Metaheuristic Algorithms with Applications

www.maa.reapress.com

Metaheur. Algor. Appl. Vol. 1, No. 1 (2024) 1–11.

Paper Type: Original Article

A Novel Metaheuristic Approach Inspired by Trees Social Relationships and Models for Fermentation Medium

Marzieh Lamtar Gholipoor[1,*], Mahmoud Alimoradi[2,4], Soheil Fakheri[3,4]

[1] Department of Chemical Engineering, Quchan Branch, Islamic Azad University, Quchan, Iran; marzieh.gholipoor@gmail.com.
[2] Department of Computer Engineering, Shafagh Institute of Higher Education, Tonekabon, Iran; mahmoud.alimoradi@shafagh.ac.ir.
[3] Department of Computer Engineering, Ayandegan Institute of Higher Education, Tonekabon, Iran; fakherisoheil@iau.ac.ir.
[4] Department of Computer Engineering and Information Technology, Lahijan Branch, Islamic Azad University, Lahijan, Iran.

Citation:

Received: 16 Aprli 2024 *Revised: 10 June 2024* *Accepted:17 July 2024*	Lamtar Gholipoor, M., Alimoradi, M., & Fakheri, S. (2024). A novel metaheuristic approach inspired by trees' social relationships and models for fermentation medium. *Metaheuristic Algorithms with Applications, 1* (1), 1-11.

Abstract

The Trees Social Relationships (TSR) metaheuristic algorithm is employed to model and optimise a fermentation medium for producing the enzyme hydantoinase by Agrobacterium radiobacter. Leveraging experimental data from the literature, we developed two neural network models. The neural network models utilised the concentrations of four medium components as inputs and provided either hydantoinase or cell concentration as a single output. The TSR algorithm was then applied to optimise the input space of the neural network models, identifying the optimal settings for maximising enzyme and cell production. This approach showcases the effective integration of neural networks with the TSR algorithm, resulting in a robust process modeling and optimisation tool.

Keywords: Trees social relationship algorithm, Neural network modeling, Fermentation process optimization, Empirical model building, Hybrid optimization approach.

1 | Introduction

Numerous factors, such as pH, temperature, ionic strength, and the concentrations of various medium components, influence the efficacy of fermentation processes. The intricate interactions among these factors often result in complex effects, necessitating detailed experimentation for accurate characterisation. Traditionally, statistical techniques like Response Surface Methodology (RSM) have been employed to manage

Corresponding Author: marzieh.gholipoor@gmail.com

these interactions, minimising the number of exhaustive experiments required. RSM aims to identify and optimise critical factors to determine the conditions that maximise the response, product yield or productivity. Through statistical experimental designs, RSM develops empirical models that relate a dependent variable (response) to independent variables (factors) [1]. The efficacy of RSM, encompassing a suite of statistical and regression techniques, is well-documented.

In recent years, a growing interest has been in leveraging non-statistical techniques, particularly Artificial Intelligence (AI), for optimising fermentation processes. Among the various AI techniques, Trees Social Relationships (TSRs) algorithms have gained significant attention as robust stochastic search and optimisation methods [2], [3]. Unlike statistical designs and empirical models, TSR algorithms can optimise fermentation conditions independently. This approach has been successfully applied to optimise the production of polyols, xylitols, and culture mediums for fed-batch insect cell cultures. Despite their effectiveness, TSR algorithms do not retain the generated information throughout the optimisation stages. In contrast, RSM provides empirical models that mathematically describe the relationships between process variables, which can be used both for optimisation and for analysing the sensitivity of the model output to each input variable. Typically, quadratic polynomials are the preferred approximating functions in RSM model building [2]-[4].

From a process modeling perspective, neural networks offer a mathematical alternative to quadratic polynomials for representing data from statistically designed experiments. Neural networks are universal function approximators capable of approximating functions to any desired degree of accuracy. This capacity makes them attractive as empirical models in response surface analysis. Optimising the input space of a neural network model can be effectively achieved using the TSR metaheuristic algorithm. A distinct advantage of the TSR algorithm is its independence from the continuity or differentiability of the objective function [5]. Recent studies have explored using neural networks and metaheuristic algorithms to model and optimise gluconic acid production from glucose. However, comparisons with RSM were absent due to the non-statistical design of the experiments. It has been demonstrated that neural networks can outperform quadratic polynomials in modeling fermentation processes, yet the networks were not utilised in the optimisation phase [6].

