AC 2008-2160: TEACHING EXPERIMENTAL DESIGN USING VIRTUAL LABORATORIES: DEVELOPMENT, IMPLEMENTATION AND ASSESSMENT OF THE VIRTUAL BIOREACTOR LABORATORY

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Teaching Experimental Design using Virtual Laboratories: Development, Implementation and Assessment of the Virtual Bioreactor Laboratory

Abstract

Presently there is a need to develop more effective ways to integrate experimental design into the engineering curriculum. To address this need, we are developing virtual laboratories that provide students a capstone experience in which they can apply experimental design in a context similar to that of a practicing engineer in industry. In a virtual laboratory, simulations based on mathematical models implemented on a computer are used to replace the physical laboratory. However, as opposed to being constructed as a direct one-to-one replacement, the virtual laboratory is intended to complement the physical laboratories in the curriculum so that certain specific elements of the experimental design process are addressed. We have previously reported on the Virtual CVD Laboratory, a simulation of an industrial-scale chemical vapor deposition (CVD) reactor. Analogously to the Virtual CVD laboratory, a Virtual Bioreactor laboratory has been developed based on an industrial scale bioreactor process. The development, implementation and assessment of the Virtual Bioreactor in the senior laboratory in Chemical, Biological and Environmental Engineering are discussed. Analysis of student surveys was undertaken to exam student metacognition of the virtual laboratory and compare their ideas of learning to the physical laboratories in the same course. Analysis shows that the experimental design, critical thinking and higher order cognition that are promoted in the Virtual CVD laboratory are manifest in the metacognitive statements of students in the Virtual BioR Laboratory. Both virtual laboratories are available for use upon request.

Introduction

In a typical laboratory class, students are tasked with taking a set of experimental measurements, analyzing the data, often in the context of underlying theory in the curriculum, and reporting the findings. This work is performed using dedicated equipment physically located in the laboratory. The pedagogical value of the hands-on experience that a laboratory provides is ubiquitously endorsed by educators;[1] however, in practice the engineering laboratory has limitations as well. The traditional mode of delivery requires large amounts of resources for a high quality student experience since students must be supervised and equipment is expensive to purchase and maintain. Moreover, versatile laboratory experiences are needed that can accommodate students enrolled via distance education. Virtual laboratories can overcome these limitations. In a virtual laboratory, students do not interact with real equipment, but rather with use computer simulations of laboratory equipment to obtain data. The virtual laboratory allows future engineers to practice the skills they will need in industry, in much the same way a flight simulator is used for training pilots.

Various uses of virtual laboratories in the engineering curricula have been reported.[2-7] The most extensive deployment of virtual laboratories of chemical processes is an impressive set of modules developed at Purdue University. Seven different laboratories based on traditional chemical engineering processes such as styrene-butadiene copolymerization[8] or hydrogen liquefaction[9] have been used. However, assessment of student learning from these modules has been sparse.

We have previously reported on the implementation of a Virtual CVD laboratory, a simulation of an industrial-scale chemical vapor deposition (CVD) reactor.[10-13] The focus of its instructional design is to complement, not replace, existing physical laboratories. The Virtual CVD laboratory provides a capstone experience in which students apply experimental design in a context similar to that of a practicing engineer with a wider design space than is typically seen in the university laboratory. Specifically, it is designed to allow students to engage more fully in certain aspects of the experimental design process such as: the experimental strategy, the analysis and interpretation of data, and the iterative process of redesign. For clarity, the following distinction of terms is made; the term "experimental design" is used to describe the more general, usually iterative, approach of addressing an open ended problem through experiment while the term "design of experiments" is reserved for that specific statistical methodology . Task analysis of "think-aloud" sessions has verified that students are engaged in the intended, iterative experimental design approach of practicing engineers.[10,11] Additionally, this laboratory experience was demonstrated to promote higher level cognition in students.

This paper addresses the development, implementation and assessment of a second virtual laboratory in the curriculum, the Virtual Bioreactor (BioR) Laboratory, which was offered in addition to the Virtual CVD laboratory. The virtual laboratories studied were delivered as part of the first quarter of the capstone laboratory sequence in the School of Chemical, Biological, and Environmental Engineering. Students completed three laboratories in this course: Ion Exchange (IX), Virtual Laboratory (VL) and Heat Exchange (HX). In the VL unit, students choose either the Virtual CVD Laboratory or The Virtual BioR Laboratory. The hypothesis of this study is that deployment of virtual laboratories in different content areas can be similarly effective, as long as the key elements of instructional design are incorporated. In particular, we wish to determine if the area of experimental design, critical thinking and higher order cognition that are promoted in the Virtual CVD laboratory are also promoted in the Virtual BioR Laboratory.

