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Review

Optimization of fermentation processes using evolutionary algorithms - A review

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Optimization of multiple objectives and constraints of fermentation process problems have been extensively studied in recent years. High-performance, robust, cost-effective and reliable computing models that provide innovative solutions to fermentation problems have been developed. This paper reviews the problems of the optimal design of batch fermentation technology and the development of computer-based solving problems using evolutionary algorithms (EAs) to generate optimal or near-optimal solutions to the problems in the fermentation industries. In this review, the latest developments of evolutionary algorithm techniques are focused and optimization of fermentation processes improvement by the techniques is presented.

Key words: Evolutionary algorithms, fermentation, optimization, optimal solution, multiple objectives, constrained optimization.

INTRODUCTION

Biotechnology industries such as pharmaceutical, agricultural, food and chemical industries are rapidly developing during the past few decades where batch operations such as cooking, drying, fermentation, evaporation and sterilization are usually carried out in batches to produce a product with uniform, consistent and reliable characteristics (Curt et al., 2007). Although optimization problems arise in a variety of situations, process optimization has been the key issue to biotechnological scale production to maintain operating conditions, increase product yields and to ensure product quality (Schmidt, 2005).

Fermentation is the basis of many industrial activities. Its processes are important field of interest for system engineering due to its complex, biological, non-linear phenomena and dynamic processes (Andres-Toro et al., 2010). Some among major problems of fermentation processes include fluctuations in the quality of the raw material, influence of temperature, long process time and biomass concentration (Liu et al., 2010; Oonsivilai and Oonsivilai, 2010). Therefore, optimization method or model is an important step to decide suitable parameters for fermentation processes which help in determining the concentration of the medium components and most suitable reaction conditions in maximizing the fermentation products and minimizing important process variables or inputs (Singh et al., 2008). Optimum design methods that combine the optimization algorithms with the computer simulations have been reported (Mohebbi et al., 2008; Abakarov et al., 2009; Guo et al., 2010).

In recent years, an important branch of biotechnology is devoted to the development of proper fermentation processes and efficient steps in the utilization of fermentation technology (Desai et al., 2008). To this effect, evolutionary algorithms (EAs) have been developed and extensively used by many researchers in the fermentation optimization (Dehuri and Mall, 2006). EAs are computer based problem–solving systems of evolutionary computation field based on principle of evolution theory. They are biological–inspired optimizing algorithms, imitating the process of natural evolution and are becoming important optimization tools for several real world applications (Rakesh and Babu, 2005). They provide a robust optimizing technique to find multiple Pareto-optimal solutions in one single simulation run

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because of their population–efficient approach to explore large search place. EAs have been used for solving both the problems of non-linear estimation and product maximization (Adeyemo, 2011). Using these algorithms in solving optimization problems, involves the development of models for the objective function(s) and constraint(s) using mathematical programming techniques.

So, with the rapid development of computer technology, several mathematical models for fermentation processes have been developed and solved using some EAs including artificial neutral networks (ANNs), genetic algorithms(GA), response surface methodology (RSM), fuzzy logic (FL) and recently developed differential evolution (DE) (Rivera et al., 2006; Dutta et al., 2005). EAs are found to be useful tools over conventional methods to deal with system modeling and optimization problems especially for those involving non-linear complex mathematical relations that integrate biological structures with computer techniques (Izadifar and Jahromi, 2007). EAs use only objective function information instead of derivatives or other auxiliary information of the problem and aim at finding the optimal from a population of points in parallel rather than from a single point which make them more useful in complex and engineering problems (Fan et al., 2006).

In the industry, the cost of fermentation process is reduced by modeling because it allows the study of various process parameters interaction through simulation and provides process understanding that helps in operational policy and posterior optimization and control application. The combination of two algorithms has been extensively studied and applied for scientific research and fermentation process. They have great potential for developing high-performance, cost-effective and reliable computing model that provide innovative solutions to problems (Ovaska et al., 2002). This paper briefly reviews the development of algorithm techniques with the concepts, methods and application of evolutionary algorithms in the field of microbiology and bioreactor engineering. The future development and application of these techniques are discussed especially in the management of fermentation processes and in decision making in the fermentation industry.

