

INTERCRITERIA DECISION ANALYSIS FOR CHOICE OF GROWTH RATE MODELS OF BATCH CULTIVATION BY STRAIN *KLUYVEROMYCES MARXIANUS* VAR. *LACTIS* MC 5

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Abstract

In this study we have developed an application of a new method for multicriteria decision analysis namely Intercriteria Decision Analysis (ICDA) method. The method is based on the apparatus of the index matrices and the intuitionistic fuzzy sets. The ICDA method gives possibility to compare some criteria or estimated by them objects. The ICDA has been used to evaluate and select growth rate models for cultivation by the strain Kluyveromyces marxianus var. lactis MC 5. Different unstructured models Monod, Mink, Tessier, Moser, Aiba, Andrews, Haldane, Luong, Edward, and Han-Levenspiel have been considered in order to explain the cell growth kinetics. The application of the ICDA for the growth rate from lactose and oxygen has shown that there are many correlation connections between the investigation models. The models have been reduced at growth rate from lactose only into tree – Mink, Tessier, and Haldane, and at growth rate from oxygen only into two – Mink, and Haldane. In this way the application of the ICDA has permitted us to investigate only the combination of models Mink, Tessier, and Haldane for lactose and Mink and Haldane for oxygen.

Key words: *intercriteria analysis, growth rate models, Kluyveromyces marxianus var. lactis MC5, intuitionistic fuzzy sets, index matrix, intuitionistic fuzzy pairs*

1. INTRODUCTION

The multicriteria decision analysis method, bears the specific name Intercriteria Decision Analysis method (Atanassov, Mavrov & Atanassova 2014) is based on two fundamental concepts: intuitionistic fuzzy sets (Atanassov 1983, 1986, 1999, 2012) and index matrices (Atanassov 1987, 1991, 2010a, 2010b, 2014). The approach employs the concept of index matrices (IMs), making particular use of some of the operations introduced over them, and the concept of intuitionistic fuzzy sets fuzziness, giving us the tools, to construct the IMs of intuitionistic fuzzy pairs (Atanassov, Szmidt & Kacprzyk 2013), defining the presence or absence of dependency/correlation between any pair of criteria within the set.

In the Atanassova et al. (2014a, 2014b) are present some interesting findings from the application of our recently developed ICDA approach to data extracted from the World Economic Forum's (WEF) Global Competitiveness Reports for the years 2008-2009 to 2013-2014 for the current 28 Member States of the European Union. Using the described approach over the data about WEF evaluations of the state of competitiveness of the 28 present EU Member States, certain dependencies are discovered to connect the 12 pillars, termed a positive and a negative consonance. The whole research and the conclusions derived are in line with WEF's address to state policy makers to identify and strengthen the transformative forces that will drive future economic growth.

In Pencheva et al. (2016) ICDA has been applied for the first time in the field of parameter identification of fermentation processes (FP) models. The ICDA implementation allowed to authors to establish relations and dependencies between two of the main genetic algorithms (GA) parameters – *numbers of individuals* and *number of generations*, on the one hand, and *convergence time*, *model accuracy* and *model parameters* on the other hand.

In Roeva et al. (2015a) ICDA is applied to establish relations and dependencies between different *model parameters*. FP of bacteria *E. coli* and yeast *S. cerevisiae* are examined and six different GA are applied for the parameter identification. Further, ICDA is applied to explore the existing relations and

dependencies of defined *model parameters* and GA outcomes – *execution time* and *objective function value* – in case of *S. cerevisiae* FP (Angelova, Roeva & Pencheva 2015) and *E. coli* FP (Roeva et al. 2015b). Moreover, ICDA is applied for establishing the relations and dependencies between GAs parameter *generation gap* on the one hand, and *convergence time*, *model accuracy* and *model parameters* on the other hand in case of *E. coli* FP (Roeva & Vassilev 2016) and *S. cerevisiae* FP (Pencheva et al. 2015). Finally, ICDA is applied to establish the relations and dependencies of considered parameters based on different criteria referred to various metaheuristic algorithms, namely hybrid schemes using GA and Ant Colony Optimization (ACO) (Roeva, Fidanova & Paprzycki 2016).

Ilkova & Petrov (2015a, 2015b, 2015c) have successfully implemented ICDA evaluating indicators of pollution of Struma and Mesta rivers and establishing the fundamental correlation between the kinetic variables fed-batch processes for *Escherichia Coli* fermentation.

In the Petrov & Ilkova (2015) ICDA has been applied for selection of the growth rate models depending on the nine unstructured models – *Monod*, *Mink*, *Tessier*, *Aiba*, *Andrews*, *Haldane*, *Luong*, *Edward* and *Han-Levenspiel* of a batch cultivations of the strain *Kluyveromyces marxianus* var. *lactis* MC 5 on five criteria – criterion for minimization in the parametric identification in the models, *statistic λ*, and relative error. The obtained results have shown that for the growth rate from *lactose* the models have been reduced only to two – *Monod* and *Mink*, and at growth rate from *oxygen* to three – *Mink*, *Tessier*, and *Haldane*. In this way the application of the ICDA has permitted us to investigate the combination of only groups of models – *Monod* for *lactose* and *Mink*, *Tessier* & *Haldane* for *oxygen*, and *Mink* with same models for *oxygen*. In this work in the parametric identification the limitation of the basic kinetic variables are not included. This can lead to a wrong identification.

In this study has examined ten unstructured models *Monod*, *Mink*, *Tessier*, *Moser*, *Aiba*, *Andrews*, *Haldane*, *Luong*, *Edward*, and *Han-Levenspiel* on 11 criteria. In the above criteria (Petrov & Ilkova 2015) we have added and the Correlation coefficient and Fisher coefficient for all kinetic variables. For removing of the uncertainty in the parametric identification restrictions of the basic kinetic process variables have been included. After that we have applied ICDA method for choice of growth rate models at batch cultivation by strain *Kluyveromyces marxianus* var. *lactis* MC 5.

2. INTERCRITERIA DECISION ANALYSIS METHOD

Theoretical framework of the proposed approach, firstly proposed in (Atanassov, Mavrov & Atanassova 2014), by slightly improving the notation from (Atanassova 2015; Atanassova et al. 2014c) is based on two fundamental concepts: intuitionistic fuzzy sets and index matrices.

Intuitionistic fuzzy sets (IFSs) defined by Atanassov (1983, 1986, 1999, 2012) represent an extension of the concept of fuzzy sets, as defined by Zadeh (1965), exhibiting function $\mu_A(x)$ defining the membership of an element x to the set A , evaluated in the interval $[0, 1]$. The difference between fuzzy sets and intuitionistic fuzzy sets is in the presence of a second function $\nu_A(x)$ defining the non-membership of the element x to the set A , where $0 \leq \mu_A(x) \leq 1$, $0 \leq \nu_A(x) \leq 1$, under the condition of $0 \leq [\mu_A(x) + \nu_A(x)] \leq 1$.

