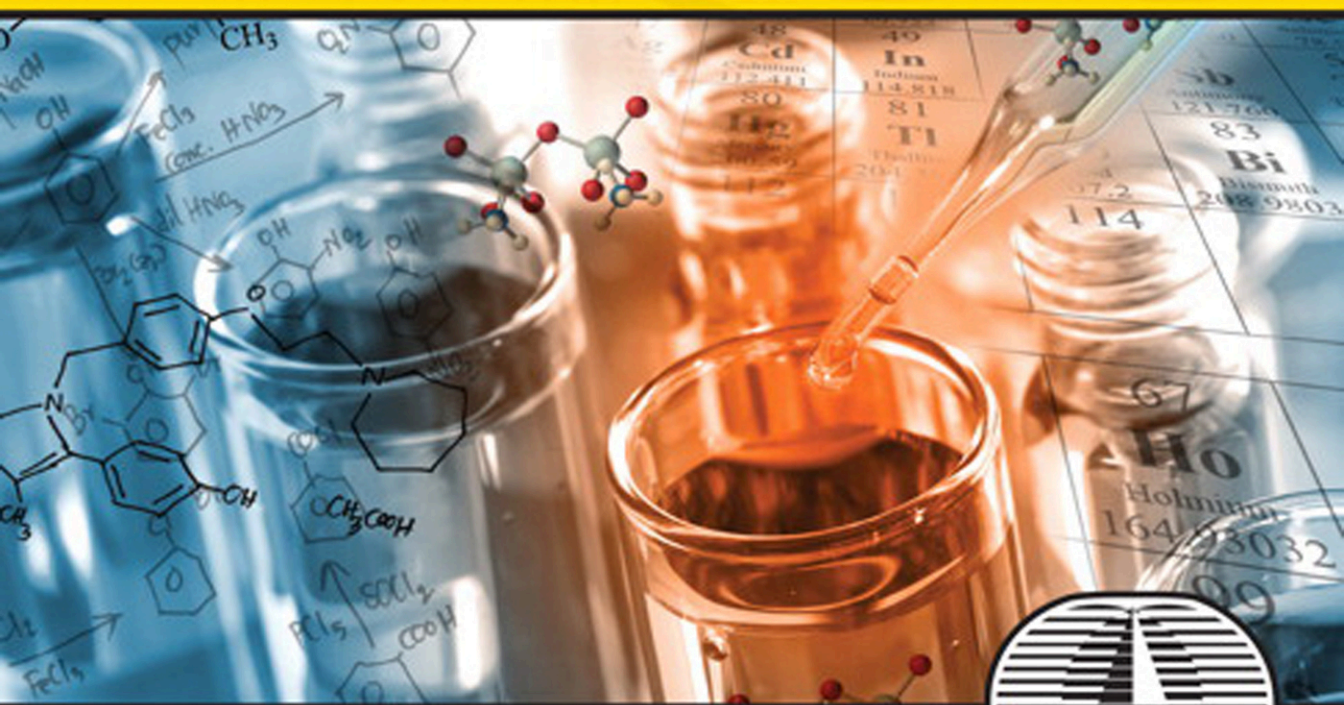


BIOPROCESS ENGINEERING

BASIC CONCEPTS

THIRD EDITION

MICHAEL L. SHULER • FIKRET KARGI • MATTHEW P. DELISA



INTERNATIONAL SERIES IN THE
PHYSICAL AND CHEMICAL ENGINEERING SCIENCES



Bioprocess Engineering

Third Edition

Bioprocess Engineering: Basic Concepts

Table of Contents

Cover

Half Title

Title Page

Copyright Page

Contents

Preface

About the Authors

Part 1 The Basics of Biology: An Engineers Perspective

1 WHAT IS A BIOPROCESS ENGINEER?

1.1. Biotechnology and Bioprocess Engineering

1.2. Differing Approaches to Research for Biologists and Engineers

1.3. The Story of Penicillin: How Biologists and Engineers Work Together

1.4. Bioprocesses: Regulatory Constraints

Suggestions for Further Reading

Questions

2 AN OVERVIEW OF BIOLOGICAL BASICS

2.1. Microbial Diversity

2.1.1. Naming Cells

2.1.2. Viruses

2.1.3. Procaryotes

2.1.4. Eucaryotes

2.2. Cell Construction

2.2.1. Amino Acids and Proteins

2.2.2. Carbohydrates: Mono- and Polysaccharides

Table of Contents

2.2.3. Lipids, Fats, and Steroids

2.2.4. Nucleic Acids, RNA, and DNA

2.3. Cell Nutrients

2.3.1. Macronutrients

2.3.2. Micronutrients

2.3.3. Growth Media

2.4. Summary

Suggestions for Further Reading

Questions

3 ENZYMES

3.1. How Enzymes Work

3.2. Enzyme Kinetics

3.2.1. Mechanistic Models for Simple Enzyme Kinetics

3.2.2. Determining Rate Parameters for Michaelis Menten Kinetics

3.2.3. Models for More Complex Enzyme Kinetics

3.2.4. Effects of pH and Temperature

3.2.5. Insoluble Substrates

3.2.6. Multiphase Enzymatic Reactions

3.3. Immobilized Enzyme Systems

3.3.1. Methods of Immobilization

3.3.2. Diffusional Limitations in Immobilized Enzyme Systems

3.3.3. Electrostatic and Steric Effects in Immobilized Enzyme Systems

3.4. Large-Scale Production of Enzymes

3.5. Medical and Industrial Utilization of Enzymes

3.6. Summary