The preliminary assessment is based on analysis of a student survey. While the overall goal in assessment of this project is to determine the ways that students learn key cognitive processes and specific domain content in a virtual environment, the preliminary assessment reported in this paper does not compare and contrast the different amount of learning achieved by the students in a virtual laboratory experience with that learned in two typical hands-on laboratory experiences. Rather, the intent of this preliminary analysis is to describe the differing student perceptions of the learning that they were to take away from the three different laboratory experiences. Students' perceptions of the learning intentions of three different laboratory experiences provide a lens into their metacognitive processes. Metacognition as a regulatory activity involves students thinking about their thinking in a way that externalizes their perceived knowledge gain and knowledge awareness.[14] Research in metacognition in engineering education has demonstrated the efficacy of providing students with learning environments that enhance students' regulation of their own learning.[15] This research sought to identify the ways that student knowledge and awareness of their own learning might evolve as they move through three structured laboratory experiences. The intent of the research is to demonstrate that the virtual laboratory provided a context in which the students' perception of the laboratory experience would move away from acquisition of technical skills and application of bounded knowledge to using conceptual systems to generalize problem solving beyond the immediate context of the laboratory problem.[16] The perspective of formative assessment processes[17] indicates that student self-assessment defines what students understand about the goals and objectives of their learning experiences. Student understanding of the goals of learning experiences is a critical element in student acquisition of the content understanding and deep cognitive and procedural skill development in higher education. Metacognition as the process of students monitoring their own learning is an important element of student learning in the engineering context.[18]

Simulation and Software Design

The Virtual BioR Laboratory is based on an industrial stirred-tank fed-batch bioreactor, as shown in Figure 1. The bioreactor can be used for different functions, such as production of a product or degradation of waste. The sequence of events that occur in the bioreactor include cleaning and sterilizing the bioreactor, loading with sterile medium, inoculation with the desired cell line, batch-growth on substrate, followed by fed-batch growth where new medium is fed to the bioreactor and the volume increases with time. Finally, the run is stopped, and the contents are emptied from the bioreactor. The simulation of the Virtual BioR is based on a mathematical model that accounts for the kinetics of the different processes that occur. Since real systems do not deterministically adhere to fundamental models, random process and measurement variation is added to the output. The mathematical model and the software architecture used in the bioreactor simulation are presented in Appendix A.

The instructor interface allows the instructor to access the Virtual BioR through the web via an instructor login. The instructor can create and monitor students' accounts (username, password, simulation). By modifying the MatLab simulation files, each account can use a different set of instructor specified parameters, such as temperature optimum, degree of substrate inhibition, maximum specific growth rate, etc. The parameters that characterize the simulated cultivation are stored in the MatLab files, so each student could be running a bioreactor with a different

