Sustainable Bioprocess Engineering: Improving Efficiency From Laboratory to Industrial Scale

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Abstract

Biological conversion can appear highly promising at laboratory scale while remaining technically unstable, resource intensive, or economically uncompetitive when transferred to industrial production. Scale changes mixing, oxygen transfer, heat removal, concentration gradients, contamination risk, instrumentation, and downstream-processing requirements, while large production volumes magnify water, energy, raw-material, and waste burdens. This editorial argues that sustainable bioprocess engineering must therefore connect biological performance with reactor engineering, process control, separations, utilities, scale-up, and economics across the full production train. Modern fermentation, continuous processing, process analytical technologies, digital models, advanced control, and intensified separations provide powerful tools, but their value depends on evidence under realistic scales and operating variability. Persistent challenges include scale-dependent physiology, titre–yield–productivity trade-offs, strain stability, mass-transfer limitations, process variability, purification burdens, and uncertain resource efficiency. Research priorities include scale-down models, continuous and intensified processing, robust monitoring, predictive digital bioprocessing, energy-efficient separations, water minimization, modular manufacturing, pilot-scale validation, and integrated techno-economic and lifecycle assessment.

Keywords: bioprocess engineering; scale-up; fermentation; process intensification; downstream processing; process analytical technology; techno-economic assessment

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1.0 Introduction

1.1 Context and Problem Framing

A successful laboratory culture establishes biological possibility, not industrial feasibility. Shake flasks and bench bioreactors provide controlled environments in which temperature, pH, oxygen availability, nutrient distribution, and contamination can be managed with comparatively little spatial heterogeneity. Large production vessels behave differently. Mixing times increase, gradients develop, oxygen transfer becomes more difficult, heat removal changes, and cells repeatedly experience fluctuating microenvironments as they circulate through the reactor. Classic scale-up studies therefore emphasize that geometric enlargement is not a neutral operation: the physical environment that surrounds a cell changes with scale (Junker, 2004; García-Ochoa & Gómez, 2009). Industrialization requires biological systems that tolerate those conditions while maintaining productivity and product quality. Standard bioprocess design principles also require explicit integration of stoichiometry, kinetics, transport, reactor configuration, and downstream constraints (Doran, 2013; Chmiel et al., 2018).

The engineering problem extends beyond fermentation. Feedstock conditioning, sterilization, media preparation, gas compression, agitation, heating and cooling, cell removal, extraction, chromatography, filtration, crystallization, drying, solvent recovery, wastewater treatment, and clean-in-place systems can dominate the resource footprint of a process. A high-yield biological reaction can still be economically weak when product concentration is low or purification is difficult. Bioprocess design must therefore connect biological performance with mass and energy balances, reactor behaviour, control systems, downstream recovery, and utilities. This is particularly important in industrial biotechnology, where commodity chemicals, fuels, proteins, food ingredients, enzymes, and biomaterials operate under very different price and purity constraints.

1.2 Why the Issue Matters

Scale-up should consequently be treated as a hypothesis-testing process rather than a late-stage engineering transfer. Takors (2012) argued that microbial scale-up affects physiology through environmental dynamics that cannot be inferred from homogeneous small reactors alone. Enfors et al. (2001) similarly demonstrated physiological responses to substrate gradients representative of large-scale cultivation. These observations motivate scale-down systems that reproduce relevant industrial heterogeneities before capital-intensive scale-up. The central position advanced here is that sustainable bioprocess engineering requires simultaneous optimization of biology, transport phenomena, process control, resource use, separations, and economics. Laboratory titres or yields are important, but they become meaningful manufacturing evidence only when the complete process can operate stably, efficiently, safely, and reproducibly at relevant scale.

2.0 Current Landscape

2.1 Bioreactor Engineering

Modern fermentation platforms span batch, fed-batch, perfusion, and continuous modes, each offering different relationships among productivity, operational complexity, contamination risk, and product consistency. Fed-batch remains dominant in many industrial processes because nutrient supply can be controlled while avoiding some washout and inhibition problems. Continuous culture can raise volumetric productivity and reduce downtime but requires stable biological performance over extended periods. In biopharmaceutical manufacturing, integrated continuous approaches have demonstrated the feasibility of linking upstream culture with downstream capture and purification (Warikoo et al., 2012; Godawat et al., 2015). Konstantinov and Cooney (2015) consequently framed continuous bioprocessing as a major manufacturing direction, although platform maturity varies among products and sectors. The continuing expansion of biopharmaceutical manufacturing further illustrates how product class and quality requirements shape process architecture (Walsh, 2018).

