An Interactive Teaching System for Bond Graph Modeling and Simulation in Bioengineering

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ABSTRACT

The objective of the present work was to implement a teaching system useful in modeling and simulation of biotechnological processes. The interactive system is based on applications developed using 20-sim modeling and simulation software environment. A procedure for the simulation of bioprocesses modeled by bond graphs is proposed and simulators containing biochemical bond graph elements are designed. These simulators are organized in libraries that exploit the modularity of the method, very useful for master students, who will be able to model and simulate complex bioprocesses. In order to evaluate the learning performance of this teaching system, an analysis was performed using a pre-test/post-test scenario, with a multiple-choice knowledge test.

Keywords

Bioengineering education, Improving classroom teaching, Interactive learning environments, Simulations, Teaching/ learning strategies

Introduction

At the university level, the teaching of bioengineering involves a variety of topics ranging from biology, biochemistry, medicine, automation, and informatics. Therefore, training in this domain is a difficult problem (Akpan, 2001; Djordjevic, Gerla, Huptych, Lhotska, & Krajca, 2010; Gonzalez-Cruz, Rodriguez-Sotres, & Rodriguez-Penagos, 2003). Within the design process of a bioengineering course, significant problems are the modeling of bioprocesses and the simulation of these complex systems (Dochain, 2008; Petre, 2006; Roman, Şendrescu, Bobaşu, Petre, & Popescu, 2011; Roman & Selişteanu, 2012; Selişteanu, Roman, & Şendrescu, 2010). Another important problem is the choice of 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.

As was demonstrated by the large number of studies, the interactive computer simulations, designed to teach complex processes, have become very popular in all domains of science education, such as physics, chemistry, and biology (Holzinger, Kickmeier-Rust, Wassertheurer, & Hessinger, 2009). Nowadays, technological developments such as computer simulations can implement more effective the so-called inquiry learning (de Jong, 2006). By using simulations to model a phenomenon, students can perform experiments by changing some variables and then observe the effects of their changes; thus, they discover the properties of the original model (de Jong, 2006). Simulations as learning tools are engaging and can be valuable for bioengineering. On the whole, a major advantage of learning with interactive simulations can be seen in the highly constructivist nature of such learning processes (Gülbahar, Madran, & Kalelioglu, 2010; Holzinger et al., 2009).

Several works, such as (de Jong, 2006; Keselman, 2003; Lawson, 2002; Manlove, Lazonder, & de Jong, 2006), reported that the students have significant problems with different inquiry learning processes: they have difficulty choosing the right variables to work with; they do not necessarily draw the right conclusions from experiments; they may have difficulty linking experimental data and hypotheses; they fail to make predictions; they make mistakes when interpreting data; and more. Therefore, research currently focuses on finding cognitive tools that help to surmount these problems and produce efficient learning situations. More precisely, computer environments can integrate these cognitive tools with the simulation (de Jong, 2006).

However, essential practical details can be lost if engineering teaching is reduced only to lectures and digital simulations, bypassing physical/biochemical experiments because of their relatively high costs (Precup, Preitl, Rădac, Petriu, Dragoş, & Tar, 2011). For that reason, most of universities try to purchase or to develop real

bioreactors (laboratory or pilot reactors); in this way the laboratories can be achieved by using real bioprocesses. Of course, it is essential to apply the theory on real bioprocesses, but in most cases this method is expensive, and in some situations there are biological risks; therefore, in many cases simulators are used (Gonzalez-Cruz et al., 2003). Linked to this approach, in the last period a lot of interactive, computer and web-based teaching systems were reported, but especially related to physics/chemistry/biology education (Bunce, VandenPlas, & Havanki, 2006; Chang, Chen, Lin, & Sung, 2008; Gibbons, Evans, Payne, Shah, & Griffin, 2004; Limniou, Papadopoulos, & Whitehead, 2009, Milrad, 2002). Consequently, the use of software simulators is common and it constitutes an alternative to real bioreactors.

Concerning the choice of a particular teaching tool for biotechnology education at undergraduate and/or master level, it is obvious that this education requires intensive training in laboratory procedures. One of the key elements is the need to allow the student to familiarize laboratory techniques in balance with regular theory (Diwakar, Achuthan, Nedungadi, & Nair, 2011). The only way to achieve this goal with low costs is to use interactive, computer, and web-based teaching systems, including virtual labs. This tendency was reported in several works of the last decade, such as (Akpan; 2001; Gibbons et al., 2004; Gonzalez-Cruz et al., 2003; Palladino, 2002; Palladino & Cosentino, 2001; Smith & Emmeluth, 2002), and in numerous recent papers (Cid & Rajal; 2011; Diwakar et al., 2011; Roman et al., 2011).

