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InterCriteria Analysis in Structural and Parameter Identification of *L-lysine* Production Model

Tatiana Ilkova, Olympia Roeva, Peter Vassilev, Mitko Petrov

Institute of Biophysics and Biomedical Engineering
Bulgarian Academy of Sciences
105 Acad. G. Bonchev Str., Sofia 1113, Bulgaria
e-mails: {tanja, olympia, mpetrov}@biomed.bas.bg,
peter.vassilev@gmail.com

Abstract: In this paper we present the approach for multicriteria decision making – InterCriteria Analysis (ICA). ICA is based on the apparatus of the index matrices and the intuitionistic fuzzy sets. We apply its idea to establish the basic kinetic relations (the model structure) based on different criteria involved in the *L-lysine* production process. The *L-lysine* amino acid produces an important substance – carnitine found in the human heart, skeletal musculature, liver and brain. Based on the ICA we confirm a mathematical model of real lysine production process. The metaheuristic technique Genetic Algorithms is used for model parameters identification.

Keywords and phrases: InterCriteria analysis, Index matrices, Genetic algorithm, Carnitine, *L-lysine*.

2000 Mathematics Subject Classification: 03E72, 93A30, 92C45.

1 Introduction

The general carnitine function is to act as "shuttle" transferring the fatty acids with a long chain through the cell membrane and the amino acids delivered to the mitochondria are used as a "fuel" for energy necessary for the human body.

The carnitine takes a part in the oxidation of the amino acids with a branched chain, prevents of forming of lactic acid in human muscles, and restrains the substances disturbing the cell wall. Also its roles in human body are: it helps the transformation of the fat in energy and reduces the bodily

weight; it increases the mental and physical working capacity; it improves the energetic security of the heart muscle; it contributes for improvement of the metabolism and it is advisable in diabetes and obesity; it overcomes the man sterility; it increases the sexual activity; it increases the steadiness to stress and it is a powerful antioxidant [9].

The amino acid carnitine is produced in the human body by the amino acid *L-lysine*. Sometimes the concentration of *L-lysine* is insufficient in the human organisms. Because of this, sometimes it has to be taken as an additional food supplement.

In this paper we examine a fermentation process for *L-lysine* production and we construct the mathematical model of the process by establishing the general relations between the basic kinetic variable of the process by using InterCriteria Analysis (ICA).

Atanassov et al. [2] introduced the ICA as an approach for multicriteria decision making. It is based on the apparatus of the Index Matrices (IMs) [4–6] and the Intuitionistic Fuzzy Sets (IFS) [7] and can be applied for decision making in different areas of science and practice. The ICA permits the comparison of some criteria or the objects estimated by them. Up to now ICA has found some successful applications in bioprocess modelling. ICA is used in the field of parameter identification of cultivation processes models. Analysis of Ant Colony Optimization (ACO) and Genetic Algorithms (GA) applications in modelling of *S. serevisiae* [1, 12, 13] and *E. coli* [14, 15] fed-batch cultivation processes have been presented.

In this paper we apply the ideas of ICA to determine a mathematical model of a fermentation process of *Brevibacterium flavum* 22LD for *L-lysine* production. For the purpose of structural and parametric identification we use GA [8].

2 InterCriteria Analysis

ICA is a method for decision making, based on IMs [4, 5, 6] and IFS [7]. The IMs are essentially new and not widely known mathematical objects that are extensions of the ordinary matrices.

Remarks on IFPs [3]. The Intuitionistic Fuzzy Pairs (IFPs) is an object in the form of an ordered pair $\langle a, b\rangle$, where $a, b \in [0, 1]$ and $a + b \leq 1$, that is used as an evaluation of an object or a process, and whose components (a and b) are interpreted respectively as degrees of membership and non-

membership to a given set, degrees of validity and non validity, degrees of correctness and non-correctness, etc.

Let us have two IFPs $x = \langle a, b\rangle$ and $y = \langle c, d\rangle$.

