

Heuristic Sensitivity Analysis for Baker's Yeast Model Parameters

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Abstract

The baker's yeast, essentially composed by living cells of *Saccharomyces cerevisiae*, used in the bread making and beer industries as a microorganism, has an important industrial role. The simulation procedure represents then a necessary tool to understand clearly the baker's yeast fermentation process. The use of mathematical models based on mass balance equations requires the knowledge of the reaction kinetics, thermodynamics, and transport and physical properties. Models may be more or less complex, however they keep the basic feature of linking observations together into some pattern.

A FORTRAN90-based program was developed to simulate the baker's yeast fermentation process in order to predict the dynamic behaviour of a well-mixed reactor. Mass balances written for all the components define a system of ordinary differential equations of initial value problem type (IVP). Considering the kinetics and the gas transfer rates relations as part of the differential system, a differential-algebraic system (DAE) can be defined. The simulation results were compared with the experimental values obtained in a laboratorial five-litre fermenter, operated in fed-batch mode.

Prior to the parameter estimation procedure, an identification of the most significant model parameters was carried out. A heuristic sensitivity analysis was performed in order to adjust the model results with the experimental data. The Meyer and Roth method was used to minimise the objective function, defined as the sum of the relative square errors between the calculated and the experimental values (associated to the state variables: biomass, glucose and ethanol).

The yield coefficients and the maximum uptake rate for glucose and oxygen were found the most significant parameters.

Keywords: heuristic sensitivity analysis, numerical simulation, parameter estimation.

1 Introduction

Real processes in the chemical, biochemical and food industry are, in their vast majority, non-linear MIMO (Multiple Input Multiple Output) systems. Their dynamics and control are difficult to study both for theoretical and practical reasons. In many cases, experiments with real industrial processes are not carried out for economy and safety reasons, and frequently on-line measurements are not available or simply they are too expensive. Advanced control strategies rely on adaptive techniques based on the knowledge of the system state. When experimental observations are missing, 'software sensors' represent a major, and often, the only alternative to allow optimal process operation to be enforced. The robustness of such sensors needs however to be tested in flexible environments where difficulties such as measurement noises, time delays and loads to the process can be readily implemented on-line [1].

Living cells of *Saccharomyces cerevisiae*, which form baker's yeast, are predominantly used in bakery and beer industries. Apart from its industrial importance and economical significance, there is a scientific interest in baker's yeast fermentation [2].

Baker's yeast production is carried out in a fed-batch fermenter with inoculums of *Saccharomyces cerevisiae* culture and a glucose solution as substrate feed. We may distinguish three metabolic pathways: respirative growth on glucose, fermentative growth on glucose and respirative growth on ethanol. Respirative pathways occur in presence of oxygen and the fermentative one in its absence (with production of ethanol) [3].

The conventional approach for process modelling is based on mass, energy and/or population balance equations. This form of modelling requires knowledge about reaction kinetics, thermodynamic, transport and physical properties.

The simulation process requires the integration of a set of non-linear differential equations, for the state variables. A set of algebraic equations, concerning mass transfer relations and kinetics laws, can be considered as part of the system to be solved, defining a differential algebraic equation (DAE) system or, alternatively included in the model, transforming the system in an initial value problem (IVP) [4-5]. The simulation model needs then to be validated with experimental data.

For an identification of the more significant model parameters a heuristic sensitivity analysis was performed. The Meyer and Roth method [6] is used to minimise the objective function, defined as the sum of the relative square errors between the calculated and the experimental values. Two steps are considered. The first one identifies the most relevant kinetics parameters and the second one, with the previous identified parameters, estimates the most relevant yield coefficients. Depending on the research interests a multi-objective analysis can be also performed without previous identification of the most relevant parameters [7].

2 Baker's yeast fermentation - Modelling approach

A deterministic model for biological well-mixed fed-batch reactors, Figure 1, is obtained by writing macroscopic balance for all the components. The simulation model also includes a set of algebraic equations, related to the mass transfer relations and to the kinetics of baker's yeast growth [3].

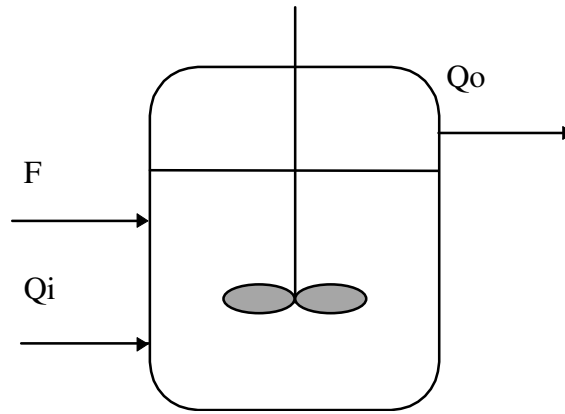
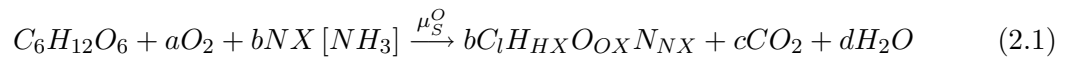


Figure 1: Fed-batch fermenter (F is liquid flow; Q_i and Q_o are gaseous flow at input and output, respectively)

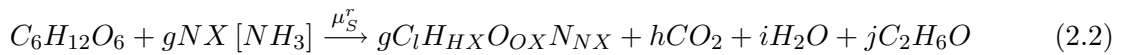
2.1 Kinetic model

Depending on the environment conditions, for instance, availability of sugar and/or oxygen, yeast growth is characterized by three metabolic pathways, respiratory and/or fermentative, namely:

respiratory growth on glucose



fermentative growth on glucose



respiratory growth on ethanol



where μ_S^O , μ_S^r , μ_E^O : specific growth rates (1/h) for the three pathways, respectively; subscripts S and E mean glucose and ethanol.