Evolutionary algorithms

Evolutionary algorithms (EAs) use several variables of a problem to provide an optimum solution. They are preferred alternative method for monitoring state variables in biotechnological processes (Soons et al., 2008). EAs techniques include the method of Neuro-computing, evolutionary computing, probabilistic computing, belief networks, fuzzy logic (FL) and chaotic computing (Huang et al., 2010). The optimization techniques that have been applied to solving biotechnology complex problems include linear programming (LP), non-linear programming (NLP), dynamic programming (DP), stochastic dynamic programming (SPD) and heuristic programming such as genetic algorithms (GA), differential evolution (DE), shuffled complex evolution, fuzzy logic (FL) and artificial neural networks (ANNs) (Adeyemo, 2011; Arranz et al., 2008; Yu and Wang, 2007; Yu et al., 2008; Lee et al., 2008).

However, the rapid development of artificial intelligence, computer technology and softwares have been found to be advantageous over the conventional methods in dealing with system modelling and optimization problems especially those involving nonlinear and complex mathematical approaches (Chen and Ramaswamy, 2002). Three evolutionary algorithms commonly used for the optimization of fermentation processes are artificial neural networks (ANNs), genetic algorithm (GA) and differential evolution (DE). They are described subsequently.

Artificial neural networks

Artificial neural networks (ANNs) model are designed to mimic the human learning processes by creating linkages between process input and output data. They also ‘learn’ how to reproduce an output from the input parameters without any prior knowledge of the relationship between them (Rosa et al., 2010). ANNs have incredible arbitrary decision boundary capabilities, capacity to adapt to different types and structure of data easily. They can predict, analyse, associate and emulate the connectivity of biological neurons to solve complex problems in the same manner as the human brain (Huang et al., 2010; Rosales-Colunga et al., 2010). ANNs model architectures and algorithms of neuro-computing have been developed and applied successfully.

In the study of theoretical aspect of ANNs, the potential and capabilities of interconnecting of several basic components based on the model of neuron was pioneered by McCulloch and Pitts (1943). Later on, the neural systems adaptation was studied by Hebb (1949). In the 1980s, Hopfield (1982) applied a particular non-linear dynamic structure to solve optimization problem. Rosenblatt (1958) coined the name perceptron and devised architecture, which are recognised as helpful tools for dynamic modeling (Huang et al., 2010). Neurons of the network are arranged into several groups called layers. ANNs can be a multi-layer neural network that has hidden and output layers.

The most commonly used neural network for solving nonlinear regression problems is the multi-layer feed-forward neural network called multi-layer perceptron (MLP). Algorithm used for the optimization problems during training of the ANNs is by means of back-propagation (BP) algorithm. It involves the minimization of performance function commonly called mean-squared-error (MSE) (Equation 1).

$$\text{MSE} \sim \sum_J \left(\bar{Y}_J - Y_J\right)^2 \quad (1)$$

ANNs have the ability to detect complex non-linear relationship between dependent and independent variables and the ability to detect all possible interaction between predicted variables. ANNs models are 'black-box' in nature, have greater computational burden and proneness to over fitting (Fernández-Navarro et al., 2010).

Genetic algorithms

Genetic algorithm is a stochastic optimization technique that searches for an optimal value of a complex objective function and are used to solve complicated optimization problems by simulation or mimicking a natural evolution process (Doganis et al., 2006). It involves repeated procedures with an initial population of potential solutions, a fitness evaluation via the application of genetic operators and the development of a new population (Goñi et al., 2008). In addition, GA has been successfully used as a tool in computer programming, artificial intelligence, optimization, neural network training and information technology since its introduction by Holland (1975) to improve the performance of simple GA (Sarkar and Modak, 2003; Fleming and Purshouse, 2002; Lee, 2000; Tsukimoto and Hatano, 2003).

GA starts with an initial set of solutions called population and each solution in a population is called chromosome or individual which are evolved through successive iterations called generations by genetic operators such as selection, crossover and mutation that mimic the principle of natural evolution (Vasant and Barsoum, 2009). "Selection" means that two individual from the whole population of individuals are selected as "parents" which depends on the value of the fitness function of each individual. "Crossover" exchanges the segments of selected parents between each other by probability. Crossover allows the exploration of the feature space to find a near to optimal solution. Mutation randomly alters the value of each element of the chromosome according to a probability called mutation probability.