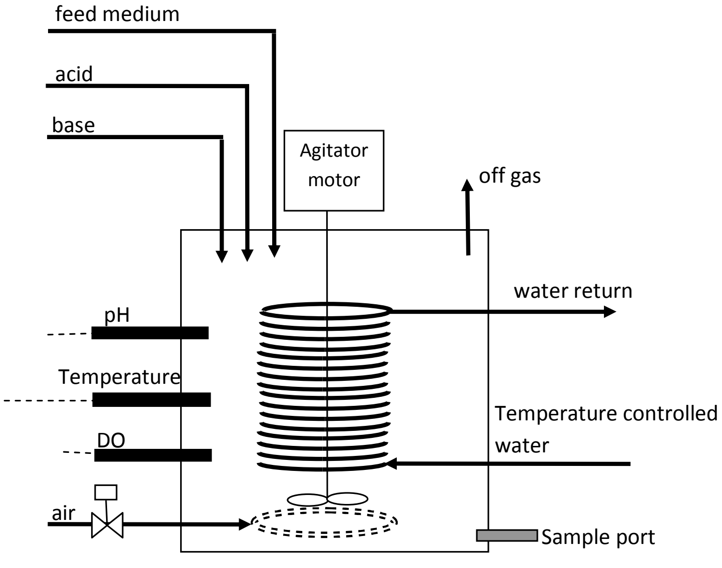
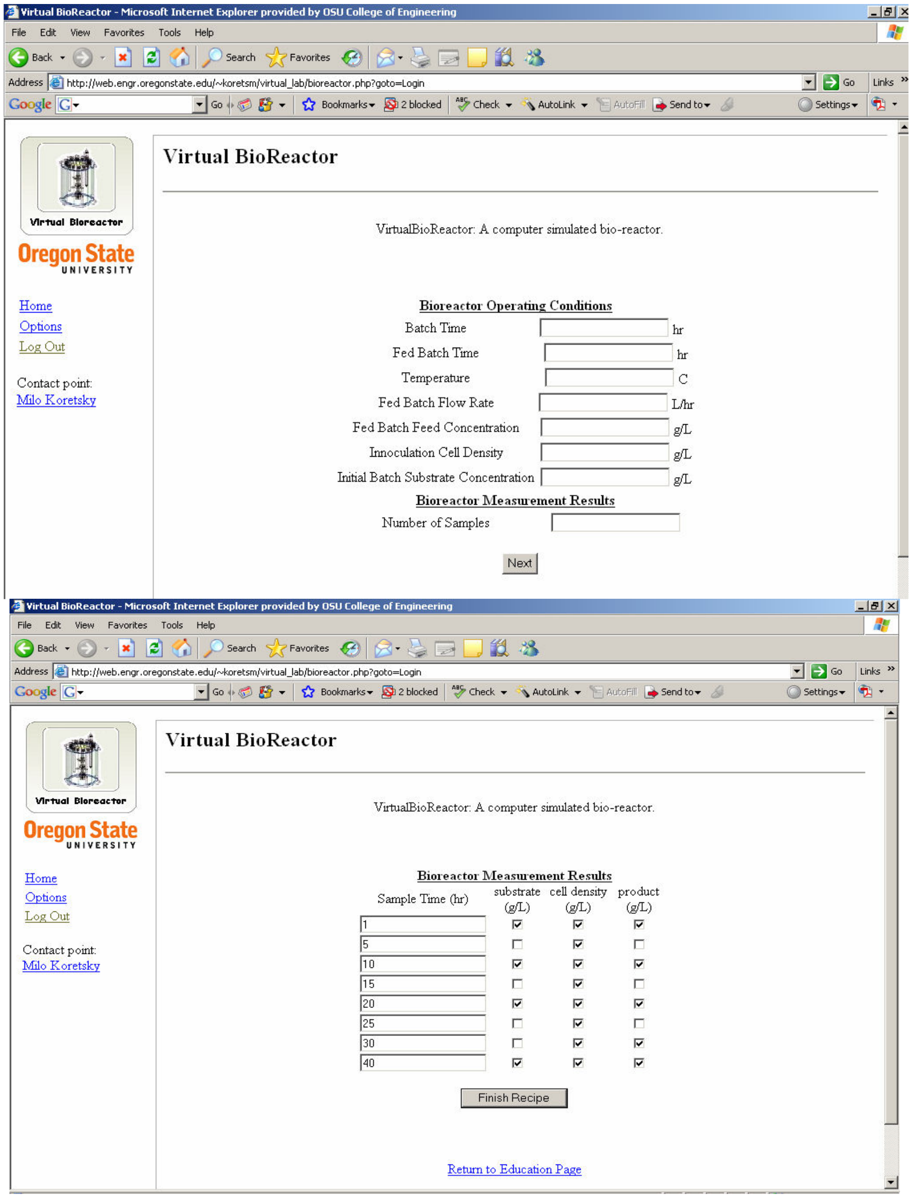


Figure 1. Schematic of a physical bioreactor.

virtual cell line. The instructor interface also provides the instructor with student progress. Student progress refers to the number of runs, conditions (recipe) of each run, time and date each run was performed, results of each run, number of measurements performed, and amount of virtual money spent.

The student interface is accessed with an instructor provided student username and password. The students are able to specify a set of conditions for a virtual bioreactor run, run the experiment, and see or download the results to excel. On the initial screen after login, students are offered four selections: (1) see previous run results, (2) see cost data, (3) run an experiment, and (4) submit final recipe. To run an experiment, the student must input process and sampling parameters as shown in the two screen shots in Figure 2.