With the increasing consumption of fossil fuels and related environmental issues, there is an urgent need to find biological substitutes for traditional petrochemical products through green biological manufacturing. Over the decades, microorganisms have been used as 'mini-factories' in biomanufacturing to leverage their diverse metabolic pathways and ability to transform a wide range of renewable raw materials into value-added compounds through fermentation. However, the use of wild-type microorganisms in industrial production is usually hindered by factors such as substrate and product toxicity [7]. Modern biotechnologies, such as genetic engineering and synthetic biology, enable the engineering of more powerful mini-factories. Successful examples include Escherichia coli, producing insulin and carotene, Saccharomyces cerevisiae, producing geraniol; Yarrowia lipolytica, producing N-acetylneuraminic acid and Bacillus subtilis, producing hyaluronic acid.

Nonetheless, the construction of mini-factories is not the ultimate goal of biomanufacturing; instead, biological fermentation and industrial production are the end goals, which present significant challenges. Engineered strains may not perform optimally in actual fermentation processes due to the lack of suitable fermentation strategies. Therefore, optimising fermentation parameters, such as medium composition and extracellular conditions, is crucial for efficiently operating these mini-factories, which is essential for fermentation [8], [9].

In practice, mathematical modeling provides rich insights that can assist in optimising fermentation processes. As approximations of reality, mathematical models can clearly represent fermentation processes, whose intrinsic complexity exceeds intuitive understanding, thus offering indispensable insight into designing, controlling, and optimising the process, as well as minimising unnecessary experimentation. However, modeling the fermentation process is challenging because each cell in the bioreactor can be viewed as a subsystem of metabolic and signaling networks. For fermentation problems, three modeling approaches are

generally used: mechanistic modeling, data-driven modeling, and hybrid modeling. Mechanistic modeling derives models from prior knowledge using notable and acknowledged equations, extracting valuable information from raw data and providing insight into underlying mechanisms. Kinetics and Constraint-Based Modeling (CBM) are the primary mechanical approaches for analysing microbial growth and metabolism.

In contrast, data-driven approaches obtain models by analysing and fitting existing data, known as black-box models, which cannot provide information about basic mechanisms without considering internal structures and phenomena [10], [11]. Machine Learning (ML) is a commonly used data-driven approach. With the advancement of omics technology and various analytical techniques, the datasets available for fermentation process modeling are rapidly growing. ML is increasingly used to interpret large-scale datasets for deeper analysis and optimisation. As a result, hybrid modeling has emerged, integrating mechanical and data-driven approaches. Recent comprehensive reviews indicate hybrid models hold promising prospects for the field [12], [13].

In addition to the complexity of microbial metabolic behavior, fermentation systems possess complex hierarchical structures comprising microorganisms and their fermentation environment, influenced by upstream and downstream operating conditions. During industrialisation, the expansion of bioreactor volumes and changes in shape alter the fermentation environment, leading to the failure of laboratory-developed fermentation strategies. Thus, as biological fermentation transitions from laboratory to industrial production, it is crucial to incorporate environmental changes in fermentation into biological models to elucidate the effects of mixing and hydrodynamics. This goal can be achieved by coupling biological models with Computational Fluid Dynamics (CFD) models [14].

This paper overviews different mathematical modeling methods and their applications in biological fermentation processes. We first introduce the primary forms of mechanistic models that describe microbial metabolism using kinetic and CBM modeling methods and their applications in biological fermentation processes. Next, we discuss approaches to building data-driven ML models and the synergistic effects of combining CBM and ML [9], [15]. Finally, we highlight the coupling of biological models with CFD models, facilitating the formation of model-based integrated tools for predicting bioreactor scale-up and culture behavior during model-assisted bioreactor operation design.

In this study, we explore the application of neural networks combined with the TSR algorithm to achieve objectives akin to RSMs. We present a comparative analysis of this hybrid approach against the standard RSM approach, focusing on their effectiveness in predicting optimal conditions for a fermentation process [16].

