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EDITORIAL

Special issue on nonlinear modeling, estimation and control of biological systems

Editorial Note

Jaime A. Moreno · Alain Vande Wouwer

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Dynamic modeling, state estimation and control are nowadays central techniques in the design, analysis, and optimization of bioprocesses in the industry, particularly with the increased importance of Process Analytical Technologies (PAT). The aim of this special issue is to account for some recent developments in the field by presenting a collection of ten articles written by distinguished colleagues who enthusiastically responded to our idea of dedicating a special issue to this subject.

The first paper by David et al. develops a nitrogen-backboned model of wine-making in standard and nitrogen-added fermentations. Nitrogen has a strong impact on the key bio-mechanisms involved during the grape-must fermentation, but also on the synthesis of flavour markers determining the aromatic profile of the wine. This paper presents a dynamical mass balance model describing the main physiological phenomena involved in standard batch fermentations, i.e., consumption of sugar and nitrogen and synthesis of ethanol. It also includes nitrogen compounds such as hexose transporters. Moreover, a common practice in wine-making is the addition of nitrogen during the fermentation to boost and shorten the process duration. A tractable representation of this boost effect is, therefore, developed as an extension of the first model. It is apparent that yeast makes a different use of nitrogen depending on the fermentation stage at which the addition is effected, balancing the regrowth of biomass and the synthesis of supplementary hexose transporters. These models are validated in line with experimental evidence deduced from extensive experimental studies.

Microalgae are often seen as a potential biofuel producer. To predict achievable productivities in the so-called raceway culturing system, the dynamics of photosynthesis has to be taken into account. In particular, the dynamical effect of inhibition by an excess of light (photoinhibition) must be represented. In the second paper by Hartmann et al., a model considering both photosynthesis and growth dynamics is proposed. This model involves three different time scales. The response of this model to fluctuating light with different frequencies is studied by slow–fast approximations. Therefore, three different regimes are identified, for which a simplified expression of the model can be derived. These expressions give a hint on productivity improvement, which can be expected by stimulating photosynthesis with a faster hydrodynamics.

The lack of sensors for some relevant state variables in fermentation processes can be coped by developing appropriate software sensors. In the third paper by Acuña et al., various Artificial Neural Network (ANN) and Support Vector Machine (SVM) models are compared when acting as software sensors of biomass concentration for a Solid-Substrate Cultivation (SSC) process. In particular, Nonlinear AutoRegressive models with eXogenous variables (NARX) and Nonlinear AutoRegressive Moving Average models with eXogenous variables (NARMAX) are considered. Results show that NARMAX-SVM outperforms the other models with a symmetric mean absolute percentage error, also called SMAPE index, under 9 for a 20 % amplitude noise. In addition, NARMAX models perform better than NARX models under the same noise conditions because of their better predictive capabilities as

J. A. Moreno
Instituto de Ingeniería, Universidad Nacional Autónoma de México, Cd. Universitaria, CP 04510 Mexico, D.F., Mexico
e-mail: JMorenoP@ii.unam.mx

A. Vande Wouwer (✉)
Service d'Automatique, Université de Mons, Boulevard Dolez 31, B-7000 Mons, Belgium
e-mail: Alain.VandeWouwer@Umons.ac.be

they include prediction errors as inputs. In the case of a perturbation of initial conditions of the autoregressive variable, NARX models exhibit better convergence capabilities. This work also confirms that a difficult to measure variable, such as biomass concentration, can be estimated online from easy to measure variables such as CO_2 and O_2 using an adequate software sensor based on computational intelligence techniques.

Determination of the observability/detectability properties of a nonlinear system is fundamental to assess the possibility of constructing observers and the properties that can be assigned to them, as e.g., the convergence rate. For linear systems this task can be solved by well-known techniques, for the case without perturbations as well as for the perturbed case. However, for nonlinear systems this study is usually a very hard task, in particular when unknown inputs and/or perturbations are present. In the fourth paper by Moreno et al., a general method to study these properties is described. It is based on a natural dynamical interpretation of the observability/detectability concepts, leading to the description of the indistinguishable dynamics (ID) of the system, i.e., a system that describes all possible indistinguishable trajectories of a plant. This dynamic system is analogous to the well-known zero dynamics of an input-state-output system and it can be studied by similar methods. The ID provides information not only about the distinguishability of the states (state observability/detectability), but also about the distinguishability of the unknown inputs (UI observability/detectability). The characterization of observability/detectability provided in this paper is very general, and it reduces to well-known tests under appropriate conditions. It also treats in the same framework observability/detectability in the presence or absence of unknown inputs. Its capabilities and feasibility are assessed by means of a few case studies related to the culture of phytoplankton in the chemostat.

