Contents

Preface to the Second Edition *XIII*
Preface to the First Edition *XV*
About the companion website *XVII*
Nomenclature *XIX*

Part I Basic Concepts and Principles *1*

1 **Introduction** *3*
1.1 Background and Scope *3*
1.2 Dimensions and Units *4*
1.3 Intensive and Extensive Properties *6*
1.4 Equilibria and Rates *6*
1.5 Batch Versus Continuous Operation *8*
1.6 Material Balance *8*
1.7 Energy Balance *9*
References *11*
Further Reading *12*

2 **Elements of Physical Transfer Processes** *13*
2.1 Introduction *13*
2.2 Heat Conduction and Molecular Diffusion *14*
2.3 Fluid Flow and Momentum Transfer *15*
2.4 Laminar Versus Turbulent Flow *18*
2.5 Transfer Phenomena in Turbulent Flow *21*
2.6 Film Coefficients of Heat and Mass Transfer *23*
Further Reading *26*

3 **Chemical and Biochemical Kinetics** *27*
3.1 Introduction *27*
3.2 Fundamental Reaction Kinetics *27*
3.2.1 Rates of Chemical Reaction *27*
3.2.1.1 Elementary Reaction and Equilibrium *28*
3.2.1.2 Temperature Dependence of Reaction Rate Constant k *29*

3.2.1.3 Rate Equations for First- and Second-Order Reactions *30*
3.2.2 Rates of Enzyme Reactions *34*
3.2.2.1 Kinetics of Enzyme Reaction *35*
3.2.2.2 Evaluation of Kinetic Parameters in Enzyme Reactions *37*
3.2.2.3 Inhibition and Regulation of Enzyme Reactions *39*
References *45*
Further Reading *45*

4 Cell Kinetics *47*
4.1 Introduction *47*
4.2 Cell Growth *47*
4.3 Growth Phases in Batch Culture *49*
4.4 Factors Affecting Rates of Cell Growth *52*
4.5 Cell Growth in Batch Fermentors and Continuous Stirred-Tank Fermentors (CSTF) *53*
4.5.1 Batch Fermentor *53*
4.5.2 Continuous Stirred-Tank Fermentor *54*
Reference *56*
Further Reading *56*

Part II Unit Operations and Apparatus for Biosystems *57*

5 Heat Transfer *59*
5.1 Introduction *59*
5.2 Overall Coefficients U and Film Coefficients h *59*
5.3 Mean Temperature Difference *62*
5.4 Estimation of Film Coefficients h *64*
5.4.1 Forced Flow of Fluids through Tubes (Conduits) *65*
5.4.2 Forced Flow of Fluids across a Tube Bank *67*
5.4.3 Liquids in Jacketed or Coiled Vessels *67*
5.4.4 Condensing Vapors and Boiling Liquids *68*
5.5 Estimation of Overall Coefficients U *68*
References *72*
Further Reading *72*

6 Mass Transfer *73*
6.1 Introduction *73*
6.2 Overall Coefficients K and Film Coefficients k of Mass Transfer *73*
6.3 Types of Mass Transfer Equipment *77*
6.3.1 Packed Column *78*
6.3.2 Plate Column *79*
6.3.3 Spray Column *79*
6.3.4 Bubble Column *79*
6.3.5 Packed- (Fixed-) Bed Column *80*
6.3.6 Other Separation Methods *80*

6.4 Models for Mass Transfer at the Interface *80*
6.4.1 Stagnant Film Model *80*
6.4.2 Penetration Model *81*
6.4.3 Surface Renewal Model *81*
6.5 Liquid Phase Mass Transfer with Chemical Reactions *82*
6.6 Correlations for Film Coefficients of Mass Transfer *84*
6.6.1 Single-Phase Mass Transfer Inside or Outside Tubes *84*
6.6.2 Single-Phase Mass Transfer in Packed Beds *85*
6.6.3 *J*-Factor *86*
6.7 Performance of Packed Column *87*
6.7.1 Limiting Gas and Liquid Velocities *87*
6.7.2 Definitions of Volumetric Coefficients and HTUs *88*
6.7.3 Mass Transfer Rates and Effective Interfacial Areas *91*
References *95*
Further Reading *95*