The metabolic pathways of fermentative growth on glucose and oxidative growth on ethanol are competitive. This competition is governed by the respiratory capacity of the cells. If the instantaneous oxygen uptake capacity exceeds the oxygen need for total respiratory glucose uptake, then, all sugar uptakes follows the respiratory pathway (2.1) with the remaining oxygen being spent on ethanol (if present) respiratory uptake (2.3). Otherwise, if the instantaneous oxygen uptake capacity is not enough, then, part of glucose uptake follows the respiratory pathway (2.1) while the remaining follows the fermentative pathway (2.2). Figure 2 illustrates the mechanism.

Several kinetics models are proposed for baker's yeast growth [8]. In this work we considered Monod type equations, following Sonnleitner and Käppeli work [9], as described and explained in [3].

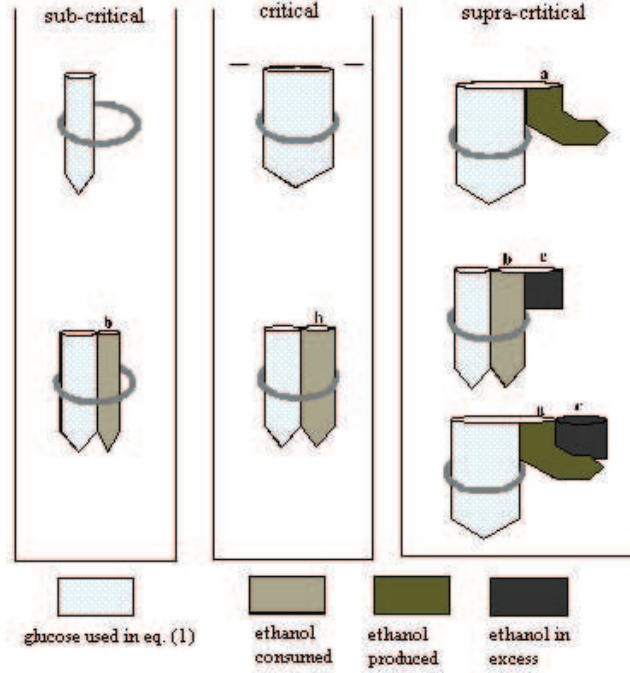


Figure 2: Metabolic mechanism of the baker yeast. The grey ring represents the respiratory bottleneck

The total specific growth rate, μ_t , is the sum of the growth rates for the three pathways

$$\mu_t = \mu_S^O + \mu_S^r + \mu_E^O. \quad (2.4)$$

The specific growth rates, μ_i , can be related to the corresponding substrate fluxes, q , and yield coefficients, Y , by

$$\mu_t = Y_{X/S}^O q_S^O + Y_{X/S}^r q_S^r + Y_{X/E}^{OE} q_E^O \quad (2.5)$$

where $Y_{X/S}^O$ and $Y_{X/S}^r$ represent the yield coefficients of biomass (X) in glucose (S) in the oxidative and fermentative phases, respectively; $Y_{X/E}^{OE}$ is the yield coefficient of biomass in ethanol (E) in the oxidative phase in ethanol.

Table 1: Baker's yeast kinetics equations for the respirative and respiro-fermentative regimes

$aq_S \leq q_O$	$\mu_S^O = Y_{X/S}^O \cdot q_S$	(2.11)
Respirative	$\mu_S^r = 0$	(2.12)
Regime	$\mu_E^O = \min(\mu_{E_1}^O, \mu_{E_2}^O)$	(2.13)
$aq_S > q_O$	$\mu_S^O = Y_{X/S}^O \cdot \frac{q_O}{a}$	(2.14)
Respiro-Fermentative	$\mu_S^r = Y_{X/S}^r \cdot (q_S - \frac{q_O}{a})$	(2.15)
Regime	$\mu_E^O = 0$	(2.16)

As ethanol uptake is influenced by the priority of glucose uptake, which functions as an inhibitor, the specific growth rate on ethanol can be described as

$$\mu_E^O = \mu_E^{\max} \frac{E}{E + K_E} \frac{K_i}{S + K_i} \quad (2.6)$$

where μ_E^{\max} is the maximal specific growth rate, K_i is the inhibition parameter and K_E is the saturation parameter.

However, this equation holds true only if there is an available respiratory capacity of the cells.

The glucose uptake, q_S , is slightly different because it follows two metabolic pathways: oxidative and fermentative

$$q_S = q_S^O + q_S^r. \quad (2.7)$$

The glucose, q_S , and oxygen, q_O , uptake follows Monod kinetics, respectively

$$q_s = q_s^{\max} \frac{S}{S + K_s} \quad (2.8)$$

$$q_O = q_O^{\max} \frac{O}{O + K_O} \quad (2.9)$$

where q_s^{\max} is the maximal specific glucose uptake rate, K_S and K_O are saturation parameters and q_O^{\max} is the maximal specific oxygen (O) uptake rate.

