Interactive Web-based Virtual Environment for Learning Single-Use Biomanufacturing Technologies

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Dr. Yakov E. Cherner, a Founder and President of ATEL, LLC, taught science, engineering and technology disciplines to high school, college and university students. He has extensive experience in writing curricula and developing educational software and efficient instructional strategies. Dr. Cherner introduced an innovative concept of multi-layered simulation-based conceptual teaching of science and technology. This instructional approach uses real-world objects, processes and learning situations that are familiar to students as the context for virtual science, engineering and technology investigations. He also proposed and implemented the pioneering concept of integrated adjustable virtual laboratories. To facilitate these methodologies for academic education, corporate and military training, his company developed new ground-breaking e-learning solutions, as well as relevant assessment and authoring tools. Dr. Cherner holds an MS in Experimental Physics, and Ph.D. in Physics and Materials Science. He published over 90 papers in national and international journals and made dozens presentations at various national and international conferences and workshops. Dr. Cherner has served as a Principal Investigator for several government-funded educational projects.

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Bruce Van Dyke received a BS in Chemistry from the University of California, San Diego (UCSD) and MS in Biochemistry from Western Washington University. He spent 17 years performing biomedical research in the Biology Department at UCSD and five years in industrial research in Seattle, Washington. After leaving industry, Bruce joined the biotechnology program at Shoreline Community College in Seattle where he developed and taught courses in biotechnology. In 2006, he was invited to join Sonia Wallman and the Northeast Biomanufacturing Center and Collaborative (NBC2) in Portsmouth, New Hampshire where he spent five years teaching in the biomanufacturing program. Bruce is currently the Chair of the Biotechnology and Compliance Program at Quincy College in Quincy, MA and a consultant for NBC2.
Abstract

This paper presents the first phase of a highly interactive, comprehensive learning environment for teaching industrial scale single-use biopharmaceutical manufacturing. This simulation-based e-learning module focuses on upstream processing, using completely disposable technology and equipment. This module can be run in the following three modes: Introduction, Practice, and Assessment.

Introduction

The adoption of single-use technologies is an increasing trend in today’s biopharmaceutical manufacturing. Disposable systems, which are easy to use and maintain, and are therefore cost efficient, will replace relatively inflexible, hard-piped equipment, including large stainless steel bioreactors and tanks. However, many life science and biotechnology companies are facing shortages in personnel skilled in single-use technologies.

To assist in training of biopharma manufacturing technicians and address the increasing demand in educational materials for disposable technologies, Quincy College (MA) has combined efforts with the Massachusetts based company ATeL for developing a highly interactive, comprehensive, online learning environment for teaching and learning the latest industrial scale, disposable biomanufacturing technologies. This project is partially supported by a Department of Labor TAACCCT Grant.

Web-based Virtual Environment

A set of interactive online modules and simulation-based virtual laboratories (v-Labs) form the core of this e-learning environment. The environment also includes online lessons, assessments, a glossary, and supporting materials.

The e-learning system design adapts and integrates cognitive information processing, systems analysis, and adult learning theories. It employs effective “learning-by-doing” and problem-based learning methodologies [1, 2]. Students process new knowledge and master complex operational and maintenance skills in such a way that it makes sense to them in their own frame of reference. According to contextual learning theory, learning skills and acquiring knowledge "in context" is the most efficient learning strategy [4, 5].

The software has a flexible multi-layered and open-ended architecture. All learning and teaching resources are based on a uniform pedagogical approach and conceptually organized in such a manner that they compliment each other and enable students to tackle the learning subject from several directions.
In this paper, only the modules developed for studying upstream processing and exploring the design of related single-use systems are discussed. Additional modules are also being developed.

The first module (Figure 1) allows students to explore the upstream process flow diagram. Student can select and expand a flowchart box and examine the process stage represented by the selected box. In the panels on the right, a step description, video clip, diagram, table, or any other relevant multimedia resource can be displayed. Each panel has a navigation bar that enables the user to switch between resources.

Figure 1. Upstream processing overall flow. A screenshot of the e-Learning Environment on single-use biomanufacturing. The panel on the left presents an expandable flowchart of upstream processing using disposable technology. A description of the selected procedure is shown in the top right panel. A video clip that demonstrates how the procedure is performed by an expert is displayed in the bottom right panel.

After reviewing the upstream process workflow, the student can explore the systems and devices utilized at each step of upstream processing in great detail. The upstream production line diagram (Figure 2) demonstrates to students that prior to cell growth in a bioreactor, the culture should be scaled-up through a series of cell culture vessels of increasing size before the use of a bioreactor. The importance of maintaining cell line-specific densities during scale-up is emphasized.

The student is able to click on any equipment and open its enlarged 3D image in a separate window. The window can be further expanded to display the equipment description and major parameters. Interactive simulations that visualize equipment operation are available
as well. These simulations also enable students to gain or enhance their skills in performing the related procedures. For example, the simulation shown in the bottom left of Figure 2 helps students master online the aseptic techniques of cell culture using spinner flasks as incubation containers, and better understand all precautions and requirements to prevent cross contamination.

