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REVIEW PAPER

INFORMATION TECHNOLOGY

Applications of Artificial Intelligence in Bioprocess Optimization: A Comprehensive Review

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ABSTRACT

Artificial intelligence (AI) is changing modern bioprocessing by offering new ways to design, monitor, and optimize complex biological systems. Traditional tools such as mechanistic models and Design of Experiment (DoE) often fall short when faced with the nonlinear behaviour and variability that are common in fermentation, cell culture, and purification processes. O, the other hand, Machine Learning (ML), Deep Learning (DL), Evolutionary Algorithms, Reinforcement Learning (RL), and Digital Twins (DT) can uncover patterns, predict outcomes, and guide decision-making with far greater accuracy. This review highlights how these AI approaches are being applied across upstream processing, downstream purification, real-time monitoring, and scale-up and put forwards some industrial case studies, including AI-assisted COVID-19 vaccine development by Pfizer and Moderna, CHO fed-batch optimization with titer increase of up to 48%, data-driven chromatography prediction with R^2 value of 0.90, GA-based feeding strategies, and AI based soft sensors for E. coli, that illustrate the practical benefits now seen in industry. The paper also puts forward some major challenges and discusses emerging trends such as autonomous digital twins, multi-omics integration, and IoT-enabled monitoring. Overall, these developments show how AI is steadily becoming a core enabler of faster, more consistent, and more efficient biomanufacturing.

Keywords: Artificial Intelligence in Bioprocessing, Machine Learning, Deep Learning, Bioprocess Optimization, Digital Twins (DTs), Upstream Processing, Downstream Processing

Bioprocessing can be considered as a core branch of modern biotechnology, that produces various products, such as vaccines, enzymes, therapeutic proteins, biofuels, etc.[1]. Bioprocessing consists of complex interactions between biological systems and physical variables, such as pH, temperature, dissolved oxygen, substrate levels, and rates of metabolism[2]. Classical modeling methods, such as

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kinetic modeling, regression analyses and others are indeed informative but are usually unable to reproduce non-linear dynamic behaviors observed in biologically active cultures at an industrial level[3]. Biological variation, heterogeneity of equipment, sensor noise, and large multi-dimensional data add to difficulties in predictions and optimizations[4]. Artificial Intelligence (AI), that teaches a computer to think like a human, allows a paradigm shift due to its ability to provide data-driven modeling, pattern detection, control, and decision-making support in real time[5]. Machine Learning (ML) and Deep Learning (DL) algorithms can identify irregularities in complex fermentation data and predict yields based on different fermentation processes[6]. Evolutionary algorithms such as genetic algorithms (GAs) provide efficient heuristic optimization tools for multi-variable problems, bacterial fermentation, and metabolic pathways[7]. Also, Reinforcement learning (RL) allows autonomous control strategies for optimizing bioreactor performance, and digital twins (DT) allows the simulation of large-scale bioprocesses[8,9]. AI has also been integrated with Internet of Things (IoT) sensors, hyperspectral imaging, and analytics to enhance its usage for monitoring, quality analysis, and environmental sustainability[10,11]. Sectors ranging from pharmaceuticals to food industries, and bio-energy are using AI-powered solutions to enhance productivity, decrease rates of errors, and speed up innovation[12]. The research paper presents a concise and comprehensive review on AI applications for bioprocess optimization together with a discussion on a few industry-scale case studies.

Objective and Scope

The primary of this study is to present a concise and comprehensive review of applications of AI in bioprocess optimization. To provide a structured analysis, this review focuses on the following specific goals:

1. Evaluating core AI methodologies relevant to bioprocessing, including Machine Learning (ML), Deep Learning (DL), Evolutionary Algorithms, Reinforcement Learning (RL), and Digital Twins (DT)
2. Assessing the practical integration of these AI applications across upstream processing, downstream purification, real-time monitoring, and scale-up procedures
3. Examining industry-scale case studies to illustrate tangible optimization benefits and performance metrics in real-world settings
4. Identifying current integration challenges, such as data quality and regulatory constraints, and discussing future technological directions

Review Methodology

To ensure a comprehensive analysis of AI applications in bioprocess optimization, a structured literature review approach was adopted to identify and evaluate relevant research.

