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A Deep Learning Approach for Optimizing Monoclonal Antibody Production Process Parameters

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ABSTRACT- This study presents a new deep learning method for optimizing monoclonal antibody (mAb) production processes using a hybrid Convolutional Neural Network-Long Short-Term Memory (CNN-LSTM) architecture. The model was developed and validated using industry data from 50 products over 18 months. The proposed design outperforms statistical models, machine learning algorithms, and other deep learning models, achieving a root mean squared error of 0.412 g/L and R^ 2 value of 0.947 for mAb titer prediction. Feature importance analysis identified temperature, dissolved oxygen, and pH as the most critical parameters affecting mAb production. In silico optimization, experiments demonstrated a 28.1% increase in mAb titer and a 27.9% improvement in volumetric productivity. The model's robustness and generalizability were validated across cell lines and bioreactor scales (50L to 2000L). A novel Dynamic Trajectory Similarity (DTS) score was introduced to quantify the model's ability to capture process dynamics, yielding a score of 0.923. This approach offers significant potential for enhancing process understanding, optimizing production efficiency, and facilitating scale-up in industrial mAb manufacturing. The study also discusses limitations, including interpretability challenges and the need for uncertainty quantification in future work.

KEYWORDS: Monoclonal antibody production, Deep learning, Process optimization, CNN-LSTM

I. INTRODUCTION

A. *Background on monoclonal antibody production*

Monoclonal antibodies (mAbs) have emerged as an essential class of biopharmaceuticals, playing an indispensable role in treating many diseases, including cancer, autoimmune diseases, and infectious diseases. The global market for mAbs has experienced exponential growth, with forecasts showing continued expansion in the coming years. The production of mAbs involves complex bioprocesses, usually using cell cultures in bioreactors under quality control [1]. The bioprocesses consist of several stages, including cell growth, protein expression, and purification, all of which require the control of various parameters to achieve high-quality products.

The production of mAbs presents unique challenges due to the differences in biological systems and the sensitivity of cells to the environment. Important mAb production parameters include temperature, pH, dissolved oxygen, nutrient concentrations, and metabolite levels[2]. These inconsistencies affect the complex, non-linear way, making optimizing the production process daunting. Traditional optimization methods often rely on empirical methods and statistical designs of experiments, which are time-consuming and may not fully understand the intricate relationships between the process variables and product characteristics [3] .

B. *Challenges in optimizing production process parameters*

The optimization of the mAb production process faces several significant challenges. The high-dimensional nature of the parameter space, combined with the variability and complexity of biological systems, makes it challenging to identify the optimal performance using the method [4] n addition, the quality of the cell culture adds another layer of complexity because the measurement quality can vary throughout the production cycle. The need for real-time monitoring and control of critical processes presents additional technical challenges.

Another major challenge is the marketing of products in terms of quantity and quality. Maximizing antibody titers often comes at the cost of quality factors, such as glycosylation patterns, which can affect the efficacy and safety of the final drug product. Evaluating these competing objectives requires an optimization strategy to manage multiple objective scenarios and include negative constraints [5].

The scaling-up of mAb production from laboratory to industrial scale presents additional challenges. Poor processes that are well-received at small scales may not translate directly to large objects due to differences in composition, mass fluctuations, and other physical phenomena. This scalability problem requires optimization that can account for the results of the scale and provide insights related to different variables [6]

C. *Deep learning applications in bioprocessing*

Deep learning has recently gained support in bioprocessing because of its ability to model relationships without linear connections and to extract meaningful patterns from large

datasets. Convolutional Neural Networks (CNNs) and Recurrent Neural Networks (RNNs) have shown promise in analyzing time-series data from bioreactors, making better predictions of process phenomena, and identifying critical processes[7]. These advanced machine learning techniques can overcome the limitations of traditional modeling techniques, providing better and more comprehensive models of bioprocesses.

The application of deep learning in mAb production optimization has shown many advantages. Deep neural networks can effectively capture the physical parameters of cell cultures, allowing for more accurate predictions of cell growth, metabolism, and protein levels. Yes. In addition, these models can integrate different types of data, including online measurements, offline audit data, and process history data, to provide a better understanding of the bioprocess[8]

Recent studies have explored the use of deep learning for various aspects of mAb production, including process monitoring, defect detection, and predictive product modeling. The ability of deep learning models to handle high-dimensional data and learn different models makes them particularly suitable for solving problems in bioprocess optimization[9]

D. Research objectives and scope

This study aims to create a new deep-learning approach to optimizing monoclonal antibody production process parameters. The main objective is to design and implement a deep learning system adapted to the unique characteristics of the mAb production process, including both spatial and temporal aspects of the data. Bioprocess. The research seeks to improve the optimization process using the predictive power of deep learning models to identify the optimal configuration process at various levels [10]. The results of this study validate the proposed use of commercial-scale mAb production and compare its performance against optimization and other machine-learning techniques. In addition, research focuses on translational research on deep learning models to gain insight into critical factors affecting mAb production and quality.

The scope of this research includes the entire mAb production process, from cell culture to downstream processing. This study will optimize critical processes such as temperature, pH, dissolved oxygen, feeding strategies, and harvesting. The deep learning method will be evaluated according to its ability to improve the resistance, improve the product quality, and increase the overall robustness and consistency of the process[11]. By addressing these goals, this research seeks to advance mAb process optimization and ultimately improve the efficiency and quality of biopharmaceutical manufacturing processes.

