Modelling and Simulation of a Fermentation Fed-batch Bioprocess via Bond Graph Approach

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Abstract: This work addresses the modelling and simulation of a baker's yeast process taking place inside a fed-batch bioreactor. The modelling procedure is based on the pseudo Bond Graph approach, and the simulation is performed by using 20sim modelling and simulation environment. First, a Bond Graph model of a prototype fed-batch bioprocess is obtained, starting from the reactions schemes and taking into account the biochemical phenomena. Then, the method is systematically applied on a complex baker's yeast fed-batch bioprocess, widely used in bio-industry. Also, numerical simulations are performed and several comparisons are presented.

Keywords: modelling, bioprocesses, Bond Graphs.

1. INTRODUCTION

From a systemic point of view, biotechnological processes have a highly nonlinear character. Although the development and implementation of process control systems in biotechnology have made remarkable progress, however, development and application of modern methods of control of these processes is slower in comparison with other areas. This delay is mainly caused by two specific features of bioprocesses. First, bioprocesses' modelling is a very difficult task. These systems contain live microorganisms and therefore their operation and growth dynamics in particular, are often difficult to understand, highly nonlinear and nonstationary. Also, reproducibility of experiments is uncertain, and the lack of accuracy of measurements can lead to a number of identification problems. Second, application of monitoring and control strategies in most cases faces the absence of a specific instrumentations, safe and cheap, for direct measurement and/or real-time monitoring of biological and biochemical variables (concentrations of biomass, substrate, metabolites).

The baker's yeast bioprocess is extensively used in bakery, beer and wine industries. Usually, baker's yeast production is carried out into Continuous Stirred Tank Bioreactors (CSTB) or into Fed-batch Bioreactors (FBB). This bioprocess is highly nonlinear and the reaction rates are quite complicated. However, some nonlinear models were developed in order to describe this process.

One of most utilized kinetic model was introduced by (Sonnleitner and Käppeli, 1986), and since then it has been used by many authors (Ferreira, 1995, Oliveira *et al.*, 1996, Lubenova and Ferreira, 2000, Georgieva *et al.*, 2001, Renard and Vande Wouwer, 2008). The Sonnleitner and Käppeli kinetic model is based on the well-known bottleneck hypothesis (Sonnleitner and Käppeli, 1986, Renard and Vande Wouwer, 2008) which assumes a limited capacity of yeast, leading to the production of ethanol under conditions of oxygen limitation and/or high glucose concentration. In practice, the analytical models of the reaction rates and/or of the specific growth rates are difficult to obtain.

Modelling of bioprocesses is a complex task; however, using the mass balance of the components inside the process and obeying some modelling rules, a dynamical state-space model can be obtained (Bastin and Dochain, 1990, Dochain, 2008, Sendrescu, 2011). An alternative to the classical modeling is the pseudo Bond Graph method (Couenne *et al.*, 2006, Heny *et al.*, 2000). This method provides a uniform manner to describe the dynamical behaviour of processes. Pseudo Bond Graphs are suitable for chemical systems due to the physical meaning of the effort and flow variables.

The Bond Graph modelling of some biological systems was reported in a few works, such as (Schnakenberg, 1981, Linkens, 1990). The Bond Graph modelling of bioprocesses is a recent research trend (Roman *et al.*, 2009, Roman *et al.*, 2010), and it is not fully exploited yet.

The present paper is an extended work of (Roman, 2010) and addresses the pseudo Bond Graph modelling of a baker's yeast bioprocess that is carried out into a FBB. First, the model of a prototype fed-batch bioprocess is obtained using the reaction schemes and taking into account the functioning of the fed-batch bioreactor. Then, in order to outline the applicability of the method, a complex model of baker's yeast bioprocess is developed. This kind of bioreactor is initially partially filled with an amount of some of the needed reactants. The other reactants are then progressively added to the reactor as and when required. The process is stopped when enough products have been accumulated.

The paper is organized as follows. In Section 2 some aspects regarding Bond Graph methodology are presented followed in Section 3 by the Bond Graph modelling of a fed-batch prototype bioprocess. Then, Section 4 is dedicated to the application of the method for the baker's yeast bioprocess.

Also, the dynamic models are achieved from the Bond Graph models. Section 5 presents several simulation results for both prototype and complex bioprocesses. The Bond Graph models are implemented by using the 20sim modelling and simulation environment (registered trademark of Control-lab Products B.V. Enschede, Netherlands), and time evolution of state variables and reaction kinetic rates are depicted. In order to integrate the systems of differential equations representing the dynamical models, several stiff and non-stiff methods were applied and some comparisons are provided. Finally, in Section 6 concluding remarks are presented.

2. FUNDAMENTS OF BOND GRAPH MODELING METHODOLOGY

The Bond Graph methodology was first introduced by H. M. Paynter, and it was developed from simple electrical and mechanical systems description (based on basic element behaviour prototypes) towards complex structures modelling with electromechanical (Thoma, 1975), hydraulic (Dauphin-Tanguy, 2000), thermal (Thoma and Ould Bouamama, 2000), chemical components (Heny *et al.*, 2000). Bond Graph method uses the effort-flow analogy to describe physical processes. Each process is described by a pair of variables, effort *e* and flow *f*, and their product is the power. Besides the power variables, two other types of variables are very important in describing dynamic systems and these variables, sometimes called energy variables, are the generalized momentum *p* as time integral of effort and the generalized displacement *q* as time integral of flow (Karnopp and Rosenberg, 1974, Thoma, 1975).