The reasons to focus on interactive computer-based teaching systems for bioengineering are many (Diwakar et al., 2011). First, as already we outlined, the experimental setup cost is a big problem. Another motivation is the need to introduce computer-based teaching systems and virtual labs, which use mathematical modeling and computational methods. From the learning perspective, such systems allow students to manipulate advanced but common-to-use simulation tools. For biotechnology, a strong motivation for the shift to computer-based-and-virtual-lab paradigm, is the explosion of data-rich information sets, which are difficult to understand without the use of analytical tools. Another reason is the increasing interest in *in silico* experimentation due to ethical considerations, risk, and complications involved in human and animal research (Diwakar et al., 2011).

Combining theory will software simulators achieves good training results. In this paper, which is an extended work of (Roman et al., 2011), we present an interactive teaching system developed by using the 20-sim modeling and simulation software environment (registered trademark of Controllab Products B.V., Netherlands). This system uses friendly graphical user interfaces and comprises sets of different experiments. First, a set of experiments with 20-sim software package is designed; the final task is to achieve bond graph prototype simulators, which can be combined to obtain simulators for complex bioprocesses. Second, a set of modeling exercises is designed to achieve the mathematical models of these prototype bioprocesses. Every experiment consists in a short tutorial, the body of experiment and several questions and tasks for master students.

These sets of modeling and simulation experiments are grouped into a teaching system, which is implemented at the University of Craiova's Department of Automation, Electronics, and Mechatronics, within the Automation of Complex Systems master program (the Bioengineering course). At the University of Craiova, the curricula and structure of this master program are organized in the electrical-engineering domain, and it follows the Bologna process (see, for example, Martins, Thiriet, Bonnaud, Hoffmann, Robert, Benlloch et al., 2008).

The proposed teaching system can be seen as a pre-laboratory setup, in which we performed both an analysis of learning performance of this teaching system, which showed promising results, and assessed the learning technique.

The paper is organized as follows. First, we provide a short introduction in the field of bioprocesses modeling via the bond graph approach. Then, we present an overview of the teaching system. As well, we examine the implementation of some prototype bioprocess simulators in a 20-sim environment and present a simulator for two interconnected bioprocesses. Subsequently, this section deals with a set of modeling exercises, which help the students to construct the mathematical model of prototype bioprocesses, obtained from bond graph simulators. The next section deals with an analysis of the learning performance of proposed teaching system. The analysis is performed by using a group of master students from the bioengineering course. The subsequent section presents several results obtained by using the analysis of variance. Finally, we present some remarks.

Technical background: Bioprocess modeling issues and bond graph approach

In industry, the bioprocesses take place inside biological reactors (bioreactors) in which several biological reactions occur simultaneously in a liquid medium (Dochain, 2008; Petre, 2006). The bioreactors can operate in three modes: continuous, fed-batch, and batch mode. A fed-batch bioreactor (FBB) initially contains a small amount of substrates and micro-organisms and is progressively filled with the influent substrates. When the FBB 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. 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 bioprocesses are characterized by several difficult issues such as strongly nonlinearity of kinetics, unavailability of cheap, online instrumentation, etc. Therefore, there are problems concerning the development of a unified modeling approach. However, even if the bioprocess modeling is a difficult task, by using the mass balance of components and obeying some modeling rules, we can obtain a dynamical state-space model (described using nonlinear differential equations) by using either classical modeling methods (Dochain, 2008) or the bond graph methodology (Roman & Selişteanu, 2012; Selișteanu et al., 2010). The bond graph method is a relative new approach for bioprocess modeling, but the results are quite encouraging, from both modeling and simulation points of view. Therefore, it is appropriate to implement teaching systems (especially for master and PhD studies) based on this approach.

The 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 varies and, therefore, the power fluctuates in time (Karnopp & Rosenberg, 1974; Thoma, 1975). A specific approach adapted to physical system particularities, the pseudo bond graph, is more suitable for the modeling of chemical and biochemical reactions due to the meaning of effort and flow variables involved whose products do not have the physical dimension of power (Dauphin-Tanguy, 2000; Thoma & Ould Bouamama, 2000). 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 (energy variables) are the generalized momentum *p* and generalized displacement *q* (Karnopp & Rosenberg, 1974).

An advantage of bond graph method over other techniques is that models of various systems belonging to different 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 bond graph concept. Causality is represented on a model by causal stroke placed perpendicular to the bond at one of its ends, indicating the direction of 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 (integral causality or derivative causality) but it is always desirable that C and I elements be in integral causality. Transformers, gyrators, and junction elements have constrainedly causality.

One of the simplest biological reactions is the micro-organism growth process (Dochain, 2008; Petre, 2006) with the next reaction scheme:

$$S \xrightarrow{\varphi} X \qquad (1)$$

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

This growth reaction represents in fact a prototype reaction, which can be found in almost every bioprocess. The dynamic of the concentrations of components from scheme (1) can be modeled considering the mass balance of

components. In the next section, we will achieve in 20-sim the bond graph models for two prototype bioprocesses: the first one for a bioprocess taking place into a batch bioreactor and the second one for a CSTB case. We will also develop a bond graph model of a bioprocess carried out in two interconnected bioreactors. These prototype simulators are built by the students in the frame of several experiments described in the following section.

