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Towards bioprocessing 4.0: Scaling sustainable innovation in the pharmaceutical bioeconomy

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THE CURRENT PHARMACEUTICAL BIOECONOMY

Bioeconomy is increasingly seen as the cornerstone for a sustainable future and for addressing global challenges such as climate change, pollution reduction, rational resource utilization, and clean energy. The consolidation of bioeconomic production structures is clearly fueled by the rate of innovations in biotechnology and life sciences as well as the level of investment, not only in industrialized countries. Despite the lack of reliable data about the current state of bioeconomy in terms of investment, inventories, facilities, and value chains, most of the projections converge to an average value of approximately USD $ 4 trillion, accounting for around 3.5% of global GDP [1,2]. Forecasts suggest that bioeconomy could exceed $7.7 trillion by 2030, but with a potential growth reaching $30 trillion under optimistic scenarios (10%–15% CAGR), that is, 26% of the world's GDP [1,3,4]. This path has been paved by the rapid adoption of biotechnology, synthetic biology, and advanced biomanufacturing [1,4]. At least 38 countries have adopted national bioeconomy strategies, reflecting some policy support, but those numbers are still small considering the size of the world's economy and market value [1,5].

In this context, the bio-based pharmaceutical sector—including biologic drugs, vaccines, and other products made via bioprocessing—represents a major and fast-growing segment. In 2024, the global biopharmaceuticals market (principally biologic medicines derived from living cells or fermentation) was valued at about $617 billion, and it is projected to double to $1.18 trillion by 2032 (8.6% CAGR) of the overall USD $2 trillion pharma market [6]. Interestingly, the pharmaceutical industry is rapidly greening its feedstocks: while in 2018 only approximately 21% of pharma's material inputs were bio-based, by 2030, as much as 38% of inputs are expected to be biomass-derived, as the sector triples in market size [2]. This reflects the deep turn toward biotechnology platforms like microbial fermentation, cell culture, and plant-based production, away from purely petrochemical processes.

Today, biotechnology has certainly redefined the production of vitamins, organic acids, and other pharmaceutical intermediates. The success of fungal production of vitamin B2 (riboflavin) from vegetable oils developed by BASF is a prime example of the insertion of a complete bioprocess substitute in pharmaceutical production. This process not only eliminated hazardous chemical waste and reduced CO_2 emissions by 30% but also cut production costs by 40% [2]. Today, 100% of the world's vitamin B2 supply (a USD $481.60 million market) is produced via fermentation rather than chemical synthesis [6]. Similar biotech processes exist for citric acid, ascorbic acid (vitamin C), succinic acid, lactic acid, and aspartic and glutamic acid are now produced via fermentation, as some well-established examples. However, such transformation had implicit challenges in scaling up biological processes to industrial levels. Laboratory-scale successes often fail to translate directly to industrial production due to differences in process dynamics, economics, and regulatory requirements.

THE SCALE-UP CHALLENGE AND THE ROLE OF BIOPROCESSING 4.0

The development of a bioprocess is inherently iterative and circular, progressing through interconnected phases of experiments at different scales, design, optimization, and implementation. As observed in Figure 1, this circular process of innovation requires the integration of many disciplines from biology to management that contribute to succeeding in the complexity of a competitive market. However, the transition from laboratory to industrial-scale bioprocesses often introduces performance challenges—for example, scale-up can cause a 10%–30% reduction in yield, titer, or productivity and even batch failures [7]. Therefore, a dedicated optimization stage is critical in bioprocess development to refine conditions and ensure robust, scalable performance. Table 1 summarizes

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such critical scale-up challenges and the engineering strategies to face them.

The challenges have been known for many years, but how to face them has evolved considerably. In the process of optimizing bioprocesses, simulation studies, either experimental or *in silico*, help to predict and mitigate scale-related issues, saving time and cost. Several strategies are increasingly catching up the attention of industry as certainly allow them to improve the performance of both new and well-established bioprocesses.

Scale-down studies enable the replication of industrial bioreactor patterns at lab scale, helping to identify scale-up effects that arise due to heterogeneities in large-volume systems, such as mixing inefficiencies and nutrient or oxygen gradients in connection to cell physiology and productivity [8,9]. Insights gained from scale-down experiments facilitate improvements in strain robustness, feeding strategies, and operation conditions, thereby enhancing process reliability. Nevertheless, accurately reproducing large-scale heterogeneities is challenging, and different configurations may emphasize distinct environmental factors, potentially yielding inconsistent results [9].

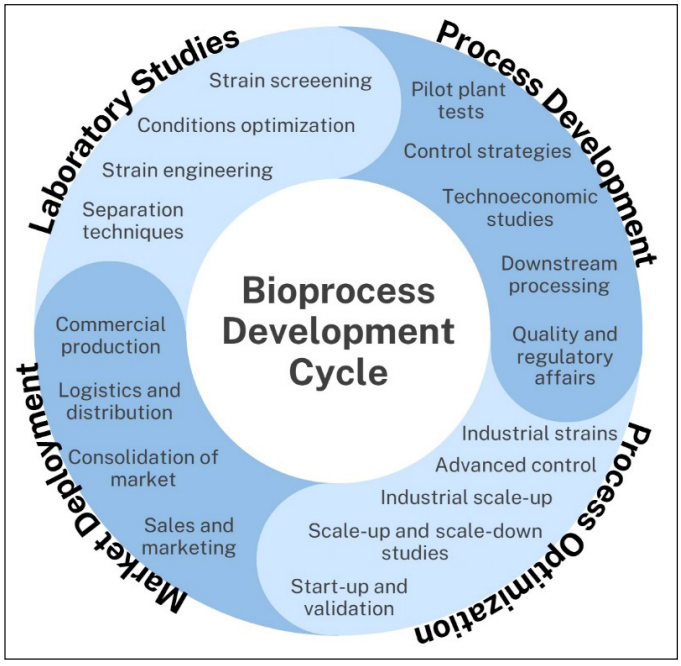

Figure 1. Innovation cycle for sustainable bioprocessing: from Laboratory Research to Industrial Scale-Up.