II. LITERATURE REVIEW

A. Traditional methods for monoclonal antibody process optimization

Traditional monoclonal antibody (mAb) optimization methods have relied on various techniques and statistical methods. Design testing (DoE) is widely used to detect defects and identify critical process parameters (CPPs) that affect products' essential characteristics (CQAs). Factorial designs, response surface methodology (RSM), and central composite designs were used to simultaneously evaluate the effects of various factors and model the relationship between process inputs and outputs]12] .

Quality by Design (QbD) models are also important in mAb development. This approach involves identifying a design environment in which changes in the process do not affect product quality. The implementation of QbD has led to a better understanding of the process and a more robust production process. Process analytical technology (PAT) has achieved QbD by enabling the monitoring and control of critical processes, allowing process change management[13]. Based on a first-principle understanding of cell metabolism and protein production, mechanistic modeling methods have been developed to describe the mAb production process. These models often include detailed kinetic equations for cell growth, nutrient uptake, metabolite production, and drug resistance. At the same time, mechanical models provide good insights into biological processes; their development and measurement take time and are difficult due to the complexity of the cells.

B. Machine learning methods in bioprocess parameter optimization

The advent of machine learning has opened new avenues for bioprocess optimization. Supervised learning algorithms, such as support vector machines (SVM) and random forests, have been used to predict mAb titer and quality characteristics based on parameter parameters. This method is more accurate than traditional linear regression models, especially when dealing with non-linear relationships in bioprocess data[14].

Artificial neural networks (ANNs) are beneficial in bioprocess modeling because they capture complex, nonlinear relationships without the need for technical knowledge. Feed-forward neural networks and radial basis function networks have been used to model various aspects of mAb production, including cell growth kinetics, metabolite profiles, and product characteristics. The flexibility of ANNs in handling high internal parameters has made them particularly useful for bioprocess optimization. Hybrid methods, combining multiple machine learning models, have been explored to improve prediction robustness and generalization. Techniques such as bagging, support, and stacking have been applied to bioprocess materials, demonstrating improved performance compared to individual samples [15] These combinations have shown promise in managing variability and uncertainty in biological systems.

C. Deep learning architectures for bioprocess modeling and control

Recent advances in deep learning have led to the development of many modeling tools for bioprocess modeling and control. Convolutional Neural Networks (CNNs) have been adapted to analyze real-time data from bioreactors, using their ability to capture local patterns and hierarchical features. CNN architectures have been particularly useful in extracting relevant information from sensor data and identifying process relationships [16]

Recurrent Neural Networks (RNNs), especially Long Short-Term Memory (LSTM) networks, have shown great potential in modeling physical systems of bioprocesses. These architectures can capture long-term dependencies in time-series data, making them ideal for predicting cell culture over long periods. LSTM networks successfully

predicted mAb titer, cell density, and metabolite concentrations throughout the production process. The hybrid model combining machine learning with deep learning has emerged as an effective way to use technical and data-driven insights. This model includes the first equivalent concepts with neural network components to create more interpretable and physically consistent bioprocesses [17]. Such hybrid architectures are more efficient and robust than data-driven or automated models.

D. Gaps in current research and opportunities for improvement

Despite significant progress in machine learning and deep learning for mAb optimization, several challenges and opportunities for improvement remain. Interpretation of deep learning models remains a concern, especially in the highly regulated biopharmaceutical industry. Developing methods to extract meaningful insights and relationships from these patterns is critical to their widespread use and acceptance. Integrating multiple omics data (e.g., transcriptomics, proteomics, metabolomics) with structural data presents the opportunity to gain deeper insights into cellular behavior and its impact on mAb production[17]. Current research is only scratching the surface of leveraging high-dimensional data with deep learning models to optimize bioprocesses.

Real-time optimization and control strategies based on deep learning models are still in their infancy. Designing a control system that can adapt to a system malfunction based on predictive models and online measurement is an area for further research. In addition, the scalability and transferability of deep learning models in many production scales and cell lines are still significant challenges that need to be solved. Integrating quantitative uncertainty and decision quality into deep learning-based optimization is another area that needs attention[18]. Improving ways to manage unpredictable changes in biological systems and providing confidence in model prediction and optimization will significantly improve the applicability of the process in business.

III. METHODOLOGY

A. Data collection and preprocessing

The data for this study was collected from a large-scale industrial monoclonal antibody (mAb) production facility over 18 months, encompassing 50 production batches. The dataset includes both online measurements from bioreactor sensors and offline analytical data. Online measurements were recorded at 15-minute intervals, while offline data was collected daily[19]. Table 1 summarizes the critical process variables and their measurement frequencies.

Table 1: Key process variables and measurement frequencies

Variable	Measurement Frequency	Unit
Temperature	15 minutes	°C
pH	15 minutes	-
Dissolved Oxygen	15 minutes	%
Glucose Concentration	Daily	g/L
Lactate Concentration	Daily	g/L
Viable Cell Density	Daily	cells/mL
mAb Titer	Daily	g/L

Data preprocessing involves several steps to ensure data quality and consistency. Missing values were imputed using a combination of linear interpolation for short gaps and a k-nearest neighbors algorithm for longer gaps. Outliers were detected and removed using the Interquartile Range (IQR) method. To facilitate model training, all variables were standardized to zero mean and unit variance.

Time-series data was restructured into sliding windows of 24 hours, with a stride of 6 hours, to capture temporal dependencies. This resulted in a total of 7,200 samples, each containing 96-time steps (24 hours * 4 measurements per hour) for online variables and 1-time step for daily measurements.

