Teaching System for Modelling and Simulation of Bioprocesses via Bond Graphs

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***Abstract*—The goal of the present work was to implement a teaching system useful in modelling and simulation of biotechnological processes. The interactive system is based on applications developed using 20sim modelling and simulation software environment. A procedure for the simulation of bioprocesses modelled by Bond Graphs is proposed and simulators containing biochemical Bond Graph elements are designed. These simulators are organised in libraries that exploit the modularity of the method, very useful for the students, which will be able to simulate complex biotechnological processes.**

Keywords-teaching systems; modelling; simulation; Bond Graphs; biotechnology

I. INTRODUCTION

The teaching of bioengineering involves a variety of topics ranging from biology, biochemistry, medicine, automatic control and informatics. Therefore, training in this field is a difficult problem [1]. In the design and the achievement of a bioengineering course, significant problems are the modelling of bioprocesses and the simulation of these complex systems [2], [3]. Another important problem is the choice of the teaching system to pass from theory to practice.

The teaching material in the field of bioengineering can be classified as: simulators, laboratory bioreactors, pilot bioreactors and industrial bioreactors. Of course, it is essential to apply the theory on real bioprocesses, but in most cases the use of this method is expensive, and in some situations there are also biological risks. For this reason, the use of software simulators is common and it constitutes an alternative to real bioreactors.

In order to achieve a good training of the students, it is very interesting and useful to combine the theory with software simulators. Using the 20sim modelling and simulation software environment (registered trademark of Controllab Products B.V., Netherlands), an interactive teaching system was created. This system uses friendly graphical user interfaces and comprises sets of different experiments. First, a set of experiments with 20sim software package is designed; the final task is to achieve Bond Graph prototype simulators, which can be combined in order to obtain simulators for complex bioprocesses. Second, a set of modelling exercises is designed to achieve the mathematical models of these prototype bioprocesses. Every experiment consists in a short tutorial, the body of the experiment and several questions and tasks for Master students.

These sets of modelling and simulation experiments are grouped into a teaching system, which is implemented at the Department of Automatic Control, University of Craiova, within the frame of Automation of Complex Systems Master programme (the Bioengineering course).

The paper is organized as follows. Section II gives an introduction in the field of bioprocesses modelling via the Bond Graph approach. In Section III, an overview of the teaching system is presented. Section IV widely examines the implementation of some prototype bioprocess simulators in 20sim environment. In addition, in this section a simulator for two interconnected bioprocesses is presented. Section V deals with the mathematical model of the prototype bioprocesses obtained from the Bond Graph simulators. Also, the set of the modelling exercises is presented. Finally, in Section VI concluding remarks are collected.

II. BIOPPROCESS MODELLING ISSUES. THE BOND GRAPH APPROACH

In industry, the bioprocesses take place inside biological reactors, also called bioreactors, in which several biological reactions occur simultaneously in a liquid medium [2], [3]. The bioreactors can operate in three modes: the continuous mode, the fed-batch mode and the batch mode [2], [3]. A Fed-Batch Bioreactor initially contains a small amount of substrates (the nutrients) and micro-organisms and is progressively filled with the influent substrates. When the Fed-Batch Bioreactor is full the content is harvested. A Batch Bioreactor is filled with the reactant mixture: substrates and micro-organisms and allows for a particular time period for the reactions inside the reactor; after some time the products are removed from the tank. In a Continuous Stirred Tank Bioreactor (CSTB), the substrates are fed to the bioreactor continuously and an effluent stream is continuously withdrawn such that the culture volume is constant.

The biotechnological processes are characterized by several difficult issues such as strongly nonlinearity of kinetics,

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the unavailability of cheap and on-line instrumentation, etc. Therefore, there are some problems concerning the development of a unified modelling approach. However, even if the bioprocess modelling is a difficult task, by using the mass balance of the components inside the process and obeying some modelling rules, a dynamical state-space model (described using nonlinear differential equations) can be obtained either using the classical modelling methods [2], either Bond Graph methodology [4], [5].

