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ARTIFICIAL INTELLIGENCE IN RECOMBINANT BIOMANUFACTURING: INTEGRATING BIOINFORMATICS AND INDUSTRIAL BIOTECHNOLOGY FOR NEXT-GENERATION THERAPEUTICS

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ABSTRACT

Artificial intelligence (AI) is emerging in recombinant biomanufacturing, where data-driven approaches are used to optimize complex biological systems. This paper reviews the integration of artificial intelligence, bioinformatics and industrial biotechnology in the recombinant production process from genetic design to large-scale processing. These approaches enhance protein engineering through structure prediction, codon optimization and functional analysis. In upstream processing, machine learning is used to support strain development, media optimization and adaptive control strategies to improve yield and product quality. For downstream operations, efficient purification is achieved through AI-based modelling of chromatographic processes and monitoring critical quality attributes in real time. This is further supported by integration with Quality by Design (QbD), Process Analytical Technology (PAT) and digital twins, enabling continuous manufacturing and real-time release testing (RTRT). Despite these gains, challenges remain, including data limitations, model interpretability, and regulatory constraints. Overall, AI-driven bioprocessing represents a transformative approach with the potential for efficient, scalable and next-generation biopharmaceutical production.

KEYWORDS: Artificial Intelligence, Recombinant Biomanufacturing, Machine Learning, Bioprocess Optimization, Quality by Design, Digital Twins.

INTRODUCTION

Recent developments of recombinant DNA technology have had a significant impact on biotechnology. These technologies enable the efficient production of therapeutic proteins, industrial enzymes and other biomacromolecules with biological activity. Recombinant DNA-based techniques aid many applications in molecular biology, such as human insulin and erythropoietin production. They also make it possible to develop genetically modified organisms for environmental and industrial bioprocesses, which play a key role in biotechnology today.[23]

Along with classical methods of genetic and process engineering, computational methods are now an indispensable aspect of the design of a biological system and the optimization of a process with respect to its accuracy and efficiency. Artificial intelligence (AI) and machine learning (ML) are some of the tools that have become important computational methods. Complex biological systems, multi-variable processes and insights from large datasets can be modeled with their help, thereby reducing experimental workload in the biotechnology industry.[17,41]

Advances in predictive modelling and intelligent control have made monitoring and automation of bioprocesses improve over time. Hybrid computational methods offer adaptive responses, which cannot easily be obtained using the traditional statistical approaches, in complex systems.[4] One of the big innovations in the field of computational biology is the field of protein structure prediction. AI-driven models like AlphaFold have proven extremely accurate in the prediction of three-dimensional structures in proteins, accelerating design cycles and allowing rational protein engineering before a large amount of experimental testing.[22]

Despite these advances, AI technologies have still not been fully integrated across the full range of recombinant biotechnology, from the genetic design to the industrial bioprocessing. Current studies mostly focus on the isolated stages, including molecular scale innovations (e.g. structure prediction) or the process scale optimization, but there is no unified framework connecting the computational design with the workflow of the scalable industrial production processes. This review addresses this gap by focusing on the integration of artificial intelligence across the entire recombinant biomanufacturing workflow, linking genetic design, upstream and downstream processing, and industrial-scale implementation. It also discusses central methodologies, barriers and future opportunities. Relevant literature was obtained from major bibliographic databases of peer-reviewed articles focusing on the application of AI, ML, and bioinformatics in the optimization of bioprocess, genetic engineering and recombinant protein production. In this regard, comprehension of this integration application of AI in the recombinant biomanufacturing workflow is vital for enhancing process efficiency, product quality and improving scalability within the industrial biotechnology sector. AI-driven recombinant biomanufacturing workflows are illustrated in Figure 1.

Historical Background of Biotechnology and Recombinant DNA

Biotechnology progressed from the primitive fermentation techniques used in the production of food and many alcoholic beverages to a scientific field that manipulates biological systems for industrial and medical purposes. The name 'biotechnology' was coined in 1919 by Karoly Ereky to refer to the process of modifying raw materials into useful products using biological processes.[12] By the mid-20th century, the potential of large-scale biological manufacturing had been demonstrated by the creation of penicillin and other antibiotics in large quantities.[11]

The molecular revolution in biotechnology started with the advent of the recombinant DNA (rDNA) technology in the early 1970s. Paul Berg made the first recombinant DNA molecule by combining DNA sequences from different species

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in vitro.[44] Shortly after, Stanley Cohen and Herbert Boyer pioneered a cloning method in which foreign genes were inserted into a bacterial plasmid so that the gene could be replicated, enabling production to take place.[10] These discoveries provided the basis for today's genetic engineering and new biotechnology.