Suggestions for Further Reading

Problems

4 HOW CELLS WORK

4.1. The Central Dogma

4.2. DNA Replication: Preserving and Propagating the Message

4.3. Transcription: Sending the Message

Table of Contents

4.4. Translation: Going from Message to Product

4.4.1. Genetic Code: Universal Message

4.4.2. Translation: How the Machinery Works

4.4.3. Posttranslational Processing: Making the Product Useful

4.5. Metabolic Regulation

4.5.1. Genetic-Level Control: Which Proteins Are Synthesized?

4.5.2. Metabolic Pathway Control

4.6. How the Cell Senses its Extracellular Environment

4.6.1. Transporting Small Molecules across Cellular Membranes

4.6.2. Role of Cell Receptors in Metabolism and Cellular Differentiation

4.7. Summary

4.8. Appendix: Example Regulation of Complex Pathways

Suggestions for Further Reading

Problems

5 MAJOR METABOLIC PATHWAYS

5.1. Bioenergetics

5.2. Glucose Metabolism: Glycolysis and the TCA Cycle

5.3. Respiration

5.4. Control Sites in Aerobic Glucose Metabolism

5.5. Metabolism of Nitrogenous Compounds

5.6. Nitrogen Fixation

5.7. Metabolism of Hydrocarbons

5.8. Biodegradation of Xenobiotics

5.9. Overview of Biosynthesis

5.10. Overview of Anaerobic Metabolism

5.11. Overview of Autotrophic Metabolism

5.12. Summary

Suggestions for Further Reading

Questions

6 HOW CELLS GROW

Table of Contents

6.1. Batch Growth

- 6.1.1. Quantifying Cell Concentration
- 6.1.2. Growth Patterns and Kinetics in Batch Culture
- 6.1.3. How Environmental Conditions Affect Growth Kinetics
- 6.1.4. Heat Generation by Microbial Growth

6.2. Quantifying Growth Kinetics

- 6.2.1. Unstructured Nonsegregated Models
- 6.2.2. Models for Transient Behavior
- 6.2.3. Cybernetic Models

6.3. Cell Growth in Continuous Culture

- 6.3.1. Specific Devices for Continuous Culture
- 6.3.2. The Ideal Chemostat
- 6.3.3. The Chemostat as a Tool
- 6.3.4. Deviations from Ideality