The IFSs itself is formally denoted by:

$$A = \{ \langle x, \mu_A(x), \nu_A(x) \rangle \mid x \in E \}$$

Comparison between elements of any two IFSs, say A and B , involves pair-wise comparisons between their respective elements' degrees of membership and non-membership to both sets.

The second concept on which the proposed method relies is the concept of index matrix, a matrix with features two index sets. The theory behind the index matrix is described in Atanassov (1987, 1991, 2010a, 2010b, 2014). Here we will start with the index matrix $\mathbf{M}$ with index sets with of m rows $\{O_1, \dots, O_m\}$ and n columns $\{C_1, \dots, C_n\}$, where for every p, q ($1 \leq p \leq m$, $1 \leq q \leq n$), O_p is an evaluated

object, C_q is an evaluation criterion, and a_{O_p, C_q} is the evaluation of the p -th object against the q -th criterion, defined as a real number or another object that is comparable according to relation R with all the rest elements of the index matrix $\mathbf{M}$.

		C_1	...	C_k	...	C_l	...	C_n
$\mathbf{M} =$	O_1	a_{O_1, C_1}	...	a_{O_1, C_k}	...	a_{O_1, C_l}	...	a_{O_1, C_n}
	$\vdots$	$\vdots$	$\ddots$	$\vdots$	$\ddots$	$\vdots$	$\ddots$	$\vdots$
	O_i	a_{O_i, C_1}	...	a_{O_i, C_k}	$\vdots$	a_{O_i, C_l}	$\vdots$	a_{O_i, C_n}
	$\vdots$	$\vdots$	$\ddots$	$\vdots$	$\ddots$	$\vdots$	$\ddots$	$\vdots$
	O_j	a_{O_j, C_1}	...	a_{O_j, C_k}	...	a_{O_j, C_l}	...	a_{O_j, C_n}
	$\vdots$	$\vdots$	$\ddots$	$\vdots$	$\ddots$	$\vdots$	$\ddots$	$\vdots$
	O_m	a_{O_m, C_1}	...	a_{O_m, C_k}	...	a_{O_m, C_l}	...	a_{O_m, C_n}

From the above requirement for comparability above, it follows that for each i, j, k it holds the relation $R(a_{O_i, C_k}, a_{O_j, C_k})$. The relation R has dual relation $\bar{R}$, which is true in the cases when relation R is false, and vice versa. For example, if R is the relation ' $>$ ', then $\bar{R}$ is the relation ' $<$ ', and vice versa.

For the needs of our decision making method, pair-wise comparisons between every two different criteria are made along all evaluated objects. During the comparison, it is maintained one counter of the number of times when the relation R holds, and another counter for the dual relation.

Let $S_{k,l}^\mu$ be the number of cases in which $R(a_{O_i, C_k}, a_{O_j, C_k})$ and $R(a_{O_i, C_l}, a_{O_j, C_l})$ are simultaneously satisfied. Let also $S_{k,l}^\nu$ be the number of cases in which $R(a_{O_i, C_k}, a_{O_j, C_k})$ and its dual $\bar{R}(a_{O_i, C_l}, a_{O_j, C_l})$ are simultaneously satisfied. As the total number of pair-wise comparisons between the object is $m(m-1)/2$, it is seen that three hold the inequalities:

$$0 \leq S_{k,l}^\mu + S_{k,l}^\nu \leq \frac{m(m-1)}{2}$$

For every k, l such that $1 \leq k < l \leq m$, and for $n \geq 2$ the following two numbers are defined:

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

Obviously, both $\mu_{C_k, C_l}, \nu_{C_k, C_l}$ are numbers in the $[0, 1]$ -interval, and their sum is also a number in this interval. What is complement to their sum one is the number π_{C_k, C_l} , which corresponds to the degree of uncertainty.

The pair, constructed from these two numbers, plays the role of the intuitionistic fuzzy evaluation of the relations that can be established between any two criteria C_k and C_l . In this way the index matrix $\mathbf{M}$ that relates evaluated objects with evaluating criteria can be transformed to another index matrix $\mathbf{M}^*$ that gives the relations among the criteria:

	C_1	$\dots$	C_n
$\mathbf{M}^* =$			
C_1	$\langle \mu_{C_1, C_1}, \nu_{C_1, C_1} \rangle$	$\dots$	$\langle \mu_{C_1, C_n}, \nu_{C_1, C_n} \rangle$
$\vdots$	$\vdots$	$\ddots$	$\vdots$
C_n	$\langle \mu_{C_n, C_1}, \nu_{C_n, C_1} \rangle$	$\dots$	$\langle \mu_{C_n, C_n}, \nu_{C_n, C_n} \rangle$

From practical considerations, it has been more flexible to work with two index matrices $\mathbf{M}^\mu$ and $\mathbf{M}^\nu$, rather than with the index matrix $\mathbf{M}^*$ of Intuitionistic Fuzzy Pairs.

The final step of the algorithm is to determine the degrees of correlation between the criteria, depending on the user's choice μ and ν . We call these correlations between the criteria: 'positive consonance', 'negative consonance' or 'dissonance'. Let $\alpha, \beta \in [0, 1]$ be the threshold values, against which we compare the values of μ_{C_k, C_l} and ν_{C_k, C_l} . We call that criteria C_k and C_l are in:

- (α, β) – positive consonance, if $(\mu_{C_k, C_l} > \alpha)$ and $(\nu_{C_k, C_l} < \beta)$;
- (α, β) – negative consonance, if $(\mu_{C_k, C_l} < \beta)$ and $(\nu_{C_k, C_l} > \alpha)$;
- (α, β) – dissonance, otherwise.

Obviously, the larger α and/or the smaller β , the less number of criteria may be simultaneously connected with the relation of (α, β) -positive consonance. For practical purposes, it carries the most information when either the *positive* or the *negative consonance* is as large as possible, while the cases of *dissonance* are less informative and are skipped.

2.1. Rules for determining the degrees of consonance and dissonance

Atanassova et al. (2014c) have discussed an important aspect of the ICDA approach related to the possibilities for defining the intuitionistic fuzzy threshold values that help discriminate between the *positive* consonance, the *negative* consonance and the *dissonance* between the criteria (**Fig. 1**).