Atanassov et al. [3] defined the following relations:

$$x < y \text{ iff } a < c \quad \text{and} \quad b < d,$$
$$x \leq y \text{ iff } a \leq c \quad \text{and} \quad b \geq d,$$
$$x = y \text{ iff } a = c \quad \text{and} \quad b = d,$$
$$x \geq y \text{ iff } a \geq c \quad \text{and} \quad b \leq d,$$
$$x > y \text{ iff } a > c \quad \text{and} \quad b < d.$$

Remarks on IMs. Atanassov [4, 5, 6] has presented the concept of IMs and has given the basic definitions and properties.

Let I be a fixed set of indices and $\mathcal{R}$ be the set of all real numbers. By IM with index sets K and $L(K, L \subset I)$, we mean the following object:

$$\left[K, L, \left\{a_{k_i,\ l_j}\right\}\right] \equiv$$

	l_1	l_2	...	l_n
k_1	a_{k_1,l_1}	a_{k_1,l_2}	...	a_{k_1,l_n}
k_2	a_{k_2,l_1}	a_{k_2,l_2}	...	a_{k_2,l_n}
$\vdots$	$\vdots$	$\vdots$		$\vdots$
k_m	a_{k_m,l_1}	a_{k_m,l_2}	...	a_{k_m,l_n}

where $K = \{k_1, k_2, \ldots, k_m\}$, $L = \{l_1, l_2, \ldots, l_n\}$, and for $1 \leq i \leq m$, and $1 \leq j \leq n : a_{k_i,l_j} \in \mathcal{R}$.

On the basis of the above definition, Atanassov [6] has introduced the new object – the Intuitionistic Fuzzy IM (IFIM) in the form:

$[K, L, \{\langle \mu_{k_i,l_j}, \nu_{k_i,l_j}\rangle\}] \equiv$

	l_1	l_2	...	l_n
k_1	$\langle \mu_{k_1,l_1}, \nu_{k_1,l_1}\rangle$	$\langle \mu_{k_1,l_2}, \nu_{k_1,l_2}\rangle$	...	$\langle \mu_{k_1,l_n}, \nu_{\mu_{k_1,l_n}}\rangle$
k_2	$\langle \mu_{k_2,l_1}, \nu_{k_2,l_1}\rangle$	$\langle \mu_{k_2,l_2}, \nu_{k_2,l_2}\rangle$	...	$\langle \mu_{k_2,l_n}, \nu_{k_2,l_n}\rangle$
$\vdots$	$\vdots$	$\vdots$		$\vdots$
k_m	$\langle \mu_{k_m,l_1}, \nu_{k_m,l_1}\rangle$	$\langle \mu_{k_m,l_2}, \nu_{k_m,l_2}\rangle$	...	$\langle \mu_{k_m,l_n}, \nu_{k_m,l_n}\rangle$

where for every $1 \leq i \leq m$, $1 \leq j \leq n : \mu_{k_i,l_j}, \nu_{k_i,l_j}$, $\mu_{k_i,l_j} + \nu_{k_i,l_j} \leq 1$, *i.e.* $\langle \mu_{k_i,l_j}, \nu_{k_i,l_j}\rangle$ is an IFP.

ICA – decision making method. Let us have an IM:

A≡

	O_1	⋯	O_k	…	O_l	…	O_n
C_1	a_{C_1,O_1}	⋯	a_{C_1,O_k}	…	a_{C_1,O_l}	…	a_{C_1,O_n}
⋮	⋮	⋮	⋮	⋮		⋮	⋮
C_i	a_{C_i,O_1}	⋯	a_{C_i,O_k}	…	a_{C_i,O_l}	…	a_{C_i,O_n}
⋮	⋮	⋮	⋮	⋮		⋮	⋮
C_j	a_{C_j,O_1}	⋯	a_{C_j,O_k}	…	a_{C_j,O_l}	…	a_{C_j,O_n}
⋮	⋮	⋮	⋮	⋮		⋮	⋮
C_m	a_{C_m,O_1}	⋯	a_{C_m,O_k}	⋯	a_{C_m,O_l}	…	a_{C_m,O_n}

where for every $p,\ q$ $(1 \le p \le m, 1 \le q \le n)$:

- C_p is a criterion, taking part in the evaluation;
- O_q is an object, being evaluated;
- a_{C_p,O_q} is a real number or another object, that is comparable about relation R with other a – object, so that for each $i,\ j,k : R\left(a_{C_k,O_i}, a_{C_k,O_j}\right)$ is defined. Let $\bar{R}$ be the inverse relation of R. For example, if "R" is the relation "<", then $\bar{R}$ is the relation ">", and vice versa.

Let $S_{l,k}^{\mu}$ be the number of cases in which $R(a_{C_k,O_i}, a_{C_k,O_j})$ and $R(a_{C_l,O_i}, a_{C_l,O_j})$ are simultaneously satisfied. Let $S_{k,l}^{\nu}$ be the number of cases in which $R(a_{C_k,O_i}, a_{C_k,O_j})$ and $\bar{R}(a_{C_l,O_i}, a_{C_l,O_j})$ are simultaneously satisfied.

Obviously,

$$S_{l,k}^{\mu} + S_{l,k}^{\nu} \le \frac{n(n-1)}{2}$$

Now, for every $k,\ l$ such that $1 \le k < l \le m$, and for $n \ge 2$, it can be defined:

$$\mu_{C_k,C_l} = \frac{2S_{k,l}^{\mu}}{n(n-1)}, \qquad \nu_{C_k,C_l} = \frac{2S_{k,l}^{\nu}}{n(n-1)}$$

Therefore, $\langle \mu_{C_k,C_l}, \nu_{C_k,C_l} \rangle$ is an IFP. The following IM can be constructed:

	C_1	⋯	C_m
C_1	$\langle \mu_{C_1,C_1}, \nu_{C_1,C_1} \rangle$	⋯	$\langle \mu_{C_1,C_m}, \nu_{C_1,C_m} \rangle$
⋮	⋮	⋮	⋮
C_m	$\langle \mu_{C_m,C_1}, \nu_{C_m,C_1} \rangle$	⋯	$\langle \mu_{C_m,C_m}, \nu_{C_m,C_m} \rangle$

It determines the degrees of correspondence between criteria $C_1, \ldots, C_m$. Here μ_{C_k,C_l} and ν_{C_k,C_l} are the degree of agreement and of disagreement, respectively.

3 Materials and Methods

The transformation of lysine to carnitine in all cells of the human body is dependent on vitamin C levels. It has been assessed that about 0.1 % of the dietary lysine is transformed to carnitine in the human organism. Carnitine is missing in a vegetable-based diet; it is only found in animal food. Because of this vegetarians who consume a lysine-deprived diet could have insufficient quantity of carnitine. The carnitine biosynthesis is shown in Fig. 1 [9].

