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Modelling and multicriteria analysis for selection of growth rate models for batch cultivation of *Kluyveromyces marxianus var. lactis* MC 5 yeast. Part II: Multi-criteria decision analysis for selecting of growth rate model

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In the second part of the work we apply the PROMETHEE II method for multi-criteria decision analysis to determine the most appropriate models of the ten unstructured models studied in the first part – *Monod, Mink, Tessier, Moser, Aiba, Andrews, Haldane, Luong, Edward* and *Han-Levenspiel* for the growth rate as a function of *lactose-only* or *oxygen-only* in the batch cultivation of the yeast *Kluyweromyces marxianus var. lactis* MC 5. The results obtained after application of PROMETHEE II method showed that the most suitable pair of models is the *Tessier* model for *lactose-only* and the *Monod* model for *oxygen-only*.

Keywords: Multi-criteria decision analysis, yeast *Kluyveromyces marxianus var. lactis* MC 5, PROMETHEE II method, growth rate models

INTRODUCTION

Multi-criteria decision analysis (MCDA) is a branch of operation research models and a well-known field of decision-making. The main objective of MCDA is to select the alternative that has the highest score according to the set of evaluation criteria [1].

There are several different methods, of which the most important are analytic hierarchy processes [2], elimination and choice expressing reality [3], multi-attribute utility theory [4], preference ranking organization methods (PROMETHEE) [5, 6], etc.

A study of various mathematical models of the specific growth rate of a batch process of yeast *Saccharomyces cerevisiae* for ethanol production was performed. The selection of the most suitable model was made using the PROMETHEE II method performed by Petrov [7].

Modelling and simulation of the process for ten unstructured models in batch cultivation of yeast *Kluyveromyces marxianus var lactis* MC 5 were performed. For the first time in modelling and simulation of this process two independent kinetic models were used, separately for *lactose* and *oxygen*, performed by Petrov [8].

In this study, the PROMETHEE II method was used to evaluate and select growth rate models for batch process of yeast *Kluyweromyces marxianus var. lactis* MC 5. After selecting the most appropriate models, the process will be simulated with the selected specific growth rate.

MATERIALS AND METHODS

Kinetic models

The kinetic models are proposed independently in [8]:

- *Biomass formation from lactose-only*

$$\begin{aligned} \frac{dX}{dt} &= \mu(S)\,X \\ \frac{dS}{dt} &= -\frac{1}{Y_{X/S}}\frac{dX}{dt} \end{aligned} \tag{1}$$

- *Biomass formation from oxygen-only*

$$\begin{aligned} \frac{dX}{dt} &= \mu(C)\,X \\ \frac{dC}{dt} &= -\frac{1}{Y_{X/C}}\frac{dX}{dt} + k_l a(C^* - C) \end{aligned} \tag{2}$$

where: t – process time, h; X – *biomass* concentration, g/L; S – *lactose* concentration, g/L; $\mu(S)$ – growth rate of biomass from *lactose-only*, h^{-1}; $Y_{X/S}$ – yield coefficients of formation of the *biomass* from *lactose*, g/g; C – *oxygen* concentration, g/L; $\mu(C)$ – growth rate of biomass from *oxygen-only*, h^{-1}; $Y_{X/C}$ – yield coefficients of formation of the *biomass* from *oxygen*, g/g; $k_l a$ – mass transfer coefficient, h^{-1}; C^* – maximal *oxygen* concentration in liquid phase, g/L.

The initial conditions of both models (Eqns. 1, 2) are: $X(0) = 0.2$ g/L, $S(0) = 44$ g/L; $C(0) = 6.65\times10^{-3}$ g/L, and $C^* = C(0)$.

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Specific growth rate models

In the first part [8] of this work, modelling and simulation of ten unstructured models was performed (Table 1): M_1 – *Monod*, M_2 – *Mink,* M_3 – *Tessier*, M_4 – *Moser*, M_5 – *Aiba*, M_6 – *Andrews*, M_7 – *Haldane*, M_8 – *Luong*, M_9 – *Edward* and M_{10} – *Han-Levenspil* to explain the cell growth kinetics.