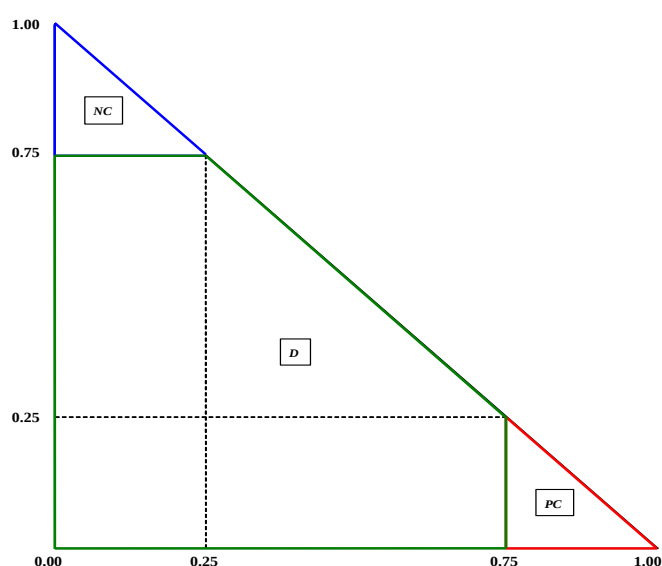


Fig. 1. The triangle of positive consonance, negative consonance and dissonance

The triangular zone for the *negative* consonance (*NC*) from **Fig. 1** corresponds to where the pairs of the criteria which exhibit *NC* will be located. Formally, this area can be expressed as:

$$NC = \{ \langle \mu, \nu \rangle \mid \mu \in [0.00, 0.25] \& \nu \in [0.75, 1.00] \& (\mu + \nu) \leq 1 \}$$

The triangular zone for *positive* consonance (*PC*) from **Fig. 1** corresponds to where the pairs of criteria which exhibit *PC* will be located. Formally, this area can be expressed as:

$$PC = \{ \langle \mu, \nu \rangle \mid \mu \in [0.75, 1.00] \& \nu \in [0.00, 0.25] \& (\mu + \nu) \leq 1 \}$$

The pentagonal zone for *dissonance* (*D*) from **Fig. 1** corresponds to the place where the pairs of criteria which are in *D* will be located. Formally, this area can be expressed as:

$$D = \{ \langle \mu, \nu \rangle \mid \mu \in [0.00, 0.75] \& \nu \in [0.00, 0.75] \& (\mu + \nu) \leq 1 \}$$

In **Table 1** we have presented only the value of the membership function (μ) for *week*, *good*, *very good*, *strong*, *very strong*, and *strict positive consonance*.

Table 1. Intuitionistic fuzzy threshold values of membership function (μ)

Level for Positive consonance	Membership function
<i>Week</i>	$0.75 \leq \mu < 0.85$
<i>Good</i>	$0.85 \leq \mu < 0.90$
<i>Very good</i>	$0.90 \leq \mu < 0.95$
<i>Strong</i>	$0.95 \leq \mu < 0.98$
<i>Very Strong</i>	$0.98 \leq \mu \leq 1.00$
<i>Strict</i>	$\mu = 1.00$

For selecting growth rate models we have to have many high values of the *membership* function (μ) because we have accepted $\alpha=0.95$ and $\beta=0.05$ in this study. The method is used for selection of growth rate models from *lactose* and *oxygen*.

3. KINETIC MODEL OF THE BATCH PROCESSES

The lactose oxidation from a natural substratum in the cultivation of *Kluyveromyces marxianus* var. *lactis* MC5 uses non-conventional whence for receiving of unicellular protein. This process is not well studied. Therefore, it does not exist a general mathematical model of the microbial synthesis, because of the extreme complexity and great variety of living activity of the microorganisms, although various models of biotechnological process and of different parts of the whey fermentation exist. On this cheese whey, which is waste product at the production of white brine cheese, oneself with what oneself receive one close cycle. The conventional model includes the dependence between concentrations of the basic energetic substrates: *lactose*, *oxygen* and *cell* concentration (Angelov et al. 1996; Viesturs et al. 2010).

The batch model is described by a perfectly mixed in bioreactor (Petrov, Ilkova & Tzonkov 2005):

$$\begin{aligned}\frac{dX}{dt} &= \rho(S, C) X \\ \frac{dS}{dt} &= -\frac{\rho(S, C)}{Y_{X/S}} X \\ \frac{dC}{dt} &= OTR - \frac{\rho(S, C)}{Y_{X/C}} X\end{aligned}\quad (1)$$

where: t – process time, h; X – biomass concentration, $\text{g}\cdot\text{L}^{-1}$; S – lactose concentration, $\text{g}\cdot\text{L}^{-1}$; C – oxygen concentration, $\text{mg}\cdot\text{L}^{-1}$; $\rho(S, C)$ – specific growth rate of the cell from lactose and oxygen,

$\rho(S, C) = \rho(S) \rho(C)$, h^{-1} ; OTR – oxygen transfer rate, $\text{mg}\cdot\text{L}^{-1}\cdot\text{h}^{-1}$; $k_L a$ – mass-transfer coefficient, h^{-1} ; φ_G – gas hold-up; C^* – mean oxygen concentration, $\text{mg}\cdot\text{L}^{-1}$; $Y_{X/S}$, $Y_{X/C}$ – yield coefficients of formation of the biomass from the lactose and the oxygen, $\text{g}\cdot\text{g}^{-1}$.

The initial conditions are given as follow: $X(0)=0.2 \text{ g}\cdot\text{L}^{-1}$, $S(0)=44 \text{ g}\cdot\text{L}^{-1}$, $C(0)=6.65\cdot 10^{-3} \text{ g}\cdot\text{L}^{-1}$, and $C^*(0)=C(0)$.

Gas hold-up (φ_G), the power input for dispersion systems the gas-liquid (P_G), and the liquid phase (P_L) are determined by the formulas (Petrov & Tzonkov 1999):

$$\varphi_G = \frac{1.98 Q_G}{(1 + 40.9 Q_G)} \left(\frac{P_G}{V} \right)^{0.2}, \quad P_G = 0.21 \left(\frac{Q_G}{N d^3} \right)^{-0.1} P_L^{0.8}, \quad \text{and} \quad P_L = 60.9 \rho N^3 d^5 \text{Re}^{-0.4}$$

where: Q_G – gas flow rate, $\text{m}^3\cdot\text{s}^{-1}$; N – agitation speed, s^{-1} ; d – impeller diameter, m; ρ – density of the cultural media, $\text{kg}\cdot\text{m}^{-3}$; Re – Reynolds number.

The gas hold-up have the following values ($d=58\times 10^{-3}$, $N=13.33 \text{ s}^{-1}$): for $Q_G=16.67\times 10^{-6} \text{ m}^3\cdot\text{s}^{-1}$, $\varphi_G=0.2305$, and for $Q_G=33.34\times 10^{-6} \text{ m}^3\cdot\text{s}^{-1}$, $\varphi_G=0.2634$.

3.1. Growth rate models

The models for the growth rate from lactose $\rho(S)$ and from oxygen $\rho(C)$ rate is unknown, so the work investigates a ten unstructured models (**Table 2**): 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-Levenspiel (Gera et al. 2008; Giridhar & Srivastava 2002; Kim et al. 2005; Saravanan et al. 2011; Sudipta & Mukherjee 2010).

