



EMERGING TECHNOLOGIES AND PROCESS INTENSIFICATION IN UPSTREAM AND DOWNSTREAM BIOPROCESSING OF BIOPHARMACEUTICALS: RECENT ADVANCES AND FUTURE PERSPECTIVES

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Abstract:

The increasing demand for biopharmaceuticals—such as monoclonal antibodies, recombinant proteins, and viral vectors—requires flexible, highly productive manufacturing platforms that ensure consistent product quality and resource efficiency. Process intensification addresses these needs by accelerating processing times and maximizing infrastructure utilization across upstream and downstream operations. Key developments include intensified fed-batch cultivation, high-density perfusion, advanced clarification, fiber- and membrane-based chromatography, and integrated continuous bioprocessing. Concurrently, digital innovations like process analytical technology, advanced process control, mathematical modelling, digital twins, and artificial intelligence play critical supporting roles. Although process intensification significantly boosts productivity, widespread adoption faces challenges, including increased buffer consumption, downstream loading bottlenecks, operational complexity, and quality constraints. Consequently, intensified strategies must be assessed from an end-to-end, whole-process perspective rather than focusing solely on isolated unit operations. The future of biopharmaceutical manufacturing relies on the targeted integration of intensified unit operations with advanced digital oversight to balance productivity, sustainability, regulatory compliance, and cost-effectiveness.

Keywords Biopharmaceuticals, Process Intensification, Upstream Processing, Downstream Processing, Continuous Biomanufacturing, Process Analytical Technology.

1. Introduction

The growing demand for monoclonal antibodies and other biopharmaceuticals has increased the need for manufacturing platforms that deliver high productivity, consistent product quality, operational flexibility, and efficient use of resources. Conventional batch and fed-batch processes remain widely established; however, their

extended processing times, large facility requirements, intensive resource consumption, and limited volumetric productivity have encouraged the development of more efficient manufacturing strategies.

Process intensification (PI) refers broadly to strategies that increase the efficiency and productivity of a manufacturing process through improvements in individual operations, process conditions, equipment, or integration between operations. In biopharmaceutical production, intensification may involve increasing viable cell density, improving cell-specific productivity, reducing the duration of production, increasing throughput, or compressing downstream purification steps. Importantly, intensification does not necessarily mean converting an entire process from batch to continuous operation. Recent approaches increasingly focus on introducing intensification selectively where it provides a measurable process benefit. Crowley *et al.* [1], for example, proposed viewing downstream intensification as a series of distinct levels that can be implemented individually or progressively integrated, rather than treating continuous manufacturing as an all-or-nothing transition.

The need for coordinated intensification becomes particularly evident when upstream and downstream operations are considered together. Increasing cell density or product titre upstream can improve volumetric productivity, but it can simultaneously increase the amount of cells, host-cell proteins, DNA, and other impurities entering downstream processing. Consequently, an improvement in one unit operation can shift the process bottleneck to another stage. Recent studies illustrate this interdependence: intensified fed-batch and perfusion approaches can increase upstream productivity, while downstream technologies such as fiber chromatography and integrated clarification are being developed to accommodate higher process loads.

Alongside physical process intensification, digital technologies are increasingly becoming part of modern bioprocess development. Process analytical technology (PAT), modelling, intensified design of experiments, advanced control, and data analytics can provide greater visibility into rapidly changing biological processes. For example, intensified DoE combined with ordinary least-squares and hybrid modelling has been demonstrated as a way of analysing dynamic process conditions and supporting process optimization [18].

Therefore, the objective of this review is to critically examine recent advances in upstream and downstream process intensification of biopharmaceutical manufacturing, with particular emphasis on intensified cell culture, perfusion, downstream purification, process integration, PAT, modelling, and digitalization. The review also considers the trade-offs associated with these technologies and discusses how selective integration may contribute to more productive, robust, economically viable, and sustainable biomanufacturing.

2. Upstream process intensification

Upstream processing determines the amount and characteristics of the biological material delivered to downstream purification. In conventional fed-batch production, cells are inoculated at comparatively low densities and undergo a prolonged growth and production phase. Intensification attempts to alter this balance by increasing the number of productive cells, shortening non-productive periods, or improving cell-specific productivity. Among the most investigated strategies are N-1 perfusion, high-density inoculation, intensified fed-batch culture, and production perfusion.

2.1 Intensification of cell culture and seed-train operations

One practical approach to upstream intensification is to move part of biomass generation from the production reactor into the preceding seed stage. In N-1 perfusion, cells are expanded under perfusion before being

transferred at a substantially higher density into the production bioreactor. This allows the production culture to begin closer to its productive phase, reducing the time required for cell growth after inoculation.