In 1982, the commercial production of human insulin in E. coli, replacing animal-derived sources of the product and enabling large-scale, safe production, was the first great rDNA-based pharmaceutical breakthrough. Since then, recombinant technology has become vital for the manufacture of vaccines, hormones, monoclonal antibodies and industrial enzymes.[23] Regulatory oversight also developed rapidly, beginning with the Asilomar Conference (1975) and subsequently formalized in the form of guidelines developed by the NIH and the Food and Drug Administration (FDA), governing the gene transfer study.[20] These developments laid the foundation for modern recombinant biomanufacturing systems.

Artificial Intelligence in Biotechnology

The concept of Artificial Intelligence (AI) is an important computational tool for analyzing intricate biological data and improving research and industrial processes in biotechnology. Artificial intelligence, including machine learning and deep learning, is widely used in genomics, proteomics and metabolomics studies, where it has been applied to patterns in data to make predictions and analyze molecular interactions and biological systems.[45] Key applications include gene annotation, prediction of protein functions, biomarker discovery and metabolic pathway analysis, which are supported through machine learning algorithms. The techniques are employed in modern bioinformatics, including systems biology, by identifying complex relationships not captured by conventional statistical procedures in large collections of data.[8] Deep learning based AlphaFold models have been able to revolutionize prediction of protein structure in three-dimensional models, which scientists can use to test their findings. This has improved the growth of the protein engineering and drug discovery field.[22] Integration of multi-omics data with AI-based models enables the analysis of cellular networks and the prediction of gene expression patterns, supporting the development of engineered microorganisms for pharmaceutical and industrial applications.[31] AI is an essential technology that contributes to data-driven innovation and enhances biological system design optimization and scalability. These advancements in artificial intelligence have laid the foundation for its application in recombinant protein engineering, where predictive modelling and data-driven approaches enable more efficient protein design and optimization.

AI in Recombinant Protein Engineering

Artificial intelligence (AI) has become an essential tool in recombinant protein engineering, enabling the design and optimization of proteins for medical and industrial applications. The process of producing recombinant proteins involves multiple steps, starting with gene design and optimizing codons and predicting protein folding and end with AI-based methods that enable scientists to study extensive data sets and determine the best protein structures which help them finish their research work faster and more effectively while spending less money.[43] AI optimizes codons by studying how they are used in various systems which include Escherichia coli and yeast and mammalian cells to predict the best codon usage that will enhance gene expression.[9] AI-based systems use deep learning methods to predict protein structure and function because they enable researchers to identify essential protein parts and beneficial mutations, which enhance enzyme functionality and therapeutic results.[22] In enzyme engineering, AI predicts mutations that improve enzyme activity and stability, as well as those that boost enzyme activity and substrate flexibility and thermal resistance, by studying sequence-structure connections.[43] The use of these methods has helped

researchers create recombinant enzymes which they now use in pharmaceuticals, food products and biofuel production.[43] AlphaFold and other advanced tools enable scientists to make precise 3D protein structure predictions, which they can verify through experiments to support their work in protein design and development.[3,39] Overall, AI improves protein design, enhances gene expression and supports advanced biopharmaceutical development. These advancements in protein design and optimization directly support upstream bioprocess development, where engineered strains and optimized expression systems enhance production efficiency. The application of AI in biomanufacturing is given in Table 1.

AI in Upstream Recombinant Bioprocess Development

Upstream bioprocess development has become a critical part of recombinant biomanufacturing, taking into consideration host selection, culture optimization and process control parameters to ensure efficient protein production. Traditional methods are often time-consuming, empirical and inefficient. Artificial intelligence (AI) offers a data-driven approach to process optimization to optimize yield and increase the control of complicated bioprocess systems.[13]

This progress is supported by advanced computational tools and methods of systems biology (such as genome-scale metabolic models, GEMs). These approaches aid in identifying the key gene targets and optimal metabolic flux for better metabolite production. As an example, an expanded heterologous expression using promoter refactoring using CRISPR-Cas9 tools and metabolic engineering of the Streptomyces coelicolor organism, resulting in significantly increased yields of oviedomycin.[16] This can be further optimized using AI to allow more accurate prediction of strain performance.