6.4. Summary

Suggestions for Further Reading

Problems

7 STOICHIOMETRY OF MICROBIAL GROWTH AND PRODUCT FORMATION

7.1. Coefficients for ATP Consumption and Oxygen

7.2. Stoichiometric Calculations

- 7.2.1. Elemental Balances
- 7.2.2. Degree of Reduction

7.3. Theoretical Predictions of Yield Coefficients

7.4. Estimation of Elemental Cell Composition

7.5. Stoichiometry by Oxidation-Reduction Half-Reactions

7.6. Thermodynamics of Biological Reactions

7.7. Summary

Suggestions for Further Reading

Problems

8 HOW CELLULAR INFORMATION IS ALTERED

Table of Contents

8.1. Evolving Desirable Biochemical Activities Through Mutation and Selection

8.1.1. How Mutations Occur

8.1.2. Selecting for Desirable Mutants

8.2. Natural Mechanisms for Gene Transfer and Rearrangement

8.2.1. Genetic Recombination

8.2.2. Transformation

8.2.3. Transduction

8.2.4. Episomes and Conjugation

8.2.5. Transposons: Internal Gene Transfer

8.3. Genetically Engineering Cells

8.3.1. Basic Elements of Genetic Engineering

8.3.2. Genetic Engineering of Higher Organisms

8.3.3. Genome Engineering

8.4. Genomics

8.4.1. Experimental Techniques

8.4.2. Computational Techniques

8.5. Summary

Suggestions for Further Reading

Problems

Part 2 Engineering Principles for Bioprocesses

9 OPERATING CONSIDERATIONS FOR BIOREACTORS FOR SUSPENSION AND IMMOBILIZED CULTURES

9.1. Choosing the Cultivation Method

9.2. Modifying Batch and Continuous Reactors

9.2.1. Chemostat with Recycle

9.2.2. Multistage Chemostat Systems

9.2.3. Fed-Batch Operation

9.2.4. Perfusion Systems

9.2.5. Membrane Bioreactors

9.3. Immobilized Cell Systems

9.3.1. Active Immobilization of Cells

9.3.2. Passive Immobilization: Biological Films

Table of Contents

9.3.3. Diffusional Limitations in Immobilized Cell Systems

9.3.4. Bioreactor Considerations in Immobilized Cell Systems

9.4. Hybrid Bioreactors: Attached and Suspended Cells

9.5. Solid-State Fermentations

9.6. Summary

Suggestions for Further Reading

Problems

10 SELECTION, SCALE-UP, OPERATION, AND CONTROL OF BIOREACTORS

10.1. Scale-Up and its Difficulties

10.1.1. Overview of Traditional Reactor Types

10.1.2. Reactors with Internal Mechanical Agitation

10.1.3. Bubble Column and Loop Reactor

10.1.4. Single-Use Bioreactors

10.1.5. Considerations in Aeration, Agitation, and Heat Transfer

10.1.6. Approaches to Scale-Up

10.1.7. Scale-Down and Microbioreactors

10.2. Bioreactor Instrumentation and Control

10.2.1. Instrumentation for Measurements of Active Fermentation

10.2.2. Using the Information Obtained

10.3. Sterilization of Process Fluids

10.3.1. The Kinetics of Death

10.3.2. Sterilization of Liquids

10.3.3. Sterilization of Gases

10.4. Summary

Suggestions for Further Reading

Problems

11 RECOVERY AND PURIFICATION OF PRODUCTS

11.1. Strategies to Recover and Purify Products

11.2. Separation of Insoluble Products

11.2.1. Filtration

Table of Contents

11.2.2. Centrifugation

11.2.3. Coagulation and Flocculation

11.3. Cell Disruption

11.3.1. Mechanical Methods

11.3.2. Nonmechanical Methods

11.4. Separation of Soluble Products

11.4.1. LiquidLiquid Extraction

11.4.2. Aqueous Two-Phase Extraction

11.4.3. Precipitation

11.4.4. Dialysis

11.4.5. Reverse Osmosis

11.4.6. Ultrafiltration and Microfiltration

11.4.7. Cross-Flow Ultrafiltration and Microfiltration

11.4.8. Adsorption

11.4.9. Chromatography

11.4.10. Electrophoresis

11.4.11. Electrodialysis

11.5. Finishing Steps for Purification

11.5.1. Crystallization

11.5.2. Drying

11.6. Integration of Reaction and Separation

11.7. Summary

Suggestions for Further Reading

Problems

12 BIOPROCESS CONSIDERATIONS IN USING ANIMAL CELL CULTURES

12.1. Structure and Biochemistry of Animal Cells

12.2. Methods Used for the Cultivation of Animal Cells

12.2.1. Basic Techniques for Animal Cell Culture

12.2.2. Growth Media

12.2.3. Growth Dynamics for Animal Cells

12.3. Bioreactor Considerations for Animal Cell Culture

Table of Contents

12.4. Bioreactor Systems for Animal Cell Culture

12.4.1. Nonstirred Reactor Systems

12.4.2. Systems for Entrapped Cells in Stirred Reactors

12.4.3. Suspended Cultures

12.5. Products of Animal Cell Cultures

12.6. Summary

Suggestions for Further Reading

Problems

13 BIOPROCESS CONSIDERATIONS IN USING PLANT CELL CULTURES

13.1. Why Plant Cell Cultures?

13.2. Plant Cells in Culture Compared to Microbes

13.3. Bioreactor Considerations

13.3.1. Bioreactors for Suspension Cultures

13.3.2. Reactors Using Cell Immobilization

13.3.3. Bioreactors for Organized Tissues

13.4. Economics of Plant Cell Tissue Cultures

13.5. Summary

Suggestions for Further Reading

Problems

14 UTILIZING GENETICALLY ENGINEERED ORGANISMS

14.1. How the Product Influences Process Decisions

14.2. Guidelines for Choosing HostVector Systems

14.2.1. Escherichia Coli

14.2.2. Gram-Positive Bacteria

14.2.3. Lower Eucaryotic Cells

14.2.4. Mammalian Cells

14.2.5. Insect CellBaculovirus System

14.2.6. Transgenic Animals

14.2.7. Transgenic Plants and Plant Cell Culture

14.2.8. Cell-Free Protein Synthesis

Table of Contents

14.2.9. Comparison of Strategies

14.3. Process Constraints: Genetic Instability

14.3.1. Segregational Loss

14.3.2. Plasmid Structural Instability

14.3.3. Host Cell Mutations

14.3.4. Growth-Rate-Dominated Instability

14.4. Avoiding Process Problems in Plasmid Design

14.5. Predicting HostVector Interactions and Genetic Instability

14.6. Regulatory Constraints on Genetic Processes

14.7. Metabolic Engineering

14.8. Synthetic and Systems Biology

14.9. Protein Engineering

14.10. Summary

Suggestions for Further Reading

Problems

15 MEDICAL APPLICATIONS OF BIOPROCESS ENGINEERING

15.1. Tissue Engineering

15.1.1. What Is Tissue Engineering?

15.1.2. Tissue-Engineered Skin Replacements

15.1.3. Chondrocyte Culture for Cartilage Replacement

15.2. Gene Therapy Using Viral Vectors

15.2.1. Models of Viral Infection

15.2.2. Mass Production of Retrovirus

15.3. Bioreactors

15.3.1. Stem Cells and Hematopoiesis

15.3.2. Extracorporeal Artificial Liver

15.3.3. Body-on-a-Chip Systems

15.4. Summary

Suggestions for Further Reading

Problems

16 BIOPROCESSES UTILIZING MIXED CULTURES

Table of Contents

- 16.1. Major Classes of Interactions in Mixed Cultures
- 16.2. Simple Models Describing Mixed-Culture Interactions
- 16.3. Mixed Cultures in Nature
- 16.4. Industrial Utilization of Mixed Cultures
- 16.5. Biological Waste Treatment
 - 16.5.1. Biological Waste-Treatment Processes
 - 16.5.2. Advanced Wastewater Treatment Systems
 - 16.5.3. Conversion of Wastewater to Useful Products
- 16.6. Summary
- Suggestions for Further Reading
- Problems

Appendix: Traditional Industrial Bioprocesses

A.1. Anaerobic Bioprocesses

- A.1.1. Ethanol Production
- A.1.2. Lactic Acid Production
- A.1.3. AcetoneButanol Production

A.2. Aerobic Processes

- A.2.1. Citric Acid Production
- A.2.2. Production of Bakers Yeast
- A.2.3. Production of Penicillins
- A.2.4. Production of High-Fructose Corn Syrup

A.3. Bioprocess Technologies: Biofuel and Bioenergy Production from Biomass

- A.3.1. Production of Liquid Fuels
- A.3.2. Production of Gaseous Fuels from Biomass
- A.3.3. Bioelectricity Generation from Wastes Using Microbial Fuel Cells

Suggestions for Further Reading

Index