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Editorial

Special Issue: Bioprocess Monitoring and Control

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Bioprocesses can be found in different areas such as the production of food, feed, energy, chemicals, and pharmaceuticals. From bio-catalysis to fermentation processes or mammalian cell cultures, different reaction systems are applied. Due to the bio-economy initiatives in different countries, the number of bioprocesses will grow further in the future. One characteristic feature of all these different bioprocesses is a complex reaction matrix where different substances play an important role. Frequently, one must deal with a three-phase system, i.e., a liquid, a gas, and a solid phase. For the optimal operation of these processes, monitoring and supervision systems are required for all phases. Additionally—although bioprocesses have been applied for several thousand years, such as the fermentation of dough—on-line measurement systems for important process variables are still rare. Although the measurement of key variables is a challenge, the control of them to guarantee optimal yields is an even greater challenge.

This Special Issue of *Processes* entitled "Bioprocess Monitoring and Control" presents novel examples of on-line monitoring and closed loop control techniques applied to different bioprocesses. The accepted manuscripts cover a range of important topics in different bioprocess areas, where microorganisms, bird's eggs, and humans are involved. Different techniques such as those for the construction of sensors, the production of a biocontrol agent, scaling up procedures, the application of observers, closed loop control, and the model-based monitoring of a downstream process are presented. The accepted manuscripts are nine original research papers and three reviews, which are summarized below.

Lisci et al. [1] studied a model-based soft sensor, which is based on the adjustable-structure geometric observer and can be used to estimate important variables in a bioreactor. The performance of this approach was compared to the performance of an extended Kalman filter. Using simulations, they were able to show that both estimators lead to good estimation performance. The geometric observer estimation is more sensitive to measurement noise, probably because of the presence of the Lie derivative in the correction term. Lisci et al. concluded that the systematic geometric approach led to the best solution for the estimation problem, giving a structure that did not depend on the correction algorithm.

Brignoli et al. [2] present a new control method for the fed-batch cultivation of *Kluyveromyces Marxianus.* They counter the problem of noise and oscillations in the control variable and address the exponential growth dynamics more effectively. Based on dielectric spectroscopy for the on-line biomass concentration measurements, the specific growth rate was estimated. Using a feedforward-feedback controller, the authors could demonstrate that the specific growth rate could be maintained at different set point values. Therefore, the feasibility of the closed loop control of the specific growth rate of yeast in long-duration fed-batch cultures was demonstrated successfully.

Abo-Zaid et al. [3] present results from tests of twenty fluorescent *Pseudomonas* isolates for their ability to produce siderophores. The assessment of their antagonistic activity against six plant pathogenic fungal isolates is demonstrated. For the promising strains, a scaling-up production of siderophores from fluorescent *Pseudomonads* was carried out. They could show that the exponential fed-batch fermentation of *P. aeruginosa* F2 and *P. fluorescens* JY3 gave higher concentrations of siderophores and biomass than

batch fermentation. Furthermore, they demonstrated that formulations of siderophore-producing fluorescent *Pseudomonads* were effective in controlling soil-borne fungi and for the stimulation of plant growth. Therefore, they concluded that bio-friendly formulations of siderophore-producing fluorescent *Pseudomonas* isolates could be used as biocontrol agents for controlling some plant fungal diseases.

Zhang et al. [4] isolated from the commercial Yanjing Natto food a bactericide-secreting Bacillus strain, i.e., *Bacillus subtilis* natto, which is potentially useful as a biocontrol agent. Upon the optimization of the growth medium for optimal bactericide secretion, the antimicrobial activity of the strain was enhanced significantly. They could demonstrate the inhibitory properties of the obtained agent against *S. aureus*, *E. coli*, and *S. typhimurium*. Using HPLC, ^{13}C-nuclear magnetic resonance, and mass spectral analyses, the structure of the purified new bactericides could be identified.

