

Optimization of Biochemical Systems Production Using Combination of Newton Method and Particle Swarm Optimization

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Abstract — In the presented paper, an improved method that combines the Newton method with Particle Swarm Optimization (PSO) algorithm to optimize the production of biochemical systems was discussed and presented in detail. The optimization of the biochemical system's production became difficult and complicated when it involves a large size of biochemical systems that have many components and interaction between chemical. Also, two objectives and several constraints make the optimization process difficult. To overcome these situations, the proposed method was proposed by treating the biochemical systems as a nonlinear equations system and then optimizes using PSO. The proposed method was proposed to improve the biochemical system's production and at the same time reduce the total of chemical concentration involves. In the proposed method, the Newton method was used to deal with nonlinear equations system, while the PSO algorithm was utilized to fine-tune the variables in nonlinear equations system. The main reason for using the Newton method is its simplicity in solving the nonlinear equations system. The justification of choosing PSO algorithm is its direct implementation and effectiveness in the optimization process. In order to evaluate the proposed method, two biochemical systems were used, which were E.coli pathway and S. cerevisiae pathway. The experimental results showed that the proposed method was able to achieve the best result as compared to other works.

Keywords— newton method; particle swarm optimization; optimization; biochemical systems; computational intelligence.

I. INTRODUCTION

Nonlinear equations system (NES) plays a vital role in scientific fields such as the chemistry field. All the chemical reactions and interconnection between chemicals use NES to model the biochemical systems. The utilization of NES helps researchers in altering and tuning the chemical reaction concentration values to optimize the desired product in biochemical systems [1]–[5]. Most of the current works transform the optimization problem (the desired product) into the process of solving NES. Solving NES requires finding all the solutions for each equation in NES. The process of solving NES is a complicated task because

normally the equations in NES are in a nondeterministic polynomial form [6]–[9]. In addition, the size of biochemical systems has an impact on solving NES because many variables will be involved in representing the chemical reactions and interconnection between chemicals in the biochemical systems.

Numerous works have been conducted in the optimization of biochemical systems [3], [4], [10]. All of them modeled the biochemical systems in NES and solved NES using optimization methods such as genetic algorithm [5], [11], differential evolution algorithm [12], [13], linear programming method [2], [14], [15], and geometric programming method [3], [16]. However, the results produced by current works are low and can be improved

[17]–[19]. In addition, current works only focus on improving the production and have not considered the total of chemical concentration [3], [4], [11], [15], [16], [20]. The production cost can be reduced if the total of chemical concentration can be reduced [2], [4]. Due to that, this study was conducted to improve the biochemical system's production, and at the same time, reduce the total of chemical concentration.

In this paper, an improved method that combines the Newton method (NM) and Particle Swarm Optimization (PSO) algorithm was proposed. The proposed method works by modeling the biochemical systems into NES. Then, NM is used in dealing with NES. Variables in NES will represent all the chemical reaction concentrations in the biochemical systems. In altering and tuning the chemical reaction concentration values, the PSO algorithm will be utilized to search the best value in producing the best result. The section of this paper is organized as follows: the following section discusses the modeling of the biochemical systems, where it tells about representing the biochemical systems into a mathematical model; followed by a section on the optimization problem, where it discusses the formulation of NES. The method section is presented afterward, where the NM, PSO algorithms and the combination of NM with PSO are presented and discussed in detail. The model and experimental data are depicted in the following section, followed by results and discussion before the paper is concluded in the conclusion section.

II. MATERIAL AND METHOD

A. Modeling of Biochemical Systems

In this study, the biochemical systems were modeled by a generalized mass action (GMA) model and have the following equation:

$$\frac{dx}{dt} = Sv(x) \quad (1)$$

Where S is referred to the stoichiometric matrix in the GMA model. The $V(x)$ is the reaction rate in the GMA model where the reaction, $V(x)$ has the following form:

$$v_i = \gamma_i \prod_j x_j^{f_{ij}} \quad (2)$$

In Equation 2, the coefficients γ_i and f_{ij} represent the rate constant and kinetic order in $V(x)$ and are derived from the Taylor series in the logarithmic space around steady state [3], [4]. These coefficients have the following form:

$$\gamma_i = |v_i|_0 \quad (3)$$

$$f_{ij} = \left| \frac{\delta v_i x_j}{\delta x_i v_j} \right| \quad (4)$$

B. Optimization Problem Statement

The optimization process of the production of biochemical systems requires the process of altering and fine-tuning the chemical concentration values in the interest of improving the production and at the same time reducing the total of chemical concentration involved. The optimization process cannot be performed randomly because

two constraints need to be followed, namely chemical constraint and steady-state constraint [4], [11].

