INTEGRATING BIOLOGICAL SYSTEMS
in the Process Dynamics and Control Curriculum

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The discipline of chemical engineering is evolving, as evidenced by the recent wave of departmental name changes that reflect both the increasing number of chemical engineering faculty involved in research on biology-oriented topics, and the fact that the percentage of chemical engineering undergraduates obtaining initial employment with companies in the biotechnology and biomedical sectors increased from 4.6% in 1998 to 10.3% in 2001-02.[1] A series of MIT-organized and NSF-sponsored workshops examined the current state of undergraduate chemical engineering education and recommended a sweeping set of changes.[2] Foremost among the proposed changes were the introduction of biology as a core science, the importance of addressing complexity, and the expanded use of the systems approach. The present discussion focuses on these three elements within the context of the traditional process dynamics and control curriculum.

The dynamics and control course, typically taught late in the junior or senior year, is a natural point for including biological systems content along with chemical process material. Due to the focus on general principles rather than specific processes, biological systems can be integrated without detracting from the coverage of more traditional applications. This expanded vision of the system dynamics and control curriculum requires the following difficult issues to be addressed: (1) how can these complex systems be introduced in a meaningful way to undergraduate chemical engineers with little background in biology?; and (2) what changes are required to include biological content without sacrificing the traditional core of process dynamics and control? The objective of this paper is to provide some practical answers to these questions using the experiences of three courses taught at our respective institutions. The first two examples illustrate the introduction of biological content into the traditional process control course, while the third example focuses on the development of a new course in which the systems approach is applied to a diverse set of biological problems.

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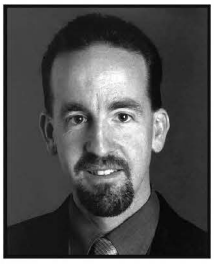

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INTEGRATION OF BIOLOGICAL SYSTEMS CONTENT

A typical process dynamics and control course covers a broad range of new material at a rather brisk pace. To produce students who can apply traditional dynamic analysis and controller design techniques is a formidable challenge even when the focus is purely on chemical process systems. The addition of biological content along with the requisite modeling and analysis techniques requires a carefully crafted course to avoid leaving students overwhelmed. A possible structure for a semester-long course is illustrated by the syllabus in Table 1, where NL is the number of lectures allotted to the specific topics listed in all caps. Bold entries represent new topics specific to biological systems. Italicized entries are theoretical topics often considered optional in a traditional course but which are viewed as important for a biologically oriented course.

The introduction of state-space models and associated analysis tools is essential for the treatment of biological systems due to their complexity (*e.g.*, high order, multivariable, highly nonlinear), which often precludes simple Laplace domain treatment. A few lectures on matrix algebra and linear state-space systems are necessary to review core material and ensure that students with deficient backgrounds understand the basic concepts. When combined with the linear systems analysis lecture, this material allows the calculation of eigenvalues to determine stability and matrix rank for the analysis of controllability and observability. The nonlinear systems theory lecture includes the traditional topic of Jacobian linearization as well as introductory coverage of phase plane analysis, multiplicity, and bifurcations. Biological systems are inherently nonlinear, given the existence of saturation phenomena, stable oscillations, etc. As such, a student must have a working knowledge of nonlinear systems to be able to identify such behavior and analyze system response in the presence of nonlinear phenomena. Without question, this topic could comprise a course unto itself. Some basic tools (*e.g.*, phase planes, limit cycles, bifurcation) are easy enough to teach in a class or two, however. These provide students with an ability to identify nonlinear system characteristics, even if they cannot design a linearizing-state feedback controller to address the underlying nonlinearity. Feedback is a concept that is introduced naturally in the context of biological system examples. The representation of biological control systems using various elements of the traditional block diagram is particularly effective. This approach, however, should be used carefully to avoid concealing the complexity of the underlying biological processes.

