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Interactive Fuzzy Programming with Preference Criteria in Multi-objective Optimization of Metabolic Pathways

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Abstract

In metabolic engineering, biochemical pathways are studied in order to optimize some desired end-products of the system. Mathematical models have been used to model the pathways and optimization algorithms have been employed to optimize the end-product of interest. A lot of work has been invested in studying single-objective problems. There are some instances, however, when more than one by-product needs to be optimized and in this case multiple objective programming must be employed. In this study, we propose the use of interactive fuzzy programming with preference criteria to solve the multi-objective problem arising from optimization in models of biochemical networks. We choose the preference criteria method due to its interactive nature that could incorporate the modeler's inputs in choosing a compromise solution. Moreover, as the ideas in preference criteria naturally lead to the definition of fuzzy membership functions, we use fuzzy programming to obtain compromise solution. We describe the method and its efficacy using an S-system model of xanthine monophosphate and guanosine monophosphate production in purine metabolism.

Keywords: fuzzy programming, preference criteria, multi-objective optimization, S-system, purine metabolism.

1 Introduction

Metabolic engineering is an interdisciplinary science that has developed as a result of advances in molecular biology and biochemistry, genetics, chemical engineering, biotechnology, mathematical modeling, and systems analysis. One major goal is the optimization of some desired metabolites that have useful industrial or pharmaceutical roles, where the engineered metabolic pathways and/or gene networks are usually performed in micro-organisms. Specifically, metabolic engineering aims to mathematically model these networks, calculate a yield of useful metabolites, and determine which parts of the network constrain the production of these metabolites [1]. Genetic engineering techniques can then be used to modify the

network in order to relieve these constraints. Once again this modified network can be modeled to calculate the new product yield. As a result, metabolic engineers are able to manipulate and grow these microorganisms to produce valuable substances on an industrial scale in a cost effective manner. Some examples include producing beer, wine, cheese, pharmaceuticals, and other biotechnology products.

Since optimization of metabolic pathways are of great biotechnological importance, the literature in this area is quite large. Some of the attempts to apply optimization criteria to metabolic networks are found in [2, 3, 4, 5, 6]. However, the instrintic nonlinearities in most metabolic systems has been a stumbling block in optimization, where results are usually scarce and confined to a small number of variables. This is in contrast to the linear domain in which a number of analytical and numerical methods are well established.

A natural bridge between the two domains is given by the Biochemical Systems Theory (BST). S-systems which is a variant of BST are highly nonlinear and able to represent all types of dynamic behavior. However, their steady state equations are linear in which methods of linear programming can easily be used. The nonlinear dynamics together with linear steady state characteristics of S-system models provides a true alternative to make optimization problems in metabolic engineering easier to solve.

A number of papers have optimized S-systems models [7, 8, 9]. However, most results are geared towards the optimization of a single by product or a single flux and very few have considered the need to optimize more than one metabolite or flux, which may often be case on real life problems. The multi-objective problem has been considered in [10] wherein the authors have considered optimizing a certain flux together with several metabolites. However, the MOP has not been extensively discussed.

In this research, we consider multi-objective optimization in S-systems. We propose to solve the MOP using the interactive fuzzy programming with preference criteria technique developed by Tapia and Murtagh [11]. We illustrate the use of the solution approach in the simplified pathway of xanthine monophosphate and guanosine monophosphate production.

2 Optimization in S-systems

Computational metabolic engineering translates metabolic networks into mathematical models and optimizes end products of these models. The translation of metabolic pathways using ordinary differential equations (ODEs) usually results in non linear systems. Biochemical Systems Theory (BST) is a mathematical modeling framework in which the reactions rates (fluxes) are represented using power law expansions in the variables of the system. One variant of BST is the S-systems in which all reactions leading to a metabolite pool are aggregated as one product of power functions and all reactions leaving the metabolite pool are likewise aggregated as one product of power functions. S-system models have the form:

$$\dot{X}_i = \alpha_i \prod_{j=1}^{n+m} X_j^{g_{ij}} - \beta_j \prod_{j=1}^{n+m} X_j^{h_{ij}}, \quad i = 1 \cdots n \tag{1}$$

where X_i, $i = 1, \cdots n$ denote the concentration of metabolite i while the α_i's and β_i's are non- negative rate constants for the production and degradation terms respectively. The g_{ij}'s and h_{ij}'s are kinetic orders which quantify the regulation effect of X_j on the production or degradation of X_i. $X_1, X_2, \cdots X_n$ are the dependent variables (e.g. metabolites) while $X_{n+1}, X_{n+2}, \cdots X_{n+m}$ are the independent variables which are controllable and have constant values throughout the model (e.g. enzymes, effectors).