2|Trees Social Relationships Algorithm

The TSR algorithm methodology is designed to leverage the social dynamics observed in tree communities to solve complex optimisation problems. Inspired by trees' interdependent and cooperative behaviors, TSR models the sharing of resources and information in a simulated environment. This novel approach integrates elements of competition and cooperation, which are crucial for the adaptation and survival of tree species in natural ecosystems [2]. The TSR algorithm begins with an initialisation phase where a population of trees is generated. Each tree represents a potential solution to the optimisation problem and is characterised by its position in the solution space. The fitness of each tree is evaluated based on the objective function of the problem, determining the quality of the solution it represents [2], [5]. In the subsequent phases, the algorithm simulates the interactions among trees, including resource sharing, competitive exclusion, and cooperative enhancement. These interactions are inspired by the natural behaviors of trees, such as root communication, canopy competition, and symbiotic relationships with other organisms.

2.1|Resource Sharing

Trees in a forest share resources through their root systems, facilitating mutual growth and survival. In TSR, this is modeled by allowing trees to exchange information about their positions and fitness values. Trees with

higher fitness values share their advantageous traits with neighboring trees, promoting the spread of beneficial characteristics throughout the population.

2.2 | Competitive Exclusion

In natural ecosystems, trees compete for sunlight, water, and nutrients. This competition drives the selection of the fittest individuals. Similarly, trees with lower fitness values are gradually excluded from the population in TSR, ensuring that only the most promising solutions are retained. This selective pressure helps to converge the population towards optimal solutions.

2.3 | Cooperative Enhancement

Trees often form symbiotic relationships with other organisms, such as mycorrhizal fungi, to enhance their growth and resilience. TSR incorporates this concept by allowing trees to form temporary alliances and pooling their resources and information to explore new regions of the solution space more effectively. This cooperative behavior increases the diversity of solutions and prevents premature convergence [2], [6].

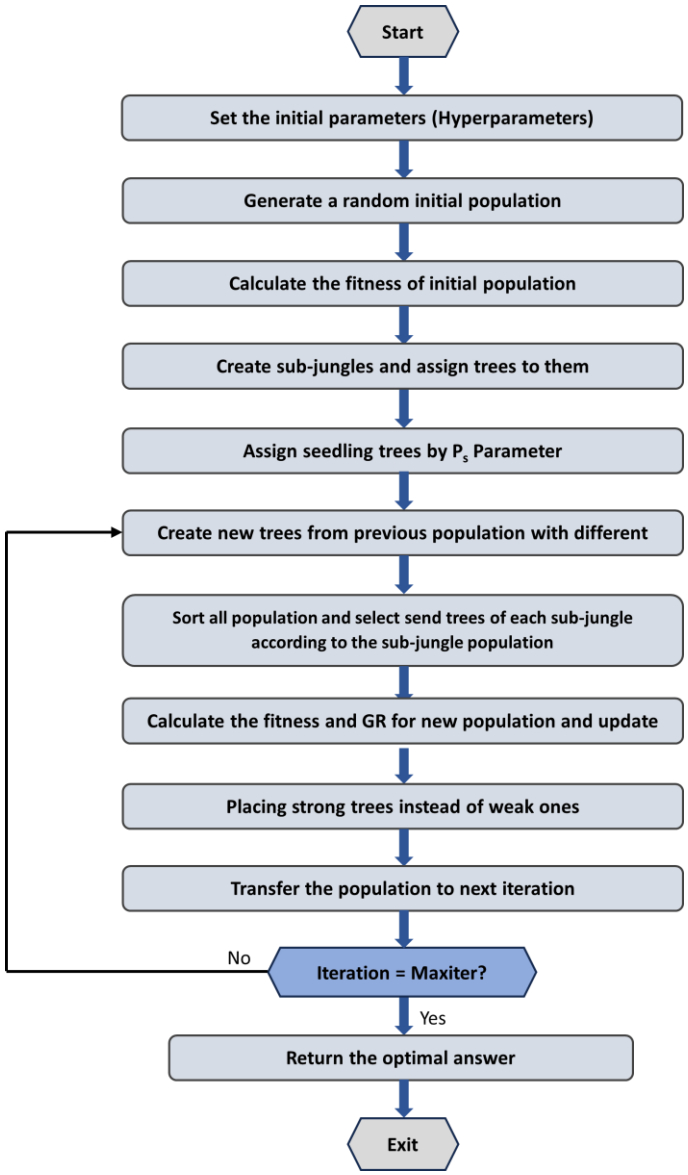

Fig. 1. Flowchart of the TSR.