Table 2. Growth rate models dependent from *lactose* or *oxygen*

Model	$\rho(S)$	$\rho(C)$	Parameters
M_1	$\rho(S) = \frac{\rho_m S}{K_S + S}$	$\rho(C) = \frac{\rho_m C}{K_C + C}$	ρ_m & K_S ρ_m & K_C
M_2	$\rho(S) = \frac{\rho_m S^2}{K_S + S^2}$	$\rho(C) = \frac{\rho_m C^2}{K_O + C^2}$	
M_3	$\rho(S) = \rho_m \left(1 - \exp\left(-\frac{S}{K_{SI}}\right) \right)$	$\rho(C) = \rho_m \left(1 - \exp\left(-\frac{C}{K_{CI}}\right) \right)$	ρ_m & K_{SI} ρ_m & K_{CI}
M_4	$\rho(S) = \frac{\rho_m S^{\alpha_M}}{K_S + S^{\alpha_M}}, \alpha_M > 0$	$\rho(C) = \frac{\rho_m C^{\alpha_M}}{K_C + C^{\alpha_M}}, \alpha_M > 0$	ρ_m, K_S & α_M ρ_m, K_C & α_M
M_5	$\rho(S) = \frac{\rho_m S}{K_S + S} \exp\left(-\frac{S}{K_{SI}}\right)$	$\rho(C) = \frac{\rho_m C}{K_C + C} \exp\left(-\frac{C}{K_{CI}}\right)$	ρ_m, K_S & K_{SI} ρ_m, K_C & K_{CI}
M_6	$\rho(S) = \frac{\rho_m S}{(K_S + S) \left(1 + \frac{S}{K_{SI}} \right)}$	$\rho(C) = \frac{\rho_m C}{(K_C + C) \left(1 + \frac{C}{K_{CI}} \right)}$	
M_7	$\rho(S) = \frac{\rho_m S}{K_S + S + \frac{S^2}{K_{SI}}}$	$\rho(C) = \frac{\rho_m C}{K_C + C + \frac{C^2}{K_{CI}}}$	
M_8	$\rho(S) = \frac{\rho_m S}{K_S + S} \left(1 - \frac{S}{S_m} \right)^n$	$\rho(C) = \frac{\rho_m C}{K_C + C} \left(1 - \frac{C}{C_m} \right)^n$	ρ_m, K_S, S_m & n ρ_m, K_C, C_m & n
M_9	$\rho(S) = \frac{\rho_m S}{K_S + S + \left(1 + \frac{S}{K} \right) \left(\frac{S^2}{K_{SI}} \right)}$	$\rho(C) = \frac{\rho_m C}{K_C + C + \left(1 + \frac{C}{K} \right) \left(\frac{C^2}{K_{CI}} \right)}$	ρ_m, K_S, K_{SI} & K ρ_m, K_O, K_{SI} & K
M_{10}	$\rho(S) = \frac{\rho_m S \left(1 - \frac{S}{S_m} \right)^n}{S + K_S \left(1 - \frac{S}{S_m} \right)^m}$	$\rho(C) = \frac{\rho_m C \left(1 - \frac{C}{C_m} \right)^n}{C + K_C \left(1 - \frac{C}{C_m} \right)^m}$	ρ_m, K_S, S_m, m & n ρ_m, K_C, C_m, m & n

In **Table 2**: ρ_m – maximum growth rate, h^{-1} ; K_S, K_C – Monod saturation constants for cell growth on *lactose* and *oxygen*, $g \cdot L^{-1}$; α_M – Moser constant; K_{SI}, K_{CI} – inhibition constants for cell growth on *lactose* and *oxygen*, $g \cdot L^{-1}$; K – constant in *Edward* model, $g \cdot L^{-1}$; S_m, C_m – critical inhibitor concentrations, above which the reactions stops, $g \cdot L^{-1}$; m, n – constants in the *Luong* and the *Han-Levenspiel* models.

3.2. System constraints of the processes

Nearly all engineering processes will have physical constraints. For the processes the *lactose* (*S*) and *oxygen* (*C*) concentration must be positive all the time; otherwise, an unrealistic solution in the identification problem will be obtained. Therefore, we have the following:

$$g_1(t, \mathbf{x}) = -S(t) \leq 0 \quad (2)$$

$$g_2(t, \mathbf{x}) = -C(t) \leq 0 \quad (3)$$

In addition, here are the following constraints for stoichiometry by the processes:

$$g_3(t, \mathbf{x}) = \frac{S(0) - S(t)}{X(t) - X(0)} - \frac{1}{Y_{X/S}} \leq 0 \quad (4)$$

$$g_4(t, \mathbf{x}) = \frac{OTR}{X(t) - X(0)} - \frac{1}{Y_{X/C}} \leq 0 \quad (5)$$

where: $\mathbf{x}$ – vector of estimated parameters, $\mathbf{x} = \mathbf{x}[\rho_m, K_S, K_{SI}, K, \dots, etc., Y_{X/S}, Y_{X/C}, k_1 a]^T$ for *lactose* and $\mathbf{x} = \mathbf{x}[\rho_m, K_C, K_{CI}, K, \dots, etc., Y_{X/S}, Y_{X/C}, k_1 a]^T$ for *oxygen* (eq. 1, and **Table 2**).

3.3. Criteria of evaluation of the model parameters

However, there is no general theory for nonlinear parameter estimation. The least-squares error is commonly used as a criterion for inspecting how close the computed profiles of the state variables are to the experimental observations. The criterion is expressed in the form below (Giridhar & Srivastava 2000):

$$SSWR = \frac{1}{N_E} \sum_{i=1}^{N_E} \sum_{j=1}^M \frac{\Delta_{ij}^2}{w_j^2} \quad (6)$$

where *SSWR* represents the sums of the squares of weighted residues; ‘*i*’ represent the number of experimental data points, $i = 1, \dots, N_E$ – number of the experiments; ‘*j*’ the number of kinetic variables, $j = 1, \dots, M$ – number of kinetics variables, $M = 3$; $\Delta_{ij} = [\mathbf{z}_e(i, j) - \mathbf{z}_m(i, j)]$ – the difference between the experimental and the model value; $\mathbf{z}_e(i, j) = [X_e(i), S_e(i), C_e(i)]$ – vector with experimental values of kinetics variables; $\mathbf{z}_m(i, j) = [X_m(i), S_m(i), C_m(i)]$ – vector with simulated values of kinetics variables; $w_j = \max_j [X_e(i), S_e(i), C_e(i)]$ – represent the weight of each variable.

If the constraints in (2)-(5) are not included in the parameter estimation problem (6), unrealistic predicted values may be found, i.e.

$$\min_{\mathbf{x}} J = SSWR + \sum_{i=1}^4 \int_{t=0}^{t_f} w_i g_i(t, \mathbf{x}) dt \quad (7)$$

where t_f – final time, $t_f = 12$ h; w_i the weight of every constraints, $w_i = 10^2$.

3.4. Criteria for model validation

The best dependences are defined by the statistical criteria: *statistic* λ ; relative error $S_L(j)$, Fisher coefficient $F_E(j)$, and experimental correlation coefficient $R^2(j)$ for all kinetics variables $j = 1, \dots, M$.

