BIOCHEMICAL ENGINEERING FUNDAMENTALS

Second Edition

James E. Bailey

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McGraw-Hill Book Company

New York St. Louis San Francisco Auckland Bogotá Hamburg
Johannesburg London Madrid Mexico Montreal New Delhi
Panama Paris São Paulo Singapore Sydney Tokyo Toronto

This book was set in Times Roman.
The editors were Kiran Verma and Cydney C. Martin.
The production supervisor was Diane Renda;
the cover was designed by John Hite;
project supervision was done by Albert Harrison, Harley Editorial Services.
Halliday Lithograph Corporation was printer and binder.

BIOCHEMICAL ENGINEERING FUNDAMENTALS

234567890 HALHAL 89876

ISBN 0-07-003212-2

Library of Congress Cataloging-in-Publication Data

Bailey, James E. (James Edwin), 1944-
Biochemical engineering fundamentals.

(McGraw-Hill chemical engineering series)
Includes bibliographies and index.
1. Biochemical engineering. I. Ollis, David F.
II. Title. III. Series
TP248.3.B34 1986 660'.63 85-19744
ISBN 0-07-003212-2

PREFACE

Processing of biological materials and processing using biological agents such as cells, enzymes, or antibodies are the central domains of biochemical engineering. Success in biochemical engineering requires integrated knowledge of governing biological properties and principles and of chemical engineering methodology and strategy. Work at the forefront captures the latest, best information and technology from both areas and accomplishes new syntheses for bioprocess design, operation, analysis, and optimization. Reaching this objective clearly requires years of careful study and practice.

This textbook is intended to start its readers on this challenging and exciting path. Central concepts are defined and explained in the context of process applications. Principles of current bioprocesses for reaction and separation are presented. Special attention is devoted throughout to the central roles of biological properties in facilitating and enabling desired process objectives. Also, process constraints and limitations imposed by sensitivities and instabilities of biological components are highlighted. By focusing on pertinent fundamental principles in the biological and engineering sciences and by repeatedly emphasizing the importance of their syntheses, the text seeks to endow its readers with a strong foundation for future study and practice. Learning fundamental properties and mechanisms on an ongoing basis is absolutely essential for long-term professional viability in a technically vibrant area such as biotechnology.

The book has been written for the first course in biochemical engineering for senior or graduate students in chemical engineering. However, selected portions of the text can provide bases for other courses in chemical, environmental, civil, or food engineering. As in the first edition, the book is presented in a systematic, logical sequence building from the most fundamental biological concepts. It is therefore well suited for self study by industrial practitioners.

To facilitate the book's accessibility for independent reading and to provide required background in a one- or two-term course taken as an elective or introduction, the text includes a self-contained presentation of key concepts from

biochemistry, cell biology, enzyme kinetics, and molecular genetics. Clearly, this treatment is intended as an introductory exposure to these topics and not as complete coverage of the life science fundamentals needed by those who will study biochemical engineering in depth or who practice in the field. Further formal or self study in biological fundamentals and practical properties is essential in these cases.

Throughout, we have tried to interweave descriptive material on the life sciences with engineering processes and analytical techniques. The implications of bioscience fundamentals for bioprocess engineering are frequently indicated in sections dealing with biological principles. Treatment of engineering analysis is presented after required descriptive, background material has been covered. Thus, enzyme kinetics and reaction engineering are introduced immediately following description of proteins and other biochemicals, and cell kinetics follows description of metabolic pathway structure, stoichiometry, and regulation.

Text examples and end-of-chapter problems provide the student with opportunities to apply the concepts presented and to broaden understanding of the subject. More than 150 problems, spanning a range of difficulty, require discussions, derivations, and/or calculations by the student.

Compelling motivations for this second edition have come from explosive developments in the biological sciences which provide revolutionary new organisms and materials with tremendous promise for new products and processes. Recombinant DNA and hybridoma technology have stimulated a new biotechnology industry. The text has been expanded and updated to present the materials and methods of gene cloning and expression and cell fusion. New process challenges and strategies for large-scale manufacture of new, ultra-pure protein products are summarized.