Interdependent variables like substrate and oxygen gradients are difficult to isolate, and the lack of comprehensive sensor data from industrial-scale tanks complicates the design of predictive lab models.

Some of the drawbacks of scale-down experimental approaches can be overcome by integrating *in silico* modeling as a complement to experimental bioprocess optimization. In this regard, computational fluid dynamics (CFD) and biological modeling are increasingly integrated to form digital twins of bioprocesses [7,9]. CFD can precisely simulate the physical environment inside bioreactors and separation equipment, revealing non-idealities such as mixing inefficiencies, oxygen transfer limitations, and shear zones. Although CFD excels at mapping abiotic factors, it lacks predictive capacity for cellular responses [10].

On the other hand, biological modeling helps to get insights about the rates of metabolite and products flow at various levels of complexity between the macroscopic and the microscopic scales, ranging from simple unstructured models to detailed structured models with intracellular compartments. While unstructured models are useful for fast calculations and basic control, they lack robustness when process conditions shift. Structured models account for physiological changes such as stress responses, storage mobilization, and metabolic regulation, offering superior extrapolative power and enabling dynamic process control, but parameter estimation and model construction are not always straightforward [10]. Constraint-based metabolic modeling (e.g., flux balance analysis) leverages stoichiometric networks to predict flux distributions under genetic or environmental perturbations, guiding media and strain optimization, but it is hard to integrate them into control strategies applicable to industries, since they prefer flexible, simple, proven, and cost-effective approaches [11].

Emerging strategies integrate CFD, kinetic, and metabolic frameworks to build multi-scale models and digital twins with the capacity to simulate intra- and extracellular phenomena, enhanced by data-driven corrections and online data from process sensors [10,12]. Although those approaches provide richer physiological data, enhance understanding, prediction, and allow the real-time control of complex bioprocesses, their utilization for a robust scale-up and bioprocess intensification is still far from massive adoption.

However, artificial intelligence (AI) may contribute to a faster adoption of those approaches driven by large sets of data. The increasing availability of high-throughput, multi-omics, and real-time sensor data difficult the construction of

Table 1. Critical scale-up challenges and engineering strategies in bio-based production.

Scale-up challenge	Impact on bioprocess	Engineering strategy
Feedstock variability	Inconsistent yields, process deviations	Standardized preprocessing, blending strategies
Oxygen transfer limitations	Reduced cell growth/productivity	Reactor design optimization, increased agitation, gas sparging
Heat transfer inefficiency	Hot spots, metabolic shifts	Advanced cooling systems, reactor geometry adjustments
Shear sensitivity of cells	Cell damage, reduced viability	Impeller design modifications, low-shear systems
Metabolite accumulation	Product inhibition, decreased yield	Process control tuning, fed-batch strategies
Downstream processing scale-up	Poor recovery rates, purity issues	Integrated process design, advanced filtration and separation technologies

mechanistic or phenomenological models integrating such volume of information and at the same time, to be responsive to generation of new data at a frequency of milliseconds [10,12]. AI's strength lies in the capacity of handling large datasets and its ability to get patterns and develop predictions based on complex superposition of mathematical and statistical models, but not in the phenomena. This is especially useful if the action is required in a short time, and the phenomenological explanation of a response or a measurement is secondary for the purpose. Once the model is trained, the computational power and the time required are very low, compared to the requirements for solving complex phenomenological models.

Therefore, the most impactful opportunity for including AI into the bioprocess innovation path is the hybrid modeling, combining the mechanistic understanding with the data-driven insights [12]. For instance, neural networks can represent unknown kinetics in a reduced metabolic model or approximate outputs of complex simulations like CFD, dramatically accelerating the solution without a complete lack of interpretability. The creation of digital twins replicating bioprocesses by integrating mechanistic and machine learning models in real-time enables model-predictive control by forecasting future process trajectories and computing optimal control actions, outperforming traditional control strategies [12]. The broader vision, which is the Bioprocessing 4.0, envisions smart, self-optimizing bioreactors, where AI anticipates process perturbations (e.g., oxygen limitation) and autonomously adjusts operation to maintain optimal performance. This paradigm change is transforming the bioprocesses development from an empirical and labor-intensive procedure to a model-informed, data-driven process.

FUTURE PERSPECTIVES

In the development of a bioeconomy, transformation of pharmaceutical industry is essential for real sustainability, driven not only by environmental and economic imperatives but also by the integration of innovative bioprocess technologies. The integration of experimental scale-up and scale-down methods, modeling, and simulation with the power of AI enables a deeper understanding and bioprocess optimization, bridging the gap between laboratory research and large-scale manufacturing. Undoubtedly, reaching the full potential of Bioprocessing 4.0 will require concerted investments in infrastructure, data integration, and workforce training. The convergence of simulation, automation, and data science promises an era of "smart biomanufacturing" systems dynamically responsive to real-time data, which can self-optimize and reduce failure risks. Bioprocessing with such capabilities will be key to accelerating the industrial deployment of next-generation bio-based pharmaceuticals, materials, food, and fuels as part of the transformative force of the global production models.

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