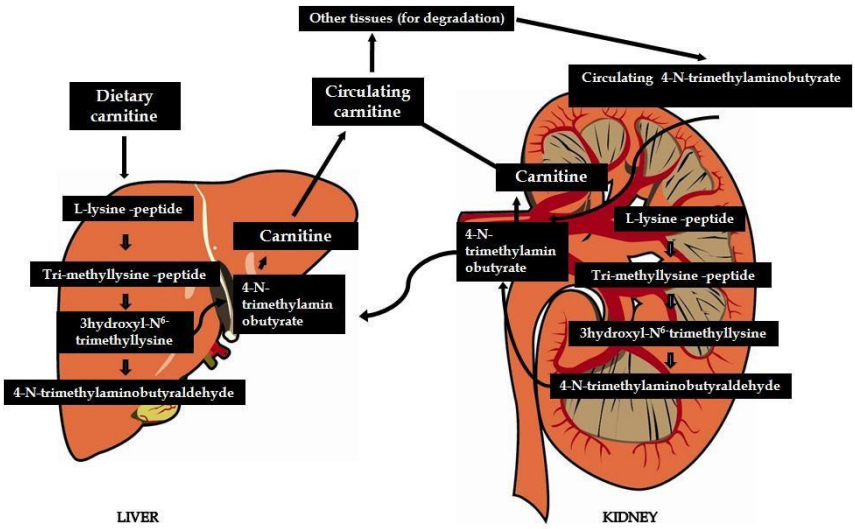


Figure 1: Carnitine biosynthesis and metabolism

Experimental investigations

Two fermentation of the strain *Brevibacterium flavum* 22LD are carried out in a 15 liter bioreactor [11, 16]. The experimental investigations are done in a bioreactor that is included in an Automatic Control System (ACS). The ACS is flexible and includes control of the following parameters of the

process: rotation speed, oxygen partial pressure, temperature, pH, foam level, gas flow rate, flow rates of the main substance.

The processes conditions are as follows: temperature – 30°C, pH = 6.8-7.6, pO_2 = 20-30%, gas flow rate – Q_G = 60 L/h; rotation speed – n = 450 min^{-1}; maximum bioreactor volume – V = 15 L.

The *L-lysine* production is a typical two-phase process for the most strains-producers. The first phase is characterized by intense accumulation of biomass and absence of the lysine biosynthetic pathway. The second phase is characterized by stunted growth and accumulation of lysine in the culture liquid. The excess threonine concentration affects negatively the activity of the dehydrogenase of β-semialdehyde of the aspartic acid and thus reduces the lysine synthesis. The addition in the culture medium of the various components at a high concentration of threonine can deflect the producers to synthesize homoserine, isoleucine, methionine, or lactic acid [16].

In this paper we will search dependence between the kinetic variables of the process: X – biomass concentration, g/L; S – substrate concentration, g/L; Tr – threonine concentration, g/L; O – oxygen concentration, g/L; L – product (lysine) concentration, g/L. We will search dependencies between these variables with the aim to find the structure of the process model.

Available experimental data for dynamics of the main process variables [11, 16] are used in the application of ICA.

4 Results and Discussion

Following [13, 15] we apply the ICA and compute the degree of agreement and the degree of disagreement ($\mu_{C_iC_j}$ and $\nu_{C_iC_j}$) for the biomass concentration, substrate concentration, oxygen concentration, threonine concentration and lysine concentration. The obtained results are shown in Table 1. In addition, the parameter k_La (volumetric oxygen mass-transfer coefficient, h^{-1}) is included in this investigation.

Also we investigate another basic characteristics for growth and biosynthesis of the strain *Brevibacterium flavum* 22LD – substrate consumption rate ($\boldsymbol{X}^{-1}(dS/dt)$) and product accumulation rate ($\boldsymbol{X}^{-1}(dL/dt)$). The results for $\mu_{C_iC_j}$ and $\nu_{C_iC_j}$ are shown in Table 2.

Table 1. The calculated values of pair $\langle \mu_{C_i C_j}, \nu_{C_i C_j} \rangle$ for the *X*, *S*, *O*, *Tr* and *L* concentrations