3.4.1. Statistic λ

Hat statistic λ has $F(M, N_E - M)$ distribution. Statistic λ is defined by (Giridhar & Srivastava 2000)

$$\lambda = \frac{(N_E - M)}{(N_E - 1)} \frac{N_E}{M} \sum_{i=1}^{N_E} \sum_{j=1}^M \frac{\Delta_{ij}^2}{S_j^2} \quad (8)$$

In the equation for calculation of S_j^2 there was a mistake. The corrected equation for determination of S_j^2 has the type:

$$S_j^2 = \frac{1}{N_E - 1} \sum_{i=1}^{N_E} (\Delta_{ij} - \Delta_j)^2, \quad \Delta_j = \frac{1}{N_E} \sum_{i=1}^{N_E} \Delta_{ij}, \quad \text{for } i = 1, \dots, N_E \text{ and } j = 1, \dots, M.$$

3.4.2. Relative error

The relative error $S_L(j)$ for every kinetic variables is determined by the following equation (Topnikov & Vavilin 1992)

$$S_L(j) = \sqrt{\frac{1}{(N_E - M)} \left(\sum_{i=1}^{N_E} \frac{\Delta_{ij}^2}{z_e^2(i, j)} \right)} \quad \text{for each } j=1, \dots, M \quad (9)$$

3.4.3. Experimental Fisher coefficient (Vuchkov & Stoyanov 1986)

$$F_E(j) = \begin{cases} \frac{S_e^2(j)}{S_m^2(j)} & \text{if } S_e^2(j) > S_m^2(j) \\ \frac{S_m^2(j)}{S_e^2(j)} & \text{if } S_m^2(j) > S_e^2(j) \end{cases} \quad \text{for each } j = 1, \dots, M \quad (10)$$

where: $S_e^2(j) = \frac{1}{N_E - 1} \sum_{i=1}^{N_E} [z_e(i, j) - \bar{z}_e(j)]^2$, and $S_m^2(j) = \frac{1}{N_E - 1} \sum_{i=1}^{N_E} [z_m(i, j) - \bar{z}_m(j)]^2$;

$$\bar{z}_e(j) = \frac{1}{N_E} \sum_{i=1}^{N_E} z_e(i, j) \quad \text{— vector with average values of experimental data of kinetics variables;}$$

$$\bar{z}_m(j) = \frac{1}{N_E} \sum_{i=1}^{N_E} z_m(i, j) \quad \text{— vector with average values of simulated data of kinetics variables.}$$

3.4.4. Experimental correlation coefficient (Vuchkov & Stoyanov 1986)

$$R_E^2(j) = \frac{\sum_{i=1}^{N_E} [z_e(i, j) - \bar{z}_e(j)][z_m(i, j) - \bar{z}_m(j)]}{\sqrt{\sum_{i=1}^{N_E} [z_e(i, j) - \bar{z}_e(j)]^2} \sqrt{\sum_{i=1}^{N_E} [z_m(i, j) - \bar{z}_m(j)]^2}} \quad \text{for each } j=1, \dots, M \quad (11)$$

Developed algorithm and program on Compaq Visual FORTRAN 90 to determine the parameters in the model (1)-(5), and computing criteria (7)-(11). For solved by a nonlinear problem (1)-(5) we are using BCPOL with double precision from IMSL Library of COMPAQ Visual FORTRAN 90 (COMPAQ Visual FORTRAN Programmer's Guide 2001).

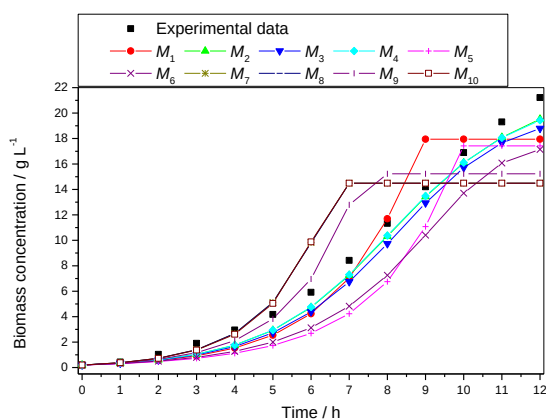
3.5. Results for investigated models

The calculated parameters in the models for the *lactose* and *oxygen* are shown in **Table 3**.

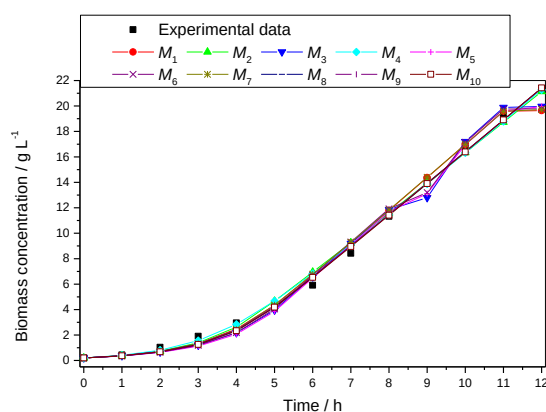
Table 3. Parameters in the models

For <i>lactose</i> , $\rho(S)$											
Model	ρ_m	K_S	K_{SI}	S_m	K	n	m	α_M	$Y_{X/S}$	$Y_{X/C}$	k_{ia}
M_1	0.510	0.101	—	—	—	—	—	—	0.403	0.342	170.522
M_2	0.977	1481.488	—	—	—	—	—	—	0.569	0.198	171.977
M_3	0.998	57.112	—	—	—	—	—	—	0.449	0.289	120.000
M_4	0.995	1011.915	—	—	—	—	—	1.887	0.550	0.215	158.070
M_5	0.579	0.123	146.963	—	—	—	—	—	0.391	0.305	189.963
M_6	0.996	32.702	191.189	—	—	—	—	—	0.396	0.177	200.894
M_7	0.656	0.003	3499.931	—	—	—	—	—	0.325	0.438	189.504
M_8	0.649	0.003	—	249.991	—	0.106	—	—	0.325	0.451	180.474
M_9	0.617	0.005	1499.980	—	61.505	—	—	—	0.342	0.408	203.595
M_{10}	0.704	0.004	—	249.976	—	0.500	0.805	—	0.325	0.493	172.111
For <i>oxygen</i> , $\rho(C)$											
Model	ρ_m	K_C	K_{CI}	S_m	K	n	m	α_M	$Y_{X/S}$	$Y_{X/C}$	k_{ia}
M_1	0.706	0.673	—	—	—	—	—	—	0.442	0.173	171.035
M_2	0.661	0.806	—	—	—	—	—	—	0.476	0.236	120.022
M_3	0.597	0.260	—	—	—	—	—	—	0.449	0.128	234.483
M_4	0.998	2.357	—	—	—	—	—	0.935	0.479	0.178	161.372
M_5	0.761	0.218	25.000	—	—	—	—	—	0.449	0.164	178.778
M_6	0.690	0.157	46.641	—	—	—	—	—	0.446	0.187	155.653
M_7	0.818	0.830	35.249	—	—	—	—	—	0.444	0.179	165.247
M_8	0.707	0.440	—	137.297	—	1.509	—	—	0.482	0.165	169.934
M_9	0.673	0.432	94.348	—	2075.152	—	—	—	0.482	0.157	177.848
M_{10}	0.767	0.615	—	47.018	—	0.992	0.829	—	0.482	0.141	201.385

The experimental and simulated results of the 10-th grown rate models for *lactose* and *oxygen* are shown in the following figures.