Although Bond Graph method applicability to chemical based processes field wasn't foreseen by the method promoters, yet it has developed in the context of enlargement of the modelling techniques from electromechanics to molecular processes. These processes' modelling is based on the so-called pseudo Bond Graph method, in which their description is no longer based on the power variables (effort and flow), or not exclusively (Thoma, 1975, Heny *et al.*, 2000, Roman *et al.*, 2009, Roman *et al.*, 2010), but on pseudo-bonds for which the product of corresponding variables has not the signification of power. Thus, a lot of chemical, thermochemical, thermofluids, technological processes were modelled based on pseudo Bond Graphs (Heny *et al.*, 2000, Roman *et al.*, 2009, Roman *et al.*, 2010). This specific approach, adapted to physical system particularities – pseudo Bond Graph – is appropriate for the modelling of processes based on chemical reactions due to the meaning of effort and flow variables (effort as concentration and flow as mass flow) involved whose product do not have the physical dimension of power. Pseudo Bond Graphs keep both the unitary characteristic and basic methodology benefits.

Among the advantages of this methodology, an important one is given by the fact that various systems belonging to different engineering domains can be modelled using only nine elements: inertial elements (I), capacitive elements (C), resistive elements (R), effort sources (Se) and flow sources (Sf), transformer elements (TF) and gyrator elements (GY), effort junctions (J0) and flow junctions (J1). Another important aspect is the causality assignment - an important concept embedded in Bond Graph theory. This refers to cause and effect relationship. Thus, as part of the Bond Graph modelling process, a causality assignment is implicitly introduced (Karnopp and Rosenberg, 1974, Thoma, 1975). Causality is graphically represented by a causal stroke placed perpendicular to the bond at one of its ends indicating the direction of the effort variable. Causal stroke assignment is independent of the power flow direction. This leads to the description of Bond Graphs in the form of state – space equation. The sources (Se and Sf) have fixed causality, the dissipative element (R) has free causality depending on the causality of the other elements of Bond Graph, and the storage elements (I, C) have preferential causality, that is integral causality or derivative causality, but it is always desirable that C and I elements to be in integral causality. Transformers, gyrators and junction elements have constrainedly causality.

Due to large application domain and complexity, the biological systems and biotechnological processes modelling represents an important challenge for the Bond Graph approach. The complexity of living world specific structure delayed the extension of Bond Graph methodology to these processes, although there are some results for biologic and biomedical systems, some of them accomplished during early period of this method (Oster, 1973, Schnakenberg, 1981), others more recent. However, the Bond Graph modelling applied to biotechnological systems is not so well explored yet, especially for those functioning in fed-batch bioreactors. This unexplored domain – bioprocesses Bond Graph modelling – can be undertaken with promising results. The obtained results regarding the modelling of batch and continuous bioprocesses constitute a starting point for the elaboration of a systematic Bond Graph modelling methodology for some classes of biotechnological processes.

3. PSEUDO BOND GRAPH MODEL OF A PROTOTYPE FED-BATCH BIOPROCESS

One of the simplest biological reactions is the micro-organisms growth process, with the reaction scheme (Bastin and Dochain, 1990, Dochain, 2008) given by:

$$S \xrightarrow{\varphi} X\,, \tag{1}$$

where S is the substrate, X is the biomass and φ is the reaction rate.

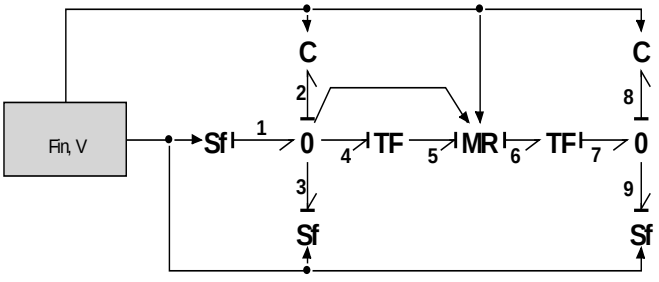

Fig. 1. Pseudo Bond Graph model of the fed-batch prototype bioprocess.

This simple growth reaction represents in fact a prototype reaction, which can be found in almost every bioprocess.

The dynamics of the concentrations of the components from reaction scheme (1) can be modelled considering the mass balance of the components. The dynamical model of the bioprocess (1) is simple, but if the reaction scheme is more complicated, the achievement of the dynamical model is difficult.

In biotechnology, pseudo Bond Graph models are accomplished starting with processes reactions schemes and using both base elements of Bond Graph methodology and pseudo bonds with effort and flow variables as concentrations and mass flows. From the reaction scheme (1) and taking into account the mass transfer through the fed-batch bioreactor, using the Bond Graph modelling characteristics, the pseudo Bond Graph model of the fed-batch bioprocess is achieved and is depicted in Fig. 1.

The directions of half arrows correspond to the run of the reaction, going out from the substrate *S* towards biomass *X*. In the Bond Graph model, the mass balances of the species involved in the bioreactor are represented by two 0-junctions: $0_{1,2,3,4}$ (mass balance for substrate *S*), $0_{7,8,9}$ (mass balance for biomass *X*).

A difficult task is the modelling of the reaction kinetics. The form of kinetics is complex, nonlinear and in many cases unknown. A general assumption (Dochain, 2008) is that a reaction can take place only if all reactants are presented in the bioreactor. Therefore, the reaction rates are necessarily zero whenever the concentration of one of the reactants is zero. In order to model the rate of reaction φ, because of the dependency of substrate and biomass concentrations, we have used a modulated two port R element, denoted $MR_{5,6}$. Mass flow of the component entering the reaction is modelled using a modulated source flow element Sf_1.