The algorithm iterates through these phases, continuously updating the population of trees based on their interactions. The balance between competition and cooperation is carefully maintained to ensure a thorough exploration of the solution space while gradually refining the population towards optimal solutions. The TSR

algorithm also includes mechanisms to handle various constraints and complexities typical of real-world optimisation problems. For example, it can incorporate boundary conditions, handle discrete and continuous variables, and adapt to dynamic changes in the problem environment. Throughout its execution, the TSR algorithm employs a feedback mechanism to monitor its performance and adjust its parameters dynamically. This self-adaptive feature enhances the algorithm's robustness and efficiency, making it suitable for a wide range of optimisation tasks. In conclusion, the TSR algorithm offers a unique and biologically inspired approach to optimisation. By mimicking trees' social interactions and adaptive behaviors, TSR provides a powerful and flexible tool for solving complex optimisation problems. Its ability to balance exploration and exploitation, along with its adaptability to diverse problem settings, underscores its potential as a valuable addition to the field of metaheuristic algorithms [2], [6]. The flowchart of the TSR method is shown in *Fig. 1*.

3|Optimising Enzyme Production with RSM and Quadratic Regression

RSM integrates statistical experimental designs with empirical model construction through regression to optimise processes or products efficiently. It enables comprehensive insights about a process from a limited number of experiments, thereby minimising costs. An empirical model, typically a quadratic polynomial, is employed to establish relationships between process responses and independent variables:

$$y = b_0 + \sum b_i x_i + \sum b_i x_i^2 + \sum b_{ij} x_i x_j + e. \quad (1)$$

Here, y denote the predicted response or outcome variable, x represents independent variablesx represents independent variables, b0, bi, bij are Regression coefficients, b0 represents the intercept or constant term and e stands for the random error component, accounting for the variability not explained by the model.

∑bixi. The sum of the linear terms where bibi are the coefficients for the independent variables xi.

∑bixi2. The sum of the squared terms where bi are the coefficients for the squared independent variables xi2.

∑bijxixj. The sum of the interaction terms where bij are the coefficients for the interaction between pairs of independent variables xi and xj [14], [16].

To pinpoint near-optimal points, practitioners typically calculate derivatives of the polynomial Equation or visualise the model's response using contour plots. Various commercial software packages facilitate the application of such quadratic models for optimising processes.

For instance, researchers applied this approach to optimise the production of hydantoinase by Agrobacterium radiobacter using a central composite design. They varied concentrations of four medium components (x1, x2, x3, and x4) within defined ranges. The experimental design levels and concentration ranges of the four independent variables are listed in *Table 1*. The resulting regression equations (see *Table 2*) successfully correlated with the enzyme and biomass concentrations (y1 and y2). The goodness of fit, as assessed by the coefficient of determination (R2), indicated a robust correlation between observed and predicted values [8], [15].

Contour plots derived from these regression equations revealed local optima within the experimental domain, identifying conditions optimal for maximising enzyme or biomass production. This methodology effectively identified specific combinations of the independent variables that led to maximum enzyme and biomass concentrations, further validated by alternative optimisation strategies such as neural network-TSR algorithm approaches (see *Table 3*).

This methodological approach underscores RSM's capability to systematically optimise processes by leveraging empirical modeling and statistical insights from experimental data [17].

Table 1. Independent variables used for the experimental step.

Variables (gl^{-1})				
Coded level	$Molasses(x1)$	$NH_4NHO_3(x2)$	$NaH_2PO_4(x3)$	$MnCl_2(x4)$
-2	7.5	0.75	7.5	0
-1	10	1	10	0.025
0	12.5	1.25	12.5	0.05
1	15	1.5	15	0.075
2	17.5	1.75	17.5	0.1

4 | Neural Network-TSR Approach

A neural network is a computational model that emulates the brain's neural architecture and learning processes. It captures the brain's learning ability by representing interconnected neurons and their synaptic weights. Neural networks function through a data-driven methodology, requiring substantial datasets for effective modeling. They consist of layers of interconnected processing units called neurons, structured in an input layer, one or more hidden layers, and an output layer [2], [14].