Description of the teaching system

The proposed teaching system implements an interactive manner in experiments' progress. These experiments allow master students to learn about biochemical reactions, reaction schemes, kinetics, types of bioreactors, bioprocess models, bond graph methodology, etc. The exercises allow the students to modify the kinetic parameters, choose the desired type of bioreactor, plot time evolution of some biological variables (biomass, substrates, products), and compare the obtained results.

In order to help the students, the experiments comprise a short tutorial (in electronic form), 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 20-sim 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 20-sim modeling and simulation environment
- Experiment no. 2: Bond graph elements in 20-sim—implementation and connectivity
- Experiment no. 3: Prototype batch bioprocess simulator in 20-sim
- Experiment no. 4: Prototype continuous bioprocess simulator in 20-sim
- Experiment no. 5: Two interconnected bioprocesses simulator

Second, a set of modeling exercises is designed via bond graph, which comprises procedures for the achievement of mathematical models:

- Exercise no. 1: Mass balances and accumulation of species in bond graph terms
- Exercise no. 2: Constitutive equations and modeling 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

Simulation experiments: Prototype simulators

Twenty-sim is an advanced modeling and simulation program (Controllab Products B.V., Netherlands) that runs under Microsoft Windows. Using 20-sim, the behavior of systems, such as electric, mechanical, hydraulic, and chemical systems or any combination of these systems can be simulated. Twenty-sim fully supports graphical modeling, allowing the design of dynamic systems in an intuitive and user-friendly way. The 20-sim software package can be used by the students for the simulation of bioprocesses modeled by bond graphs. These simulators are organized in libraries that exploit the modularity of the method, which is very useful for the students, who will be able finally to understand and to simulate complex bioprocesses. Next, the core issues of experiments 3, 4 and 5 will be shortly presented.

Prototype simulators for batch and continuous bioprocesses

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

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

to the run of 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 accumulation of components *S* and *X* in the bioreactor is represented by bonds 1 and 7 and are modeled using capacitive elements C. For the modeling of yield coefficients, TF elements were used (Roman & Selişteanu, 2012). A difficult task is the modeling of 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 continuous bioprocess (experiment no. 4), the substrate is fed to CSTB continuously, and an effluent stream is continuously withdrawn such that the culture volume is constant. From the reaction scheme (1) and taking into account the mass transfer, using the bond graph modeling procedure, the pseudo bond graph model is achieved and is given in Figure 2. The mass balances of components 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*).

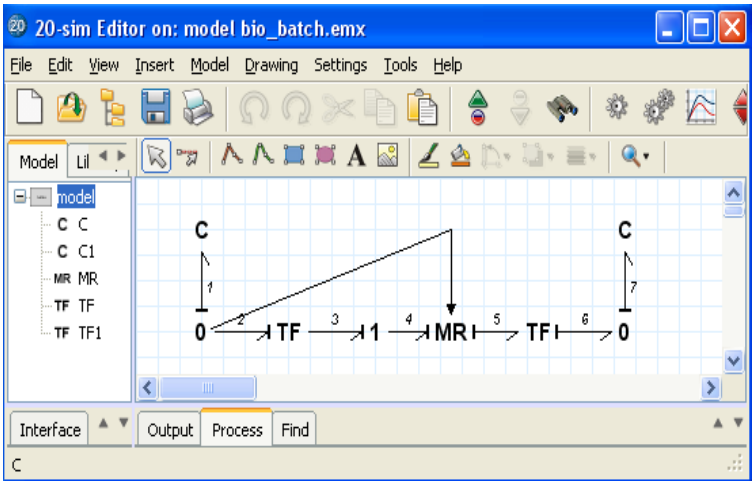

Figure 1. The 20-sim simulator of the batch prototype biotechnological process

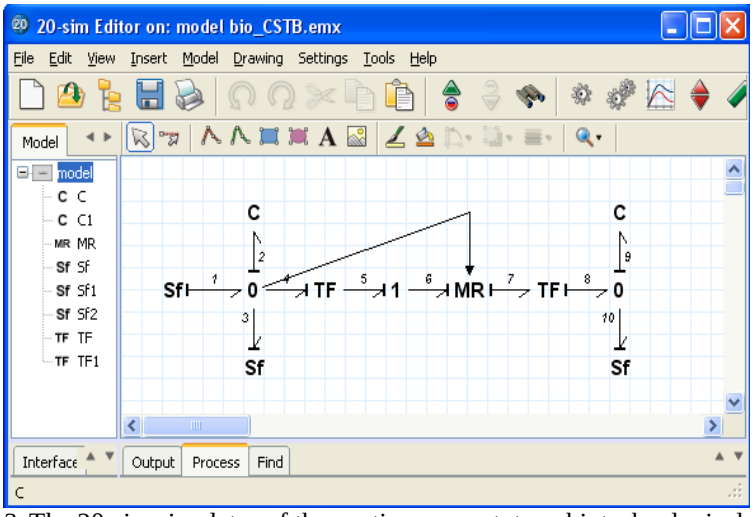

Figure 2. The 20-sim simulator of the continuous prototype biotechnological process

A modulated two-port resistive element $MR_{6,7}$ was used to model the kinetics. Mass flow of the component entering the reaction is modeled using a source flow element Sf_1. The output flows of the reaction components are modeled by using flow sources represented by bonds 3 and 10: Sf_3, Sf_{10}. The accumulation of substrate and biomass in CSTB is represented by bonds 2 and 9, and they are modeled using capacitive elements C (Roman & Selişteanu, 2012).