	X	***S***	***L***	***Tr***	***O***	$k_L a$
X		⟨0.02, 0.78⟩	⟨0.89, 0.05⟩	⟨0.79, 0.15⟩	⟨0.25, 0.50⟩	⟨0.33, 0.28⟩
S	⟨0.02, 0.78⟩		⟨0.94, 0.01⟩	⟨0.94, 0.00⟩	⟨0.56, 0.36⟩	⟨0.35, 0.30⟩
L	⟨0.89, 0.05⟩	⟨0.94, 0.01⟩		⟨0.02, 0.71⟩	⟨0.79, 0.19⟩	⟨0.28, 0.37⟩
Tr	⟨0.79, 0.15⟩	⟨0.94, 0.00⟩	⟨0.02, 0.71⟩		⟨0.51, 0.20⟩	⟨0.35, 0.21⟩
O	⟨0.25, 0.50⟩	⟨0.56, 0.36⟩	⟨0.79, 0.19⟩	⟨0.51, 0.20⟩		⟨0.55, 0.08⟩
$k_L a$	⟨0.33, 0.28⟩	⟨0.35, 0.30⟩	⟨0.28, 0.37⟩	⟨0.35, 0.21⟩	⟨0.55, 0.08⟩	

Table 2. The calculated values of pair $\langle \mu_{C_i C_j}, \nu_{C_i C_j} \rangle$ for the *X*, *O*, $X^{-1}(dS/dt)$ and $X^{-1}(dL/dt)$ concentrations

	X	***O***	$X^{-1}(dS/dt)$	$X^{-1}(dL/dt)$
X		⟨0.88, 16⟩	⟨0.18, 0.64⟩	⟨0.83, 0.14⟩
O	⟨0.88, 0.16⟩		⟨0.79, 0.07⟩	⟨0.88, 0.22⟩
$X^{-1}(dS/dt)$	⟨0.18, 0.64⟩	⟨0.79, 0.07⟩		⟨0.89, 0.11⟩
$X^{-1}(dL/dt)$	⟨0.83, 0.14⟩	⟨0.88, 0.22⟩	⟨0.89, 0.11⟩	

With the help of the results presented in Table 1 and Table 2 we will search the dependencies between the basic kinetic variable of the process. At first we will discuss the relation between the biomass, substrate and product (lysine).

4.1. Structural Identification of the Model

Dependencies for the biomass

The results show that the relations between biomass and threonine, i.e. pair $\langle \mu, \nu \rangle$ is ⟨0.79, 0.15⟩ (Table 1), with a small uncertainty $\pi = 0.06$. There is dependence between *X* and *Tr*. It is known that *Breviberium* are auxotrophy mutants. Absence of threonine and methionine in the culture lead to the cessation of their growth [11, 16]. In accordance to this and to achieve results the threonine is included to the Monod kinetics (Monod's equation) as a growth limiting factor:

$$\frac{dX}{dt} = \varepsilon X$$

where ε is the specific growth rate:

$$\varepsilon = \frac{k_1 Tr}{k_2 + Tr} \tag{1}$$

where here and further k_i are kinetic coefficients.

Dependencies for the substrate

The obtained relation between substrate and biomass – the pair $\langle \mu, \nu \rangle$ is $\langle 0.02, 0.78 \rangle$, with too large uncertainty $\pi = 0.245$. In this case we do not conclude, based on ICA, that there is a relation between the substrate and biomass.

Let us look at the relation $X^{-1}(dS/dt)$ to $X^{-1}(dL/dt)$. The pair $\langle \mu, \nu \rangle$ is $\langle 0.89, 0.11 \rangle$ (Table 2), and uncertainty is $\pi = 0$. In this case, based on ICA results, we include dL/dt in the equation for the dynamics of S. Following [16] the carbon source consumption could be defined by biomass growth, maintaining the biomass in active form and lysine accumulation:

$$\frac{dS}{dt} = -k_3 \varepsilon X - k_4 X - k_5 \frac{dL}{dt}$$

In case of extracellular product accumulation, the substrate limitation for the product synthesis is considerable. Here the carbon is almost 50% of the lysine molecular mass $C_5H_{14}O_2N_2$ and the 30-40 g/L concentration of lysine at the end of the batch process is needed to achieve high sugar utilization.