In a neural network, neurons in the hidden layers are crucial as they facilitate the network's ability to learn complex relationships between inputs and outputs by adjusting synaptic weights. The inputs to each neuron in the hidden and output layers are aggregated and transformed via an activation function, commonly the sigmoid function. Training the network involves determining these adjustable weights through an iterative process, often using the backpropagation algorithm. This algorithm minimises the error between the network's predictions and actual outputs by iteratively adjusting weights to reduce discrepancies. The process continues until the error satisfies a predetermined threshold, effectively fitting a multi-dimensional curve to the data [14].

For our study, two neural network models were developed to simulate fermentation. Each model comprised a single output neuron (for hydantoinase or biomass concentration) and four input neurons representing the concentrations of four medium components.

Optimising neural network models with conventional techniques, such as gradient-based methods, is challenging due to the difficulty of computing model derivatives. The TSR metaheuristic algorithm provides a novel and efficient alternative. Inspired by the social interactions and relationships among trees in a forest, TSR utilises these natural strategies to navigate the solution space effectively.

The TSR algorithm begins by initialising a population of potential solutions analogous to a forest of trees. Each solution, or tree, is evaluated for its fitness using an objective function - in this case, the neural network models. TSR mimics tree behaviors such as seed dispersion, growth, and competition to explore the solution space. The algorithm identifies promising regions through these interactions and refines the search for optimal solutions. This process continues iteratively, balancing exploration and exploitation until an optimal or near-optimal solution is found [2], [14].

The neural network models and TSR algorithm utilised in this study were implemented in MATLAB and executed within a Microsoft Windows environment. This combination leverages the strengths of neural networks in modeling complex data relationships and the optimisation power of the TSR algorithm to enhance the performance and accuracy of fermentation process simulations [2], [12].

Table 2. Regression equations for dependent variables.

Dependent variables	Best fitness	R^2
Hydantoinase (Uml^{-1})	$y_1 = 34.58 + 1.139x_1 - 0.409x_2 + 1.126x_3 + 1.825x_4 - 2.962x_1^2 - 1.328x_2^2 - 2.356x_3^2 - 2.308x_4^2 + 1.092x_1x_2 - 0.365x_1x_3 - 0.739x_1x_4 + 0.552x_2x_3 - 2.033x_2x_4 - 1.655x_3x_4$.	0.799

Biomass ($\mathrm{mg\ ml^{-1}}$)	$y_2 = 1.69 + 0.02x_1 - 0.48x_2 - 0.055x_3 - 0.045x_4 - 0.144x_1^2 - 0.102x_2^2 - 0.11x_3^2 - 0.069x_4^2 + 0.066x_1x_2 + 0.007x_1x_3 + 0.013x_1x_4 + 0.552x_2x_3 - 0.042x_2x_4 - 1.655x_3x_4.$	0.812

Table 3. Maximum hydantoinase and biomass identified by quadratic polynomial and neural network models and the optimum input sets that result in the maximum output values.

Model	Dependent Variable	Independent variables ($\mathbf{gl^{-1}}$) $\mathbf{Molasses(x1)}$	$\mathbf{NH_4NHO_3(x2)}$	$\mathbf{NaH_2PO_4(x3)}$	$\mathbf{MnCl_2(x4)}$
Quadratic polynomial	y1 = 35.39	12.36	1.04	12.14	0.07
Neural network	y1 = 39.29	11.95	0.75	15.99	0.08
Quadratic polynomial	y2 = 1.69	12.75	1.3	14.23	0.04
Neural network	y2 = 1.92	14.76	1.53	12.25	0.02

5|Results and Discussion

5.1|Neural Network Modeling

The initial step in neural network modeling involves designing the network's topology. Various design parameters influence performance, including the activation function, training algorithm, learning rate, momentum, number of hidden layers, neurons per hidden layer, initial weights, and training duration. Feed-forward neural networks with a single hidden layer of sufficient neurons are known to approximate any continuous nonlinear function accurately. However, selecting other design parameters often involves empirical rules and trial and error, as network topology is typically problem-specific.

In this study, we configured two neural networks with a 4-6-1 structure (four input neurons, six neurons in one hidden layer, and one output neuron) after preliminary experimentation. To prevent overtraining, the dataset of 30 experimental runs was divided into a training set (27 runs) and a validation set (3 runs). The training set optimised the network weights, while the validation set evaluated predictive capabilities. Training data spanned the lower and upper bounds of the output neurons (y1 and y2).

