Dynamic macroscopic modeling of intracellular glycogen accumulation in yeast fed-batch cultures

Summary:
The general context of this study concerns yeast cell cultures in fed-batch bioreactors, i.e. within reactors which are fed over time with liquid culture medium containing the required components for an efficient yeast growth. There exist a lot of applications, from baker’s yeast production to the one of therapeutic molecules, or biofuels. The general goal of this master thesis is to mathematically analyze the key factors influencing the accumulation of glycogen (GLY) within Saccharomyces cerevisiae cells cultured in bioreactor, and to deduce feeding profiles which allow maximizing this accumulation. Several studies have proved the key role of storage carbohydrates, like glycogen or trehalose (TRE), whose accumulation allows increasing yeast cell resistance to diverse stresses caused by the surrounding environment. The main goal is to build a dynamic macroscopic mathematical model which allows predicting the time profiles of S. cerevisiae yeast concentration, of the main extracellular species involved in the bioreactor culture medium (glucose, ammonium, ethanol) and of intracellular GLY. This dynamic macroscopic model will have the following features: description of overflow metabolism phenomena, description of glucose and ammonium coordinated uptakes, description of intracellular GLY accumulation. It will be developed based on former results obtained at 3BIO-BioControl (A. Richelle et al., Computers and Chemical Engineering, 61, 220-233, 2014) and on recent results we obtained for modeling intracellular TRE accumulation (A. Huet et al., IFAC PapersOnLine, 55-20, 391-396, 2022). The model will be used to determine the optimal bioreactor feeding conditions which maximize GLY accumulation. Parameter identification and model validation will be performed based on experimental data available at 3BIO-BioControl (and possibly data collected from new experimental campaigns). This work is part of a collaboration with Puratos and Vesale Pharma companies within the framework of the SuNuP project about “Optimization of fermentation and drying conditions of microorganisms in order to develop dry and active sourdoughs, starters and probiotics” (https://www.wagralim.be/en/nos-projets-innovation/sunup).
Software sensor for intracellular carbohydrate concentration in yeast fed-batch cultures

Summary:
The context of this research is the same as in the first master thesis topic. In this case, the goal is to build a software sensor for the online estimation of intracellular concentration of carbohydrates (trehalose TRE and/or glycogen GLY). This needs the choice of
- a dynamical model linking the measured and unmeasured state variables;
- a state observer that will provide the online state estimation based on that dynamical model and some available measurements.

The dynamical model will consist of an adapted version of the model recently developed in our research group. The state observer will consist of an Extended Kalman Filter (EKF) or, eventually, on another nonlinear state estimation technique. The observability of the model, i.e. the possibility to estimate the state variables based on the available measurements, will be analyzed for different subsets of measured state variables (among biomass, glucose, ammonium and ethanol concentrations). The developed EKF will be validated on experimental data available at 3BIO-BioControl (and possibly data collected from new experimental campaigns). This work is part of a collaboration with Puratos and Vesale Pharma companies within the framework of the SuNuP project about “Optimization of fermentation and drying conditions of microorganisms in order to develop dry and active sourdoughs, starters and probiotics” (https://www.wagralim.be/en/nos-projets-innovation/sunup).

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Metabolic modeling of intracellular carbohydrates accumulation in yeast fed-batch cultures

Summary:
The context of this research is the same as in the first master thesis topic. The difference is that, instead of considering dynamic macroscopic modeling, the goal is to build a metabolic network with input fluxes for glucose and ammonium uptakes, output fluxes for ethanol and biomass production and intracellular fluxes for describing the main intracellular metabolisms (glycolysis, TCA cycle, pentose phosphate pathway,
fermentation, amino acid metabolism, transport reactions). Especially, the accumulation of trehalose (TRE) and/or glycogen (GLY) among the carbohydrates will be included in the network. A metabolic network including all the aforementioned fluxes, with the exception of those concerning TRE and GLY, has been proposed in a recent PhD thesis in the 3BIO-BioControl group (José Plaza, 2020). A first goal will be to include a more detailed description of carbohydrates metabolism and especially TRE and GLY accumulation. Metabolic Flux Analysis (MFA) and Flux Variability Analysis (FVA) will then be performed on the new metabolic network based on experimental data available at 3BIO-BioControl (and possibly data collected from new experimental campaigns). The second goal will consist in analyzing the results so as to determine the culture conditions, i.e. glucose and nitrogen uptake rates, that could lead to increasing the intracellular TRE and/or GLY accumulation. Prof. José Plaza (Universidad del Valle, Cali, Colombia) will co-supervise this work.

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Analysis and development of methods for estimating the fluxes in food webs describing the Vietnamese marine ecosystem

Summary:
The analysis of marine ecosystems involves food webs which describe the mass flows between different trophic compartments. For low trophic levels, these compartments are phytoplankton, zooplankton, bacteria, detritus, etc., while for higher trophic levels they concern different fish species which are directly linked to the former levels through the zooplankton they predate. Quantifying these web flows allows understanding the behavior of many types of marine and coastal ecosystems and the impact of natural and anthropogenic changes (climate, fishery intensity, nutrient enrichment, etc.). Similarly, to metabolic networks, food webs are generally underdetermined as the number of unmeasured web fluxes is higher than the available linear equality constraints (mass balances and available measurements). Even by considering the inequality constraints representing physiological constraints like lower and upper bounds on bacterial growth efficiency or detritus degradation rate, it is not possible to determine unique values for the web fluxes. Linear Inverse Models (LIMs) consist of the set of equality and inequality equations which link the web fluxes (van Oevelen et al., Ecosystems, 13, 32-45, 2010). Different algorithms have been proposed to tackle the underdeterminacy problem. Simple linear programs can provide the lower and upper bounds for each of the web fluxes. Sampling algorithms allow to compute the mean flux distribution and the marginal distribution of each flux. The first goal of this work is to improve the Vietnamese ecosystem model proposed by Anh et al. (Estuarine, Coastal and Shelf Science, 165, 226-236, 2015), especially with new data/information from Nha Trang Ocean Institute and other bibliographical references. The second goal is to test and/or develop different algorithms for
determining the food web flows in the aforementioned marine ecosystem, with a special focus on sampling algorithms.

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