Dependencies for the biomass to oxygen

It is known [16] that for all fermentation cycle around 30 g oxygen are spent for 1 L cultural broad. The saturation concentration of the dissolved oxygen is 6.1 mg/L. The low solubility, on the one hand, and high requirements of the medium of oxygen, on the other hand, require high aeration of the medium during cultivation. Taking into account the role of carbon sources and oxygen concentrations [16] in the kinetic model (1) additional parts are added – a part accounting activation of oxygen increase and decrease, proportional to the consumption of sugars

$$\varepsilon_1 = \frac{k_1 \, Tr \, O}{(k_2 + Tr)(k_3 + S_0 - S)(k_4 + O)} \qquad (2)$$

where S_0 denotes concentration of substrate in the feeding solution, g/L.

Dependencies for the lysine and threonine

The lysine accumulation is function of the biomass. The ICA results confirm the dependence between biomass and lysine – the pair $\langle \mu, \nu \rangle$ is $\langle 0.89, 0.05 \rangle$, with an insignificant uncertainty of $\pi = 0.06$. Let us look at the relation of the lysine to the substrate from Table 1. The pair $\langle \mu, \nu \rangle$ is $\langle 0.94, 0.01 \rangle$ again with an insignificant uncertainty of $\pi = 0.05$. Also from Table 2 the relation of the lysine to the substrate is evident – the pair $\langle \mu, \nu \rangle$ is $\langle 0.89, 0.11 \rangle$, with uncertainty $\pi = 0$. The obtained results show the dependence between lysine

and substrate and biomass. The dependence between the lysine and oxygen is also established: ⟨0.79, 0.19⟩. Following the ICA results and [16] the dynamics of the lysine concentration has the form:

$$\frac{dL}{dt} = \vartheta\, X$$

where ϑ is the specific consumption rate of substrate, h^{-1}:

$$\vartheta = \frac{k_8\, S\, O}{(k_9 + S)(k_{10} + S)(k_{11} + O)(k_{12} + O)}$$

The threonine consumption is available only in case of biomass growth. The ICA results show the dependence between threonine and biomass (see *Dependencies for the biomass*) and between threonine and substrate (⟨μ, ν⟩ ⟨0.94, 0.00⟩). Based on the obtained results the equation for the threonine has the following form:

$$\frac{dTr}{dt} = k_{13}\frac{dX}{dt} = k_{13}\,\varepsilon_1\, X$$

Finally the oxygen dynamics should be defined. For ICA results (see Table 1) the relation between X and O shows that they do not have a strong positive relation – ⟨0.25, 0.50⟩, with a large uncertainty of π = 0.25. Following Table 2 the relation between them is the pair ⟨μ, ν⟩ ⟨0.88, 0.11⟩ with small uncertainty. This second experiment (Table 2) gives better results and we can confide the oxygen consumption depends on the biomass concentration.

The oxygen consumption is dependent also on the lysine accumulation (already explained). The relation between oxygen and lysine (Table 1) is ⟨0.79, 0.19⟩, with small uncertainty of π = 0.02. From Table 2 the relation between oxygen and $X^{-1}(dL/dt)$ is the pair ⟨μ, ν⟩: ⟨0.88, 0.22⟩, with π = 0.

Based on the analysis of the results, the dynamics of the oxygen concentration has the form:

$$\frac{dO}{dt} = -k_{14}\,\varepsilon_1\, X - k_{15}X - k_{16}\vartheta\, X + k_{17}(O^* - O)$$

where rate k_{17} (also the volumetric oxygen mass-transfer coefficient (k_La)) is oxygen feed up during the fermentation and O^* is saturation oxygen concentration.

In *Brevibacterium flavum* 22LD fermentation process the dynamics of the main process variables based on mass balance [16] and ICA results are presented as follows:

$$\frac{dX}{dt} = \varepsilon_1 X$$
$$\frac{dS}{dt} = -k_5\varepsilon_1 X - k_6 X - k_7\vartheta X$$
$$\frac{dL}{dt} = \vartheta X$$
$$\frac{dTr}{dt} = k_{13}\,\varepsilon_1 X$$
$$\frac{dO}{dt} = -k_{14}\,\varepsilon_1 X - k_{15}X - k_{16}\vartheta X + k_{17}(O^* - O)$$

4.2. Parameter Identification of the Model

Based on the available experimental data for the main process variables – *X*, *S*, *O*, *Tr* and *L* model parameter identification is fulfilled using GA.