AI is widely used in culture media optimisation. The limiting effects of the non-linear behaviour of multiple media components restrict the power of traditional design-of-experiments (DoE) approaches. Machine learning models, including explainable approaches such as SHAP, have identified key factors, including metal ions, such as iron (Fe) and zinc (Zn), that control charge variant distributions in CHO cell cultures, critical quality attributes (CQAs) in biopharmaceutical manufacture.[13] These models improve predictive accuracy, media optimization, and process understanding.

In addition to optimizing strain and media, the use of AI in controlling complex bioprocesses in real time and enables adaptive control in dynamic environments. AI-driven adaptive control in the system, as in Pichia pastoris bioprocesses, shows better process stability and dynamic optimization in various process conditions.[14] Soft sensors are a combination of process measurements and mechanistic or machine learning models (e.g. cell density, dissolved oxygen and metabolite concentrations). They can estimate important parameters, such as viral titer in the production of recombinant adeno-associated virus (rAAV), which are difficult to measure experimentally.[19] These methods improve stability, reproducibility and product quality, and they lower costs, thereby enabling automated and data-driven biomanufacturing. These upstream advancements directly influence downstream processing efficiency and overall product quality in biomanufacturing systems. Despite these advancements, AI-driven upstream optimization remains limited by biological variability and dependence on high-quality training data. In addition, model predictions may not always translate effectively across different host systems and large-scale manufacturing conditions. An AI-driven upstream bioprocessing workflow is illustrated in Figure 2.

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AI in Downstream Processing and Chromatographic Optimization

Recent advances in resin design, ligand chemistry and process modelling improve the scalability, robustness and selectivity of chromatography in downstream bioprocessing of biotherapeutics.[30] Chromatography is evolving into a predictive, data-driven process, where artificial intelligence (AI) can be applied to train machine learning models to predict retention behaviour, binding interactions and elution profiles, reducing reliance on trial-and-error approaches.[26] Adsorption isotherms can be rapidly estimated using artificial neural networks (ANNs) in a fraction of the time; coupled with automation and mechanistic models, then reproducibility and scalability are boosted.[24] Hybrid approaches, such as QSRR-ANN models, are more accurate in the prediction of liquid chromatography as compared to the traditional methods.[35]

AI-based soft sensors using multi-sensor data enable real-time prediction of critical quality attributes (CQA), such as product quantity, purity and potency, thereby reducing the need for offline laboratory analysis and facilitating the faster decision-making process on process-related factors.[5] Moreover, the combination of process analytical technology (PAT) and digital twins enables uninterrupted biomanufacturing with real time monitoring, adaptive control and dynamic optimization of process parameters, such as flow rate and concentration. This approach minimizes variability, increases yield, and enables real-time release testing (RTRT), providing a robust and automated manufacturing framework.[33] Together with upstream optimization, these downstream advancements contribute to a fully integrated and intelligent biomanufacturing pipeline. However, AI applications in downstream processing are limited by the complexity of separation mechanisms and the availability of high-quality datasets. Additionally, model transferability across different chromatographic systems and scales remains a key challenge. An AI-integrated downstream bioprocessing workflow is illustrated in Figure 3.

AI-Driven Process Integration and Quality by Design (QbD)

Quality by Design (QbD), as defined in ICH Q8(R2), focuses on developing mechanistic and statistical models of the relationship between critical process parameters (CPPs) and critical quality attributes (CQAs) in order to attain reproducible quality products.[21] Traditional QbD models usually include design of experiments (DoE) and multivariate analysis, but struggle to model complex non-linear and multidimensional interactions that occur in bioprocess systems. Artificial intelligence (AI), specifically machine learning (ML), enables data-based modelling of multifactorial CPP-CQA interactions, enabling accurate predictions, reducing the experimental burden and developing robust design spaces.[38]

The combination of artificial intelligence (AI) and Process Analytical Technology (PAT) advances QbD toward real-time process monitoring and control. Near infrared (NIR) and Raman spectroscopy are advanced sensing platforms. When combined with ML algorithms, it's possible to develop soft sensors for the estimation of CQAs in real-time and for the estimation of key process variables. Multi-sensor-based data integration provides higher model robustness. It also supports adaptive control strategies for dynamic process optimization in a continuous biomanufacturing system.[18,40]