Stepper *et al.* [2] demonstrated this concept by combining pre-stage perfusion with ultra-high seeding density in a CHO-cell fed-batch process. Their system reached high cell densities during the perfusion stage and subsequently achieved approximately 1.9-fold higher product titre within an equivalent runtime while maintaining comparable product quality. The strategy was also transferred to pilot-scale reactors, demonstrating its potential beyond small-scale process development.

Capacitance-based monitoring can further support N–1 perfusion by providing online information about viable cell density and enabling more responsive process control [3].

This approach is particularly attractive for established manufacturing platforms because the production reactor can continue to operate in fed-batch mode. Therefore, the process can gain some advantages of intensification without requiring complete conversion to a continuous production system.

2.2 Intensified fed-batch cultivation

Rather than replacing fed-batch manufacturing, intensification can also be introduced within the existing platform. Intensified fed-batch processes generally combine higher inoculation density with optimized feeding, culture conditions, or productivity-enhancing strategies. Their major advantage is that the underlying fed-batch infrastructure can often be retained, making the transition comparatively straightforward.

Schulze *et al.* [4] demonstrated rapid intensification of an established CHO fed-batch process by combining N–1 perfusion with high inoculation density and a productivity-enhancing supplementation strategy. The resulting intensified process increased space-time yield from 0.28 to 0.55 g/L/day, while maintaining product quality.

More recently, Wolnick *et al.* [6] examined high-inoculation-density fed-batch processing for two complex molecular formats produced in CHO cells. Product concentrations increased by approximately 33% and 109%, respectively, compared with the corresponding low-inoculation-density processes, while similar product-quality attributes were maintained. Similar intensification strategies have combined one-step inoculum production with high-seeded fed-batch cultivation to reduce the time required for biomass generation [5].

These studies demonstrate that intensification does not necessarily require a completely new manufacturing platform. However, increased cell density and productivity can also increase metabolic demands and the quantity of material entering downstream operations. Therefore, an intensified fed-batch process should be assessed not only by final titre but also by culture stability, product quality, downstream capacity, and overall resource consumption.

2.3 Perfusion-based production

In perfusion culture, fresh medium is continuously supplied while spent medium containing the product is removed, with a cell-retention system maintaining a high concentration of cells inside the bioreactor. Unlike conventional fed-batch culture, where production eventually ends as the culture reaches its operational limits, perfusion can maintain high viable cell densities over extended periods.

The major attraction of production perfusion is therefore its ability to achieve high volumetric productivity within relatively compact bioreactor volumes. However, the advantage is accompanied by increased medium requirements and greater dependence on reliable cell-retention and process-control systems. An important consideration is therefore productivity per unit of resource, rather than productivity alone. If increased output

requires disproportionately greater medium consumption, the economic or environmental benefit of intensification may be reduced.

Product quality must also be considered. Liang *et al.* [7] investigated the effect of process intensification on the homogeneity of an IgG1:κ monoclonal antibody during perfusion culture, highlighting that intensified operation should be evaluated alongside product attributes rather than solely by increases in production rate.

Perfusion-based intensification has also been investigated for viral-vector production, where high-cell-density cultivation can be coupled with integrated clarification to increase process efficiency [8].

Thus, perfusion represents a powerful intensification strategy, but its suitability depends on the molecule, cell line, retention technology, medium requirements, process-control capability, and downstream capacity.



Figure 1: Evolution of biopharmaceutical manufacturing

Table 1: Comparison of conventional and intensified biopharmaceutical processing

Parameter	Conventional batch/ fed-batch	Intensified/ continuous
	Discontinuous	Continuous/semi-continuous
Cell density	Moderate-high	High-very high
Volumetric productivity	Moderate	Generally higher
Production cycle	Longer	Potentially shorter
Equipment utilization	Lower	Higher
Facility footprint	Generally larger	Potentially smaller
Media/buffer requirement	Moderate-high	Process dependent
Intermediate holds	Multiple	Reduced
Automation	Moderate	High
PAT requirement	Increasing	Highly important
Process complexity	Lower	Higher
Integration	Limited	High
Regulatory experience	Extensive	Developing
Major advantage	Robust and established	High productivity/integration
Major limitation	Lower productivity and utilization	Complexity and control requirements

3. Downstream process intensification

The increase in upstream productivity creates a corresponding requirement for efficient downstream processing. Higher cell densities and product concentrations can increase the quantity of cells, DNA, host-cell proteins, and other impurities entering the purification train. Consequently, downstream processing can become the limiting step if its capacity is not increased alongside upstream production.