Fig. 2 and *Fig. 3* depict the network-calculated hydantoinase and biomass concentrations for both training and validation data, compared to experimental data. Solid circles represent network-trained outputs, while open circles denote network-predicted outputs for validation set inputs. The neural networks fit the training data well and accurately predicted validation data. Polynomial regression equations (*Eq. (2)* and *Eq. (3)*), shown as triangles in *Fig. 2* and *Fig. 3*, provided less accurate predictions, highlighting neural networks' superior modeling capability in response surface analysis.

5.2|Optimisation by TSR Algorithm

It can be optimised once a robust neural network model is established across the independent variables' ranges. For the fermentation example, we used the TSR algorithm to optimise the input space of the neural network models and determine optimum hydantoinase and biomass concentrations.

One suggestion for improving performance is to use fuzzy logic, specifically a fuzzy-split range control system for the fermentation process. Fuzzy logic emulates human reasoning and translates this thought process into mathematical rules for problem-solving and decision-making. Unlike the precise and numerical nature of computer logic, the rules and linguistic variables used in human decision-making are often vague. These linguistic terms are mathematically represented as membership functions [18].

The TSR algorithm's performance is influenced by design parameters such as initial population size, parent selection, seed dispersion rate, growth rate, and number of generations. Experimentation showed that the TSR algorithm is robust to parameter variations, with population size and number of generations significantly

affecting performance. Using a population of 50-100, neural network responses converged to optimal values within 200-500 generations.

Table 3 presents the results, including input conditions yielding maximum output values. The neural network models identified maximum achievable hydantoinase and cell concentrations of 39.29 U ml−1 and 1.92 mg ml−1, respectively, 11-14% higher than those identified by polynomial equations. This difference underscores the importance of accurate response surface approximation for optimisation.

Different optimum conditions arose from models with varying accuracy. To verify that differences were not due to the optimisation method, we used TSR to optimise polynomial equations, obtaining similar results to derivative calculations of *Eq. (1)* and *Eq. (2)*. This consistency confirms that polynomial models' optimal conditions are not dependent on the optimisation method.

Quadratic polynomial models are frequently used for fermentation optimisation but may lack accuracy. Our study demonstrates that higher-order polynomials or neural networks are necessary for accurate response surface modeling, preventing suboptimal conditions. Accurate model selection in RSM is crucial for effective process optimization.

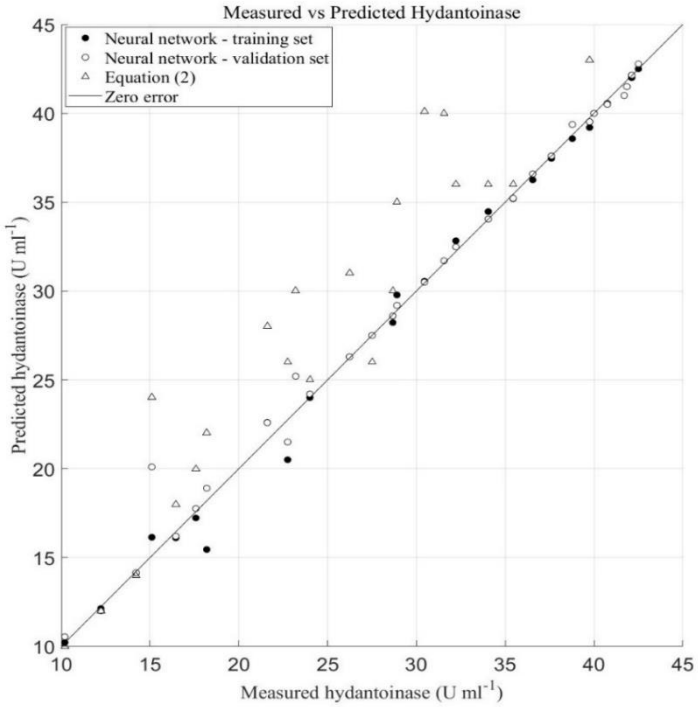

Fig. 2. Comparison of hydantoinase production predicted by the neural network and Eq. (2) with actual hydantoinase production.