From (2.1), it can be seen that the oxidative glucose uptake depends on the availability of dissolved oxygen, and may be defined as

$$q_s^o = \frac{q_O^O}{a} \quad (2.10)$$

where a is the stoichiometric coefficient of the oxygen in the respiratory pathway of glucose and q_O^O is the oxygen uptake on glucose.

Two situations may occur: excess of oxygen that implies no fermentative growth of biomass or lack of oxygen and consequently excess of glucose that implies no respiratory growth on ethanol.

Table 1 resumes mathematically the two situations that coexist [10].

Two auxiliary equations, (2.17) and (2.18), must be added for the estimation of the specific growth rate on ethanol, defined as:

$$\mu_{E_1}^O = \mu_E^{max} \frac{E}{E + K_E} \frac{K_i}{S + K_i} \quad (2.17)$$

and

$$\mu_{E_2}^0 = \frac{Y_{X/O}^{OE}}{Y_{X/E}^{OE}} (q_O - a_{QS}) . \quad (2.18)$$

The relevant kinetic data were taken from Sonnleitner and Käppeli [9] and [11].

2.2 Mechanistic model

Considering that the yield coefficients, Y 's, are constant and the dynamics of the gas phase can be neglected, the following set of differential equations was obtained:

mass balance for the biomass

$$\frac{dX}{dt} = (\mu_S^O + \mu_S^r + \mu_E^O - D) X \quad (2.19)$$

mass balance for the sugar

$$\frac{dS}{dt} = \left(-\frac{\mu_S^O}{Y_{X/S}^O} - \frac{\mu_S^r}{Y_{X/S}^r} \right) X + (S_f - S) D \quad (2.20)$$

where S_f is the substrate concentration in the feed and D is dilution rate (ratio feed rate/volume),

mass balance for the ethanol

$$\frac{dE}{dt} = \left(\frac{\mu_S^r}{Y_{X/E}^r} - \frac{\mu_E^O}{Y_{X/E}^{OE}} \right) X - DE \quad (2.21)$$

mass balance for the oxygen

$$\frac{dO}{dt} = \left(-\frac{\mu_S^O}{Y_{X/O}^O} - \frac{\mu_E^O}{Y_{X/O}^{OE}} \right) X - DO + OTR \quad (2.22)$$

mass balance for the carbon dioxide

$$\frac{dC}{dt} = \left(\frac{\mu_S^O}{Y_{X/C}^O} + \frac{\mu_S^r}{Y_{X/C}^r} + \frac{\mu_E^O}{Y_{X/C}^{OE}} \right) X - DC - CTR \quad (2.23)$$

accumulation of the working volume during the fed-batch process

$$\frac{dV}{dt} = DV \quad (2.24)$$

The gas transfer rates are given by:

$$OTR = K_L^O a(O^* - O) \quad (2.25)$$

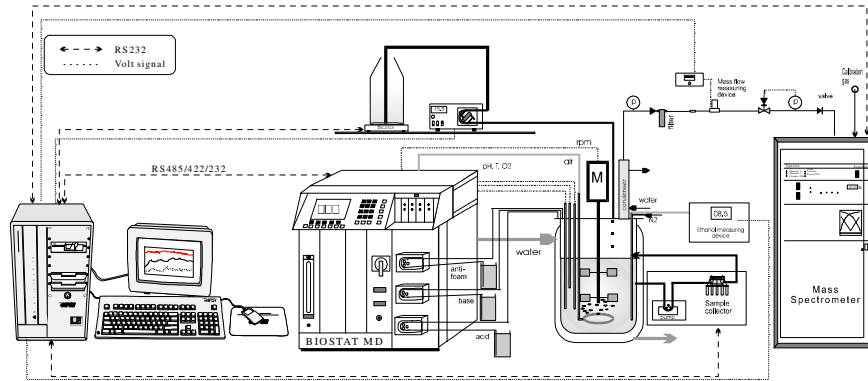


Figure 3: Experimental set-up for baker's yeast production

$$CTR = K_L^C a(C - C^*) \quad (2.26)$$

where $K_L^i a$ are overall mass transfer coefficients for oxygen and carbon dioxide and O^* and C^* are the corresponding equilibrium concentrations.

The set of equations (2.19–2.24) defines an IVP model and the set of equations (2.19–2.24, 2.25–2.26, 2.11–2.13 or 2.14–2.16) defines a DAE model [5]. These two different approaches were presented and discussed elsewhere [4].

3 Experimental set-up

In this section a brief description of the experimental set-up is presented. For more details see [12-13]. Figure 3 illustrates the macro experimental set-up used comprising a five-litre fermenter with temperature control, aeration and agitation. It is equipped with sensors for on-line measurement of environment variables, such as: temperature, pH and concentration of dissolved oxygen. These variables are monitored and controlled by a direct digital control unit (DCU, Biostat MD). Each variable has its own control loop, with appropriate parameters, which can be modified by the user or through the supervisor computer. The DCU actuates in each final control element, as for example, acid and base pumps for pH control. The pumps and electrodes calibration is done with help of this control unit.

The fed-batch fermentation starts with a two and a half litre volume substrate medium and an inoculum of 0.5 l, added through a peristaltic pump in a profile dictated by a control law. The substrate addition is monitored with the help of a balance, by means of mass variation of the glass that contains the glucose solution. The feeding ends when the maximum volume is attained (the fermentation time is about 15 to 20 hours).

