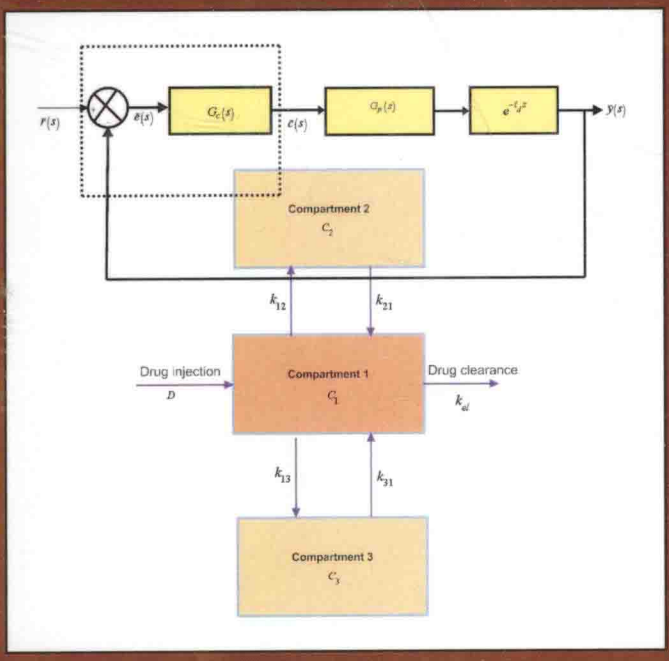
Control of Biological and Drug-Delivery Systems

for Chemical, Biomedical, and Pharmaceutical Engineering



LAURENT SIMON

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CONTROL OF BIOLOGICAL AND DRUG-DELIVERY SYSTEMS FOR CHEMICAL, BIOMEDICAL, AND PHARMACEUTICAL ENGINEERING

LAURENT SIMON
Otto H. York Department of Chemical, Biological and Pharmaceutical Engineering
New Jersey Institute of Technology

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PREFACE

The control of biological and drug-delivery systems is critical to providing a long and healthy life to millions of people worldwide. In living systems, maintenance of homeostasis is credited to several control mechanisms (e.g., positive and negative feedback loops). Researchers in systems biology and controlled-release devices continue to use dynamics and control theory to increase their understanding of cell behavior, to treat diseases, and to develop drug administration protocols.

As the need to develop and commercialize bio-based products becomes more prevalent, chemical engineering departments throughout the nation have begun to shift their focus from a curriculum centered on the knowledge of chemical plant operations to a program that includes biological and pharmaceutical applications. Consequently, a multidisciplinary approach is mandatory to help ensure that chemical engineering graduates secure employment in industries where expertise in bioprocess and drug delivery is needed.

This textbook combines knowledge of process dynamics and basic control theory to analyze processes in the chemical, biomedical, and pharmaceutical engineering fields. Chemical process control topics, such as external disturbances, transfer functions, and input/output models, will be covered and enhanced by examples selected in the focus areas. Armed with this information, students will be in a strong position to address issues and to solve problems that dominate both fields (i.e., biological sciences and release devices).

Because most textbooks published in these areas are written for graduate-level study, undergraduate chemical engineering students are not exposed to diversified problems in biological sciences. This book is the first of its kind to provide biological and drug-delivery applications for dynamics and control concepts taught at the undergraduate level.

An expected result of the proposed perspective is an enrichment of fundamental concepts and the development of an application-oriented environment that gives students broader career choices and a competitive edge in the job market. The new outlook is also indispensable in developing technologies and in providing effective medicine to millions of people in need of gene therapies, heart–lung bypasses and dialysis machines. Although written primarily for undergraduate chemical and biomedical engineering students, this book's focus on drug-delivery systems and its coverage of a wide range of topics in the biological sciences is expected to appeal to a large audience in pharmaceutical engineering and systems biology.

