dynamic responses will be quantified using metabolomics approaches together with carbon labeling. Kinetic modeling will be applied to identify the in-vivo kinetics of storage carbohydrate metabolism. This model will improve the understanding of the kinetics involved in storage carbohydrate metabolism and its regulation in S. cerevisiae.

Applicants should have a strong background in chemical/biochemical engineering and microbial physiology. Candidates need to hold a MSc degree in biotechnology resp. life science oriented disciplines (with engineering). Furthermore the candidate should have a vivid interest in experimental research in the field of industrial fermentation in connection with theoretical developments especially mathematical modeling. Candidates are expected to have good communicative skills and team spirit. Furthermore fluency in English is a requirement for this position.

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