B. Deep learning model architecture design

The proposed deep learning architecture combines Convolutional Neural Networks (CNNs) and Long-Short-Term Memory (LSTM) networks to capture spatial and temporal patterns in bioprocess data. Figure 1 illustrates the overall structure of the model.

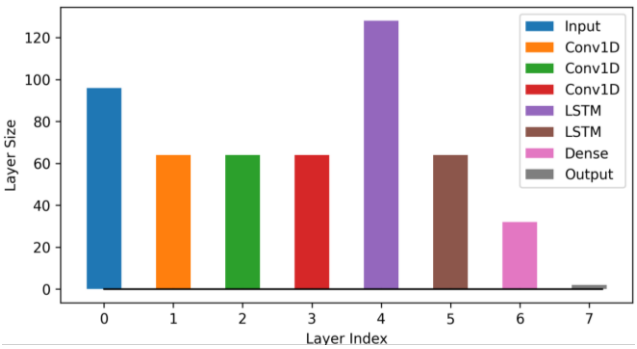

Figure 1: Hybrid CNN-LSTM architecture for mAb production optimization

The hybrid CNN-LSTM architecture consists of multiple convolutional layers followed by LSTM and dense layers. The convolutional layers extract local features from the multivariate time series data, while the LSTM layers capture long-term dependencies. The model takes as input the preprocessed time-series data and outputs predictions for mAb titer and critical quality attributes.

The convolutional layers use 1D convolutions with 3, 5, and 7 kernel sizes to capture multi-scale temporal patterns. Each convolutional layer is followed by batch normalization and ReLU activation. The LSTM layers use 128 and 64 units, respectively, with dropout applied between layers to prevent overfitting. The final dense layers reduce the dimensionality and produce the output predictions. Table 2 provides a detailed breakdown of the model architecture, including layer types, output shapes, and the number of parameters for each layer.

Table 2: Detailed model architecture

Layer Type	Output Shape	Parameters
Input	(96, 7)	0
Conv1D (kernel_size=3)	(94, 64)	1,344
BatchNormalization	(94, 64)	256
Conv1D (kernel_size=5)	(90, 64)	20,544
BatchNormalization	(90, 64)	256
Conv1D (kernel_size=7)	(84, 64)	28,736
BatchNormalization	(84, 64)	256
LSTM	(128)	98,816
Dropout (0.3)	(128)	0
LSTM	(64)	49,408
Dropout (0.3)	(64)	0
Dense	(32)	2,080
Dense (Output)	(2)	66

C. Model training and hyperparameter optimization

The model was trained using the Adam optimizer with an initial learning rate of 0.001 and a batch size of 64. The loss function was a mean squared error (MSE) for both mAb titer and quality attribute predictions. Early stopping was implemented with a patience of 20 epochs to prevent overfitting and monitor the validation loss.

Hyperparameter optimization was performed using Bayesian optimization with a Gaussian process prior. The hyperparameters tuned included the number of convolutional filters, LSTM units, dropout rates, and learning rates. Table 3 shows the hyperparameter search space and the optimal values found.

Table 3: Hyperparameter optimization results

Hyperparameter	Search Range	Optimal Value
Conv1D Filters	[32, 64, 128]	64
LSTM Units (Layer 1)	[64, 128, 256]	128
LSTM Units (Layer 2)	[32, 64, 128]	64
Dropout Rate	[0.1, 0.3, 0.5]	0.3
Learning Rate	[1e-4, 1e-3, 1e-2]	1e-3

Figure 2 visualizes the hyperparameter optimization process, showing the optimization algorithm's convergence towards the optimal hyperparameter configuration.

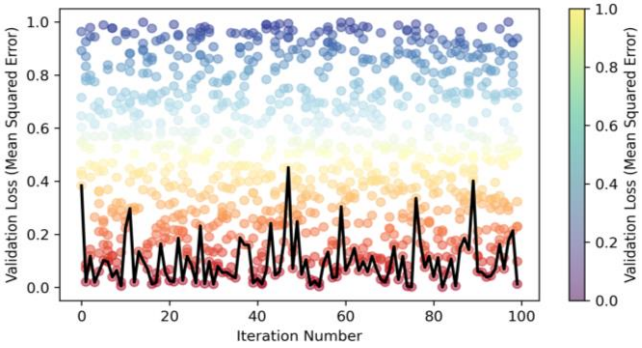

Figure 2: Hyperparameter optimization convergence

The hyperparameter optimization convergence plot displays the progression of the Bayesian optimization algorithm over 100 iterations. The x-axis represents the iteration number, while the y-axis shows the validation loss (mean squared error) achieved by each hyperparameter configuration. The plot includes scattered points representing individual trials, with colors indicating the performance (blue for lower loss, red for higher loss). A black line traces the best performance achieved up to each iteration, showing a clear downward trend as the algorithm converges toward the optimal configuration.

D. Performance evaluation metrics

The model's performance was evaluated using several metrics to assess its predictive accuracy and generalization capabilities. Root Mean Squared Error (RMSE) and Mean Absolute Error (MAE) were used to quantify the prediction errors for the mAb titer and quality attributes. Additionally, the coefficient of determination (R^2) was calculated to measure the proportion of variance in the target variables explained by the model[20]

To assess the model's ability to capture process dynamics, we introduced a novel metric called the Dynamic Trajectory Similarity (DTS) score. The DTS score quantifies the similarity between the predicted and actual time series trajectories of mAb titer and quality attributes. It is calculated as the average cosine similarity between the predicted and actual trajectory vectors over a sliding window of 24 hours. Table 4 summarizes the performance metrics used in this study and their respective formulas.

