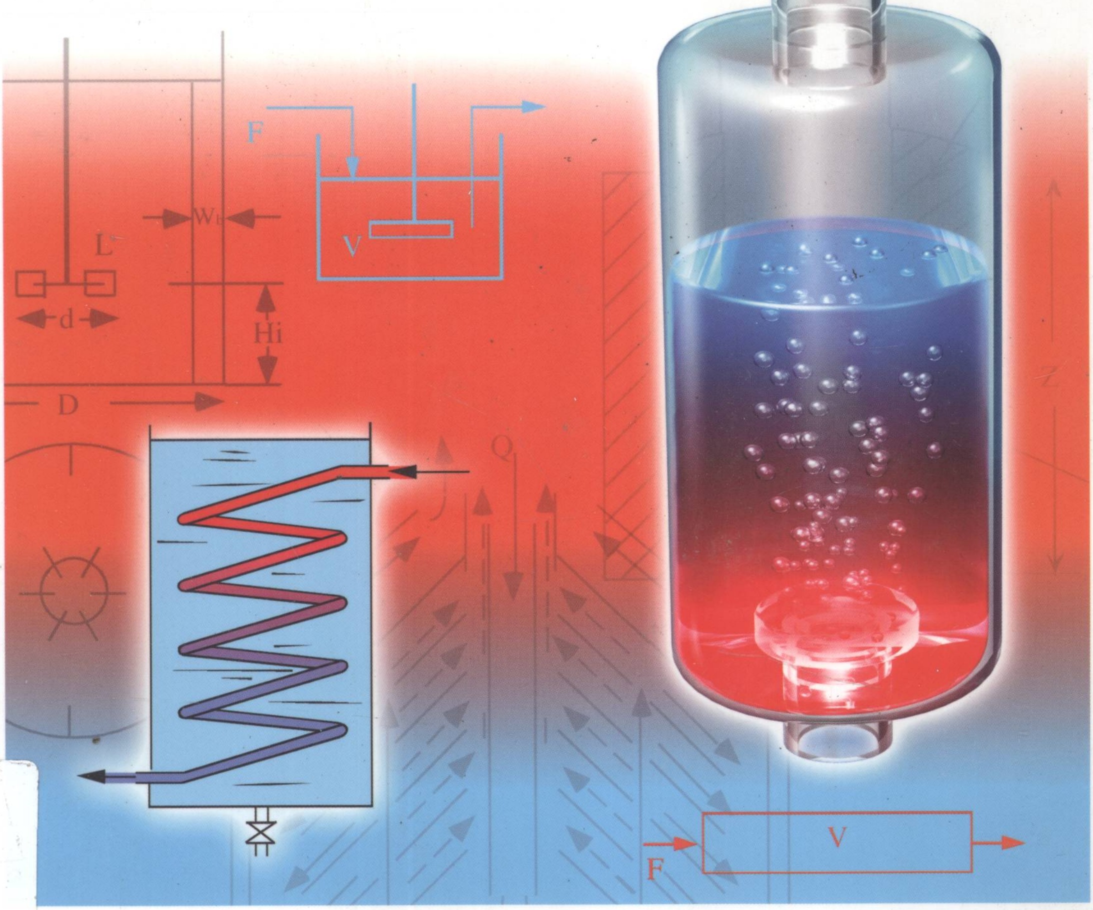
Shigeo Katoh and Fumitake Yoshida

WILEY-VCH

Biochemical Engineering

A Textbook for Engineers, Chemists and Biologists



Shigeo Katoh and Fumitake Yoshida

Biochemical Engineering

A Textbook for Engineers, Chemists and Biologists

WILEY-VCH

WILEY-VCH Verlag GmbH & Co. KGaA

The Authors

Prof. Shigeo Katoh
Kobe University
Graduate School of Science
and Technology
Kobe 657-8501
Japan

Prof. Fumitake Yoshida †
Sakyo-ku Matsugasaki
Yobikaeshi-cho 2
Kyoto 606-0912
Japan

Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek
Die Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at http://dnb.d-nb.de

Printed in the Federal Republic of Germany
Printed on acid-free paper

Cover Design Formgeber, Eppelheim
Typesetting Macmillan Publishing Solutions, Bangalore, India
Printing Strauss GmbH, Mörlenbach
Bookbinding Litges & Dopf Buchbinderei GmbH, Heppenheim

ISBN: 978-3-527-32536-8

Shigeo Katoh and Fumitake Yoshida

Biochemical Engineering

Related Titles

S. Lutz, U.T. Bornscheuer (Eds.)

Protein Engineering Handbook

2009

ISBN: 978-3-527-31850-6

A. Seidel-Morgenstern (Ed.)

Membrane Reactors

Distributing Reactants to Improve Selectivity and Yield

2009

ISBN: 978-3-527-32039-4

S.I. Sandler

Chemical, Biochemical, and Engineering Thermodynamics

2006

ISBN: 978-0-471-66174-0

K. Buchholz, V. Kasche, U.T. Bornscheuer

Biocatalysts and Enzyme Technology

2005

ISBN: 978-3-527-30497-4

Preface

Bioengineering can be defined as the application of the various branches of engineering, including mechanical, electrical, and chemical engineering, to biological systems, including those related to medicine. Likewise, biochemical engineering refers to the application of chemical engineering to biological systems. This book is intended for use by undergraduates, and deals with the applications of chemical engineering to biological systems in general. In that respect, no preliminary knowledge of chemical engineering is assumed.

Since the publication of the pioneering text *Biochemical Engineering*, by Aiba, Humphrey and Mills in 1964, several articles on so-called "biochemical" or "bioprocess" engineering have been published. Whilst all of these have combined the applications of chemical engineering and biochemistry, the relative space allocated to the two disciplines has varied widely among the different texts.

In this book, we describe the application of chemical engineering principles to biological systems, but in doing so assume that the reader has some practical knowledge of biotechnology, but no prior background in chemical engineering. Hence, we have attempted to demonstrate how a typical chemical engineer would address and solve such problems. Consequently, a simplified rather than rigorous approach has often been adopted in order to facilitate an understanding by newcomers to this field of study. Although in Part I of the book we have outlined some very elementary concepts of chemical engineering for those new to the field, the book can be used equally well for senior or even postgraduate level courses in chemical engineering for students of biotechnology, when the reader can simply start from Part II. Naturally, this book should prove especially useful for those biotechnologists interested in self-studying chemical bioengineering. In Part III, we provide descriptions of the applications of biochemical engineering not only to bioprocessing but also to other areas, including the design of selected medical devices. Moreover, to assist progress in learning, a number of worked examples, together with some "homework" problems, are included in each chapter.

I would like to thank the two external reviewers, Prof. Ulfert Onken (Dortmund University) and Prof. Alois Jungbauer (University of Natural Resources and

Biochemical Engineering: A Textbook for Engineers, Chemists and Biologists
Shigeo Katoh and Fumitake Yoshida

ISBN: 978-3-527-32536-8

Applied Life Sciences), for providing invaluable suggestions. I also thank the staff of Wiley-VCH Verlag for planning, editing and producing this book. Finally I thank Kyoko, my wife, for her support while I was writing this book.

Shigeo Katoh

Nomenclature*

A	Area (m^2)
a	Specific interfacial area ($m^2\,m^{-3}$ or m^{-1})
b	Width of rectangular conduit (m)
C	Concentration (kg or kmol m^{-3}, g or mol cm^{-3})
C_n	Cell number density (m^{-3})
C_p	Heat capacity (kcal $°C^{-1}$ or kJ K^{-1})
$\mathbf{C}_x$	Cell mass concentration (kg m^{-3})
Cl	Clearance of kidney or hemodialyzer ($cm^3\,min^{-1}$)
c_p	Specific heat capacity (kJ $kg^{-1}\,K^{-1}$ or kcal $kg^{-1}\,°C^{-1}$)
D	Diffusivity ($m^2\,h^{-1}$ or $cm^2\,s^{-1}$)
$\mathbf{D}$	Tank or column diameter (m)
Dl	Dialysance of hemodialyzer ($cm^3\,min^{-1}$)
d	Diameter (m or cm)
d_e	Equivalent diameter (m or cm)
E	Enhancement factor = k*/k(–)
E	Internal energy (kJ)
E_a	Activation energy (kJ $kmol^{-1}$)
E_D, E_H, E_V	Eddy diffusivity, Eddy thermal diffusivity, and Eddy kinematic viscosity, respectively ($m^2\,h^{-1}$ or $cm^2\,s^{-1}$)
E_f	Effectiveness factor
F	Volumetric flow rate (–) ($m^3\,h^{-1}$ or $cm^3\,s^{-1}$ or min^{-1})
f	Friction factor
G_m	Fluid mass velocity (kg $h^{-1}\,m^{-2}$)
G_V	Volumetric gas flow rate per unit area (m h^{-1})
g	Gravity acceleration (= 9.807 m s^{-2})
H	Henry's law constant (atm or Pa $kmol^{-1}$ (or kg^{-1}) m^3)
H	Height, Height per transfer unit (m)
H	Enthalpy (kJ)
Hs	Height equivalent to an equilibrium stage (–)
Ht	Hematocrit (%)
h	Individual phase film coefficient of heat transfer (W $m^{-2}\,K^{-1}$ or kcal $h^{-1}\,m^{-2}\,°C^{-1}$)

* Some symbols and subscripts explained in the text are omitted.

Biochemical Engineering: A Textbook for Engineers, Chemists and Biologists
Shigeo Katoh and Fumitake Yoshida

ISBN: 978-3-527-32536-8

J	Mass transferf flux (kg or kmol h^{-1} m^{-2})
J_F	Filtrate flux (m s^{-1}, m h^{-1}, cm min^{-1} or cm s^{-1})
K_L	Consistency index (g cm^{-1} s^{n-2} or kg m^{-1} s^{n-2})
K	Overall mass transfer coefficient (m h^{-1} or cm s^{-1})
K	Distribution coefficient, Equilibrium constant (–)
K_m	Michaelis costant (kmol m^{-3} or mol cm^{-3})
k	Individual phase mass transfer coefficient (m h^{-1} or cm s^{-1})
k	Reaction rate constant (s^{-1}, m^3 $kmol^{-1}$ s^{-1} etc.)
k_M	Diffusive membrane permeabilty coefficient (m h^{-1} or cm s^{-1})
L	Length (m or cm)
L_v	Volumetric liquid flow rate per unit area (m h^{-1})
m	Partition coefficient (–)
N	Mass transfer rate per unit volume (kmol or kg h^{-1} m^{-3})
N	Number of revolutions (T^{-1})
N	Number of transfer unit (–)
N	Number of theoretical plates (–)
N_i	Number of moles of i component (kmol)
n	Flow behavior index (–)
n	Cell number (–)
P	Total pressure (Pa or bar)
P	Power requirement (kj s^{-1} or W)
p	Partial pressure (Pa or bar)
Q	Heat transfer rate (kcal/h or kJ/s or W)
Q	Total flow rate (m^3 s^{-1})
q	Heat transfer flux (W m^{-2} or kcal h^{-1} m^{-2})
q_p	Adsorbed amount (kmol kg^{-1})
R	Gas law constant atm l $gmol^{-1}$ K^{-1}, (= 0.08206 kJ $kmol^{-1}$ K^{-1}, etc.)
R	Hydraulic resistance in filtration (= 8.314 m^{-1})
R, **r**	Radius (m or cm)
r_p	Sphere-equivalent particle radius (m or cm)
r_i	Reaction rate of *i* component (kmol m^{-3} s^{-1})
T	Temperature (K)
t	Temperature (°C or K)
t	Time (s)
U	Overall heat transfer coefficient (kcal h^{-1} m^{-2} $°C^{-1}$ or W m^{-2} K^{-1})
U	Superficial velocity (m s^{-1} or cm s^{-1})
u	Velocity (m s^{-1} or cm s^{-1})
V	Volume (m^3)
V_{max}	Maximum reaction rate (kmol m^{-3} s^{-1})
v	Velocity averaged over conduit cross section (m s^{-1} or cm s^{-1})
v_t	Terminal velocity (m s^{-1})
W	Work done to system (kJ/s or W)
W	Mass flow rate per tube (kg s^{-1} or g s^{-1})
W	Peak width (m^3 or s)
w	Weight (kg)

x Thickness of wall or membrne (m or cm)
x_i Mole fraction (–)
x Fractional conversion (–)
$Y_{x/s}$ Cell yield (kg dry cells/kg substrate consumed)
y Distance (m or cm)
y Oxygen saturation (% or –)
Δy_f Effective film thickness (m or cm)
Z Column height (m)
z Height of rectangular conduit of channel (m or cm)

Subscripts

G Gas
i Interface, Inside, Inlet
L Liquid
o Outside, Outlet
0 Initial

Superscripts

* Value in equilibrium with the other phase

Greek letters

α Thermal diffusivity ($m^2 h^{-1}$ or $cm^2 s^{-1}$)
α Specific cake resistance ($m\,kg^{-1}$)
γ Shear rate (s^{-1})
ε Void fraction (–)
ε Gas holdup (–)
ϕ Thiele modulus (–)
κ Thermal conductivity ($W\,m^{-1}\,K^{-1}$ or $kcal\,m^{-1}\,h^{-1}\,°C^{-1}$)
μ Viscosity (Pa s or $g\,cm^{-1}\,s^{-1}$)
μ Specific growth rate (h^{-1})
ν Kinematic viscosity $= \mu/\rho$ ($cm^2 s^{-1}$ or $m^2 h^{-1}$)
Π Osmotic pressure (atm or Pa)
ρ Density ($kg\,m^{-3}$)
σ Surface tension ($kg\,s^{-2}$)
σ Reflection coefficient (–)
σ Standard deviation (–)
τ Shear stress (Pa)
τ Residence time (s)
ω Angular velocity (s^{-1})

Dimensionless numbers

$(Bo) = (g\,D^2\,\rho/\sigma)$	Bond number
$(Da) = (-r_{a,max}/k_L\,A\,C_{ab})$	Damköhler number
$(Fr) = [U_G\,/(g\,D)^{1/2}]$	Froude number
$(Ga) = (g\,D^3/\nu^2)$	Galilei number
$(Gz) = (W\,G_p/\kappa\,L)$	Graetz number
$(Nu) = (h\,d/\kappa)$	Nusselt number
$(Nx) = (F/D\;L)$	Unnamed
$(Pe) = (v\,L/E_D)$	Peclet number
$(Pr) = (c_p\mu/\kappa)$	Prandtl number
$(Re) = (d\,v\,\rho/\mu)$	Reynolds number
$(Sc) = (\mu/\rho\,D)$	Schmidt number
$(Sh) = (k\,d/D)$	Sherwood number
$(St) = (k/v)$ or $(h/c_p\,v\,\rho)$	Stanton number

Contents

Preface *XI*
Nomenclature *XIII*

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*

2 Elements of Physical Transfer Processes *13*
2.1 Introduction *13*
2.2 Heat Conduction and Molecular Diffusion *13*
2.3 Fluid Flow and Momentum Transfer *14*
2.4 Laminar versus Turbulent Flow *18*
2.5 Transfer Phenomena in Turbulent Flow *21*
2.6 Film Coefficients of Heat and Mass Transfer *22*
References *25*

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*

Biochemical Engineering: A Textbook for Engineers, Chemists and Biologists
Shigeo Katoh and Fumitake Yoshida

ISBN: 978-3-527-32536-8

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*

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 *50*
4.5 Cell Growth in Batch Fermentors and Continuous Stirred-Tank Fermentors (CSTF) *52*
4.5.1 Batch Fermentor *52*
4.5.2 Continuous Stirred-Tank Fermentor *54*
References *55*

Part II Unit Operations and Apparatus for Bio-Systems *59*

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) *64*
5.4.2 Forced Flow of Fluids Across a Tube Bank *66*
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 *71*

6 Mass Transfer *73*
6.1 Introduction *73*
6.2 Overall Coefficients κ and Film Coefficients k of Mass Transfer *73*
6.3 Types of Mass Transfer Equipment *77*
6.3.1 Packed Column *77*
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 Columns *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*

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 *101*
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 *107*
7.3.1 Gas Holdup *107*
7.3.2 Interfacial Area *107*
7.3.3 Mass Transfer Coefficients *108*
7.3.3.1 Definitions *109*
7.3.3.2 Measurements of k_La *109*
7.4 Mechanically Stirred Tanks *112*
7.4.1 General *112*
7.4.2 Power Requirements of Stirred Tanks *113*
7.4.2.1 Ungassed Liquids *114*
7.4.2.2 Gas-Sparged Liquids *115*
7.4.3 k_La 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 *120*
7.5 Gas Dispersion in Stirred Tanks *120*
7.6 Bubble Columns *120*
7.6.1 General *121*
7.6.2 Performance of Bubble Columns *121*
7.6.2.1 Gas Holdup *122*
7.6.2.2 k_La *122*
7.6.2.3 Bubble Size *122*

7.6.2.4 Interfacial Area *a* 123
7.6.2.5 k_L 123
7.6.2.6 Other Correlations for k_La 123
7.6.2.7 k_La and Gas Holdup for Suspensions and Emulsions 123
7.7 Airlift Reactors 125
7.7.1 IL Airlifts 125
7.7.2 EL Airlifts 125
7.8 Packed-Bed Reactors 127
7.9 Microreactors [29] 127
References 131

8 Membrane Processes 133
8.1 Introduction 133
8.2 Dialysis 134
8.3 Ultrafiltration 135
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

9 Cell–Liquid Separation and Cell Disruption 145
9.1 Introduction 145
9.2 Conventional Filtration 146
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 the 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 162
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 Multi-Stage 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 178
11.6.3 Resolution Between Two Elution Curves 178
11.6.4 Gel Chromatography 179
11.6.5 Affinity Chromatography 181
References 183

Part III Practical Aspects in Bioengineering 187

12 Fermentor Engineering 187
12.1 Introduction 187
12.2 Stirrer Power Requirements for Non-Newtonian Liquids 189
12.3 Heat Transfer in Fermentors 191
12.4 Gas–Liquid Mass Transfer in Fermentors 193
12.4.1 Special Factors Affecting k_La 194
12.4.1.1 Effects of Electrolytes 194
12.4.1.2 Enhancement Factor 194
12.4.1.3 Presence of Cells 194
12.4.1.4 Effects of Antifoam Agents and Surfactants 195
12.4.1.5 k_La in Emulsions 195
12.4.1.6 k_La in Non-Newtonian Liquids 197
12.4.2 Desorption of Carbon Dioxide 198
12.5 Criteria for Scaling-Up Fermentors 199
12.6 Modes of Fermentor Operation 202
12.6.1 Batch Operation 202
12.6.2 Fed-Batch Operation 203
12.6.3 Continuous Operation 204
12.6.4 Operation of Enzyme Reactors 206
12.7 Fermentors for Animal Cell Culture 207
References 209

13 Downstream Operations in Bioprocesses 211
13.1 Introduction 211
13.2 Separation of Microorganisms by Filtration and Microfiltration 213
13.2.1 Dead-End Filtration 214

13.2.2 Cross-Flow Filtration 216
13.3 Separation by Chromatography 218
13.3.1 Factors Affecting the Performance of Chromatography Columns 218
13.3.1.1 Velocity of Mobile Phase and Diffusivities of Solutes 218
13.3.1.2 Radius of Packed Particles 219
13.3.1.3 Sample Volume Injected 220
13.3.1.4 Column Diameter 220
13.3.2 Scale-Up of Chromatography Columns 221
13.4 Separation in Fixed Beds 222
13.5 Sanitation in Downstream Processes 224
References 209

14 Medical Devices 227
14.1 Introduction 227
14.2 Blood and Its Circulation 227
14.2.1 Blood and Its Components 227
14.2.2 Blood Circulation 228
14.3 Oxygenation of Blood 230
14.3.1 Use of Blood Oxygenators 230
14.3.2 Oxygen in Blood 231
14.3.3 Carbon Dioxide in Blood 233
14.3.4 Types of Blood Oxygenator 234
14.3.5 Oxygen Transfer Rates in Blood Oxygenators 235
14.3.5.1 Laminar Blood Flow 236
14.3.5.2 Turbulent Blood Flow 236
14.3.6 Carbon Dioxide Transfer Rates in Blood Oxygenators 242
14.4 Artificial Kidney 242
14.4.1 Human Kidney Functions 243
14.4.2 Artificial Kidneys 245
14.4.2.1 Hemodialyzer 245
14.4.2.2 Hemofiltration 246
14.4.2.3 Peritoneal Dialysis 246
14.4.3 Mass Transfer in Hemodialyzers (cf. Section 8.2) 247
14.5 Bioartificial Liver 251
14.5.1 Human Liver 251
14.5.2 Bioartificial Liver Devices 251
References 254

Appendix 255

Index 257