Table 1. Tested growth rate models dependent on *lactose* or *oxygen*

Model	$\mu(\mathbf{Z})$
$M_1(\mathbf{Z})$	$\mu(\mathbf{Z}) = \dfrac{\mu_m^{\mathbf{Z}}\,\mathbf{Z}}{K_{\mathbf{Z}} + \mathbf{Z}}$
$M_2(\mathbf{Z})$	$\mu(\mathbf{Z}) = \dfrac{\mu_m^{\mathbf{Z}}\,\mathbf{Z}^2}{K_{\mathbf{Z}} + \mathbf{Z}^2}$
$M_3(\mathbf{Z})$	$\mu(\mathbf{Z}) = \mu_m^{\mathbf{Z}}\left(1 - \exp\left(-\mathbf{Z} / K_{\mathbf{Z}I}\right)\right)$
$M_4(\mathbf{Z})$	$\mu(\mathbf{Z}) = \dfrac{\mu_m^{\mathbf{Z}}\,\mathbf{Z}^{\alpha_M}}{K_{\mathbf{Z}} + \mathbf{Z}^{\alpha_M}},\ \alpha_M > 0$
$M_5(\mathbf{Z})$	$\mu(\mathbf{Z}) = \dfrac{\mu_m^{\mathbf{Z}}\,\mathbf{Z}}{K_{\mathbf{Z}} + \mathbf{Z}} \exp\left(-\mathbf{Z} / K_{\mathbf{Z}I}\right)$
$M_6(\mathbf{Z})$	$\mu(\mathbf{Z}) = \dfrac{\mu_m^{\mathbf{Z}}\,\mathbf{Z}}{(K_{\mathbf{Z}} + \mathbf{Z})\left(1 + \mathbf{Z} / K_{\mathbf{Z}I}\right)}$
$M_7(\mathbf{Z})$	$\mu(\mathbf{Z}) = \dfrac{\mu_m^{\mathbf{Z}}\,\mathbf{Z}}{K_{\mathbf{Z}} + \mathbf{Z} + \mathbf{Z}^2 / K_{\mathbf{Z}I}}$
$M_8(\mathbf{Z})$	$\mu(\mathbf{Z}) = \dfrac{\mu_m^{\mathbf{Z}}\,\mathbf{Z}}{K_{\mathbf{Z}} + \mathbf{Z}}\left(1 - \mathbf{Z} / \mathbf{Z}_m\right)^n$
$M_9(\mathbf{Z})$	$\mu(\mathbf{Z}) = \dfrac{\mu_m^{\mathbf{Z}}\,\mathbf{Z}}{K_{\mathbf{Z}} + \mathbf{Z} + \left(1 + \mathbf{Z} / K\right)\left(S^2 / K_{\mathbf{Z}I}\right)}$
$M_{10}(\mathbf{Z})$	$\mu(\mathbf{Z}) = \dfrac{\mu_m^{\mathbf{Z}}\,\mathbf{Z}}{\mathbf{Z} + K_{\mathbf{Z}}} \dfrac{\left(1 - \mathbf{Z} / \mathbf{Z}_m\right)^n}{\left(1 - \mathbf{Z} / \mathbf{Z}_m\right)^m}$

In Table 1: $\mathbf{Z} = [S, C]^{\mathrm{T}}$ – vector with basic energetic substrates *lactose* and *oxygen*, respectively; $\mu_m^{\mathbf{Z}}$ – maximum growth rate for *lactose* and *oxygen*, respectively, h^{-1}; $K_{\mathbf{Z}}$ – *Monod* saturation constants for cell growth on *lactose* and *oxygen*, g/L; α_M – *Moser* constant; $K_{\mathbf{Z}I}$ – inhibition constants for cell growth on *lactose* and *oxygen*, g/L; K – constant in *Edward* model, g/L; $\mathbf{Z}_m$ – critical inhibitor concentrations, above which the reactions stops, g/L; m, n – constants in the *Luong* and the *Han-Levenspiel* models.

Criteria using PROMETHEE II method

The criteria used in the PROMETHEE II method are the same as those used in [8]: $C_1(S)$ / $C_1(C)$ – criteria for evaluation of kinetic parameters; $C_2(S)$ / $C_2(C)$ – *statistic* λ; [$C_3^{'}(X)$ and $C_4(S)$] or [$C_3^{''}(X)$ and $C_4(C)$] – relative error (S_L) for the kinetics variables (X, S) or (X, C); [$C_5^{'}(X)$ and $C_6(S)$] or [$C_5^{''}(X)$ and $C_6(C)$] – experimental Fisher coefficient for the kinetic variables (X, S) or (X, C); [$C_7^{'}(X)$ and $C_8(S)$] or [$C_7^{''}(X)$ and $C_8(C)$] – experimental correlation coefficient R^2 for kinetic variables (X, S) or (X, C).