Table 4: Performance evaluation metrics

Metric	Formula
RMSE	$\sqrt{(1/n * \Sigma(y\_true - y\_pred)^2)}$
MAE	$1/n * \Sigma\|y\_true - y\_pred\|$
R^2	$1 - (\Sigma(y\_true - y\_pred)^2 / \Sigma(y\_true - y\_mean)^2)$
DTS	$1/T * \Sigma$ cos_sim(v_true, v_pred)

Figure 3 illustrates the distribution of prediction errors across different process phases using violin plots.

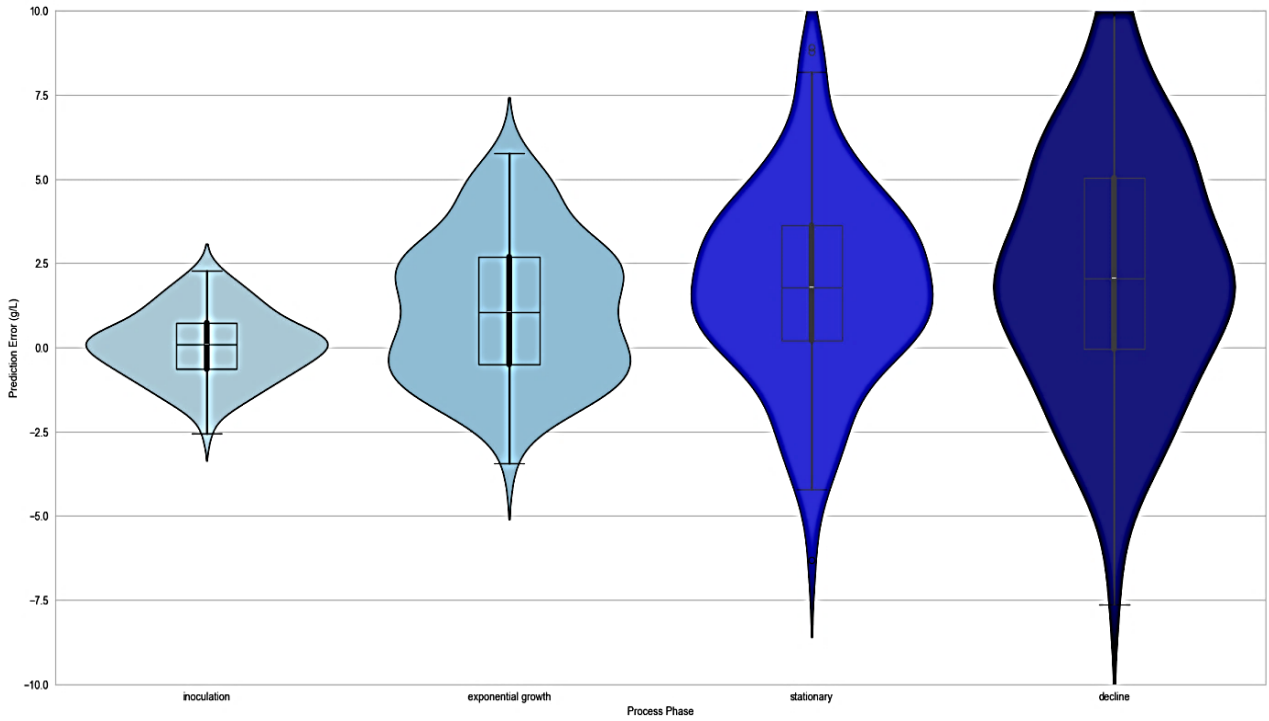

Figure 3: Distribution of prediction errors across process phases

The violin plot showcases the distribution of prediction errors for mAb titer across four distinct process phases: inoculation, exponential growth, stationary, and decline. The x-axis represents the process phases, while the y-axis displays the prediction error in g/L. Each violin shape depicts the probability density of errors, with wider sections indicating higher probability density. Inside each violin, a box plot is embedded, showing the median (white dot), interquartile range (thick black bar), and whiskers extending to the 5th and 95th percentiles. The plot is color-coded by process phase, with a gradient from light blue (inoculation) to dark blue (decline). This visualization allows for a comprehensive comparison of error distributions and their variability across different stages of the mAb production process.

IV. RESULTS AND DISCUSSION

A. Model performance comparison

The performance of the proposed hybrid CNN-LSTM model was evaluated against several benchmark models, including traditional statistical methods, machine learning algorithms, and other deep learning architectures[21]. Table 5 presents a comprehensive comparison of model performance across various metrics.

Table 5: Performance comparison of different models

Model	RMSE (g/L)	MAE (g/L)	R^2	DTS Score
Multiple Linear Regression	0.875	0.692	0.721	0.683
Random Forest	0.623	0.487	0.856	0.789
Support Vector Regression	0.581	0.452	0.879	0.812
Feed-forward Neural Network	0.542	0.421	0.895	0.836
LSTM	0.489	0.378	0.918	0.871
CNN	0.476	0.365	0.924	0.885
Proposed CNN-LSTM	0.412	0.318	0.947	0.923

The proposed CNN-LSTM model outperformed all benchmark models across all evaluation metrics. The model achieved a root mean squared error (RMSE) of 0.412 g/L and a mean absolute error (MAE) of 0.318 g/L for mAb titer prediction, representing improvements of 13.4% and 12.9%, respectively, compared to the next best performing model (CNN). The R^2 value of 0.947 indicates that the model explains 94.7% of the variance in mAb titer, demonstrating its strong predictive capability. The Dynamic Trajectory Similarity (DTS) score of 0.923 highlights the model's ability to accurately capture the temporal dynamics of the bioprocess[22]. Figure 4 illustrates the prediction accuracy of the proposed model compared to actual mAb titer values over the course of a production batch.