Throughout the topic sequence in Table 1, a number of examples serve to highlight the breadth of opportunities for application of the theoretical concepts presented in the course. Table 2 provides a list of potential case studies. For each

TABLE 1

Proposed Syllabus for a Biologically Oriented Dynamics and Control Course

NL=number of lectures • all caps=topic area • bold=new topics • italicized=optional topics

NL	Topics
4	DYNAMIC MODELING Principles of fundamental modeling; chemical and **biological process examples**; introduction to empirical modeling
7	LINEAR AND NONLINEAR SYSTEMS ANALYSIS *Matrix algebra and linear state-space systems*; linear systems theory; introduction to nonlinear systems theory; dynamic simulation; chemical and **biological process examples**; introduction to the Laplace transform
7	FEEDBACK SYSTEMS Basic principles of feedback; **physiological control systems**; **homeostasis as a setpoint-free feedback system**; **feedback in biochemical reaction networks**; closed-loop response analysis; servo vs. load behavior; feedback control of chemical process systems; **closed-loop drug delivery**
8	FEEDBACK CONTROL SYNTHESIS Basic principles of model-based controller design; PID controller design and tuning; advanced single-variable control techniques; multivariable control techniques; *model predictive control*; chemical and **biological process examples**
4	ADVANCED TOPICS *Large-scale systems and plantwide control; parameter estimation and experimental design; state estimation*; **introduction to systems biology**

TABLE 2

Possible Case Studies for the Process Dynamics and Control Course

Chemical Processes Continuous and/or fed-batch polymerization reactor; distillation column; continuous pulp digester; paper machine; simple plantwide example (*e.g.*, reactor and separator); semiconductor process (*e.g.*, lithography); photovoltaic film processing; fuel cell
Biotechnological Systems Continuous and/or fed-batch fermentor; yeast energy metabolism; cell stress response (*e.g.*, heat shock); eukaryotic cell cycle; bacterial chemotaxis
Biomedical Systems Baroreceptor vagal reflex (blood pressure control system); insulin-dependent diabetic patient (glucose-insulin metabolism/control); circadian rhythm gene regulatory network; anesthesia control; drug delivery for HIV treatment; drug delivery for cancer treatment

topic where examples are listed in the syllabus, two chemical process and two biological system examples could be used to develop lecture materials, in-class exercises, and recitation problems. Ideally the biological problems are divided equally between the biotechnology and biomedical lists.

A major conclusion of the MIT-organized education workshops was that multiscale phenomena should be incorporated throughout the undergraduate chemical engineering curriculum.[2] A useful connection between the traditional chemical and biological examples listed in Table 2 is the wide range of time and length scales at which these systems can be analyzed. Polymerization reactor models can be developed using input-output representations,[3] detailed descriptions of the individual polymer particles and their interactions,[4-6] or a variety of scales in between.[7-9] Analogous models can be developed for microbial fermentors where lumped descriptions of cellular processes are provided by unsegregated models[10-13] and detailed descriptions of the individual cells are provided by cell population models.[14] While the introduction of biological systems content is not necessarily required to illustrate these concepts, we feel that an integrated program of chemical and biological examples will reinforce key concepts and demonstrate that these diverse examples are conceptually similar.

UMASS CHE 446: INCORPORATING BIOTECHNOLOGY

The process dynamics and control course at the University of Massachusetts (<http://www.ecs.umass.edu/che/che446/>) has traditionally focused on Laplace transform methods and chemical process applications. This course usually represents the only extensive exposure to dynamic modeling and feedback control in the undergraduate curriculum. Biological systems were chosen as an appropriate vehicle for introducing the key elements of biological transformations, multiscale phenomena, and systems-level analysis identified in the MIT-sponsored education workshops.[2] Rather than completely change the existing course content, a more conservative approach based on the integration of biological systems and the requisite analysis techniques was pursued.

The current syllabus for the UMass course (ChE 446) is shown in Table 3, where new topics introduced in the past two years are italicized. The first few weeks are focused on fundamental modeling because undergraduate students typically have little experience formulating dynamic balance equations. Two biological examples—a continuous yeast fermentor model and a structured yeast cell model—are introduced and revisited throughout the semester. Both time domain and Laplace domain analysis techniques receive extensive coverage. A major focus is the formulation and stability analysis of linear state-space models. Engineered and natural-feedback systems are introduced in parallel to highlight their common features and unique properties. While most of the material on single-loop controller synthesis is traditional, an introduction to time domain controller design and analysis techniques is provided to parallel the Laplace domain methods. The final few weeks are focused on multivariable control systems with an emphasis on linear model predictive control.