2.2 Process Intensification

Scale-up science increasingly combines transport measurements with computational and biological analysis. Oxygen-transfer capacity remains central for aerobic systems because low oxygen solubility makes gas–liquid transfer a common bottleneck (García-Ochoa & Gómez, 2009). Mixing and substrate gradients can create local starvation, overflow metabolism, by-product formation, and stress responses. Scale-down reactors reproduce selected heterogeneities so that strains and control strategies can be evaluated before manufacturing-scale operation (Neubauer & Junne, 2010). More recent analyses integrate flow-field models with cellular physiology to understand how circulation through industrial vessels creates repeated environmental transitions (Wang et al., 2020). Industrial-perspective scale-down research and organism-lifeline analysis reinforce the need to reproduce dynamic large-scale exposures rather than only average vessel conditions (Noorman, 2011; Haringa et al., 2016; Wang et al., 2021).

2.3 Monitoring and Control

Digitalization is also changing process development. Process analytical technology combines in-line, on-line, and at-line measurements with multivariate analysis to improve process understanding and control. Spectroscopy, soft sensors, biomass probes, metabolite measurements, and advanced data analytics can provide information that was previously available only through delayed laboratory assays. Mechanistic models and hybrid models can then support state estimation, control, and scale-up. Gernaey et al. (2010) describe how mechanistic modelling can structure knowledge across fermentation processes, while Mandenius and Gustavsson (2015) show how sensor strategies can convert biological variability into actionable process information. PAT frameworks for biopharmaceuticals similarly emphasize real-time measurement, multivariate understanding, and control of critical quality attributes (Rathore et al., 2010).

2.4 Downstream Processing

Downstream processing has simultaneously become a major focus of intensification. For many bioproducts, separation rather than fermentation determines both cost and environmental burden. Membrane operations, continuous chromatography, integrated clarification, aqueous extraction, selective adsorption, crystallization, and in-situ product removal can reduce unit operations or improve recovery. In biopharmaceuticals, continuous downstream strategies seek to match the productivity gains of continuous upstream processing; in industrial biotechnology, similar logic applies to low-value products that cannot tolerate energy-intensive purification. The key shift is from optimizing individual unit operations toward integrated production trains.

3.0 Critical Challenges

3.1 Scale-Up Uncertainty

Scale-dependent biological behaviour remains the most fundamental challenge. Industrial vessels develop concentration gradients because mixing, reaction, and transport occur on comparable timescales. Cells may therefore cycle between substrate excess and limitation, high and low dissolved oxygen, or different pH environments. These fluctuations can change metabolic fluxes, stress responses, by-product formation, and recombinant-protein quality. Lara et al. (2006) describe how microorganisms effectively live with environmental heterogeneity in large bioreactors, while scale-down research demonstrates that short exposures can have cumulative consequences. Strains optimized only under homogeneous laboratory conditions may therefore be poorly matched to manufacturing reality. High-cell-density cultivation makes these interactions particularly acute because oxygen, heat, and substrate demands rise rapidly with biomass concentration (Riesenberg & Guthke, 1999).

Oxygen transfer, mixing, and heat removal impose interconnected physical constraints. Increasing agitation can improve mixing and gas transfer but raises power demand and shear; increasing gas flow can improve oxygen delivery but complicate foaming and off-gas handling. High-cell-density cultures intensify these constraints because oxygen uptake and heat generation rise with biomass concentration. Scale-up criteria such as constant power per volume, tip speed, mixing time, or mass-transfer coefficient cannot generally be satisfied simultaneously (Junker, 2004). Sustainable design requires identifying which physical variables most strongly affect biology and product quality rather than applying a universal scaling rule.

