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Editorial

Advanced Modeling of Biomanufacturing Processes

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The multi-layered and complex nature of cellular regulation enhances the need for advanced computational methodologies that can serve as scaffolds for organizing experimental data to facilitate the inference of meaningful relationships [1]. First-principle-type unstructured models have been successfully used to monitor, predict, and optimize cell culture performance in biomanufacturing processes. However, such model-based approaches have not been widely adopted by the bioprocess industry due to clear limitations [2]: (i) inconsistencies in the utilized growth kinetics, leading to conflicting conclusions; (ii) lack of correlation/connectivity with the critical quality attributes (CQAs) of downstream unit operations; and (iii) limited information on the impact of process parameters (i.e., shear stress, DO_2, DCO_2, pH, osmolality) on product and broth quality. Therefore, despite outstanding research developments in biotechnology, the sophisticated mathematical toolset that led to the explosive growth of manufacturing capacity in traditional chemical industries, known as process systems engineering (PSE), has not been widely applied to the biomanufacturing industry [3]. Consequently, the design and optimization of industrial biomanufacturing processes remains heavily reliant on manual and evidence-based approaches [4].

At the other end of the spectrum, mathematical models for biological systems developed over the last decades have been central in the understanding, improvement, and optimization of biological systems [5]. Knowledge of the metabolic state of a cell and its response to various stimuli and extracellular conditions can offer significant insight into its regulatory functions, as well as assist in identifying pathways and targets that could be manipulated using synthetic biology tools [6]. Metabolic engineering and systems biology study the interactions between all known metabolic reactions in an organism, and their application has yielded significant insight into the regulatory elements of central carbon metabolism [7]. However, they are computationally intensive approaches, rendering their use impractical for on-line industrial applications. To date, several challenges remain before detailed kinetic models reach the degree of maturity required for conventional use in industrial-scale biomanufacturing applications.

In recent years, hybrid integrated knowledge and data-driven modeling approaches have revealed the potential to further unlock bioprocess performance by utilizing increasingly sophisticated machine learning algorithms to mitigate the limitations of traditional knowledge-based modes [8]. Data-driven approaches allow the identification of patterns and correlations that may not be apparent through traditional modeling alone. The synergy between mathematical modeling and machine learning facilitates real-time optimization and fosters adaptive and responsive bio-based technologies [9]. Combined with the contemporary popularity of artificial intelligence (AI), machine learning, and data mining tools, these hybrid approaches have provided a platform for clear communication between modelers and process engineers and have contributed to the increased adoption of model-based approaches in industrial biomanufacturing [10]. What is presently lacking is availability of novel engineering approaches able to integrate, organize, and guide experimental (and modeling) information across multiple unit operations, all the way from the strain

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design and selection phase to the purification and/or formulation of the end product. This shortage of advanced modeling tools also affects the techno-economic and life cycle (LCA) analyses of new bio-based processes and products, using plant-wide steady-state modeling approaches [11].

This Special Issue of *Processes*, entitled "Advanced Modeling of Biomanufacturing Processes" (accessed on 26 January 2024), aims to advance the degree of maturity of model-based approaches in industrial biomanufacturing, presenting developments in seven research articles and two dedicated reviews. These cover a range of applications across different sectors such as biopharmaceuticals, high-added value biochemicals, and biomaterials. Initially, Gibson et al. present a model-based evaluation of the effect of buffer management on bioprocess efficiency to facilitate the design of sustainable biopharmaceutical manufacturing processes. A detailed non-replicated full factorial design model is employed to identify the impact of buffer management on a monoclonal antibody production process at a large scale. The study demonstrates the potential to significantly reduce process mass intensity among the investigated strategies. In an attempt to describe cellular behavior, Krumm et al. apply a simple segmented model to systematically analyze the superiority of a high-seeding density fed-batch process compared to conventional feeding strategies. The model was validated as a predictive tool for improving the feeding policy and harvest viability of the system and used to derive optimal fed-batch feeding strategies.

Venturing beyond antibodies, Gómez-Aldapa et al. employ a design of experiments (DoE) approach to derive a predictive response surface model (RSM) that was used to optimize the production of isopentyl acetate from whey components. The model was able to identify optimal operating conditions in terms of substrate concentration, allowing the efficient exploitation of this low-cost substrate. Shifting the research focus to downstream processing, Puga-Córdova et al. focused on separating 2-phenylethanol, produced during whey fermentation. An additional objective was to evaluate the economic potential of the process. By using a steady-state simulator, the authors showed that the developed separation protocol possesses, beyond adequate efficiency, a large economic potential. Luna et al. explore the potential of hybrid knowledge and data-driven models to optimize the fermentative production of polyhydroxyalkanoates (PHAs). Specifically, a novel hybrid model was developed and applied to simulate the dynamic evolution of growth and uptake rates in microbial cells. Various operating conditions were investigated, including both single- and dual-nutrient-limited growth, in order to identify conditions that maximize the intracellular accumulation of the biopolymer. Meimaroglou et al. combine both deterministic (i.e., method of moments) and stochastic (i.e., kinetic Monte Carlo) components to study the hydrolysis and polycondensation reactions of saccharides. Their innovative modeling framework successfully simulated the formation of polysaccharides with high polymerization degrees. Finally, Nedjhioui et al. apply a series of multi-factorial designs to minimize the risks and hazards for both the environment and humans, during kerosene recovery. This multi-objective optimization framework identified optimal operational conditions and provided in depth insights on the physicochemical properties of this complex system.

In the first review of this Special Issue, Penloglou et al. analyze both technical and economic aspects of nanocellulose production from lignocellulosic biomass. A detailed plant-wide simulation model is used to calculate the most important key performance indicators (KPIs), and compare them with the present state of the art. Thus, a comprehensive overview of the current state of nanocellulose production is provided, highlighting the main challenges to be addressed in future research. Finally, Tsipa et al. review available mathematical models for microbial fuel cells, developed and used for their design, control, and optimization. In this framework, an advanced bio-based model is also presented, able to link gene regulation of specific metabolic pathways to microbial growth. This multi-scale modeling approach enables a more accurate prediction and estimation of substrate biodegradation mechanisms, microbial growth kinetics, and gene-enzyme expression patterns.

In conclusion, as is showcased by the nine publications of the present Special Issue, advanced mathematical modeling of biomanufacturing processes and separation technologies is a cornerstone for achieving sustainability and efficiency in the modern era. The ability to quantitatively represent biochemical and biological systems, as well as optimize bioprocesses and anticipate challenges, positions mathematical modeling and simulation as indispensable tools in the advancement of industrial-scale applications of biotechnology. As the pursuit of innovative solutions to meet the growing demands for bio-based products intensifies, the integration of rigorous multi-scale mathematical frameworks will undoubtedly play a crucial role in shaping the future of the bio-economy.

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

List of Contributions

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