Chemical constraint refers to an optimal range of the chemical concentration that must remain. This is due to the survival of cells, whereby if the chemical concentration is outside the optimum range, the functionality of the cells will not work. Thus, they will not be able to produce chemical reactions. Meanwhile, the steady-state constraint refers to a condition where the biochemical is in static and forces all GMA models to become equal to 0. Therefore, Equation 1 becomes as follows:

$$\frac{dx_n}{dt} = [Sv(x)_1, Sv(x)_2, \dots, Sv(x)_n = 0] \quad (5)$$

Where this situation is derived from the process of solving NES. Due to that, the optimization of biochemical systems production can be considered as solving NES. Thus it makes Equation 5 become as follows [6], [21]:

$$f(x) = [f(x)_1, f(x)_2, \dots, f(x)_n] \quad (6)$$

where $x = (x_1, x_2, \dots, x_n)$ is n variable in NES and $f(x)_1, f(x)_2, \dots, f(x)_n$ are the functions in NES. Therefore, the optimization problem statement can be formulated as follows:

$$\max f_1 = V \quad (7)$$

$$\min f_2 = \left(\sum_{j=1}^n x_j \right) \quad (8)$$

s.t. satisfying

$$S(v)_i = 0 \quad i = 1, 2, 3, \dots, n \quad (9)$$

$$x_j^l \leq x_j \leq x_j^u \quad j = 1, 2, 3, \dots, m \quad (10)$$

where Equation 7 is the production of biochemical systems, Equation 8 is the total of chemical concentration involved, Equation 9 is the steady-state constraint, while Equation 10 is the chemical constraint.

C. Newton Method

NM is an algorithm that is commonly used for solving NES because it offers many advantages such as it is very easy and simple to be applied in solving NES [22], and its convergence speed is fast [8]. In the proposed method, the biochemical systems were transformed into NES, where it enabled NM to solve NES. Consider NES in a matrix form:

$$f(x) = 0 \quad (11)$$

Where $F(x) = (f_1, f_2, f_3, \dots, f_n) F: D \rightarrow R^n$ is the convex subset of R^n , $x \in D$ and $x \in D$ and $F: D \rightarrow R^n$ is continuously differentiable in $D \subseteq R^n$. For any initial vector $x^{(0)}$ close to x^* where x^* is the solution of Equation 11, the NM will produce the sequence of vectors using $\{x^{(k)}\}_{k=0}$ and the step in the NE is given in Fig 1.

```

1 Repeat
2   Step 1: Initial guess  $p^{(0)}$ 
3   Step 2: Solve  $J(p^k + s^k) = F(p)^k$  or  $S(p)^k$ 
4   Step 3: Compute  $p^{(k+1)} = x^k + s^k$ 
5 Until converge to the solution

```

Fig 1. Step in the Newton method

D. Particle Swarm Optimization

Kennedy and Eberhart [23] who were inspired by the natural behavior of animal foraging such as flocks of birds, schools of fish or swarms of bees introduced the PSO algorithm. The PSO algorithm uses the movement of a population of particles to change their position with time. The movement of each particle is based on the optimization problem, where the movement is based on the best position found. In the iteration of the PSO algorithm, when a newly improved position is found, it replaces the current best position. The process is continued until a satisfactory solution is found.