After the implementation of bond graphs, the students can use all the facilities of 20-sim environment to add or to remove elements, to run simulations, to modify various parameters, to obtain and to analyze the evolution of biological variables (also, the dynamical state-space models can be obtained according to the procedures described in next subsections).

A simulator for two interconnected bioprocesses

In order to exploit the modularity of bond graph approach, embedded in the 20-sim 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 (Dochain, 2008; Roman & Selişteanu, 2012). In practice, this bioprocess takes place inside CSTBs or in the so-called sequencing batch reactors. Usually, the activated sludge bioprocesses operate in at least two interconnected tanks, as in Figure 3: an aerator in which degradation of 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 bioreactor, while the surplus biomass is removed. The reaction may be described by a simple autocatalytic aerobic microbial growth that can be represented by the reaction scheme:

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

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

In bond graph terms, the mass balances of 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 component involved in the settler is given by one 0-junction: $0_{16,17,18}$. The accumulations of species *S*, *C*, and *X* in bioreactor are represented by bonds 3, 8, 14, and 17, they are modeled using capacitive elements *C*. For the modeling of the reaction rate a two-port modulated R element, $MR_{11,12}$, was used. Mass flows of the components entering the reaction are modeled using flow source elements Sf_1 and Sf_6. Also, the mass flow of recycled biomass is modeled using Sf_{16}. 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 modeled 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 (Roman & Selişteanu, 2012).

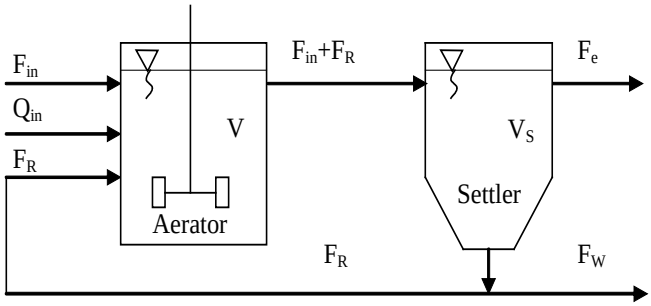

Figure 3. Schema of the activated sludge wastewater treatment bioprocess

The simulator presented in Figure 4 can be implemented by the students either by using the whole bond graph step-by-step procedure or by connecting the corresponding libraries for two continuous prototype processes (as in Fig. 2) interconnected into a cascade structure as in the schema from Figure 3.