A great advantage of S-systems is they can capture any differentiable nonlinearities [12] but at the same time they have steady states that are characterized by systems of linear equations upon logarithmic transformation (See Chapter 6 of [13] for a detailed discussion on this). Hence, optimization in S-system models requiring operations at steady state conditions is represented by a linear program which allows the use of a straightforward simplex algorithm.

Sensitivity analysis of S-systems shows that changes in independent variables cause the system to assume a new steady state. The new steady state is characterized by new metabolic levels and flux levels. Hence, the aim in optimizing metabolic pathways is to determine which enzyme activities should be altered and by what degree such that the new steady state is optimal in some sense.

The optimization task with S-systems is as follows.

$$\begin{array}{l} \max\limits_{y \in R^{n+m}} f(y) \\ \text{subject to} \\ i) \text{ steady state equations (expressed in logarithms of variables)} \\ ii) \ \text{constant}_{\text{a}} \ \leq \ \ln(\text{dependent or independent variable}) \ \leq \ \text{constant}_{\text{b}} \\ iii) \ \text{constant}_{\text{c}} \ \leq \ \ln(\text{flux}_{\text{i}}) \ \leq \ \text{constant}_{\text{d}} \\ iv) \ \ln\left(\dfrac{\text{flux}_{\text{j}}}{\text{flux}_{\text{k}}}\right) <= \text{constant}_{\text{e}} \end{array} \tag{2}$$

where $f(y)$ is either a flux of the model or a dependent variable (in logarithmic form). The constraints $i)$ to $iv)$ define a feasible decision subspace $Y \subseteq R^{n+m}$ of the $n+m$-dimensional real space [14, 7, 8, 9]. A linear program for metabolic networks in S-systems may contain some or all of the constraints but it should always contain an objective function. Constraint *(i)* ensures that the optimized system is in a steady state, no matter what the altered independent variables are. In addition to the steady state constraints, the linear program may include other components: constraint *(ii)* forces the variables to stay within certain limits, constraint *(iii)* is the analogous constraint on the fluxes and constraint *(iv)* forces the ratio of two fluxes flux_j and flux_k to remain below a certain limit.

Linear programming models are easily solved with readily available linear optimization programs. These programs are usually well behaved and are able to deal with thousands of variables and constraints.

3 MOMP in S-systems

Most optimization in S-systems deals with a single goal that is to maximize yield. However, in many real life situations, a single goal may be unrealistic, and any optimal solution must strike a balance among different goals. In this paper, we consider a situation wherein more than one by product of the network should be optimized hence we consider an MOP.

An MOP with k objective functions in S-systems can be written as:

$$\begin{array}{l}\max\limits_{y\in R^{n+m}} \mathbf{f}(y) = [f_1(y), f_2(y), \cdots, f_k(y)] \\ \text{subject to} \\ i) \text{ steady state equations (expressed in logarithms of variables)} \\ ii) \text{ constant}_{\text{a}} \leq \ln(\text{dependent or independent variable}) \leq \text{constant}_{\text{b}} \\ iii) \text{ constant}_{\text{c}} \leq \ln(\text{flux}_{\text{i}}) \leq \text{constant}_{\text{d}} \\ iv) \ln\left(\dfrac{\text{flux}_{\text{j}}}{\text{flux}_{\text{k}}}\right) \leq \text{constant}_{\text{e}}\end{array} \tag{3}$$

In comparison with (2), we now have k objective functions but with the same formulation of the constraints. The objectives in (3) (and MOPs in general) are usually conflicting so that not all objectives can simultaneously arrive at their optimal levels. Thus, instead of a unique solution to the problem which is typically the case in the single-objective problem (2), the solution to (3) is not unique and consists of a (possibly infinite) set of nondominated solutions. We have the following definition of a non dominated solution.

Definition 1. *A vector of decision variables, y^* is a nondominated point if and only if there does not exist y such that*

$$\begin{array}{c} f_i(y) \geq f_i(y^*), i = 1, \ldots k \\ f_j(y) > f_j(y^*), \textit{ for some } j \end{array}$$

The image of a nondominated point is a nondominated solution.

The main goal here is to reach a compromise solution among the set of nondominated solutions.