The quantities exiting from the reaction are modelled using also modulated flow sources elements Sf represented by bonds 3 and 9. This approach was imposed by the dependency of these elements on F_{in} - the input feed rate (l/h), and on *V* – volume of the bioreactor (l).

From the constitutive equations of Sf-elements we obtain:

$$f_3 = e_3 Sf_3, \quad f_9 = e_9 Sf_9. \tag{2}$$

The accumulations of substrate and biomass in the FBB are represented by bonds 2 and 8, and are modelled using capacitive elements C, with the constitutive equations:

$$e_2 = q_2 / C_2 = (\int_t (f_1 - f_3 - f_4)dt) / C_2, \tag{3}$$

$$e_8 = q_8 / C_8 = (\int_t (f_7 - f_9)dt) / C_8. \tag{4}$$

Using the constitutive relations of transformer elements $TF_{4,5}$ and $TF_{6,7}$ the relations for flows f_4 and f_7 are obtained: $f_4 = k_{4,5} f_5$, $f_7 = f_5 / k_{6,7}$, with $k_{4,5}$ and $k_{6,7}$ the transformers modulus, which are in fact yield coefficients of the bioprocess (their values equal one for this fed-batch bioprocess).

In fact, e_2 is the substrate concentration, which will be denoted with *S* (g/l), e_8 is the biomass concentration *X* (g/l), f_5 is proportional to φ and *V*, $C_2 = C_8 = V$ (l) with $Sf_3 = Sf_9 = F_{in}$.

Therefore, from (3) and (4) we will obtain the dynamical model of the fed-batch bioprocess:

$$\begin{aligned} V\frac{dS}{dt} &= V \cdot \dot{S}(t) = F_{in}S_{in} - F_0 S - \varphi V, \\ V\frac{dX}{dt} &= V \cdot \dot{X}(t) = -F_0 X + \varphi V, \\ \frac{dV}{dt} &= \dot{V}(t) = F_{in}. \end{aligned} \tag{5}$$

The model (5) expresses the equations of mass balance for the reaction scheme (1).

Taking into account that the dilution rate $D = F_{in} / V$, the dynamical behaviour of the concentrations can be easily obtained from (5):

$$\begin{aligned} \dot{S}(t) &= DS_{in} - DS - \varphi, \\ \dot{X}(t) &= -DX + \varphi, \\ \dot{V}(t) &= F_{in}. \end{aligned} \tag{6}$$

The reaction rate can be expressed as (Bastin and Dochain, 1990):

$$\varphi(S, X) = \mu(S, X) \cdot X, \tag{7}$$

where μ is the specific growth rate.

Concerning the modelling of the specific growth rate, there exist many models. The form of the specific growth rate depends on the particular bioprocess that takes place inside the FBB; a lot of kinetic laws were found: Monod, Haldane, Contois, Tessier, etc. A detailed description of the reaction kinetics is given in (Bastin and Dochain, 1990). For example, for the Monod model, the kinetic expression is as follows (Bastin and Dochain, 1990):

$$\mu(S) = \mu^*\left(S/(K_m + S)\right), \tag{8}$$

where μ^* represents the maxim specific growth rate and K_m the Michaelis-Menten constant.

Another possible form is represented by the Haldane model (Selişteanu *et al.*, 2007):

$$\mu(S) = \mu_0\left(S/(K_M + S + S^2/K_i)\right), \tag{9}$$

where μ_0 represents the maxim specific growth rate, K_M the Michaelis-Menten constant and K_i the inhibition constant.

4. MODELING OF BAKER'S YEAST BIOPROCESS

Next, the same procedure as in previous section will be used in order to obtain the Bond Graph model of a baker's yeast fed-batch bioprocess. Living cells of *Saccharomyces cerevisiae*, which form baker's yeast, are predominantly used in bakery, beer and wine industries. Nowadays, with the achievement of modern gene technology, *S. cerevisiae* are increasingly used as host organisms for producing recombinant proteins (production of insulin for diabetics, vaccines, etc.) (Georgieva *et al.*, 2001).

Baker's yeast production is carried out into fed-batch fermenters with inoculums of *S. cerevisiae* culture and a glucose solution as substrate feed. Three metabolic pathways can be detected: 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, associated with ethanol production (Sonnleitner and Käppeli, 1986).

The reaction scheme of the baker's yeast production process was introduced by (Sonnleitner and Käppeli, 1986), and since then it has been used by many authors (Ferreira, 1995, Oliveira *et al.*, 1996, Lubenova and Ferreira, 2000, Georgieva *et al.*, 2001, Renard and Vande Wouwer, 2008):

$$S + C \xrightarrow{\mu_s^o} X + G\,,\quad S \xrightarrow{\mu_s^r} X + E + G\,,\quad E + C \xrightarrow{\mu_e^o} X + G\,. \qquad (10)$$

In the reaction schemes (10), S is the glucose, X the biomass, E the ethanol, C is the dissolved oxygen, and G the dissolved carbon dioxide.

The first reaction scheme represents the respiratory growth on glucose; the second reaction scheme the fermentative growth on glucose, and finally the third reaction represents the respiratory growth on ethanol. μ_s^o, μ_s^r, and μ_e^o are three specific growth rates that reflect the capacity of the baker's yeast to exploit three catabolic pathways for energy and material sources.