The knowledge of liquid phase composition, in terms of state variables, is obtained by measuring the following variables: biomass, glucose, dissolved ethanol, oxygen and carbon dioxide. Each variable are measured and analysed by specific sensors and methodologies.

A computer and other hardware are linked to the DCU in order to implement data acquisition, monitoring and open and closed control loop strategies (in open loop to impose constant or variable feed flow and in closed loop to test PID laws and adaptive control algorithms). In

order to overcome the difficulties of off-line measures of biomass and glucose, the supervisor computer also determines their concentration by on-line estimation techniques.

4 Heuristic sensitivity analysis

As the baker's yeast fermentation is a highly non-linear system, differences in experimental and simulation results are significant. In order to overcome this problem, some of the model parameters are adjusted using an optimization technique based on Meyer and Roth method [6]. The objective function to be minimised, (4.27), is the sum of the errors associated to biomass, glucose and ethanol. Only three of the five state variables are used due to limitations on the optimization solver.

$$F_{obj} = \sum_{i=1}^{nexp} \left(\frac{X_i^{mod} - X_i^{exp}}{X_i^{exp}} \right)^2 + \sum_{i=1}^{nexp} \left(\frac{S_i^{mod} - S_i^{exp}}{S_i^{exp}} \right)^2 + \sum_{i=1}^{nexp} \left(\frac{E_i^{mod} - E_i^{exp}}{E_i^{exp}} \right)^2 \quad (4.27)$$

where subscripts *exp* and *mod* refer to experimental and simulation model results, respectively; *nexp* is the number of experimental points.

In order to quantify the performance of parameters estimation a new variable is defined, mean error, \overline{Er} :

$$\overline{Er} = \sqrt{\frac{F_{obj}}{3 \ nexp}} \quad (4.28)$$

being constant 3 the number of state variable considered in (4.27).

In the overall model (mechanistic and kinetics) there are 17 parameters to be studied (9 yield coefficients *Y* and 8 kinetic parameters). As previously mentioned only three state variables are considered in the optimization methodology. Biomass, glucose and ethanol are chosen due to their relevant role in the fermentation process. As a consequence, also only three parameters can be estimated simultaneously. As a first approach, an identification of the most relevant parameters in the model was performed. In this sense, relevant means the measure of their effect on the model. Heuristic sensitivity analyses were performed based on empiric evaluation of results. The first heuristic analysis calculates the most relevant kinetics parameters. The second heuristic analysis, with the previously identified kinetics parameters, estimates the most relevant yield coefficients. The methodology followed is described in the next section.

5 Modelling Simulation procedure

The simulation programs used for the sensitivity analysis of baker's yeast fed-batch production were developed in FORTRAN90 (adaptation of some subroutines described in [6]). All simulations were performed in a Pentium PC platform.

Five experiments were carried out with the initial conditions presented in Table 2. The experiments are named as EXPC0*i*, where *i* equal 1, 3, 4, 6 and 7. All the experiences were performed in the experimental set-up (Figure 3) previously described. EXPC07, considered for comparison purpose, was run in batch (*F*=0 l/h) and the others were performed as fed-batch

Table 2: Initial conditions in the five experiences

EXPC0i	S_f (g/l)	F (l/h)	Initial values					
			V (l)	X (g/l)	S (g/l)	E (g/l)	O (g/l)	C (g/l)
EXPC01	25	0.10	3.30	0.297	1.276	0.810	0.0066	0.0020
EXPC03	100	0.15	2.75	1.545	0.292	2.933	0.0066	0.0020
EXPC04	5	0.15	2.75	1.400	25.443	3.800	0.0066	0.0020
EXPC06	25	0.15	2.75	1.455	0.000	1.836	0.0066	0.0020
EXPC07	0	0	2.75	0.222	21	0.333	0.0066	0.0020

Table 3: Kinetics parameters in the sensitivity analysis run

<i>Simulation</i> <i>Run</i>	q_s^{max}	q_o^{max}	μ_e^{max}
0*	3.5	0.256	0.17
1	10.0	0.256	0.17
2	3.5	1.0	0.17
3	3.5	0.256	10.0
4	0.35	0.256	0.17
5	3.5	0.256	0.01
6	3.5	0.01	0.17

* literature values [9, 11].

fermentations, for different substrate flows (F). These values were chosen taking into account the set-up limitations.

6 Results and Discussion

In order to identify the most significant model parameters, several simulation runs were performed, changing one parameter at a time, and having as a reference the literature values [9, 11]. Due to their important role in the model definition, the kinetics parameters, q_s^{max} , q_o^{max} and μ_e^{max} , are the first to be chosen for sensitivity analysis. Table 3 resumes the values used (empirically assumed) in each simulation performed. Run 0 corresponds to the literature values.

Figure 4 shows the biomass (X), glucose (S) and ethanol (E) profiles obtained with the kinetics parameters presented in Table 3 (subscripts 0 to 6 correspond to the simulation runs). The dot points correspond to experimental data and the lines to simulation values.