To accommodate the new material on biological systems and time domain techniques, material previously covered in the course had to be de-emphasized or virtually eliminated. Topics that received reduced coverage included transfer function models, Laplace domain analysis and design techniques, advanced single-loop control strategies, and traditional chemical process examples. Frequency domain techniques received very limited coverage. While these topics are admittedly important, a broader view of dynamic systems and feedback

TABLE 3
Syllabus for UMass Course ChE 446: Process Control
NL=number of lectures italicized=new topics all caps=topic area

NL	Topics
5	FUNDAMENTAL MODELING Basic principles; chemical process examples (nonisothermal chemical reactor; *binary flash unit; binary distillation column); biochemical system examples (continuous fermentor model; metabolically structured yeast cell model)*
7	DYNAMIC SYSTEM ANALYSIS *Linear algebra (solution of matrix equations, state-space models; eigenvalues and eigenvectors); time domain analysis (basic stability concepts, linearization of nonlinear models, linear stability analysis, continuous fermentor example);* Laplace transforms; transfer function models; empirical models; *parameter estimation*
6	FEEDBACK SYSTEMS Process control systems; *biological feedback systems (engineered vs. natural feedback systems, yeast sulfate assimilation pathway, baroreceptor vagal reflex)*; closed-loop transfer functions; closed-loop stability
7	FEEDBACK CONTROL SYNTHESIS PID-controller tuning; internal model control; *time domain controller design (state feedback, pole placement, model matching, continuous fermentor example)*; feedforward control; cascade control
5	MULTIVARIABLE CONTROL Control loop interactions; decentralized control; *discrete-time models (discretization of continuous-time models, convolution models, prediction models); model predictive control (controller design and tuning, constraint handling, real-time optimization, continuous fermentor example)*

control was deemed to be more important given current trends in the chemical engineering profession. In fall 2003, each student was asked to evaluate the biological systems content using a score ranging from "5" if they strongly agreed the objective was achieved to "1" if they strongly disagreed the course objective was achieved. Results obtained from the 21 respondents are summarized in Table 4. The average scores are similar to those obtained for the other course objectives, thereby indicating that the biological content was successfully integrated into the course.

PITT CHE 0500: INTRODUCING BIOMEDICINE

The biology component in the Systems Engineering I: Dynamics Modeling course (ChE 0500, <http://sage.che.pitt.edu/~che0500>) at Pittsburgh focuses on the analysis of, and controller synthesis for, biomedical systems at the whole-organism level. By integrating the research activities in modeling and control of diabetic and cancer case studies within the undergraduate class, students are exposed to a novel application area. This format has resulted in a steady flow of undergraduates interested in undergraduate research, and an increased interest in graduate study. Students at Pitt were posed the same questions as those at UMass; responses can be found in Table 4. While confidence in dynamic balance construction is not as high as that shown in the UMass course, the other questions return similar quantitative responses indicating that the biomedical topics were well received.

ChE 0500 is approached from a model-based perspective; approximately half of the course is focused on modeling systems using both fundamental and empirical approaches, in both continuous and sampled-data (*i.e.*, discrete) domains. From the fundamental modeling perspective, the students are taught to distinguish pharmacokinetics (the time profile of a drug) from pharmacodynamics (the disease dynamics, effect of the drug on the disease, and toxicity) in much the same way valve dynamics and process output response are captured by separate blocks in a block diagram. The remainder of the course focuses on the model-based synthesis and analysis of classical and advanced control systems, as in Table 1.

As a case study, consider the insulin-dependent diabetic patient depicted in Figure 1. Fundamental model construction introduces students to the key variables of the diabetic-patient problem and demonstrates the utility of skills developed elsewhere in the curriculum (*e.g.*, dynamic mass balance with reaction, transport resistance) in the modeling of biomedical problems. Students then work with this model, or suitable lower-order approximations,[15] throughout the semester on in-class problems, homework, etc.

The case study method[16] is commonly employed in teaching to facilitate in-depth treatment of problems in limited