Downstream process intensification therefore focuses on increasing throughput, reducing processing steps, improving material utilization, and integrating purification operations. Current approaches include intensified clarification, continuous and multi-column chromatography, membrane-based separation, fiber chromatography, and alternative capture technologies.

3.1 Intensified clarification

Harvest clarification is responsible for removing cells and cellular debris from the harvested culture before subsequent purification. Conventional clarification may involve combinations of centrifugation and depth filtration. When upstream cultures are intensified, however, the increased solids concentration can place greater demands on clarification capacity.

Intensified clarification approaches have been developed to handle the increased solids load associated with high-cell-density cultures while maintaining efficient product recovery [9].

An important example comes from the work of Anderson *et al.* [10], where fiber-based chromatographic technologies were integrated with a chromatographic clarification device to intensify monoclonal-antibody purification. The authors found that conventional depth filtration was insufficient for optimal operation of the

fiber Protein A step because contaminant loading contributed to premature fouling. Incorporating chromatographic clarification reduced this problem and enabled the intensified downstream sequence to operate effectively.

3.2 Fibre-based continuous capture chromatography

Protein A chromatography remains a major capture step for monoclonal antibodies. Conventional resin-based chromatography relies heavily on diffusion and sequential processing steps, which can limit throughput and increase buffer requirements.

Fiber chromatography offers an alternative based on more rapid convective transport. Anderson *et al.* [10] used multiple fiber-based devices to compress a monoclonal-antibody purification sequence. Their intensified process increased overall yield from 60% to 70%, while the authors estimated substantial productivity improvements at several purification stages and a reduction in buffer consumption.

These findings suggest that process intensification can involve more than simply increasing the speed of an individual chromatography step. Combining clarification, capture, and polishing technologies can reduce the number of operations and intermediate handling steps.

3.3 Membrane-based purification

Membrane-based technologies are attractive for intensified downstream processing because they can provide high-throughput separation using convective rather than purely diffusive transport. Membrane adsorbers and membrane chromatography can therefore support rapid processing and may be suitable for continuous or semi-continuous operation.

Recent experimental studies have demonstrated the potential of membrane chromatography for high-throughput mAb purification and charge-variant separation, while also highlighting the importance of optimizing loading, flow conditions, and membrane capacity [11].

Continuous downstream configurations have also demonstrated the feasibility of integrating chromatography operations to reduce processing interruptions and improve process continuity [14].

However, their implementation is not without limitations. Binding capacity, membrane fouling, pressure development, product recovery, membrane lifetime, and molecule-specific behaviour must be considered during process development. Consequently, membrane-based purification should be evaluated in relation to the complete purification train rather than solely on its processing speed.

3.4 Alternative capture technologies

Alternative capture methods such as aqueous two-phase extraction (ATPE) have been investigated as possible approaches for simplifying product recovery and reducing dependence on conventional chromatography. Their potential lies in combining separation and concentration within a relatively compact operation.

However, phase behaviour, impurity partitioning, recovery, scalability, and molecule-specific performance remain important challenges. Therefore, such technologies are better viewed at present as potential complementary strategies rather than universal replacements for established Protein A-based capture.

Table 2: Selected technologies used for upstream and downstream process intensification

Technology	Stage	Main principle	Major advantage	Major limitation
N-1 perfusion	Upstream	High-density seed expansion	Higher inoculation density	Operational complexity
Intensified fed-batch	Upstream	High-density culture + optimized feeding	Higher space-time yield	Metabolic/product-quality effects
Production perfusion	Upstream	Continuous nutrient supply/product removal	Very high productivity	Media requirement
Capacitance-based control	Upstream	Online VCD monitoring	Dynamic perfusion control	Sensor/model dependency
Intensified clarification	Downstream	High-throughput solids removal	Handles high cell-density harvest	Fouling/scale-up
Multi-column chromatography	Downstream	Parallel column operation	Better resin utilization	Complex switching
Membrane chromatography	Downstream	Convective adsorption	High throughput	Fouling/capacity
ATPE	Downstream	Partition-based separation	Continuous capture potential	Process maturity
PAT	Both	Real-time monitoring	Better control	Analytical complexity
Digital twin	Both	Virtual process representation	Prediction/optimization	Model validation
AI/ML	Both	Data-driven prediction	Advanced optimization	Data quality/interpretability

4. Integrated and continuous bioprocessing

Process intensification becomes more meaningful when improvements in individual operations are considered as part of the complete manufacturing train. An intensified upstream process may produce more concentrated material, while downstream operations must be capable of processing that material without creating new bottlenecks. This has encouraged the development of integrated and continuous approaches in which multiple unit operations are connected and coordinated.