Virtual BioReactor

VirtualBioReactor: A computer simulated bio-reactor.

Bioreactor Operating Conditions

Batch Time		hr
Fed Batch Time		hr
Temperature		C
Fed Batch Flow Rate		L/hr
Fed Batch Feed Concentration		g/L
Innoculation Cell Density		g/L
Initial Batch Substrate Concentration		g/L

Bioreactor Measurement Results

Number of Samples

Virtual BioReactor

VirtualBioReactor: A computer simulated bio-reactor.

Bioreactor Measurement Results

Sample Time (hr)	substrate (g/L)	cell density (g/L)	product (g/L)
1	☑	☑	☑
5	☐	☑	☐
10	☑	☑	☑
15	☐	☑	☐
20	☑	☑	☑
25	☐	☑	☐
30	☐	☑	☑
40	☑	☑	☑

Figure 2. Student Interface – Input boxes for run and sample parameters.

It is in the student interface that the Virtual BioR Laboratory differs significantly from the Virtual CVD laboratory. The Virtual CVD student interface offers a 3D graphical user interface designed to look like a typical semiconductor manufacturing environment, including a clean room with reactor consoles and process and metrology bays. Future efforts will be made to develop an analogous student interface for the Virtual BioR Laboratory. In the meantime, we plan to investigate the effect of the different interfaces on student learning.

Implementation

The Virtual BioR Laboratory was delivered in Fall 2007 during the required senior laboratory course (ChE/BioE/EnvE 414) at OSU for students majoring in Chemical Engineering (ChE), Bioengineering (BioE), and Environmental Engineering (EnvE). The virtual laboratory project was the second of three projects delivered during the 10-week quarter. The other two were traditional physical laboratories (ion exchange chromatography and double-pipe heat exchanger). ChE students had a choice between the Virtual CVD and Virtual BioR laboratories; all BioE and EnvE students were assigned the Virtual BioR Laboratory.

The majority of the students selecting the Virtual BioR Laboratory were simultaneously taking a Bioreactors course (BIOE 458). BIOE 458 is required for BIOE and ENVE students and for CHE students with a declared option in Biochemical Engineering. This course completed treatment of batch and fed-batch operation as the Virtual Bioreactor Laboratory was beginning.

A total of 53 students were enrolled in the senior laboratory course, which included 32 ChE, 14 BioE, and 7 EnvE students. About half of the ChE students selected the Virtual BioR Laboratory, giving 37 students total for that laboratory. The remaining 16 ChE students selected the Virtual CVD Laboratory). The students self-organized into 9 teams of three students and 5 teams with two students for the Virtual BioR Laboratory. Each team was tasked to develop optimal operating conditions for pilot cultivation. They were instructed to find operating conditions that maximize volumetric productivity in the bioreactor.

The Virtual BioR Laboratory project instructional design mirrored that developed for the Virtual CVD Laboratory including deliverables consisting of: a design memorandum and instructor coaching session that was completed prior to the students performing virtual experiments, a project update memo, a project journal, a written report and an oral presentation. The structure and intent of the assignments were the same, and only differed in the specific content of the process (bioreactor verses CVD). For the Virtual BioR, students could select one of two scenarios: (1) production of recombinant protein product by yeast, or (2) degradation of a recalcitrant waste product by a consortium of bacteria. Simulation parameters were varied to represent each case, and varied for each student team.

To execute a bioreactor run, the students had to specify seven parameters: batch time, fed-batch time, initial cell concentration, initial substrate concentration, cultivation temperature, and fed-batch feed rate and concentration. In addition, the sampling times and (virtual) assays to be per performed on each sample were input. The cell concentration, substrate concentration, and product concentration assays were available. Several costs were assigned to each run, and are itemized in Table 1.

Table 1. Virtual Costs Associated with a Virtual BioR Run

Cost Category	Details	Cost
Run	reactor set-up (cleaning, sterilization, calibration), labor and medium	$2,000/run
Hourly operation	labor and medium	$200/hr
Cell concentration measurement	labor, reagents	$25
Substrate concentration measurement		$75
Production concentration measurement		$75
Bioreactor overfill	cleaning, lost production time, labor	$4,000

Prior to receiving their username and password, student teams were required to meet with the instructor to deliver their design memorandum. During this meeting the instructor read the memorandum and advised students on their experimental design approach. If the memorandum did not provide the initial run parameters and a clear strategy for initial data analysis and selection of the subsequent run parameters, the students had to rewrite the memorandum before receiving their username and password. About half of the Virtual BioR teams had to rewrite their memorandum. Students approached the project by investigating one factor at a time, using design of experiments (DOE) matrix to evaluate the effect of input parameters, and/or using their content knowledge about the processes (growth, dilution to feed) and phenomena (temperature dependence, substrate inhibition) known to occur in a bioreactor.

At the completion of the three week project, the students had run a total of 237 Virtual BioR runs, taking 7,449 measurements, at a virtual cost of $2,894,815, as shown in Table 2. The BioE students perform a small-scale (3 L), but similar in duration, yeast fed-batch physical bioreactor laboratory in the next course in the senior laboratory series (BioE 415). Of course in the physical laboratory, due to complexity and time restrictions, only one run is performed, so they are unable to use the results from their physical bioreactor experiment to influence the design of the next bioreactor run, as they do in the Virtual BioR Laboratory.

Table 2. Fall 2007 Virtual Bioreactor Laboratory.

Group	# Runs	Measurements	Cost
1	7	384	$187,800
2	10	543	$116,625
3	12	309	$88,465
4	12	384	$103,050
5	12	435	$119,725
6	14	420	$259,500
7	16	543	$225,825
8	17	330	$129,150
9	17	636	$207,500
10	21	636	$297,500
11	21	237	$179,875
12	22	429	$220,875
13	25	1242	$356,950
14	31	921	$401,975
	237	7449	$2,894,815

During this Fall 2007 implementation, initial cell concentration was included as a parameter that the students could adjust. In reality, selecting a very large initial cell concentration would have significant impact on cost - essentially another bioreactor would be required to supply the inoculum culture. Some students recognized this and maintained a reasonable inoculation concentration based on realistic constraints, while some inoculated to the maximum cell density to achieve higher volumetric productivities. In future delivery, an upper limit on initial cell density will be imposed.

Assessment

The mixed methodological perspective of this research is grounded in a phenomenological perspective of ascertaining how students who are engaged in the virtual laboratory as a learning environment make sense of their experiences. This research sought to address the following question:

> To what extent do students perceive differing learning outcomes in physical and virtual laboratory experiences?

The data collected was student self reports of their perceptions of their laboratory activities. A set of survey questions was provided to the students in ChE/BioE/EnvE 414 senior laboratory class in Fall 2007 as an assignment. The survey questions were asked after the students had completed each of the three laboratories to gather their perceptions of their learning experiences. The timing was, in general, as soon as possible after the final laboratory report for that given laboratory had been turned in. There were, in some cases, overlap in that the content for the next laboratory had commenced. The following questions were asked after each laboratory session:

1. What do you think the instructors intended you to learn by doing the (Ion Exchange, Virtual, Heat Exchange) laboratory?
2A. What content do you need to know to do this lab?
2. What is the most important skill you have developed from doing the lab?
5A. How would you explain this laboratory experience to a first year student?
5. When you close your eyes and picture the lab experiment, what do you see?

This research focuses on the results of the analysis of Question 1 to determine whether or not the students' perspectives of instructor intent for the laboratory differed in the context of the physical versus virtual laboratory experiences.

Survey responses were entered into a spreadsheet and coded by the three researchers. An initial set of codes was identified by the principal investigator based on the focus of the research program on student cognition and the basic conditions of the laboratory experiences. In order to address the issue of bias, one of the researchers was from an independent agency that specializes in evaluation. An inductive set of codes was independently determined by this researcher based on concepts that emerged from the first reading of the student survey responses. Coded sections of the first survey from both researchers were compared to identify multiple common terms and few differences. The final set of codes used to analyze the surveys reconciled the two approaches and is provided in Table 3. The responses were coded by placing student statements into coding categories and the order of those statements within the student response was recorded.

A qualitative judgment of the extent to which the response of the student invoked substantive cognitive processes was made based on the entire response by the student. Students were rated *Low* or *High* if they were believed to be exhibiting cognitive processes at the lower level or higher level, respectively. For example, a student response could be assigned to a low level when it only referred explicitly to 'experiment' or 'experimental design.' Conversely, student responses were assigned to a high level when they referred explicitly to the multiple steps that they had to take to determine how to determine the response to the question posed by the laboratory or if the student referenced the use of conceptual knowledge together with problem-solving or experimental design processes. The following response is an example of one that was rated as High by the three researchers:

Table 3. Coding Structure for Student Survey Question 1.