Literature Search Strategy

An extensive literature search was conducted across major scientific databases, including Scopus, Web of Science, IEEE Xplore and PubMed using keywords such as “Artificial Intelligence in Bioprocessing”, “Machine Learning”, “Deep Learning”, “Bioprocess Optimization”, “Digital Twins (DT)”, “Upstream Processing” and “Downstream Processing”.

Inclusion and Exclusion Criteria

This review study prioritized recent peer-reviewed research and industrial reports that demonstrated practical AI applications such as data-driven modelling, advanced PAT and augmented control in bio manufacturing. Studies that lacked empirical data or focusing solely on theoretical models without practical bioprocess relevance were excluded.

Data Extraction and Synthesis

Selected literature was categorized by the specific AI methodology and the targeted bioprocessing state with special emphasis put on extracting quantitative performance metrics from industrial case studies to validate practical efficacy.

3. Overview of AI Methods Relevant to Bioprocessing

AI technologies cover a wide range of computational methodologies that include capabilities to learn from data, recognize complex patterns, and optimize decision-making[13]. The next subsections give a summary on the main AI-technologies implemented in bioprocess engineering:

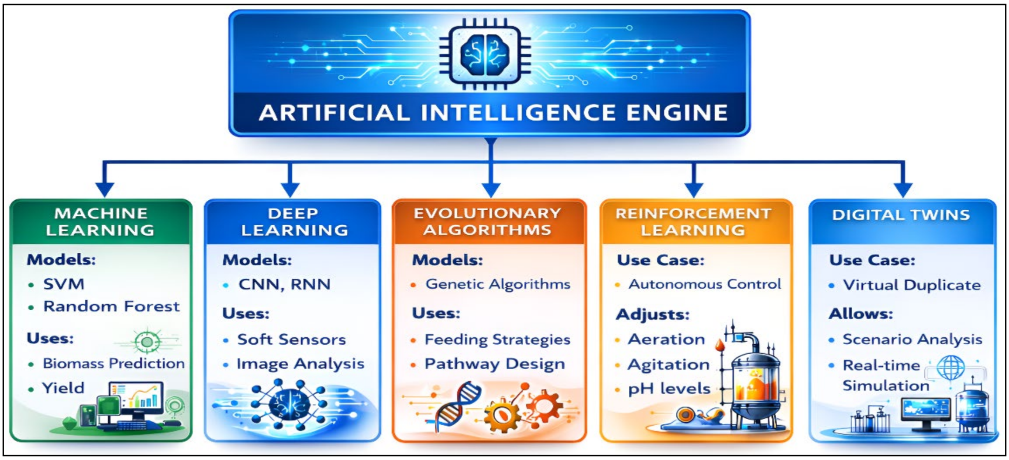

Fig. 1: Mapping AI Methodologies to Bioprocess Challenges

Fig. 1 illustrates the mapping of specific Artificial Intelligence methodologies to their targeted bioprocess applications. Distinct computational architectures are aligned with their optimal use cases, ranging from data-driven yield prediction to autonomous control and virtual process simulation.

Data-Driven Modelling: Machine Learning (ML) and Deep Learning (DL)

ML offers statistical capabilities that are able to learn from historical data to perform classification, prediction, or regression[13]. Supervised machine learning models including Support Vector Machines (SVMs), Random Forest (RF), and Gradient Boosting (GB), are widely used for bioprocess predictions including biomass concentration, product level, and detection of contaminations[14]. Unsupervised machine learning algorithms including Clustering and Principal Component Analysis (PCA) are applicable to similarity analysis, anomaly detection, and dimensionality reduction for large-scale fermentation data[15]. It has also been demonstrated that Least Absolute Shrinkage and Selection Operator (LASSO) based models can predict monoclonal antibody yields using complex morphology data for Chinese Hamster Ovary (CHO) cells with hundreds of morphology descriptors[16]. These models show how well ML is able to provide biologically relevant discoveries using large datasets.