Coolbaugh *et al.* [15] demonstrated the feasibility of an end-to-end integrated continuous monoclonal-antibody process at pilot scale. Their system incorporated major upstream and downstream operations, including perfusion, virus removal filtration, ultrafiltration, diafiltration, and formulation. The process operated for 25 days and produced 4.9 kg of drug substance from a 100-L perfusion bioreactor, providing an important demonstration that multiple manufacturing operations can be linked into an integrated platform.

Economic and process-design analyses indicate that facility design, equipment requirements, development costs, and manufacturing scale can influence the potential benefits of continuous processing [15,16].

For this reason, hybrid manufacturing may offer a practical intermediate approach [19]. Established batch operations can be retained where they are robust and economically advantageous, while selected operations can be intensified or connected where they provide measurable benefits.

Crowley *et al.* [1] similarly argue for a progressive view of downstream intensification, in which individual intensified operations can be implemented independently and subsequently integrated.

5. Process analytical technology and advanced process control

As bioprocesses become faster and more interconnected, conventional offline sampling may not provide sufficient information for timely process decisions. Process Analytical Technology (PAT) addresses this limitation by providing real-time or near-real-time information about process variables and, where possible, product-related attributes.

Measurements such as pH, dissolved oxygen, viable cell density, capacitance, glucose, lactate, conductivity, turbidity, pressure, and product concentration can be used to understand process behaviour. PAT therefore becomes particularly important in intensified systems, where changes in culture conditions or downstream operation can occur rapidly.

Process analytical technologies and data analytics can provide information that supports monitoring, prediction, and control of intensified bioprocesses [17,21].

The value of PAT is increased further when measurements are connected to mathematical models and automated control systems. Instead of merely observing a process, the information can be used to adjust feeding, perfusion rates, process conditions, or downstream operation in response to changing process behaviour.

5.1 Intensified design of experiments and modelling

Traditional experimental approaches often investigate one factor at a time or use relatively static process conditions. Intensified design of experiments (iDoE) provides a way of studying changing process conditions within the same cultivation experiment.

Nold *et al.* [18] demonstrated iDoE for mammalian biopharmaceutical production by examining changes in factors such as temperature and dissolved oxygen across different process phases. Their work combined experimental data with ordinary least-squares and hybrid modelling, showing how model-based analysis can help interpret interactions between changing process variables and identify conditions for process optimization.

5.2 Digital twins and AI/ML

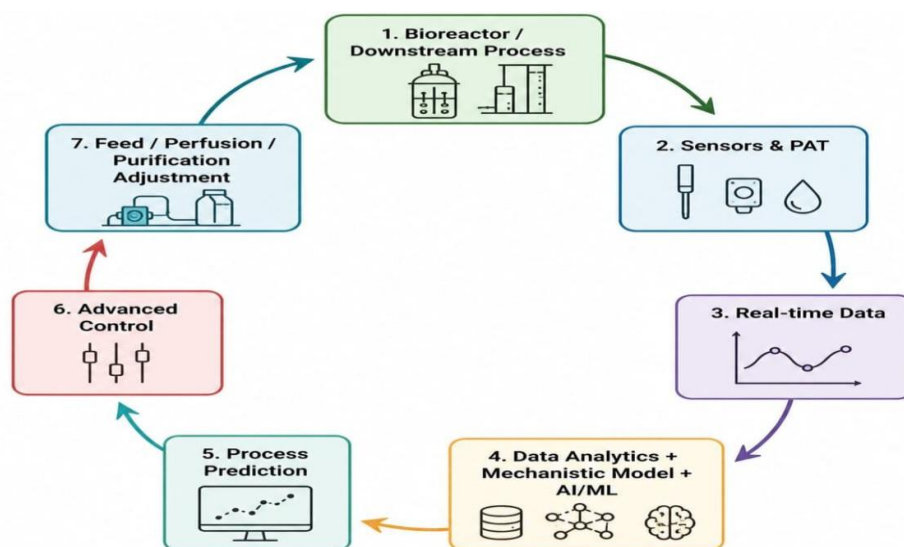


Figure 2: PAT-Digital Twin-AI/ML-Advanced Control loop

Digitalization extends process intensification beyond equipment and unit operations by connecting process data with computational models. AI and machine-learning approaches can complement mechanistic models by identifying complex relationships within large process datasets. Potential applications include prediction of cell growth and product titre, detection of process deviations, optimization of feeding strategies, and prediction of quality-related outcomes. However, digital tools should not be considered independent replacements for process knowledge. Their usefulness depends on the quality and representativeness of training data, model validation, interpretability, and the ability to maintain reliable performance when manufacturing conditions change [20,21,22].