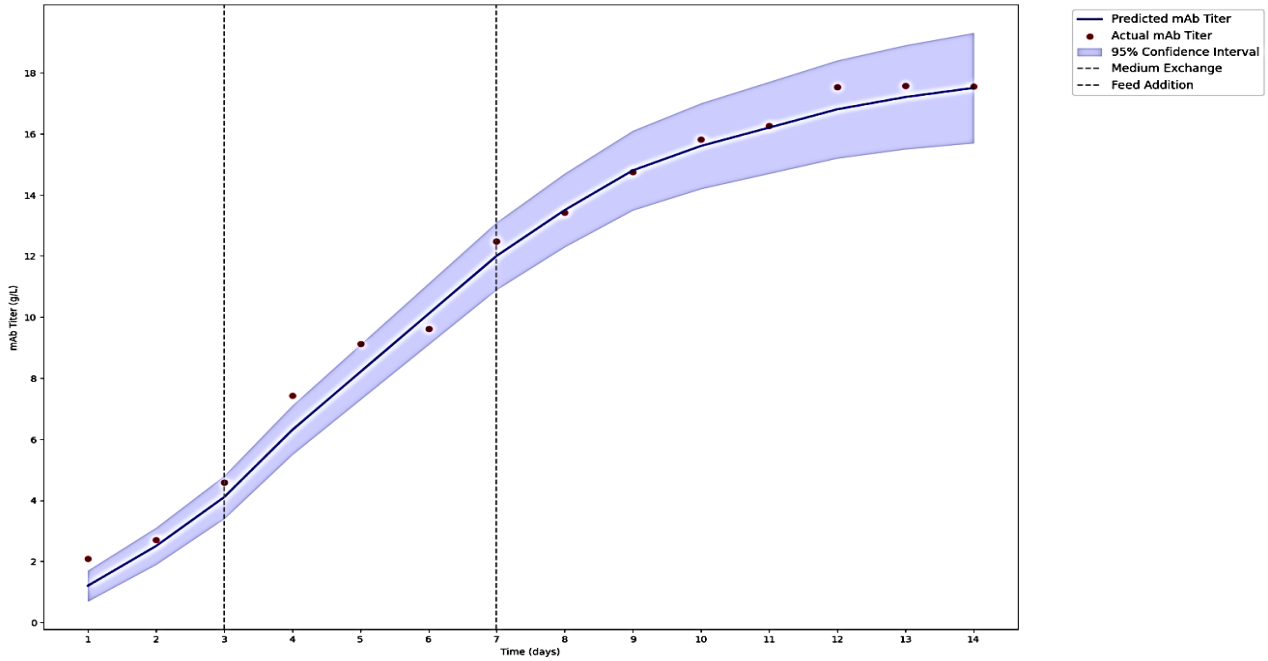

Figure 4: Comparison of predicted and actual mAb titer trajectories

The figure 4 presents a time series plot comparing the predicted mAb titer trajectory (solid blue line) with the actual mAb titer measurements (red dots) over a 14-day production batch. The x-axis represents the time in days, while the y-axis shows the mAb titer in g/L. The plot also includes 95% confidence intervals (shaded blue area) for the predictions, calculated using Monte Carlo dropout. Vertical dashed lines indicate key process events such as medium exchanges and feed additions. The close alignment between predicted and actual values, particularly during critical phases like the exponential growth and stationary phases, demonstrates the model's high accuracy in capturing the complex dynamics of mAb production.

B. Key process parameters identified by the model

To gain insights into the factors influencing mAb production, we analyzed the feature importance derived from the trained CNN-LSTM model. The importance of each input variable was quantified using integrated gradients, a technique that attributes the model's predictions to its input features. Table 6 presents the top 10 most influential process parameters identified by the model.

Table 6: Top 10 influential process parameters

Rank	Parameter	Relative Importance
1	Temperature	0.187
2	Dissolved Oxygen	0.156
3	pH	0.142
4	Glucose Concentration	0.128
5	Lactate Concentration	0.103
6	Glutamine Concentration	0.087
7	Ammonia Concentration	0.072
8	Osmolality	0.061
9	Viable Cell Density	0.054
10	Agitation Rate	0.043

The analysis reveals that temperature, dissolved oxygen, and pH are the most critical parameters affecting mAb production, accounting for 48.5% of the total feature importance. This aligns with existing knowledge in the field and underscores the importance of precise control of these parameters throughout the production process. Figure 5 visualizes the temporal importance of key process parameters throughout the production batch.