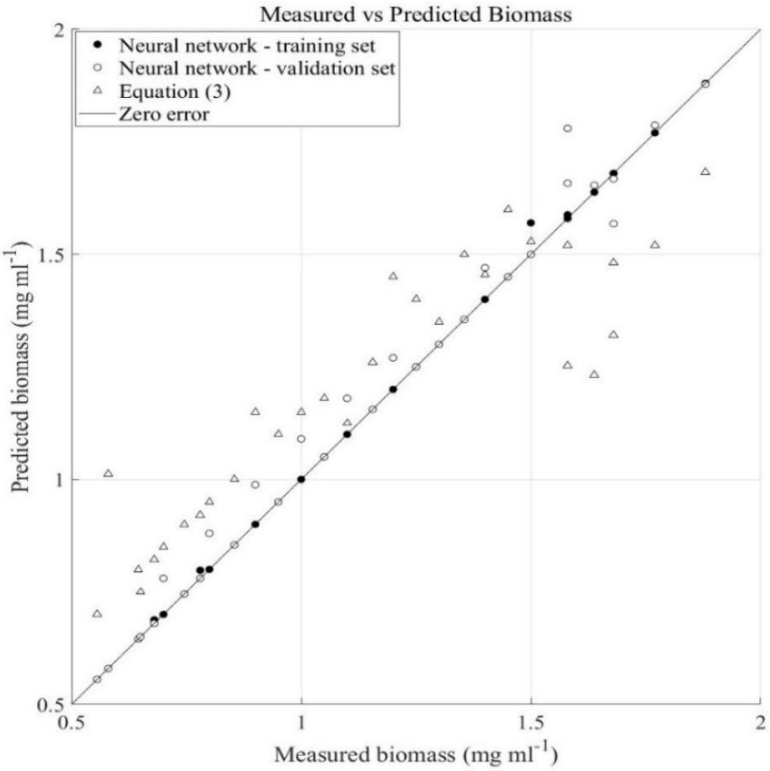

Fig. 3. Comparison of biomass production predicted by the neural network and Eq. (3) with actual biomass production.

Conclusion

Empirical model building in the standard RSM approach often involves fitting quadratic polynomials to data derived from statistically designed experiments. However, quadratic polynomials may not always adequately approximate the true response surface of a process. This study found that neural networks better fit experimental data than conventional quadratic polynomials.

The input space of a neural network model can be effectively optimised using the TSR algorithm, which does not require the objective function to be continuous or differentiable. The hybrid neural network-TSR algorithm approach described in this work offers a viable alternative to the standard RSM approach for modeling and optimising fermentation processes. This integration demonstrates improved accuracy and optimisation capability, making it a promising method for complex empirical modeling tasks.

Author Contribution

Conceptualization, M. L. Gh., M. A and S. F.; Methodology, S. F.; Software, M. L. Gh.; Validation, M. A. and M. L. Gh.; formal analysis, S. F; investigation, M. A; resources, M. L. Gh.; data maintenance, M. A; writing-creating the initial design, S. F; writing-reviewing and editing, S. F and M. A.; visualization, M. A. project management. All authors have read and agreed to the published version of the manuscript.

Funding

It is declared that this research involved no external funding and was undertaken solely with the researchers' own means.

Data Availability

All the data are available in this paper.

Conflicts of Interest

The authors declare no conflict of interest.

References

[1] Hemraj S. Nandanwar, R. P., & Hoondal, G. S. (2013). (D)-p-hydroxyphenylglycine production by thermostable D-hydantoinase from Brevibacillus parabrevis-PHG1. *Biocatalysis and biotransformation*, *31*(1), 22–32. DOI:10.3109/10242422.2012.755962

[2] Alimoradi, M., Azgomi, H., & Asghari, A. (2022). Trees social relations optimization algorithm: A new swarm-based metaheuristic technique to solve continuous and discrete optimization problems. *Mathematics and computers in simulation*, *194(C)*, 629–664. DOI:10.1016/j.matcom.2021.12.010

[3] Sharon Mano Pappu, J., Gummadi, S. N., & Jayabalan, T. (2022). Modeling and optimization of microbial production of xylitol. *Role of microbes in industrial products and processes*, 223–254. DOI:10.1002/9781119901198.ch9