3.2 Energy and Water Demand

Process variability and biological stability create a third challenge. Genetic drift, plasmid loss, phage contamination, adventitious organisms, raw-material variation, inoculum history, and sensor error can all affect performance. Continuous systems can magnify the consequences of slow biological change because cultures remain active for long periods. Robust monitoring and contamination barriers are therefore essential. The problem is not solely achieving a high average yield, but maintaining a validated operating region over time and across batches, sites, operators, and raw-material lots.

3.3 Contamination and Robustness

Titre, yield, and productivity also create difficult trade-offs. A strain may achieve high yield at low growth rate, high productivity at the expense of by-product formation, or high titre only with costly feeding and oxygen demand. These metrics then interact with downstream recovery: higher titre can reduce separation volume, but impurities or broth rheology may become more challenging. Straathof (2011) emphasized that recovery of fermentation products must be considered during pathway and process selection, particularly for bulk chemicals. Upstream optimization that ignores purification can therefore make the total process worse. Biocatalytic-process economics likewise show that catalyst productivity, lifetime, recovery, and product concentration must be assessed together (Tufvesson et al., 2011).

3.4 Techno-Economic Viability

Water, energy, and economics ultimately determine whether scale-up is sustainable. Sterilization, aeration, agitation, evaporation, distillation, drying, refrigeration, and cleaning can create large utility demands. Disposable technologies may reduce water and cleaning but increase material use. Modular facilities can reduce capital exposure but may lose economies of scale. Techno-economic studies such as Humbird et al. (2011) show how conversion yield, feedstock cost, enzyme use, solids handling, and product recovery jointly determine commercial

feasibility. Sustainability claims should therefore be tested using full process inventories rather than biological conversion efficiency alone. Green-process metrics and sustainable-bioprocess frameworks provide complementary methods for relating resource consumption to functional output (Heinzle et al., 2006; Sheldon, 2017).

4.0 Discussion and Priorities

4.1 Integrative Discussion

Sustainable bioprocess engineering is best understood as optimization of a production train rather than optimization of a microorganism. Upstream changes propagate downstream. A more concentrated feed may improve reactor productivity but increase viscosity and mixing demand; a new strain may raise titre but secrete difficult impurities; a continuous culture may increase throughput while requiring more sophisticated contamination detection. Conversely, an energy-efficient separation can change the acceptable range of fermentation titre. These interactions mean that biological and process engineering decisions should be made iteratively.

Process intensification is valuable when it reduces total resources or improves control, not merely when equipment becomes smaller. Stankiewicz and Moulijn (2000) introduced process intensification as a route to substantially more efficient chemical processing, and its logic has increasingly influenced bioprocessing. Continuous production, integrated unit operations, in-situ recovery, and high-cell-density cultivation can reduce inventories and increase productivity, but complexity can shift into automation, cleaning, validation, and control. The relevant question is whether intensification improves whole-system performance under realistic reliability requirements. The same principle underlies process-intensification approaches that combine smaller equipment, integration, and improved transfer without assuming that intensification is automatically sustainable (Boodhoo & Harvey, 2013; Woodley, 2017).

Digital bioprocessing can support this integration by connecting models, sensors, and control. Mechanistic models capture mass balances and transport constraints; data-driven models can estimate difficult-to-measure states; hybrid models combine both. Yet a digital representation is only useful when it is calibrated against process-relevant data and updated as scale or equipment changes. Sustainable manufacturing therefore depends on an evidence chain linking strain phenotype, hydrodynamics, sensor data, control actions, separation performance, resource use, and economics. Model-based upstream development also demonstrates how predictive tools can accelerate process understanding when their assumptions are linked to experimental data (Kornecki & Strube, 2018).

Complementary scholarship informing this synthesis includes Rathore (2009); and Wang (2015). These works broaden the evidentiary base considered across the field.

4.2 Research and Practice Priorities

A first priority is better scale-down and scale-up methodology. Laboratory systems should reproduce the temporal patterns of substrate, oxygen, pH, and shear that cells experience in large equipment rather than only matching average values. Computational fluid dynamics, tracer studies, and cellular response measurements can help identify the industrial heterogeneities that matter most. Scale-up evidence should state explicitly which similarity criteria are preserved and which are sacrificed.