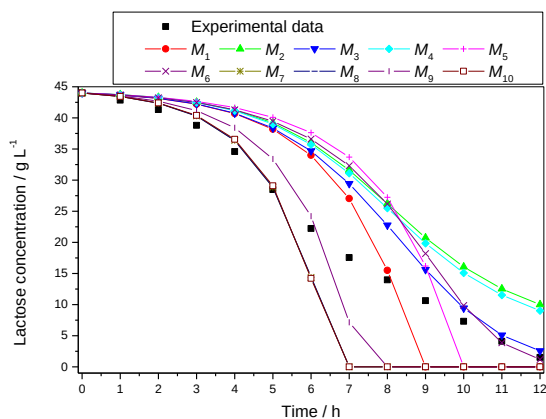


a) from lactose

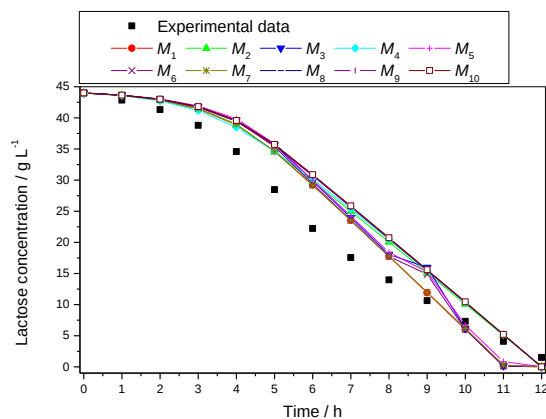


b) from oxygen

Fig. 2. Biomass concentration dependent on *lactose* and from *oxygen*

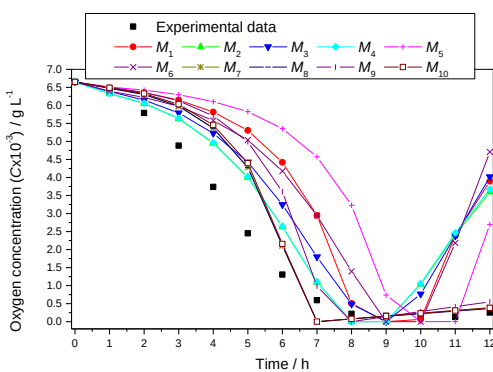


a) from lactose

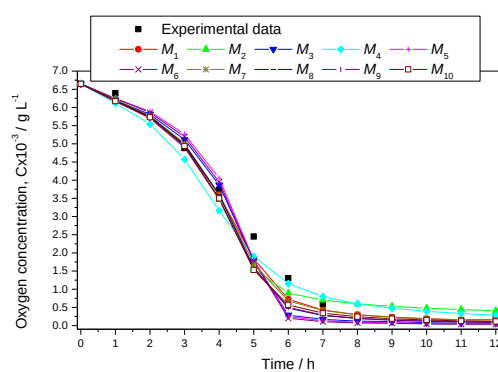


b) from oxygen

Fig. 3. Lactose concentration dependent on *lactose* and from *oxygen*



a) from lactose



b) from oxygen

Fig. 4. Oxygen concentration dependent on *lactose* and from *oxygen*

The figures (**Fig. 2a – Fig. 4a**) for the growth rate models dependent only from *lactose* present that there is a discrepancy between the experimental and simulated data for the kinetic variable. For example: the models of *Monod* (M_1), *Aiba* (M_5), *Edward* (M_9), and *Han-Levenspiel* (M_{10}) do not good reflect the real situation.

When the growth rate dependent only from *oxygen* (**Fig. 2b – Fig. 4b**) there is a different situation. All investigated models describe very good the experimental values of the kinetic variables of the process. These results show that the influence of the oxygen on the *cell growth kinetics* is more than on the *lactose*.

4. APPLICATION OF THE ICDA FOR SELECTION OF GROWTH RATE MODELS

The criterions (7)-(11) was used to determine correlations between models (**Table 2**) with ICDA, i.e. $C_1 = \min_x J \times 10^{-3}$ (eq.10); $C_2 = \lambda$ (eq. 11); $C_{(k=3,4,5)} = S_L(j)$, (eq. 12); $C_{(k=6,7,8)} = F_E(j)$, (eq. 13); $C_{(k=9,10,11)} = R^2(j)$, (eq. 14), $j = 1, \dots, M$. Now, we can construct the IMs of growth rate dependent on *lactose* (A_1) and *oxygen* (A_2). The elements $a_{M_p C_q}$ of the IMs A_1 and A_2 for every criterion (C_q), $q = 1, \dots, 11$ and model (M_p), $p=1, \dots, 10$ are shown below:

Index matrix A_1 for *lactose*

$A_1 =$	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	C_{11}
M_1	112.702	187.163	0.337	0.689	7.368	1.031	1.234	1.042	0.976	0.948	0.859
M_2	84.845	449.330	0.276	1.996	7.260	1.038	1.223	1.088	0.999	0.963	0.916
M_3	81.921	378.425	0.308	0.464	7.438	1.070	1.006	1.105	0.998	0.959	0.900
M_4	82.044	436.126	0.274	1.776	7.423	1.040	1.185	1.089	0.999	0.964	0.912
M_5	170.726	268.108	0.479	0.757	6.023	1.066	1.158	1.022	0.975	0.910	0.809
M_6	137.605	338.939	0.444	0.526	7.871	1.192	1.024	1.094	0.992	0.935	0.843
M_7	68.607	169.285	0.381	0.783	0.720	1.156	1.286	1.105	0.893	0.965	0.971
M_8	68.339	168.705	0.380	0.783	0.679	1.157	1.285	1.107	0.893	0.965	0.971
M_9	68.461	166.819	0.311	0.735	1.143	1.103	1.281	1.095	0.930	0.970	0.944
M_{10}	70.387	168.845	0.384	0.783	0.719	1.154	1.288	1.112	0.893	0.964	0.969

Index matrix A_2 for *oxygen*

$A_2 =$	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	C_{11}
M_1	9.661	160.551	0.163	0.484	0.305	1.008	1.084	1.001	0.996	0.982	0.996
M_2	13.137	190.459	0.156	0.439	1.398	1.012	1.003	1.045	0.998	0.982	0.991
M_3	14.328	170.228	0.202	0.512	0.498	1.001	1.076	1.046	0.995	0.977	0.993
M_4	13.113	189.073	0.117	0.453	1.110	1.014	1.006	1.077	0.998	0.980	0.995
M_5	14.719	172.930	0.219	0.475	0.584	1.003	1.071	1.065	0.996	0.978	0.992
M_6	13.751	166.366	0.203	0.485	0.632	1.003	1.079	1.063	0.995	0.980	0.992
M_7	10.107	159.249	0.173	0.475	0.323	1.005	1.083	1.008	0.996	0.983	0.995
M_8	15.568	212.655	0.177	0.463	0.366	1.004	1.006	1.024	0.998	0.978	0.994
M_9	15.338	215.903	0.167	0.461	0.355	1.002	1.005	1.015	0.998	0.978	0.994
M_{10}	15.739	212.285	0.178	0.467	0.317	1.004	1.005	1.012	0.999	0.977	0.993

Now, let see the index matrixes $\mathbf{A}_1$ and $\mathbf{A}_2$. The criteria of evaluation of the model parameters (C_1) is changed in the interval $C_1 \in [68.339, 170.726]$ for *lactose*, and in the interval $C_1 \in [9.661, 15.739]$ for *oxygen*. The relative errors $C_{(k=3,4,5)}$ for every kinetic variable M is changed in the interval $C_{(k=3,4,5)} \in [0.274, 7.871]$ for *lactose*, and $C_{(k=3,4,5)} \in [0.117, 1.398]$ for *oxygen*.