A review of interactive techniques in solving MOPs is given in [15]. Tapia and Murtagh propose the use of the preference criteria technique in [16]. Some researches have formulated the MOP as fuzzy programming problem wherein the aspiration levels for the objectives are given by fuzzy set membership functions [17, 18, 19, 20].

In this paper, we use the proposed approach of Tapia and Murtagh [11] which reformulates the multi-objective decision problem as fuzzy programming problem but suggests a convenient way of expressing aspiration levels as preference information known as preference criteria and percentages of achievement (which are concepts taken from [16]) of the objectives as useful in providing decision making aids. The notions of preference criteria and percentages of achievement are used to define fuzzy membership functions. These functions express the degree of imprecision of the decision maker's (DM) indicated (fuzzy) aspiration levels for the objective relative to their actual levels of attainment. In our case, the DM can be the modeler, experimentalist or the metabolic engineer.

4 The Use of Interactive Fuzzy Programming with Preference Criteria in Solving MOPs

During the interactive process of solving the MOP (3), the DM has the option to identify a finite number of non-dominated solutions that satisfy a preference structure. We collect these favoured solutions into a set denoted as

$$U = \{\mathbf{f}(y_u^*), u = 1, 2 \ldots r\} \ ,$$

where $r \geq k$ and k is the number of objective functions. The DM has the task of selecting his best compromise solution from this set. This involves setting up $k+1$ selection criteria, $C(i), i = 1, 2 \ldots k+1$. The first k criteria are of the form

$$C(i): \quad 0 \leq pc_i - E_i \leq pa_i \leq 100, i = 1, 2, \ldots, k \ ,$$

where $0 \leq pc_i \leq 100$ is the ith preference criterion defined by the DM. This models the DM's desire to attain the optimal value of objective i in (3). A value of pc_i closer to 100 means a higher preference to optimize f_i, while a value closer to zero means a lower preference for f_i. While pa_i is the percentage of achievement of the ith objective function in (3) and is given by:

$$pa_i = \left[1 - \frac{f_i(y^{i*}) - f_i(y)}{f_i(y^{i*}) - f_i^-}\right] * 100\% \tag{4}$$

where y^{i*} is the solution when we optimize only the ith objective function in (3) subject to the same set of constraints. The value of pa_i signifies the closeness of the ith objective's computed value at y to the true minimum $f_i(y^{i*})$ over the range of values between f_i^- and $f_i(y^{i*})$. E_i is the ith non-negative underachievement size that the DM is willing to accept for the ith objective function.

The $(k+1)$th criterion is given by

$$C(k+1): \quad 0 \leq \sum_{i=1}^{k} (pa_i^g - pa_i) \leq E_g$$

where pa_i^g is the global percentage of achievement for the ith objective function which can be obtained from the optimal solution of the following mathematical program:

$$\begin{aligned} &\max \ \sum_{i=1}^{k} pa_i \\ &\text{subject to the same constraints as in (3) .} \end{aligned} \tag{5}$$

E_g is the maximum non-negative value difference accepted by the DM between the sum of the global percentages of achievement and the sum of the actual percentages of achievement of all the k objective functions.

The best compromise solution should meet the requirement that the $k+1$ selection criteria, $C(j), j = 1, 2, \ldots, k+1$, be satisfied simultaneously. These selection criteria can be regarded as expressions of the DMs' aspiration level for the ith objective function. We want to search for a best compromise solution in which the percentage of achievement, pa_i, of the ith objective function is better or at least equal to the DM's aspiration level expressed in terms of the preference criterion, pc_i and E_i.

The best compromise solution is likewise expected to be a point at which the sum of the actual percentages of achievement of the objective functions and the sum of the global percentages of achievement which are optimal solutions of (5) differs only by at most a non-negative magnitude, E_g. The global percentages of achievement represent a point in the attainable objective space that is optimally situated with respect to the ideal point whose coordinates are the optimum values of all the objectives.

From the $k+1$ selection criteria, $C(j)$, we now define the membership function of a nondominated solution as

$$\frac{pa_i - pc_i + E_i}{100 - pc_i + E_i} \ . \tag{6}$$

Each nondominated solution can be considered to be a member of a fuzzy set whose degree of membership can be calculated using (6), whose values range from 0 to 100. A solution with a higher membership value is considered to be a strongly desirable solution.