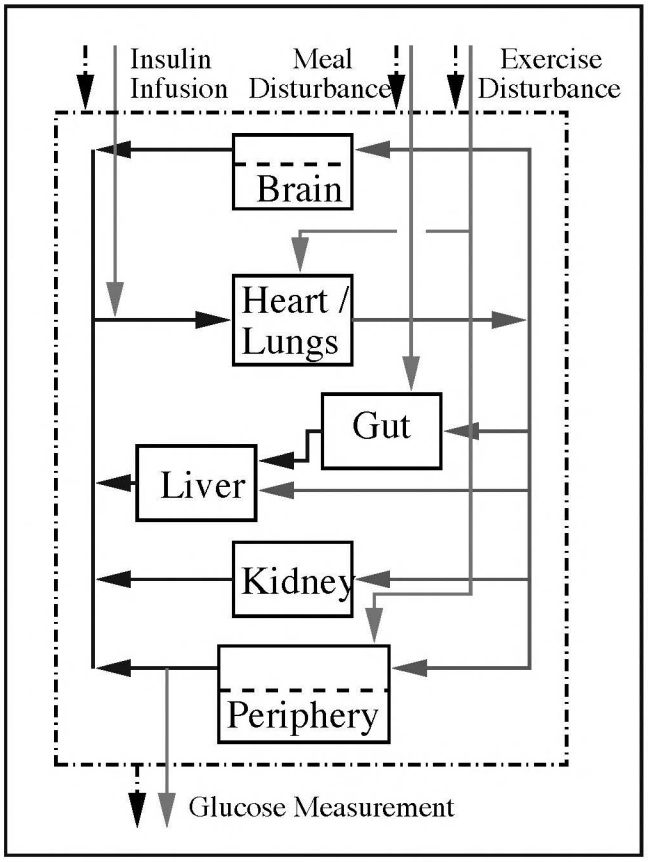

Figure 1. *Open-loop schematic of the diabetic patient. Small solid blocks represent the fundamental model, with manipulated input insulin delivery rate, meal disturbance, exercise disturbance, and glucose concentration measurement.*

TABLE 4
Student Responses to Biological Systems Content in the UMass (21 respondents) and Pitt (17 respondents) Process Control Courses

	Score	
Question	**UMass**	**Pitt**
I can construct a dynamic model of a biological system.	3.83	3.23
I can perform dynamic system analysis and controller design in the time domain.	3.78	3.71
I can apply dynamic system analysis techniques to biological systems to evaluate properties such as stability.	3.89	3.76
I can describe the relevance of feedback control theory to biological systems.	3.83	3.77

classroom time. An added benefit would be to use a unifying application, thereby allowing students to focus their attention on a single problem. The diabetic patient is one such problem, and case studies from the literature have been mapped onto the course outline (Table 1). The map in Table 5 provides a guide to focused literature reading that allows biomedically motivated problems to be quickly brought into the classroom. Case study-specific tables of this form are most useful to faculty who are not dynamics and control experts, but who are responsible for teaching the course, because the dynamics and control class is a challenging course for nonexperts to teach. A collection of these paper-topic maps, for traditional and biological case studies, would provide those teaching the dynamics and control course with a variety of examples tailored to each section of the course.

UCSB CHE 154: A COURSE IN SYSTEMS BIOLOGY

In addition to the required dynamics and control course, described earlier, there is a demand in many chemical engineering programs for elective courses that facilitate specialization in either systems engineering or biotechnology/biomedical engineering. At UCSB, a new course was offered in the spring 2004 quarter entitled Engineering Approaches to Systems Biology (ChE 154/BMSE 255). The course is taught at a dual level (seniors and new graduate students), and fulfills the track requirement for both systems and biology emphases in the undergraduate chemical engineering program. The current syllabus is listed in Table 6, detailing the topics for a single-quarter course (20 lectures of duration 75 minutes).

TABLE 5
Integration of Sample Case Study (insulin-dependent diabetic patient) with Course Outline Topics

DATA-DRIVEN MODELING Sorensen FOTD,[23] Bolie two-state linear,[15] Bergman "minimal" model[24]
FIRST PRINCIPLES MODELING Physiologically based pharmacokinetic/pharmacodynamic[18, 23]
LINEAR SYSTEMS ANALYSIS Bolie two-state linear ODEs[15]
LINEAR SYSTEMS ANALYSIS w/ LINEARIZATION Linearize and analyze Bergman "minimal"[24]
DYNAMIC SIMULATION All models, including AIDA as a different performance classification[15, 18, 23-26]
FEEDBACK SYSTEMS Glucose-insulin interactions[15]; nonlinear feedback response[24]; healthy pancreas response[23, 27]
CLOSED-LOOP ANALYSIS Sorensen healthy patient[23]
PID CONTROL Controller design from FOTD,[23] low-order ODEs,[15] and linearized systems and/or effects of nonlinearity[24]
ADVANCED CONTROL Feedforward for meal disturbances[28] and exercise,[29] with simple[15, 24] or complex[23] case studies
MULTIVARIABLE CONTROL MISO (glucose and insulin inputs; G, I, and exercise inputs)[30] or MIMO (glucose and insulin control) for a variety of systems[15, 23, 24]
MODEL PREDICTIVE CONTROL Linear MPC in analytical[15] or data-driven[31] forms; MPC with a linearized model[23, 24, 32, 33]; nonlinear MPC if desired[23, 24, 32-34]