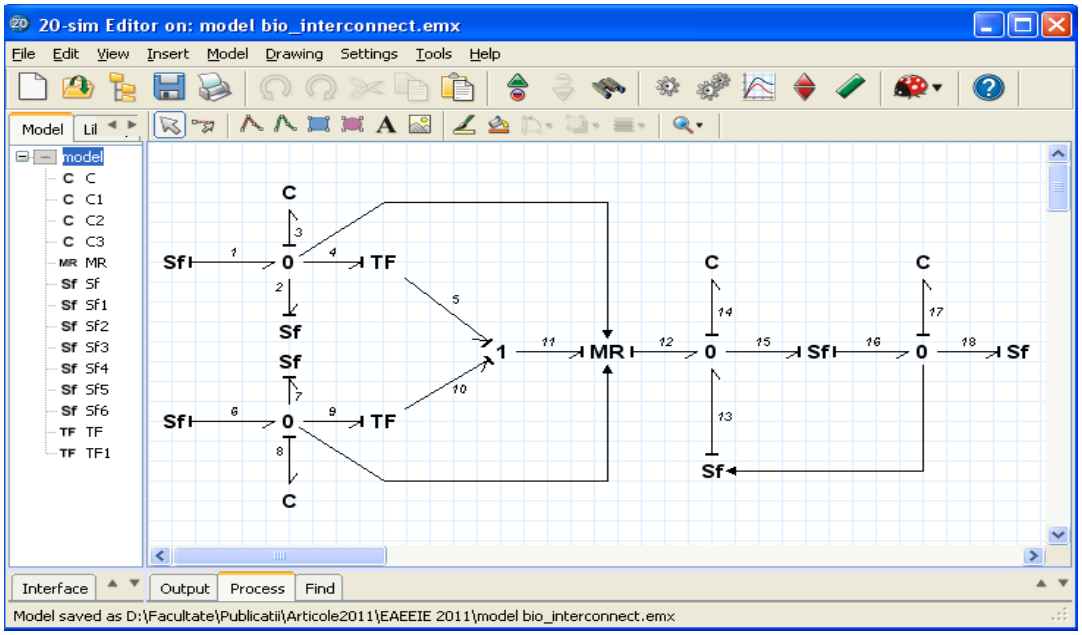

Figure 4. 20-sim simulator of two interconnected bioprocesses

Bond graph models of prototype bioprocesses and modeling exercises

In the second set of exercises, students can use the simulators obtained in the first set to develop dynamical models of bioprocesses. The exercises structure is the same as in the case of 20-sim experiments: short tutorials, main, and questions. The mathematical models are obtained via bond graph by writing the characteristic equations for both elements and junction structure and taking into account the constructive and process characteristics in mathematical terms. All the ingredients required for the design of mathematical models are studied by the students within exercises 1 and 2. After that, in the exercises 3, 4, and 5 the 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.

The mathematical model of batch bioprocess

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

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

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

(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 is obtained:

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

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

$$\frac{dS}{dt} = -\varphi, \quad \frac{dX}{dt} = \varphi. \tag{5}$$

Even if this system seems to be a simple one, the kinetics given by reaction rate φ can be very complex. The behavior of mathematical model (in the form (4) or in the form of concentrations' dynamics (5)) is studied by the students, who can use the 20-sim facilities to plot and to analyze the time evolution of main biological variables. As an example, in Figure 5, the profiles of biomass and substrate concentrations are presented as they are obtained from 20-sim. The students can observe the typical behavior of this process: the consumption of substrate associated with biomass production. They can change the form of kinetics, the values of some parameters, and the solver of differential equations (the type of solver can be crucial for stiff systems. See, for example, Figure 6).

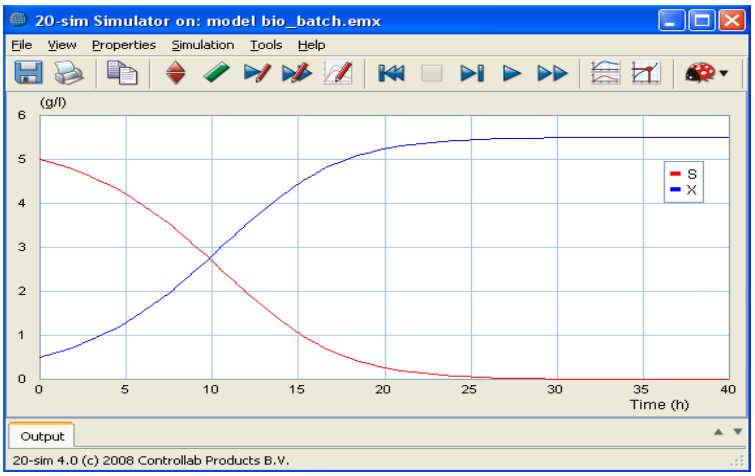

Figure 5. Evolution of concentrations in the case of the batch prototype bioprocess

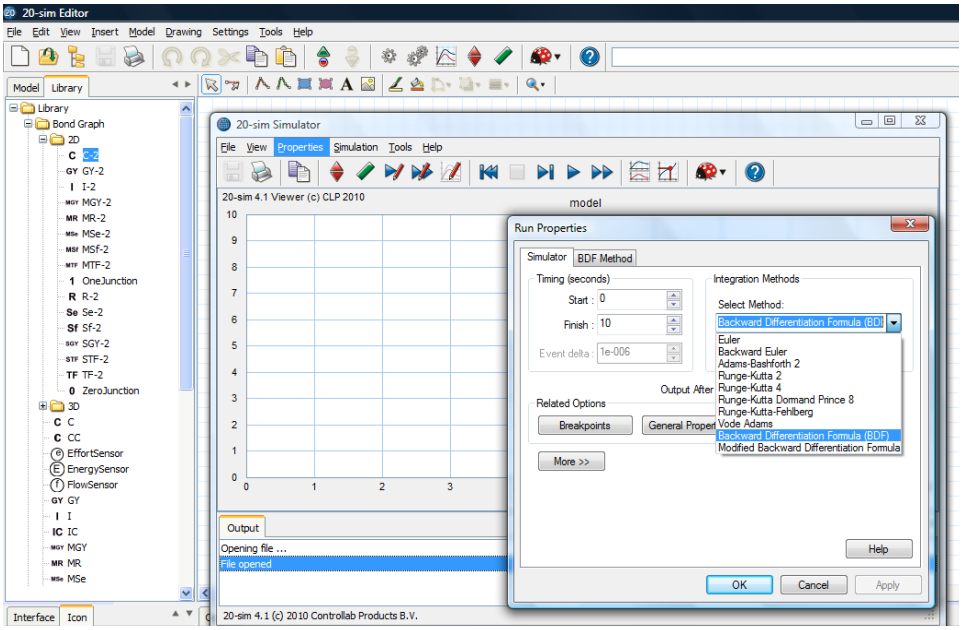

Figure 6. Setting the solver in 20-sim

The mathematical model of continuous bioprocess

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

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

$$e_2 = \frac{1}{C_2} q_2 = \frac{1}{C_2} \int_t (f_1 - f_3 - f_4) dt, \; e_9 = \frac{1}{C_9} q_9 = \frac{1}{C_9} \int_t (f_8 - f_{10}) dt. \quad (6)$$

(ii) The significance of bond graph elements is as follows: e_2 is the substrate concentration S (g/l), e_9 the biomass concentration X (g/l), f_6 is $\varphi \cdot V$, $C_2 = C_9 = V$ (l) is the reactor volume, $Sf_3 = Sf_{10} = F_0$, with F_0 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} the influent substrate concentration (g/l).

