

# Contents

## Part I Mammalian Cells

<b>1 Mammalian Cell Culture Technology: An Emerging Field</b> .....	3
D. Eibl, R. Eibl, and R. Pörtner	
1.1 Definition and History.....	3
1.2 Fields of Application and Products from Mammalian Cells.....	6
1.3 Future Prospects .....	8
1.4 Exercises.....	9
References .....	9
Complementary Reading.....	11
<b>2 Characteristics of Mammalian Cells and Requirements for Cultivation</b> .....	13
R. Pörtner	
2.1 Differences Between Mammalian Cells, Plant Cells and Microbes: Consequences of These Differences .....	13
2.2 Types of Mammalian Cells .....	14
2.2.1 From Primary Cells to Permanent (Established) Cell Lines .....	15
2.2.2 Hybridom Cells for Production of Monoclonal Antibodies .....	17
2.2.3 Culture Collections and Cell Banking.....	20
2.3 Culture Media .....	21
2.4 Characteristics of Cell Growth and Metabolism.....	24
2.4.1 Short Introduction to Cell Metabolism .....	24
2.4.2 Glucose, Glutamine and Amino Acids as Carbon and Energy Source .....	26
2.4.3 The Effects of Lactate and Ammonia .....	29
2.4.4 Oxygen Uptake and Carbon Dioxide Production.....	31
2.5 Kinetic Modelling of Cell Growth and Metabolism .....	32
2.5.1 Introduction to Kinetic Modelling for Mammalian Cells .....	32
2.5.2 Set-Up of an Unstructured Model.....	33

2.5.3	Structured Models .....	44
2.5.4	Conclusions for Set-Up of a Kinetic Model.....	45
2.6	Questions and Problems.....	46
	List of Symbols .....	47
	References.....	47
	Complementary Reading .....	53
<b>3</b>	<b>Bioreactors for Mammalian Cells: General Overview.....</b>	<b>55</b>
	D. Eibl and R. Eibl	
3.1	Technical Terminology: Bioreactor/Fermentor, Bioreactor Facility.....	56
3.2	Suitable Bioreactor Types for Mammalian Cell Cultures.....	57
3.2.1	Categorization, Functional Principle, Possible Fields of Application.....	57
3.2.2	Bioreactor Trends and the Increasing Acceptance of Disposables .....	66
3.3	Special Case: Bioreactors for Patient-Specific Therapies Based on Functional Tissue and Stem Cells.....	69
3.3.1	Bioreactors for Growing 3D Tissues.....	70
3.3.2	Bioreactors for Large-Scale Expansion and Differentiation of Stem Cells.....	72
3.4	Conclusions.....	73
3.5	Questions and Problems.....	74
	List of Abbreviations and Symbols.....	74
	References.....	75
	Complementary Reading .....	82
<b>4</b>	<b>Special Engineering Aspects .....</b>	<b>83</b>
	P. Czermak, R. Pörtner, and A. Brix	
4.1	Cell Damage by Shear and Aeration.....	83
4.1.1	General Aspects .....	83
4.1.2	Model Analysis .....	85
4.1.3	Cell Damage in Bioreactors .....	92
4.2	Oxygen Supply.....	102
4.2.1	Introduction .....	102
4.2.2	Limitations for Oxygen Transfer.....	105
4.2.3	Oxygen Supply Systems (Aeration Systems) .....	108
4.2.4	Consequences for Reactor Design and Operation.....	120
4.3	Immobilization of Cells .....	122
4.3.1	Carriers for Cell Immobilization .....	123
4.3.2	Encapsulation .....	134

4.4	Culture Modes.....	136
4.4.1	Principles of Culture Modes.....	136
4.4.2	Examples of Different Culture Modes .....	141
4.4.3	Process Strategies for Fed-Batch .....	147
4.4.4	Process Strategies Applied in Industrial Processes .....	149
4.5	Monitoring and Controlling in Animal Cell Culture .....	152
4.5.1	Temperature.....	152
4.5.2	pH.....	153
4.5.3	Oxygen Partial Pressure .....	154
4.5.4	Carbon Dioxide Partial Pressure .....	156
4.5.5	Metabolites and Products .....	156
4.5.6	Cell Density and Viability .....	159
4.5.7	Agitation.....	160
4.6	Questions and Problems.....	160
4.6.1	Problem .....	160
4.6.2	Problem .....	160
	List of Symbols .....	162
	References.....	164
	Complementary Reading .....	171
<b>5</b>	<b>Bioreactor Design and Scale-Up.....</b>	<b>173</b>
	G. Catapano, P. Czermak, R. Eibl, D. Eibl, and R. Pörtner	
5.1	Bioreactor Design .....	173
5.1.1	Bioreactors for Suspended Cells .....	176
5.1.2	Fixed Bed and Fluidized Bed Bioreactors: Design, Performance and Scale-Up.....	199
5.1.3	Membrane Bioreactors .....	217
5.1.4	Disposable Bioreactors.....	242
5.2	Selection of Bioreactor and Operation Mode .....	245
5.3	How to Grow Mammalian Cells from Cryopreserved Vial to Production Bioreactor.....	246
5.4	Questions and Problems.....	249
	List of Symbols .....	250
	References.....	253
	Complementary Reading .....	259
<b>Part II Special Applications</b>		
<b>6</b>	<b>Insect Cell-Based Recombinant Protein Production.....</b>	<b>263</b>
	W. Weber and M. Fussenegger	
6.1	Insect Cell Culture .....	263
6.2	Special Aspects: Engineering Baculoviruses as Vectors.....	264
6.3	Bioreactor Concepts.....	267

6.4	Process Design .....	268
6.4.1	Optimization of Nutrient Supply .....	268
6.4.2	Optimization of Production Kinetics .....	268
6.5	Applications .....	270
6.6	Current Trends in Insect Cell-Based Protein Production .....	270
6.6.1	Elimination of Product Protein Proteolysis .....	273
6.7	Limitations .....	273
	References .....	274
	Complementary Reading .....	276
<b>7</b>	<b>Bioreactors for Bioartificial Organs</b> .....	<b>279</b>
	G. Catapano	
7.1	Introduction.....	279
7.2	Cells for Bioartificial Organs .....	280
7.2.1	Expression of the Adult Cell Phenotype .....	283
7.3	Bioreactor Design for Bioartificial Organs .....	285
7.3.1	Extravascular (EV) Bioreactors .....	289
7.3.2	Intravascular (IV) Bioreactors.....	295
7.3.3	Membrane Immunoprotection in Bioartificial Organs .....	302
7.4	Commercial Bioreactors and Applications .....	304
	List of Symbols .....	310
	References.....	311
<b>8</b>	<b>Plant Cell-Based Bioprocessing</b> .....	<b>315</b>
	R. Eibl and D. Eibl	
8.1	Plant Cell Culture Basics .....	316
8.1.1	Characteristics of Plant Cells and Culture Conditions .....	316
8.1.2	Media.....	317
8.1.3	Plant Cell Culture Types and Their In Vitro Initiation.....	319
8.1.4	Routine Working Methods in Plant Cell Cultivation .....	326
8.2	Bioreactors for Plant Cell Cultures .....	330
8.2.1	General Considerations .....	330
8.2.2	Suitable Bioreactors for Plant Cell Suspension Cultures .....	332
8.2.3	Suitable Bioreactors for Hairy Roots .....	335
8.3	Approaches to Improving Productivity in Plant Cell-Based Bioprocessing.....	340
8.4	Application Examples and Potential Active Agent Candidates .....	342
8.5	Conclusions.....	343
8.6	Questions and Problems.....	344

Contents	xi
List of Abbreviations and Symbols.....	345
References.....	347
Complementary Reading .....	356
<b>Index</b> .....	<b>357</b>