In the following, we will consider the fed-batch operation of the bioprocess. From the reaction scheme (10), and considering the mass transfer through the bioreactor, using the modelling procedure described in the previous section, the pseudo Bond Graph model of the bioprocess is achieved. This model is presented in Fig. 2.

The directions of the half arrows in the Bond Graph correspond to the progress of the reactions, going out from the components S and C towards X and G for the first reaction, from S towards X, E and G for the second reaction, and from E and C towards X and G for the third reaction.

In Bond Graph terms, the mass balances of the species involved in the bioreactor are represented by five 0-junctions: $0_{1,2,3,4,33}$ (mass balance for C), $0_{6,7,8,9,20}$ (mass balance for S), $0_{13,14,15,24,37}$ (mass balance for X), $0_{17,18,19,26,39}$ (mass balance for G), and $0_{28,29,30,31}$ (mass balance for E). The constitutive relations of these junctions are:

$$f_2 = f_1 - f_3 - f_4 - f_{33}\,,\quad f_7 = f_6 - f_8 - f_9 - f_{20}\,,$$
$$f_{14} = f_{13} - f_{15} + f_{24} + f_{37}\,,\quad f_{18} = f_{17} - f_{19} + f_{26} + f_{39}\,,$$
$$f_{29} = f_{28} - f_{30} - f_{31}\,.$$

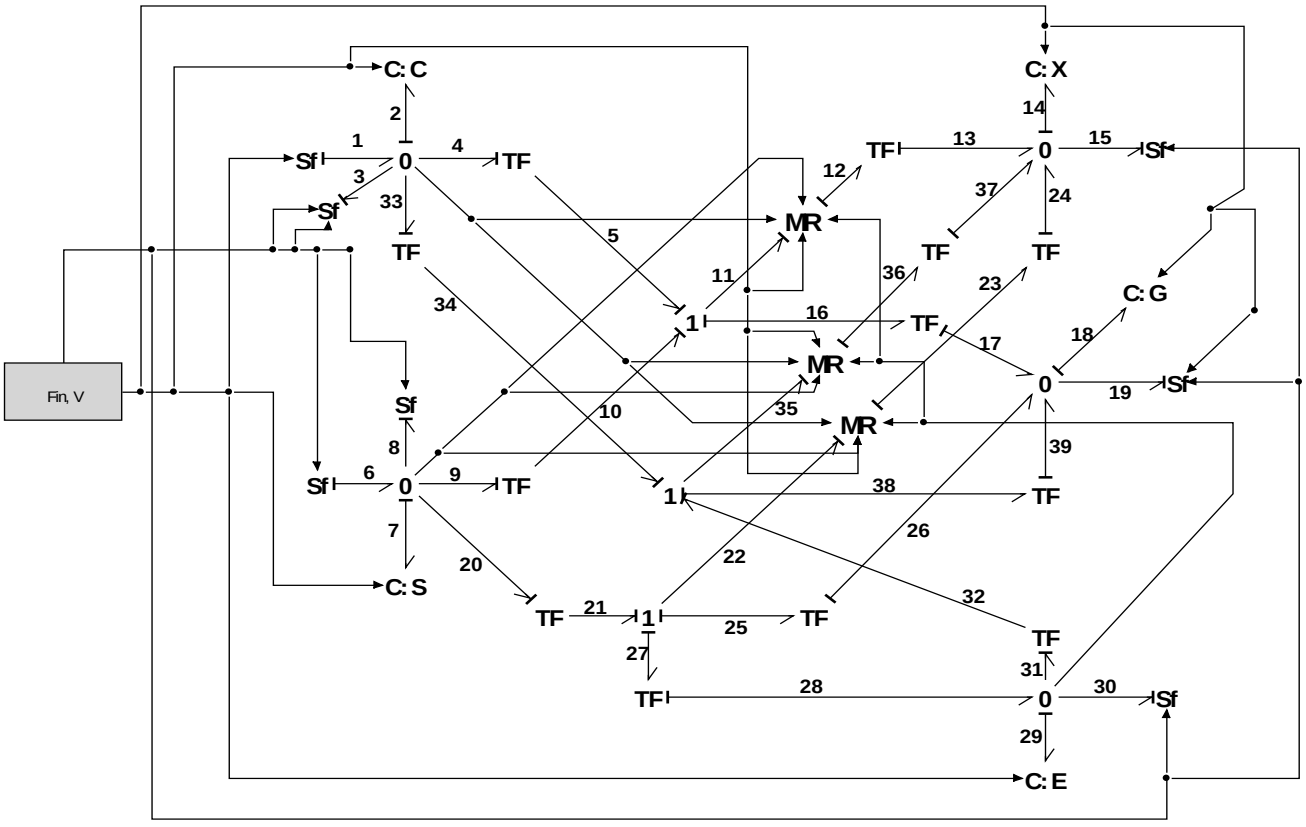

Fig. 2. Pseudo Bond Graph model of the baker's yeast bioprocess.