In the proposed method, a population of particles represents the variables in NES. Each particle is generated randomly and can be formulated as follows:

$$P_m = \{p_{m1}, p_{m2}, p_{m3}, \dots, p_{mn}\} \quad (12)$$

Where m is the number of particles p while n is the number of variables in NES. Each particle, p_{mn} , is generated within specific ranges of p_{mn}^u and p_{mn}^l , where p_{mn}^u is the upper range and p_{mn}^l is lower range and has the following form:

$$p_{mn} = p_{mn}^u - p_{mn}^l \quad (13)$$

In every iteration, all particles will change their position by following the current best particle, V_{best} and the best in the population V_{gbest} . The movement of particle to a new location is based on their velocity and is defined as follows:

$$v_{m+1} = wv_m + c_1rand_1(v_{best} - v_m) + c_2rand_2(v_{gbest} - v_w) \quad (14)$$

Where w is inertia weight factor, c_1 and c_2 are acceleration constant (this study set c_1 and c_2 to 2), $rand_1$ and $rand_2$ is a random value in the range [0,1]. The new position for a particle is given as follows:

$$p_{m+1} = p_m + v_{m+1} \quad (15)$$

The best solution is found when the number of iteration is achieved, or the acceptable fitness value is discovered. The V_{gbest} position is considered the best solution. The pseudo code of PSO is given in Fig 2.

```

1 Begin
2   iteration (t) = 0
3   initialize particles p(t)
4   evaluate p(t)
5   Repeat (not terminate)
6     t = t + 1;
7     update weights
8     select pBest for each particle
9     select gBest from p(t-1)
10    calculate particle velocity p(t)
11    update particle position p(t)
12    evaluate particle p(t)
13  Until converge to the solution
14 End

```

Fig 2. The pseudo code of PSO

E. Combination of Newton Method and Particle Swarm Optimization

This section discusses the combination of NM and PSO. In the proposed method, NM was used in solving NES, while PSO was utilized in altering and fine-tuning the variables in NES. Fig. 3 shows the proposed method in a flow chart form. The steps involved in the proposed method are listed below.

1) *Step 1:* Initialize the first iteration (t) of particles p(t). Each particle is generated randomly using Equation 12. Each particle represents the variables in NES.

2) *Step 2:* Evaluate the particles. In this step, all particles are being evaluated. Firstly, all particles will be decoded into variables in NES. Then, NM is used to solve NES. A termination condition will be applied to identify whether the chemical constraint is followed or not. If the variables are following the chemical constraint in NES, the variables in NES will proceed to Step 4; otherwise, the variables in NES will move forward to the next step. Lines 1 – 5 in Fig. 1 gives the evaluation process of the variables in NES.

3) *Step 3:* Improve the particle. This step concerns the optimization process of the solution. The PSO operation is involved in this step, as given by lines 6 – 11 in Fig. 2. Before the PSO operation is applied, the variables in NES need to be encoded into a particle form. The objective of this step is to discover the best solution. Then all the particles go back to Step 2.

4) *Step 4:* Return the best particle. In this step, the best particle discovered during the iteration process will be given.

F. Model and Experimental Data

In order to test the capability of the proposed method, a simple program was developed based on jMetal [24] and JAMA version 1.3. Two biochemical systems were used, namely the optimization of *trp* in *E.coli* pathway and the optimization of ethanol production in *S. cerevisiae* pathway.

