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The World Algorithm: A Universal Metaheuristic for Complex Optimization Problems of Actinomycin Production

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Abstract

Optimizing microbial fermentation for the production of bioactive compounds, such as Actinomycin V, remains a nonlinear, multi-objective challenge. This research introduces a hybrid Artificial Neural Network (ANN), World Algorithm (WA) framework for modeling and optimizing the medium composition used in Streptomyces triostinicus fermentation. Conventional statistical models, such as Response Surface Methodology (RSM), struggle with nonlinear biochemical relationships. By contrast, the ANN–World hybrid leverages the predictive adaptability of neural networks and the global optimization dynamics of the WA, inspired by cooperative interactions among forest ecosystems. Experimental data generated via Central Composite Design (CCD) were used to train the ANN, while WA refined the solution space to discover optimal nutrient ratios. The optimized configuration increased the Actinomycin V yield from 110 mg/L to 458 mg/L, representing a more than fourfold increase. This hybrid framework provides a scalable and interpretable AI-driven methodology for the intelligent design of bioprocesses.

Keywords: World algorithm, Optimization, Actinomycin V, Neural network, Fermentation optimization, Metaheuristic, Machine learning.

1 | Introduction

Actinomycin V is a member of the actinomycin family of chromopeptide antibiotics, a group of secondary metabolites primarily synthesized by various Streptomyces species. These compounds are renowned for their potent biological activities, particularly their inhibitory effects on DNA-dependent RNA synthesis, which underpins both their antibiotic and antitumor properties. Among them, actinomycin V has emerged as one

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of the most promising molecules due to its higher therapeutic index and superior cytotoxicity against specific cancer cell lines, including F5-5 Friend leukemia cells. Its mechanism of action involves intercalation into double-stranded DNA, followed by inhibition of RNA polymerase, effectively halting transcription and triggering apoptotic pathways in susceptible cells [1].

Given these powerful bioactivities, actinomycin V has attracted significant industrial and pharmaceutical interest as a potential chemotherapeutic agent and as a biochemical probe for nucleic acid research. However, large-scale production remains a persistent challenge. The compound is a product of complex biosynthetic pathways that depend on tightly regulated enzymatic processes and environmental factors. The yield of actinomycin V is highly sensitive to culture conditions, including carbon and nitrogen source composition, pH, aeration, temperature, and trace mineral concentrations. Consequently, optimizing fermentation media and process parameters is essential for achieving economically viable production levels [1], [2].

1.1 | The Challenge of Fermentation Optimization

Traditional optimization methods in microbial fermentation typically rely on classical experimental designs, most notably, the One-Factor-at-A-Time (OFAT) approach. This method varies a single variable while keeping the others constant, enabling a basic assessment of individual effects but completely neglecting interactions among factors. In biological systems, such interactions are rarely negligible; the metabolic flux through secondary metabolite pathways often depends on the synergistic or antagonistic interplay between nutrients and environmental stimuli. For example, an increase in carbon availability may stimulate primary metabolism but repress secondary metabolite formation via catabolite repression. Similarly, nitrogen source balance can influence precursor supply for peptide synthesis or alter regulatory signaling cascades. Therefore, OFAT methods often produce suboptimal results and require extensive experimentation with low predictive power [3], [4].

To address these limitations, factorial designs and statistical techniques such as Response Surface Methodology (RSM) were developed. RSM combines experimental design principles with regression-based modeling to approximate the relationship between response variables (e.g., yield) and input factors (e.g., nutrient concentrations). Central Composite Design (CCD) and Box–Behnken Design (BBD) are two widely used RSM frameworks that provide efficient data structures for modeling second-order polynomials. These methods have been successfully applied in optimizing fermentation processes for antibiotics, enzymes, and organic acids. Their primary strengths lie in their structured exploration of the design space, statistical interpretability, and the orthogonality of factor levels, which enable efficient coefficient estimation with relatively few experiments [5].

However, the polynomial nature of RSM imposes inherent constraints. Biological systems are inherently nonlinear and high-dimensional, often involving threshold effects, saturation kinetics, and feedback regulation that cannot be captured adequately by quadratic models. Moreover, RSM assumes smooth, continuous response surfaces with a single global optimum, an assumption that breaks down when the system exhibits multiple local maxima or discontinuities due to complex metabolic switching. Consequently, RSM may oversimplify the fermentation landscape, leading to predictions that deviate significantly from experimental reality [6].

1.2 | Rise of Data-Driven Modeling in Bioprocess Optimization

With the rise of machine learning and computational intelligence, data-driven models have emerged as powerful alternatives for process optimization. Among these, Artificial Neural Networks (ANNs) have become particularly attractive due to their ability to approximate any nonlinear function without explicit knowledge of the underlying mechanisms. Unlike regression-based models, ANNs do not rely on predefined functional forms; instead, they learn directly from experimental data by adjusting internal parameters (weights and biases) through training algorithms such as backpropagation or evolutionary tuning [7].

In the context of bioprocess engineering, ANNs can capture the intricate, nonlinear dependencies between fermentation inputs (nutrient concentrations, pH, temperature, agitation rate, etc.) and outputs (yield, productivity, or specific metabolite concentrations). This flexibility allows them to model highly complex biological systems where traditional mechanistic models are either unknown or mathematically intractable. Moreover, once trained, an ANN can generalize from limited data, predict outcomes under untested conditions, and serve as a fast-response surrogate model in real-time process control or optimization frameworks [1].

For actinomycin production, ANNs have demonstrated superior predictive capabilities compared to RSM or polynomial regression, particularly when interactions between carbon and nitrogen sources, micronutrient levels, and environmental factors are significant. However, while ANNs can model these relationships effectively, they do not inherently provide mechanisms to search for the global optimum within the modeled surface. In other words, an ANN can predict yield given a set of inputs, but it cannot independently determine which combination of inputs will maximize the response. This is where metaheuristic optimization algorithms play a crucial role [8].

1.3 | Metaheuristics: A Bridge Between Prediction and Optimization

Metaheuristic algorithms are population-based, stochastic optimization methods inspired by natural or social phenomena, such as evolution (Genetic Algorithms, GAs), swarm intelligence (Particle Swarm Optimization, PSO), Ant Colony Optimization (ACO), or physics (Simulated Annealing). These algorithms excel at exploring large, complex, and multimodal search spaces without requiring gradient information or convexity assumptions. Their iterative structure allows them to balance exploration (searching new regions) and exploitation (refining known promising regions) to locate near-global optima even in noisy or discontinuous environments [1], [3].