Through Figure 4, it is clear that runs 4 and 6 change significantly the profiles (x4 and x6 profiles for biomass, s4 and s6 for glucose, and e4 and e6 for ethanol). These simulation runs correspond to the decrease on q_s^{max} and q_o^{max} kinetics parameters, respectively for glucose and oxygen (Table 3). For further study, these two parameters were identified to be the most

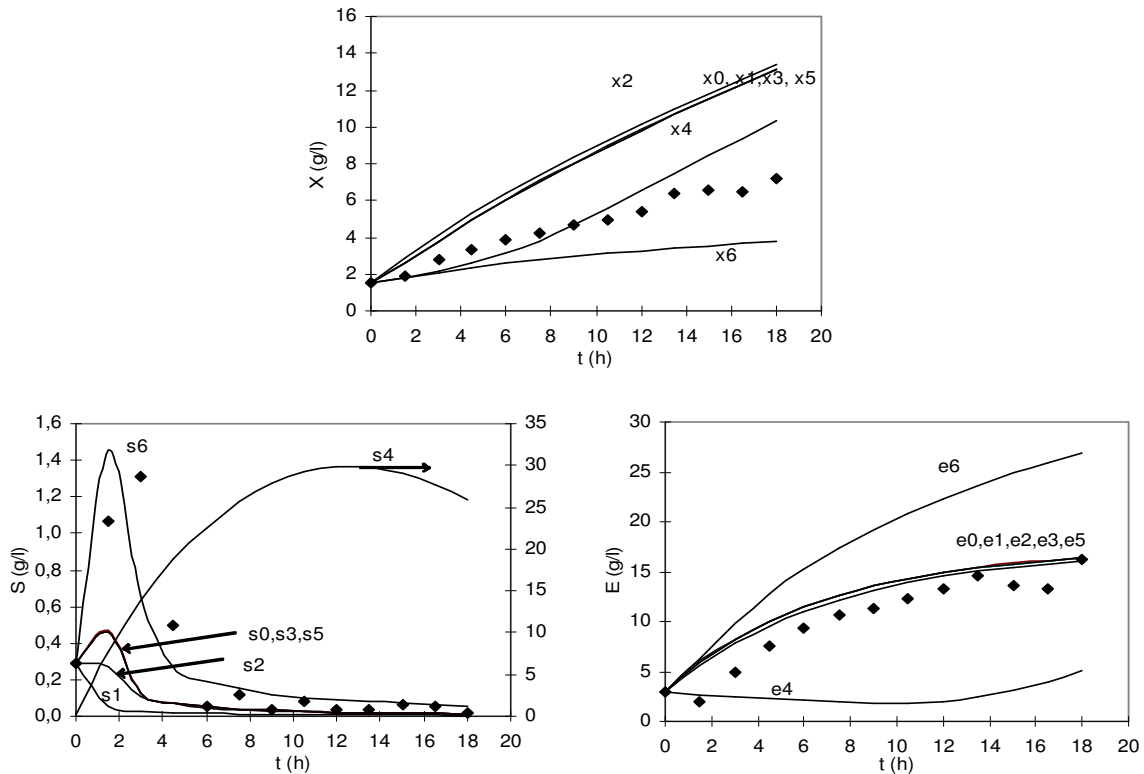


Figure 4: Biomass(X), glucose(S) and ethanol (E) profiles for the seven runs with the kinetics parameters presented in Table 3. The dot points correspond to experimental data and the lines to simulation values. Subscripts 0 to 6 correspond to the simulation runs.

relevant for baker's yeast production. The maximum specific growth rate on ethanol, μ_e^{max} , does not influence simulation state variables profiles (the x_0 , x_3 and x_5 profiles for biomass, the s_0 , s_3 and s_5 profiles for glucose and the e_0 , e_3 and e_5 profiles for ethanol are coincident).

Table 4 resumes the estimated values, for the two relevant parameters, q_s^{max} and q_o^{max} obtained in each run. The mean values of all the estimates and the literature values are also shown. These mean values enable an easily comparison with the literature ones. The objective function (4.27) and the mean error (4.28) obtained in each experiment are also presented.

There is in fact a large difference in the results obtained in the five experiences. The mean value for maximum uptake in glucose, q_s^{max} is similar to the literature but, q_o^{max} is approximately half of the value in the literature. Considering maximum glucose uptake parameter, it varies from 0.79 in EXPC04 to 8.31 in EXPC01. Taking into account the initial conditions in each run (Table 2) it is clear that as sugar concentration in feed stream decreases from 25 g/l in EXPC01 to 5 g/l in EXPC04, the glucose uptake also decreases sharply.

For a better understanding of the influence of these parameters in the X , S and E profiles, a graphical representation for EXPC03 was considered, Figure 5. The subscript (1) refers to literature parameters, (2) to the estimated values and (3) to the mean of estimated values of q_s^{max} and q_o^{max} . The dot points correspond to the experimental data.

Even with the estimated values for that experience, x_2 , s_2 and e_2 profiles in Figure 5,

Table 4: Estimated values for q_s^{max} and q_o^{max} , objective function and mean error in the five experiences under the initial conditions described in Table 2.

<i>Experiment</i>	q_s^{max}	q_o^{max}	<i>Objective Function</i> (4.27)	<i>Mean Error</i> (4.28)
EXPC01	8.31	0.154	9.35	0.490
EXPC03	3.16	0.114	11.54	0.544
EXPC04	0.79	0.071	3.33	0.304
EXPC06	4.65	0.184	6.90	0.421
EXPC07	1.78	0.1625	11.72	0.571
Mean	3.74	0.137		
Literature [9, 11]	3.5	0.256		

there are still a significant difference between the model and experimental results. Therefore, a second heuristic sensitivity analysis was carried out in order to improve the results for experiment EXPC03.