Moreover, digital twin frameworks are an essential step in process integration, though the integration of mechanistic models, real-time PAT data, and Artificial Intelligence analysis (AI) to virtually model bioprocesses, allowing proactive adjustment of process parameters in response to disturbances. This capability helps to increase the robustness of the process, scalability and the transition to continuous manufacturing systems.[33]

Real-time release testing (RTRT) broadens the QbD paradigm to include a shift from end product testing to the model-based verification of quality assurance. It enables real-time prediction of CQAs and early detection of deviations. AI and ML models using PAT data streams support rapid decision-making. This approach helps to optimize the efficiency of the process and product quality and is consistent with the regulatory requirements for advanced manufacturing and Industry 4.0-driven biomanufacturing systems.[25] This integrated framework connects upstream and downstream processes, enabling a fully coordinated and intelligent biomanufacturing system. However, AI-driven QbD implementation is limited by challenges in model interpretability and regulatory acceptance. Additionally, real-time validation and standardization of AI-based models remain critical barriers. An AI-driven process integration workflow is illustrated in Figure 4.

Multidimensional Challenges in AI-Driven Bioprocessing Systems

The interrelation of data, modelling, integration, regulatory and industrial factors limits the application of machine learning (ML). Nonlinearity, a high level of variability and a lack of high-quality bioprocess data reduce model robustness and scalability, and the black-box nature of advanced ML models hinders interpretability and regulatory acceptance.[6,32,34] Moreover, poor generalizability across different process conditions restricts the reliability of models. Bias and overfitting vulnerability require constant validation and monitoring.[6,32] Its implementation in practice is constrained by difficulty in integrating it with PAT automation and GMP frameworks, the high infrastructure and expertise requirements.[2,36] Evolving regulatory frameworks further complicate transparency, lifecycle management, and global harmonization of AI-based systems.[28,37] On an industrial scale, AI governance, workforce readiness, and failure to match moral and regulatory codes are some of the crucial challenges. This limits large-scale adoption, although AI has the potential to transform Industry 4.0 bioprocessing.[27,25] Addressing these challenges is essential for enabling the effective integration of AI across the entire biomanufacturing workflow. Challenges vs solutions in AI bioprocessing are presented in Table 2.

Future Directions and Opportunities of AI in Bioprocessing

The future of AI in bioprocessing lies in the integrated data-driven intelligence, advanced automation, and adaptive systems. New technologies such as digital twins and predictive modelling are expected to drive significant advancements in the design and control of bioprocesses, enabling real-time and scalable optimisation for decision-making.[1,29] Concurrently, synthetic data generation and big data analytics help overcome limitations related to data scarcity and variability, improving model robustness across biological systems.[15,42] The integration of AI into sustainable biomanufacturing systems will also support the transition to resource-efficient and environmentally sustainable manufacturing.[36,25] It is important to note that evolving regulatory frameworks emphasizing transparency, lifecycle validation and risk-based governance will become essential to ensure safe and trustworthy implementation of AI-driven systems.[28,37] All these innovations together represent a paradigm shift towards smart, autonomous, and Industry 4.0-enabled bioprocessing, where such implementation of AI will not only result in operational efficiency but also shape the future biopharmaceutical innovation. These future developments further reinforce the importance of integrating AI across all stages of biomanufacturing systems.

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Table 1: Applications of AI in Biomanufacturing.

Area	AI technique	Application	Benefits	Reference
Protein Engineering	Deep Learning	Structure prediction	Faster protein design	(22)
Upstream	ML, SHAP, ANN	Media optimization, Process control	Improved yield and quality, Better stability	(13,14)
Downstream	ANN, ML	Chromatography optimization	Efficient purification	(24)
QbD	ML, Digital Twins	Process modelling	Improved process understanding	(38)

Table 2: Challenges vs Solutions in AI Bioprocessing

Challenge	AI-Based solution	Reference
Limited and variable data	Synthetic data generation and data augmentation	(6,15,42)
Poor model interpretability	Explainable AI, SHAP models	(32,34)
Overfitting and low generalization	Model validation and hybrid modelling	(6,32)
Integration with industrial systems	PAT integration and automation	(2,36)
Regulatory and compliance issues	Risk-based validation and AI governance	(28,37)