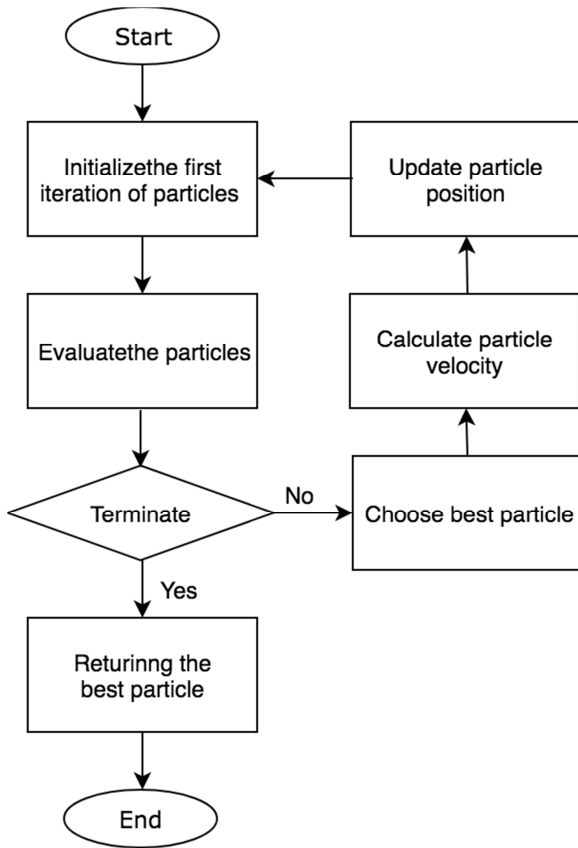


Fig 3. The proposed method in a flow chart form

$$\begin{aligned}
 4 &\leq x_5 \leq 10 \\
 500 &\leq x_6 \leq 5000 \\
 0 &\leq x_8 \leq 1000
 \end{aligned}$$

2) *Biochemical systems 2: S.cerevisiae Pathway*: For the second biochemical systems, *S.cerevisiae* pathway, the proposed method attempts to optimize ethanol production. A study by Galazzo and Bailey [26] explained this pathway in detail. The NES of *S.cerevisiae* pathway can be formulated as follows:

$$\begin{aligned}
 V_{in} - V_{HK} &= 0 \\
 V_{HK} - V_{PFK} - V_{Carb} &= 0 \\
 V_{PFK} - V_{GAPD} - 0.5V_{Gro} &= 0 \\
 2V_{GAPD} - V_{PK} &= 0 \\
 2V_{GAPD} + V_{PK} - V_{HK} - V_{Carb} - V_{PFK} - V_{ATPase} &= 0
 \end{aligned}$$

where all the variable V has the following values:

$$\begin{aligned}
 V_{in} &= 0.8122X_2^{-0.2344}Y_1 \\
 V_{HK} &= 2.8632X_1^{0.7464}X_5^{0.0243}Y_2 \\
 V_{PFK} &= 0.5232X_2^{0.7318}X_5^{-0.3941}Y_3 \\
 V_{Carb} &= 8.904 \times 10^{-4}X_2^{8.6107}Y_6 \\
 V_{GAPD} &= 7.6092 \times 10^{-2}X_3^{0.6159}X_5^{0.1308}Y_4 \\
 V_{Gro} &= 9.272 \times 10^{-2}X_3^{0.05}X_4^{0.533}X_5^{-0.0822}Y_7 \\
 V_{PK} &= 9.471 \times 10^{-2}X_3^{0.05}X_4^{0.533}X_5^{-0.0822}Y_5 \\
 V_{ATPase} &= X_5X_8
 \end{aligned}$$

The optimization problem statement of this pathway is given as follows:

$$\begin{aligned}
 \max f_1 &= V_{PK} \\
 \min f_2 &= \sum_{j=1}^6 x_j + \sum_{j=1}^6 y_j
 \end{aligned}$$

s.t. satisfying

$$\begin{aligned}
 x_j^{0.8} &\leq x_j \leq x_j^{1.2} \quad j = 1,2,3,4,5 \\
 y_j^0 &\leq y_j \leq y_j^{50} \quad j = 1,2,3,4,5,8
 \end{aligned}$$

III. RESULTS AND DISCUSSIONS

In producing the best result, several experiments were performed. Several parameter settings were involved because the PSO algorithm has many parameter settings. In producing the best result, the parameter setting is as follows: the number of iteration, the maximum number is 100 for both pathways; the number of solution is 100 for both pathways, and the weight factor is 0.5 for *E.coli* pathway and 0.4 for *S.cerevisiae* pathway. Meanwhile, for NM, the fixed value of parameters, which is the number of iteration, is set to 100 and 10^{-6} for tolerance value.

The best result produced by the proposed method for *E.coli* pathway is given in Table 1. Also, the comparison with other works is also given in Table 1. From the table, it is found that the proposed method produced the same amount of *trp*, similar to the studies performed by [3], [20], which is 3.95. For the total of chemical concentration, it can be seen that the proposed method was able to reduce more as compared to other works with 6016.01. From this observation, it can be concluded that the proposed method performed better than the other works in the *E.Coli* pathway.