The same simulation program was employed, considering the initial conditions described in Table 2. The parameters referred below were selected and their values were changed arbitrary. This second analysis concludes that:

- q_s^{max} – only influences glucose profile;
- μ_e^{max} – not relevant;
- q_o^{max} – influences on the reverse order biomass and ethanol;
- K_{La} – influences on the reverse order biomass and ethanol;
- K_s – only influences glucose profile;
- K_o – influences on the reverse order biomass and ethanol;
- K_e and K_i – not relevant;
- Yield coefficients – $Y_{x/s}^r$, $Y_{x/e}^r$, $Y_{x/s}^o$ and $Y_{x/o}^o$ are relevant.

Considering EXPC03, with q_s^{max} and q_o^{max} values previously estimated an optimization run is performed in order to adjust $Y_{x/s}^r$ and $Y_{x/e}^r$ values. Figure 6 shows the new profiles obtained for biomass (X), glucose (S) and ethanol (E).

Comparing Figure 5, profiles (2), and Figure 6, there is a significant improvement; *i.e.* the experimental data is better adjusted by the model behavior.

In Table 5 the estimated and literature values for $Y_{x/s}^r$, $Y_{x/e}^r$ obtained are presented with the objective function and the mean error obtained.

With the new values for these four parameters, q_s^{max} , q_o^{max} , $Y_{x/s}^r$, $Y_{x/e}^r$, an optimization run is then performed in order to estimate $Y_{x/s}^o$ and $Y_{x/o}^o$. Figure 7 shows the best results attained

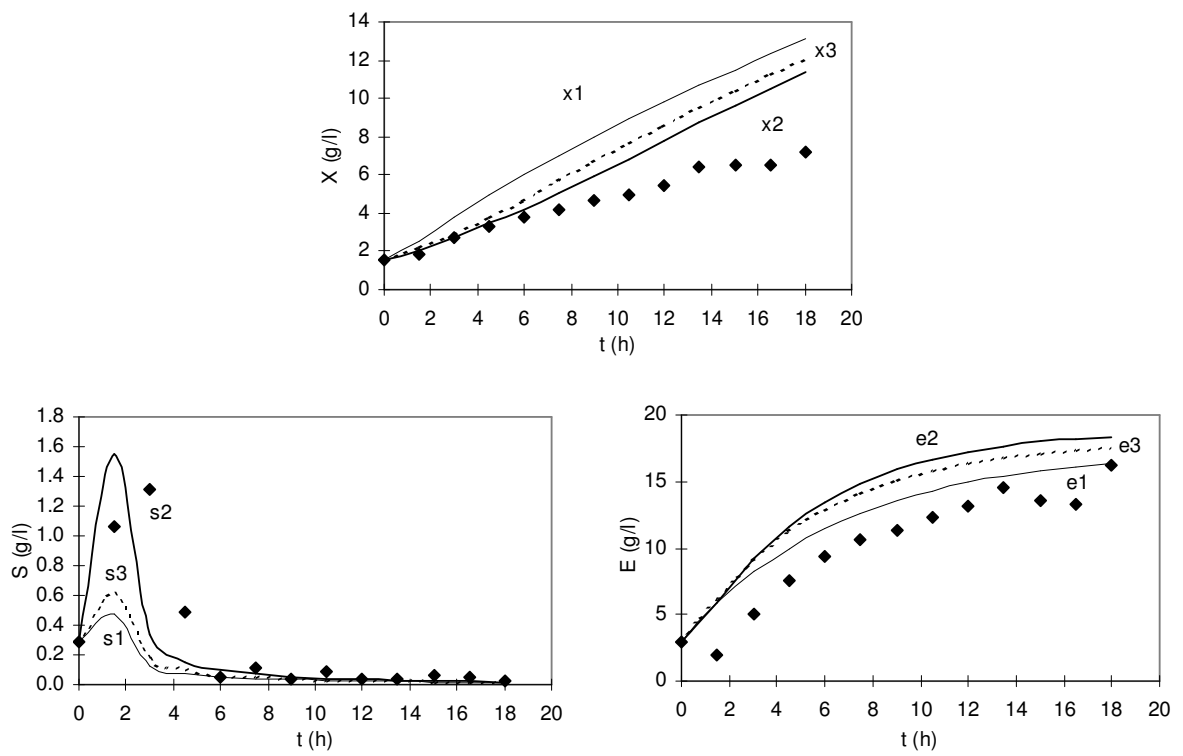


Figure 5: Biomass (X), glucose (S) and ethanol (E) profiles in experiment EXPC03. The subscript (1) refers to literature parameters, (2) to the estimated values and (3) to the mean of estimated values of $q_{x/s}^r$ and q_o^{max} . The dot points correspond to experimental data.