[4] Wari, E., Zhu, W., & Liu, X. (2015). Genetic algorithms applications in the food process industry. In IIE annual conference. *Proceedings. Institute of industrial and systems engineers (IISE)*, (pp. 288-297). https://www.proquest.com/openview/885118ef4fbd523f7d708ce84b146e0b/1?pq-origsite=gscholar&cbl=51908

[5] Daliri, A., Asghari, A., Azgomi, H., & Alimoradi, M. (2022). The water optimization algorithm: A novel metaheuristic for solving optimization problems. *Applied intelligence*, *52*(15), 17990–18029. DOI:10.1007/s10489-022-03397-4

[6] Daliri, A., Alimoradi, M., Zabihimayvan, M., & Sadeghi, R. (2024). World hyper-heuristic: A novel reinforcement learning approach for dynamic exploration and exploitation. *Expert systems with applications*, *244*(10), 122931. DOI:10.1016/j.eswa.2023.122931

[7] Herring, R., & Paarlberg, R. (2016). The political economy of biotechnology. *Annual review of resource economics*, *8*(8), 397–416. DOI:10.1146/annurev-resource-100815-095506

[8] Brinc, M., & Belič, A. (2019). Optimization of process conditions for mammalian fed-batch cell culture in automated micro-bioreactor system using genetic algorithm. *Journal of biotechnology*, 20(300), 40–47. DOI:10.1016/j.jbiotec.2019.05.001

[9] Zhou, T., Reji, R., Kairon, R. S., & Chiam, K. H. (2023). A review of algorithmic approaches for cell culture media optimization. *Frontiers in bioengineering and biotechnology*, *11*, 1195294. DOI:10.3389/fbioe.2023.1195294

[10] Pham, P. V. (2018). Medical biotechnology: techniques and applications. In *Omics technologies and bio-engineering* (pp. 449–469). Elsevier. DOI:10.1016/B978-0-12-804659-3.00019-1

[11] Yamaji, H. (2014). Suitability and perspectives on using recombinant insect cells for the production of virus-like particles. *Applied microbiology and biotechnology*, *98(5)*, 1963–1970. DOI:10.1007/s00253-013-5474-9

[12] Kim, G. B., Kim, W. J., Kim, H. U., & Lee, S. Y. (2020). Machine learning applications in systems metabolic engineering. *Current opinion in biotechnology*, *64*, 1–9. DOI:10.1016/j.copbio.2019.08.010

[13] Alimoradi, M., Zabihimayvan, M., Daliri, A., Sledzik, R., & Sadeghi, R. (2022). Deep neural classification of darknet traffic. In *Artificial intelligence research and development* (pp. 105–114). IOS Press. DOI:10.3233/FAIA220323

[14] Riordon, J., Sovilj, D., Sanner, S., Sinton, D., & Young, E. W. K. (2019). Deep learning with microfluidics for biotechnology. *Trends in biotechnology*, *37*(3), 310–324. DOI:10.1016/j.tibtech.2018.08.005

[15] Chen, W. H., Uribe, M. C., Kwon, E. E., Lin, K. Y. A., Park, Y. K., Ding, L., & Saw, L. H. (2022). A comprehensive review of thermoelectric generation optimization by statistical approach: Taguchi method, analysis of variance (ANOVA), and response surface methodology (RSM). *Renewable and sustainable energy reviews*, *169*(C), 112917. DOI:10.1016/j.rser.2022.112917

[16] Aziz, K., Mamouni, R., Kaya, S., & Aziz, F. (2024). Low-cost materials as vehicles for pesticides in aquatic media: A review of the current status of different biosorbents employed, optimization by RSM approach. *Environmental science and pollution research*, *31*(28), 39907–39944. DOI:10.1007/s11356-023-27640-8

[17] Andoh, A., Imaeda, H., Aomatsu, T., Inatomi, O., Bamba, S., Sasaki, M., … Fujiyama, Y. (2011). Comparison of the fecal microbiota profiles between ulcerative colitis and Crohn's disease using terminal restriction fragment length polymorphism analysis. *Journal of gastroenterology*, *46*(4), 479–486. DOI:10.1007/s00535-010-0368-4

[18] Khajehkhasan, S., & Fakheri, S. (2020). A new method based on operational strategies for early detection of breast cancers. *Innovation management and operational strategies*, *1*(2), 187–201. DOI:10.22105/imos.2021.266543.1027