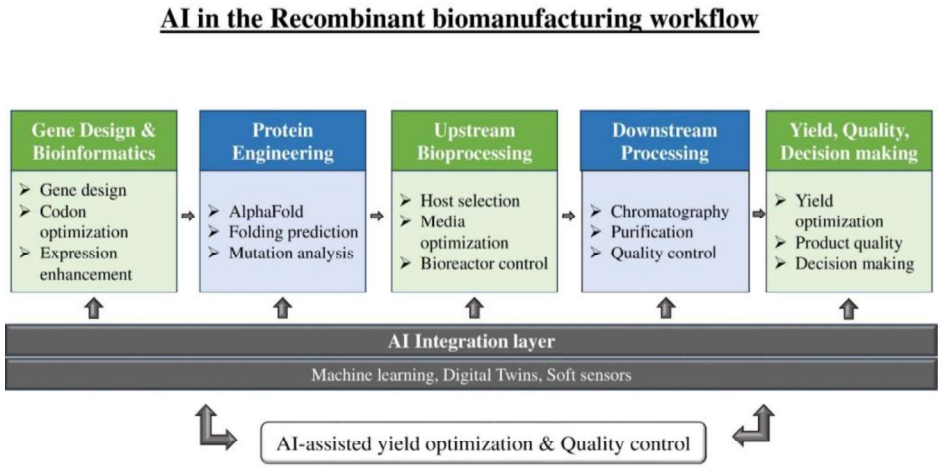

Figure 1: AI-driven recombinant biomanufacturing workflow.

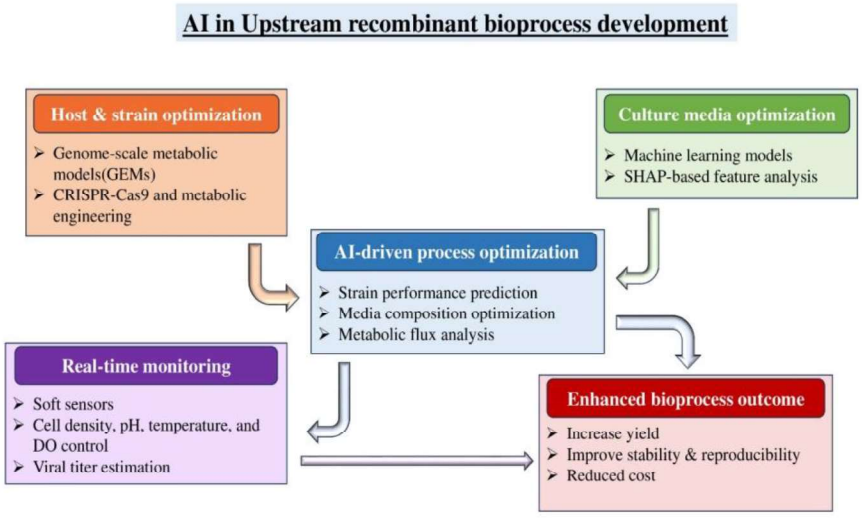

Figure 2: AI-driven upstream bioprocessing workflow illustrating strain optimization, media design, process control, and real-time monitoring.