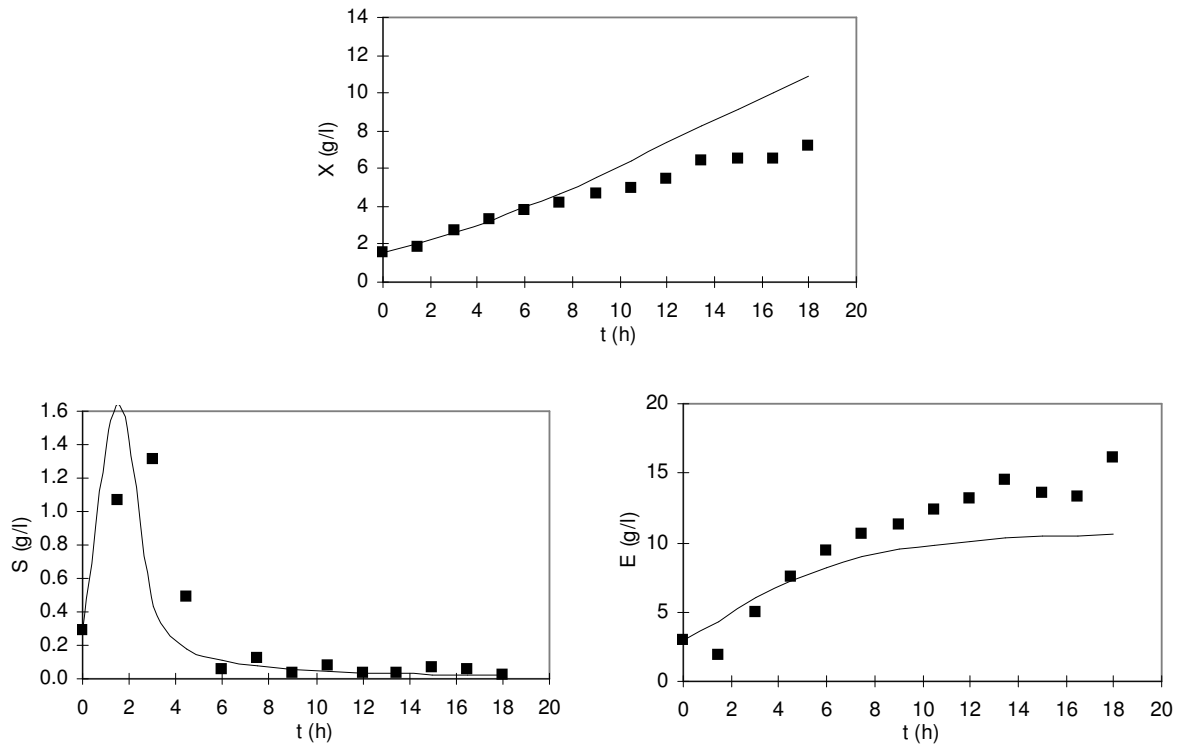


Figure 6: Biomass (X), glucose (S) and ethanol (E) in EXPC03 with q_s^{max} , q_o^{max} , $Y_{x/s}^r$, $Y_{x/e}^r$ estimated values (line) and experimental data (dot).

Table 5: Estimated values for $Y_{x/s}^r$ and $Y_{x/e}^r$ and objective function and mean error obtain for EXPC03.

<i>Experiment</i>	$Y_{x/s}^r$	$Y_{x/e}^r$	<i>Objective Function</i> (4.27)	<i>Mean Error</i> (4.28)
EXPC03	0.04	0.16	7.30	0.433
Literature [9, 11]	0.05	0.10		

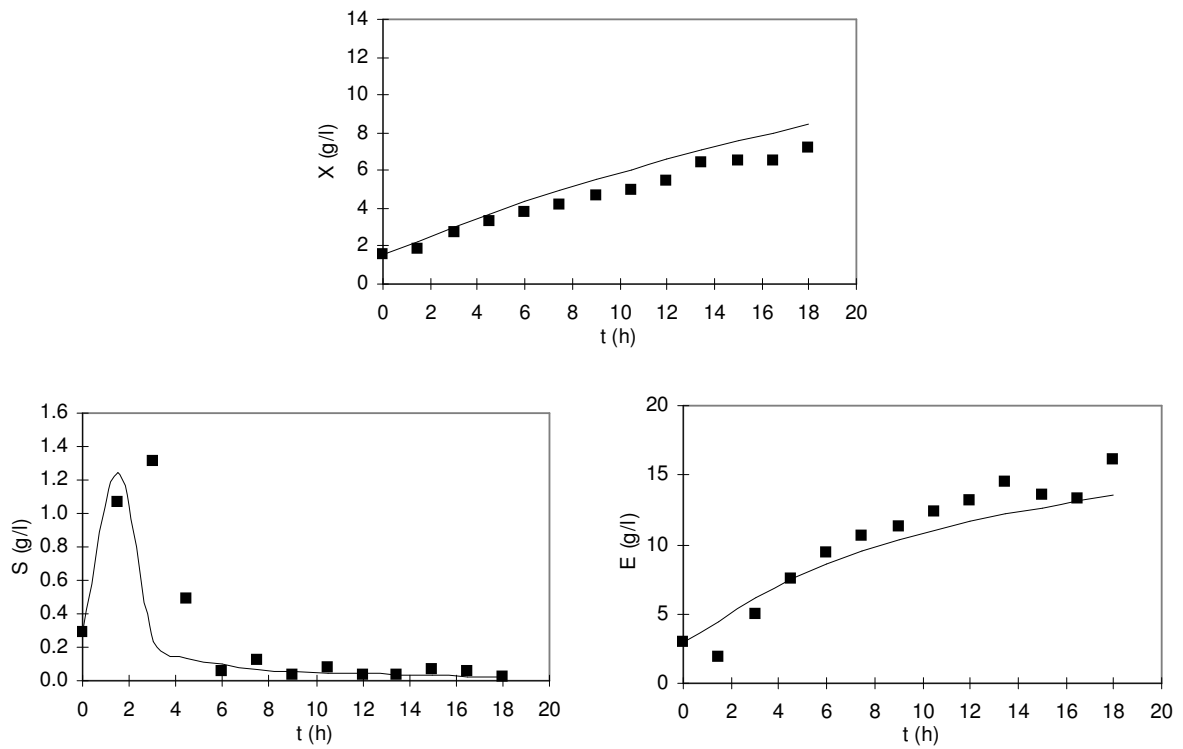
for this new experiment. Biomass and ethanol are significantly improved. However, glucose behavior in the first four hours is slightly worst than the one obtained without $Y_{x/s}^o$ and $Y_{x/o}^o$ estimates (Figure 6). We must point out that the six parameters were adjusted in pairs.