The criteria C_2 and $C_6 - C_{11}$ are statistical. They are used for the model validation. Their experimental values are changed in the intervals:

$C_2 \in [16.819, 449.330]$, $C_{6-8} \in [1.006, 1.288]$, and $C_{9-11} \in [0.893, 0.999]$ for *lactose*;

$C_2 \in [159.246, 215.903]$, $C_{6-8} \in [1.001, 1.084]$, and $C_{9-11} \in [0.995, 0.999]$ for *oxygen*.

The theoretical values of C_2 and $C_6 - C_{11}$ are given from statistical tables (Vuchkov & Stoyanov 1986).

Fisher coefficient for C_2 (Statistic λ) is $F_{(3,10)}^\lambda = 3.71$. For Fisher coefficients ($C_6 - C_8$) are $F_{(10, 3)} = 8.79$, and for correlation coefficients ($C_9 - C_{11}$) the tabular value is $R_{(10)} = 0.576$.

The $C_2 > F_{3,10}^\lambda = 3.71$, the experimental Fisher coefficients ($C_6 - C_8$) are in interval $C_6 - C_8 \in [1.001, 1.228] < F_{10,3} = 8.79$, and the experimental correlation coefficients ($C_9 - C_{11}$) are in interval $C_9 - C_{11} \in [0.893, 0.999] > R_{(10)} = 0.576$.

The presented results can be seen that in terms of the criteria for validation ($C_2, C_6 - C_{11}$) all growth rate models dependent from *lactose* or *oxygen* are adequate.

Application of ICDA will show who criteria will be dropped out from the investigation.

4.1. ICDA for growth rate from lactose

The values of membership function (μ) and non-membership function (ν) have been calculated with the help of the software developed by our colleagues for the realization of the method.

The index matrix $\mathbf{A}_1^\mu$ for $\rho(S)$ has the following form:

$\mathbf{A}_1^\mu =$	M_1	M_2	M_3	M_4	M_5	M_6	M_7	M_8	M_9	M_{10}
M_1		0.891	0.964	0.891	0.982	0.945	0.800	0.800	0.927	0.800
M_2	0.891		0.855	1.000	0.873	0.836	0.691	0.691	0.818	0.691
M_3	0.964	0.855		0.855	0.945	0.982	0.764	0.764	0.891	0.764
M_4	0.891	1.000	0.855		0.873	0.836	0.691	0.691	0.818	0.691
M_5	0.982	0.873	0.945	0.873		0.964	0.818	0.818	0.945	0.818
M_6	0.945	0.836	0.982	0.836	0.964		0.782	0.782	0.909	0.782
M_7	0.800	0.691	0.764	0.691	0.818	0.782		1.000	0.873	1.000
M_8	0.800	0.691	0.764	0.691	0.818	0.782	1.000		0.873	1.000
M_9	0.927	0.818	0.891	0.818	0.945	0.909	0.873	0.873		0.873
M_{10}	0.800	0.691	0.764	0.691	0.818	0.782	1.000	1.000	0.873	

The triangle of IFs for growth rate from *lactose* only in the real borders of μ and ν are shown in **Fig. 5**.

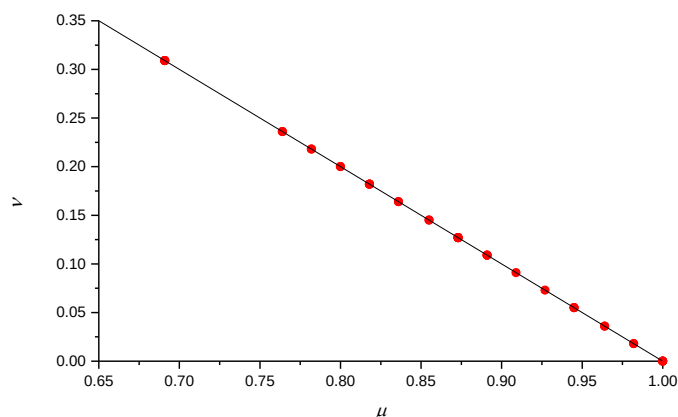


Fig. 5. Intuitionistic fuzzy triangle for growth rate dependent on *lactose*

The comparatively high value of the membership function $\mu \in [0.691, 1.000]$, the low value of non-membership function $\nu \in [0.000, 0.309]$, and the zero uncertainty $\pi = 0$ (matrix A_1^μ) show that the models investigated which depend on *lactose* are dependent on each other, as well.

The index matrix A_1^μ and **Fig. 5** shows there are a *strict* ($\mu = 1.0$, $\nu = 0.0$, $\pi = 0.0$), *very strong* ($\mu \geq 0.98$, $\nu \leq 0.02$, $\pi = 0.0$), and *strong* ($\mu \geq 0.95$, $\nu \leq 0.05$, and $\pi = 0.0$) positive consonance for an considerable part of the models.

The model M_1 has *strong* consonance with M_3 , and *very strong* with M_5 . From this triad models M_1 and M_5 (**Fig. 2a**) can be eliminated. The model M_2 has *strict* consonance with M_4 , therefore M_4 drops off, that is more complex – it has one parameter more.

The model M_6 has *strong* consonance with M_5 , and *very strong* with M_3 . But we have already chosen M_3 , and have rejected M_5 , therefore we can eliminate also M_6 .

The model M_7 is in *strict* consonance with models M_8 and M_{10} . From this it therefore we can reject the models M_8 and M_{10} (**Fig. 2a** – **Fig. 4a**) and the model M_7 remain. The model M_9 is in *dissonance* with all rest, but it does not reflect the experimental results (**Fig. 2a** – **Fig. 4a**). Therefore it drops off from the investigation.

In conclusion we can say that the models M_1 , M_4 , M_5 , M_6 , M_8 , M_9 , and M_{10} drop off, remain M_2 , M_3 , and M_7 .

So the application of ICDA for determination of the correlation between the growth rate models from *lactose* $\rho(S)$ gives us an opportunity to reduce the models investigated to three – *Mink* (M_2), *Tessier* (M_3), and *Haldane* (M_7). They will participate in a combination with the obtained models for $\rho(C)$ after application of the ICDA for growth rate from *oxygen*.

