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Culture conditions optimization of hyaluronic acid production by *Streptococcus zooepidemicus* based on radial basis function neural network and quantum-behaved particle swarm optimization algorithm

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ABSTRACT

This study aimed to optimize the culture conditions (agitation speed, aeration rate and stirrer number) of hyaluronic acid production by *Streptococcus zooepidemicus*. Two optimization algorithms were used for comparison: response surface methodology (RSM) and radial basis function neural network coupling quantum-behaved particle swarm optimization algorithm (RBF-QPSO). In RBF-QPSO approach, RBF is employed to model the microbial HA production and QPSO algorithm is used to find the optimal culture conditions with the established RBF estimator as the objective function. The predicted maximum HA yield by RSM and RBF-QPSO was 5.27 and 5.62 g/l, respectively, while a maximum HA yield of 5.21 and 5.58 g/l was achieved in the validation experiments under the optimal culture conditions obtained by RSM and RBF-QPSO, respectively. It was indicated that both models provided similar quality predictions for the above three independent variables in terms of HA yield, but RBF model gives a slightly better fit to the measured data compared to RSM model. This work shows that the combination of RBF neural network with QPSO algorithm has good predictability and accuracy for bioprocess optimization and may be helpful to the other industrial bioprocesses optimization to improve productivity.

1. Introduction

Fermentation processes are used to produce various substances in the pharmaceutical, chemical and food industries. The performance of fermentation processes depends on many factors, including pH, temperature, ionic strength, agitation speed, and aeration rate in the aerobic fermentation [1]. To achieve the best performance of fermentation processes, various process optimization strategies were developed by scientists. The most frequently used optimization strategy is “one-at-a-time” strategy [2]. This approach is not only time consuming, but also ignores the combined interactions between physio-chemical parameters [3].

In contrast, response surface methodology (RSM), which includes factorial design and regression analysis, seeks to identify and optimize significant factors to maximize the response (cell density, high yields of the desired metabolic products or enzyme levels in the microbial system). RSM yields a model, which describes the relationship between the independent and dependent variables of the processes. The most widely used simulating models are second-order polynomials [4,5], and now RSM has been widely applied in the bioprocess optimization [6,7].

In the last decade, artificial intelligence (AI) has emerged as an attractive tool for developing non-linear empirical models especially in situations wherein the development of conventional empirical models becomes impractical [8]. The most commonly used AI are artificial neural networks (ANNs). ANNs are superior and more accurate modeling techniques when compared to RSM and represent the nonlinearities in a much better way [2]. The most frequently used ANNs is a radial basis function (RBF) neural network. As a variant of feed-forward ANNs, RBF neural network is a universal function approximator under certain general conditions [9], and provides a mathematical alternative to the quadratic polynomial derived from statistically designed experiments [8]. The ability to approximate functions to any desired degree of accuracy makes RBF neural network preferable for use as empirical models to RSM [10]. RBF has already been successfully

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applied to a large diversity of applications including interpolation [11], chaotic time-series modeling [12], and system identification [13].

Recently, we developed a novel evolutionary technique: quantum-behaved particle swarm optimization (QPSO) algorithm [14–16]. QPSO algorithm is a powerful stochastic search and global optimization technique, and can be used to optimize process conditions without the need of statistical designs and empirical models. Different from particle swarm optimization (PSO) algorithm, QPSO algorithm is globally convergent and can find out the global optima more efficiently and quickly [14–17]. However, there are no reports about the applications of QPSO algorithm in the bioprocess optimization.

Hyaluronic acid (HA) is a linear glycosaminoglucan polysaccharide composed of repeating disaccharide units of alternative D-glucuronic acid (GlcUA) and *N*-acetylglucosamine (GlcNAc) [18]. With such biological and physico-chemical properties as biocompatibility, lubricity, viscoelasticity and high water-holding capacity, HA has been widely applied in biomedical, cosmetic, food and healthcare fields [19–21]. Conventionally HA was extracted from animal tissue like rooster combs, and now is increasingly produced by microbial fermentation with a much lower production cost. Oxygen mass transfer is an important limiting factor for microbial HA production as a typical high-viscosity fermentation, and how to break the bottleneck of oxygen mass transfer for HA fermentation is a key issue for the enhancement of HA production [22]. The agitation speed, aeration rate and stirrer number are the main factors influencing the mixing efficiency and oxygen mass transfer, therefore, the optimization of agitation speed, aeration rate and stirrer number are very important for the microbial HA production.