The GA have already proved effective in solving complex, non-linear optimization tasks. GA operators and parameters, applied for the considered here parameter identification procedures, are as follows:

- encoding – binary
- crossover – double point
- mutation – bit inversion
- selection – roulette wheel selection
- fitness function – linear ranking

and

- generation gap – 0.97
- crossover rate – 0.70
- mutation rate – 0.1
- number of individuals – 100
- number of generations – 100

The optimization criterion is presented as a minimization of a distance measure *J* between experimental and model predicted values of process variables (*X*, *S*, *O*, *Tr* and *L*), represented by the vector *y*:

$$J = \sum_{i=1}^{n}\sum_{j=1}^{m}\left\{\left[y_{exp}(i) - y_{mod}(i)\right]_j\right\}^2 \rightarrow min$$

where J is the optimization criterion, n – number of measurements for each process variable, m – number of process variables, y_{exp} – experimental data vector, y_{mod} – model predicted data vector.

Matlab environment is used of parameter identification procedures and a script contained the necessary instructions for *Genetic Algorithm Toolbox* [8] has been also developed.

The initial conditions of the process are:

$X(0)$ =3.0 g/L; $S(0)$ = 100.0 g/L;

$Tr(0)$ = 80.0 g/L; $O(0)$ = 6.1 mg/L.

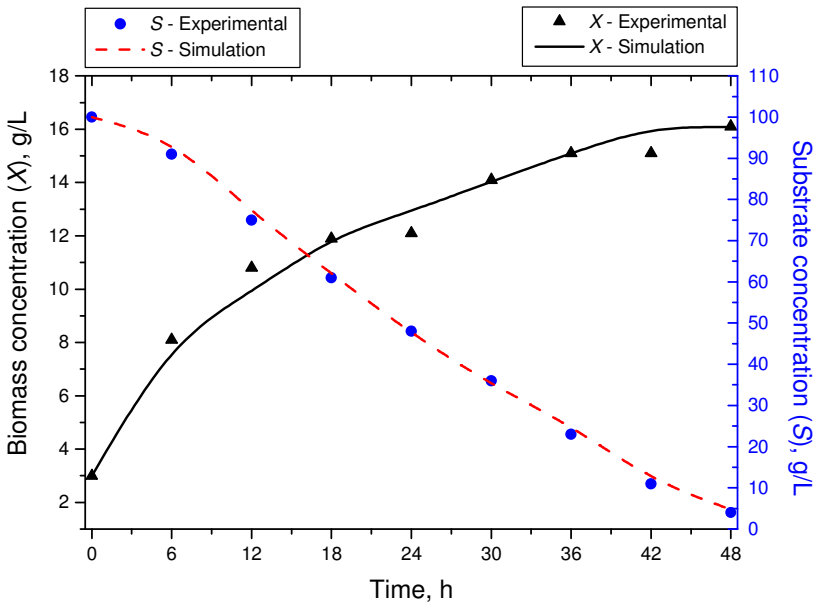
The obtained model parameters estimates are as follows:

k_1 = 20.80, k_2 = 42.00, k_3 = 28.00, k_4 = 1.1, k_5 = 1.01, k_6 = 0.07,

k_7 = 0.51, k_8 = 62.0, k_9 = 28.0, k_{10} = 37.0, k_{11} = 4.0, k_{12} = 0.12,

k_{13} = 6.1, k_{14} = 448.0, k_{15} = 22.0, k_{16} = 209.0, k_La = k_{17} = 120.0.

The results show (Fig. 2) that the model fit very well with the experimental data.