The estimated and literature values for $Y_{x/s}^r$, $Y_{x/e}^r$ are presented in Table 6 in addition with the respective objective function and the mean error.

Globally, it is apparent that a variability of the microorganisms metabolic behavior has, in a mathematically point of view, a relation to the variability of the characteristic parameters, namely yield coefficients and kinetics values [14].

Table 6: Estimated values for $Y_{x/s}^o$ and $Y_{x/e}^o$ and objective function and mean error obtain for EXPCO3.

<i>Experiment</i>	$Y_{x/s}^r$	$Y_{x/e}^r$	<i>Objective Function</i> (4.27)	<i>Mean Error</i> (4.28)
EXPCO3	0.86	0.63	5.68	0.385
Literature [9, 11]	0.49	1.20		

Figure 7: Biomass (X), glucose (S) and ethanol (E) in EXPCO3 with q_s^{max} , q_o^{max} , $Y_{x/s}^r$, $Y_{x/e}^r$, $Y_{x/s}^o$ and $Y_{x/o}^o$ estimated values (line) and experimental data (dots).

7 Conclusions

A deterministic model for fed-batch baker's yeast production was presented. The mathematical model, differential mass balance equations together with mass transfer and kinetics equations, considered as an IVP problem, was simulated in a FORTRAN90 based system.

The theoretical model was validated with a data set corresponding to five experimental open loop runs: four in fed-batch operation mode and one in batch mode.

As a significant discrepancy between simulated and experimental results was verified, there was a need for parameter estimation. In order to decide which parameters were the most relevant in model performance, a heuristic sensitivity analysis was taken. The maximum uptake rate for glucose and oxygen and the yield coefficients were seen to be the most significant model parameters. The number of parameter to be estimated at the same time was a software limitation (maximum three).

The apparent variability in microorganism behaviour motivates the thirst for process knowledge and understanding.

8 Suggestions for further research

As the optimization routine has a limitation in the number of parameters that can be estimated together (three) we are now starting a different method for estimating a larger number of parameters (depending only upon the experimental data available on each run), using a Minimum Square technique [15]. So, with the experimental fed-batch baker's yeast results, related to initial conditions (inputs) and final concentrations (outputs), yield coefficients and kinetic parameters are to be estimated together.

Nomenclature

C	dissolved carbon dioxide concentration	(g/l)
C^*	carbon dioxide saturation concentration	(g/l)
E	ethanol concentration	(g/l)
\overline{Er}	mean error	
F_{obj}	objective function	
K_i	inhibition parameter	
K_{La}^i	a overall mass transfer coefficient for component i	(1/h)
O	dissolved oxygen concentration	(g/l)
O^*	oxygen saturation concentration	(g/l)
S	glucose concentration	(g/l)
S_e	glucose concentration in the feed	(g/l)
V	liquid volume of reactor	(l)
X	biomass concentration	(g/l)
$Y_{x/s}^o$	yield coefficient biomass/glucose in oxidative pathway in glucose	
$Y_{x/s}^r$	yield coefficient biomass/glucose in fermentative pathway in glucose	
$Y_{x/e}^r$	yield coefficient biomass/ethanol in fermentative pathway in glucose	
$Y_{x/e}^{oe}$	yield coefficient biomass/ethanol in oxidative pathway in ethanol	
$Y_{x/o}^o$	yield coefficient biomass/oxygen in oxidative pathway in glucose	
$Y_{x/o}^{oe}$	yield coefficient biomass/oxygen in oxidative pathway in ethanol	
$Y_{x/c}^o$	yield coefficient biomass/carbon dioxide in oxidative pathway in glucose	
$Y_{x/c}^r$	yield coefficient biomass/carbon dioxide in fermentative pathway in glucose	
$Y_{x/c}^{oe}$	yield coefficient biomass/carbon dioxide in oxidative pathway in ethanol	

Small letters

a	a is the stoichiometric coefficient of the oxygen in the respiratory pathway of glucose	
n_{exp}	number of experimental points	
q_o	total oxygen uptake	(1/h)
q_O^O	oxygen uptake on glucose	(1/h)
q_s	total glucose uptake	(1/h)
q_s^{max}	maximum glucose uptake	(1/h)
q_s^o	glucose uptake in the oxidative pathway	(1/h)
q_s^r	glucose uptake in the fermentative pathway	(1/h)
q_e^o	ethanol uptake in the oxidative pathway	(1/h)
q_o^{max}	maximum oxygen uptake	(1/h)
t	time	(h)

Greek symbols

μ	specific growth rate	(1/h)
μ_e^{max}	maximum oxidative specific growth rate on ethanol	(1/h)
μ_e^o	oxidative specific growth rate on ethanol	(1/h)
μ_{max}	maximum specific growth rate	(1/h)
μ_s^r	fermentative specific growth rate on glucose	(1/h)
μ_s^o	oxidative specific growth rate on glucose	(1/h)

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