

Table of contents

CONTRIBUTORS	13
1 INTRODUCTION TO FERMENTATION	
1.1 Introduction	15
1.2 Types of fermentation	16
1.2.1 Biomass production	16
1.2.2 Cell products or enzymes	19
1.2.3 Biotransformation	19
1.3 Bioreactor design	19
1.4 Bioreactor process	22
References	25
2 BATCH AND CONTINUOUS GROWTH	
2.1 Growth	26
2.2 Measurement of microbial growth (direct)	29
2.2.1 Cell dry weight measurement	29
2.2.2 Total cell number	32
2.2.3 Viable cell number	34
2.2.4 Absorbance	35
2.2.5 Packed cell volume	37
2.3 Measurement of microbial growth (indirect)	37
2.3.1 Measurement of cellular components	37
2.3.2 Bioluminescence, ATP measurement	38
2.3.3 Substrate consumption or product formation	38
2.3.4 Fluorescence spectroscopy	38
2.3.5 Viscosity	41
2.3.6 Gaseous exchange	42
2.3.7 Impedance	43
2.3.8 Heat evolution	44

2.4	Kinetics of cell growth in batch culture	45
2.4.1	The specific growth rate (μ)	47
2.4.2	The substrate utilization rate	48
2.4.3	Product formation rate	49
2.4.4	Biomass and product yields	50
2.4.5	Productivity	54
2.4.6	The effect of substrate concentration on the specific growth rate (μ)	55
2.4.7	The effect of temperature on growth rate	61
2.4.8	Effect of pH on the growth rate	62
2.5	Continuous culture	63
2.5.1	Chemostat theory	64
2.5.2	The relationship between dilution rate and cell concentration	64
2.5.3	The relationship between dilution rate and substrate concentration	69
2.5.4	The fundamental equations of continuous culture	70
2.5.5	The critical dilution rate	71
2.5.6	Productivity	72
2.5.7	Determination of maximum growth rate and maintenance energy	73
2.5.8	Deviations from ideal chemostat behaviour	74
2.5.9	Modifications to the basic chemostat system	75
2.5.10	Advantages of continuous culture over batch culture	80
2.5.11	Disadvantages of continuous culture compared to batch culture	80
2.5.12	Applications of continuous culture	81
2.5.13	Continuous enrichment culture	81
2.5.14	Fed-batch culture	83
2.5.15	Filamentous organisms	84
2.5.16	List of symbols	85
	References	86

3 MIXING AND MASS TRANSFER

3.1	Introduction	88
3.2	Mass transfer	89
3.2.1	Oxygen transfer	89
3.2.2	Measurement of $K_L a$	91
3.2.2.1	Steady state — oxygen balance method	91
3.2.2.2	Dynamic methods	91
3.2.3	Correlations for $K_L a$ — stirred tanks	92
3.2.4	Correlations for $K_L a$ — airlift bioreactors	94
3.2.5	Gas hold-up	95
3.2.6	Liquid mixing	96
3.3	Theory of mixing	96
3.3.1	Characterization of agitation	97
3.3.2	Types of agitators	99

3.3.3	Agitation in a stirred tank	101
3.3.4	Effect of gas and solids on power consumption	102
3.4	Rheological properties	104
3.4.1	Rheological classification	104
3.4.1.1	Newtonian fluids	105
3.4.1.2	Non-Newtonian fluids	105
3.4.2	Shear in stirred tank bioreactors	106
3.4.2.1	Time average shear or laminar shear	106
3.4.2.2	Turbulent shear	107
3.4.3	Shear in airlift bioreactors	108
3.5	List of symbols	109
	References	110
4	BIOREACTOR DESIGN	
4.1	Introduction	112
4.2	Types of bioreactor	113
4.2.1	Stirred-tank bioreactors	114
4.2.2	Airlift bioreactors	116
4.3	Heat transfer	118
4.4	Scale-up	121
4.4.1	Stirred-tank bioreactors	121
4.4.2	Airlift bioreactors	123
4.5	List of symbols	123
	References	125
5	AIRLIFT BIOREACTORS	
5.1	Introduction	126
5.2	Design and construction of the airlift-loop reactor	126
5.3	Hydrodynamics	128
5.4	Three-phase flow	134
5.5	Mixing	135
5.6	Oxygen transfer	143
5.6.1	Isobaric method	144
5.6.2	Non-isobaric model	145
5.6.3	Oxygen transfer in a three-phase flow	150
5.7	List of symbols	153
	References	155
6	BIOREACTOR INSTRUMENTATION AND CONTROL	
6.1	Introduction	158
6.2	Bioreactor sensor characteristics	160
6.3	Temperature measurement and control	166
6.4	Principles of dissolved oxygen measurement and control	170