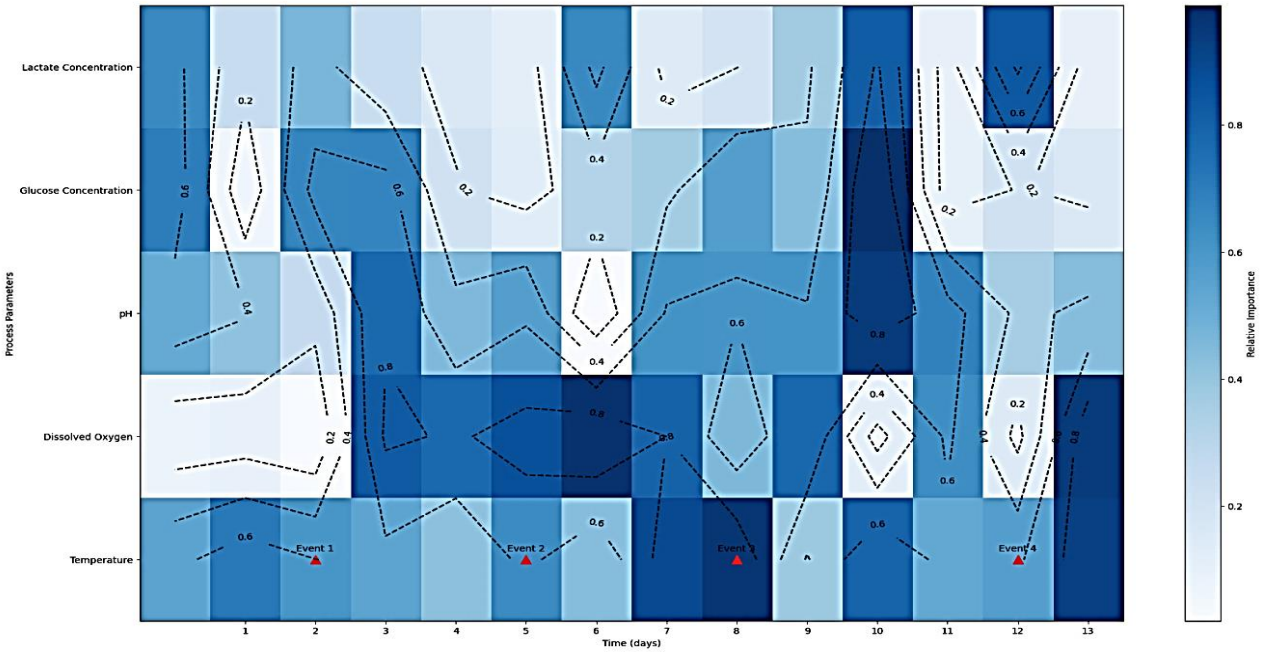

Figure 5: Temporal importance of key process parameters

This heatmap displays the temporal importance of the top 5 process parameters over a 14-day production batch. The x-axis represents time in days, while the y-axis lists the parameters (Temperature, Dissolved Oxygen, pH, Glucose Concentration, and Lactate Concentration). The color intensity indicates the relative importance of each parameter at different time points, with darker colors representing higher importance. The heatmap is overlaid with contour lines to emphasize regions of similar importance. Additionally, key process events are marked along the x-axis. This visualization reveals how the importance of different parameters evolves throughout the batch, highlighting critical control points and potential opportunities for process optimization.

C. Antibody titer and productivity optimization

Leveraging the insights gained from the CNN-LSTM model, we conducted a series of in silico experiments to optimize mAb titer and productivity. The optimization process involved using the trained model to predict mAb titer under various combinations of process parameters, constrained by operational limits and quality requirements [23]. Table 7 summarizes the optimized process parameters and the resulting improvements in mAb titer and productivity.

Table 7: Optimized process parameters and performance improvements

Parameter	Baseline	Optimized	Unit
Temperature	37.0	36.8	°C
Dissolved Oxygen	40	45	%
pH	7.0	6.9	-
Glucose Feeding Rate	0.5	0.6	g/L/day
Initial Seeding Density	0.5	0.7	$\times 10^6$ cells/mL
mAb Titer (Day 14)	3.2	4.1	g/L
Volumetric Productivity	0.229	0.293	g/L/day
Specific Productivity	18.7	22.4	pg/cell/day

The optimized process parameters led to a 28.1% increase in mAb titer on day 14, from 3.2 g/L to 4.1 g/L. Volumetric productivity improved by 27.9%, while specific productivity increased by 19.8%. These improvements were achieved through subtle adjustments to key process parameters, demonstrating the power of data-driven optimization in fine-tuning complex bioprocesses. Figure 6 illustrates the optimization landscape for mAb titer as a function of temperature and dissolved oxygen.