Category	The student indicates the instructor's intent was
Communication/Documentation (COMM)	Written and oral communication development, report writing, reporting results to clients.
Situated Nature (SN)	Place the experiment in the context of their future professional environments or scenarios.
Lab Protocol/Skills (SKILL)	Develop specific techniques and skills of hands on experimental work, encounter concepts in a hands-on environment, or address safety issues. This category is only marked when the student is specific.
Specific Content – literal (CONT)	Learn the specific topics or content within that laboratory assignment or reinforce understanding of content learned in lecture classes, e.g., resin capacity in ion exchange.
Team Skills (TEAM)	Learn how to work effectively with others as part of a team
Experimental Design (EXP)	Learn nature of designing experiments including the process of identifying the problem, designing the data collection method to address the problem, analyzing the results and making decisions. A low level response to this simply identified experimental design as an outcome
Understanding/Critical thinking (CRIT)	Develop ways that the experience they have in the laboratory is useful in a general sense, i.e., to other experiments and helps develop their higher level critical and creative thinking skills.

> I believe that the virtual lab was intended to simulate a complicated process where one could perform many more experiments than if it were a real lab. It was focused on the analysis and synthesis aspects of understanding because the data was easily obtained but the real question was what does it mean about the input parameters and how should it direct further testing.

A response rated as Low by all researchers is:

> The objective was to learn to work effectively as a team, and to design an experiment where optimization is essential.

Finally, a response that received different ratings from the reviewers is:

> I believe that the instructors intended us to learn about project management. With this, we can encompass both the need for scheduling, thinking ahead, and seeing where the strengths of each team members lies before tackling a project that we are given. This lab simulates more of a real life project than most labs because we are given minimum details and are expected to find data out instead of it just being given to us. We are to deal with unexpected situations such as using bad parameters and figuring out what is wrong with our decisions.

The number of coded statements in each category was summed across all of the student surveys for each of the three researchers. Inter-rater reliability was determined by comparing the code distributions in each of the coding categories. An inter-rater reliability rating, which measures homogeneity, is useful when analyzing the same data by two or more raters/interviewers so as to establish the extent of consensus on the use of the instrument or analysis process by those who administer it. Cohen's Kappa (κ) is used to assess inter-rater reliability if there are just two raters. Intraclass correlation (ICC) is used to measure inter-rater reliability for more than two raters. ICC may be conceptualized as the ratio of between-groups variance to total variance. The inter-rater reliability for Question 1 among the three raters is reported in Table 4.

Levels of inter-rater reliability range between 0 and 1.0. Reliability estimates in the range of 0.70 are considered acceptable, and the levels for Question 1 on the Ion Exchange Laboratory and Virtual Laboratory are within the acceptable range. The low level of correlation among the raters on the Heat Exchange Laboratory experience is somewhat problematic. It is not clear the extent to which the differences among the raters reflect variability in the student responses. It is believed these ratings could be improved by methodical reviewer preparation.

Table 4. Inter-Rater Reliability of High/Low Coding

Laboratory	Reliability Coefficient
Ion Exchange	0.775
Virtual	0.746
Heat Exchange	0.583

The analysis of student perceptions was determined by calculating the percentages of students whose statements were identified in each of the coding categories. Percentages of coding frequency were determined by summing the number of times a particular code was assigned to the student responses across the sample of 43 students who agreed to participate in the study. For this analysis, student statements were assigned to a code only once even if the student made multiple statements that addressed the same category.

One check on the integrity of the coding analysis was made by assigning each statement of the students' responses to a specific coding category. The percent of codes in each coding category was then determined by dividing the number of statements in each category by the total number of coded statements. The distribution pattern of the coded statements remained essentially the same as the previous analysis.