(iii) Therefore, from (6) and taking into account the constitutive relations of junction elements, the dynamical model 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 (1). The dynamical behavior of concentrations can be easily obtained from (7). From the equation of continuity $F_{in} = F_0$ and using the so-called dilution rate $D = F_{in} / V = 1 / t_r$, where t_r is the medium residence time, equations (7) become:

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

The behavior of mathematical model (in th e form [7] or in the form of concentrations' dynamics [8]) is studied by the students. By using the 20-sim capabilities, the evolution of main biological variables can be analyzed. As an example, in Figure 7 the profiles of biomass and substrate concentrations are presented as they are obtained from 20-sim. The students can change the form of kinetics, the values of some biological and simulation parameters, etc.

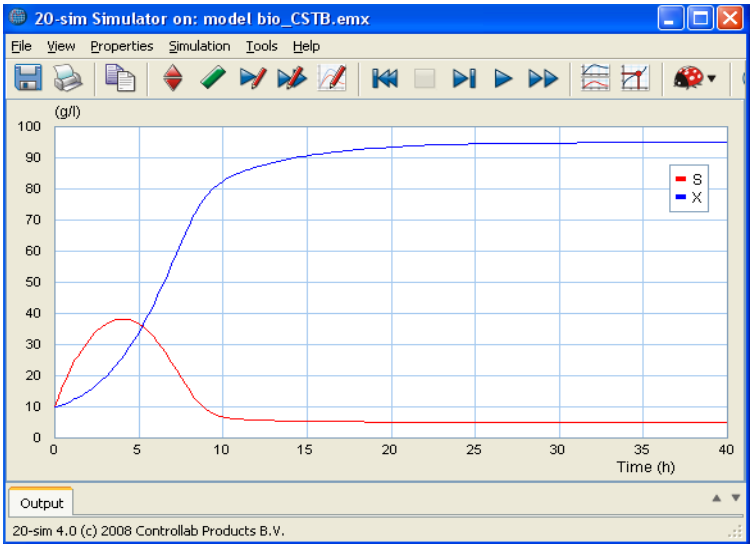

Figure 7. Time profiles of concentrations: The continuous prototype bioprocess

Analysis of learning performance

Participants and experimental condition

To evaluate the impact of the teaching system, we compared the learning performance by using two learning conditions: (i) a traditional theoretical set of lessons, which includes classical text descriptions, static images,

mathematical issues, etc., and (ii) the proposed computer-based interactive teaching system that covers the same learning content. The so-called null hypothesis would be that the different learning conditions do not imply different learning performance (Holzinger et al., 2009). The comparison was achieved with a procedure based on pre-tests and post-tests. The learning performance was measured using a multiple-choice test. To accomplish this study, 44 master students from Automation of Complex Systems master program (second year of study, 2010–2011, bioengineering) at the University of Craiova were used. Thirty-one men and thirteen women participated.

To assess knowledge and learning performance, a pre-test/post-test scenario was used, with a multiple-choice knowledge test, including twenty questions about the modeling of bioprocesses. Each of these questions represented a significant aspect of the discipline and demanded a systematic understanding to ensure choosing the correct answer. Every question included five possible answers; checking none, one, or more alternatives could be correct. The minimum score was 0 and the maximum score was 20. The pre-test and post-test used the same questions, but presented in different order. Because the complexity of the full teaching system, the tests focused only on a pair of experiment/modeling exercise. For example, one of these pairs contains Experiment 3: "Prototype batch bioprocess simulator in 20-sim" and Exercise 3: "Mathematical model of the prototype batch bioprocess acquired via bond graph." These tests can be seen as a kind of pre-laboratory training, useful for the students in order to deal more easily with the real equipment, such as laboratory or pilot bioreactors (in our case, the bioengineering laboratory is equipped with a BIOSTAT Sartorius bioreactor [Nisipeanu, Bunciu, & Stănică, 2011]).

Procedure

The students were requested to provide biographical data and to complete the pre-tests to assess the prior knowledge in bioprocess modeling field. Then, the students were randomly divided into two groups, one denoted T (for the first learning condition, traditional) and one by C (the second learning condition, computer-based). Each group consists of 22 students (group T: 17 men and 5 women, and group C: 14 men and 8 women). Group T was provided with hard copies of the lessons set, and the participants from group C used the PCs from the classroom, with full access to the interactive teaching system. Both groups were given the same amount of time to learn. After a short pause, the students were asked to complete the post-tests. The entire procedure took about 110 min, which is a standard time period.