4.2. ICDA for growth rate from oxygen

The computing index matrix A_2^μ for $\rho(C)$ has the following form:

$A_2^\mu =$	M_1	M_2	M_3	M_4	M_5	M_6	M_7	M_8	M_9	M_{10}
M_1		0.800	0.964	0.800	0.945	0.945	0.964	0.945	0.945	0.945
M_2	0.800		0.836	1.000	0.855	0.855	0.836	0.855	0.855	0.855
M_3	0.964	0.836		0.836	0.982	0.982	1.000	0.982	0.982	0.982
M_4	0.800	1.000	0.836		0.855	0.855	0.836	0.855	0.855	0.855
M_5	0.945	0.855	0.982	0.855		1.000	0.982	0.964	0.964	0.964
M_6	0.945	0.855	0.982	0.855	1.000		0.982	0.964	0.964	0.964
M_7	0.964	0.836	1.000	0.836	0.982	0.982		0.982	0.982	0.982
M_8	0.945	0.855	0.982	0.855	0.964	0.964	0.982		1.000	1.000
M_9	0.945	0.855	0.982	0.855	0.964	0.964	0.982	1.000		1.000
M_{10}	0.945	0.855	0.982	0.855	0.964	0.964	0.982	1.000	1.000	

The triangle of IFs for growth rate from oxygen only in the real borders of μ and ν is shown in **Fig. 6**.

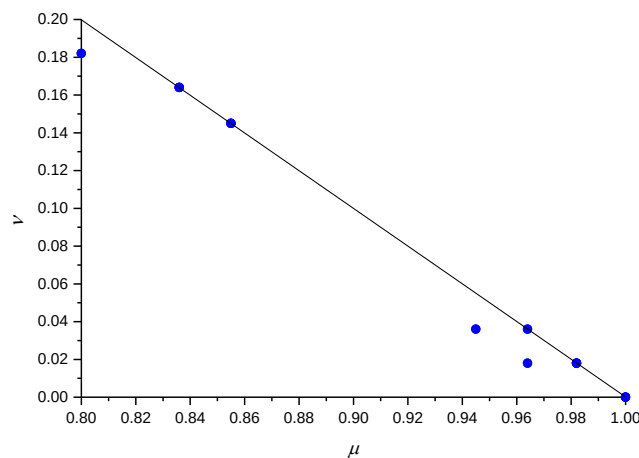


Fig. 6. Intuitionistic fuzzy triangle for growth rate dependent on oxygen

The comparatively high value of membership function $\mu \in [0.8, 1.0]$, the value of non-membership function $\nu \in [0.000, 0.182]$, and very small uncertainty $\pi = 0.018$ (matrix A_2^μ and **Fig. 6**) shows the investigated models that depend on oxygen are also dependent on each other.

The index matrix A_2^μ and **Fig. 6** shows there is a *strict* ($\mu = 1.0$, $\nu = 0.0$, $\pi = 0.0$), *very strong* ($\mu \geq 0.98$, $\nu \leq 0.02$, $\pi = 0.0$), and *strong* ($\mu \geq 0.95$, $\nu \leq 0.05$, and $\pi = 0.0$) positive consonance, the more models have.

The model M_7 has *strong* consonance with M_1 , *strict* consonance c M_3 , and *very strong* consonance with M_5 , M_6 , M_8 , M_9 , and M_{10} . Only with the models M_2 and M_4 it is in *dissonance*. That shows the model M_7 is our first choice, but the rest (M_1 , M_3 , M_5 , M_6 , M_8 , M_9 , and M_{10}) model was rejected from

the investigations. But the model M_2 has *strict* consonance with M_4 . Therefore, M_4 can be eliminated from the investigations.

The application of ICDA for determination of the correlation between the growth rate models from oxygen $\rho(C)$ gives us an opportunity to reduce the models investigated from ten to only two – *Mink* (M_2), and *Haldane* (M_7).

The combination from models for specific growth rate $\rho(S, C)$ of the process are divided in two groups in dependence from the oxygen model:

$$\begin{aligned} \text{First group: } & \left. \begin{array}{l} M_{1.1} : \text{Mink for } \rho(S) \\ M_{1.2} : \text{Tessier for } \rho(S) \\ M_{1.3} : \text{Haldane for } \rho(S) \end{array} \right\} \& \text{Mink for } \rho(C) \\ \\ \text{Second group: } & \left. \begin{array}{l} M_{2.1} : \text{Mink for } \rho(S) \\ M_{2.2} : \text{Tessier for } \rho(S) \\ M_{2.3} : \text{Haldane for } \rho(S) \end{array} \right\} \& \text{Haldane for } \rho(C) \end{aligned}$$

The models for specific growth rate $\rho(S, C)$ of the processes are shown in **Table 4**.

Table 4. Specific growth rate $\rho(S, C)$ for processes

Model	First Group
$M_{1.1}$	$\rho(S, C) = \frac{\rho_m S^2}{(K_s + S^2)} \frac{C^2}{(K_c + C^2)} \quad (12)$
$M_{1.2}$	$\rho(S, C) = \rho_m \left(1 - \exp\left(-\frac{S}{K_{SI}}\right) \right) \frac{C^2}{(K_c + C^2)} \quad (13)$
$M_{1.3}$	$\rho(S, C) = \frac{\rho_m S}{(K_s + S + S^2 / K_{SI})} \frac{C^2}{(K_c + C^2)} \quad (14)$
Model	Second Group
$M_{2.1}$	$\rho(S, C) = \frac{\rho_m S^2}{(K_s + S^2)} \frac{C}{(K_c + C + C^2 / K_{CI})} \quad (15)$
$M_{2.2}$	$\rho_m \left(1 - \exp\left(-\frac{S}{K_{SI}}\right) \right) \frac{C}{(K_c + C + C^2 / K_{CI})} \quad (16)$
$M_{2.3}$	$\rho(S, C) = \frac{\rho_m S}{(K_s + S + S^2 / K_{SI})} \frac{C}{(K_c + C + C^2 / K_{CI})} \quad (17)$

The final choice will be made after repeated identification and application of the ICDA for the model (12)-(17). This will be developed in another paper from the authors.

CONCLUSIONS

The application of the ICDA for determination of the correlation connections between the growth rate models from *lactose* has shown that *seven* models can be eliminated from all *ten* initial models. Only the models of *Mink*, *Tessier*, and *Haldane* have remained. The investigation of the correlation connections at the growth rate models from *oxygen* has shown that we can eliminate *eight* models. Models of *Mink*, and *Haldane* remain that have been included in the general model.

The application of ICDA for establishment of correlation connection between different models for the specific the growth rate proved to be very useful. In this way of using of ICDA we can say for *negative consonance*, this means that the model was not correctly chosen (they do not reflect the real situation) and for this aim we have to search another description of the process.

In our next work on parametric identification we will determine the obtained models which are most appropriate for the specific growth rate, by using the ICDA.

The full picture of the model of the process will be clear when we carry out the identification and fed-batch processes and make a simultaneous identification of batch and fed-batch processes.

ACKNOWLEDGMENTS

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