![Virtual Single-Use Biomanufacturing](image)

**Figure 2. Upstream processing in detail.** Top left: an interactive diagram shows an entire chain of disposable equipment used in upstream processing. Top right: a panel displays the description of the technological step that is facilitated by the selected equipment. Bottom right: an enlarged 3D-image of the selected equipment. Bottom left: a fragment of the software interface that allows the student to master operational skills online.

The combination of interactive simulations with synchronized multimedia learning resources helps the student master operational and maintenance skills online and prepare for more efficient performance of a similar task in the actual laboratory or in their workplace.

Simulations demonstrate how to prepare for operating a single-use bioreactor (Figure 3, left). They also allow students to load a disposable bag into the virtual bioreactor, using a computer mouse and a keyboard. Step-by-step instructions to complete this procedure are also displayed (Figure 3, top right). Students can watch how a bag is being loaded by an experienced biomanufacturing technician (Figure 3, bottom right).
**Figure 3.** Loading a disposable bag into a bioreactor. An example of an assembly exercise for a virtual single-use bioreactor. Instructions for loading a disposable bag are displayed in the top right panel. A video presenting preparation of a disposable bag is shown in the bottom right panel.

**Figure 4.** Controlling a bioreactor. An interface for mastering skills in process control and virtual single-use bioreactor operation. The table in the top right panel displays the current process parameters. The parameter highlighted in red is outside the setpoint range and the system is in the alarm state. The table shown in the bottom right window enables the user to specify process setpoints and allowed deviation ranges.
E-Learning modules enable students to learn how to operate equipment and control processes. The screenshots presented in Figure 4 illustrate monitoring of cell growth in a 2000 L single-use bioreactor. Cell growth in a bioreactor requires steady state conditions. Therefore, the student must initially use a pop-up table (Figure 4, bottom right) to specify optimal values of the process parameters and allowed deviation ranges. During cell growth, any parameter outside the set limit is highlighted in red (Figure 4, top right) and the program sends a warning message. The student has to decide how to fix the problem (e.g. add base, adjust temperature, add antifoam, etc).

The online modules which form the core of the virtual laboratory can be run in three modes: Introduction, Practice, and Assessment. The Introduction mode introduces students to the major processes and equipment operation. In this mode, students can observe step-by-step disposable upstream processing procedures and get familiar with design, functions and interconnections of major production systems and devices.

The Practice mode enables students to perform interactive virtual experiments that match experimental tasks which students will face in their biomanufacturing college labs and workplaces. If a student enters an incorrect process control parameter, the system flags it for correction. In addition, students can collect and handle data from the virtual process. Detailed step-by-step on-screen instructions guide students through the online experiments. Various online textbooks, presentations, technical manuals, Standard Operating Procedures (SOPs), audio, video and other multimedia educational resources, which are associated with the experiments and address the education and training needs of biopharmaceutical technicians, are instantly available to the students for just-in-time learning.

In the Assessment mode, performance-based and sequential tests help students to self-evaluate their knowledge and progress. Students are required to complete technical processes with minimal or no instruction. The program tracks the user’s actions, grades system-generated quizzes, and records the elapsed time.

At any one time, 48 Quincy College students use the virtual e-learning modules in their required biomanufacturing and compliance courses, alongside hands-on laboratory experiments. Virtual experiments are performed prior to actual experiments in preparation for hands-on practice in the college laboratory. Soon, this program will be available free of charge, allowing numerous students to benefit.

Upstream processing, as discussed above, can be broken down as follows:

- **Scale-up**: Grow cells in several increasing increments, from frozen stocks, to plates, to stirred cell flasks, to wave bags, and, finally, to a bioreactor. Students need to know cell line-specific requirements (titer (cell density), media, growth rates, gas requirements) and calculate required titer for plating and expansion. Additionally, students are required to identify each connector and its function on the stirred cells, wave bags, and bioreactor bags, and to assemble equipment and setup software.

- **Analytical techniques (Quality Control)**: Daily sampling to monitor approximately ten parameters to determine the health of the culture. The module will require students to
  - Understand acceptable ranges for each assay
  - Perform each assay
Analyse data
Determine the health of each culture

- Harvest: Remove cells from bioreactor via sterile filtration (ultra filtration, tangential flow filtration).

Online assignments are extremely helpful in teaching students the correct order of events for successfully performing real experiments, and give them confidence in their ability to properly perform these procedures. The students study subjects and practice technical hands-on skills online at their own pace, when and where they chose, without the risk of wasting valuable laboratory materials and time. In addition, students are able to repeat virtual experiments several times within a reasonable time frame.

Blended learning, using the combination of virtual activities and actual disposable equipment in the college laboratory, helps students better understand the procedures they perform, and enhances students’ comprehension of the underlying chemical and biological processes. In addition, Quincy College biomanufacturing faculty use the interactive animations for lesson demonstrations.

We believe that the combination of online and hands-on learning ensures integration of theoretical knowledge and practical skills, and enhances students’ understanding of workplace performance. Our future plans include thorough testing to evaluate the effectiveness of the virtual labs as teaching tools, and comparing the impact on student learning from hybrid labs versus the sole use of hands-on labs or virtual labs.

References: