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Editorial

Special Issue “Modelling and Optimal Design of Complex Biological Systems”

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At present, complex biological processes are used in many industrial areas. Furthermore, they are increasingly used within real environmental refineries whose objectives are producing biomolecules or recovering nutrients and energy within circular economy cycles. Modeling has become prevalent in optimizing bioprocesses. To minimize building and/or operational costs, optimal design that conceives optimal configurations of processes or methods to interconnect several reactors has developed rapidly. To this end, tools from modeling, control, simulation, and, in a more general way, dynamical systems theory are essential for addressing optimization challenges.

The Special Issue, “Modeling and Optimal Design of Complex Biological Systems”, provides research studies related to these critical research areas, briefly discussed below.

Aerobic and anaerobic systems for nutrient removal

This review study [1] focuses on the globally used anaerobic digestion (AD) process that conventionally transforms biodegradable organics (e.g., agricultural residues, food waste, wastewater treatment sludge) into energy-rich biomethane and nutrient-rich biosolids under anaerobic environmental conditions. The paper presents a broad overview of the historical context of AD modeling and comments on the current state of the art concerning the theory, applications, and technologies that comprise or exist alongside models for research and practice. The use of models for AD is envisaged to become even more critical in the context of the climate emergency, the need for intelligent management of resources, and the provision of resilient infrastructure that generates and processes these resources.

A two-step model of the anaerobic digestion process is mathematically and numerically studied in [2]. The model describes the hydrolysis and methanogenesis phases applied to waste digestion with a high solid matter content. The hydrolysis step is considered a limiting step in this process that uses the Contois growth function for the bacteria responsible in the first degradation step. The Haldane growth rate is used for the methanogenesis step since it is inhibited by the first reaction’s product (also the substrate for the second one). The existence and stability properties of the equilibrium points are investigated. The operating diagrams concerning the dilution rate and the input substrate concentrations are established and discussed.

A model of a biodenitrification process in a spatially-distributed bioreactor is considered in [3], taking into account the limitation of kinetics by the carbon source and oxidized nitrogen. The model is described by a system of four diffusion–convection–reaction equations for which the existence and uniqueness of a global solution are shown. The system is approximated by a standard finite element method that satisfies an optimal a priori error estimate. Results are obtained for three forms of the growth function (single substrate limiting form, “multiplicative” form, and “minimum” form) and are compared to each



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other. Numerical simulations indicate that the “minimum” model provides results closer to the experimental data.

The article [4] proposes a multivariable adaptive feedback control for highly uncertain continuous anaerobic digestion processes to regulate the volatile fatty acids (VFA) concentration, the strong ions concentrations, and the total and intermediate alkalinities. The controller is a robust multiple-input, multiple-output (MIMO) control. The proposed control scheme is experimentally tested and validated in a pilot plant anaerobic digester, consisting of a 0.982 m³ up-flow fixed-bed bioreactor, located in LBE-INRAE, Narbonne, France. The structure of the control scheme takes into account the high nonlinearity of the AD process, the unknown microbial growth kinetics, and its parameter uncertainty. A Luenberger observer is used in the control scheme to estimate the biomass concentrations (which cannot be measured), together with the kinetics and yield coefficients. Demonstrably, the proposed MIMO control is robust in the face of parameter uncertainty, unknown kinetics, and pH variations, as well as in measuring disturbances.

A general approach for kinetics monitoring of a class of biotechnological processes is proposed in [5]. This class of processes is characterized by a relationship between measured and estimated parameters that guarantees the synthesis of an asymptotically stable software sensor (SS) design. The originality of this approach lies in (i) the presentation of the process kinetics with two unknown time-varying parameters with clear physical meaning, (ii) the derivation of a linear structure of the SS using logarithmic transformations of these parameters that facilitate stability analysis, and (iii) the derivation of stable fourth- and fifth-order structures of the SS, satisfying conditions for asymptotical stability. As a case study, monitoring the kinetics of processes conducted in stirred tank reactors is investigated. A new tuning procedure is derived, resulting in a choice of only one design parameter. Experimental data with *Bacillus subtilis* fed-batch cultivations demonstrate the proposed procedure’s effectiveness.

Microalgae systems for the treatment of water and the production of biomolecules

Microalgae have attracted increasing attention during the last decade as an efficient, versatile, and renewable way to harvest solar energy; uses include the production of biofuels, pigments, food ingredients, and even wastewater treatment. Cultivation of microalgae inevitably involves the application of dynamic conditions—even if a continuous culture is implemented—as a result of natural illumination changes during the day. Moreover, microalgae cultivation typically takes several days or weeks, during which changes in environmental conditions are expected. Therefore, microalgae represent a relevant case study when determining the effects of delays on the behavior of microbial populations. The work [6] studies the existence of delays in the response of a microalgae population when exposed to changes in energy and carbon sources and a growth inhibitor. *Chlorella vulgaris* is used to conduct the study, considering that this is a well-known microalga with various purposes and applications. Results show no appreciable delays exist when microalgae undergo changes in the intensity of incident light. For changes in carbon source concentration (inorganic carbon), a slight delay is detected in the range of minutes. Finally, when exposing microalgae to inhibitory concentrations of ammonia, a significant delay of several hours is observed.