Generally, the GA optimization method can be summarized as shown in Figure 1 (Marchitan et al., 2010). The initial set of random solutions representing the population ($X_1^{(k)}$, $X_2^{(k)}$, . . . $X_q^{(k)}$) where q is population size and k is the generations (iteration number). Chromosome (each individual in the population) $X_j^{(k)}$ represents a single set of input variables that gives a solution to the problem (Equation 2).

$$X_j^{(k)} = (X_{j,1}^{(k)}, X_{j,2}^{(k)}, \ldots \ldots X_{j,n}^{(k)}) \quad (2)$$

Where n is the number of input variables, $X_{j,2}^{(k)}$ is one of the genes. Solutions are represented in encoded form as binary strings or real code. According to GA terminology, the fitness function is identical with the objective function in mathematical programming terminology. The stopping criterion is verified after computation of all fitness value for each individual chromosome, if the stopping criterion is not satisfied, then, selection of some individuals from the current population based on ranking and sorting of the fitness values called parent chromosomes ($X_1^{(k)}$, $X_2^{(k)}$, ... $X^{(k)}_{(q-s)}$) is done and are used for the generation of new chromosomes (offspring) that form the next generation population ($X_1^{(k+1)}$, $X_2^{(k+1)}$, ... $X^{(k+1)}_{(q)}$). Hence, at the end of several generations, the optimal solution converges (Marchitan et al., 2010; Thakur et al., 2010).

Differential evolution

Although, many EAs have been developed but they are still time consuming. In order to overcome this disadvantage, Storn and Price (1995) introduced the evolutionary strategy called differential evolution (DE) and have been successfully applied to the optimization of some well-known non-differentiable, non-linear and non-convex function (Storn, 1997). DE is a very simple population based stochastic function minimizer or maximizer which is very powerful at the same time. It has efficient straightforward features that make it very attractive for numerical optimization. DE combines simple arithmetical operators with the operators of selection, crossover and mutation to evolve from a randomly generated starting population to a final solution. They perform mutation based on the distribution of the solutions in the current population. DE uses a greedy and less stochastic approach to solve problems than the classical evolutionary algorithms (Liu and Wang, 2010; Mariani et al., 2008; Angira and Babu, 2006; Babu and Angira, 2006).

The crucial idea behind DE is a scheme to generate the trial parameter vectors that is completely self-organizing and adds the weighted differences between two population vectors to a third vector thereby no separate probability need to be used. Some of the successful applications of DE have been reported in the literatures which include; batch fermentation process, optimization of non-linear chemical processes, optimization of process synthesis and design problems, optimization of biomass pyrolysis and optimal design of shell and tube heat exchangers (Angira and Babu, 2006; Babu and Angira, 2006; Babu et al., 2005; Babu and Chaurasia, 2003). Among the DE's advantages are its simple structure, speed, robustness and ease to use and it can be used for optimizing functions with real variables and many local optimal (Khademi et al., 2009).

Some applications of evolutionary algorithms to fermentation

In recent years, application of GA to the optimal control of

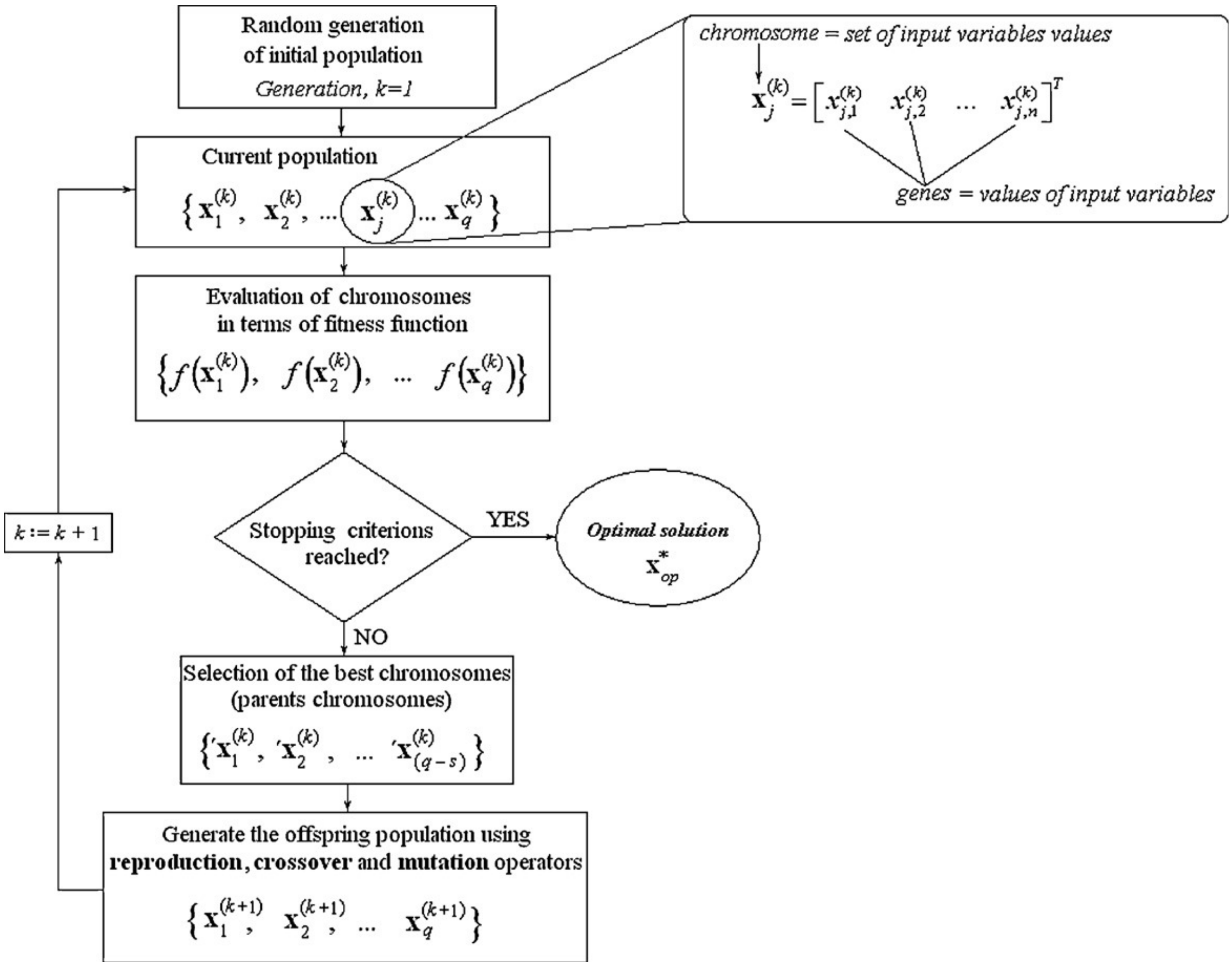

Figure 1. The principal steps of a typical GA.

agricultural and food production systems have been observed and reported in a number of literatures. Andres-Toro et al. (2010) demonstrated how GA provides an optimum temperature profile for industrial beer fermentation process to obey certain constraints. A non–linear mathematical model with eight state and one control variables in a continuous time was developed with the objective of minimizing time without quality loss. In this research, GA provides an optimum temperature profile for the short time beer fermentation process and the non-dominated solutions were obtained from the model results using simple genetic algorithm and hill-climbing algorithm application to the GA profile. A methodology of feature selection in chromatograms of polyphenolic compounds, obtained from a high performance liquid chromatography with aligned photodiodes detector (HPLC-DAD) for wine classification purposes based on genetic algorithms has been proposed by Beltra´n et al. (2005). It was demonstrated that the application of this methodology to Chilean wine variety classification problems, using genetic algorithm gives the percentage of correct classification of 94.19%.