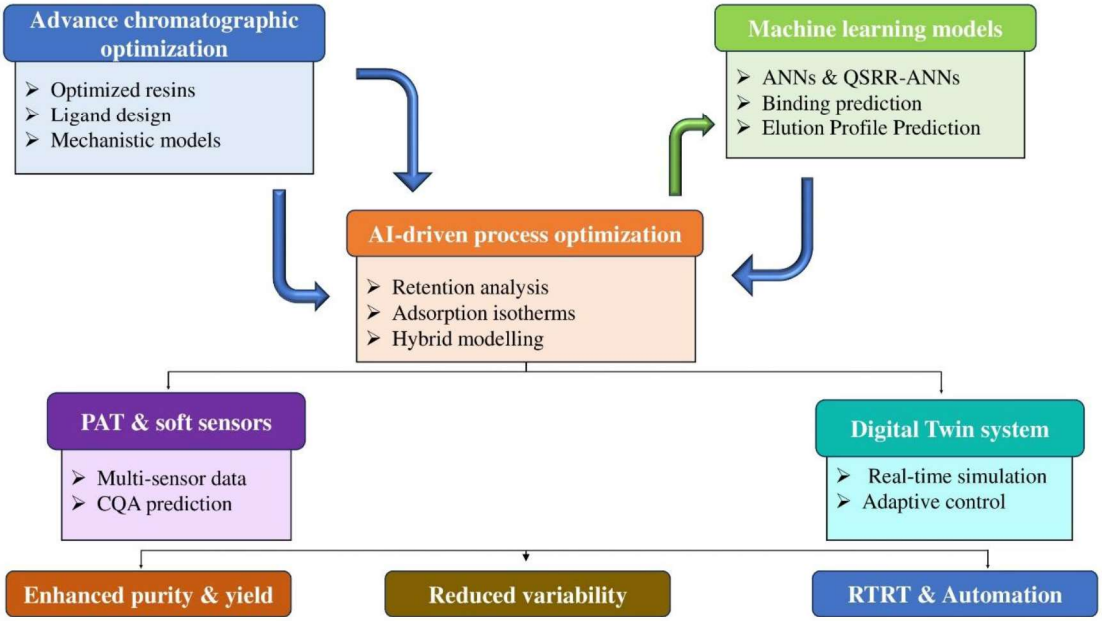

Figure 3: AI-integrated downstream bioprocessing workflow showing chromatography optimization and real-time CQA monitoring.

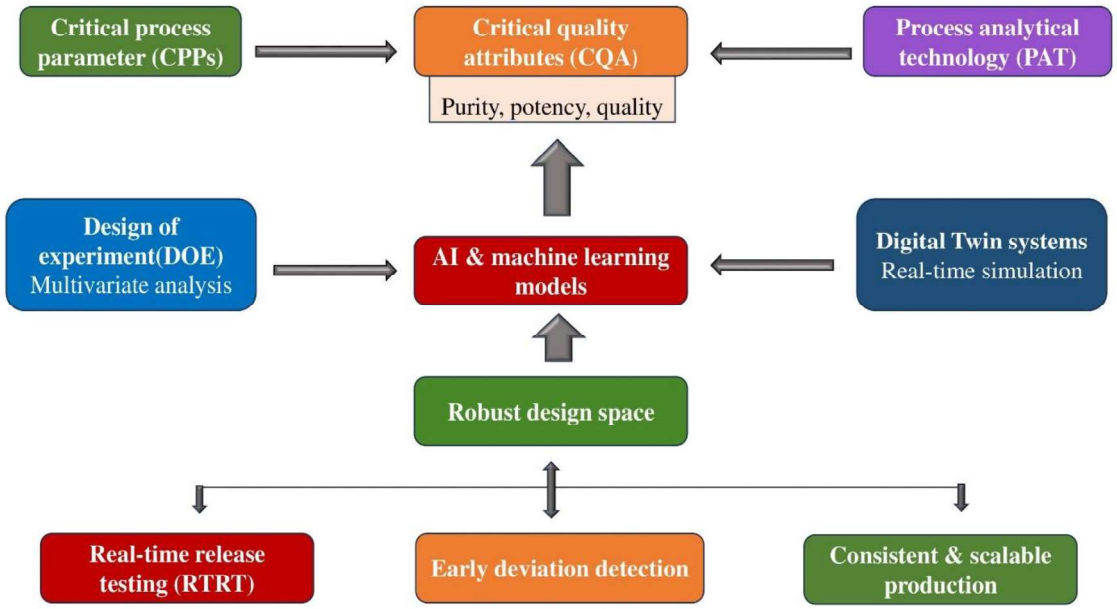

Figure 4: AI-driven process integration workflow illustrating QbD, PAT, and real-time bioprocess control.

CONCLUSION

Artificial intelligence is transforming recombinant bioprocessing by enabling optimization of protein engineering, upstream and downstream processes, as well as an integrated quality framework such as QbD and PAT. AI enhances process efficiency and product quality while supporting the transition toward continuous and automated biomanufacturing systems. The advancement of autonomous AI systems is supported by developments in explainable

AI and digital twins, which address challenges related to data limitations, model interpretability, and regulatory compliance. This is expected to enable intelligent, reliable, next-generation biopharmaceutical production through AI-driven bioprocessing systems.

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