Bond Graph method uses the effort-flow analogy to describe physical processes. A Bond Graph consists of subsystems linked together by lines representing power bonds. Each process is described by a pair of variables, effort *e* and flow *f*, and their product is the power. The direction of power is depicted by a half arrow. In a dynamic system the effort and the flow variables, and hence the power fluctuate in time [6], [7]. A specific approach adapted to physical system particularities – the Pseudo Bond Graph – is more suitable for the modelling of processes based on chemical and biochemical reactions due to the meaning of effort and flow variables involved whose product do not have the physical dimension of power [8], [9]. Pseudo Bond Graphs keep both the unitary characteristic and basic methodology benefits. Two other types of variables are important in describing dynamic systems and these variables, sometimes called energy variables, are the generalized momentum *p* and generalized displacement *q* [6].

An advantage of Bond Graph method over other techniques is that models of various systems belonging to different engineering domains can be expressed using a set of 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). I, C, and R elements are passive elements because they convert the supplied energy into stored or dissipated energy. Se and Sf elements are active elements because they supply power to the system and TF, GY, 0 and 1-junctions are junction elements that serve to connect I, C, R, Se and Sf, and constitute the junction structure of Bond Graph model.

The concept of causality is an important concept of Bond Graph models. Causality is represented on a model by 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.

One of the simplest biological reactions is the micro-organisms growth process [2], with the next reaction scheme:

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

with S the substrate, X the biomass and φ the reaction rate.

This simple growth reaction represents in fact a prototype reaction, which can be found in almost every bioprocess. The dynamic of the concentrations of components from reaction scheme (1) can be modelled considering the mass balance of the components. In Section IV, the pseudo Bond Graph models for two prototype bioprocesses will be achieved in 20sim: the first one for a bioprocess taking place into a batch bioreactor and the second one for a CSTB case. Also, a Bond Graph model of a bioprocess carried out in two interconnected bioreactors is derived. These prototype simulators are built by the students in the frame of several experiments described in the next section.

III. Short Description of the Teaching System

The proposed system allows an interactive manner in progress of the experiments. These experiments allow Master students to learn about: biochemical reactions, reaction schemes, bioprocess kinetics, types of bioreactors, bioprocess models, Bond Graph methodology, etc. The exercises allow modifying kinetic parameters, to choose the desired type of bioreactor (batch, fed-batch, continuous), to plot the time evolution of some biological variables (biomass, substrates, products), to compare the obtained results. This system uses friendly graphical user interfaces designed in 20sim.

In order to help the Master students, the experiments comprise a short tutorial, which must be read on the beginning of an experiment and a small quiz, useful for checking the students' knowledge after the experiment.

First, a set of experiments with 20sim software package is designed; the final task is to obtain Bond Graph prototype simulators, which can be combined in order to obtain simulators for complex bioprocesses:

- Experiment no. 1: "Basics of 20sim modelling and simulation environment"
- Experiment no. 2: "Bond Graph elements in 20sim – implementation and connectivity"
- Experiment no. 3: "Prototype batch bioprocess simulator in 20sim"
- Experiment no. 4: "Prototype continuous bioprocess simulator in 20sim"
- Experiment no. 5: "Two-interconnected bioprocesses simulator"

Second, a set of modelling exercises is designed via Bond Graph approach, which comprises procedures for the achievement of mathematical models of the prototype bioprocesses:

- Exercise no. 1: "Mass balances and accumulation of species in Bond Graph terms"
- Exercise no. 2: "Constitutive equations and modelling of reaction rates"
- Exercise no. 3: "Mathematical model of the prototype batch bioprocess acquired via Bond Graph approach"
- Exercise no. 4: "Mathematical model of the prototype continuous bioprocess obtained via Bond Graph"
- Exercise no. 5: "Mathematical model of two interconnected bioprocesses"

IV. Simulation Experiments – Prototype Simulators

20-sim is an advanced modelling and simulation program that runs under Microsoft Windows. Using 20-sim, the behaviour of dynamic systems, such as electric, mechanical, hydraulic and chemical systems or any combination of these systems can be simulated. 20-sim fully supports graphical modelling, allowing the design of dynamic systems in an intuitive and user friendly way [10].