6. Critical analysis: Does intensification always mean better performance?

This is the section I would definitely keep, because your department specifically asks for critical discussion.

A major limitation of evaluating process intensification only through productivity is that higher product output does not necessarily indicate better overall process performance. An intensified process may reduce production time but simultaneously increase media consumption, process complexity, equipment requirements, or downstream loading. Therefore, the benefits of intensification need to be assessed across the entire manufacturing system.

For example, intensified fed-batch culture can increase productivity while retaining much of the existing manufacturing infrastructure, whereas perfusion can achieve high cell densities but may require continuous medium supply and more sophisticated process control. Similarly, intensified downstream technologies can shorten purification operations but may introduce new requirements for synchronization, sensor integration, and fouling control.

This systems-level perspective is supported by the emerging literature on process intensification, which increasingly treats intensification as a combination of selectively improved unit operations rather than a simple transition from batch to continuous manufacturing [1,15,16,19].

6.1 Digitalization of biopharmaceutical manufacturing

Digitalization is increasingly linking process measurements with mechanistic models, data analytics, and automated decision-making. These technologies can support process development, prediction, fault detection, optimization, and control, thereby extending process intensification from physical equipment and unit operations to data-driven process management [18,20,21,22].

6.2 Productivity versus resource consumption

Productivity should therefore be evaluated alongside resource requirements. Media, buffers, water, energy, single-use components, and waste generation all contribute to the economic and environmental performance of a manufacturing process. A useful example is fiber-based downstream intensification. Anderson *et al.* [10] reported increased yield together with an estimated reduction in buffer use for their intensified purification process, illustrating that an effective intensification strategy can improve both productivity and material efficiency.

In contrast, the high medium requirements associated with some perfusion processes demonstrate why increased volumetric productivity alone cannot define process efficiency [7].

6.3 Digital twins

A digital twin is a dynamic computational representation of a physical manufacturing process that can be continuously informed by process data. In biopharmaceutical manufacturing, digital twins can support virtual experimentation, process optimization, fault prediction, and advanced control. Their practical implementation

depends on model accuracy, data quality, validation, interoperability, and maintenance of model performance under changing process conditions [22].

6.4 Artificial Intelligence (AI) and Machine Learning (ML)

Artificial intelligence (AI) and machine learning (ML) can identify complex relationships between process variables and biological outcomes. Potential applications include prediction of cell growth and product titre, early detection of process deviations, quality prediction, feeding optimization, chromatography optimization, and predictive maintenance. Hybrid approaches that combine mechanistic process knowledge with data-driven models may provide a balance between predictive capability, interpretability, and process understanding [20,21].

7. Challenges

Although process intensification can improve productivity and reduce processing time, its implementation also introduces several challenges. Higher cell densities and faster processing can place greater demands on downstream purification, process control, and equipment. Maintaining stable operating conditions is particularly important in intensified and continuous systems, where small disturbances can affect the overall process [6,7,15,16]. Product quality must also remain a priority. Changes in culture conditions or intensified operating modes may influence critical quality attributes such as glycosylation, aggregation, and charge variants [6,7].

Another challenge is the cost and complexity associated with sensors, automation, specialized equipment, modelling, and validation. Continuous processing also requires reliable monitoring, data integrity, process synchronization, and appropriate regulatory strategies [15,16,17].

8. Future perspectives

The future of biopharmaceutical manufacturing is likely to focus on selective and integrated process intensification rather than converting every operation to continuous processing. Intensified upstream and downstream technologies can be combined with conventional operations wherever this provides a practical advantage. Further development of PAT, digital twins, AI/ML, and advanced process control could enable faster detection of process changes and more informed operating decisions. At the same time, sustainability will become increasingly important, with greater attention to water, energy, media, buffer, waste, and single-use material consumption [1,15,16,19].

9. Conclusion

Overall, recent advances in bioprocessing are making biopharmaceutical manufacturing more efficient, flexible, and better controlled. Process intensification, continuous manufacturing, PAT, and digital technologies are helping improve productivity while reducing time and resource requirements. The integration of modelling and AI/ML further supports real-time monitoring, prediction, and process optimization. However, challenges related to scalability, process complexity, data quality, and regulatory acceptance still need to be addressed. Continued development and integration of these technologies will play an important role in building more robust and sustainable biopharmaceutical manufacturing processes.

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