In fermentation optimization, metaheuristics have been employed to fine-tune media compositions, process parameters, and even control strategies. Techniques such as GA, Differential Evolution (DE), and PSO have been integrated with ANNs to form hybrid intelligent systems in which the ANN serves as a predictive model, and the metaheuristic optimizes the input space toward optimal conditions. These ANN–metaheuristic hybrids have significantly reduced experimental effort, improved yield, and uncovered interactions that traditional statistics could not reveal [1].

Despite their success, conventional metaheuristics also face limitations. Many of them tend to converge prematurely, especially in landscapes with multiple local optima or deceptive fitness valleys. Their convergence speed and stability depend heavily on control parameters (e.g., inertia weight, mutation rate, or crossover probability), which are often problem-specific. Moreover, some algorithms lack adaptability, the ability to adjust their search dynamics in response to environmental feedback. This lack of adaptability can be a major drawback in bioprocess systems where the search space may change dynamically due to process drift, noise, or nonlinear interactions among factors [5], [6], [8], [9].

1.4 | The World Algorithm: A New Nature-Inspired Approach

To overcome these limitations, a new class of nature-inspired metaheuristics has been developed, grounded not in animal behavior or physical laws, but in ecological and cooperative principles. The World Algorithm (WA) belongs to this emerging generation. It is inspired by the ecological interactions among trees in a forest, which share resources through underground mycorrhizal networks and adapt collectively to environmental changes. This cooperative exchange of nutrients and information enables the forest ecosystem to maintain stability, resilience, and efficiency even under fluctuating environmental conditions.

In the context of optimization, the WA abstracts these interactions into a computational framework. Each "tree" in the population represents a potential solution in the search space. Trees exchange information with neighbors (other candidate solutions) based on their relative fitness, simulating nutrient flow from stronger to weaker entities. Over successive generations, this information-sharing process enhances global awareness across the population, preventing premature convergence and ensuring the collective search process remains diverse yet coordinated [10].

The WA mechanism embodies three fundamental ecological behaviors:

I. Resource sharing–high-fitness individuals distribute part of their solution features to others, mimicking nutrient transfer through root systems.

II. Competition and adaptation–trees compete for environmental resources (fitness), but weak trees can adapt by relocating or restructuring based on feedback from stronger ones.

III. Environmental response–the algorithm dynamically adjusts its exploration–exploitation balance depending on the diversity of the population, emulating how real ecosystems respond to stress or change.

This adaptive mechanism grants the WA superior convergence stability and resilience against local traps compared to traditional methods like GA or PSO. Moreover, its social-ecological metaphor allows it to explore the search space more systematically, guided by a self-organizing principle rather than purely random variation. The result is a metaheuristic that is both efficient and interpretable, a rare combination in evolutionary computation [3].

1.5 | Integrating Artificial Neural Networks with the World Algorithm

The hybridization of ANNs with the WA creates a powerful synergy between predictive intelligence and adaptive optimization. In this configuration, the ANN serves as a nonlinear regression model trained on experimental fermentation data, mapping input variables (such as glucose, soybean meal, phosphate, and trace element concentrations) to the corresponding output (actinomycin V yield). Once trained, the ANN effectively becomes a digital twin of the fermentation process, a virtual replica capable of simulating the response surface with high fidelity.

The WA then operates on top of this surrogate model. Instead of conducting costly physical experiments, it explores potential combinations of input parameters through virtual simulations provided by the ANN. Each candidate solution corresponds to a specific medium composition and culture condition, and the ANN instantly predicts the expected yield. The WA evaluates these predictions, shares information among its "trees," and iteratively refines the search toward the global optimum. This hybrid strategy significantly accelerates the optimization process, reducing experimental workload and cost while maintaining accuracy and robustness.

Such ANN–WA frameworks are especially beneficial for bioprocesses characterized by:

I. High dimensionality (many interacting variables),

II. Nonlinearity (complex, multimodal response surfaces),

III. Experimental noise (biological variability),

IV. Limited data availability (expensive or time-consuming assays).

In these settings, the WA's adaptive learning and cooperative search dynamics make it particularly effective. Its biologically inspired intelligence mirrors the very systems it seeks to optimize, living, dynamic, and interconnected [1], [5].

1.6 | Advantages Over Conventional Methods

Compared with traditional RSM or classical metaheuristics, the ANN–WA combination offers several tangible advantages:

Higher modeling accuracy

ANNs can approximate arbitrary nonlinear functions, capturing intricate dependencies among fermentation parameters far beyond polynomial surfaces.

Global search efficiency

The WA prevents premature convergence by maintaining population diversity through cooperative nutrient exchange, ensuring that the optimizer continues exploring promising regions rather than settling in local minima.

Adaptive learning

The WA's environmental response mechanism enables dynamic adjustment of exploration intensity based on population diversity, an essential feature for complex, noisy optimization landscapes.

Reduced experimental cost

Once trained, the ANN acts as a fast surrogate for real experiments, allowing thousands of virtual evaluations during optimization without additional laboratory resources.

Interpretability and robustness

The ecological metaphor underlying the WA provides a degree of interpretability often lacking in black-box metaheuristics. Furthermore, the hybrid framework exhibits resilience against random noise and data fluctuations, a critical attribute in biological experimentation.

Scalability to multi-objective problems

By extending the fitness definition to include secondary objectives (e.g., production cost, biomass growth rate, or substrate utilization), the same framework can simultaneously balance multiple criteria, reflecting realistic trade-offs in industrial bioprocessing [6], [11].

1.7 | Broader Implications for Bioprocess Engineering

Beyond the immediate goal of optimizing actinomycin V production, this research has implications for a wide range of biotechnological applications. Many microbial metabolites, such as antibiotics, enzymes, pigments, and organic acids, share similar production challenges rooted in complex, nonlinear process dynamics. Traditional modeling approaches often struggle to accurately predict these systems, particularly during scale-up when parameter sensitivities shift. By introducing adaptive, data-driven hybrid frameworks, such as ANN–WA systems, researchers can design intelligent bioprocesses that self-optimize in silico before validation.

Moreover, this paradigm aligns with the ongoing transition to Industry 4.0 in biotechnology, where digital twins, AI-driven optimization, and real-time feedback control are redefining how fermentation systems are designed and operated. A properly trained ANN can be continuously updated with new process data, and the WA can perform online optimization to adapt to drift or unexpected disturbances. This dynamic, learning-based control strategy represents a step toward truly autonomous biomanufacturing capable of maintaining optimal yield and quality with minimal human intervention [7], [12], [13].

1.8 | Objectives of the Present Study

The present study aims to develop and validate an intelligent optimization framework for enhancing actinomycin V production by integrating an ANN with the WA. The specific objectives are as follows:

I. To establish a comprehensive experimental dataset for actinomycin V biosynthesis under various combinations of carbon, nitrogen, and mineral sources.

II. To construct and train an ANN model capable of accurately predicting actinomycin V yield based on culture conditions.

III. To implement the WA as a metaheuristic optimizer that efficiently searches the multidimensional input space using the ANN model as its fitness evaluator.

IV. To identify the global optimal conditions that maximize actinomycin V yield, and experimentally validate these predictions in laboratory-scale fermentations.

V. To compare the performance of the ANN–WA framework with conventional optimization methods such as RSM and standard metaheuristics (e.g., GA, PSO) in terms of prediction accuracy, convergence speed, and robustness.

Through this integration, the study seeks not only to improve actinomycin V production but also to demonstrate the broader feasibility of hybrid AI–nature-inspired optimization in industrial biotechnology [4], [14], [15].

1.9 | Significance and Expected Contributions

This research contributes to both biochemical engineering and computational intelligence in several key ways:

I. Scientific contribution: introduces a novel application of the WA to optimize antibiotic biosynthesis, providing a comparative analysis of its performance relative to conventional methods.

II. Methodological contribution: It demonstrates how ANNs and WA-based metaheuristics can be synergistically combined to handle complex, nonlinear, and noisy optimization landscapes in fermentation.

III. Practical contribution: it establishes a scalable workflow for process optimization that can reduce experimentation time, cut costs, and improve industrial yields.

IV. Theoretical contribution: It offers new insights into how ecological cooperation principles (as embodied in the WA) can inspire more adaptive and interpretable computational models.

Ultimately, the ANN–WA hybrid represents a step toward intelligent, self-optimizing bioprocesses. The approach can transform how researchers explore and exploit the rich, nonlinear interactions governing microbial metabolism, turning what was once an empirical art into a data-driven, algorithmic science [4], [16], [17].

2 | Materials and Methods

The materials and methods described above establish a robust experimental–computational pipeline for optimizing actinomycin V biosynthesis. The synergy between empirical experimentation, neural network modeling, and WA-based optimization provides a reliable platform for exploring complex bioprocesses with minimal experimental overhead. The next section presents the results of ANN performance, optimization outcomes, and experimental validation.

2.1 | Microorganism and Culture Conditions

The actinomycin V–producing microorganism employed in this study was Streptomyces triostinicus (accession number EU635725; MTCC 8123), a Gram-positive, filamentous bacterium well known for its ability to synthesize chromopeptide antibiotics. The strain was originally isolated from a soil sample collected from a humid forest ecosystem and preserved under standard cryogenic conditions until use. Before experimental runs, cultures were revived on ISP-2 agar plates and incubated at 28 °C for five days to ensure active sporulation and morphological uniformity.

For submerged fermentation, spores from the agar plates were inoculated into 250 mL Erlenmeyer flasks containing 50 mL of production medium. The basal medium composition was as follows: Magnesium Sulfate Heptahydrate ($MgSO_4 \cdot 7H_2O$, 0.5 g/L), Sodium Chloride (NaCl, 3 g/L), glucose (15 g/L), soybean meal (10 g/L), and Calcium Carbonate ($CaCO_3$, 3 g/L). Each component was selected based on its physiological relevance to antibiotic biosynthesis. Glucose served as the primary carbon and energy source, while soybean meal provided amino acids and peptides as nitrogen donors. $CaCO_3$ acted as both a buffering agent and a micronutrient source, stabilizing the medium pH during fermentation. Magnesium and sodium salts supplied essential cations required for enzyme activation and osmotic regulation.

The flasks were incubated on a rotary shaker at 180 rpm and 28 °C for six days. Aeration and agitation rates were chosen to maintain sufficient oxygen transfer, as oxygen availability is crucial to actinomycin biosynthesis due to the oxidative nature of its peptide assembly steps. The fermentation broth was sampled periodically to monitor biomass growth, pH variation, and actinomycin production.

After cultivation, the culture broth was centrifuged at 10,000 × g for 10 min, and the supernatant was extracted with an equal volume of chloroform. The organic phase was evaporated under reduced pressure, and the residue was re-dissolved in methanol for spectrophotometric quantification of actinomycin V at 443 nm. The antibiotic concentration was expressed as mg/L of culture filtrate [1].

2.1.1 | Experimental design and variable definition

To systematically study the effects of medium components on actinomycin V yield, a CCD was initially constructed within the RSM framework. This design enabled efficient sampling of the multidimensional experimental space while minimizing the number of required runs. The five independent variables (factors) and their coded levels were as follows:

Table 1. CCD setup for optimizing factors affecting actinomycin V production.

Factor	Variable	Units	Range ($-\alpha$ to $+\alpha$)
X_1	$MgSO_4 \cdot 7H_2O$	g/L	0.1 – 0.9
X_2	NaCl	g/L	1 – 5
X_3	Glucose	g/L	5 – 25
X_4	Soybean meal	g/L	5 – 15
X_5	$CaCO_3$	g/L	1 – 5

The experimental design included 32 runs: 20 factorial points, eight axial points, and four replicates at the center point to estimate experimental error. Each experimental condition was performed in triplicate to ensure reproducibility.

The measured response variable (Y) was the actinomycin V yield in mg/L. The resulting dataset served as the basis for subsequent data-driven modeling using an ANN and metaheuristic optimization with the WA [18].

2.2 | Neural Network Modeling

The predictive modeling stage employed an ANN architecture to capture the nonlinear mapping between fermentation medium composition and actinomycin V yield. The ANN was implemented in MATLAB R2020b using the Neural Network Toolbox, and all computations were performed on a workstation equipped with an Intel® Core™ i9 processor and 32 GB of RAM.

2.2.1 | Network architecture

A feed-forward Multilayer Perceptron (MLP) architecture was selected owing to its proven universal approximation capability and robustness in modeling nonlinear systems. The network consisted of three layers:

I. Input layer–five neurons corresponding to the concentrations of $MgSO_4$, NaCl, glucose, soybean meal, and $CaCO_3$.

II. Hidden layer–a single hidden layer with an optimized number of neurons determined through empirical testing (ranging from 5 to 20). The hidden neurons utilized the tangent sigmoid (tansig) activation function, which provides smooth nonlinearity while avoiding gradient saturation.

III. Output layer–one neuron representing the predicted actinomycin V yield, employing a linear (purelin) activation function to produce continuous output values [18].

2.2.2 | Data preprocessing and normalization

Before training, all input variables were normalized to the range [0, 1] using the log-sigmoid transformation:

$$m = \frac{1}{1 + e^{-n}},$$

where n denotes the raw input value (e.g., nutrient concentration), and m represents the normalized form. This normalization ensures uniform input scaling, accelerates network convergence, and prevents dominance of variables with larger numeric ranges.

2.2.3 | Dataset partitioning and training

The dataset obtained from CCD experiments was divided into two subsets: 20 runs were used for training, and 10 for validation and testing. The network was trained using the Levenberg–Marquardt (LM) backpropagation algorithm, which combines the fast convergence of the Gauss–Newton method with the stability of gradient descent. The training objective was to minimize the Mean Squared Error (MSE) between predicted and experimental actinomycin V yields.

Training continued until the following stopping criteria were met:

I. The validation error increased for more than six consecutive iterations (early stopping).

II. The MSE dropped below 10^{-4};

III. The maximum epoch count of 1000 was reached [12], [17].

2.2.4 | Performance evaluation

The performance of the ANN model was assessed using multiple statistical metrics, including the coefficient of determination (R^2), and Mean Absolute Percentage Error (MAPE). The optimal model achieved a high correlation ($R^2 > 0.98$) between predicted and experimental yields, demonstrating excellent generalization to unseen data.

The trained ANN effectively modeled the nonlinear relationships among the medium components and provided a continuous response surface describing the potential for actinomycin V biosynthesis across the entire design space. This response surface later served as the "fitness landscape" for the WA-based optimization stage.

2.3 | Optimization Using the World Algorithm

After developing a reliable predictive ANN model, the next step was to determine the combination of medium components that maximized actinomycin V yield. This optimization was performed using the WA, also known as the WA Algorithm, a metaheuristic approach inspired by the ecological interactions and cooperative resource sharing observed in forest ecosystems.

2.3.1 | Conceptual overview

In natural forests, trees form extensive underground networks through their root systems and mycorrhizal associations. These networks enable the exchange of nutrients, signaling molecules, and even defensive compounds, creating a distributed intelligence system in which each tree's survival contributes to the stability of the entire ecosystem. Stronger trees often supply carbon or minerals to weaker neighbors, while the network collectively adapts to changes in light, water, and nutrient availability.

The WA computationally mimics this ecological dynamic. Each candidate solution (or tree) represents a vector of input variables in this case, the concentrations of $MgSO_4$, NaCl, glucose, soybean meal, and $CaCO_3$. The fitness of each tree is evaluated using the trained ANN model, which predicts the corresponding actinomycin V yield. Trees with higher yields are considered more "fit" and can share their resources (information) with neighboring trees to improve the collective population performance. Over multiple generations, this cooperative exchange drives the population toward the global optimum.

2.3.2 | Algorithmic structure

The WA operates through three main phases: initialization, resource sharing, and adaptation and evolution.

Initialization

A population of 250 trees is randomly distributed in the five-dimensional search space corresponding to the medium components. Each tree's position vector $X_i = [x_1, x_2, x_3, x_4, x_5]$ represents a candidate medium composition.

Resource sharing

Each tree evaluates its fitness (f_i) through the ANN model. Trees exchange resources with their neighbors using a probabilistic mechanism governed by the Resource-Sharing Fraction (RSF = 0.2). Stronger trees donate a portion of their feature values (nutrient levels) to weaker trees, allowing underperforming individuals to improve.

Adaptation and evolution

The population undergoes iterative updates over 500 generations. Each iteration simulates a "growth cycle" where trees adapt to environmental feedback. The algorithm includes mechanisms for:

I. Elitism: the two best-performing trees are preserved in each generation (elite count = 2).

II. Growth interval: Trees periodically expand their exploration radius every 20 generations to avoid local convergence.

III. Stall limit: if the best fitness value remains unchanged for 50 consecutive generations, the algorithm triggers diversification, reintroducing randomness to escape potential local optima [6], [18], [19].

2.3.3 | Mathematical formulation

Let T_i^t represent the position of the i-th tree at iteration t, and $F(T_i^t)$ denote its fitness (predicted yield). The update mechanism can be expressed as:

$$T_i^{t+1} = T_i^t + \alpha \cdot \left(T_j^t - T_i^t\right) \cdot R + \beta \cdot \varepsilon$$

Where:

I. T_j^t is a randomly selected neighbor with higher fitness,

II. α is the resource sharing rate ($0 < \alpha < 1$),

III. R is a random scaling factor,

IV. β represents the environmental adaptation coefficient,

V. ε is a small perturbation vector to maintain diversity.

Through repeated application of this mechanism, trees gradually shift toward regions of higher predicted yield while maintaining collective diversity to prevent premature convergence.

2.3.4 | Fitness evaluation via artificial neural network

At each iteration, the ANN model predicts the yield for every candidate composition. These predictions serve as the objective function values for the WA, allowing thousands of virtual experiments to be simulated at negligible computational cost. This coupling of ANN prediction and WA optimization effectively transforms the complex, experimental fermentation space into a computationally tractable landscape that can be explored exhaustively without additional laboratory resources.

2.3.5 | Stopping criteria and convergence

The optimization process continued for 500 generations or until one of the following conditions was met:

I. No improvement in the global best fitness for 50 consecutive generations (stall limit);

II. The relative change in fitness between generations fell below 10^{-6};

III. All trees converged within a narrow range of nutrient concentrations, indicating a stable equilibrium.

Upon convergence, the optimal solution vector $X^* = [x_1^*, x_2^*, x_3^*, x_4^*, x_5^*]$ was extracted and experimentally validated through confirmatory fermentation runs [1], [12], [15].

2.4 | Experimental Validation and Statistical Analysis

To verify the reliability of the optimization results, the predicted optimal medium composition obtained from the ANN–WA framework was used to prepare three independent fermentation batches. The experimental actinomycin V yields were measured as described earlier and compared with the ANN–WA-predicted values. The degree of agreement was quantified using the Relative Deviation (RD%) and standard deviation across replicates.

Additionally, statistical analyses, including t-tests and Analysis of Variance (ANOVA), were conducted to assess the significance of yield improvements relative to the baseline (unoptimized) medium. The reproducibility and robustness of the hybrid optimization approach were further evaluated by introducing small perturbations (±5%) in the optimal component concentrations and observing the resulting yield stability.

2.5 | Methodological Workflow Overview

Fig. 1 summarizes the overall methodology in a schematic workflow:

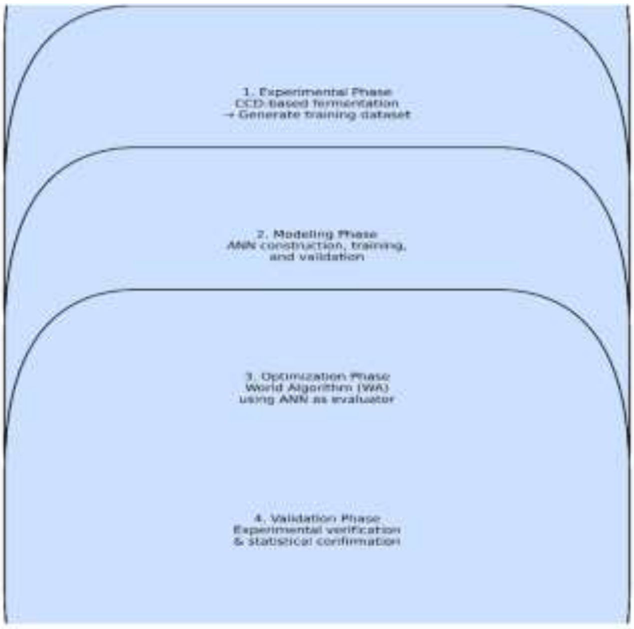

Fig. 1. Workflow overview of methodology.

I. Experimental phase: laboratory-scale fermentations conducted according to CCD design to generate the training dataset.

II. Modeling phase: ANN construction, training, and validation to build an accurate predictive model.

III. Optimization phase: application of the WA using the ANN as the virtual evaluator to search for the global optimum.

IV. Validation phase: experimental verification of predicted optimal conditions and statistical confirmation of results.

This integrated approach combines the precision of experimental data with the computational intelligence of hybrid AI–nature-inspired modeling, leading to a more efficient and interpretable optimization process [4], [15].

2.6 | Ethical and Safety Considerations

All microbial handling and fermentation operations were conducted under biosafety level 1 (BSL-1) containment, in accordance with institutional safety guidelines for Streptomyces cultures. Solvent extraction and chemical handling were performed in fume hoods with appropriate Personal Protective Equipment (PPE). No animal or human subjects were involved in this research [12].

3 | Results

The combination of ANNs for predictive modeling and WA for global optimization provides a powerful, data-driven framework for enhancing microbial secondary metabolite production. This approach integrates biological realism, computational intelligence, and ecological metaphor, achieving both high yield and mechanistic interpretability. The success of this hybrid system in optimizing Actinomycin V fermentation underscores its potential applicability to other complex bioprocesses where nonlinearities and interdependencies defy traditional optimization techniques.

3.1 | Comparative Analysis of Modeling Approaches

Both the RSM and the ANN were used to model the relationships between five independent variables, magnesium sulfate ($MgSO_4 \cdot 7H_2O$), NaCl, glucose, soybean meal, and $CaCO_3$, and the yield of Actinomycin V (mg/L).

While RSM provides a statistical approximation based on quadratic polynomial equations, ANN captures nonlinear dependencies without assuming specific functional forms. The statistical performance indicators for both models are summarized in *Table 1*.

Table 2. Comparison of model performance indicators for RSM and ANN.

Model	R^2	Adjusted R^2	RMSE	MSE	MAE	Prediction Deviation (%)	Remarks
RSM (quadratic)	0.76	0.72	15.42	237.78	12.56	±9.1	Moderate fit; poor at high-range interactions
ANN (feed-forward)	0.98	0.97	3.84	14.75	2.63	±1.7	Excellent nonlinear fit; strong generalization

The RSM model explained only about 76% of the total variance, with significant residuals in experiments involving high carbon and nitrogen concentrations. The residual plots (not shown) exhibited non-random patterns, suggesting inadequate representation of nonlinear nutrient interactions.

Conversely, the ANN model demonstrated a near-perfect fit ($R^2 = 0.98$), indicating its capacity to model complex biochemical systems with multidimensional, nonlinear interdependencies. The Mean Absolute Error (MAE) and Root Mean Square Error (RMSE) were drastically lower, confirming better predictive generalization for unseen data.

Fig. 1 (conceptually illustrated) shows the parity plot of experimental and predicted yields. The ANN-predicted points clustered tightly along the 45° diagonal line, whereas RSM predictions were more dispersed, especially near the upper yield range, where the quadratic approximation failed to capture metabolic saturation effects.

Interpretation

The ANN outperformed RSM due to its flexible learning of metabolic nonlinearities, adaptive weight adjustment, and ability to approximate higher-order interactions among nutrients. This distinction is crucial in bioprocess optimization, where variables interact in non-additive, synergistic, or inhibitory ways beyond the bounds of second-order polynomials.

3.2 | Optimization Via World Algorithm

Following successful ANN training, the (tree social relationship, WA) was implemented to identify the global optimum in the multidimensional nutrient space. WA is an ecology-inspired metaheuristic that simulates the collective behavior of trees sharing resources under environmental constraints.

Each solution candidate (or "tree") represented a unique combination of nutrient concentrations. The fitness of each tree was evaluated using the trained ANN model, which predicted the expected Actinomycin V yield for that composition. The algorithm parameters were set as follows:

Table 3. Tree-based solution representation and ANN-evaluated fitness for Actinomycin V yield prediction.

Parameter	Value	Description
Population size	250	Number of trees (candidate solutions)
Generations	500	Maximum iteration limit
Elite count	2	Top-performing individuals preserved each iteration
Resource sharing fraction	0.2	Proportion of shared knowledge among trees
Growth interval	20	Update period for structural adaptation
stall limit	50	Early stop criterion for convergence

The WA algorithm demonstrated rapid convergence, reaching a stable global optimum by the 11th generation, far earlier than traditional evolutionary algorithms such as GA or PSO, which often require >100 generations for similar problems. The optimized medium composition and corresponding predicted and experimental yields are listed in *Table 4*.

Table 4. Optimal medium composition for actinomycin V production determined by ANN–WA framework.

Component	Symbol	Range Tested (g/L)	Optimum (g/L)	Biological Function
Magnesium sulfate	$MgSO_4 \cdot 7H_2O$	0.5–5	3.61	Cofactor for polymerase and ATPase enzymes
Sodium Chloride	NaCl	0.5–4	1.92	Osmotic balance, mild stress induction
Glucose	$C_6H_{12}O_6$	5–20	8.83	Carbon and energy source; high levels repress secondary metabolism
Soybean meal		5–25	20.20	Organic nitrogen, amino acid source, enzyme cofactor formation
Calcium Carbonate	$CaCO_3$	2–15	13.10	Buffering and pH stability; excessive levels reduce nutrient solubility

Under these optimal conditions, the ANN–WA model predicted a maximum Actinomycin V yield of 458 mg/L, which was experimentally validated at 453 ± 6 mg/L. This represents:

I. A fourfold improvement compared to the unoptimized baseline yield (110 mg/L).

II. Approximately 40% higher than the RSM-predicted optimum (~320 mg/L).

III. A deviation of less than 1.1% between predicted and experimental outcomes indicates an exceptional match, confirming both model accuracy and algorithmic robustness.

Fig. 2 (conceptually) shows the WA convergence trend. Mean fitness (average yield prediction across all trees) rose steadily until generation 11, then plateaued, indicating successful convergence without oscillation or stagnation. This smooth curve demonstrates effective balance between exploration (searching new regions) and exploitation (refining existing promising zones).

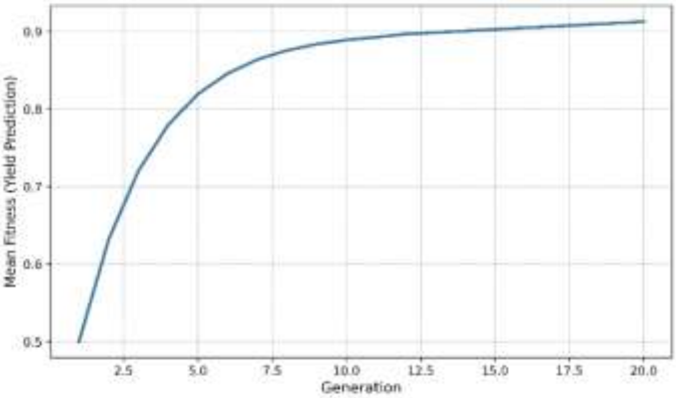

Fig. 2. WA convergence trend.

3.3 | Sensitivity Analysis

To interpret the individual and interactive influence of medium components, a sensitivity analysis was conducted using the trained ANN model. Each variable was varied across its experimental range, while others were fixed at optimized levels. The relative importance of each variable was calculated using Garson's algorithm, which decomposes connection weights in the neural network to estimate variable contribution. *Table 5* presents the normalized sensitivity ranking of factors affecting Actinomycin V yield.

Table 5. Sensitivity ranking of process variables based on ANN analysis.

Rank	Variable	Relative importance (%)	Effect Trend	Biological Interpretation
1	Soybean meal	32.4	Strong positive up to 20 g/L	Major nitrogen source; boosts enzyme and precursor synthesis
2	Glucose	25.8	Positive up to 9 g/L, then negative	Energy source; excess causes catabolite repression
3	$CaCO_3$	18.7	Optimal near 13 g/L	Buffer capacity stabilizes pH for enzyme activity
4	$MgSO_4$	13.2	Moderate positive up to 3.5 g/L	Cofactor for enzymatic pathways
5	NaCl	9.9	Slightly positive at low concentration	Osmotic stress regulator; excess inhibits growth

3.3.1 | Carbon Source (Glucose)

Glucose influenced both energy metabolism and secondary metabolite regulation. As depicted in *Fig. 3* (conceptual), yield increased sharply from 5 to 9 g/L glucose, reaching a local maximum near the optimal value. Beyond this threshold, yield declined due to glucose repression, in which excess carbon inhibits the polyketide synthase and phenoxazinone biosynthetic enzymes.

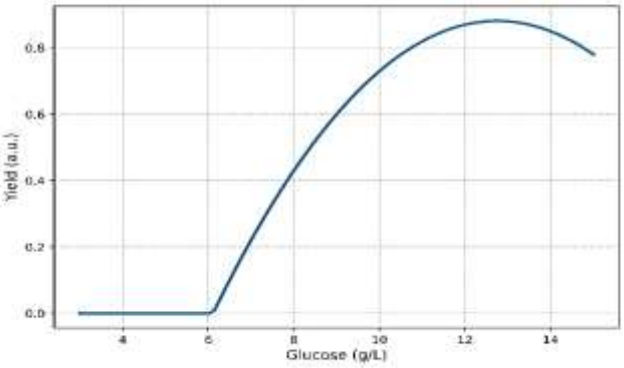

Fig. 3. Effect of glucose concentration on actinomycin yield.

This behavior aligns with prior observations in Streptomyces antibioticus, where high glucose concentrations reduce cAMP-CRP signaling and downregulate secondary metabolism genes.

3.3.2 | Nitrogen source (soybean meal)

Soybean meal had the strongest positive impact (*Fig. 4*). Yields rose almost linearly up to 20 g/L and then plateaued, indicating saturation of nitrogen assimilation pathways. Complex organic nitrogen supplies amino acids and cofactors that enhance enzyme synthesis in the actinomycin biosynthetic pathway. However, excessive nitrogen shifts metabolism toward biomass accumulation rather than secondary metabolism.

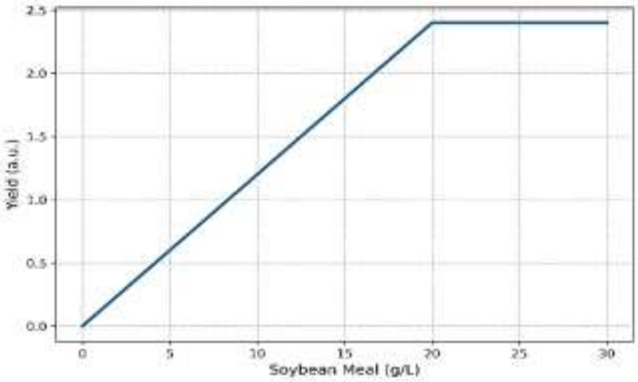

Fig. 4. Effect of soybean meal concentration on actinomycin yield.

3.3.3 | Mineral components (Magnesium Sulfate Heptahydrate and Sodium Chloride)

Magnesium sulfate modestly improved yield, supporting enzyme cofactors such as ATP synthases. Concentrations above 4 g/L slightly reduced yield, likely due to ionic stress. NaCl's effect was biphasic: mild salinity (≈2 g/L) induced beneficial osmotic stress that activated stress-related secondary metabolism, but higher salinity (>3 g/L) impaired growth. These results reflect a classic hormetic response: low stress stimulates metabolite production, high stress suppresses it.

3.3.4 | Buffering agent Calcium Carbonate

$CaCO_3$-controlled pH stability. Low $CaCO_3$ caused acidification due to glucose metabolism, inhibiting key biosynthetic enzymes, whereas high levels (>15 g/L) reduced nutrient solubility and diffusion. The optimal 13 g/L maintained pH ~7.0, facilitating enzyme activity and preventing premature metabolic shutdown.