Under stress conditions, microalgae are known to accumulate large amounts of neutral lipids and carbohydrates, which can be used for biofuel production. However, online measurement of microalgal biochemical composition is a difficult task, which makes the microalgal process rather difficult to manage. In the fifth paper by Mairet et al., an adaptive interval observer is proposed for the online estimation of neutral lipid and carbohydrate quotas in microalgae. The observer is based on a change of coordinate that involves a time varying gain. A dynamics for the gain is introduced, whose trajectory converges toward a predefined optimal value (which maximizes the convergence rate of the observer). The observer performance is illustrated with experimental data of *Isochrysis* sp. cultures under nitrogen limitations and day–night cycle. The proposed observer design appears to be a suitable robust estimation technique.

Feeding strategies for a Sequential Batch Reactor (SBR) are studied in the sixth paper by Gajardo et al. with the objective of reaching a given (low) level of substrate as fast as possible while not exceeding a certain volume of water. Inside the SBR, several species compete for a single substrate and this objective leads to a minimal time control problem where the control variable is the feeding rate. The latter is a bounded measurable function of time plus possible impulses associated to instantaneous dilution. Extremal trajectories of singular arc type are characterized as the strategies keeping the substrate at a constant level. Therefore, the optimal feeding strategies are composed of only three types of feeding phases: dilution, manipulation of the pump to keep the substrate concentration constant and turning off the pump so that the substrate concentration decreases down to some level. These three phases can be combined in infinitely many ways, but attention is paid in this study to two particular cases: the immediate one impulse strategy, which consists of filling up the tank with a single dilution and then wait, and the singular arc strategy, which consists of reaching, as fast as possible, a given level of substrate and then actuate the pump to keep this concentration constant until the tank of the reactor is completely filled. Numerical studies are presented, which can guide the practitioners to decide for one of the two strategies for particular settings of the SBR.

The seventh paper by Pcolka and Celikovsky considers the optimal control problem of a bioreactor used for penicillin production. Penicillin production optimization can be viewed as a fixed initial state, free time interval and free final state problem. Optimization is achieved using a nonlinear gradient method, and attention is focused on the selection of the best method to compute the search step size. Three families of methods are compared, including fixed-step, parabola-minimizing, and general-curve minimizing families.

In the framework of environment preservation, microalgae biotechnology appears as a promising alternative for CO_2 mitigation. Advanced control strategies can be further developed to maximize biomass productivity, by maintaining these microorganisms in bioreactors at optimal operating conditions. The eighth paper by Tebbani et al. proposes the implementation of Nonlinear Predictive Control combined with an on line estimation of the biomass concentration, using dissolved carbon dioxide concentration measurements. First, optimal culture conditions are determined so that biomass productivity is maximized. To cope with the lack of online biomass concentration measurements, an interval observer for biomass concentration estimation is built and described. This estimator provides a stable accurate interval for the state trajectory and is further included in a Nonlinear Model Predictive Control framework that regulates the biomass concentration at its optimal value. The proposed methodology is applied to cultures of the microalgae Chlorella vulgaris in a laboratory-scale continuous photobioreactor. Performance and robustness of the proposed control strategy are assessed through experimental results.

Two additional papers have been published in a regular issue of Bioprocess and Biosystems Engineering.

The first one (and ninth in this collection of articles) by Sieber et al., titled "A method for the reconstruction of unknown non-monotonic growth functions in the chemostat" (doi:10.1007/s00449-013-0912-8), considers a generic single-species chemostat model, and proposes an adaptive control law that allows one to identify unstable steady states of the open-loop system without the a priori knowledge of the growth function. It is then shown how one can use this control law to trace out (reconstruct) the whole graph of the growth function. The process of tracing out the graph can be performed either continuously or stepwise. Even in the case of two species in competition, which is not directly accessible with this approach due to the lack of controllability, feedback control improves identifiability of the nondominant growth rate.

Finally, the last paper by Bayen and Mairet ("Minimal time control of fed-batch bioreactor with product inhibition", doi:10.1007/s00449-013-0911-9) is devoted to the minimal time control problem of fed-batch bioreactors, in the presence of an inhibitory product, which is released by the biomass proportionally to its growth. A growth rate with substrate saturation and product inhibition is first considered, and it is proved that the optimal strategy is fill and wait (bang-bang). Jin growth rate, which takes substrate and product inhibition into account, is then studied. For this type of growth function, the existence of singular arc paths defining singular strategies is demonstrated. Several configurations are addressed depending on the parameter set. For each case, an optimal feedback control of the problem (of bang-bang or bang-singular-bang type) is proposed. These results are obtained by formulating the initial model as a planar system through the use of conservation laws. Thanks to Pontryagin's maximum principle, Green's theorem, and properties of the switching function, the optimal synthesis can be achieved. A methodology is also proposed to implement the optimal feeding strategies.

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