20sim modelling and simulation software package can be used by the Master students for the development of procedures for the simulation of biotechnological processes modelled by Bond Graphs. These simulators are organised in libraries that exploit the modularity of the method, very useful for the students, which will be able finally to understand and to simulate complex biotechnological processes.

Next, the core issues of the experiments 3, 4 and 5 will be shortly presented.

A. Prototype Simulators for Batch and Continuous Bioprocesses

After they read short tutorials, the students start each experiment that consists in the implementation in 20sim of the Bond Graph elements (Sf, C, TF, etc.) by using libraries, tools and interactive menus. The prototype Bond Graph simulators are obtaining starting from the reaction scheme (1) and by taking into consideration the bioprocess type (for example batch or continuous).

In the case of the batch bioreactor (experiment no. 3), there is no influent into or effluent stream from the bioreactor and the biomass X is periodically collected. For the development of the Bond Graph model of this bioprocess, the reaction scheme (1) and the mass transfer through the batch bioreactor are taken into account. The prototype is obtained and placed into a special implementation window of the 20sim environment – see Fig. 1.

The directions of half arrows correspond to the run of the reaction, going out from the substrate S towards biomass X. The mass balances of the components involved in the bioreactor are represented by 0-junctions. Thus, we will have two 0-junctions corresponding to substrate S and biomass X. The accumulations of components S and X in the bioreactor are represented by bonds 1 and 7 and are modelled using capacitive elements C. For the modelling of the yield coefficients TF elements were used [4], [5].

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 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, a modulated two-port R element, denoted $MR_{4,5}$, was used.

For the case of the continuous bioprocess (experiment no. 4), the substrate is fed to the bioreactor continuously and an effluent stream is continuously withdrawn such that the culture volume is constant.

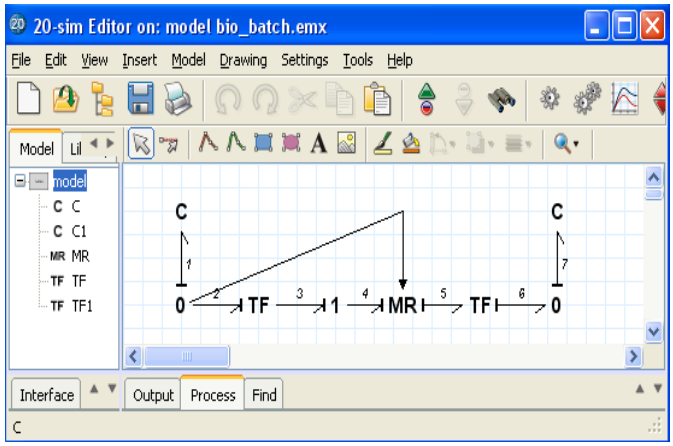

Figure 1. 20sim simulator of the batch prototype bioprocess.

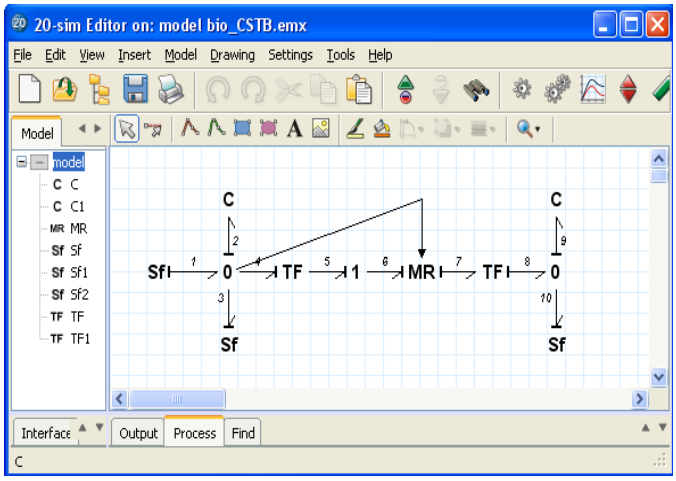

Figure 2. 20sim simulator of the continuous prototype bioprocess.