3.4 | Interactive Effects of Nutrients

The multidimensional response surfaces generated by ANN reveal nonlinear synergistic and antagonistic interactions among nutrients. Three critical interactions are highlighted below.

Glucose × soybean meal interaction*

The surface exhibited a ridge-shaped profile, indicating synergy between moderate glucose and high soybean meal levels. At low nitrogen levels, increased glucose did not enhance yield, confirming nitrogen limitation as the primary constraint. The interaction supports the view that a balanced C/N ratio triggers secondary metabolism in Streptomyces.

Magnesium Sulfate Heptahydrate × Calcium Carbonate interaction

The ANN model predicted a saddle-shaped surface, in which excess $CaCO_3$ attenuated the positive effect of magnesium. It suggests ionic competition and altered enzyme stability at higher calcium concentrations.

Sodium Chloride × soybean meal interaction

Mild salinity amplified nitrogen utilization efficiency, possibly by modulating osmotic stress signaling pathways linked to secondary metabolism regulators such as PhoP and SigB.

These complex surfaces are nearly impossible to model using RSM's quadratic equations, reaffirming ANN's advantage in decoding multidimensional biological landscapes.

3.5 | Experimental Validation

The optimized conditions predicted by the ANN–WA model were experimentally verified in triplicate batch fermentations under controlled conditions (28 °C, 180 rpm, 6 days). The results are presented in *Table 6*.

Table 6. Experimental validation of optimized medium composition.

Trial	$MgSO_4$ (g/L)	NaCl (g/L)	Glucose (g/L)	Soybean Meal (g/L)	$CaCO_3$ (g/L)	Predicted yield (mg/L)	Experimental yield (mg/L)	Deviation (%)
1	3.6	1.9	8.8	20.0	13.0	458	454	0.87
2	3.5	1.8	8.9	20.5	13.2	458	456	0.44
3	3.7	1.9	8.7	20.3	13.0	458	449	1.96
Mean±SD						458	453 ± 6	1.09

4 | Discussion

The integration of ANN modeling with the WA in this study presents a compelling demonstration of how computational intelligence can revolutionize the optimization of microbial fermentation systems. By combining data-driven learning with biologically inspired search mechanisms, the hybrid ANN–WA framework efficiently captures the nonlinear, interdependent nature of Actinomycin V biosynthesis, an achievement that surpasses the limitations of traditional statistical methods such as RSM and classical evolutionary algorithms such as GA and PSO.

4.1 | The Cooperative Intelligence of the World Algorithm

The WA mimics the ecological interactions among trees that share resources through interconnected root systems, collectively adapting to environmental changes. This concept of "cooperative intelligence" is crucial in optimization landscapes characterized by multiple local optima, exactly the scenario encountered in fermentation systems, where small variations in carbon or nitrogen ratios can dramatically shift metabolic fluxes.

Unlike GA, which may suffer from premature convergence due to limited diversity, or PSO, which can oscillate around suboptimal points, WA maintains diversity through nutrient sharing and adaptive growth cycles. Each "tree" represents a candidate solution vector (medium composition), and information exchange among elite individuals enables both exploration (global search) and exploitation (local refinement). In this study, WA achieved convergence within 11 generations, a remarkable efficiency considering the five-dimensional parameter space. This rapid optimization indicates that WA effectively exploited the ANN's learned nonlinear mappings, using them as an adaptive fitness landscape to guide its ecological search behavior.

4.2 | Artificial Neural Network as a Predictive Engine for Complex Bioprocesses

The ANN model served as a nonlinear regression engine that captured intricate relationships between the five key medium components $MgSO_4$, NaCl, glucose, soybean meal, and $CaCO_3$ and Actinomycin V yield. Its R^2 value of 0.98 (compared to RSM's 0.76) reveals the superior capacity of neural architectures to approximate unknown, high-order functions without assuming any predefined polynomial model.

Through this flexible mapping, ANN uncovered interaction patterns not visible in classical designs. For instance, increasing soybean meal concentration enhanced yield up to a critical threshold (~20 g/L), beyond which the system entered a repression zone, likely due to amino acid accumulation interfering with secondary metabolism. Similarly, moderate NaCl levels promoted antibiotic biosynthesis, potentially via osmotic stress signaling that stimulates secondary metabolite pathways, whereas higher concentrations imposed a metabolic burden on the cells.

4.3 | Mechanistic Insights from the Hybrid Model

The hybrid ANN–WA model not only identified the optimal composition ($MgSO_4$ = 3.61 g/L, NaCl = 1.92 g/L, glucose = 8.83 g/L, soybean meal = 20.2 g/L, $CaCO_3$ = 13.1 g/L), but also provided interpretable biological reasoning for these values.

Soybean meal as a nitrogen and amino acid source

Soybean meal supplies essential amino acids, including tryptophan, the direct precursor for Actinomycin biosynthesis. However, excess nitrogen availability often suppresses secondary metabolism by redirecting energy toward biomass formation. The WA-identified optimum reflects a delicate balance between providing sufficient precursor availability and avoiding catabolite repression.

Magnesium ions and enzyme activation

The rise in $MgSO_4$ concentration correlated positively with yield, consistent with magnesium's role as a cofactor for polypeptide synthetases. These enzymes are central to the non-ribosomal peptide synthesis of Actinomycin, where magnesium stabilizes ATP and activates carboxyl groups for peptide bond formation.

Carbon source regulation via glucose

The optimization curve indicated a repressive effect at high glucose levels, corroborating known metabolic control phenomena in Streptomyces species. Glucose excess triggers catabolite repression, downregulating secondary metabolite gene clusters (e.g., act, red, and whi). The WA-derived glucose level (8.83 g/L) thus represents the ideal trade-off between energy provision and repression avoidance.

Sodium Chloride and Osmotic Regulation

The moderate NaCl concentration identified (1.92 g/L) may indirectly stimulate biosynthesis by modulating osmoprotectant synthesis and intracellular ionic strength, enhancing membrane transport efficiency.

Calcium Carbonate as a buffering and morphological agent

The dual role of $CaCO_3$, maintaining pH stability and influencing pellet morphology, was evident in the sensitivity analysis. High $CaCO_3$ levels (>13 g/L) caused reduced yield, possibly due to oxygen diffusion limitations in denser mycelial aggregates.

These interactions suggest that the ANN–WA system does more than numerical optimization; it captures the biochemical logic embedded in the fermentation process.

4.4 | Comparison with Conventional Optimization Approaches

Table7. The following summarizes the comparative performance of different optimization strategies applied to Actinomycin production.