In this work, RBF neural network coupling QPSO algorithm (RBF-QPSO) was used to optimize the mixing performance of HA production by *Streptococcus zooepidemicus*. Three independent process variables including agitation speed, aeration rate, and stirrer number were considered for optimization. The optimization objective was to achieve the maximum HA yield at an optimal combination of three independent variables. The RBF neural network was used to develop the mathematical function of HA production with agitation speed, aeration rate, and stirrer number. Then QPSO algorithm was used to execute the optimization task to achieve the maximum HA yield. RSM was also used for optimization in comparison with RBF-QPSO approach.

2. Model structures

2.1. Response surface methodology (RSM)

RSM combines statistical experimental designs and empirical models developing by regression with a purpose of process or product optimization. Statistical experimental design is a powerful method for accumulating information about a process efficiently and rapidly from a small number of experiments, thereby minimizing experimental costs. An empirical model is then used to relate the response of the process to some independent variables. This usually entails fitting a quadratic polynomial to the available data by regression analysis. The general form of the quadratic polynomial is:

$$y = b_0 + \sum b_i x_i + \sum b_i x_i^2 + \sum b_{ij} x_i x_j + e \tag{1}$$

where y is the predicted response, x_i and x_j stand for the independent variables, b_0 is the intercept, b_i and b_j are regression coefficients, and e is a random error component.

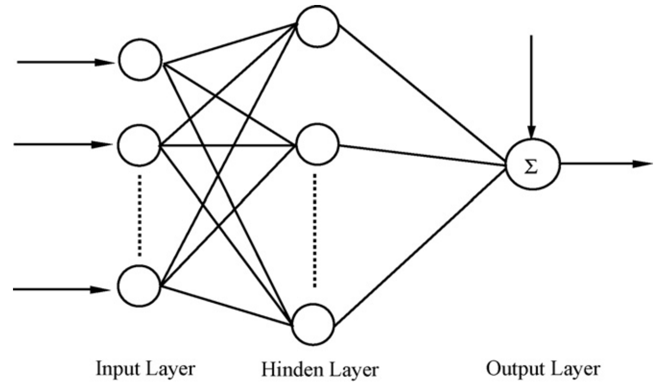

Fig. 1. Structure of RBF neural network for process modeling.

2.2. RBF neural network

RBF neural network is structured by embedding radial basis function with a two-layer feed-forward neural network. Such a network is characterized by a set of inputs and a set of outputs. In between the inputs and outputs there is a layer of processing units called hidden units. Each of them implements a radial basis function. The architecture of RBF network is shown in Fig. 1.

Mathematically RBF neural network can be formulated as

$$g(x) = \sum_{k=1}^{m} \lambda_k \varphi_k(||x - c_k||) \tag{2}$$

where m is the neuron number of hidden layer, which is equal to cluster number of training set. $||x - c_k||$ represents the distance between the data point x and the RBF center c_k. λ_k is the weight related with RBF center c_k. Therefore, the output of RBF neural networks is a weighted sum of the hidden layer's activation functions. Various functions have been tested as activation functions for RBF networks. Here we adopt the most commonly used Gaussian RB functions as basis functions shown in Eq. (3):

$$\varphi_k(x) = \frac{R_k(x)}{\sum_{i=1}^{m} R_i(x)} \tag{3}$$

$$R_k(x) = \exp\left(-\frac{||x - c_k||^2}{2\sigma_k^2}\right) \tag{4}$$

In Eq. (4), σ_k indicates the width of the kth Guassian RB functions. One of the σ_k selection methods is shown as follows.

$$\sigma_k^2 = \frac{1}{M_k} \sum_{x \in \theta_k} |||x - c_k||^2 \tag{5}$$

where θ_k is the kth cluster of training set, and M_k is the number of sample data in the kth cluster.

2.3. QPSO algorithm

As a population-based evolutionary technique, PSO system simulates the knowledge evolvement of a social organism, in which individuals (particles) represent the candidate solutions to the problem at hand and fly through a multidimensional search space to find out the optima or sub-optima [23]. The particle evaluates its position to a goal (objective function) at every iteration, and the particles in a local neighborhood share memories of their "best" positions. These memories are used to adjust particle velocities and their subsequent positions.

In the original PSO with M particles in the D-dimensional search space, each particle can be represented by the position vector