The following fuzzy model is proposed to find a compromise solution with a high membership value as this would be the most satisficing solution to the DM.

$$
\begin{aligned}
&\max Z \\
&\text{subject to for } i = 1, 2 \dots k, \\
&(i)\ \frac{pa_i - pc_i + E_i}{100 - pc_i + E_i} \geq Z \\
&(ii)\ 0 \leq pc_i - E_i \leq pa_i \leq 100 \\
&(iii)\ 1 - \sum_{i=1}^{k} \frac{(pa_i^g - pa_i)}{E_g} \geq Z \\
&(iv)\ 0 \leq \sum_{i=1}^{k} (pa_i^g - pa_i) \leq E_g \\
&(v)\ pa_i = \left[1 - \frac{f_i(y^{i*}) - f_i(y)}{f_i(y^{i*}) - f_i^-}\right] * 100 \\
&(vi)\ f_i^- \neq f_i(y^{i*}) \\
&(vii)\ \mathbf{f}(y) = (f_1, f_2, \dots f_k) \in F
\end{aligned}
\tag{7}
$$

where

$f_i(y^{i*})$ = max f_i subject to the contraints of (3)

f_i^- = $\min\limits_{1 \leq j \leq k} \left\{ f_i(y^{j*}) \right\}$

pc_i, $i = 1, \cdots k$ are input preference criteria

E_i, $i = 1, \cdots k$ and E_g are input underachievement sizes accepted by the DM

pa_i^g $i = 1, \cdots k$ are the global percentages of achievement of the objective function which are calculated from (5).

F is the attainable objective space corresponding to the feasible region, Y, defined by the constraints of (3).

The fuzzy model (7) is intended to be used interactively and iteratively. For each objective function f_i, the DM is first asked to input a preference criteria pc_i and underachievement tolerance values E_i. The DM is likewise asked to input E_g, which is the maximum nonnegative tolerance value which represents the difference between the sum of all global percentages of achievement and the sum of all percentages of achievement acceptable to him. Model (7) is then solved; if the problem is infeasible, the DM is asked for a new set of parameters. Once a feasible solution is found, then the optimal value of Z as well as the corresponding nondominated solution to MOP are presented to the DM. If the DM is satisfied with the solution then the problem is considered solved otherwise he is asked for a new set of inputs. The proposed algorithm for the solution of (3) using preference criteria in fuzzy programming can be written symbolically as follows:

Step 0. Formulate the fuzzy model (7) in relation to the MOP (3).

Step 1. Ask the DM to input pc_i, $i = 1, 2 \ldots k$; E_i, $i = 1, 2 \ldots k$; and E_g

Step 2. Solve (7). If it is infeasible then go to Step 1, otherwise present to the DM the resulting value of Z and its corresponding nondominated solution for (3). If the DM selects a preferred solution, STOP; if the DM is not satisfied, go to Step 1.

5 Optimization on a Model of Xanthine Monophosphate and Guanosine Monophosphate Production

To illustrate the use of the proposed method, we consider the optimization problem on the purine metabolic pathway involving xanthine monophosphate (XMP) and guanosine monophosphate (GMP) as given in [14]. Many organisms have metabolic pathways that synthesize and breakdown purines. The optimization problem in [14] is a single-objective problem and we add some additional objective functions to extend the problem to a multi-objective one. The single objective problem involves maximizing the yield of XMP and GMP, which are flavor enhancing purine nucleotides and are used as food additives. As shown in Figure 1, XMP and GMP are intermediates in the production of nucleic acids from 5-phosphoriboribosyl-α-1-pyrophosphate (PPRP).