Chen et al. (2002) introduced the use of GA for identifying the unknown parameters of seventh-order nonlinear model of fed-batch culture of hybridoma cells on-line and to optimize feed rate control profiles for glucose and glutamine. The results proved GA to be a good alternative method for solving on-line identification and optimization problems. GA coupled with neural networks (NNs) was developed for the medium optimization of Xylitol fermentation by *Candida mogii* with high yield. Xylitol is of high value to pharmaceutical, food and chemical industries. Xylitol use is limited due to high production costs and this has encouraged the development of new technologies that enables lower production costs. To this effect, Baishan et al. (2003) optimized the concentration of six medium components within 50 experiments and 40 emulate experiments to give a maximum yield of xylitol production by *C. mogii* with minimum use of medium content with GA after the NNs was trained.

Etschmann et al. (2004) optimized the temperature and 13 medium constituents within 98 parallel experiments to give maximum yield of 2-phenylethanol (2-PE) from bio-conversion of L-phenylalanine (L-Phe) with *Kluyveromyce marxianus* CBS 600 using GA optimization method. An increase of 87% 2-PE concentration was achieved compared to the non-optimized medium within four generations plus an additional temperature screening. The study showed that, product yield in enzyme and whole cell biocatalyst can be improved not only by addition of enzyme but also by medium engineering using genetic algorithm even in the presence of complex medium components. Therefore, implementing medium engineering at an early stage of research may reveal unpredicted phenomena, it thereby reduces the production time and increases the rate of production.

In another study, a mathematical model was developed for the bioprocess optimization of a newly isolated *Pseudomonas* sp. that has a high specific growth rate under submerged fermentation system using genetic algorithm. The proposed model was applied to the protease production rate, reaction time and other parameters like initial inoculum size, initial substrate concentration. Simulation results demonstrated that, the genetic algorithms technique was successfully applied for both parameters estimation and product maximization. The fed-batch fermentation increases protease production by *Pseudomonas* sp. in a reduced reaction time while sustaining the growth rate (Dutta et al., 2005). Polysaccharides that are produced by plants, algae and bacteria are commercially used as food additives and in pharmaceuticals. Lactic acid bacteria produce exopolysaccharides (EPS) that have health stimulating properties such as immunity stimulation, anti-ulcer and cholesterol reduction.

A hybrid methodology comprising the Plackett-Burman (PB) design method, ANN based modelling and GA was developed to enhance the optimization of media and inoculums volume for the exopolysaccharides production by *Lactobacillus plantarum* isolated from the fermented *Eleusine coracan*. PB was used to identify the most three influential media components; ANN was generated for approximating the non-linear relationship between the fermentation operating variables and the yield. Then, the input parameters of ANN model was optimized using the GA based process optimization to obtain the maximum EPS yield in the batch fermentation (Desai et al., 2006). The support vector machines (SVM) model for penicillin fermentation processes was developed with industrial data and simulation done by RGA for fitting function. It was demonstrated that the optimal control strategy improves the penicillin titer of the fermentation process by 22.88%, compared with the routine operation (Xuejin et al., 2010). An on-line tracking and estimation of a penicillin fed-batch fermentation process by unscented Kalman filter (UKF) state space model with support vector machines method was compared with mechanistic state model to simulate the accuracy of penicillin fed-batch fermentation by Wang et al. (2010). The results indicate that the proposed method is an effective approach to address the problem of on-line estimation of fed-batch fermentation processes.

Recently, a developed EA called differential algorithm (DE) has been reported in the literatures. Khademi et al. (2009) investigated the performance of methanol synthesis and cyclohexane dehydrogenation in a thermally coupled heat exchanger reactor using differential evolution method. Oonsivilai and Oonsivilai (2010) presented the application of DE algorithm to a constrained optimization problem of fermentation process. A temperature profile was applied to drive the process to obey certain constraints during the beer fermentation process. The effect of temperature profile for beer fermentation process was designed and estimated by kinetic model to minimize the operation time and to optimize the quality of beer. Seven decision variables were considered which includes ethanol and sugar; by-products like ethyl acetate and diacetyl; three components of the biomass (dead, active, and latent). The results show that DE is an easy method to incorporate the prior knowledge and the operation performance for the optimization of the batch process. In another study, Tagawa (2009) used differential evolution technique for the optimization of balanced SAW filters design problems.