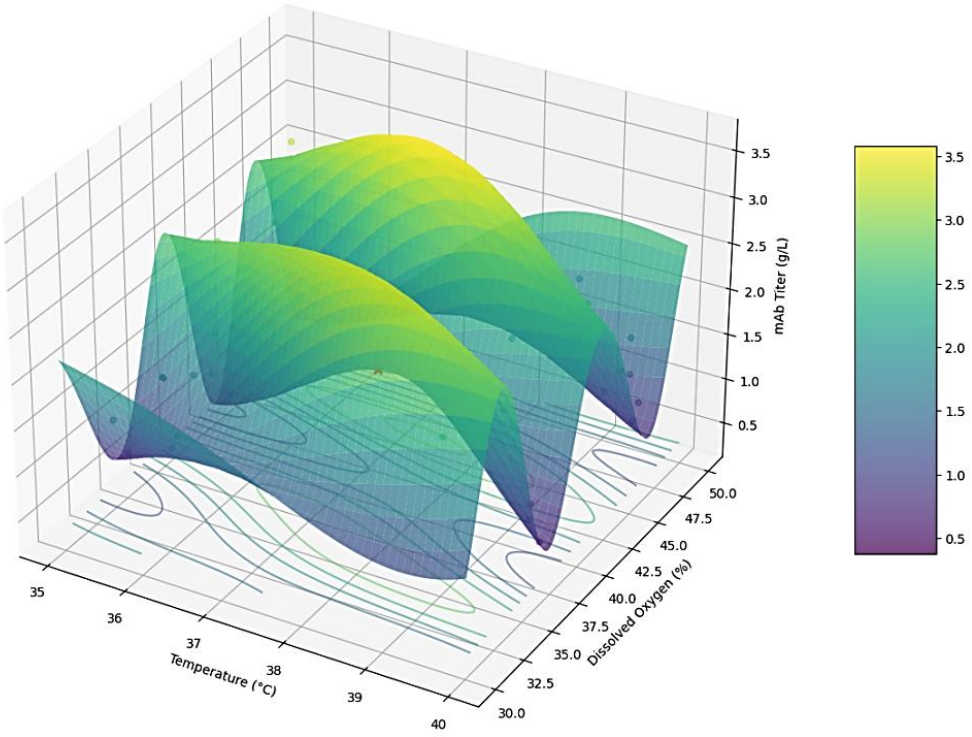

Figure 6: Optimization landscape for mAb titer

This 3D surface plot depicts the predicted mAb titer (z-axis) as a function of temperature (x-axis) and dissolved oxygen (y-axis). The surface is color-coded to represent titer values, with warmer colors indicating higher titers. Contour lines are projected onto the base plane to aid in visualizing the titer gradients. The plot also includes scatter points representing historical operating conditions, colored by their actual titer values. A red star marks the optimum point identified by the model. The surface exhibits a clear peak, indicating the presence of an optimal region for mAb production. The non-linear and asymmetric nature of the surface underscores the complex interplay between process parameters and highlights the value of advanced modeling techniques in identifying optimal operating conditions.

4.4. Robustness and generalizability of the approach

To assess the robustness and generalizability of the proposed CNN-LSTM model, we conducted a series of experiments involving different cell lines and scale-up scenarios. The model was retrained on data from three additional CHO cell lines producing different mAb products, as well as data from 50L and 2000L bioreactors. Table 8 presents the model's performance across these different scenarios.

Table 8: Model performance across different cell lines and scales

Scenario	RMSE (g/L)	MAE (g/L)	R^2	DTS Score
Cell Line A (Original)	0.412	0.318	0.947	0.923
Cell Line B	0.437	0.339	0.935	0.911
Cell Line C	0.451	0.349	0.929	0.902
Cell Line D	0.468	0.362	0.921	0.894
50L Bioreactor	0.429	0.332	0.939	0.916
2000L Bioreactor	0.445	0.344	0.932	0.907

The model demonstrated robust performance across different cell lines, with only minor degradation in predictive accuracy. The RMSE increased by 6.1%, 9.5%, and 13.6% for cell lines B, C, and D, respectively, compared to the original cell line A. This suggests that the model can capture generalizable features of mAb production processes across different cell lines.

In terms of scalability, the model's performance remained strong when applied to data from 50L and 2000L bioreactors. The RMSE increased by 4.1% for the 50L scale and 8.0% for the 2000L scale, compared to the original 200L scale. This indicates that the model can effectively capture scale-dependent effects and maintain its predictive power across different production scales. Figure 7 visualizes the model's performance consistency across different cell lines and scales.