From the reaction scheme (1) and taking into account the mass transfer through the CSTB, using the Bond Graph modelling procedure, the pseudo Bond Graph model of the continuous bioprocess is achieved and is given in Fig. 2.

For the model presented in Fig. 2, the mass balances of the components involved in the bioreactor are represented by two 0-junctions: $0_{1,2,3,4}$ (mass balance for S), and $0_{8,9,10}$ (mass balance for biomass X). A modulated two-port resistive element $MR_{6,7}$ was used to model the reaction kinetics. Mass flow of the component entering the reaction is modelled using a source flow element Sf_1. The output flows of the reaction components are modelled by using flow sources represented by bonds 3 and 10, i.e. Sf_3, Sf_{10}. The accumulations of substrate and biomass in the CSTB are represented by bonds 2 and 9, and they are modelled using capacitive elements C [4], [5].

After the implementation of Bond Graphs, the students can use all the facilities of the 20sim environment to add or to remove elements, to run simulations, to modify various parameters of the systems, to obtain and to analyse the dynamic evolution of biological variables (also, the dynamical state-space mathematical models of the biotechnological processes can be obtained – accordingly to the procedures described in Section V).

B. A Simulator for Two Interconnected Bioprocesses

In order to exploit the modularity of the Bond Graph approach, embedded in the 20sim package, the students can realize more complex simulators, by using the prototypes. Next, an example of such simulator is shortly described (experiment no. 5).

The activated sludge bioprocess is an aerobic process of biological wastewater treatment [3], [11]. In practice, this bioprocess takes place inside CSTBs or in the so-called Sequencing Batch Reactors. Usually, in wastewater treatment plants, the activated sludge bioprocesses operate in at least two interconnected tanks, like in Fig. 3: an aerator in which the biological degradation of the pollutants takes place and a sedimentation tank (settler) in which the liquid is clarified, that is the biomass is separated from the treated wastewater. Part of the settled biomass is fed back to the bioreactor, while the surplus biomass is removed from the process.

The reaction in the bioreactor may be described by a simple autocatalytic aerobic microbial growth that can be represented by the following reaction scheme:

$$k_1 S + k_2 C \xrightarrow{\varphi \leftarrow} X \qquad (2)$$

where S, X and C are respectively the pollutant, the biomass and the dissolved oxygen, φ is the reaction rate and k_1 and k_2 are the yield coefficients.

In Bond Graph terms, the mass balances of the components involved in the aerator are represented by three 0-junctions: $0_{1,2,3,4}$ (mass balance for S), $0_{6,7,8,9}$ (mass balance for C), and $0_{12,13,14}$ (mass balance for X), and the mass balance of the component involved in the settler is given by one 0-junction: $0_{16,17,18}$.

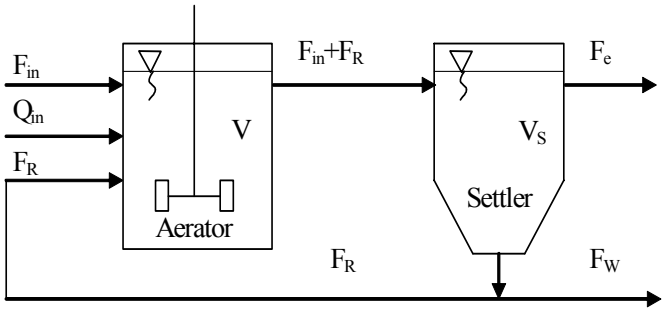

Figure 3. Schema of the activated sludge bioprocess.