The effect of nitrate and perchlorate on selenate reduction in a batch reactor was investigated by Kim et al. [5]. They selectively enriched selenate-reducing bacteria in bench-scale sequencing batch reactors, which were seeded with activated sludge, and operated them semi-continuously in parallel for more than one and a half months. They show that complete selenate and nitrate reduction can be accomplished simultaneously. Kim et al. concluded that selenate-reducing bacteria are capable of enduring the competition associated with the reduction of other oxyanions and electron donors without significant inhibition after appropriate acclimation.

Jafari et al. [6] studied a bioleaching process for the extraction of metals from a flotation concentrate. In their contribution, results regarding the influence of two typical flotation frothers on the sensitivity of bacteria in the mesophilic mixed culture are presented. As a traditional mixed mesophilic microorganism culture, *Acidithiobacillus ferrooxidans*, *Leptospirillum ferrooxidans*, and *Acidithiobacillus thiooxidans* were used. By increasing the dosage of the frothers, they could show a negative correlation with bacterial activities. However, the mixed culture showed a lower sensitivity to the toxicity of the frothers than the examined pure cultures.

Feidl et al. [7] investigated the monitoring of monoclonal antibody breakthrough curves in chromatographic downstream operations. As a measurement system, they used a Raman spectrometer connected to the process by a self-developed flow cell. An extended Kalman filter was developed by complementing the measurement information with information coming from a lumped kinetic model. Feidl et al. demonstrate in their contribution that this approach allows the estimation of the antibody concentrations with reduced noise and increased robustness.

For the incubation of bird eggs, Youssef et al. [8] developed a model predictive controller to regulate the heating power. They used several IR radiators divided into three zones to adjust the eggshell temperatures individually in each zone. To test and implement the developed controller, four full incubation trials were performed. The authors could demonstrate that the controllers were able to follow the reference trajectory defined for each individual zone. They could keep the air temperature constant, although the eggshell temperatures within the middle zone were different from those in the sidelong zones.

That we as humans are also part of a kind of bioprocess and have to be maintained under optimal conditions is considered by Youssef et al. [9]. They propose an adaptive occupant-based predictive controller for a heating, ventilation, and air conditioning system using a predictive classification model to provide an optimal indoor climate with respect to temperature and humidity. To estimate the individual metabolic rates of 25 participants, three input variables—aural temperature, heart rate, and average skin heat-flux—were used. The least squares support vector machine technique was applied to predict the individual's thermal sensation. Based on that, they recommend an adaptive model predictive controller to adjust the indoor climate.

Without reliable sensors, the control of processes is not possible. Krywko-Cendrowska et al. [10] emphasize the importance of monitoring in general but also for bioprocesses. They review examples of well-defined conjugated macromolecules based on an oligo(arylene-ethynylene) skeleton used for sensor applications and discuss their relevance and their perspectives, not only for biological samples. In the review, they focus exclusively on examples of uniform macromolecules.

Noll et al. [11] summarize the most important models for physiological, biochemical, and physical properties governed by temperature. A timeline of the publication of different temperature models is presented as are the pro and cons of mechanistic and empirical models. In their review, a toolset for the future exploitation of temperature as a control variable for optimization, monitoring, and control applications in bioprocess engineering is presented.

Galvanauskas et al. [12] emphasize in their review the importance of the control of the specific growth rate because this enables the improvement of the quality and reproducibility of bioprocesses. Requirements are given that must be met to successfully implement the specific growth rate control system. Furthermore, recommendations are presented for the selection of particular control systems for specific biotechnological processes.

The articles in this Special Issue highlight the diversity of bioprocesses and new applications in the development and management of these processes. Especially for closed loop control, the reliability of the measurements is central. Beside the measurements, the applicability of the models is equally important. They must provide the required accuracy in estimating bioprocess variables. The articles in this Special Issue show a major step forward towards efficient bioprocesses but in the future further research is still needed. The papers from this Special Issue can be accessed at the following link: https://www.mdpi.com/journal/processes/special_issues/bioprocess_control.

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