DL is characterized by neural networks with multiple computational layers, excels at modelling highly non-linear and high-dimensional systems[17]. In bioprocessing, for example, DL architectures such as, Convolutional Neural Networks (CNNs) and Recurrent Neural Networks (RNNs), have been applied to analyze data from spectroscopy, sensor streams, and cell culture images[18,19]. The primary applications where CNNs perform well include hyperspectral data analysis, microbial morphology, and automatic quality assessment[20]. DL can also contribute importantly to modeling metabolic pathways, predicting production rates, or optimizing strain design, particularly for simulations using genome-scale metabolic models[21].

Optimization and Autonomous Control: Evolutionary and Reinforcement Learning

Evolutionary algorithms such as genetic algorithms (GAs) are powerful optimization techniques inspired by the natural selection and have been often applied in optimizing fermentation conditions[22], metabolic pathways[23], and bioreactor operation[24]. In industrial settings, GAs have been integrated with hybrid ML systems for dynamic optimization of fermentation parameters in insulin production[26] and ethanol fermentation[25].

Reinforcement Learning (RL) learns optimal control moves while interacting with bioprocess environments and can find its applications in dynamic control processes. It has promising applications for automation in feed control, aeration control, and pH control, which are basically controlled by Proportional Integrate Derivative (PID) controllers[8,27,28]. Historically, work on AI-based bioreactor control using automated state estimation dates back many years, and many current ideas within reinforcement learning are extensions of this[28].

Advanced Frameworks: Digital Twins (DT) and Explainable AI (XAI)

Digital Twins or DTs are virtual duplicates that are representative of physical bioprocesses and are able to perform data integration, predictive control and simulation in real-time[29]. Mammalian cell culture has used DTs to simulate nutrient consumption, cell growth, and metabolic profiles with high accuracy [30]. The DT frameworks combine data from sensors, mechanistic models, and ML algorithms to enable scenario analyses that do not interfere with real-time processes[31].

With AI increasingly being integrated into regulated industries like pharmaceuticals and food processing, interpretability becomes a requirement. Tools for Explainable AI (XAI), such as Shapley Additive exPlanations (SHAP) and Local Interpretable Model-agnostic Explanations (LIME), improve the interpretability of AI models in decision-making, thus making it easier for bioprocess engineers to better understand the importance of a variable or behavior[32].

Applications of AI in Bioprocess Optimization

The applications of AI in bioprocessing can be seen in upstream processing, downstream purification, environment sensing, and scale-up[9]. Fig. 2 illustrates the sequential flow of physical processes—from upstream fermentation to downstream purification—integrated with a continuous feedback loop of Digital Twins and IoT sensors for real-time process control and predictive optimization.

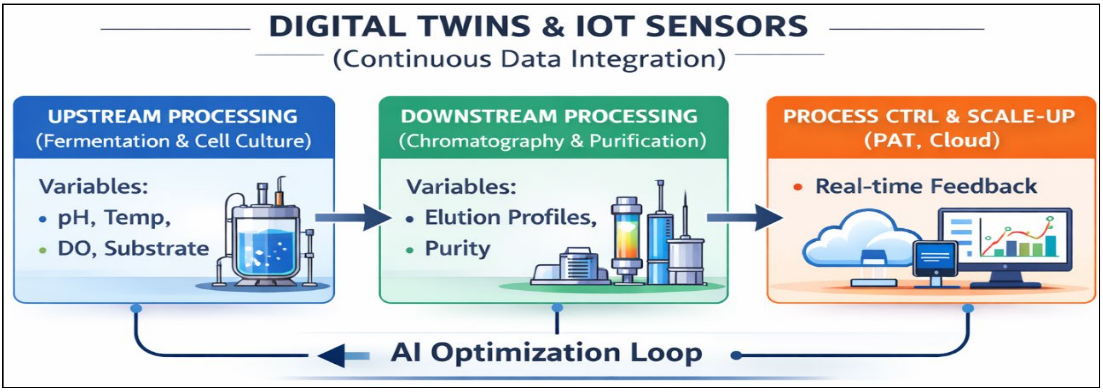

Fig. 2: The AI-Driven Biomanufacturing Life-cycle

Some important areas where AI has applications are enlisted below:

Core Bioprocessing Operations: Fermentation and Downstream Purification

Fermentation involves microorganisms where the growth factors and end products can be affected by a number of complex factors[33]. AI helps in the entire fermentation process by analyzing data from various sensors and making predictions as to how fermentation process can be optimized by using various patterns and variables[34]. In addition, ML models are applied for predicting biomass and product yields as part of recombinant protein production processes, using variables including temperature, dissolved oxygen, pH, and substrate concentration[35]. Neural Networks can analyze sensor data to help overcome substrate inhibition and optimize nutritional strategies[36]. Genome-scale models that are integrated with AI are able to identify metabolic barriers much more effectively and provide guidance on strain improvement[37]. In the case of solid-state fermentation (SSF), Artificial Neural Networks (ANNs) models have proven more effective than polynomial regression for optimizing enzymatic production, including amylase production in *Rhizopus microsporus var. oligosporus*[38]. Moreover, precision fermentation using AI technology is also working to bring innovations in microbial strain engineering, metabolic engineering, and new food ingredients[39].

Downstream processing remains one of the most expensive steps in biomanufacturing, particularly the purification of monoclonal antibodies (mAb)[40]. AI assists in enhancing chromatographic separation through elution profile optimization, breakthrough curve prediction, and improvement in assessment of resin performances[41]. Models based on ML techniques can also calculate yields and purities for Protein A Chromatography processes, take into consideration operating variables such as flow rates, load densities, buffer mixtures, and capacities for binding[42]. Hybrid models that combine both data-driven and mechanistic models improve procedures for loading and cycles, introducing a new level of accuracy that further leads to reducing experimental work[43]. DTs have also been employed to model column behavior and optimize purification procedures, permitting wash and elution conditions to be varied online for calculation[44]. Soft sensors using neural networks can also calculate the concentration for products in cases where inline sensors are not present or where destructive tests are needed for concentration calculation[45]. In High-Performance Liquid Chromography (HLPC), AI algorithms are equally applied to identify peaks and impurities within HPLC analysis to ensure quality control[46].

Process Monitoring, Control and Scale-Up

Primarily, Advanced PAT technology using AI can improve online monitoring for both fermentation and cell culture processes[34]. Conversely, Hyperspectral Imaging (HIS) and ML can assess rates for biomass, lipids, morphology, and nutrient exhaustion in microbial and algal cultures, while AI models trained with HSI data can also provide high resolution for monitoring contamination, substrate uptake, and growth phase predictions[47]. The spectroscopic data provided by InfraRed (IR) spectrometry, including near-IR, mid-IR, Raman, and fluorescent spectrometry, has many variables to analyze and is well-posed for ML modeling efforts[49]. DL models like CNNs perform better than classical chemometrics in extraction and prediction tasks, as reported in various studies[50] and thus it can be said that these tools reduce the need for invasive sampling and improve process robustness.

Classical process control is predominantly dependent on PID control, which has difficulty with nonlinear processes in biotechnology applications[2]. AI-based control strategies utilize learned dynamics from previous production cycles and simulations to provide predictions for adjustments related to aeration, agitation, feed rate, and pH and Reinforcement Learning provides adaptive control strategies, where machines can develop control policies by constantly learning from experience to ensure optimal production and optimal yields or products[51,52]. AI integration with IoT can provide cloud-based supervisory control capabilities, where data from sensors can contribute to monitoring, warning, and decision making[52]. For fermentation plants, AI has reduced intervention in normal operations and ensured consistency in processes[53].