Another interesting example is by Mariani et al. (2008) that determined the apparent thermal diffusivity of banana during the drying process as a function of the moisture content and temperature using DE as the optimization technique to obtain parameters of two functions through an inverse method. The proposed mathematical model for the thermal diffusivity considered the effects of shrinkage and transient heat transfer at surface during drying, cooling and freezing of fruits in a continuous system as an important aspect of food processing operation. It was demonstrated that a small change in the moisture content of banana caused an abrupt change in the apparent thermal diffusivity that decreases as the moisture content reduces or decreases. A number of studies have been conducted and reported in the literatures that explore, analyse and discuss the new approach for the estimation of apparent thermal diffusivity of foods at different drying temperature (Lima et al., 2002; Queiroz and Nebra, 2001).

An adaptive version of DE algorithm developed by Yüzgeç (2010) was introduced to the optimization of feeding profile for an industrial scale baker's yeast fermentation process to maximize the amount of the biomass and minimize the ethanol production during fermentation process. The proposed DE algorithms were compared with the classical genetic algorithm presented by Yüzgeç et al. (2009) for the same fermentation process and the result showed that, DE algorithm have better performance than the classical GA. Modified version of DE algorithm to improve efficiency and robustness are well presented in the literatures (Ali and Torn, 2004; Sun et al., 2004; Brest et al., 2006; Babu and Jehan, 2003). Trigonometric differential evolution algorithm (TDE) as an improved version of differential evolution was proposed by Fan and Lampinen (2003). In the development of TDE algorithm, trigonometric mutation operation was embedded into DE algorithm, to enhance the convergence rate and robustness of DE algorithm. The results showed that, the convergence rate of TDE was higher than the DE algorithm. This is supported by the work of Angira and Alladwar (2005, 2007) where both DE and TDE were used for solving dynamic optimization problems. The performance of TDE was found to be efficient and significantly faster than the original DE algorithm.

Application of ANNs in biotechnology and biological engineering are very wide. ANNs have been applied in solving problems in food processing, quality and safety, soil and water, ecology and natural resources, chemical application and other areas. These applications have been developed through classification modelling and prediction, control, simulation, parameter estimation detection, data clustering, data fusion and optimization (Huang et al., 2010). The two important elements in the optimal control include a reliable optimization algorithm and an accurate process model that reflect process changes, as well as the correlation of fermentation parameters. Becker et al. (2002) uses dynamic neural networks as a tool for the online optimization of industrial fermentation because of the nonlinearity of fermentation processes and the lack of correlation between biologic response and process parameters. Artificial neural network models of the rumen fermentation pattern in dairy cattle were carried out by Craninx et al. (2008). Some other researchers also adopted artificial neural networks (ANN) to model fermentation processes (Zuo and Wu, 2000; Xiong and Zhang, 2005).

Chen and Ramaswamy (2002) presented the application of coupled neural networks and GA techniques for modelling and optimization of variables retort temperature (VRT) thermal processing for conduction heated foods. The objective was to analyse the effects of VRT function parameters on process time, average quality retention, and surface cook value. The results showed the effectiveness and the reliability of ANN-GA intelligence technique for optimization of VRT processing in food industry to improve the quality of canned foods and reduce the process time compared to the conventional thermal processing. Other examples of ANN and GA hybridization for process optimization have been reported and successfully applied in evaluating the relative significance of variables and optimization of the target metabolites production in biotechnology and industrial chemistry (Mutihac and Mutihac, 2008; Desai et al., 2008). Rivera et al. (2010) proposed artificial neural network-based software sensors (ANN-SS), that allows an on-line measurement of some process variables with an estimation algorithm that provide on-line estimates of immeasurable variables, model parameters or to overcome measurement delay.