The accumulations of species *C*, *S*, *X*, *G* and *E* in the bioreactor are represented by bonds 2, 7, 14, 18 and 29, and are modelled using capacitive elements C. The constitutive equations of C-elements are obtained using constitutive relations of 0-junction, and they have the following form:

$$\begin{aligned} e_2 &= q_2 / C_2 = (\int_t (f_1 - f_3 - f_4 - f_{33})dt) / C_2, \\ e_7 &= q_7 / C_7 = (\int_t (f_6 - f_8 - f_9 - f_{20})dt) / C_7, \\ e_{14} &= q_{14} / C_{14} = (\int_t (f_{13} - f_{15} + f_{24} + f_{37})dt) / C_{14}, \\ e_{18} &= q_{18} / C_{18} = (\int_t (f_{17} - f_{19} + f_{26} + f_{39})dt) / C_{18}, \\ e_{29} &= q_{29} / C_{29} = (\int_t (f_{28} - f_{30} - f_{31})dt) / C_{29}, \end{aligned} \quad (11)$$

where C_2, C_7, C_{14}, C_{18} and C_{29} are the parameters of C-elements: $C_2 = C_7 = C_{14} = C_{18} = C_{29} = V$, with V being the bioreactor volume (l).

The components flows exiting from the reaction are modelled using flow sources elements Sf represented by bonds 3, 8, 15, 19 and 30; the constitutive equations of these elements are:

$$f_3 = e_3 Sf_3, \; f_8 = e_8 Sf_8, \; f_{15} = e_{15} Sf_{15}, \quad (12)$$

$$f_{19} = e_{19} Sf_{19}, \; f_{30} = e_{30} Sf_{30}, \quad (13)$$

with Sf_3, Sf_8, Sf_{15}, Sf_{19}, Sf_{30} parameters of Sf-elements:

$$\begin{aligned} &Sf_3 = Sf_8 = Sf_{15} = Sf_{30} = F_{in}, \\ &Sf_{19} = K_V K_L a V + F_{in} \end{aligned} \quad (14)$$

where F_{in} is the input feed rate (l/h), and K_V is a transfer coefficient.

Mass flows of the components entering the reaction are modelled using two flow sources elements Sf_1 and Sf_6. The transformer elements $TF_{4,5}$, $TF_{9,10}$, $TF_{12,13}$, $TF_{16,17}$, $TF_{20,21}$, $TF_{23,24}$, $TF_{25,26}$, $TF_{27,28}$, $TF_{31,32}$, $TF_{33,34}$, $TF_{36,37}$, $TF_{38,39}$ were introduced to model the yield coefficients $k_i, i = \overline{1,12}$.

For the modelling of the reaction rates φ_1, φ_2, φ_3 we used three modulated multiport R-element, $MR_{11,12}$, $MR_{22,23}$, and $MR_{35,36}$. The constitutive relations of MR elements imply that:

$$f_{12} = \mu_s^0 V e_{12}, \; f_{23} = \mu_s^r V e_{23}, \; f_{36} = \mu_e^0 V e_{36}. \quad (15)$$

The signification of Bond Graph elements is as follows: e_2 is the substrate concentration C (g/l), e_7 - the glucose concentration S (g/l), e_{14} - the biomass concentration X (g/l), e_{18} is the product concentration G (g/l), e_{29} is the ethanol concentration E (g/l), $f_1 = K_L a C^* V$ (where $K_L a$ is the mass transfer coefficient and C^* the equilibrium concentration of the dissolved oxygen), $f_6 = F_{in} S_{in}$ where F_{in} is the input feed rate (l/h), S_{in} is the glucose concentration on the feed (g/l). Taking into account all these aspects, from (11) we will obtain the dynamical model of the baker's yeast bioprocess:

$$\begin{aligned} V \cdot \dot{C}(t) &= K_L a (C^* - C) V - F_{in} C - k_1 \varphi_1 V - k_2 \varphi_3 V, \\ V \cdot \dot{S}(t) &= F_{in} S_{in} - F_{in} S - k_3 \varphi_1 V - k_4 \varphi_2 V, \\ V \cdot \dot{X}(t) &= k_5 \varphi_1 V - F_{in} X + k_6 \varphi_2 V + k_7 \varphi_3 V, \\ V \cdot \dot{G}(t) &= k_8 \varphi_1 V - (K_V K_L a V + F_{in}) G + k_9 \varphi_2 V + k_{10} \varphi_3 V, \\ V \cdot \dot{E}(t) &= k_{11} \varphi_2 V - F_{in} E - k_{12} \varphi_3 V. \end{aligned} \quad (16)$$

Taking into account that the dilution rate $D = F_{in} / V = 1 / t_r$, with t_r - medium residence time, the above equations become:

$$\begin{aligned} \dot{C}(t) &= K_L a (C^* - C) - DC - k_1 \varphi_1 - k_2 \varphi_3, \\ \dot{S}(t) &= DS_{in} - DS - k_3 \varphi_1 - k_4 \varphi_2, \\ \dot{X}(t) &= k_5 \varphi_1 - DX + k_6 \varphi_2 + k_7 \varphi_3, \\ \dot{G}(t) &= k_8 \varphi_1 - (K_V K_L a + D) G + k_9 \varphi_2 + k_{10} \varphi_3, \\ \dot{E}(t) &= k_{11} \varphi_2 - DE - k_{12} \varphi_3. \end{aligned} \quad (17)$$

For the reaction rates of the baker's yeast bioprocess there exist many possible models (Sonnleitner and Käppeli, 1986, Oliveira *et al.*, 1996, Georgieva *et al.*, 2001, Renard and Vande Wouwer, 2008). However, the process of yeast growth on glucose with ethanol production is generally described by the next three metabolic reactions (Sonnleitner and Käppeli, 1986). First, the reaction rate of respiratory growth on glucose, and the associated specific growth rate are (Renard and Vande Wouwer, 2008):

$$\varphi_1 = \mu_s^0 \cdot X, \; \mu_s^0 = \min(\mu_s, \mu_{c\max} / k_5), \quad (18)$$

where the kinetic terms associated with the glucose consumption μ_s and with the respiratory capacity $\mu_{c\max}$ are modelled by Monod-type laws: $\mu_s = q_{s\max} S / (S + K_s)$, $\mu_{c\max} = q_{c\max} C / (C + K_c)$, with $q_{s\max}$ and $q_{c\max}$ the maximal values of the specific growth rates of glucose and oxygen, and K_s and K_c the saturation parameters for glucose and oxygen uptake, respectively.

Second, the reaction rate of the fermentative growth on glucose, and the associated specific growth rate are (Renard and Vande Wouwer, 2008):

$$\varphi_2 = \mu_s^r \cdot X, \; \mu_s^r = \max(0, \mu_s - \mu_{c\max} / k_5). \quad (19)$$

Finally, if the oxidation capacity is sufficiently high to oxidize both ethanol and glucose, then their consumption is possible (Georgieva *et al.*, 2001). Then, the reaction rate of the respiratory growth on ethanol, and the specific growth rate are (Renard and Vande Wouwer, 2008):

$$\varphi_3 = \mu_e^0 \cdot X, \quad (20)$$

$$\mu_e^0 = \max(0, \min(\mu_e, (\mu_{c\max} - k_5 \mu_s) / k_6)), \quad (21)$$

where μ_e is the potential ethanol oxidative rate, modelled by Monod-type law: $\mu_e = q_{e\max} E / (E + K_e)$, with $q_{e\max}$ the maximal value of the ethanol specific growth rate, and K_e the saturation parameter for growth on ethanol.

5. SIMULATION RESULTS

The obtained Bond Graph models of the prototype and baker's yeast bioprocesses were simulated using 20sim environment. For the simulation of the fed-batch operation a typical time profile of the input feed rate is considered - see Fig. 3. In the same picture, the time profile of the bioreactor volume was depicted. The simulation results of the time evolution of reaction rate, and of substrate and biomass concentrations respectively are shown in Figs. 4 and 5 when the specific growth rate is of the Monod type (7), and in Figs. 6 and 7 when the specific growth rate is of the Haldane form (8), which takes into account the inhibitory action of the substrate concentration.

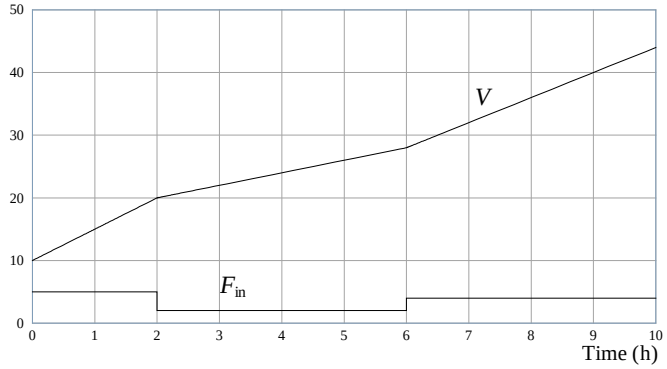

Fig. 3. Time profiles of the input feed rate (l/h) and of the volume (l).

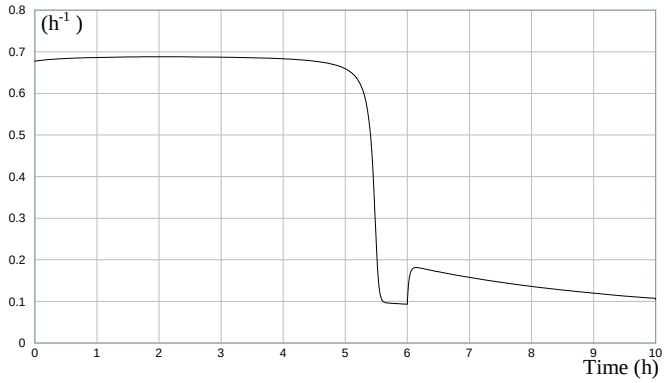

Fig. 4. Evolution of specific growth rate μ - Monod.

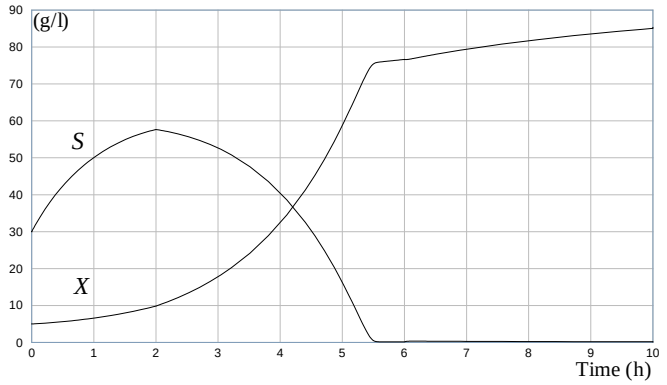

Fig. 5. Time evolution of concentrations - prototype fed-batch bioprocess – Monod.

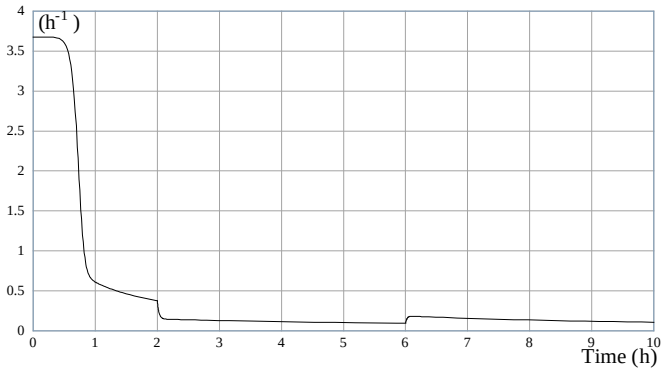

Fig. 6. Evolution of specific growth rate μ - Haldane.

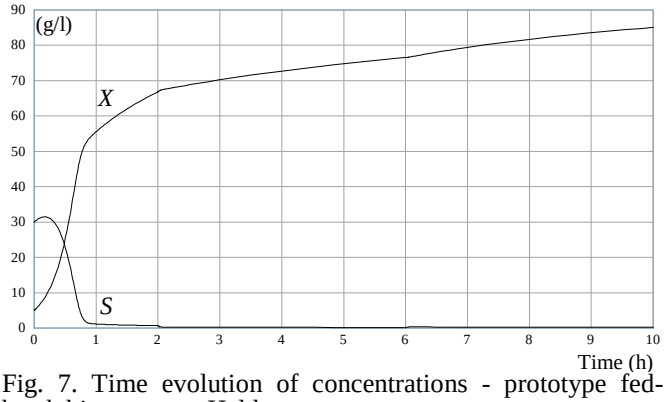

Fig. 7. Time evolution of concentrations - prototype fed-batch bioprocess – Haldane.

For the simulation of the prototype fed-batch bioprocess the following parameters were used: $\mu^* = 0.7$ (h^{-1}), K_m = 1 (g/l), $\mu_0 = 6$ (h^{-1}), K_M = 10 (g/l), K_i = 100 (g/l), S_{in} = 100 (g/l).

For the case of baker's yeast bioprocess the simulations were performed for the parameters given by (Sonnleitner and Käppeli, 1986). The values of these parameters were obtained from real experiments. However, the obtained Bond Graph model is a qualitative one, which allows the development of some simulation experiments.

Fig. 8 shows the feed rate profile imposed to the process. As shown in Fig. 9, the specific growth rates related to ethanol production and consumption switch alternatively from zero to positive values and are not at any instant simultaneously positive. Fig. 10 depicts the time evolution of specific growth μ_s^r. The profiles of the state variables are plotted in Figs. 11, 12, and 13.

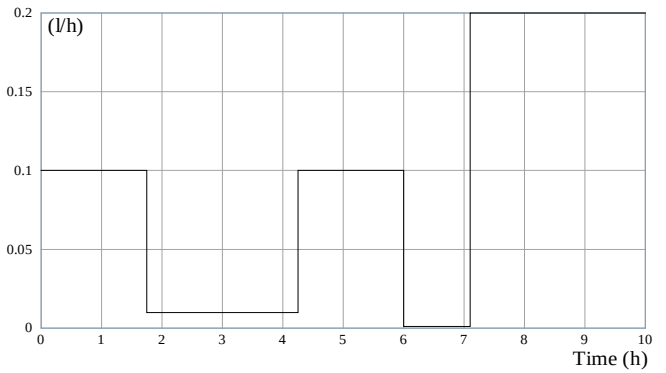

Fig. 8. Time profiles of the input feed rate – baker's yeast bioprocess.

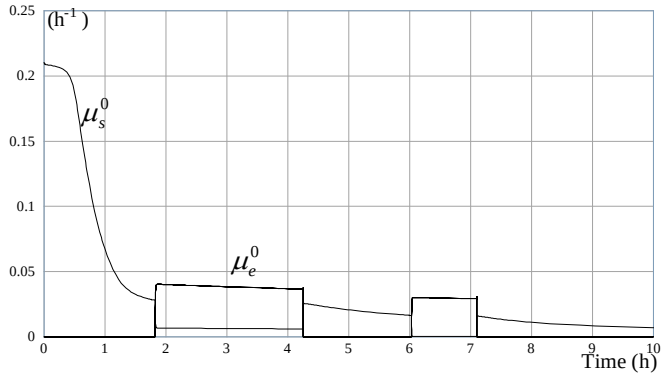

Fig. 9. Evolution of specific growth rates μ_s^0 and μ_e^0.

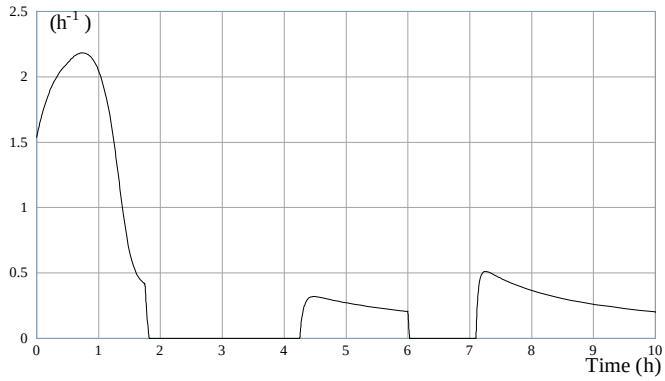

Fig. 10. Evolution of specific growth rate μ_s^r.