TABLE 6
Syllabus for UCSB Course: ChE 154 – Engineering Approaches to Systems Biology

NL	Topics
6	CELLULAR REGULATION Central dogma; genome sequences; genome expression; genomic circuits; protein, metabolic, signaling networks; high throughput biological data; biological databases
6	MATH MODELING AND SYSTEMS ANALYSIS TOOLS Modeling strategies; boolean models; nonlinear ODE models; discrete stochastic models; systems biology modeling packages; network analysis—robustness, identifiability; design of experiment issues
6	BIOSYSTEMS CASE STUDIES Bacterial chemotaxis; lambda phage virus; circadian rhythm gene network; signal transduction in apoptosis; synthetic biological circuits
2	COURSE PROJECTS Midterm progress reports; final presentations

The course focuses on the emerging problems in systems biology and computational biology. There is a substantial level of effort being invested in these areas in both academia and industry, and the demand for training of students has increased in proportion. These advances have been facilitated by developments in both computational modeling and high throughput biology—enabling a systematic approach to analyzing complexity in biophysical networks that was previously untenable. These studies provide increasingly detailed insights into the underlying networks, circuits, and pathways responsible for the basic functionality and robustness of biological systems. They also create new and exciting opportunities for the development of quantitative and predictive modeling and simulation tools. Model development involves translating identified biological processes into coupled dynamical equations that are amenable to numerical simulation and analysis. These equations describe the interactions between various constituents and the environment, and involve multiple feedback loops responsible for system regulation and noise attenuation and amplification.

The discipline of "systems biology" has emerged in response to these challenges,[17] and combines approaches and methods from systems engineering, computational biology, statistics, genomics, molecular biology, biophysics, and other fields. The recurring themes include: (i) integrative viewpoints toward unraveling complex dynamical systems, and (ii) tight iterations between experiments, modeling, and hypothesis generation. In response, there have been a number of courses introduced in a variety of departments across the country that address elements of systems biology and computational biology. These have been targeted at both undergraduate and graduate audiences, and in some cases involve continuing education participants from industry. The balance of topics in the syllabus in Table 6 is approximately one-third on basic cellular regulation, one-third on applications of systems engineering tools to biological problems, and one-third on detailed case studies to illustrate current methodologies and future challenges. Although the UCSB curriculum is based on quarters, the same general template could be extended to a semester-long course without significant modification.

Assignments for this course consist of short homework problems, primarily at the beginning of the course, and a major course project. The project entails a midterm progress report, a final presentation, and a written report. The case study offers a mechanism to tailor the course to a diverse student population—seniors work in teams with a reduced scope, while graduate students work as individuals on a more detailed project.

OPEN ISSUES

Laplace Domain Methods

Traditional process control courses emphasize Laplace transform methods for analyzing and designing feedback systems. While traditional analysis may be facilitated by Laplace domain representations, the applicability of these methods to the complex systems commonly encountered in biological problems is severely limited. Biological systems are inherently nonlinear with phenomena ranging from protein interactions in gene regulatory networks to adaptation in systemic reflexes. Furthermore, modeling of biological systems at resolutions below the macroscopic scale often leads to high-state dimension.[14, 18] As is evident from Table 1, Laplace domain methods have been de-emphasized and frequency domain techniques have been effectively removed from the proposed curriculum. While we do not dispute their potential value, transform-based methods introduce conceptual difficulties that cause many students to lose their physical insights and view the material as applied mathematics. On the other hand, the syllabus in Table 1 is sufficiently flexible that limited coverage of frequency domain methods at the expense of other topics is possible.

Time Domain Methods

Complex dynamic system models are most effectively formulated and analyzed in the time domain using conservation equations. Consequently, the syllabus in Table 1 focuses on linear and nonlinear state-space models. Connections with the corresponding Laplace domain concepts can be introduced as appropriate (*e.g.*, stability via eigenvalues vs. poles). On the other hand, the Laplace transform is a particularly useful tool for single-input, single-output (SISO) systems with time delay and/or zero dynamics. We acknowledge that analytical treatment of zeros in the time domain is more involved than the corresponding Laplace methods. Time domain analysis of transportation and measurement delays is most conveniently performed using a discretized framework based on state augmentation. Because this approach can lead to potentially large state dimensions, evaluating student understanding of this material can be challenging. A possible solution is to use a combination of relatively simple exam questions and more detailed homework problems. While control system design issues can be addressed using continuous state-space models, we believe that a discrete-time framework is preferred for introducing data-driven model identification and sampled-data systems. Recent results have shown that a properly tuned SISO model predictive controller cannot be outperformed by a conventional proportional-integral-derivative (PID) controller.[19] Because we expect this fact to be reflected in industrial practice, the syllabus in Table 1 offers increased exposure to controller synthesis techniques based on discrete-time representations such as step response models. While a comprehensive treatment is beyond the scope of this course, model predictive control (MPC) should be foremost among the topics covered due to its industrial importance. As outlined in the UMass course syllabus (see Table 3), the introduction of MPC necessitates limited discussion of real-time optimization and draws on the discrete-time modeling tools discussed above.