7 **Bioreactors** *97*
7.1 Introduction *97*
7.2 Some Fundamental Concepts *98*
7.2.1 Batch and Continuous Reactors *98*
7.2.2 Effects of Mixing on Reactor Performance *99*
7.2.2.1 Uniformly Mixed Batch Reactor *99*
7.2.2.2 Continuous Stirred-Tank Reactor (CSTR) *99*
7.2.2.3 Plug Flow Reactor (PFR) *100*
7.2.2.4 Comparison of Fractional Conversions by CSTR and PFR *101*
7.2.3 Effects of Mass Transfer Around and within Catalyst or Enzymatic Particles on the Apparent Reaction Rates *102*
7.2.3.1 Liquid Film Resistance Controlling *102*
7.2.3.2 Effects of Diffusion within Catalyst Particles *103*
7.2.3.3 Effects of Diffusion within Immobilized Enzyme Particles *105*
7.3 Bubbling Gas–Liquid Reactors *106*
7.3.1 Gas Holdup *106*
7.3.2 Interfacial Area *107*
7.3.3 Mass Transfer Coefficients *108*
7.3.3.1 Definitions *108*
7.3.3.2 Measurements of $k_L a$ *109*
7.4 Mechanically Stirred Tanks *111*
7.4.1 General *111*
7.4.2 Power Requirements of Stirred Tanks *113*
7.4.2.1 Ungassed Liquids *113*
7.4.2.2 Gas-Sparged Liquids *114*
7.4.3 $k_L a$ in Gas-Sparged Stirred Tanks *116*
7.4.4 Liquid Mixing in Stirred Tanks *118*
7.4.5 Suspending of Solid Particles in Liquid in Stirred Tanks *119*
7.5 Gas Dispersion in Stirred Tanks *120*

7.6 Bubble Columns *120*
7.6.1 General *120*
7.6.2 Performance of Bubble Columns *121*
7.6.2.1 Gas Holdup *121*
7.6.2.2 $k_L a$ *122*
7.6.2.3 Bubble Size *122*
7.6.2.4 Interfacial Area a *122*
7.6.2.5 k_L *123*
7.6.2.6 Other Correlations for $k_L a$ *123*
7.6.2.7 $k_L a$ and Gas Holdup for Suspensions and Emulsions *124*
7.7 Airlift Reactors *125*
7.7.1 IL Airlifts *125*
7.7.2 EL Airlifts *126*
7.8 Packed-Bed Reactors *127*
7.9 Microreactors *127*
References *131*
Further Reading *132*

8 Membrane Processes *133*
8.1 Introduction *133*
8.2 Dialysis *134*
8.3 Ultrafiltration *136*
8.4 Microfiltration *138*
8.5 Reverse Osmosis *139*
8.6 Membrane Modules *141*
8.6.1 Flat Membrane *141*
8.6.2 Spiral Membrane *142*
8.6.3 Tubular Membrane *142*
8.6.4 Hollow-Fiber Membrane *142*
References *143*
Further Reading *143*

9 Cell–Liquid Separation and Cell Disruption *145*
9.1 Introduction *145*
9.2 Conventional Filtration *145*
9.3 Microfiltration *147*
9.4 Centrifugation *148*
9.5 Cell Disruption *151*
References *153*

10 Sterilization *155*
10.1 Introduction *155*
10.2 Kinetics of Thermal Death of Cells *155*
10.3 Batch Heat Sterilization of Culture Media *156*
10.4 Continuous Heat Sterilization of Culture Media *158*

10.5 Sterilizing Filtration *161*
References *164*

11 Adsorption and Chromatography *165*
11.1 Introduction *165*
11.2 Equilibria in Adsorption *165*
11.2.1 Linear Equilibrium *165*
11.2.2 Adsorption Isotherms of Langmuir Type and Freundlich Type *166*
11.3 Rates of Adsorption into Adsorbent Particles *167*
11.4 Single- and Multistage Operations for Adsorption *168*
11.5 Adsorption in Fixed Beds *170*
11.5.1 Fixed-Bed Operation *170*
11.5.2 Estimation of the Break Point *171*
11.6 Separation by Chromatography *174*
11.6.1 Chromatography for Bioseparation *174*
11.6.2 General Theories on Chromatography *176*
11.6.2.1 Equilibrium Model *176*
11.6.2.2 Stage Model *177*
11.6.2.3 Rate Model *177*
11.6.3 Resolution Between Two Elution Curves *178*
11.6.4 Gel Chromatography *179*
11.6.5 Affinity Chromatography *181*
11.7 Biorecognition Assay *183*
11.7.1 Antigen Recognition by an Antibody *183*
11.7.2 Enzyme-Linked Immunosorbent Assay (ELISA) *183*
References *187*
Further Reading *187*