The results of the coding for the Ion Exchange Laboratory, the Virtual Laboratory and the Heat Exchange Laboratory are shown in Tables 5-7. The percentage of statements that were selected by each researcher for the categories reported in Table 3 is shown. There is a clear difference between the Virtual Laboratory and the two physical laboratories. The number of high cognition statements (HIGH) is approximately double in the Virtual Laboratory (20 vs. 11) where nearly half the student responses exhibit this characteristic. Previous research has demonstrated the Virtual CVD Laboratory promotes high level cognition.[10,11] Thus, the level of student metacognition in the combined virtual laboratories is consistent with the findings of the Virtual CVD Laboratory, alone. Similarly, the statements that were coded as experimental design (EXP)

Table 5. Survey results from coding of Question 1 for the Ion Exchange Laboratory

Researcher	COM	SN	SKILL	CONT	TEAM	EXP	CRIT	Low	High
1	51%	30%	58%	49%	21%	7%	42%	31	12
2	53%	23%	47%	40%	16%	28%	26%	30	13
3	53%	33%	51%	47%	21%	5%	51%	30	13
Mean %	53%	29%	52%	45%	19%	13%	40%	30 70%	13 30%

Table 6. Survey results from coding of Question 1 for the Virtual Laboratory

Researcher	COM	SN	SKILL	CONT	TEAM	EXP	CRIT	Low	High
1	2%	40%	9%	7%	16%	62%	64%	22	21
2	2%	30%	0%	9%	14%	75%	52%	26	17
3	20%	27%	0%	18%	16%	64%	77%	21	22
Mean %	8%	32%	3%	11%	15%	67%	64%	23 53%	20 47%

Table 7. Survey results from coding of Question 1 for the Heat Exchange Laboratory

Researcher	COM	SN	SKILL	CONT	TEAM	EXP	CRIT	Low	High
1	12%	21%	56%	23%	2%	35%	51%	32	11
2	9%	21%	42%	37%	5%	51%	26%	38	5
3	14%	16%	56%	56%	5%	28%	58%	33	10
Mean %	12%	19%	51%	39%	4%	38%	45%	34 79%	9 21%

averages 67% for the Virtual Laboratory. This value is significantly higher than the physical laboratories which have average values of 13% and 38%, respectively, and again is consistent with the instructional design and the learning observed in the Virtual CVD laboratory. Moreover, there is a significant improvement in awareness of experimental design from first physical laboratory to second physical laboratory. The average number of statements that identify experimental design increases threefold. Thus, there is evidence that students are carrying their awareness gained from their experience in the virtual laboratory back to the physical laboratory. The critical thinking (CRIT) is also higher in the virtual laboratories than in the physical laboratories (64% vs. 43%). Again, this increase is consistent with the premise that the virtual laboratories promote high level cognition. In contrast, the lab protocol/skills (SKILL) are the highest rated in physical laboratories while insignificant in the Virtual Laboratory (52% vs. 3%). This result is consistent with the notion that the physical laboratories play an important role in developing haptic skills.[11] These contrasts between students perceptions of the virtual and physical laboratories were likely mediated, to some extent, by the corresponding delivery in lecture. Finally, both situated nature (SN) and team (TEAM) are approximately equal in the first physical laboratory and the virtual laboratory, and both rate significantly higher than in the second physical laboratory. It is unclear what is prompting the lower responses in the latter case; perhaps, fatigue of students, instructor or researcher. This third laboratory has the lowest score for inter-rater reliability.

Conclusion

The Virtual Laboratory experiment in the capstone senior laboratory in the School of Chemical, Biological and Environmental Engineering was modified in Fall 2007 to include the choice of a second virtual laboratory, the Virtual BioR Laboratory. The instructional design of the Virtual BioR Laboratory was based on the more established Virtual CVD laboratory, including elements such as a design memorandum and instructor coaching session that was completed prior to the students performing virtual experiments, a project update memo, a project journal, a written report and an oral presentation. Students were also charged for runs so that they had to make good choices in their experimental design and stayed out of the "video game" mode. While the types of cognition of students using the Virtual BioR Laboratory still needs to be directly measured, a survey revealed their metacognition about the goals of the learning during this project. Analysis of metacognitive statements of students show enhanced awareness of experimental design, and greater occurrences of critical thinking and higher order cognition. These statements are consistent with the type of learning that has been measured for the Virtual CVD Laboratory. If the type of learning depends only on the instructional design and is, indeed, independent of the specific content of a specific virtual laboratory, these types of laboratories could be developed over a wide array of content areas, and have a large impact on student learning in the capstone laboratory.