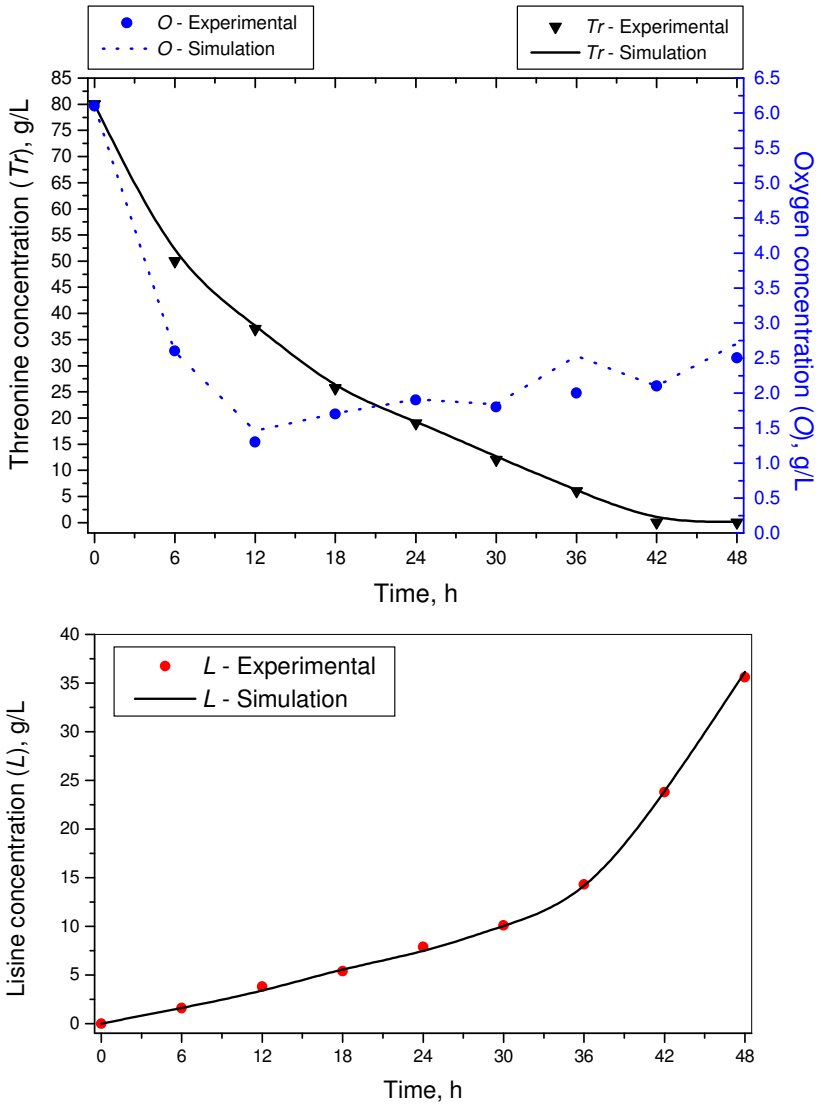


Fig. 2 Comparison between a model simulated and a real *Brevibacterium flavum* 22LD fermentation process

5 Conclusion

Carnitine is studied extensively in part because of the important role it plays in fatty acid oxidation and energy production. Amino acid *L-lysine* promotes cell division and is necessary for carnitine production. *Brevibacterium flavum* is considered the most suitable organism for the lysine production. In this paper we examine a *Brevibacterium flavum* 22LD fermentation process for *L-lysine* production.

We have used ICA as a method for decision making in the modeling of the *Brevibacterium flavum* 22LD fermentation process. The aim of the paper was to establish the basic dependencies between the different kinetic variable of the process. Based on ICA results and known kinetic relations we have confirmed mathematical structure of the considered fermentation process. After that we have made a parametric identification of this bioprocess. Applying Genetic Algorithms we have done model parameter identification. The results have shown that the model fits very well with the experimental data.

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