1) *Biochemical systems 1: E.coli Pathway*: For the first biochemical systems, *E.coli* pathway, the proposed method attempted to optimize the *trp* production. A detail explanation of this pathway can be found in the works performed by Xiu et al. [25]. The NES of *E.coli* pathway can be formulated as follows:

$$\begin{aligned}
 V_{11} - V_{12} &= 0 \\
 V_{21} - V_{22} &= 0 \\
 V_{31} - V_{32} - V_{33} - V_{34} &= 0
 \end{aligned}$$

where all the variable V has the following values:

$$\begin{aligned}
 V_{11} &= 0.6403X_3^{-5.87 \times 10^{-4}}X_5^{-0.8332} \\
 V_{12} &= 1.0233X_1X_4^{0.0035}X_{11}^{0.9965} \\
 V_{21} &= X_1 \\
 V_{22} &= 1.4854X_2X_4^{-0.1349}X_{12}^{0.8651} \\
 V_{31} &= 0.5534X_2X_3^{-0.5573}X_6^{0.5573} \\
 V_{32} &= X_3X_4 \\
 V_{33} &= 0.9942X_3^{7.0426 \times 10^{-4}}X_7 \\
 V_{34} &= 0.8925X_3^{3.5 \times 10^{-6}}X_4^{0.9760}X_8X_9^{-0.0240}X_{10}^{-3.5 \times 10^{-6}}
 \end{aligned}$$

The optimization problem statement of this pathway is given as follows:

$$\begin{aligned}
 \max f_1 &= V_{34} \\
 \min f_2 &= \sum_{j=1}^6 x_j + x_8
 \end{aligned}$$

s.t. satisfying

$$\begin{aligned}
 x_j^{0.8} &\leq x_j \leq x_j^{1.2} \quad j = 1,2,3 \\
 0 &\leq x_4 \leq 0.00624
 \end{aligned}$$

TABLE I
THE RESULTS OBTAINED IN *E. COLI* PATHWAY

| Work by | F_1 | F_2 |
|-----------------------------------|-------------|----------------|
| Marin-Sanguino <i>et al.</i> [16] | 3.06 | 6016.38 |
| Vera <i>et al.</i> [15] | 3.06 | 6016.38 |
| Xu [3] | 3.95 | 6016.57 |
| Ismail <i>et al.</i> [5] | 3.95 | 6016.22 |
| This work | 3.95 | 6016.01 |

For the *S.cerevisiae* pathway, the best result produced by the proposed method is given in Table 2. The comparison with other works is also listed in Table 2. The proposed method was able to produce the highest ethanol production with 52.59 when compared to other works. Furthermore, the proposed method was able to achieve the minimum total of chemical concentration with 295.34. As a conclusion, the proposed method was able to perform better than the other works.

TABLE II
THE RESULTS OBTAINED IN *S.CEREVISIAE* PATHWAY

| Work by | F_1 | F_2 |
|------------------------------|--------------|---------------|
| Rodriguez <i>et al.</i> [11] | 52.08 | 295.27 |
| Xu [3] | 52.12 | 297.66 |
| Ismail <i>et al.</i> [5] | 52.57 | 297.38 |
| This work | 52.59 | 295.34 |

IV. CONCLUSION

In this work, an improved method based on the NM and PSO algorithms was proposed. The proposed method aimed to overcome the optimization problem in biochemical systems production. The problems that arise in the optimization process are two objectives that need to be considered; and the size of biochemical systems. In dealing with the problems, the presented study was conducted by combining the NM and PSO algorithms. The proposed method viewed the biochemical systems as NES. Then, NM was used to solve NES, while the PSO algorithm was utilized to alter and fine-tune the variables in NES. Two biochemical systems were used, namely the optimization of *trp* in *E.coli* pathway and the optimization of ethanol production in *S. cerevisiae* pathway, to measure the performance of the proposed method. The experimental results showed that the performance of the proposed method outperformed the results produced by other works. In conclusion, the proposed method was able to overcome the optimization problem in biochemical systems and performed better as compared to other works. For future work, the proposed method could be improved by referring to various other works available such as [27]–[30].

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