Multivariable Control

While most traditional courses treat multivariable systems as a straightforward extension of SISO systems, a more comprehensive approach that addresses the unique challenges of multivariable controller design is warranted. A formal introduction to decentralized control would support the systems viewpoint of multivariable processes—a set of optimal SISO feedback loops generally does not result in overall system optimality. Another advantage of introducing MPC is that multivariable system complexity is handled in a transparent and systematic manner. Students can gain appreciation for the effects of constraints and optimization-based methods for constraint compensation.

Robustness

A critical topic in the analysis of both process control systems and biological regulation is robustness. While the remarkable levels of robust performance attained in nature are enviable from an engineering perspective, this issue is not widely appreciated in biology. The critical importance of robustness in understanding disease states, as well as evolution and development, motivates its incorporation in the system dynamics and control curriculum. While a detailed theoretical treatment[20] is beyond the scope of a typical undergraduate course, key concepts of robustness can be emphasized using simple tools such as sensitivity analysis—effectively capturing the gains from uncertain system elements to the controlled output or performance measure. Students would be well positioned to evaluate parametric sensitivities using state-space models in the proposed curriculum. Robustness analysis could also be used to study closed-loop strategies such as redundancy, feedback, filtering, and modular protocols commonly used in nature.

Nonlinear Analysis and Control

Most biological systems are not adequately described by linear dynamic models since nonlinear effects such as saturation phenomena are ubiquitous. Consequently, linear and linearization-based analysis techniques are rarely sufficient. Nonlinear analysis techniques, such as phase plane analysis and bifurcation theory (see Table 3), can be introduced explicitly, thereby exposing students to theoretical concepts and analysis tools with wider applicability than Laplace domain methods. Nonlinear phenomena are also common in industrial plants, and linear control methodologies often require specialized tools to handle strong nonlinearities. Linear controllers exhibit poor performance for some nonlinear processes (*e.g.*, high purity distillation columns) and completely fail for particularly difficult processes (*e.g.*, those displaying input multiplicity). Given increased exposure to linear MPC in the revised curriculum, a brief introduction to nonlinear MPC is entirely feasible.

Teaching Control for Nonexpert Faculty

Our experience indicates that the process dynamics and control class is not a popular choice as a teaching assignment among nonexperts in the field. This lack of interest is due to a variety of issues, including the mathematical complexity of the material and the significant focus on feedback controller synthesis. An additional concern is that the material is challenging to students, who have had limited exposure to dynamical systems prior to this course. The syllabus in Table 1 represents a significant departure from the traditional controller-synthesis-dominated course to a more balanced presentation of system dynamics and feedback.

A notable benefit of the proposed syllabus is the degree of potential customization. While our focus has been on the introduction of biological systems content, the treatment of other application areas such as advanced materials can be accomplished in a similar manner. This flexibility provides an excellent opportunity for instructors to integrate their research interests into the course. In fact, the three courses described here were heavily influenced by the work performed in our research groups. Possible benefits of such integration include: (i) increasing the diversity of application examples by encouraging nonexperts to teach the course; and (ii) introducing students to cutting-edge research that influences their perception of the field and may affect their future career directions.

SUMMARY

Biological processes have assumed an increasingly important role in chemical engineering research and practice. Modifications of the existing chemical engineering curriculum are necessary to provide undergraduate students the needed exposure to this emerging field. We believe that the capstone process dynamics and control course provides an excellent opportunity to integrate biological systems content and draw parallels with chemical process applications that have been the traditional focus of this course. This paper provides a summary of work on this problem at our respective institutions.