AI assists in scale-up by predicting microbiological growth, Oxygen Transfer Rate (OTR), and mixing ability for various scales[55]. Neural networks can also reveal scale-specific variables and bridge differences in sheer stress to decrease trial-and-error procedures common in tech transfer processes[56,57]. The combination of CFD and ML has constructive simulation capabilities for mixing and mass transfer reactions to assist bioreactor design and scale-up procedures[3,58].

Industrial Case Studies

The below sub-sections discuss some of the top examples from the industry where AI-assisted bioprocessing resulted in optimized performance, which is supported by appropriate metrics as well.

5.1 AI in Vaccine Production and Mammalian Cell Culture

In the case of vaccine production, mRNA (messenger Ribonucleic Acid) vaccine development efforts such as Pfizer and Moderna were substantially facilitated by antigen development and clinical trials by the use of artificial intelligence during the time of the COVID-19 pandemic[59]. ML models were helpful in evaluating large datasets of viral sequences, immune responses, and structural features to rapidly prioritize vaccine candidates and thereby contributing to record-breaking development timelines, from decades and years to months[59]. In addition, predictive analytics solutions that were developed using AI were also applied to improve patient enrolment for clinical trials and it should be noted that conventional vaccine development faces attrition rates of over 80% from preclinical development to market authorization[59]. Additionally, it has also been observed that integrated computational tools based on machine learning have the ability to screen data from high-throughput techniques to provide optimal antigen and adjuvant pairings and formulations to allow for better parameter searches and optimization of vaccine strategies not just in COVID-19 but other vaccines as well[59]. These AI based techniques are now often used to expedite what would otherwise be time-consuming processes in vaccine development, such as antigen selection and preclinical testing to ensure that vaccines can be developed faster and not take decades or years[59].

The application of AI model assisted optimization approaches has brought about major advancements in industrial fed-batch processes of CHO cell culture in predicting the titers of monoclonal antibodies by understanding complex factors such as temperature change, feed rate, dissolved oxygen, and nutrient[71]. Utilizing these models, an optimization process identified unusual sets of parameters, which were then experimentally confirmed to result in increases of as much as 48% in residual monoclonal antibody (mAb) titers and 20 to 30% greater productivity in cell-specific yields, in comparison to the baseline processes[71]. This methodology that uses ML models also resulted in a substantially lower number of exploratory bio-reactor runs than traditional DoE approaches. More than 40% fewer experiments were conducted to accomplish this task. So, we can say that biomanufacturing processes can be made more efficient[71].

AI-Driven Downstream Processing and Chromatography

Machine learning techniques have come out to be very helpful in downstream purification processes as it can predict chromatographic retention and optimal separation conditions. In[61], researchers trained models such as Random Forest (RF) and Gradient Boosting (GB) on large retention datasets in order to learn how compound structure and solvent parameters can influence elution profiles. The resulting models achieved high predictive accuracy with a R^2 value of 0.90, thus enabling reliable in-silico selection of solvent systems and gradient conditions before an experiment. This enabled reduction of 50% to 70% scouting experiments typically needed in traditional scouting to be eliminated and went on to significantly reduce the time needed for purification thus enabling higher success rates. Hence, AI reduced development inefficiencies in chromatographic methods by significantly narrowing down the search space in experiments and delivering precise estimates of retention related to varied chemical structures[61].

Optimization of Microbial Fermentation and Feeding Strategies

In[35], researchers present a DL framework for real-time prediction of biomass accumulation in *E. coli* recombinant protein fermentations using only online critical process parameters (CPPs). Working with eleven 1-L stirred-tank fermentations, the authors trained RNN and Long Short-Term Memory (LSTM) architectures on 11 Critical Process Parameters (CPPs), including pH, dissolved oxygen, temperature, agitation speed, oxygen or air flows, four pump activities, and induction state, encoded as sliding windows of 20 time points. OD600, a spectrophotometric measurement used to estimate cell concentration in microbial cultures and measured hourly, was interpolated using a sixth-degree polynomial and linear mean blending, achieving an interpolation accuracy of R^2 (Coefficient of Determination) of 99.93%. Model evaluation via leave-one-out cross-validation demonstrated strong predictive performance with average Root Mean Square Error (RMSE) values of 4.10 for LSTM and 4.00 for RNN and an average final-yield errors, REFY value of 7.52% and 7.21%, respectively, against a mean final OD600 of 51.30 ± 6.76. In