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Appendix A. Mathematical Model and Software Architecture

The growth of cell and synthesis of production for an aerobic reaction is as follows:

cells + substrate + oxygen ➔ more cells + product + CO_2

The simulation of biomass growth, substrate consumption, and product synthesis is based on a reaction kinetic expression (Monod growth) with substrate inhibition (Eq. 1):

$$\mu = \frac{\mu_{max}}{\left(1+\frac{K_S}{S}\right)\left(1+\frac{S}{K_I}\right)} \qquad (1)$$

Where μ is the specific growth rate [hr^{-1}], μ_{max} is the maximum specific growth rate, S is the substrate concentration [g/L], K_s is the Monod constant [g/L], and K_I [unitless] is the substrate inhibition constant. Substrate inhibition refers to the substrate inhibiting the growth rate of the cells.

Four simultaneous ordinary differential equations describe the change in cell (X, g/L), substrate and product (P, g/L) concentration and volume (V, L) with time (t, hr) (Eq. 2-5).

$$\frac{dX}{dt} = \mu X - \frac{FX}{V} \qquad (2)$$

$$\frac{dS}{dt} = \frac{F(S_f - S)}{V} - \frac{\mu}{Y_{x/s}} \qquad (3)$$

$$\frac{dP}{dt} = \frac{\mu X Y_{P/S}}{Y_{X/S}} - \frac{FP}{V} \qquad (4)$$

$$\frac{dV}{dt} = F \qquad (5)$$

The fed-batch feed rate and substrate concentration are denoted by F [L/hr] and S_f (g/L), respectively. This development imposes constant yield coefficients of biomass ($Y_{X/S}$, g X/g S) and product ($Y_{P/X}$, g P/g X) produced per substrate consumed. In subsequent development, variable yield coefficients can be implemented to better represent a physical bioreactor.

In addition to substrate inhibition, temperature dependant growth was simulated by making the maximum specific growth rate a function of temperature (Eq. 6).

$$\mu_{max}(T) = A_3\left(A_1 e^{\frac{-E_a}{RT}} - A_2 e^{\frac{-E_d}{RT}}\right) \qquad (6)$$

T is the temperature [K], E_a and E_d are the activation energies [kcal/mol] for growth and thermal death, respectively, R is the gas constant, and A1, A2 and A3 are proportionality constants.

The cell concentration reaches in a physical bioreactor reaches a maximum due to limitations in oxygen delivery at high cell concentrations or accumulation of inhibitory metabolites. A limit on maximum achievable cell density in the bioreactor was imposed with a linear decrease in growth rate as the cell concentration approached the maximum, In addition to temperature dependant growth, substrate inhibition, and maximum achievable cell density, other phenomena could be easily included in the virtual bioreactor simulation such as temperature dependant protein product degradation and product inhibition.

The volume of the bioreactor has been set to 5,000 L. This was selected for flexibility, in that this bioreactor volume can realistically be typical for yeast or bacterial pilot scale commercial reactors or a production scale mammalian cell bioreactor. To implement these scenarios, only the parameters in the simulation need to be modified to represent the characteristics of yeast, bacterial, or mammalian cell cultivations.

The Virtual BioR Laboratory software design contains several components. An overview is shown in Figure A1. Students access the Virtual BioR through a web interface encoded in php, data is stored in a MySQL database, and the simulation is performed in MatLab. The process simulation in the vCVD is implemented in C++. By coding the Virtual BioR simulation in MatLab, we have empowered instructors to more easily refine and change the simulation properties for successive years classes, or even for individual students.

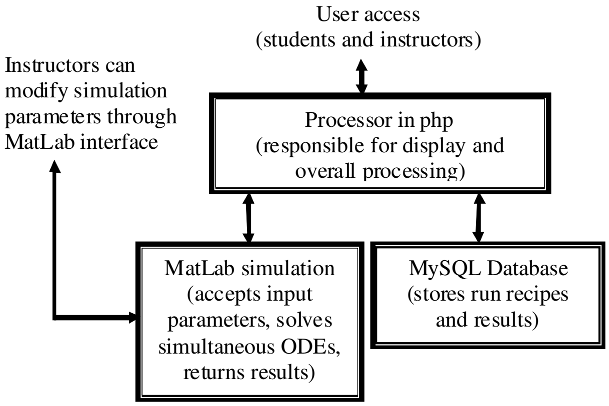

Figure A1. Virtual Bioreactor Architecture