It has been demonstrated that, ANN-GA is more accurate to access the optimum concentrations of the significant variables than response surface methodology (RSM) (Erenturk and Erenturk, 2007; Garcia-Gimeno et al., 2005; Huang and Xia, 2007; Izadifar and Jahromi, 2007; Singh et al., 2009; Wang and Wan, 2009). Guo et al. (2010) applied Plackett–Burmanand central composite designs to optimize the medium for ethanol production by *Clostridium autoethanogenum* with carbon monoxide as sole carbon source and genetic algorithm was employed to access the optimum concentration of ethanol predicted by RSM and ANN. The results showed that, ANN-GA model performed better than RSM model in the optimization of ethanol production over time. In another study, comparism of RSM and ANNs application was demonstrated by Zhang et al. (2010). A novel optimization coupling conditions technique based on ANN, as compared with RSM was developed to improve the effect of pH, carbodiimide concentration and coupling time on the activity yield of immobilized cellulose. Both simulation and prediction results showed the accuracy of 9.7% of ANN model as compared to the yield activity of RSM. The maximum activity yield obtained from ANN model showed a perfect agreement with the experimental activity yield.

Recently, reactive extraction has attracted attention as a promising technique for the recovery of various substances from liquid streams such as alcohols (Kuzmanovic et al., 2006), carboxylic acids (Cas et al., 1998; Jun et al., 2007; Hong and Hong, 2000; Poposka et al., 2000; Poposka et al., 1998), phenols (Li et al., 2006), aldehydes (Babic et al., 2009) and for separation of the biologically active products in biotechnological applications (Likidis and Schügerl, 1988; Reschke and Schügerl, 1984). Several important studies on the influence of diluents on amine extraction of carboxylic acids are reported (Kyuchoukov et al., 2001; Senol, 2004; Tik et al., 2001). Marchitan et al. (2010) compared RSM and ANN modelling for the optimization of reactive extraction in other to maximize the extraction efficiency of tartaric acid from aqueous solution using experimental design and to improve the performance of the existing system. As the case study, the extraction of tartaric acid from aqueous solution with Amberlite LA-2(amine) dissolved in organic solvent was investigated. The efficiency extraction was modelled and optimized as a function of input variables such as pH of feed solution, tartaric acid and amine concentration. The evolution profile of optimization search by RSM-GA was compared to ANN-GA. GA model was employed for the maximization of the RSM fitness function and the scope of optimization was not totally achieved by RSM-GA for the reactive extraction.

On the other hand, the reactive extraction efficiency of 96.08% was obtained when ANN-GA modeling method was used compared to 83.06% optimum yield by RSM-GA hybrid. The results showed that, ANN-GA have the ability to overcome the limitation of quadratic polynomial model in solving optimization problem. Both models was used for the construction of response output surface plots in order to reveal the influence of input variables on extraction efficiency, as well as to figure out the interaction effects between variables.

CONCLUSION

EAs are different from conventional algorithms for non-linear optimization since they use only objective function information instead of derivatives or other auxiliary information of the problem. Hybridization of two or three techniques to generate new model structure and parameters has continued to be a major trend in application of EAs to the optimization of important state variables in food and biotechnological processes. Although, genetic algorithm based optimization has proved to be a good and often superior technique for solving bioprocess optimization problems as such GA find global minimum solution instead of local minimum but DE have proved to be significantly fast and robust technique due to its ability to use real code instead of binary coding (though some GAs also use real code) GA algorithm uses for optimization functions. It is recommended that DE be used to solve some optimization problems in the fermentation processes and compare the results with that of GA to establish DE's superiority when it comes with speed.

Although, ANNs techniques have their own limitations which restrict them as a substitute to traditional method but with time, fusion of ANNs with other training algorithms to design new bioprocesses as well as to improve the existing ones will be developed in order to overcome more industrial application problems in the future. It can be expected that in the next decade SVMs will be more actively used in food science, biotechnology and engineering due to its fast growing interest and advantages over ANNs (Vapnik, 1999) (Vapnik, 1995).

Compared with ANNs, SVMs model have advanced soft computing development that often produce high classification accuracies with less effort or time in setting up control parameters. Hence, many real-world optimization problems involve the satisfaction of multiple conflicting objectives. EAs have improved the performance of function in most situations in food industry but it is believed that more research should be carried out to reach a better understanding of how to design the parameters and rules of EAs in fermentation processes. Many of the studies mentioned in this review used different types of EA techniques for biotechnological processes. It is believed that this review will help in the improvements of industries and regular beer development.

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