The accumulations of species S, C, and X in the bioreactor are represented by bonds 3, 8, 14, and 17 and they are modelled using capacitive elements C.

For the modelling of the reaction rate a two-ports modulated R element, $MR_{11,12}$, was used. Mass flows of the components entering the reaction are modelled using flow source elements Sf_1 and Sf_6. Also, the mass flow of the recycled biomass is modelled using Sf16. The transformer elements $TF_{4,5}$, and $TF_{9,10}$ were introduced to model the yield coefficients.

The output flows of the components exiting from the reaction are modelled using flow sources elements Sf represented by bonds 2, 7, 15, 18. The output flow of component X from Aerator is an input flow for Settler [11].

The simulator presented in Fig. 4 can be implemented by the Master students either by using the whole Bond Graph step by step procedure, or by connecting the corresponding libraries for two continuous prototype bioprocesses (of the type described in Fig. 2) interconnected into a cascade structure as in the schema from Fig. 3.

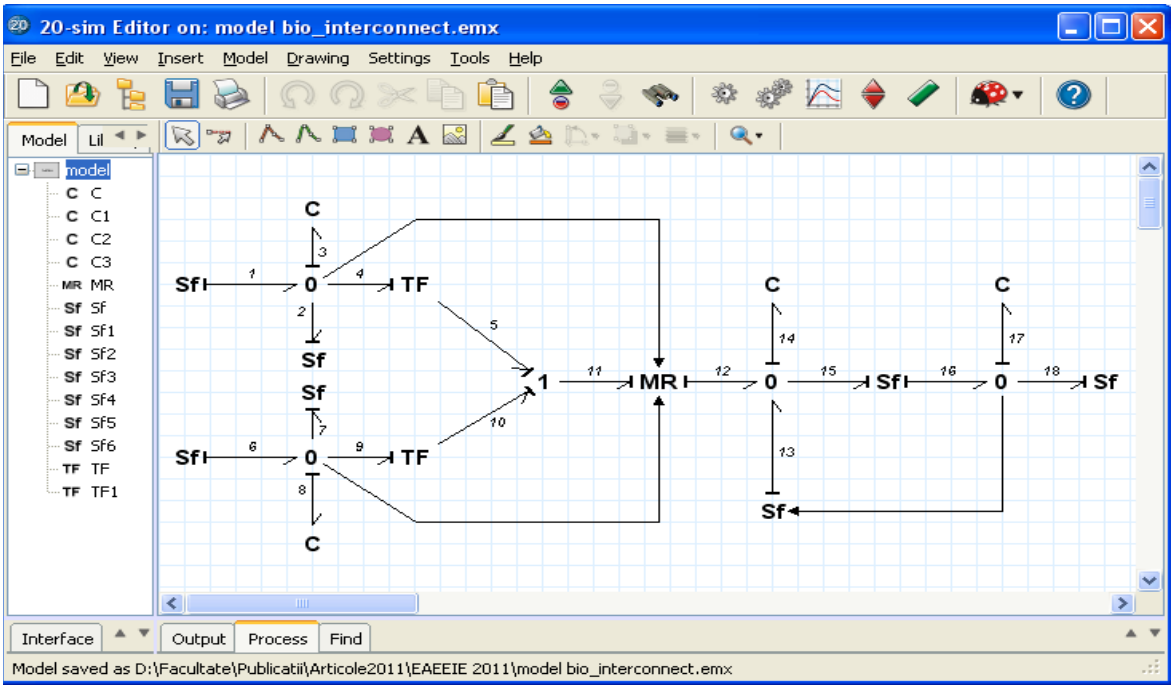

Figure 4. The simulator of the two-interconnceted bioprocesses.