6.5	Principles of pH/redox measurement and control	178
6.5.1	pH	178
6.5.2	Redox potential	183
6.6	Detection and prevention of foam	184
6.7	Determination of biomass	186
6.8	Ion-specific electrodes	187
6.9	Biosensors	188
6.10	List of symbols	192
	References	193
7	BIOREACTOR OFF-GAS ANALYSIS	
7.1	Introduction	195
7.2	Generalized gas balance equations	196
7.3	Steady-state balancing	199
7.3.1	Mass balance calculation	200
7.3.2	Sources of error	202
7.4	Derived quantities based on combined gas analysis and gas mass balancing techniques	205
7.4.1	$K_L a$ determination	205
7.4.2	Volumetric uptake and production rates	206
7.4.3	Specific uptake and production rates	206
7.4.4	Integrated uptake and production quantities	206
7.4.5	Yield coefficients	207
7.4.6	Specific growth rate	207
7.4.7	Estimation of biomass, based on carbon balancing	207
7.4.8	Elemental balancing methods	208
7.5	Gas analysers	211
7.6	List of symbols	219
	References	220
8	METHODS AND STRATEGIES FOR FERMENTATION CONTROL	
8.1	Introduction to control	222
8.1.1	The control loop	222
8.1.2	Analogue and digital control	222
8.1.3	The control algorithm — PID control	223
8.1.4	Time-proportioned control	225
8.2	Physical control of the fermentation	226
8.2.1	Temperature	226
8.2.2	Airflow	226
8.2.3	Pressure	227
8.2.4	Agitation	227
8.2.5	pH control	227
8.2.6	Dissolved oxygen	227
8.2.7	Fermenter content	228

8.2.8	Feeding	228
8.2.9	Vent gas analysis	229
8.3	Introduction to computers for control	229
8.3.1	Interfacing	229
8.3.2	The function of the computer for fermentation	229
8.3.3	Sequencing and direct digital control (DDC)	230
8.3.4	Supervisory control	230
8.3.5	Data logging and handling	231
8.4	Control strategy for fermentation	231
8.4.1	Estimation of biomass	232
8.4.2	Handling noisy measurements	232
8.4.3	Biological control — feedback and feedforward	233
8.4.4	Adaptive control and adaptive models	233
8.4.5	Fault diagnosis	234
8.4.6	The empirical approach to improved control	234
8.5	List of symbols	235
	General references	236
9	MODELLING AND SIMULATION OF FERMENTATION PROCESSES	
9.1	Modelling	237
9.2	Digital simulation	240
9.3	Formulation and solution of problems by simulations	240
9.4	Numerical solution	242
9.5	Digital simulation programming languages	243
9.6	ISIM (interactive simulation language)	243
9.7	List of symbols	251
	References	253
10	STERILIZATION	
10.1	Introduction	254
10.2	Microbial death	254
10.3	Effect of temperature on death rate	255
10.4	Decimal reduction time	257
10.5	Batch sterilization cycle	261
10.6	Moist heat, steam	263
10.7	Large-scale sterilization	264
10.8	Continuous sterilization	265
10.8.1	Steam injection	265
10.8.2	Indirect steam heating	266
10.9	Filtration	268
10.9.1	Depth filters	268
10.9.2	Exclusion filters	268
10.10	Other methods of sterilization	268
10.10.1	Dry heat	268
10.10.2	Pasteurization and Tyndallization	269

10.10.3	Chemicals	269
10.10.4	Ionizing radiation	269
10.11	List of symbols	270
	References	270
11	PLANT AND ANIMAL CELL BIOREACTORS	
11.1	Introduction	271
11.2	Plant cells	272
11.2.1	Plant cell bioreactors	272
11.2.2	Characteristics of plant cell suspensions	273
11.2.3	Plant cell bioreactor requirements	276
11.2.4	Plant cell bioreactor design	278
11.2.5	Plant cell bioreactor operation	279
11.2.6	Alternative cultures for plant cells	281
	References	283
11.3	Animal cells	287
11.3.1	Animal cell bioreactors	287
11.3.2	Animal cell bioreactor operation	289
11.3.3	Animal cell bioreactor design	291
11.3.3.1	Attached growth systems	291
11.3.3.2	Suspended growth systems	294
11.3.3.3	Immobilized cell systems	296
	References	298
12	EXPERIMENTAL RESULTS	
12.1	Introduction	302
12.2	Aerobic batch culture of <i>Saccharomyces cerevisiae</i> , using 2% glucose as a carbon source	302
12.2.1	Calibration of pH probes	302
12.2.2	Calibration of dissolved oxygen probes	303
12.2.3	Sampling	304
12.2.4	Absorbance	304
12.2.5	Dry weight determinations	304
12.2.6	Total cell number	306
12.2.7	Viable cell count	307
12.2.8	Ethanol determinations	309
12.2.9	Glucose determinations	310
12.2.10	Experimental results	311
12.2.11	Alternative cultures	314
12.3	Continuous culture: the chemostat culture of <i>Saccharomyces cerevisiae</i> growing under glucose limitation	315
12.3.1	Determination of the culture volume of a chemostat	316
12.3.2	Procedure	318
12.3.3	Experimental results	319

12.3.4	Determination of $\mu_{\max}$ by wash-out	322
12.4	Determination of mixing times in bioreactors	323
12.5	Determination of overall oxygen transfer coefficient (K_{La})	324
12.5.1	Procedure	324

INDEX	328
-------	-----

Dr S. W. Carley-Smith	Department of Chemical Engineering City School of Engineering West Sussex BN14 4GH, UK
Dr K. C. Chitt	Department of Mechanical and Process Engineering University of Strathclyde Sheffield S1 2SN, UK
Dr I. J. Dunn	Technische Universiteit Delft, P.O. Box 5046 2600 CA Delft, The Netherlands
Dr F. J. Ingham	Department of Chemical Engineering University of Bradford Bradford BD7 1ET, UK
Dr I. W. Marison	Institute of Chemical Engineering Switzerland Institute of Technology CH-8570 Fribourg, Switzerland
Dr A. H. Sleg	Department of Chemical Engineering University of Twente Enschede 7500, The Netherlands
Dr P. Verhaert	TNO Caroten, P.O. Box 8000 3720 GA Wageningen, The Netherlands RAB AA Wageningen, The Netherlands RAB AN Wageningen, The Netherlands