Background of PROMETHEE II method

The basic principle of PROMETHEE II is based on a pair-wise comparison of alternatives along each recognized criterion. Alternatives were evaluated according to different criteria, which had to be maximized or minimized. The implementation of the PROMETHEE II required two additional types of information [5, 6]:

- *Selection of the Weight*

Determination of the weight is an important step in most of the multi-criteria methods. PROMETHEE II assumes that the decision-maker is able to weigh the criteria appropriately, at least when the number of criteria is not too large.

- *Selection of the Preference Function*

For each criterion, the preference function translates the difference between the evaluations obtained by two alternatives into a preference degree, ranging from zero to one. In order to facilitate the selection of a specific preference function, Brans and Vincke [5] propose six basic types: Type I – Usual criterion; Type II – U-shape criterion; Type III – V-shape criterion; Type IV – Level criterion; Type V – linear with an indifference criterion; and Type VI – Gaussian criterion.
The decision-making process using the PROMETHEE method consists of five steps, which are described in detail in [5, 6].

- *The Software Packages*

In our work, we used the new PROMETHEE-GAIA Academic Edition software to solve the multi criteria decision making problem, called Visual PROMETHEE by PROMETHEE-GAIA.net [9], and developed under the guidance of B. Mareschal.

RESULTS AND DISCUSSION

The modelling and simulation results for *lactose-only*, and *oxygen-only* are described in detail in [8].

Tables 2 and 3 show the results for the criteria by which the models (M_1 – M_{10}) are validated.

Table 2. Criteria for models validation from *lactose-only*

Models	$C_1(S)$	$C_2(S)$	$C_3^{'}(X)$	$C_4(S)$	$C_5^{'}(X)$	$C_6(S)$	$C_7^{'}(X)$	$C_8(S)$
$M_1(S)$	13.8827	151.8377	0.2262	0.5030	1.0125	1.1676	0.9864	0.9754
$M_2(S)$	9.6736	**204.1643**	0.2058	**0.6288**	1.0598	**1.0253**	**0.9744**	0.9920
$M_3(S)$	10.6736	**151.3657**	0.1982	0.3879	1.0220	1.1364	**0.9869**	0.9819
$M_4(S)$	9.2521	175.7246	0.1960	0.3883	1.0471	1.0591	0.9790	0.9894
$M_5(S)$	14.0315	151.7896	0.2274	0.5067	1.0124	1.1690	0.9863	0.9752
$M_6(S)$	13.9697	151.9010	0.2270	0.5051	1.0129	1.1684	0.9863	0.9753
$M_7(S)$	13.9765	152.1378	0.2272	0.5045	1.0130	1.1681	0.9864	0.9752
$M_8(S)$	13.8925	151.7663	0.2262	0.5036	1.0128	1.1679	0.9864	0.9754
$M_9(S)$	**14.1648**	151.9544	**0.2289**	0.5087	**1.0118**	**1.1698**	0.9863	**0.9749**
$M_{10}(S)$	**6.0574**	184.7091	**0.1641**	**0.1845**	**1.0694**	1.0313	0.9853	**0.9944**

Table 3. Criteria for model validation from *oxygen-only*

Models	$C_1(C)$	$C_2(C)$	$C_3^{''}(X)$	$C_4(C)$	$C_5^{''}(X)$	$C_6(C)$	$C_7^{''}(X)$	$C_8(C)$
$M_1(C)$	0.6734	**154.5335**	0.1612	0.5992	1.0127	1.0174	**0.9992**	0.9986
$M_2(C)$	1.5593	163.0421	0.1864	**0.9618**	1.0187	1.0155	**0.9988**	**0.9963**
$M_3(C)$	1.0059	161.9099	0.1748	0.8047	1.0141	1.0203	0.9991	0.9978
$M_4(C)$	**0.6727**	156.9493	**0.1596**	0.6473	**1.0115**	1.0223	**0.9992**	**0.9988**
$M_5(C)$	1.1461	160.2555	0.1818	0.2635	1.0174	1.0178	0.9989	0.9975
$M_6(C)$	1.4423	**172.3611**	**0.2021**	0.2539	1.0223	1.0235	0.9989	0.9969
$M_7(C)$	**1.6108**	169.1571	0.1941	0.2713	1.0195	**1.0286**	0.9989	0.9965
$M_8(C)$	1.1806	165.3167	0.1869	**0.2492**	1.0218	1.0164	0.9989	0.9975
$M_9(C)$	1.1256	159.8748	0.1812	0.2646	1.0176	1.0169	0.9989	0.9975
$M_{10}(C)$	1.0604	163.3446	0.1855	0.2611	**1.0226**	**1.0111**	0.9990	0.9978

Here it is time to specify that for criteria C_1 – C_6 we are looking for min., and for criteria C_7 and C_8 – for max. The best values of all criteria are marked in green. The maximum values for criteria C_1 – C_6 and the minimum values for criteria C_7 and C_8 are marked in red.