Part III Practical Aspects in Bioengineering *189*

12 Fermentor Engineering *191*
12.1 Introduction *191*
12.2 Stirrer Power Requirements for Non-Newtonian Liquids *193*
12.3 Heat Transfer in Fermentors *195*
12.4 Gas–Liquid Mass Transfer in Fermentors *197*
12.4.1 Special Factors Affecting $k_L a$ *198*
12.4.1.1 Effects of Electrolytes *198*
12.4.1.2 Enhancement Factor *198*
12.4.1.3 Presence of Cells *199*
12.4.1.4 Effects of Antifoam Agents and Surfactants *199*
12.4.1.5 $k_L a$ in Emulsions *199*
12.4.1.6 $k_L a$ in Non-Newtonian Liquids *201*
12.4.2 Desorption of Carbon Dioxide *202*
12.5 Criteria for Scaling-Up Fermentors *204*
12.6 Modes of Fermentor Operation *206*

12.6.1 Batch Operation *207*
12.6.2 Fed-Batch Operation *207*
12.6.3 Continuous Operation *209*
12.6.4 Operation of Enzyme Reactors *211*
12.7 Fermentors for Animal Cell Culture *213*
References *214*
Further Reading *215*

13 Instrumentation and Control of Bioprocesses *217*
13.1 Introduction *217*
13.2 Instrumentation of Bioprocesses *218*
13.2.1 Process Variables and Sensors in Bioprocess Operations *218*
13.2.1.1 Physical Variables *220*
13.2.1.2 Chemical Variables *221*
13.2.1.3 Biochemical Variables *222*
13.3 Control of Bioprocesses *223*
13.3.1 Schematic View of Instrumentation and Control of Bioprocesses *223*
13.3.2 Principles of Control Systems Used for Bioprocesses *224*
13.3.2.1 Closed-Loop System with Feedback *224*
13.3.2.2 Algorithms for Manipulation of Control Variables *225*
13.3.3 Examples of Bioprocess Control *229*
13.3.3.1 pH and Temperature Control *229*
13.3.3.2 DO Control *230*
13.3.3.3 Respiratory Quotient *230*
13.3.3.4 pH Stat *231*
13.3.3.5 DO Stat *231*
13.4 Advanced Control of Bioprocesses *231*
13.4.1 Optimization and Control of Bioprocesses *232*
13.4.2 Application of Artificial Intelligence (AI) Technology to Bioprocess Control *232*
13.4.2.1 Fuzzy Control *232*
13.4.2.2 Artificial Neural Network *233*
13.4.2.3 Expert System *233*
References *234*
Further Reading *234*

14 Downstream Operations in Bioprocesses *235*
14.1 Introduction *235*
14.2 Separation of Microorganisms by Filtration and Microfiltration *238*
14.2.1 Dead-End Filtration *238*
14.2.2 Cross Flow Filtration *240*
14.3 Separation by Chromatography *242*
14.3.1 Factors Affecting the Performance of Chromatography Columns *242*

14.3.1.1 Velocity of Mobile Phase and Diffusivities of Solutes *242*
14.3.1.2 Radius of Packed Particles *243*
14.3.1.3 Sample Volume Injected *243*
14.3.1.4 Column Diameter *244*
14.3.2 Scale-Up of Chromatography Columns *245*
14.4 Separation in Fixed-Beds *246*
14.5 Sanitation in Downstream Processes *247*
References *248*
Further Reading *249*

15 Medical Devices *251*
15.1 Introduction *251*
15.2 Blood and Its Circulation *251*
15.2.1 Blood and Its Components *251*
15.2.2 Blood Circulation *253*
15.3 Oxygenation of Blood *254*
15.3.1 Use of Blood Oxygenators *254*
15.3.2 Oxygen in Blood *255*
15.3.3 Carbon Dioxide in Blood *256*
15.3.4 Types of Blood Oxygenators *258*
15.3.5 Oxygen Transfer Rates in Blood Oxygenators *259*
15.3.5.1 Laminar Blood Flow *259*
15.3.5.2 Turbulent Blood Flow *260*
15.3.6 Carbon Dioxide Transfer Rates in Blood Oxygenators *265*
15.4 Artificial Kidney *266*
15.4.1 Human Kidney Functions *266*
15.4.2 Artificial Kidneys *268*
15.4.2.1 Hemodialyzer *268*
15.4.2.2 Hemofiltration *270*
15.4.2.3 Peritoneal Dialysis *270*
15.4.3 Mass Transfer in Hemodialyzers (cf. 8.2) *271*
15.5 Bioartificial Liver *275*
15.5.1 Human Liver *275*
15.5.2 Bioartificial Liver Devices *276*
References *278*

Appendix A: Conversion Factors for Units ***279***

Appendix B: Solutions to the Problems ***281***

Index ***295***