The textbook is organized so that theory is accompanied by illustrations in several areas. Chapter 1 outlines the role of process dynamics and control in a number of disciplines and a brief overview of instrumentations. Chapter 2 introduces mathematical modeling based on the physical knowledge of a system. In Chapter 3, techniques are developed to linearize process models around nominal points. The concept of deviation variables is also introduced. Stability considerations and phase diagrams are addressed in Chapter 4. The properties of the Laplace operator are described in Chapter 5. Laplace transforms of several functions and ordinary and partial differential equations are computed. Techniques for inverting Laplace transforms are provided in Chapter 6. Partial fraction expansion and the residue theorem are applied to obtain closed-form solutions for differential equations. Chapter 7 discusses derivations of transfer functions from input–output models. This approach is fundamental for controller analysis and design. Physical systems, represented by ordinary and partial differential equations, are discussed. Dynamic behaviors of open-loop systems that are introduced in Chapter 8 deal with rational and transcendental transfer functions. Strategies to derive reduced-order models are also presented. In Chapter 9, control methodologies are developed. The emphasis is placed on three widely used feedback controllers: the proportional, proportional–integral, and proportional–integral–derivative controllers. In Chapter 10, frequency response analyses are studied and methods to draw Bode and Nyquist plots are described. Techniques to analyze the stability of feedback systems are developed in Chapter 11. Examples from biological processes are provided to illustrate the implementation of these tools. In Chapter 12, tuning guidelines for feedback controllers are provided. The Smith predictor, a model-based method to help reduce the effects of dead time on closed-loop performance, is discussed in Chapter 13. Using this structure, the controller acts on a delay-free response. The fundamentals of cascade and feedforward control designs are covered in Chapter 14. Both architectures provide methods for lessening the impact of disturbances on the controlled

variable. A technique for determining a relaxation time for lumped- and distributed-parameter systems is explained in Chapter 15. Based on Laplace transforms, the time to reach a steady-state value can be estimated. Examples of optimum control and design problems encountered in biomedicine are presented in Chapter 16.

This textbook is the result, in part, of my experience as an instructor of process control. I have expertise in process dynamics and control, bioprocesses, and drug-delivery systems and have written over 35 refereed articles and book chapters on biotechnology, controlled release, and mathematical modeling. My unique experiences in teaching biotransport to biomedical and chemical engineering students have exposed me to an assortment of problems that are relevant to both disciplines. My perspective on process dynamics and control has been enriched by courses such as Introduction to Biotechnology and Pharmaceutical Engineering Fundamentals. For additional information, visit my website http://www.laurentsimon.com or http://web.njit.edu/~lsimon/.

LAURENT SIMON

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L. S.

CONTENTS

CHAPTER 1

INTRODUCTION

Examples, pertinent to the application of process control in some areas of bioprocessing and drug delivery, are outlined below to underscore the ubiquitous nature of this technology. Concepts of disturbance variables, set points, manipulated variables, and controlled variables are introduced. Block diagrams are drawn to describe processes. A list of hardware and software required to implement control algorithms is also included.

1.1 THE ROLE OF PROCESS DYNAMICS AND CONTROL IN BRANCHES OF BIOLOGY

Biology deals with the study of living organisms and vital processes. A close examination of cellular functions reveals a sophisticated mechanism and a remarkable control system. The cells, fundamental units in all living things, are responsible for growth, maintenance, and reproduction. Branches of biology, such as biotechnology and physiology, have witnessed a substantial growth in the application of control theories to guide research and to promote discovery.

1.1.1 Applications in Biotechnology

The dynamics of bacterial growth, for example, involve *in vivo* and *in vitro* reactions (i.e., bioreactions). A microorganism, inoculated into a sterilized

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medium, undergoes a lag, an exponential growth phase, a stationary phase, and a death phase. Cell proliferation occurs in a bioreactor, a critical unit operation in biopharmaceutical, biochemical, and activated sludge processes, to name a few [1]. In the lag phase, there is little or no evidence of cell division as the bacteria adjust to their new environment. In microbial cell cultivation, the length of the lag phase can be attributed to the type and age of the microorganism, the size of the inoculum, the temperature of the medium, and nutrient concentration. As cells divide in a bioreactor, their number grows in an exponential fashion. An equilibrium phase (i.e., stationary phase) is achieved as the rate at which cells die is equal to the rate at which they divide. For *in vitro* processes, the lack of nutrients, pH changes, and reduced oxygen are among the factors that may explain why some cells enter the stationary phase. In the death phase, the number of viable cells decreases as nutrients deplete and lytic enzymes start to accumulate. Process dynamics and control can be applied, in biotechnology, to identify the factors that influence cell growth and help devise a procedure for maximizing the production of high-valued proteins. An efficient system needs to consider the different growth phases because of the diverse patterns and kinetics exhibited by the cells. Distinct methods are required depending on the production of (1) primary metabolites, excreted in the exponential growth phase, or (2) secondary metabolites, generated as the cells approach the stationary phase.