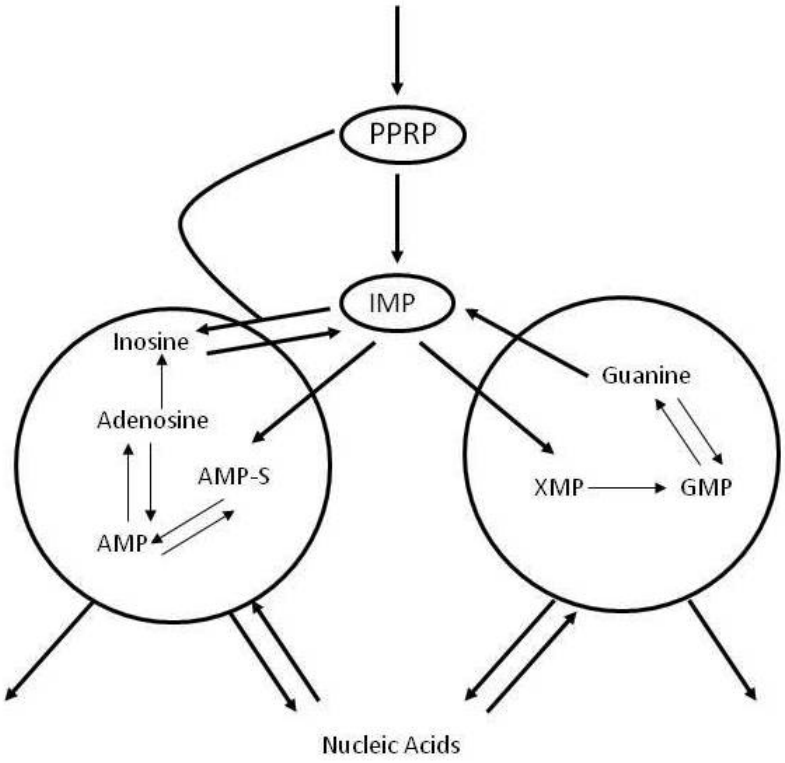

Figure 1: Simplified pathway of XMP and GMP synthesis taken from [14].

In order to translate Figure 1 into a mathematical S-system form, we define the variables and reaction fluxes as follows. PPRP is represented as X_1, inosine monophosphate (IMP) is represented as X_2, the adenylates and inosine are aggregated as X_3 and XMP and guanylates are aggregated as X_4. The regulatory mechanisms that affect the system of purine metabolism are accounted as illustrated in Figure 2. As seen also in Figure 2, the central branchpoint of the purine metabolism is IMP and the production and the conversions into other intermediates are strongly regulated by feedback inhibition. (As shown by the negative signs beside the fluxes (arrows).)

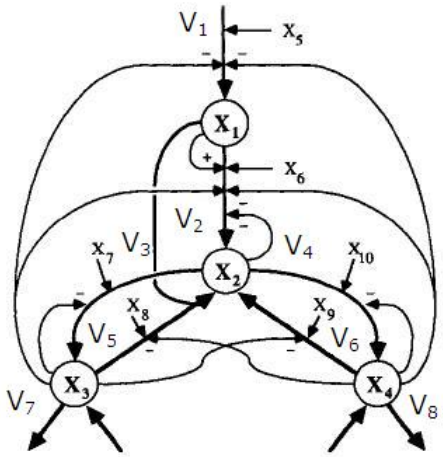

Figure 2: Definition of variables for an S-system model of the pathway in Figure 1.

Since the S-system is a canonical method for translating biochemical networks to models, the network in Figures 1 and 2 are formulated in a straightforward manner (see Chapter 3 of [13]). The S-system representation has 4 dependent and 6 independent variables and is given by

$$\begin{aligned}
\dot{X}_1 &= 900X_3^{-0.5}X_4^{-0.5}X_5 - 10X_1^{0.5}X_2^{-0.1}X_3^{-0.2}X_4^{-0.2}X_6 \\
\dot{X}_2 &= 10X_1^{0.5}X_2^{-0.1}X_3^{0.1}X_4^{-0.5}X_6X_8X_9 - 100X_2^{0.5}X_3^{-0.5}X_4^{-0.5}X_7X_{10} \\
\dot{X}_3 &= 200X_2^{0.5}X_3^{-0.5}X_7 - 10X_1^{0.1}X_3X_4^{-1}X_8 \\
\dot{X}_4 &= 30X_2^{0.5}X_4^{-0.5}X_{10} - 100X_4^{-1}X_4X_9 \ .
\end{aligned} \tag{8}$$

The independent variables $X_5, X_6, X_7, X_8, X_9, X_{10}$ are all equal to 1 and all parameters (rate constants and kinetic orders) are obtained from literature [14]. The system (8) has a unique stable steady state given in column 1 of Table 1.

An application of the above model is to maximize the steady-state concentration of X_4 (i.e., the concentration of GMP and XMP) by determining optimal values of the control or independent variables. One constraint is that all metabolite pools must remain within a certain range about their original concentrations and the processes in the network cannot be changed to an arbitrary degree, which implies constraints on the control variables. It is also required that the metabolite pools of PPRP (X_1), IMP (X_2), and the adenylates (X_3) must remain within 10% of their original concentrations. The independent variables

are limited to values between 20% and five times their basal values. The linear program in logarithmic coordinates for (8) has the following form:

$$\begin{array}{l}\max\ y_4\\ \text{subject to}\\ 0.5y_1 - 0.1y_2 + 0.3y_3 + 0.3y_4 - y_5 + y_6 = \ln(90)\\ 0.5y_1 - 0.6y_2 + 0.6y_3 + y_6 - y_7 + y_8 + y_9 - y_{10} = \ln(10)\\ 0.1y_1 - 0.5y_2 + 1.5y_3 - y_4 - y_7 + y_8 = \ln(20)\\ 0.5y_2 + y_3 - 1.5y_4 - y_9 + y_{10} = \ln\left(\frac{10}{3}\right)\\ \ln(4.9) \le y_1 \le \ln(6.0)\\ \ln(192) \le y_2 \le \ln(234)\\ \ln(2176) \le y_3 \le \ln(2660)\\ \ln(0.2) \le y_5, y_6, y_7, y_8, y_9, y_{10} \le \ln(5)\end{array} \tag{9}$$

where $y_i = \ln(X_i) \quad i = 1, \cdots 10$.

We now extend the problem into a multi-objective form. To this end, we also optimize the dependent variable X_3 and the flux V_2. Since the purpose of this paper is to illustrate how the technique is applied, we give no attention to the biological significance of the two additional objectives. Our MOP for (8) has the form

$$\begin{array}{l}\max\limits_{y}(f_1(y), f_2(y), f_3(y))\\ \text{subject to the same constraints in (9)}\\ \\ \text{where}\\ f_1 = y_4\\ f_2 = 0.5y_1 - 0.1y_2 + 0.1y_3 - 0.5y_4 + y_6 + y_8 + y_9\\ f_3 = y_3\ .\end{array} \tag{10}$$

We formulate a fuzzy model (7) in relation to the MOP model (10). We solve the fuzzy model using AIMMS software [21]. The following parameter values obtained from the single-function optimization computations for each objective function in (10) are used:

$$\begin{array}{ll} f_1(y^{1*}) = 6.273 & f_1^- = 6.050\\ f_2(y^{2*}) = 3.577 & f_2^- = -2.665\\ f_3(y^{3*}) = 7.886 & f_3^- = 7.685\end{array}$$

and $(pa_1^g + pa_2^g + pa_3^g) = 261.4$, which is obtained from the solution in (5).

Now, to illustrate our proposed method, suppose the DM has the following input preferences: $pc_1 = 80$, $pc_2 = 60$, $pc_3 = 60$, $E_1 = 10$, $E_2 = 5$, $E_3 = 5$ and $E_g = 5$. This means that the DM favors objective 1 over the other 2 objectives. Column 2 of Table 1 gives us the solution to (7) where $X_i = \exp(y_i)$.

It can be observed that the optimized values are indeed improvements of the steady state values, where the concentration of each metabolite and flux V_2 all increased. To obtain the above metabolite concentrations and flux value, all the enzymes should be altered accordingly. The concentration of X_5 should be increased from its steady state concentration of 1 to 1.051 and the concentration of X_6 should be decreased from 1 to .958. While the concentrations of the other independent variables should be increased from 1 to 5. If the DM is satisfied with these results then we terminate the algorithm otherwise we ask the DM to input a new set of preferences.

Variable Name	Steady State Values	Optimized Values
Independent and Dependent Variables		
X_1	5.42	6
X_2	213	234
X_3	2417	2631
X_4	482	526
X_5	1	1.051
X_6	1	.958
X_7	1	5
X_8	1	5
X_9	1	5
X_{10}	1	5
Model Flux		
V_2	1.352	9.14

Table 1: Steady state and optimized concentrations of the all the variables and flux V_2

6 Conclusion

In this paper, we consider the need to optimize more than one by product of metabolic pathways which results into solving MOPs of S-systems. In solving the MOPs, we propose to use the interactive fuzzy programming with preference criteria technique. This technique is chosen due to its interactive nature. It allows a DM to input his preferences in the from of preference criteria and underachievement tolerance values which are used in selection criteria that provide a convenient way to define fuzzy membership functions. These membership functions it turn determine which nondominated solution is selected.

We illustrate the technique using the simplified pathway of xanthine monophosphate and guanosine monophosphate production. Since the purpose of this paper is to illustrate how the technique works, we did not give too much importance into the biological significance of our multi-objective optimization. However, in our future work, we intend to apply multi-objective optimization to some existing and more complicated models such as the fermentation pathway in *Saccharomyces cerevisiae* (yeast) [8] and citric acid production pathway in *Aspergillus niger* (fungus) [9].

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