Some cases of fermentations, high OD600 values of 63.4 were reached, and the mass of the inclusion bodies was as large as 13.5g, thus showing substantial batch-to-batch variability. The models captured OD600 trends well, particularly later in fermentations, though prediction errors increased for atypical CPP trajectories. By providing accurate, data-driven estimates of growth and yield in near real-time, the study highlights the potential of recurrent neural networks for soft sensing, early deviation detection, and enhanced decision support in microbial bioprocessing[35].

Genetic Algorithm (GA) based optimization has recently been applied to mammalian cell-culture feeding strategies to improve the productivity in biopharmaceutical processes. In[80], researchers used an in-silico framework combining Design of Dynamic Experiments (DoDE), semi-parametric bioprocess modeling, and a GA optimizer to identify optimal glucose and glutamine feeding profiles for an IgG-producing cell line. The GA explored thousands of dynamic feed trajectories and converged on nutrient-delivery schedules that improved culture performance relative to standard strategies. Simulation based experiment agreement showed that GA-optimized profiles increased predicted antibody titer by 18 to 25%, improved nutrient-use efficiency, and reduced the probability of nutrient accumulation–related inhibitory effects by over 30%[80]. The approach also decreased experimental burden by up to 50%, as many sub-optimal feeding schedules were eliminated through computational screening alone. Hence, it shows that the concept of evolutionary optimization being used to identify non-intuitive dynamic methods of feeding that can optimize productivity in a bioprocess[80].

AI Tools, Simulation Frameworks, and Computational Platforms

Contemporary bioprocess engineering has at its disposal a broad spectrum of AI and simulation tools that supports prediction, optimization, control, and digital twin development. The below table of mentions some tools and their application to the field of bioprocessing has been presented in the table below:

Table 1: Major AI and Modeling Tools Used in Bioprocess Optimization

Tool / Framework	Category	Application in Bioprocessing	Key References
TensorFlow / PyTorch	Deep Learning	Image analysis, spectroscopy interpretation, time-series prediction	[62]
MATLAB / Simulink	ML, Control Systems	Soft sensors, bioreactor control simulations, hybrid modeling	[63]
SciKit-Learn	ML Toolkit	Supervised/unsupervised learning, batch classification, anomaly detection	[63]
CADET	Chromatography Simulation	Mechanistic chromatography modeling, DT development	[64]
OptFlux / COBRA Toolbox	Metabolic Modeling	Genome-scale metabolic modeling, strain engineering	[65]
Aspen Plus	Chemical Process Simulation	Integration with hybrid ML for scale-up and techno-economic analysis	[66]
SuperPro Designer	Bioprocess Simulation	Facility-level optimization, economics, process integration	[67]
KNIME / RapidMiner	Workflow Automation	Data preprocessing, feature engineering, model deployment	[68]
LabView IoT + Custom Soft Sensors	Real-Time Monitoring	Remote monitoring, PAT integration, sensor fusion	[69]

It can be used both in research and for the development of industrial applications due to the flexibility it has to offer. Also, an increase in integration of ML models with mechanistic models in Chromatography Analysis and Design Environment (CADET), Constraint-Based Reconstruction and Analysis (COBRA), and Aspen systems reflects a shift toward hybrid modeling paradigms with higher predictive fidelity.

Challenges and Limitations

Along with the advantages, there are some challenges that occur in the integration of AI in Bioprocessing, and some of those are discussed in this section.