The study [7] is devoted to parameter estimation of a dynamic model for cultures of the microalgae *Scenedesmus obliquus* using datasets collected in batch photo-bioreactors operated with various initial and light illumination conditions. Measurements of biomass, intracellular substrate quota, extracellular substrate, and chlorophyll concentrations are collected from nine batch experiments differing by their initial and light exposition conditions. The parameters of a dynamic model are then estimated using a weighted least squares approach, and the uncertainty in the parameters is estimated based on the Fisher Information Matrix. Monte Carlo studies allow the model cross-validation against datasets not used in the identification procedure. The dynamic model is exploited in a simulation study demonstrating the potential benefits of a Nonlinear Model Predictive Control (NMPC) for

optimizing biomass production in a continuous photo-bioreactor, acting simultaneously on the dilution rate and the light intensity.

A new model is proposed in [8] to represent the combined effect of light, oxygen concentration, and temperature (LOT-model) on microalgae growth to account for the oxidative stress affecting the cultures. The model is validated with experimental data for several species, such as *Chlorella minutissima*, *Chlorella vulgaris*, *Dunaliella salina*, *Isochrysis galbana*, and it shows a strong impact of oxygen concentration on productivity, depending on temperature. The LOT-model is proven to accurately fit several experimental data sets at equilibrium or dynamical conditions with an average error lower than 5.5%. It reveals that oxygen may play a substantial role in microalgae productivity. Since oxygen concentration in the medium is directly (solubility) or indirectly (photosynthesis) related to temperature and light, it is clear that this parameter must be monitored more attentively and systematically along the cultures. The proposed modeling approach can support advanced control strategies to reduce the productivity lost due to oxygen accumulation.

The water cycle algorithm (WCA), which is a metaheuristic method inspired by the movements of rivers and streams toward the sea in nature, is adapted and applied, for the first time, in [9] to solve the parameter identification problem of fermentation process (FP) models. A series of identification procedures of two different FP models are carried out to verify the WCA effectiveness. The bacteria *E. coli* and the yeast *S. cerevisiae* are chosen as case studies due to their impact on different industrial fields. To confirm the superiority of WCA, a comparison is made with the results obtained by the genetic algorithm (GA), another population-based technique that is a proven and promising alternative to conventional optimization methods. It is demonstrated that WCA results are more accurate compared to GA results. Considering that WCA is simple in terms of coding, implementation, and its confirmed superiority, it is concluded that WCA is an efficient and powerful algorithm for the parameter identification of complex nonlinear FP models.

Complex interconnections of biosystems for energy production

A new mathematical model describing a biotechnological process of simultaneous hydrogen and methane production by anaerobic digestion is proposed in [10]. The process is conducted in two connected, continuously stirred bioreactors. The proposed model is developed by adapting and reducing the well-known Anaerobic Digester Model No 1 (ADM1). Mathematical analysis of the model is performed, involving the existence and uniqueness of positive and uniformly bounded solutions, computation of equilibrium points, and investigation of their local stability concerning practically essential input parameters: the dilution rates D_1 and D_2 in the two bioreactors. The investigation of the hydrogen and methane flow rates, Q_{H_2} and Q_{CH_4} , on steady-state operation demonstrates the existence of maxima at some values of the dilution rates D_1 and D_2 , respectively. An optimal ratio of the working volumes of both bioreactors equal to 4.42 is obtained using the adapted model coefficients values, utilizing a criterion for maximizing the bioenergy production. The elaborated web-based software allows checking different model-based optimization and control strategies that could contribute to designing and engineering a real process.

Optimizing the continuous fermentation process is essential to increasing efficiency and decreasing cost, especially for complicated biochemical processes described by substrate and product inhibition. The optimum design (minimum volume) of CSTRs in series, assuming substrate and product inhibition, is determined in [11]. The optimum substrate concentration in the feed to the first reactor is determined for N reactors in series. The nonlinear, constrained optimization problem is solved using the MATLAB function *fmincon*. It is found that the optimum design is more beneficial at high substrate conversion and a medium level of feed substrate concentration. The percentage reduction in the total volume using the optimum design compared to the equal-volume design (R%) is determined as a function of substrate conversion and substrate concentration in the feed to the first reactor. For $N = 2, 3, 4,$ and 5 reactors in series, the maximum R% values achieved are 35%, 54%,

62%, and 66%, respectively. The obtained R% values agree with experimental data available in the literature for ethanol fermentation.

Conflicts of Interest: The authors declare no conflict of interest.

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