The use of computer-based simulators as pre-laboratory training is in accordance with cognitive load theory and constructivism (Kirschner, 2001; Kirschner, 2002; Limniou et al, 2009; Shiland, 1999). The entire procedure implies that the master students: (a) do not receive a massive amount of information at the same time, (b) have enough time to handle the useful information, (c) construct their new information based on the previous knowledge, (d) confirm or reject their initial hypothesis, and (e) think on bond graph method related to biochemical phenomena.

Additionally, we distributed some questionnaires to the entire group of 44 students, providing a number of statements about traditional/computer-based teaching approach, their interest in bioengineering, understanding of theoretical and practical problems previously studied (pre-requirements), their interest in real/simulated experiments before and after bioengineering course and so on.

Results and discussion

First, the results concerning the pre-tests are presented in Table 1. The mean scores and standard deviations were calculated by using simple routines provided in Matlab (The MathWorks, Inc., USA). As was expected, no significant differences were found between the two groups (T and C). In group T, the mean score in pre-test was M = 11.63, and the standard deviation SD = 1.43. In group C, the results were: M = 11.95, SD = 1.64. As reported in various references, the gender issues related to learning conditions and learning performance are interesting (Caspi, Chajut, & Saporta, 2008; Franzoni & Assar, 2009). The results obtained in the frame of our pre-test show that the women from both T and C groups scored better than the men from the two groups. See Table 1.

However, the results obtained at the post-test were quite different with respect to pre-test (Table 2). For the group T, the mean score was M = 15.13, SD = 1.28, while for the group C we have M = 16.77, SD = 1.50. As expected, the results obtained by both groups are higher than in pre-tests. It is interesting that the results obtained by the men from

group C are much better than the results obtained by the men from group T, which can mean that male students are more comfortable with computer-based training than they are with the traditional theoretical approach. As a conclusion, we can see that in the post-test, the group C resulted in a higher mean score than group T. Also, an interesting interaction of learning condition and gender was found for the post-tests.

Table 1. Results obtained in pre-test related to learning conditions and gender

Test type	Group	Mean score M	Standard deviation SD
Pre-test	T	11.6364	1.4325
	C	11.9545	1.6469
	T – women	12.8000	1.9235
	T – men	11.2941	1.1048
	C – women	12.1250	1.2464
	C – men	11.8571	1.8752

Table 2. Results obtained in post-test related to learning conditions and gender

Test type	Group	Mean score M	Standard deviation SD
Post-test	T	15.1364	1.2834
	C	16.7727	1.5097
	T – women	16.2000	1.4832
	T – men	14.8235	1.0744
	C – women	16.7500	1.3887
	C – men	16.7857	1.6257

In order to achieve a more appropriate statistical analysis, we apply the univariate analysis of variance (ANOVA), by using Statistics Toolbox, provided by Matlab. First, we computed the learning performance (i.e., the score in post-test compared with the score in pre-test), for both groups T and C. The results are presented in Figures 8 and 9, where the standard one-way ANOVA tables are given. The columns represent: SS (the sums of squares), df (degrees of freedom), MS (mean squares: SS/df), F statistic, and prob>F (the p value). ANOVA revealed a significant effect for both groups, ($F = 72.85$, $p \approx 0$, and $F = 102.32$, $p \approx 0$), as expected.

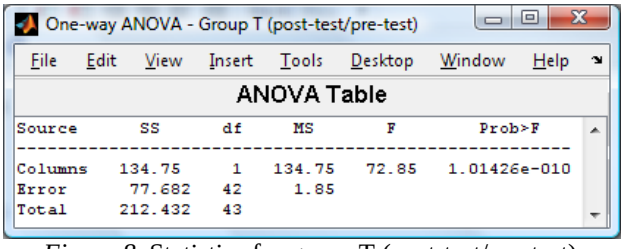

Figure 8. Statistics for group T (post-test/pre-test)

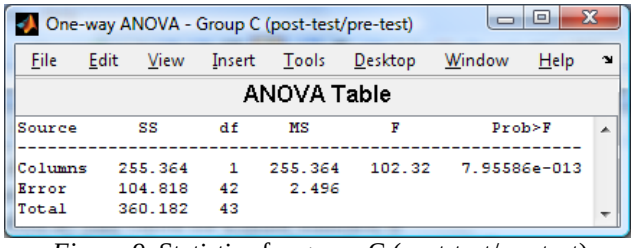

Figure 9. Statistics for group C (post-test/pre-test)