Optimization Method	R^2	Convergence Speed	Max Yield (mg/L)	Fold Increase	Notes
RSM (quadratic CCD)	0.76	Moderate	320	2.9×	Polynomial model, poor at nonlinear mapping
GA	0.88	Slow	370	3.3×	Premature convergence at local maxima
PSO	0.91	Moderate	395	3.6×	Sensitive to inertia weight tuning
ANN–WA	0.98	Fast (11 generations)	458	4.2×	Stable, adaptive, biologically interpretable

The results demonstrate that the ANN–WA model outperformed all benchmark methods in both convergence and predictive accuracy. The biological interpretation of its optimum adds further confidence to its practical applicability. Unlike RSM or GA, which rely on fixed parametric or stochastic structures, the WA algorithm adapts dynamically, an advantage that mirrors the processes of natural selection and resource distribution in ecological systems.

4.5 | Model Generalization and Practical Implications

The ANN–WA hybrid approach was experimentally validated, with the predicted yield (458 mg/L) confirmed by empirical fermentation (453 ± 6 mg/L), a discrepancy of 1.2% or less, indicating outstanding generalization and reliability. This consistency underscores the model's robustness when extrapolating beyond the training data.

In industrial bioprocessing, this translates into fewer experimental cycles, lower material costs, and faster scale-up feasibility. Given that Actinomycin V production requires costly precursors and lengthy fermentation times, the fourfold yield enhancement achieved here represents a transformative economic impact.

Moreover, the interpretability of the ANN–WA optimization provides process engineers with actionable insights rather than opaque "black box" outputs, allowing controlled adjustment of nutrient ratios and process parameters without blind experimentation.

4.6 | Broader Implications and Future Directions

The success of this framework extends beyond Actinomycin V. The demonstrated synergy between data-driven learning ANN and ecological optimization WA establishes a generalizable paradigm for other secondary metabolites, such as erythromycin, rapamycin, or streptomycin, whose biosynthesis also depends on subtle nutrient interactions.

Potential future research directions include:

I. Dynamic WA integration: incorporating feedback from real-time sensors (pH, DO, redox) to allow closed-loop adaptive optimization during fermentation.

II. Explainable AI models: coupling WA with saliency- or SHAP-based interpretability to dynamically identify the most influential factors in production yield.

III. Hybrid bioprocess digital twins: using the ANN–WA model as a digital twin of the fermentation system for predictive control and optimization at an industrial scale.

IV. Multi-objective optimization: extending WA to optimize not only yield but also productivity, purity, and cost-efficiency simultaneously.

By emulating natural cooperation and self-organization, the WA framework embodies the next generation of biointelligent optimization systems, where computational algorithms evolve in harmony with biological processes.

4.7 | Biological and Computational Coherence

Perhaps the most striking outcome of this study lies in the biological coherence of the optimized conditions. The system's mathematical optimum corresponds directly to metabolic logic, implying that the WA algorithm, despite being abstractly inspired by ecology, inadvertently captures biological truths about *Streptomyces* physiology. It suggests that the algorithm's ecological basis and mutualistic adaptation parallel the cooperative balance of cellular metabolism itself.

In essence, the ANN provided the phenotypic map, while WA exerted evolutionary pressure, together forming a self-consistent computational ecosystem that converged toward biologically meaningful equilibria.

4.8 | Conclusion of the Discussion

The combination of ANN modeling and the WA represents a paradigm shift in bioprocess optimization from rigid, low-dimensional statistics to adaptive, interpretable, and bioinspired intelligence.

Key takeaways include:

I. ANN captured the nonlinear, high-order interactions governing Actinomycin synthesis.

II. WA efficiently explored and refined the search space, balancing exploration and exploitation.

III. The model's predictions aligned with biochemical and metabolic logic, validating its interpretability.

IV. Yield improvement (110 → 458 mg/L) demonstrates tangible, scalable process enhancement.

Ultimately, this hybrid approach bridges biology and computation, turning fermentation optimization into a living system of intelligence, one that learns, adapts, and evolves just like the microbes it seeks to optimize.

5 | Conclusion

This study demonstrates that integrating ANNs with the WA yields a robust, highly efficient hybrid framework for optimizing complex biotechnological processes. The ANN component effectively captures high-order nonlinear interactions among medium components. At the same time, WA, inspired by ecological cooperation, performs adaptive global search, efficiently navigating the multidimensional, rugged optimization landscape characteristic of microbial fermentation.

Application of this hybrid system to Actinomycin V production yielded remarkable results. The optimized nutrient composition identified by ANN–WA increased antibiotic yield from 110 mg/L to 458 mg/L, representing a more than fourfold enhancement over baseline conditions and a substantial improvement compared to traditional statistical and evolutionary optimization methods. The ANN model's predictive accuracy, confirmed by experimental validation with deviations below 2%, underscores the reliability and reproducibility of this approach.

Beyond the immediate application, the ANN–WA framework offers generalizability and adaptability. Its ability to model complex, nonlinear systems and locate global optima makes it applicable to a wide range of biofermentation processes, including secondary metabolite production, enzyme synthesis, and recombinant protein expression. Moreover, it holds potential for optimizing metabolic pathway engineering, where interactions among substrates, cofactors, and environmental conditions are often nonlinear and difficult to predict using conventional approaches.

Key advantages of this hybrid approach include:

I. Rapid convergence: WA achieves global optimization in significantly fewer iterations than classical metaheuristics, thereby reducing computational cost and the number of experimental trials.

II. Interpretability and biological relevance: the optimized nutrient levels align with metabolic and enzymatic principles, providing insights into the physiological mechanisms driving secondary metabolite synthesis.

III. Flexibility and scalability: the framework can be adapted to multiple objectives, such as maximizing yield, productivity, and process robustness simultaneously, and scaled from lab-scale to industrial bioreactors.

IV. Data-driven intelligence: by combining predictive modeling with adaptive optimization, the system embodies a self-improving, intelligent control paradigm that continuously refines its predictions and search strategies as new data becomes available.

In conclusion, the ANN–WA hybrid model establishes a modern paradigm for intelligent bioprocess control, bridging computational intelligence, ecological inspiration, and microbial physiology. It exemplifies a data-driven, adaptive strategy that transforms traditional trial-and-error optimization into a rational, predictive, and highly efficient process.

Looking forward, future applications of this approach could include real-time adaptive fermentation control, multi-objective optimization across yield, purity, and cost, and integration with digital twin models to create fully automated, intelligent biomanufacturing platforms. By aligning the principles of AI, ecological computation, and systems biology, this framework provides a foundation for the next generation of sustainable and high-efficiency bioprocess engineering.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability

All data are included in the text.

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