- *Data Quality and Availability:* The challenges encountered when using bioprocess data are noisy measurements, missing data points, variations from one batch to another, and insufficient sensor coverage. Bioprocess data can be considered to be of low volume and high variance and thus makes it difficult to develop models that can be generalized because bioprocess data do not belong to the same type of applications as image processing, which involves tasks of deep learning. The volume of the data due to their size makes deep learning impossible without the concept of transfer learning and the generation of[5,70,71].
- *Model Interpretability and Validation:* AI models, especially deep neural networks, often function as black boxes. In regulated sectors such as biopharmaceutical manufacturing, interpretability is essential for compliance, validation, and risk analysis. Explainable AI methods help bridge this gap, but regulatory acceptance still remains a challenge[72,73].
- *Integration with Legacy Equipment and Systems:* A large number of fermentation facilities depend on existing control systems and equipment that are not optimized for AI integration. The processing of high-frequency readings from sensors and cloud connectivity may also be costly. Industrial applications require harmonization of IT, operational, and automation engineering perspectives[74,75].
- *Regulatory and Validation Constraints:* Pharmaceutical manufacturing is governed by strict regulations such as current International Council for Harmonisation (ICH) Q8 to Q12, and Food and Drug Administration (FDA) PAT guidelines. Decisions that are taken using AI models must be validated rigorously, with full traceability and risk assessment. A lack of clear regulatory frameworks for AI-enabled control further slows the adoption of AI in bioprocessing[76].
- *Workforce Skills and Organizational Readiness:* Bioprocess engineers may not be at par with these AI systems and lack training in ML, data science, and automation, creating organizational resistance. An effective AI implementation requires interdisciplinary collaboration, dedicated data engineering teams, and sustained investment[77,78].

Future Prospects

AI is expected to become increasingly foundational to next-generation bioprocessing. Some key emerging directions include:

- *Digital Twins for Closed-Loop Control:* Future DTs will transition from predictive simulation models towards autonomous closed-loop optimization, in which the DT will self-update its state through sensor data and AI-driven predictions[79] and it could result in greatly reduced experimentation time and improved batch success rates.

- *Multi-Omics Integration with AI:* The genome, transcriptome, proteome, and metabolome provide valuable information about the state of the cell. AI models that are capable of combine multi-omics information will be used in the improved strain engineering and metabolic pathway and product formation prediction[79].
- *Edge AI and IoT-Enabled Bioprocess Monitoring:* The edge computing capability will enable ML algorithms to be executed directly from the device in the case of IoT sensors or the bioprocess control unit[79] and will be especially valuable in distributed biofuel or agricultural bioprocessing systems.
- *Autonomous Bioprocess Operations:* By combining the power of RL, DTs, and high-frequency PATs, it will be possible to develop partially to fully automated bioreactor systems that can: change the flow rates dynamically, optimize aeration/pH conditions, predict failures, and monitor quality[80].

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CONCLUSION

AI has evolved from a supplementary analytics tool to a foundational driver of next-generation bioprocess optimization. Across upstream, downstream, and process-control operations, AI systems now enable precise prediction, early deviation detection, enhanced product quality, and significant reductions in development time. The industrial case studies in this review show the depth of AI's use in developing COVID-19 vaccines, CHO fed-batch processes achieving up to 48% titer gains with 40% fewer experiments, chromatography optimization eliminating up to 70% of scouting runs, GA-optimized feeding strategies improving antibody titers by 25%, and recurrent neural-network soft sensors enabling near real-time prediction of E. coli biomass. It demonstrates that AI not only accelerates process development but also uncovers non-intuitive, high-performance operating conditions that classical approaches often overlook. However, there are some challenges such as, data quality, model transparency, regulatory acceptance, and integration with older equipment. Still, progress in explainable AI, hybrid mechanistic–AI modeling, and digital-twin platforms is helping move the field forward. As technologies like reinforcement learning, multi-omics AI, and edge-enabled PAT systems mature, bioprocessing is likely to become increasingly automated and reliable. Overall, we can say that, AI is positioned to play a major role in shaping the next generation of industrial biomanufacturing, making processes faster, smarter, and more resilient.

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