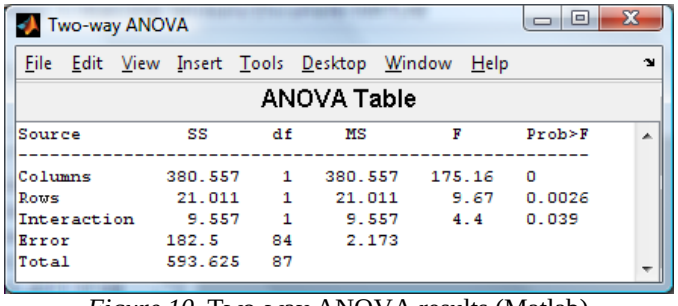

Figure 10. Two-way ANOVA results (Matlab)

Tests of Within-Subjects Contrasts—SPSS

Measure: MEASURE_1

Source	Learning	TestType	Type III Sum of Squares	df	Mean Square	F	Sig.
Learning	Linear		21,011	1	21,011	5,238	,033
Error (Learning)	Linear		84,239	21	4,011		
TestType		Linear	380,557	1	380,557	1403,731	,000
Error (TestType)		Linear	5,693	21	,271		
Learning * TestType	Linear	Linear	9,557	1	9,557	74,519	,000
Error (Learning*TestType)	Linear	Linear	2,693	21	,128		

Figure 11. Two-way ANOVA results: Tests of within-subjects contrasts (SPSS)

	Test Value					
	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
T - pre	38,102	21	,000	11,63636	11,0012	12,2715
T - post	55,317	21	,000	15,13636	14,5673	15,7054
C - pre	34,048	21	,000	11,95455	11,2244	12,6847
C - post	52,110	21	,000	16,77273	16,1034	17,4421

Figure 12. Confidence intervals: results obtained with SPSS

However, the repeated single factor analysis of variance is not quite suitable for this experiment because this kind of analysis can miss possible interaction effects. Because here we have a repeated measurements design, repeated measurements are taken of the same individuals, and it is necessary to establish a within-subject effect. More precisely, averaging over all individuals as if they were independent may give misleading results. Therefore, a two-way ANOVA was performed by using the Matlab environment. The results are plotted in Figure 10. The purpose of two-way ANOVA is to find out whether data from several groups have a common mean.

One-way ANOVA and two-way ANOVA differ in that the groups in two-way ANOVA have two categories of defining characteristics instead of one. In Figure 10, the columns in the source represent the effects related to the pre-test and post-test, and the rows represents the effects related to the learning condition (T and C groups). As can be observed, the p-value for the pre-test/post-test effect is zero (to four decimal places). This is a strong indication that the scores obtained by the students differ from the pre-test to the post-test. The p-value for the learning condition effect is 0.0026, which is also highly significant. This indicates that the C group is out-performing the T group in the obtained scores. There does not appear to be strong interaction between learning condition and test type.

In order to compare these results with another statistical computing environment, we also used the SPSS package (general linear model—repeated measurements). The tests of within-subjects contrasts are given in Figure 11. As you can see the results are similar. The confidence intervals computed with SPSS are presented in Figure 12.

The ANOVA can be performed if the homoscedasticity and normality of the data is checked. The data normality was tested by using an adaptation of the Kolmogorov-Smirnov test—more precisely, the Lilliefors test—provided by the Matlab. Also, the homogeneity of variance was checked by using the Breusch-Pagan test.

It is interesting to check whether the effect of learning method treatment depends on gender. This approach calls for a two-way factorial with repeated measures in a mixed model. However, this kind of analysis is more complex for our particular experiment, because the data concerning the gender are unbalanced for the considered groups. Therefore, the analysis for gender issues is based only on the descriptive statistics presented in Tables 1 and 2.

Concerning the assessment of learning technique, the results obtained from the questionnaires completed by the students are presented in Table 3. The highest interest is in real bioreactor experiments, but the difference between

real experiments and simulators is quite small. Once the new methods of bioengineering training were used, the students' results were better, both during the semester and at the exam.

Table 3. Assessment of learning technique and interest in bioengineering

	Before bioengineering course and experiments			After bioengineering course and experiments		
	High	Medium	Low	High	Medium	Low
Interest in bioengineering	39%	54%	7%	74%	22%	4%
Understanding of theoretical problems previously studied	35%	44%	21%	73%	20%	7%
Understanding of practical problems previously studied	29%	40%	31%	70%	24%	6%
Interest in traditional theoretical methods	28%	53%	19%	32%	54%	14%
Interest in 20-sim simulators	40%	43%	17%	74%	21%	5%
Interest in real bioprocess experiments	71%	23%	6%	84%	14%	2%

Conclusions

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

This study confirmed the results of previous research on exploratory learning using interactive simulations. Still, it is necessary to offer additional assistance on the correct use of a simulation before beginning to learn with the computer-based teaching system. In future research, the evaluation of proposed teaching tool can be further improved. The implementation of the proposed bioengineering teaching system resulted in significantly higher learning performance than traditional learning conditions. The results pointed out that, with some exceptions, these effects are independent of individual learning strategies but not necessarily of gender.

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 bioprocess modeling and simulation issues. The package can be extended with new experiments, and can be seen as a pre-laboratory training system.

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