The proposed curriculum allows biological content and time domain concepts to be introduced in a synergistic manner without adversely affecting the coverage of traditional material. As outlined in the proposed syllabus, this requires a decrease in time spent on traditional topics such as PID controller synthesis, Laplace transform techniques, and frequency response analysis. Advances in feedback controller tuning (*e.g.*, autotuning and model-based methods) combined with the availability of simulation/analysis tools (*e.g.*, MATLAB, LabVIEW) bring into question the need for extensive treatment of pencil-and-paper analytical techniques that are rarely employed, even at the graduate level. While focused time on these topics has been reduced in the name of incorporating biology, it should also be noted that the analysis tools introduced in the dynamics and control class are applicable to problems beyond biological systems. Hence, students are no less prepared for "traditional" industrial positions, and they are certainly more equipped for positions in pharmaceuticals and systems biology.

A key hurdle that must be overcome is the lack of instructional materials to support the new process dynamics and control curriculum. For the courses outlined above, the authors are using new textbooks (*System Modeling in Cell Biology*, MIT Press) or have developed supplementary materials to complement existing textbooks. Researchers in process dynamics and control can contribute in a variety of ways. The construction of extended case studies such as Table 5 for various applications would ease the burden on nonexperts teaching the course. Software tools such as the Process Control Modules[21] and Java-based Control Modules[22] are well suited for introducing traditional concepts and applications. New software tools are needed to expose chemical engineering undergraduates to biological complexity and to allow the application of theoretical concepts to representative biological systems. Ongoing efforts, such as those organized by MIT and the CACHE Corporation, are focused on the development of biologically focused systems courses. A task force headed by the second author of this paper is currently working on course revisions as well as software module development as a means to integrate biological content throughout the chemical engineering curriculum. More details on this effort will be made available at <http://www.cache.org>.