Application of PROMETHEE II method

Selection of the weight

Criteria C_1 – C_4 are the most important. That is why for them we choose double weight (in %): w_j = 17%, j = 1, ..., 4 in comparison with criteria C_5 – C_8: w_j = 8%, j = 5, ..., 8. The sum of all weights fulfils the condition: $\Sigma w_j = 100\%$, j = 1, …, 8.

Selection of the Preference Function

Choosing a preference function is a very important task. In this work, we have chosen to have a strict preference for the alternative with the highest value. For this reason, Type I – usual criterion has been chosen for all criteria. Its function is preferably shown in Fig. 1.

$$p(x) = \begin{cases} 0 & x \le 0 \\ 1 & x > 0 \end{cases}$$

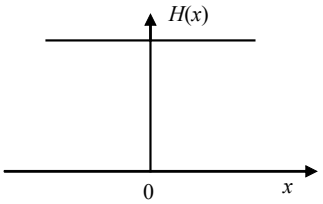

Fig. 1. Type I – Usual criterion

We used PROMETHEE Academic Edition software [9] to solve the multi-criteria decision making problem. The results for different growth rate models when a PROMETHEE II method was applied are shown in Table 4.

The models with the highest Rank (Table 4) for growth rate are: model M_3 (*Tessier*) for *lactose-only* and model M_1 (*Monod*) for *oxygen-only*:

$$\mu(S,C) = \mu_{\max}\,(1 - \mathrm{EXP}(-S/K_S))\,\frac{C}{(K_C + C)} \qquad (3)$$

Table 4. Results after application of the PROMETHEE II method

Lactose-only				
Rank	Action	ϕ	ϕ^+	ϕ^-
1	***M*3(*S*)**	**0.5556**	**0.7778**	**0.2222**
2	$M_{10}(S)$	0.3889	0.6944	0.3056
3	$M_4(S)$	0.2407	0.6204	0.3796
4	$M_1(S)$	0.2315	0.5926	0.3611
5	$M_8(S)$	0.1944	0.5741	0.3796
6	$M_2(S)$	-0.1852	0.4074	0.5926
7	$M_6(S)$	-0.2222	0.3796	0.6019
8	$M_7(S)$	-0.3056	0.3333	0.6389
9	$M_5(S)$	-0.3241	0.3241	0.6481
10	$M_9(S)$	-0.5741	0.2037	0.7778
Oxygen-only				
Rank	Action	ϕ	ϕ^+	ϕ^-
1	***M*1(*C*)**	**0.5833**	**0.7870**	**0.2037**
2	$M_4(C)$	0.5648	0.7778	0.2130
3	$M_3(C)$	0.1852	0.5648	0.3796
4	$M_9(C)$	0.1759	0.5833	0.4074
5	$M_5(C)$	0.1389	0.5648	0.4259
6	$M_{10}(C)$	0.0926	0.5185	0.4259
7	$M_8(C)$	-0.1111	0.4167	0.5278
8	$M_6(C)$	-0.4815	0.2593	0.7407
9	$M_7(C)$	-0.5000	0.2315	0.7315
10	$M_2(C)$	-0.6481	0.1574	0.8056

The kinetic model of the process has the form:

$$\begin{aligned} \frac{dX}{dt} &= \mu(S,C)\,X \\ \frac{dS}{dt} &= -\frac{1}{Y_{X/S}}\frac{dX}{dt} \\ \frac{dC}{dt} &= -\frac{1}{Y_{X/C}}\frac{dX}{dt} + k_l a(C^* - C) \end{aligned} \quad , \qquad (4)$$

The criteria for the model (Eqn. 4) differ from the criteria used in modelling and simulation of the process independently of *lactose* and *oxygen*. In this case, instead of eight criteria we have eleven. This is because we already have three kinetic variables of the process (*X*, *S* and *C*):

- C_1 – criteria for evaluation of kinetic parameters in model;
- C_2 – *statistic* λ;
- $C_3(X)$, $C_4(S)$, $C_5(C)$ – relative error (S_L) for the kinetic variables of the model;
- $C_6(X)$, $C_7(S)$, $C_8(C)$ – experimental Fisher coefficients for the kinetic variables of the model;
- $C_9(X)$, $C_{10}(S)$, $C_{11}(C)$ – experimental correlation coefficients R^2 for kinetic variables of the model.

Criteria (C_1) for evaluation of kinetic parameters in the model (Eqns. 4) are determined by the following dependence:

$$C_1 = \frac{1}{N}\sum_{i=1}^{N}\left(\frac{(X_e(t_i)-X_m(t_i))^2}{X^2_{e\max}} + \frac{(S_e(t_i)-S_m(t_i))^2}{S^2_{e\max}} + \frac{(C_e(t_i)-C_m(t_i))^2}{C^2_{e\max}}\right) \qquad (5)$$

where: C_1 – sums of the squares of weighted residuals; N – number of the experiments; t_i – time partitions, h; $X_e(t_i), S_e(t_i), C_e(t_i)$ – measurement values of kinetic variables, g/L; $X_m(t_i), S_m(t_i), C_m(t_i)$ – simulated values with models of kinetics variables, g/L; $X^2_{e\max}, S^2_{e\max}, C^2_{e\max}$ – maximal measurement values of kinetic variables, g/L.

In the next part of the work a simulation of the model will be performed.

Simulation

An algorithm and program of COMPAQ Visual FORTRAN 90 [10] were developed in order to identify the parameters in the model (Eqn. 4**)** for batch cultivation process of yeast *Kluyweromyces marxianus var. lactis* MC 5. For solving the nonlinear problem for computing criteria C_1, we used a direct search method, a subroutine BCPOL with double precision from IMSL Math/Library [11]. All computations were performed using HexaCore AMD Phenom II X6 1075T, 3 GHz, 8 GB RAM, Windows XP operating system (32 bit).

The calculated values of the kinetic parameters in the model are shown in Table 5.

Table 5. Calculated values of kinetic parameters

Parameter	Search bound	Value
$\mu_{\max}$	[0.1, 1.0]	0.7405
K_S	[0.01, 5.0]	0.0101
K_C	[0.1, 7.0]×10^{-3}	0.4654×10^{-3}
$Y_{X/S}$	[0.1, 1.5]	0.4334
$Y_{X/C}$	[0.1, 5.0]	3.9101
k_la	[80.0, 180]	164.0484

The calculated values of the model validation criteria ($C_1 - C_{11}$) are as follows: $C_1 = 6.83\times10^{-3}$; $C_2 = 149.84$; $C_3 = 0.188$; $C_4 = 0.340$; $C_5 = 0.428$; $C_6 = 1.05$; $C_7 = 1.06$; $C_8 = 1.01$; $C_9 = 0.987$; $C_{10} = 0.994$; $C_{11} = 0.997$.

The criteria C_2, and $C_6 - C_{11}$, are statistical. The theoretical values of C_2 and $C_6 - C_{11}$ are given from statistical tables [12]. Fisher coefficient for C_2 (*Statistic* λ) is $F_T^{\lambda}(2,11) = 4.04$. Fisher coefficients for criteria $C_6 - C_8$ are $F_T(11,2) = 19.40$, and correlation coefficient for criteria $C_9 - C_{11}$ is $R^2_T(11) = 0.684$ for level of significance $\alpha = 0.01$. The experimental Fisher coefficients criteria are $C_2 > F_T^{\lambda}(2,11) = 4.04$ and$(C_6 - C_8) < F_T(11, 2) =$

19.40. The experimental correlation coefficients criteria are $(C_9 - C_{11}) > R_T^2(11) = 0.684$.

From the comparison of the criteria $(C_2, C_6 - C_{11})$ for validation of the model with their tabular values, it can be seen that it is adequate and can be used for modelling.

The following figures show the experimental and simulated results for the concentration of biomass, lactose and oxygen.

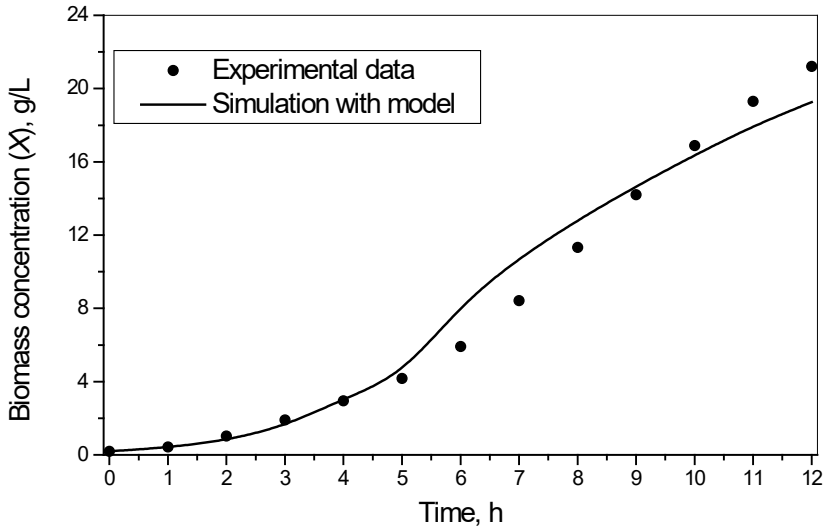

Fig. 2. Experimental and simulated results for biomass concentration

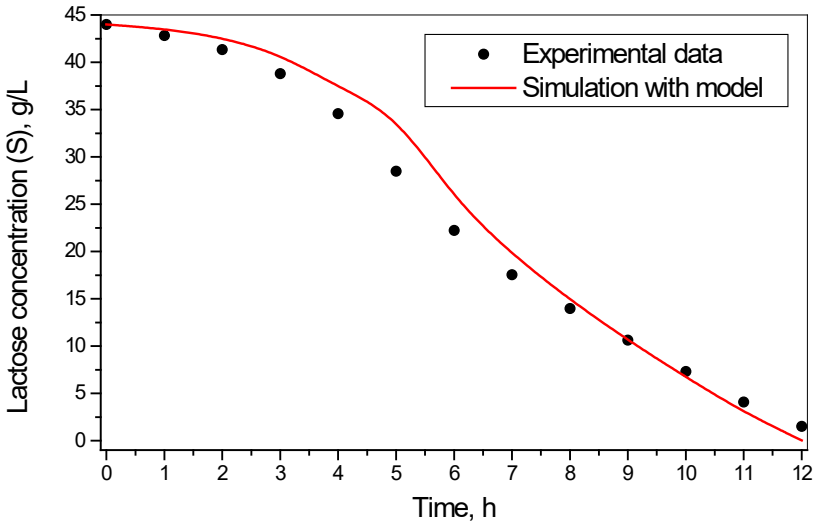

Fig. 3. Experimental and simulated results for *lactose* concentration

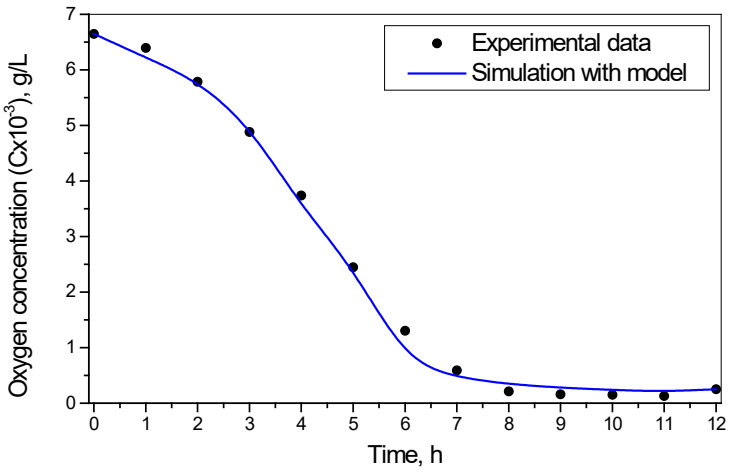

Fig. 4. Experimental and simulated results for *oxygen* concentration

From the results obtained in the process simulation (Figs. 2 - 4), it can be seen that the selected model of the specific growth rate well describes the experimental and model results.

CONCLUSIONS

The application of the PROMETHEE II method has shown that the most suitable pair of models is the *Tessier* model for *lactose-only* and the Monod model for *oxygen-only*. The *Tessier-Monod* specific process growth model is adequate and can be used for modelling.

In our future work, a multi-objective parameter estimation for the six fermentations and sensitivity analysis in batch cultivation of yeast *Kluyveromyces marxianus var. lactis* MC 5 will be performed. In this way the optimal values of the kinetic parameters will be determined for the model used for modelling, optimisation and optimal processes control.

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