Second, intensified and continuous bioprocesses require long-duration validation. Integrated continuous manufacturing can improve productivity and equipment utilization (Warikoo et al., 2012), but robust evidence should include contamination control, steady-state stability, transition management, cleaning, start-up and

shutdown, and disturbance recovery. Pilot and demonstration campaigns should be long enough to expose slow biological drift and fouling phenomena that short laboratory runs miss.

Third, process analytical technologies and advanced control should become routine elements of scale-up. Sensors should target critical process variables and critical quality attributes rather than produce data for its own sake. Soft sensors, spectroscopic measurements, and multivariate models should be validated across feedstock lots and process scales. Advanced control strategies should be tested under realistic disturbances and sensor failure, not only nominal operation.

Fourth, downstream processing deserves equal emphasis with strain and reactor development. Energy-efficient membranes, selective recovery, continuous chromatography, phase-separation strategies, crystallization, and in-situ product removal should be assessed early. Product recovery should inform metabolic engineering targets because a modest improvement in titre may be less valuable than a change that simplifies separation. This is especially important for dilute bulk products and complex biological matrices.

Fifth, water and energy minimization should be designed across utilities and cleaning systems. Heat integration, water reuse, lower-temperature separations, closed-loop cleaning, and electrified utilities can reduce environmental burdens. Resource targets should be reported per functional unit of product and should include realistic recovery efficiencies rather than idealized laboratory assumptions.

Finally, techno-economic and lifecycle assessment should be integrated with process development. Sustainability evaluations should use scale-appropriate mass and energy balances and explore uncertainty in yield, equipment cost, feedstock price, utilities, product price, and scale. Pilot-scale evidence is especially valuable because it narrows uncertainty between bench data and commercial design. A process should not be described as sustainable solely because its catalyst is biological; sustainability must emerge from the complete manufacturing system.

4.3 Implications for the Journal's Scope

The journal should encourage research that bridges biological innovation with the engineering evidence required for industrial manufacturing. Studies of engineered strains, enzymes, cell lines, or pathways are most valuable when their process implications are made explicit through reactor performance, scale-down testing, separability, resource consumption, or pilot-scale data. Likewise, process-engineering studies should connect transport, sensors, control, and separations to biological performance rather than treating fermentation as a generic unit operation.

Particular value lies in work on scale-up methodology, continuous and intensified bioprocessing, process analytical technology, digital bioprocessing, advanced control, low-energy separations, water minimization, modular manufacturing, and integrated environmental-economic assessment. Negative scale-up results and comparative pilot studies should be considered scientifically important because they identify constraints that laboratory optimization alone cannot reveal. The central scholarly standard should be credible translation from biological promise to stable and resource-efficient production.

4.4 Conclusion

Industrial bioprocessing fails when laboratory biology and manufacturing engineering are treated as separate stages. Scale changes the physical environment experienced by cells, while the economics and environmental performance of a process depend heavily on operations that occur before and after biological conversion. The resulting challenge is inherently integrative: strains, reactors, sensors, control, separations, utilities, and supply chains must function as one production system.

Sustainable scale-up therefore requires more than maintaining yield in a larger vessel. It requires stable biology under realistic gradients, efficient transfer of oxygen and heat, reliable monitoring, controlled variability, energy- and water-conscious purification, and economic performance supported by pilot evidence. The strongest future bioprocess research will connect molecular and microbial innovation to these manufacturing conditions from the beginning. Laboratory success becomes industrial progress only when the full process can operate reproducibly, efficiently, safely, and at a cost and resource intensity that support sustained production.

5.0 Declarations

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Prof. Helena Brooks and Dr. Gilbert Hughes contributed to the conceptual development, literature synthesis, critical interpretation, drafting, and revision of the editorial.

5.2 Funding

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5.3 Competing Interests

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5.4 Data Availability

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5.5 AI Use Disclosure

Generative AI was used to support literature organization and language drafting during preparation of this editorial. The authors remain responsible for independently verifying the accuracy of the arguments, citations, references, and final submitted text in accordance with the publisher's policy.

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