Editorial

Special Issue: Mathematical Modeling and Control of Bioprocesses

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This Special Issue (SI) of Processes on Mathematical Modeling and Control of Bioprocesses (MMCB) contains papers focusing, on the one hand, on mathematical modeling of biological processes at different scales ranging from microscopic to macroscopic levels and, on the other hand, on model-based estimation, optimization and control of these processes.

1. Mathematical Modeling of Biological Processes at Microscopic Scale

At the microscopic scale, metabolic networks are often used to model cell behavior in different culture conditions. Three papers of the SI on MMCB are focused on metabolic network modeling. One of the major issues with models based on metabolic networks is their underdetermination, in the sense that the number of unknown intracellular fluxes to be determined is usually higher than the number of available equations corresponding to the mass balances and the available measurements. Bogaerts and Vande Wouwer [1] review various methods to tackle this underdetermination, among which are flux pathway analysis, flux balance analysis, flux variability analysis and sampling of the flux solution space. One of these methods, namely Dynamic Flux Balance Analysis, is used by Shen and Budman [2] to infer metabolite concentrations for which hardware measurements are not available. A variable structure system, describing different regions of the state space, is introduced and a set membership-based approach is used to estimate the unmeasured concentrations from few available measurements. To completely circumvent the abovementioned problem of system underdetermination, Bastin et al. [3] use relatively simple macroscopic models that allow obtaining a unique flux distribution to describe VERO cell behavior in different bioreactor culture conditions, e.g., exponential growth phase or substrate-limited growth phase. Such models could be used to develop feedback control strategies in fed-batch or perfused bioreactors.

2. Mathematical Modeling of Biological Processes at Macroscopic Scale

At a more macroscopic scale, four papers of the SI on MMCB focus on dynamic models for describing different processes, i.e., production of biopolymers [4], production of biopesticides [5], biodegradation [6] and biorefinery of second-generation biomass [7]. Duvigneau et al. [4] propose a new kinetic model for describing the production of the bio-copolymer poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV), which has a broad range of applications and is easier to process than the classical homopolymer poly(3-hydroxybutyrate). Given the coupling of CO_2 online measurements in the exhaust gas to biomass production, the model allows for predicting the composition and current yield of PHBV along the process. Monroy et al. [5] propose and compare different kinetic models for three different strains of *Bacillus thuringiensis* ssp *Kurstaki*, a microorganism used for the production of biopesticides. The main goal of the model is to estimate the total protein productivity, yield and titer. Based on several experimental datasets, a dynamical model is finally selected with the Akaike information criterion. Dimitrova and Zlateva [6]

propose a mathematical model for the biodegradation of a phenol and cresol mixture in a continuously stirred bioreactor, with a specific growth rate that involves sum kinetics with interaction parameters (SKIP) and inhibition effects. The global stabilizability of the model dynamics towards equilibrium points is analyzed and illustrated with numerical examples. Sbarciog et al. [7] propose a biorefinery model that integrates several processes, among which are steam refining, anaerobic digestion, ammonia stripping and composting. The overall goal is the model-based optimization of the process. The authors illustrate with simulation results the potential to efficiently produce oligosaccharides, lignin, fibers, biogas, fertilizer and compost from real collected biowaste.

3. Model-Based Estimation, Optimization and Control of Biological Processes

This SI on MMBC also focuses attention on recent developments in monitoring and optimization of biological systems, where mathematical models can of course play an important role, as reflected by four articles.

Sokač et al. [8] review the application of mathematical modeling and optimization for enhancing composting, which is a complex process whose efficiency is influenced by temperature, pH, moisture content, C/N ratio, particle size, nutrient content and oxygen supply. In [9], Djema et al. derive optimal control strategies based on the Pontryagin maximum principle in order to ensure the domination of the strain of interest in cultures of microalgae in the chemostat described by the Droop model. Sari [10] considers one-step and two-step models of anaerobic digestion together with a large class of growth functions encountered in applications, and studies their operating diagrams as a function of the dilution rate and inlet concentration, so as to define the best operating conditions for biogas production. In [11], Wallocha and Popp present an off-gas-based software sensor for real-time biomass estimation in continuous single-use bioreactors with CHO cell lines. They discuss the interest of considering viable cell volume concentration (instead of the density) as cell size or volume can have a direct impact on oxygen demand.

Finally, two articles are devoted to controller design and implementation, addressing important practical aspects of bioprocess control strategy deployment.

Colin-Robles et al. [12] consider the maximization of the hydrogen production rate in a microbial electrolysis cell. Using the golden section search optimization algorithm coupled with a robust super-twisting controller, the cell is brought to the maximum of a static performance map. The proposed optimization strategy is embedded in an FPGA throughout different digital architectures that are executed in parallel without hardware sharing. In [13], Butkus et al. propose a gain scheduling approach, which is based on controller input/output signals only and does not require additional online measurements of cultivation process variables for the adaptation of controller parameters. The approach is used to control dissolved oxygen concentration in a bioreactor operated in fed-batch mode.

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