It is also necessary to regulate the environmental conditions (e.g., temperature, pH, dissolved oxygen [DO], and limiting nutrient) that affect the reactions occurring within the cells in order to achieve a desired outcome (e.g., product yield, cell concentration). The goal of process control is defined in these terms by Boudreau and McMillan [1]:

> Process control attempts to influence the individual sophisticated internal reactions of billions of cells by controlling their extracellular environment.

DO control is crucial in the cultivation of aerobic cells in bioreactors. Oxygen is required in aerobic respiration to produce energy, in the form of adenosine triphosphate (ATP), from glucose or another organic substrate. The energy consumed by the cells helps them to carry reactions, make products, reproduce, transport nutrients, and change locations. The control of DO in bioprocesses requires careful consideration and an understanding of process dynamics. For example, fermentations aimed at producing antibiotics can be highly viscous, which may lead to fluctuation in the DO concentration in the bioreactor [2]. Advanced algorithms, incorporating the kinetic data, were applied in real time to control DO in the production of aminoglycoside antibiotics from *Streptomyces*.

Figure 1.1 shows DO control when a mouse hybridoma cell line was used to produce an antibody against a tissue-type plasminogen activator (t-PA). Only some of the peripherals are shown in the schematic. Sampling and inoculum ports, humidifiers, and moisture traps are usually included. This product

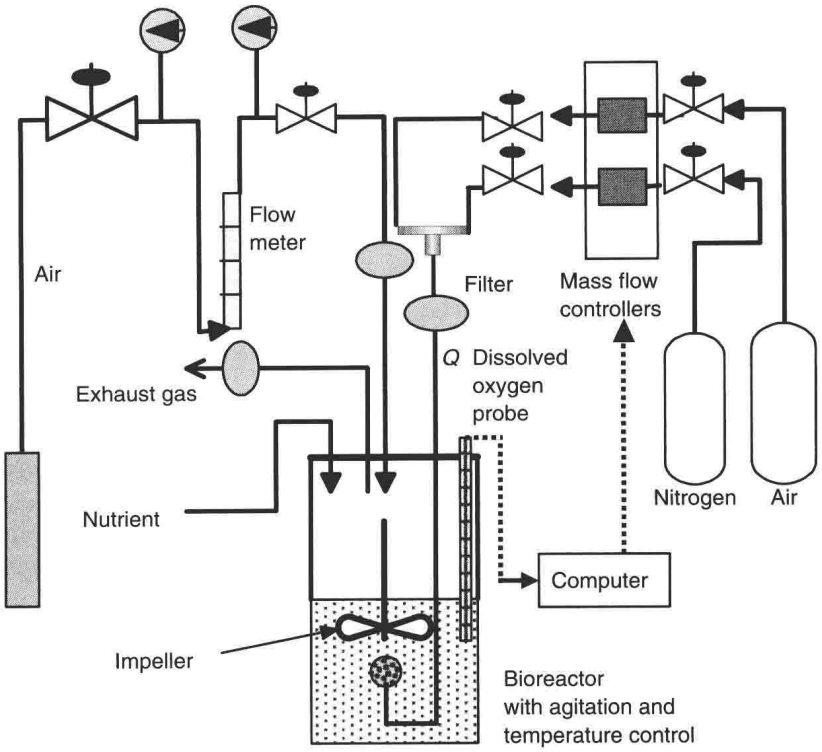

Figure 1.1. Schematic diagram for the control of dissolved oxygen.

(t-PA) has important clinical applications in heart attack research. A control strategy that depends on manipulating the airflow in the sparger, or the agitation, would not work because the hybridoma cells lack a protective cell wall and, as a result, are highly sensitive to shear forces. The basic idea is to disturb the growth environment minimally by keeping the stirring speed and gas flow rate constant. Signals from the DO probe are sent to the computer that stores a control design algorithm (i.e., control law). The computer/controller sends instructions to the mass flow controllers (MFCs) to vary the flow rates of nitrogen (F_{N2}) and air (F_{air}) while keeping a constant total gas flow rate ($Q = F_{N2} + F_{air}$). To design the control law properly, it is important to understand how the hybridoma cells respond to changes in the DO concentration and the dynamics of the DO probe. For these reasons, a fundamental knowledge of process dynamics is a critical step in control design. A *block diagram*, usually drawn to represent the system (Fig. 1.2), is a schematic representation of the interconnections or relationships among variables and processes that make up the control system. The actual DO concentration in the bioreactor is read by the DO probe, which feeds a signal to a *comparator*. The difference between a reference value, set by the operator, and the input signal is