

Table of Contents

TABLE OF CONTENTS.....	V
PREFACE.....	XI
PART I PRINCIPLES OF BIOREACTOR MODELLING.....	1
NOMENCLATURE FOR PART I.....	3
1 MODELLING PRINCIPLES.....	9
1.1 FUNDAMENTALS OF MODELLING.....	9
1.1.1 Use of Models for Understanding, Design and Optimization of Bioreactors	9
1.1.2 General Aspects of the Modelling Approach.....	10
1.1.3 General Modelling Procedure.....	72
1.1.4 Simulation Tools.....	75
1.1.5 Teaching Applications.....	75
1.2 DEVELOPMENT AND MEANING OF DYNAMIC DIFFERENTIAL BALANCES. . . .	16
1.3 FORMULATION OF BALANCE EQUATIONS.....	21
1.3.1 Types of Mass Balance Equations.....	27
1.3.2 Balancing Procedure.....	23
1.3.2.1 Case A. Continuous Stirred Tank Bioreactor.....	24
1.3.2.2 Case B. Tubular Reactor.....	24
1.3.2.3 Case C. River with Eddy Current.....	25
1.3.3 Total Mass Balances.....	33
1.3.4 Component Balances for Reacting Systems.....	34
1.3.4.1 Case A. Constant Volume Continuous Stirred Tank Reactor.....	35
1.3.4.2 Case B. Semi-continuous Reactor with Volume Change.....	37
1.3.4.3 Case C. Steady-State Oxygen Balancing in Fermentation.....	38
1.3.4.4 Case D. Inert Gas Balance to Calculate Flow Rates.....	39
1.3.5 Stoichiometry, Elemental Balancing and the Yield Coefficient Concept..	40
1.3.5.1 Simple Stoichiometry.....	40
1.3.5.2 Elemental Balancing.....	42
1.3.5.3 Mass Yield Coefficients.....	44

1.3.5.4	Energy Yield Coefficients.....	45
1.3.6	<i>Equilibrium Relationships</i>	46
1.3.6.1	General Considerations.....	46
1.3.6.2	Case A. Calculation of pH with an Ion Charge Balance.....	47
1.3.7	<i>Energy Balancing for Bioreactors</i>	49
1.3.6.3	Case B. Determining Heat Transfer Area or Cooling Water Temperature.....	52
2	BASIC BIOREACTOR CONCEPTS.....	55
2.1	INFORMATION FOR BIOREACTOR MODELLING.....	55
2.2	BIOREACTOR OPERATION.....	56
2.2.7	<i>Batch Operation</i>	57
2.2.2	<i>Semicontinuous or Fed Batch Operation</i>	58
2.2.3	<i>Continuous Operation</i>	60
2.2.4	<i>Summary and Comparison</i>	63
3	BIOLOGICAL KINETICS.....	67
3.1	ENZYME KINETICS.....	68
3.1.1	<i>Michaelis-Menten Equation</i>	68
3.1.2	<i>Other Enzyme Kinetic Models</i>	73
3.1.3	<i>Deactivation</i>	76
3.1.4	<i>Sterilization</i>	76
3.2	SIMPLE MICROBIAL KINETICS.....	77
3.2.7	<i>Basic Growth Kinetics</i>	77
3.2.2	<i>Substrate Inhibition of Growth</i>	80
3.2.3	<i>Product Inhibition</i>	81
3.2.4	<i>Other Expressions for Specific Growth Rate</i>	81
3.2.5	<i>Substrate Uptake Kinetics</i>	83
3.2.6	<i>Product Formation</i>	85
3.2.7	<i>Interacting Microorganisms</i>	86
3.2.7.1	Case A. Modelling of Mutualism Kinetics.....	88
3.2.7.2	Case B. Kinetics of Anaerobic Degradation.....	89
3.3	STRUCTURED KINETIC MODELS.....	91
3.3.1	<i>Case Studies</i>	93
3.3.1.1	Case C. Modelling Synthesis of Poly- β -hydroxybutyric Acid (PHB).....	93
3.3.1.2	Case D. Modelling of Sustained Oscillations in Continuous Culture.....	94
3.3.1.3	Case E. Growth and Product Formation of an Oxygen-Sensitive <i>Bacillus-subtilis</i> Culture.....	97
4	BIOREACTOR MODELLING.....	101
4.1	GENERAL BALANCES FOR TANK-TYPE BIOLOGICAL REACTORS.....	101
4.1.1	<i>The Batch Fermenter</i>	103
4.1.2	<i>The Chemostat</i>	104
4.1.3	<i>The Fed Batch Fermenter</i>	106
4.1.4	<i>Biomass Productivity</i>	109
4.1.5	<i>Case Studies</i>	109

4.1.5.1	Case A. Continuous Fermentation with Biomass Recycle.....	110
4.1.5.2	Case B. Enzymatic Tanks-in-series Bioreactor System.....	112
4.2	MODELLING TUBULAR PLUG FLOW BIOREACTORS.....	113
4.2.1	Steady-State Balancing.....	113
4.2.2	Unsteady-State Balancing for Tubular Bioreactors.....	115
5	MASS TRANSFER.....	117
5.1	MASS TRANSFER IN BIOLOGICAL REACTORS.....	117
5.1.1	Gas Absorption with Bioreaction in the Liquid Phase.....	117
5.1.2	Liquid-Liquid Extraction with Bioreaction in One Phase.....	118
5.1.3	Surface Biocatalysis.....	118
5.1.4	Diffusion and Reaction in Porous Biocatalyst.....	779
5.2	INTERPHASE GAS-LIQUID MASS TRANSFER.....	119
5.3	GENERAL OXYGEN BALANCES FOR GAS-LIQUID TRANSFER.....	123
5.3.7	Application of Oxygen Balances.....	725
5.3.1.1	Case A. Steady-State Gas Balance for the Biological Uptake Rate.....	125
5.3.1.2	Case B. Determination of $K_L a$ Using the Sulfite Oxidation Reaction.....	126
5.3.1.3	Case C. Determination of $K_L a$ by a Dynamic Method.....	126
5.3.1.4	Case D. Determination of Oxygen Uptake Rates by a Dynamic Method.....	128
5.3.1.5	Case E. Steady-State Liquid Balancing to Determine Oxygen Uptake Rate.....	129
5.3.1.6	Case F. Steady-State Deoxygenated Feed Method for $K_L a$	130
5.3.1.7	Case G. Biological Oxidation in an Aerated Tank.....	131
5.3.1.8	Case H. Modelling Nitrification in a Fluidized Bed Biofilm Reactor.....	133
5.4	MODELS FOR OXYGEN TRANSFER IN LARGE SCALE BIOREACTORS.....	137
5.4.1	Case Studies for Large Scale Bioreactors.....	739
5.4.1.1	Case A. Model for Oxygen Gradients in a Bubble Column Bioreactor.....	139
5.4.1.2	Case B. Model for a Multiple Impeller Fermenter.....	140
6	DIFFUSION AND BIOLOGICAL REACTION IN IMMOBILIZED BIOCATALYST SYSTEMS.....	145
6.1	EXTERNAL MASS TRANSFER.....	146
6.2	INTERNAL DIFFUSION AND REACTION WITHIN BIOCATALYSTS.....	149
6.2.7	Derivation of Finite Difference Model for Diffusion-Reaction Systems.....	151
6.2.2	Dimensionless Parameters from Diffusion-Reaction Models.....	154
6.2.3	The Effectiveness Factor Concept.....	755
6.2.4	Case Studies for Diffusion with Biological Reaction.....	757
6.2.4.1	Case A. Estimation of Oxygen Diffusion Effects in a Biofilm.....	157
6.2.4.2	Case B. Complex Diffusion-Reaction Processes (Biofilm Nitrification)....	157
7	AUTOMATIC BIOPROCESS CONTROL FUNDAMENTALS.....	161
7.1	ELEMENTS OF FEEDBACK CONTROL.....	161
7.2	TYPES OF CONTROLLER ACTION.....	163
7.2.7	On-Off Control.....	163
7.2.2	Proportional (P) Controller.....	164
7.2.3	Proportional-Integral (PI) Controller.....	765

7.2.4	Proportional-Derivative (PD) Controller.....	766
7.2.5	Proportional-Integral-Derivative (PID) Controller.....	767
7.3	CONTROLLER TUNING.....	169
7.3.1	Trial and Error Method.....	769
7.3.2	Ziegler-Nichols Method.....	769
7.3.3	Cohen-Coon Controller Settings.....	770
7.3.4	Ultimate Gain Method.....	777
7.4	ADVANCED CONTROL STRATEGIES.....	172
7.4.1	Cascade Control.....	772
7.4.2	Feed Forward Control.....	775
7.4.3	Adaptive Control.....	174
7.4.4	Sampled-Data Control Systems.....	774
7.5	CONCEPTS FOR BIOPROCESS CONTROL.....	175
7.5.7	Selection of a Control Strategy.....	776
7.5.2	Methods of Designing and Testing the Strategy.....	775
REFERENCES.....		181
REFERENCES CITED IN PART I.....		181
RECOMMENDED TEXTBOOKS AND REFERENCES FOR FURTHER READING.....		184
PART II DYNAMIC BIOPROCESS SIMULATION EXAMPLES AND THE BERKELEY MADONNA SIMULATION LANGUAGE. 191		
8 SIMULATION EXAMPLES OF BIOLOGICAL REACTION PROCESSES USING BERKELEY MADONNA.....193		
8.1	INTRODUCTORY EXAMPLES.....	193
8.1.1	Batch Fermentation (<i>BATFERM</i>).....	795
8.1.2	Chemostat Fermentation (<i>CHEMO</i>).....	799
8.1.3	Fed Batch Fermentation (<i>FEDBAT</i>).....	204
8.2	BATCH REACTORS.....	209
8.2.1	Kinetics of Enzyme Action (<i>MMKINET</i>).....	209
8.2.2	Lineweaver-Burk Plot (<i>LINEWEAV</i>).....	212
8.2.3	Oligosaccharide Production in Enzymatic Lactose Hydrolysis (<i>OLIGO</i>).....	215
8.2.4	Structured Model for <i>PHB</i> Production (<i>PHB</i>).....	279
8.3	FED BATCH REACTORS.....	224
8.3.1	Variable Volume Fermentation (<i>VARVOL</i> and <i>VARVOLD</i>).....	224
8.3.2	Penicillin Fermentation Using Elemental Balancing (<i>PENFERM</i>).....	250
8.3.3	Ethanol Fed Batch <i>Diauxic</i> Fermentation (<i>ETHFERM</i>).....	240
8.3.4	Repeated Fed Batch Culture (<i>REPFED</i>).....	245
8.3.5	Repeated Medium Replacement Culture (<i>REPLCUL</i>).....	249
8.3.6	Penicillin Production in a Fed Batch <i>Fermenter</i> (<i>PENOMY</i>).....	255
8.4	CONTINUOUS REACTORS.....	257
8.4.1	Steady-State Chemostat (<i>CHEMOSTA</i>).....	257
8.4.2	Continuous Culture with Inhibitory Substrate (<i>CONINHIB</i>).....	267
8.4.3	Nitrification in Activated Sludge Process (<i>ACTNITR</i>).....	267

8.4.4	Tubular Enzyme Reactor (<i>ENZTUBE</i>).....	272
8.4.5	Dual Substrate Limitation (<i>DUAL</i>).....	275
8.4.6	Dichloromethane in a Biofilm Fluidized Sand Bed (<i>DCMDEG</i>).....	280
8.4.7	Two-Stage Chemostat with Additional Stream (<i>TWOSTAGE</i>).....	286
8.4.8	Two Stage Culture with Product Inhibition (<i>STAGED</i>).....	290
8.4.9	Fluidized Bed Recycle Reactor (<i>FBR</i>).....	295
8.4.10	Nitrification in a Fluidized Bed Reactor (<i>NITBED</i>).....	299
8.4.11	Continuous Enzymatic Reactor (<i>ENZCON</i>).....	305
8.4.12	Reactor Cascade with Deactivating Enzyme (<i>DEACTENZ</i>).....	308
8.4.13	Production of <i>PHB</i> in a Two-Tank Reactor Process (<i>PHBTWO</i>).....	314
8.5	OXYGEN UPTAKE SYSTEMS.....	318
8.5.1	Aeration of a Tank Reactor for Enzymatic Oxidation (<i>OXENZ</i>).....	318
8.5.2	Gas and Liquid Oxygen Dynamics in a Continuous Fermenter (<i>INHIB</i>).....	321
8.5.3	Batch Nitrification with Oxygen Transfer (<i>NITRIF</i>).....	327
8.5.4	Oxygen Uptake and Aeration Dynamics (<i>OXDYN</i>).....	331
8.5.5	Oxygen Electrode for K_La (<i>KLADYN</i> , <i>KLAFIT</i> and <i>ELECTFIT</i>).....	335
8.5.6	Biofiltration Column with Two Inhibitory Substrates (<i>BIOFILTDYN</i>).....	342
8.5.7	Optical Sensing in Microtiter Plates (<i>T1TERDYN</i> and <i>TITERBIO</i>).....	349
8.6	CONTROLLED REACTORS.....	354
8.6.1	Feedback Control of a Water Heater (<i>TEMPCONT</i>).....	354
8.6.2	Temperature Control of Fermentation (<i>FERMTEMP</i>).....	358
8.6.3	Turbidostat Response (<i>TURBCON</i>).....	363
8.6.4	Control of a Continuous Bioreactor, Inhibitory Substrate (<i>CONTCON</i>).....	367
8.7	DIFFUSION SYSTEMS.....	371
8.7.1	Double Substrate Biofilm Reaction (<i>BIOFILM</i>).....	371
8.7.2	Steady-State Split Boundary Solution (<i>ENZSPLIT</i>).....	377
8.7.3	Dynamic Porous Diffusion and Reaction (<i>ENZDYN</i>).....	383
8.7.4	Oxygen Diffusion in Animal Cells (<i>CELLDIFF</i>).....	388
8.7.5	Biofilm in a Nitrification Column System (<i>NITBEDFILM</i>).....	393
8.8	MULTI-ORGANISM SYSTEMS.....	400
8.8.1	Two Bacteria with Opposite Substrate Preferences (<i>COMMENSA</i>).....	400
8.8.2	Competitive Assimilation and Commensalism (<i>COMPASM</i>).....	406
8.8.3	Stability of Recombinant Microorganisms (<i>PLASMID</i>).....	411
8.8.4	Predator-Prey Population Dynamics (<i>MIXPOP</i>).....	417
8.8.5	Competition Between Organisms (<i>TWOONE</i>).....	422
8.8.6	Competition between Two Microorganisms in a Biofilm (<i>FILMPOP</i>).....	425
8.8.7	Model for Anaerobic Reactor Activity Measurement (<i>ANAEMEAS</i>).....	433
8.8.8	Oscillations in Continuous Yeast Culture (<i>YEASTOSC</i>).....	441
8.8.9	Mammalian Cell Cycle Control (<i>MAMMCELLCYCLE</i>).....	445
8.9	MEMBRANE AND CELL RETENTION REACTORS.....	451
8.9.1	Cell Retention Membrane Reactor (<i>MEMINH</i>).....	451
8.9.2	Fermentation with Pervaporation (<i>SUBTILIS</i>).....	455
8.9.3	Two Stage Fermentor With Cell Recycle (<i>LACMEMRECYC</i>).....	464
8.9.4	Hollow Fiber Enzyme Reactor for Lactose Hydrolysis (<i>LACREACT</i>).....	470
8.9.5	Animal Cells in a Fluidized Bed Reactor (<i>ANIMALIMMOB</i>).....	477

9	APPENDIX: USING THE BERKELEY MADONNA LANGUAGE..	483
9.1	A SHORT GUIDE TO BERKELEY MADONNA.....	483
9.2	SCREENSHOT GUIDE TO BERKELEY MADONNA.....	488
10	ALPHABETICAL LIST OF EXAMPLES.....	497
11	INDEX.....	499