V. PROTOTYPE BIOPROCESSES BOND GRAPH MODELS AND MODELLING EXERCISES

In the second set of exercises, the students can use the simulators obtained in the frame of the first set, in order to develop the dynamical models of bioprocesses. The structure of the exercises is the same as in the case of 20sim experiments: short tutorials, main procedure and questions.

The mathematical models are obtained via Bond Graph approach 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.

All the ingredients required for the design of the mathematical models are studied by the students within the exercises 1 and 2. After that, in the exercises 3, 4 and 5 the Master students learn how to build the mathematical models for the prototype bioprocesses and the activated sludge bioprocess (interconnected bioprocesses), respectively. To illustrate the procedure, in the following the main body of exercises 3 and 4 will be shortly described.

A. The Mathematical Model of Batch Bioprocess

By using the next procedure, the students obtain the mathematical model of the batch bioprocess (in the frame of exercise 3).

(i) The constitutive equations of C-elements are as follows:

$$\begin{aligned} e_1 &= \frac{1}{C_1} q_1 = \frac{1}{C_1} \int_t (-f_2) dt, \\ e_7 &= \frac{1}{C_7} q_7 = \frac{1}{C_7} \int_t (f_6) dt. \end{aligned} \tag{3}$$

(ii) From the constitutive relations of 1-junction ($1_{3,4}$) and MR element, we obtain: $f_3 = f_4$, f_4 being proportional to the reaction rate φ and V.

(iii) Using the constitutive relations of transformer elements and taking into account the signification of Bond Graph elements, the dynamical model of batch bioprocess is obtained:

$$\begin{aligned} V \frac{dS}{dt} &= V \cdot \dot{S}(t) = -\varphi V, \\ V \frac{dX}{dt} &= V \cdot \dot{X}(t) = \varphi V. \end{aligned} \tag{4}$$

(iv) The model (4) expresses the equations of mass balance for the reaction scheme (1). The dynamical behaviour of the concentrations of components can be easily obtained from the system (4):

$$\begin{aligned} \frac{dS}{dt} &= -\varphi, \\ \frac{dX}{dt} &= \varphi. \end{aligned} \tag{5}$$

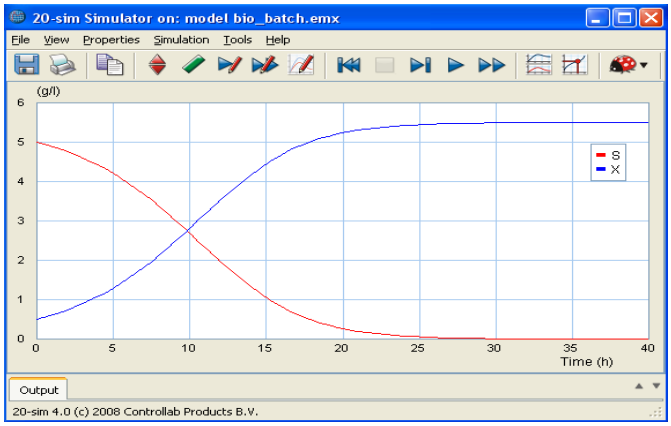

Figure 5. Time profiles of concentrations in the case of the batch prototype bioprocess.

Even if this system seems to be a simple one, the nonlinear kinetics given by the reaction rate φ can be very complex.

The behaviour of the mathematical model (in the form (4) or in the form of concentrations' dynamics (5)) is studied by the students, which can use the 20sim facilities to plot and to analyse the time evolution of main biological variables. As an example, in Fig. 5 the time profiles of biomass and substrate concentrations are presented as they are obtained from 20sim. The students can observe the typical behaviour of this bioprocess: the consumption of substrate associated with biomass production. The students can change the form of the reaction kinetics, the values of some parameters, and also the solver of the differential equation (the type of solver can be crucial for stiff systems).

B. The Mathematical Model of Continuous Bioprocess

In the frame of exercise 4, the students obtain the mathematical model of the continuous bioprocess, by using the same Bond Graph modelling procedure as in the batch case.