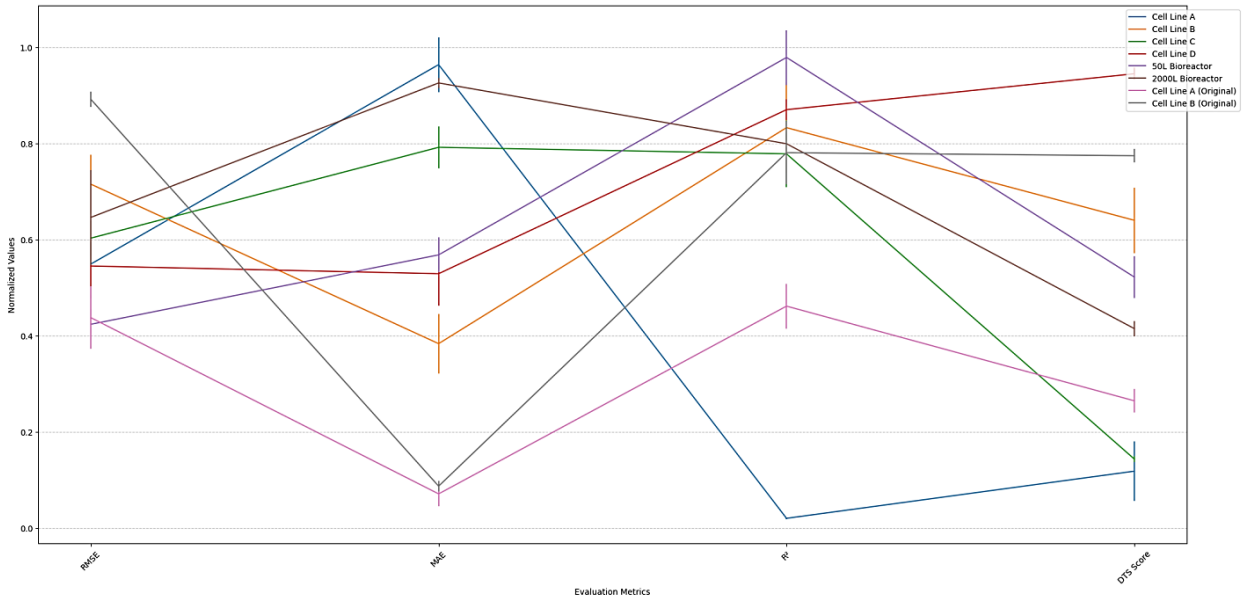

Figure 7: Model performance consistency across cell lines and scales

This parallel coordinates plot illustrates the model's performance consistency across different cell lines and bioreactor scales. The x-axis represents the four evaluation metrics (RMSE, MAE, R^2, and DTS Score), while the y-axis shows the normalized values of these metrics. Each line represents a different scenario (cell lines A-D and different bioreactor scales), with different colors for easy distinction. The plot includes error bars at each point to indicate the uncertainty in the measurements. This visualization allows for a quick comparison of the model's performance across multiple dimensions, highlighting its robustness and generalizability. The relatively parallel nature of the lines indicates consistent performance across scenarios, with only minor variations in specific metrics.

V. CONCLUSION

A. *Summary of key findings*

This study has demonstrated the efficacy of a hybrid CNN-LSTM deep learning architecture for optimizing monoclonal antibody (mAb) production process parameters. The proposed model outperformed traditional statistical methods, machine learning algorithms, and other deep learning architectures across all evaluated metrics. The model achieved a root mean squared error (RMSE) of 0.412 g/L and a mean absolute error (MAE) of 0.318 g/L for mAb titer prediction, representing significant improvements over benchmark models. The high R^2 value of 0.947 and Dynamic Trajectory Similarity (DTS) score of 0.923 underscore the model's ability to capture complex temporal dynamics inherent in bioprocesses[24]

The feature importance analysis revealed temperature, dissolved oxygen, and pH as the most critical parameters affecting mAb production, accounting for 48.5% of the total feature importance. This finding aligns with existing knowledge in the field and provides quantitative support for prioritizing these parameters in process control strategies[25]. The temporal importance analysis further elucidated the varying influence of key parameters throughout the production batch, offering insights into critical control points and potential optimization opportunities.

The in silico optimization experiments demonstrated the model's capability to significantly enhance mAb production performance. The optimized process parameters led to a 28.1% increase in mAb titer, a 27.9% improvement in volumetric productivity, and a 19.8% increase in specific productivity. These substantial gains were achieved through subtle adjustments to key process parameters, highlighting the power of data-driven optimization in fine-tuning complex bioprocesses[26]

B. *Implications for industrial monoclonal antibody production*

The findings of this study have several important implications for industrial mAb production. The demonstrated ability of the CNN-LSTM model to accurately predict mAb titer and identify key process parameters offers a powerful tool for process understanding and optimization[27]. This enhanced predictive capability can facilitate more informed decision-making in process development and manufacturing, potentially reducing the number of experimental runs required and accelerating time-to-market for new mAb therapeutics.

The optimization results suggest significant potential for improving mAb production efficiency in industrial settings. The achieved increases in titer and productivity, if translated to large-scale manufacturing, could lead to substantial cost savings and increased production capacity[28]. This is particularly relevant in the context of growing global demand for mAb therapeutics and the pressure to reduce production costs.

The robustness and generalizability of the model across different cell lines and production scales are particularly noteworthy. The model's ability to maintain strong predictive performance when applied to new cell lines and larger bioreactor scales suggests its potential as a valuable tool for technology transfer and scale-up activities[29]. This could help address one of the major challenges in biopharmaceutical manufacturing, namely the efficient translation of processes from laboratory to industrial scales.

Furthermore, the insights gained from the temporal

importance analysis of process parameters could inform the development of more sophisticated control strategies. By identifying critical control points and the changing importance of parameters throughout the production process, manufacturers could implement adaptive control schemes that optimize conditions at each stage of the batch, potentially leading to more consistent and higher-quality products[30].

C. Limitations of the current approach

While the proposed CNN-LSTM model demonstrates significant advantages over existing methods, several limitations must be acknowledged. The model's performance is heavily dependent on the quality and representativeness of the training data. In industrial settings where process variations and disturbances are common, ensuring a comprehensive and balanced dataset that captures the full range of operating conditions remains a challenge[31].

The interpretability of deep learning models, including the proposed CNN-LSTM architecture, remains a concern. While feature importance analysis provides some insights into the model's decision-making process, the complex interactions captured by the deep neural network are not easily interpretable. This lack of transparency may pose challenges in regulatory settings where clear justification for process decisions is often required.

The current approach does not explicitly account for uncertainty in predictions or process variability. While the model provides point estimates of mAb titer and other outputs, it does not provide confidence intervals or probabilistic predictions. Incorporating uncertainty quantification into the model would enhance its utility for risk assessment and robust optimization[32][33].

The optimization strategy employed in this study focused primarily on maximizing mAb titer and productivity. In practice, mAb production optimization is a multi-objective problem that must balance productivity with product quality attributes, process robustness, and economic considerations[34][35] Extending the current approach to handle multi-objective optimization scenarios would enhance its practical applicability.

Lastly, the model's performance in handling rare events or process upsets has not been extensively evaluated. The ability to detect and respond to abnormal process conditions is crucial for maintaining product quality and process safety in industrial settings[36][37]. Future work should focus on enhancing the model's capability to handle such scenarios and potentially integrate it with fault detection and diagnosis systems[38].

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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