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REFERENCES

1. AIChE, 2001-2002 initial placement of chemical engineering graduates <http://www.aiche.org/careerservices/trends/ placement.htm> (2002)
2. Massachusetts Institute of Technology, *Frontiers in Chemical Engineering Education Initiative* <http://web.mit.edu/che-curriculum> (2003)
3. Parker, R.S., D. Heemstra, F.J. Doyle III, R.K. Pearson, and B.A. Ogunnaike, "The Identification of Nonlinear Models for Process Control Using Tailored 'Plant-Friendly' Input Sequences," *J. Proc. Control*, **11**, Sp. Issue SI:237-250 (2001)
4. Immanuel, C.D., C.F. Cordeiro, S.S. Sundaram, E.S. Meadows, T.J. Crowley, and F.J. Doyle III, "Modeling of Particle Size Distribution in Emulsion Co-Polymerization: Comparison with Experimental Data and Parametric Sensitivity Studies," *Comp. Chem. Eng.*, **26,** 1133-1152, (2003)
5. Semino, D., and W.H. Ray, "Control of Systems Described by Population Balance Equations – I. Controllabity Analysis," *Chem. Eng. Sci.*, **50**(11), 1805-1824 (1995)
6. Semino, D., and W.H. Ray, "Control of Systems Described by Population Balance Equations – II. Emulsion Polymerization with Constrained Control Action," *Chem. Eng. Sci.*, **50**(11) 1825-1839 (1995)
7. Congalidis, J.P., J.R. Richards, and W.H. Ray, "Feedforward and Feedback Control of a Solution Copolymerization Reactor," *AIChE J.*, **35**(6) 891-907 (1989)
8. Uppal, A., W.H. Ray, and A.B. Poore, "On the Dynamic Behavior of Continuous Stirred Tank Reactors," *Chem. Eng. Sci.*, **29**, 967-985, (1974)
9. Daoutidis, P., M. Soroush, and C. Kravaris, "Feedforward/Feedback Control of Multivariable Nonlinear Processes," *AIChE J.*, **36**(10) 1471-1484 (1990)
10. Henson, M.A., and D.E. Seborg, "Nonlinear Control Strategies for Continuous Fermentors," *Chem. Eng. Sci.*, **47,** 821-835 (1992)
11. Chang, Y.K., and H.C. Lim, "Experimental and Simulation Studies of Multivariable Adaptive Optimization of Continuous Bioreactors Using Bilevel Forgetting Factors," *Biotech. Bioeng.*, **34**, 577-591 (1989)
12. Semones, G.B., and H.C. Lim, "Experimental Multivariable Adaptive Optimization of the Steady-State Cellular Productivity of a Continuous Baker's Yeast Culture," *Biotech. Bioeng.*, **33**,16-25 (1989)
13. DiBiasio, D., H.C. Lim, and W.A. Weigand, "Experimental Investigation of Stability and Multiplicity of Steady States in a Biological Reactor," *AIChE J.*, **27**, 284-292 (1981)
14. Henson, M.A., "Dynamic Modeling of Microbial Cell Populations," *Current Opinion in Biotechnology*, **14**, 460-467 (2003)
15. Bolie, V.W., "Coefficients of Normal Blood Glucose Regulation," *J. Appl. Physiol.*, **16**, 783-788 (1961)
16. Mustoe, L.R., and A.C. Croft, "Motivating Engineering Students by Using Modern Case Studies," *Int. J. Eng. Ed.*, **15**, 469-476 (1999)
17. Kitano, H., "Systems Biology: A Brief Overview," *Science*, **295**,1662-1664 (2002)
18. Parker, R.S., J.H. Ward, N.A. Peppas, and F.J. Doyle III, "Robust H_∞ Glucose Control in Diabetes Using a Physiological Model," *AIChE J.*, **46**, 2537-2549 (2000)
19. Pannocchia, G., N. Laachi, and J.B. Rawlings, "A Fast, Easily Tuned, SISO, Model Predictive Controller, *Proc. DYCOPS* (2004)
20. Skogestad, S., and I. Postlethwaite, *Multivariable Feedback Control*, John Wiley & Sons, New York (1996)
21. Doyle, F.J. III, R.S. Parker, and E.P. Gatzke, "Process Control Modules: A Software Laboratory for Control Design," *Prentice Hall International Series in the Physical and Chemical Engineering Sciences*, PH PTR, Upper Saddle River, NJ (2000)
22. Yang, D.R., and J.H. Lee, "Process Control Education Software Using Java Applet," AIChE Annual Meeting, <http://dot.che.gatech.edu/Information/research/issicl/che4400/ javamodule.html> (2002)
23. Sorensen, J.T., "A Physiologic Model of Glucose Metabolism in Man and its Use to Design and Assess Improved Insulin Therapies for Diabetes," Ph.D. thesis, Department of Chemical Engineering, MIT, (1985)
24. Bergman, R.N., L.S. Phillips, and C. Cobelli, "Physiologic Evaluation of Factors Controlling Glucose Tolerance in Man," *J. Clin. Invest.*, **68**, 1456-1467 (1981)
25. Lehmann, E.D., T. Deutsch, E.R. Carson, and P.H. Sonksen, "AIDA: An Interactive Diabetes Advisor," *Comp. Meth. Prog. Biomed.*, **41**,183-203 (1994)
26. Agar, B.U., G. Birol, and A. Cinar, "Virtual Experiments for Controlling Blood Glucose Level in Type 1 Diabetes," in *Proc. Second Joint EMBS/BMES Conf.*, p. 2609 (2002)
27. Nomura, M., M. Shichiri, R. Kawamori, Y. Yamasaki, N. Iwama, and H. Abe, "A Mathematical Insulin-Secretion Model and its Validation in Isolated Rat Pancreatic Islets Perfusion," *Comput. Biomed. Res.*, **17**, 570-579 (1984)
28. Lehmann, E.D., and T. Deutsch, "A Physiological Model of Glucose-Insulin Interaction in Type 1 Diabetes Mellitus," *J. Biomed. Eng.*, **14**, 235-242 (1992)
29. Lenart, P.J., and R.S. Parker, "Modeling Exercise Effects in Type 1 Diabetic Patients," Proceedings of the 15th IFAC World Congress on Automatic Control, Barcelona (2002)
30. Parker, R.S., E.P. Gatzke, and F.J. Doyle III, "Advanced Model Predictive Control (MPC) for Type 1 Diabetic Patient Blood Glucose Control," in *Proc. American Control Conf.*, Volume 5, pp. 3483-3487 (2000)
31. Parker, R.S., F.J. Doyle III, and N.A. Peppas, "A Model-Based Algorithm for Blood Glucose Control in Type 1 Diabetic Patients," *IEEE Trans. Biomed. Eng.*, **46**(2) 148-157 (1999)
32. Parker, R.S., F.J. Doyle III, and N.A. Peppas, "The Intravenous Route to Blood Glucose Control," *IEEE Eng. Med. Biol.*, **20**, 65-73 (2001)
33. Lenart, P.J., and R.S. Parker, "Glucose Control During Exercise in Type I Diabetic Patients," Proceedings of the Topical Conference on Bioinformatics and Genomics, AIChE Annual Meeting (2001)
34. Florian, J.A. Jr., and R.S. Parker, "Empirical Modeling for Glucose Control in Diabetes and Critical Care," *Eur. J. Control*, **11** (2005) ❐