(i) The accumulations of substrate and biomass in the CSTB represented by bonds 2 and 9, and modelled using capacitive elements C, give the following constitutive relations:

$$\begin{aligned} e_2 &= \frac{1}{C_2} q_2 = \frac{1}{C_2} \int_t (f_1 - f_3 - f_4) dt, \\ e_9 &= \frac{1}{C_9} q_9 = \frac{1}{C_9} \int_t (f_8 - f_{10}) dt. \end{aligned} \tag{6}$$

(ii) The signification of Bond Graph elements is as follows: e_2 is the substrate concentration S (g/l), e_9 is the biomass concentration X (g/l), f_6 is $\varphi \cdot V$, $C_2 = C_9 = V$ (l) is the volume of the bioreactor, $Sf_3 = Sf_{10} = F_0$, where F_0 is the output flow (l/h), and $f_1 = F_{in} S_{in}$, where F_{in} is the influent substrate flow (l/h) and S_{in} is the influent substrate concentration (g/l).

(iii) Therefore, from (6) and taking into account the constitutive relations of junction elements, the dynamical model of the continuous bioprocess can be obtained:

$$V \cdot \frac{dS}{dt} = F_{in} S_{in} - F_0 S - \varphi V,$$
$$V \cdot \frac{dX}{dt} = -F_0 X + \varphi V. \quad (7)$$

(iv) The model (7) expresses the equations of mass balance for the reaction scheme (1). The dynamical behaviour of the concentrations can be easily obtained from (7). From the equation of continuity $F_{in} = F_0$ and using the so-called dilution rate $D = F_{in} / V = 1/t_r$, with t_r - medium residence time, the equations (7) become:

$$\frac{dS}{dt} = DS_{in} - DS - \varphi,$$
$$\frac{dX}{dt} = -DX + \varphi. \quad (8)$$

The behaviour of the mathematical model (in the form (7) or in the form of concentrations' dynamics (8)) is studied by the students. By using the 20sim capabilities, the time evolution of main biological variables can be analysed. As an example, in Fig. 6 the time profiles of biomass and substrate concentration are presented as they are obtained from 20sim. The students can change the form of the reaction kinetics, the values of some biological and simulation parameters, etc.

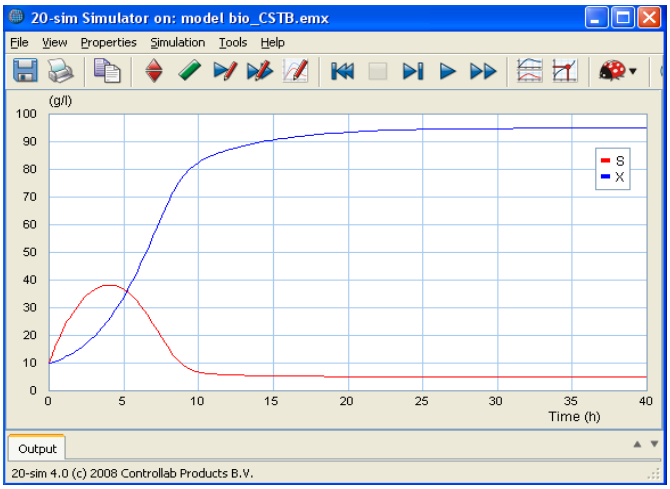

Figure 6. Evolution of concentrations - the continuous prototype bioprocess.

VI. Conclusion

The advances in information technology provide new means for the improvement of learning technologies. The presented teaching system allows an improvement in bioengineering education and training. The experiments touch on the important problems for biotechnological processes. The system has didactic properties such as modularity of the package, friendly graphical user interfaces and so on.

As the use of real bioreactors is expensive and even dangerous, the exploitation of software simulators constitutes a good alternative. The interactive system helps Master students to understand different biotechnological process modelling and simulation issues. The package can be extended with new experiments.

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