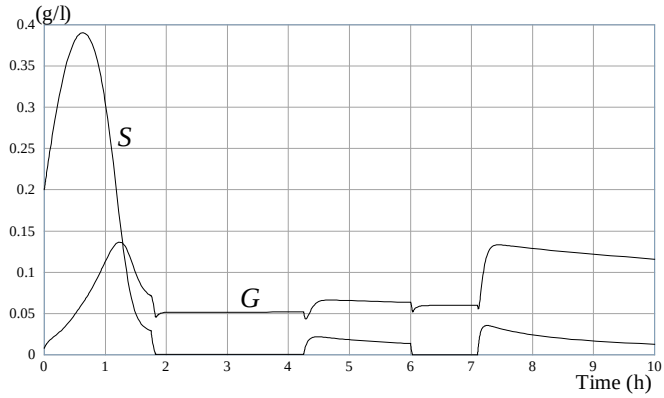

Fig. 11. Time profile of substrate and dissolved carbon dioxide concentrations.

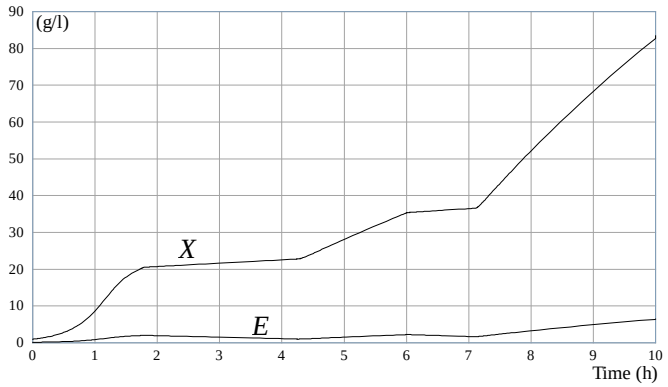

Fig. 12. Evolutions of biomass and ethanol concentrations.

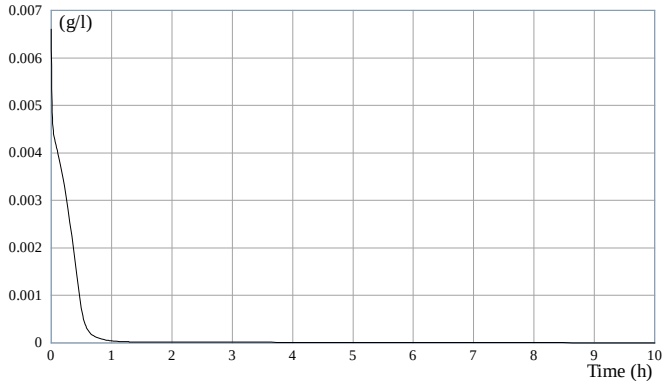

Fig. 13. Time profile of the dissolved oxygen concentration.

The last simulations were focused on the comparison of three integration methods. For example, in Figs. 14 and 15 the time profiles of the dissolved growth rate and of the dissolved carbon dioxide concentration obtained with three different methods were provided (non-stiff: Euler, Runge-Kutta 4, and stiff: Modified Backward Differentiation Formula).

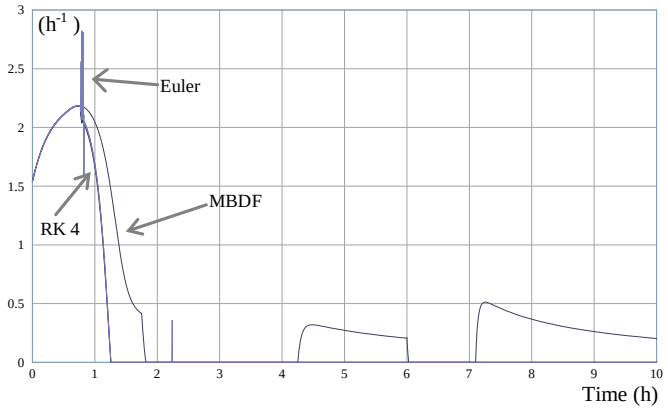

Fig. 14. The profiles of dissolved growth rate μ_s^r – different integration methods.

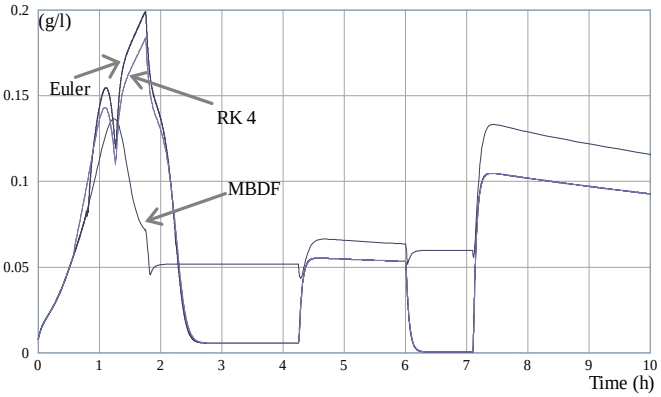

Fig. 15. The profiles of dissolved carbon dioxide concentration – different integration methods.

From these figures it can be notices that good results are obtained with Modified Backward Differentiation Formula integration method for both dissolved growth rate evolution and dissolved carbon dioxide concentration.

6. CONCLUSION

Due to the inherent diversity of the biotechnological processes, there are some problems concerning the development of a unified modelling approach. In this paper, a systematic procedure was used in order to develop the pseudo Bond Graph models of a prototype fed-batch bioprocess and of a nonlinear baker's yeast process, widely used in bioindustry. Also, the dynamic models of these complex bioprocesses were obtained starting from the pseudo Bond Graph model, by writing the characteristic equations for both elements and junction structure and taking into account the constructive and process characteristics of the systems in mathematical terms. The simulation of Bond Graph models by comparing the results obtained using different integration methods showed good results for stiff methods.

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