Several engineering topics have received greater emphasis in the second edition. This is immediately apparent from the new chapters on separation processes, bioprocess instrumentation and control, and bioprocess economics. Important new topics such as metabolic stoichiometry, multiphase reactor engineering, and animal and plant cell reactor technology have also been integrated into the earlier text.

In addition, the opportunity of preparing a second edition has enabled numerous improvements in organization and presentation of material included in the first edition. This contributes, for example, to more concise yet more informative description of background material, and to a more systematic approach to stoichiometry, kinetics, and bioreactor design. The importance of coalescence and dispersion processes in multiphase reactor contacting exemplifies another area of enhanced presentation.

Cogent and critical comments on the second edition from Michael Shuler, Douglas Lauffenberger, Peter Reilly, Frances Arnold, Donald Kirwan, and Elmer Gaden provided many improvements. Numerous colleagues and current and former students including Dinesh Arora, Ruben Carbonell, Douglas Clark, Kathy Dennis, Jorge Galazzo, L. Gary Leal, Sun Bok Lee, Harold Monbouquette, Mustafa Ozilgen, Steven Peretti, Alex Seressiotis, Robert Siegel, Friedrich Srienc, and Gregory Stephanopoulos contributed ideas, background research, and/or new

homework exercises to the second edition. To those who contributed in numerous ways to the first edition, including Peter Reilly, Elmer Gaden, Harold Bungay, Murray Moo-Young, and George Tsao, we again offer our thanks. Of course the authors take full responsibility for any errors, and welcome comments and suggestions from readers.

This book would not exist without the patient, steadfast efforts of April Olson, Kathy Lewis, Heidi Youngkin, Sandra Cantrell, Bessie See, and Kathy Cannady who typed the several drafts. Hundreds of hours of proofreading assistance were generously donated by Doug Axe, Nancy da Silva, Jorge Galazzo, Chris Guske, Justin Ip, Anne McQueen, Kim O'Connor, Steve Peretti, Mike Prairie, Todd Przybycien, Ken Reardon, Jin-Ho Seo, Alex Seressiotis, Jackie Shanks, Friedrich Srienc, and Dane Wittrup. Finally, we would like to extend our heartfelt gratitude to many friends, colleagues, students, and sponsors who have stimulated our development as biochemical engineers in the years since the first edition. They are in many ways the true authors of this book.

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David F. Ollis

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CHAPTER

ONE

A LITTLE MICROBIOLOGY

Small living creatures called *microorganisms* interact in numerous ways with human activities. On the large scale of the biosphere, which consists of all regions of the earth containing life, microorganisms play a primary role in the capture of energy from the sun. Their biological activities also complete critical segments of the cycles of carbon, oxygen, nitrogen, and other elements essential for life. Microbes are also responsible for many human, animal, and plant diseases.

In this text we concentrate primarily on mankind's use of microbes. These versatile biological catalysts have served mankind for milennia. The ancient Greeks credited the god Dionysus with invention of fermentation for wine making, and the "Monument bleu," which dates from 7000 B.C., shows beer brewing in Babylon. Fermented foods such as cheese, bread, yoghurt, and soy have long contributed to mankind's nutrition. Late in the 19th century, the work of Pasteur and Tyndall identified microorganisms as the critical, active agents in prior fermentation practice and initiated the emergence of microbiology as a science. From these beginnings, further work by Buchner, Neuberg, and Weizmann led to processes for production of ethanol, glycerol, and other chemicals in the early 20th century.

In the 1940s complementary developments in biochemistry, microbial genetics, and engineering ushered in the era of antibiotics with tremendous relief to mankind's suffering and mortality. This period marks the birth of *biochemical engineering*, the engineering of processes using catalysts, feedstocks, and/or