国外名校名著

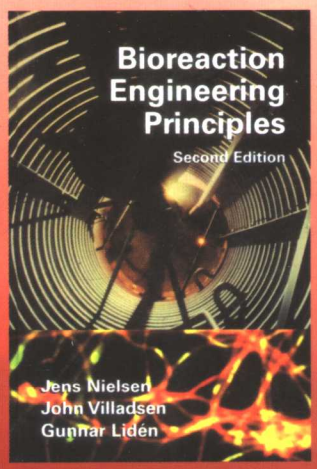
BIOREACTION ENGINEERING PRINCIPLES

Second Edition

生物反应工程原理

第二版（英文影印版）

Jens Nielsen, John Villadsen, Gunnar Lidén



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前　言

随着中国社会主义现代化建设进入新的阶段，以高质量的高等教育培养千百万专门人才，迎接新世纪的挑战，是实现“科教兴国”战略的基础工程，也是完成“十五”计划各项奋斗目标的重要保证。为切实加强高等学校本科教学并提高教学质量，教育部于2001年专门下发文件提出12条意见，对高等学校教学工作从认识、管理、教师队伍到教学方法和教学手段等给予指导。文件强调，按照“教育要面向现代化、面向世界、面向未来”的要求，为适应经济全球化和科技国际化的挑战，本科教育要创造条件使用英语等外语进行公共课和专业课教学。

在文件精神指导下，全国普通高等学校尤其是重点高校中兴起了使用国外教材开展教学活动的潮流。如生物技术与工程、环境科学与工程、材料科学与工程及作为其学科基础理论重要组成部分的化学技术和化学工程技术又是这股潮流中最为活跃的领域之一。在教育部“化工类专业人才培养方案及教学内容体系改革的研究与实践”项目组及“化工类专业创新人才培养模式、教学内容、教学方法和教学技术改革的研究与实践”项目组和“全国本科化学工程与工艺专业教学指导委员会”的指导和支持下，化学工业出版社及时启动了引进国外名校名著的教材工程。

出版社组织编辑人员多次赴国外学习考察，通过国外出版研究机构对国外著名的高等学校进行调查研究，搜集了一大批国际知名院校的现用教材选题。他们还联络国内重点高校的专家学者组建了“国外名校名著评价委员会”，对国外和国内高等本科教学进行比较研究，对教材内容质量进行审查评议，然后决定是否引进。他们与国外许多著名的出版机构建立了联系，有的还建立了长期合作关系，以掌握世界范围内优秀教材的出版动态。

以其化学化工专业领域的优势资源为基础，化学工业出版社的教材引进主要涉及化学、化学工程与工艺、环境科学与工程、生物技术与工程、材料科学与工程、制药工程等专业，对过程装备与控制工程、自动化等传统专业教材的引进也在规划之中。

他们在影印、翻译出版国外教材的过程中，注意学习国外教材出版的经验，提高编辑素质，密切编读联系，整合课程体系，更新教材内容，科学设计版面，提高印装质量，更好地为教育服务。

在化工版“国外名校名著”系列教材即将问世之际，我们不仅感谢化学工业出版社为高等教育所做的努力，更应赞赏他们严谨认真的工作作风。

中国科学院院士，天津大学教授

余国琮

2002年8月

Preface

This is the second edition of the text "Bioreaction Engineering Principles" by Jens Nielsen and John Villadsen, originally published in 1994 by Plenum Press (now part of Kluwer).

Time runs fast in Biotechnology, and when Kluwer Plenum stopped reprinting the first edition and asked us to make a second, revised edition we happily accepted. A text on bioreactions written in the early 1990's will not reflect the enormous development of experimental as well as theoretical aspects of cellular reactions during the past decade.

In the preface to the first edition we admitted to be newcomers in the field. One of us (JV) has had 10 more years of job training in biotechnology, and the younger author (JN) has now received international recognition for his work with the hottest topics of "modern" biotechnology. Furthermore we are happy to have induced Gunnar Lidén, professor of chemical reaction engineering at our sister university in Lund, Sweden to join us as co-author of the second edition. His contribution, especially on the chemical engineering aspects of "real" bioreactors has been of the greatest value.

Chapter 8 of the present edition is largely unchanged from the first edition. We wish to thank professor Martin Hjortso from LSU for his substantial help with this chapter.

As was the case for the first edition numerous people helped us by carefully reviewing individual chapters. Professor Lars K Nielsen of University of Queensland was a constant sparring partner, both in Australia and lately as a visiting professor at DTU. The help of Dr. Mats Åkesson and of our PhD students, in particular Mikkel Nordkvist, Thomas Grotkjær, Jochen Förster and Morten Skov Hansen is also gratefully acknowledged. MSc student Rebecca Munk Vejborg was of great help in her careful editing of the final version of the manuscript.

All three authors are chemical engineers by education, and we followed in the footsteps of other chemical engineers who "converted" to biotechnology, but retained their passion for a quantitative treatment of problems from the physical world. One of the greatest innovators of biochemical engineering, professor James E. Bailey was also a chemical engineer by education. We wish to dedicate this book to the memory of this eminent scientist, who was a close colleague and a friend (of the senior author for more than 35 years), and whose work is admired by all three of us. If the pages of this book could inspire some students in the way Jay Bailey inspired hundreds of chemical engineering and biochemical engineering students we could hope for no better reward.

John Villadsen and Jens Nielsen
BioCentrum-DTU

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List of Symbols

Symbols that are defined and used only within a particular Example, Note, or Problem are not listed. It should be noted that a few symbols are used for different purposes in different chapters. For this reason more than one definition may apply for a given symbol.

a	Cell age (h)
a	Specific interfacial area (m^2 per m^3 of medium)
a_d	Specific interfacial area (m^2 per m^3 of gas-liquid dispersion)
a_{cell}	Specific cell surface area (m^2 per gram dry weight)
$\mathbf{A}$	Matrix of stoichiometric coefficients for substrates, introduced in Eq. 7.2
$b(y)$	Breakage frequency (h^{-1})
Bi	Biot number, given by Eq. (10.59)
$\mathbf{B}$	Matrix of stoichiometric coefficients for metabolic products, introduced in Eq. 7.2
c_i	Concentration of the ith chemical compound (kg m^{-3})
c_i^*	Saturation concentration of the ith chemical compound (kg m^{-3})
c	Vector of concentrations (kg m^{-3})
C_{ij}	Concentration control coefficient of the jth intermediate with respect to the activity of the ith enzyme
C_i^J	Flux control coefficient with respect to the activity of the ith enzyme
$\mathbf{C}^*$	Matrix containing the control coefficients [defined in Eq. (6.44)]
d_b	Bubble diameter (m)
δ_f	Thickness of liquid film (m)
d_{mean}	Mean bubble diameter (m)
d_{mem}	Lipid membrane thickness (m)
d_s	Stirrer diameter (m)
d_{Sauter}	Mean Sauter bubble diameter (m), given by Eq. (10.18)
D	Dilution rate (h^{-1}), given by Eq. (3.1)
D_{max}	Maximum dilution rate (h^{-1})
D_{mem}	Diffusion coefficient in a lipid membrane (m^2 s^{-1})
D_{eff}	Effective diffusion coefficient (m^2 s^{-1})
D_i	Diffusion coefficient of the ith chemical compound (m^2 s^{-1})
Da	Damköhler number, given by Eq. (10.37)
e_0	Enzyme concentration (g enzyme L^{-1})
E_g	Activation energy of the growth process in Eq. (7.27)
$\mathbf{E}$	Elemental matrix for all compounds
$\mathbf{E_c}$	Elemental matrix for calculated compounds
$\mathbf{E_m}$	Elemental matrix for measured compounds
$f(y,t)$	Distribution function for cells with property y in the population, Eq. (8.1)
$\mathbf{F}$	Variance-covariance matrix
g	Gravity (m s^{-2})
G	Gibbs free energy (kJ $mole^{-1}$)
G^0	Gibbs free energy at standard conditions (kJ $mole^{-1}$)
ΔG_{ci}	Gibbs free energy of combustion of the ith reaction component (kJ $mole^{-1}$)

ΔG_d	Gibbs free energy of denaturation (kJ mole^{-1}), Eq. (7.28)
ΔG^0_{ci}	Gibbs free energy of combustion of the *i*th reaction component at standard conditions (kJ mole^{-1})
ΔG^0_f	Gibbs free energy of formation at standard conditions (kJ mole^{-1})
Gr	Grashof number, defined in Table 10.6
h	Test function, given by Eq. (3.52)
$h(y)$	Net rate of formation of cells with property y upon cell division (cells h^{-1})
$h^+(y)$	Rate of formation of cells with property y upon cell division (cells h^{-1})
$h^-(y)$	Rate of disappearance of cells with property y uponcell division (cells h^{-1})
H_A	Henry's constant for compound A (atm L mole^{-1})
ΔH_{ci}	Enthalpy of combustion of the ith reaction component (kJ mole^{-1})
ΔH^0_f	Enthalpy of formation (kJ mole^{-1})
$\mathbf{I}$	Identity matrix (diagonal matrix with 1 in the diagonal)
$\mathbf{J}$	Jacobian matrix, Eq. (9.102)
k_0	Enzyme activity (g substrate [g enzyme]$^{-1}$ h^{-1})
k_i	Rate constant (e.g. kg kg^{-1} h^{-1})
k_g	Mass transfer coefficient for gas film (e.g. mole atm^{-1} s^{-1} m^{-2})
k_l	Mass transfer coefficient for a liquid film surrounding a gas bubble (m s^{-1})
k_la	Volumetric mass transfer coefficient (s^{-1})
k_s	Mass transfer coefficient for a liquid film surrounding a solid particle (m s^{-1})
K_a	Acid dissociation constant (moles L^{-1})
K_l	Overall mass transfer coefficient for gas-liquid mass transfer (m s^{-1})
K	Partition coefficient
K_{eq}	Equilibrium constant
K_m	Michaelis constant (g L^{-1}), Eq. (6.1)
m	Amount of biomass (kg)
m	Degree of mixing, defined in Eq. (11.1)
m_{ATP}	Maintenance-associated ATP consumption (moles ATP [kg DW]$^{-1}$ h^{-1})
m_s	Maintenance-associated specific substrate consumption (kg [kg DW]$^{-1}$ h^{-1})
$M_n(t)$	The *n*th moment of a one-dimensional distribution function, given by Eq. (8.9)
n	Number of cells per unit volume (cells m^{-3}), Eq. (8.1)
N	Stirring speed (s^{-1})
N_A	Aeration number, defined in Eq. (11.9)
N_f	Flow number
N_p	Power number, defined in Eq. (11.5)
p	Extracellular metabolic product concentration (kg m^{-3})
p_A	Partial pressure of compound A (e.g. atm)
$p(y, y^*, t)$	Partitioning function, Eq. (8.5)
P_i	Productivity of species *i* in a chemostat (e.g. kg m^{-3} h^{-1})
P	Dimensionless metabolic product concentration
P	Permeability coefficient (m s^{-1})
P	Power input to a bioreactor (W)
P_g	Power input to a bioreactor at gassed conditions (W)
$\mathbf{P}$	Variance-covariance matrix for the residuals, given by Eq. (3.46)
Pe	Peclet number, defined in Table 10.6
q^t_A	Volumetric rate of transfer of A from gas to liquid (moles L^{-1} h^{-1})
$q_{A,Obs}$	Observed volumetric formation rate of A (kg m^{-3} h^{-1}), Eq. (10.45)
q_x	Volumetric rate of formation of biomass (kg DW m^{-3} h^{-1})
$\mathbf{q}$	Volumetric rate vector (kg m^{-3} h^{-1})
$\mathbf{q}^t$	Vector of volumetric mass transfer rates (kg m^{-3} h^{-1})

Q	Number of morphological forms
Q	Heat of reaction (kJ mole^{-1})
Q_1	Fraction of repressor-free operators, given by Eq. (7.52)
Q_2	Fraction of promotors being activated, given by Eq. (7.58)
Q_3	Fraction of promoters, which form complexes with RNA polymerase, in Eq. (7.60)
r	Specific reaction rate (kg [kg DW]$^{-1}$ h^{-1})
r	Enzymatic reaction rate (Chapter 6) (g substrate L^{-1} h^{-1})
r_{ATP}	Specific ATP synthesis rate (moles of ATP [kg DW]$^{-1}$ h^{-1})
$\mathbf{r}$	Specific reaction rate vector (kg [kg DW]$^{-1}$ h^{-1})
$\mathbf{r}_s$	Specific substrate formation rate vector (kg [kg DW]$^{-1}$ h^{-1})
$\mathbf{r}_p$	Specific product formation rate vector (kg [kg DW]$^{-1}$ h^{-1})
$\mathbf{r}_x$	Specific formation rate vector of biomass constituents (kg [kg DW]$^{-1}$ h^{-1})
$\mathbf{r}(\mathbf{y},t)$	Vector containing the rates of change of properties, in Eq. (8.2)
R	Gas constant (=8.314 J K^{-1} mole^{-1})
R	Recirculation factor
$\mathbf{R}$	Redundancy matrix, given by Eq. (3.39)
$\mathbf{R}_r$	Reduced redundancy matrix
Re	Reynolds number, defined in Table 10.6
s	Extracellular substrate concentration (kg m^{-3})
$\mathbf{s}$	Extracellular substrate concentration vector (kg m^{-3})
s_f	Substrate concentration in the feed to the bioreactor (kg m^{-3})
S	Dimensionless substrate concentration
ΔS	Entropy change (kJ mole^{-1} K^{-1})
Sc	Schmidt number, defined in Table 10.6
Sh	Sherwood number, defined in Table 10.6
t	Time (h)
t_c	Circulation time (s)
t_m	Mixing time (s)
T	Temperature (K)
$\mathbf{T}$	Total stoichiometric matrix
$\mathbf{T}_1$	Stoichiometric matrix corresponding to non-measured rates in rows of $\mathbf{T}^T$
$\mathbf{T}_2$	Stoichiometric matrix corresponding to known rates of $\mathbf{T}^T$
u_b	Bubble rise velocity (m s^{-1})
u_i	Cybernetic variable, given by Eq. (7.41)
u_s	Superficial gas velocity (m s^{-1})
$\mathbf{u}$	Vector containing the specific rates of the metamorphosis reaction (kg kg^{-1} h^{-1})
v	Liquid flow (m^3 h^{-1})
v_e	Liquid effluent flow from the reactor (m^3 h^{-1})
v_f	Liquid feed to the reactor (m^3 h^{-1})
v_g	Gas flow (m^3 h^{-1})
v_i	Flux of reaction i (kg [kg DW]$^{-1}$ h^{-1})
v_{pump}	Impeller induced flow (m^3 s^{-1})
$\mathbf{v}$	Flux vector, i.e. vector of specific intracellular reaction rates (kg [kg DW]$^{-1}$ h^{-1})
V	Volume (m^3)
V_d	Total volume of gas-liquid dispersion (m^3)
V_g	Dispersed gas volume (m^3)
V_l	Liquid volume (m^3)
V_y	Total property space, Eq. (8.2)
w_i	Cybernetic variable, given by Eq. (7.42)
x	Biomass concentration (kg m^{-3})
X	Dimensionless biomass concentration

X_i	Concentration of the ith intracellular component (kg [kg DW]$^{-1}$)
$\mathbf{X}$	Vector of concentrations of intracellular biomass components (kg [kg DW]$^{-1}$)
$\mathbf{y}$	Property state vector
Y_{ij}	Yield coefficient of *j* from *i* (kg *j* per kg of *i* or C-mole of *j* per kg of *i)*
Y_{xATP}	ATP consumption for biomass formation (moles of ATP [kg DW]$^{-1}$)
Z_i	Concentration of the ith morphological form (kg [kg DW]$^{-1}$)

Greek Letters

α_{ji}	Stoichiometric coefficients for substrate i in intracellular reaction j
β_{ji}	Stoichiometric coefficient for metabolic product i in intracellular reaction i
$\dot{\gamma}$	Shear rate (s^{-1})
γ_{ji}	Stoichiometric coefficient for intracellular component *i* in intracellular reaction *j*
Γ	Matrices containing the stoichiometric coefficients for intracellular biomass components
δ	Vector of measurement errors in Eq. (3.41)
Δ	Matrix for stoichiometric coefficients for morphological forms
ε	Gas holdup (m^3 of gas per m^3 of gas-liquid dispersion)
ε	Porosity of a pellet
ε_{ji}	Elasticity coefficients, defined in Eq. (6.37)
ε	Vector of residuals in Eq. (3.44)
E	Matrix containing the elasticity coefficients
η	Dynamic viscosity (kg m^{-1} s^{-1})
η_{eff}	Internal effectiveness factor, defined in Eq. (10.46)
π_i	Partial pressure of compound i (atm)
θ	Dimensionless time
κ_i	Degree of reduction of the *i*th compound
μ	The specific growth rate of biomass (h^{-1})
μ_{max}	The maximum specific growth rate (h^{-1})
μ_q	The specific growth rate for the *q*th morphological form (kg DW [kg DW]$^{-1}$ h^{-1})
ρ_{cell}	Cell density (kg wet biomass [m^{-3} cell])
ρ_l	Liquid density (kg m^{-3})
σ	Surface tension (N m^{-1})
σ^2	Variance
τ	Space time in reactor (h)
τ_s	Shear stress (N m^{-2})
τ_t	Tortuosity factor, used in Eq. (10.43)
Φ	Thiele modulus, given by Eq. (10.49)
Φ_{gen}	Generalized Thiele modulus, given by Eq. (10.55)
$\psi(X)$	Distribution function of cells, Eq (8.8)

Abbreviations

ADP	Adenosine diphosphate
AMP	Adenosine monophosphate
ATP	Adenosine triphosphate
CoA	Coenzyme A
DNA	Deoxyribonucleic acid
E_c	Energy charge

EMP	Embden-Meyerhof-Parnas
FAD	Flavin adenine dinucleotide (oxidized form)
FADH,	Flavin adenine dinucleotide (reduced form)
FDA	Food and Drug Administration
F6P	Fructose-6-phosphate
GTP	Guanosine triphosphate
G6P	Glucose-6-phosphate
MCA	Metabolic control analysis
NAD+	Nicotinamide adenine dinucleotide (oxidized form)
NADH	Nicotinamide adenine dinucleotide (reduced form)
NADP+	Nicotinamide adenine dinucleotide phosphate (oxidized form)
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced form)
PEP	Phosphoenol pyruvate
PP	Pentose phosphate
PSS	Protein synthesizing system
PTS	Phosphotransferase system
PYR	Pyruvate
P/O ratio	Number of molecules of ATP formed per atom of oxygen used in the oxidative phosphorylation
RNA	Ribonucleic acid
mRNA	Messenger RNA
rRNA	Ribosomal RNA
tRNA	Transfer RNA
RQ	Respiratory quotient
R5P	Ribose-5-phosphate
TCA	Tricarboxylic acid
UQ	Ubiquinone

Contents

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1

Bioreaction Engineering: From Bioprocess Design to Systems Biology

Biotechnology is a key factor in the development and implementation of processes for the manufacture of new food products, animal feedstuffs, pharmaceuticals, and a number of speciality products through the application of microbiology, enzyme technology, and engineering disciplines such as reaction engineering and separation technology. With the introduction of the so-called "new" biotechnologies since 1970, directed manipulation of the cell's genetic machinery through recombinant DNA techniques and cell fusion became possible. This has fundamentally expanded the potential for biological systems to make important biological molecules that cannot be produced by other means. Existing industrial organisms can be systematically altered to produce useful products in cost-efficient and environmentally acceptable ways. Thus, progress in genetic engineering has led to directed genetic changes through recombinant DNA technology, which allows a far more rational approach to strain improvement than by classical methods. This is referred to as *metabolic engineering* (Bailey, 1991), and in recent years, metabolic engineering has been applied for improvement of many different microbial fermentation processes (Ostergaard *et al.*, 2000; Nielsen, 2001). Initially, metabolic engineering was simply the technological manifestation of molecular biology, but with the rapid development in new analytical techniques, in cloning techniques, and in theoretical tools for analysis of biological data, it has become possible to rapidly introduce directed genetic changes and subsequently analyze the consequences of the introduced changes at the cellular level. Often the analysis will point towards an additional genetic change that may be required to further improve the cellular performance, and metabolic engineering therefore involves a cyclic operation with a close integration between analysis of the cellular function and genetic engineering.

The pervasive influence that biotechnology is bound to have on everyday life in the 21st century is recognized by scientists, industrialists, and politicians in industrialized countries and certainly also in the less industrially developed countries of the world, where biotechnology will lead to revolutionary changes in traditional agricultural economies. In order to reap the benefits of development in biology there is, however, an urgent need for industrial microbiologists with experience in solving quantitative problems, particularly as applied to industrial bioreactors. Such persons have traditionally been referred to as biochemical engineers or bioprocess engineers. They should ideally combine a generalist's knowledge of the major topics in molecular biology, microbial physiology, and process engineering with an expert's insight into one particular field.

Traditionally biochemical engineers had an important function in the design and scale up of bioprocesses. Today they are heavily involved also in the very early design phase of a new process, as it has become of utmost importance to apply an integrated process design wherein the prospective production organism is made fit for large scale operation even at the early stages of laboratory strain development. Thus, biochemical engineers have been very active in the rapid progress of metabolic engineering. Teams of engineers and biologists will be responsible for the implementation of an integrated approach to process design. It is therefore important that main stream biologists obtain some insight into quantitative analysis of cellular function and bioreactor operation, and that biochemical engineers continue to learn more about fundamental biological processes.

Besides their role in process design and in metabolic engineering, biochemical engineers must also play an increasing part in fundamental biological research. The genome of a large number of organisms has been completely sequenced, and it has become a major research goal both to assign function to all genes in the genome, referred to as *functional genomics*, and to understand how all the components within the cellular system interact. This can only be done through the use of complex mathematical models, and this field is referred to as *systems biology* (see Fig. 1.1).

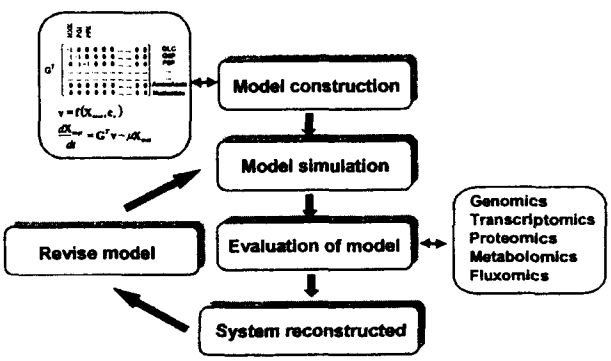

Figure 1.1 Schematic representation of systems biology.
Based on empirical data and knowledge of cellular function a mathematical model is proposed. The model is used to simulate the overall cell function, and model simulations are compared with experimental data. Experimental data may be obtained from: 1) Genomics; information about the genomic sequence; 2) Transcriptomics; data on the expression of all genes obtained by measurement of the complete mRNA pool using DNA arrays; 3) Proteomics; data on all available proteins in the cell obtained by 2D-gel electrophoresis or protein chips; 4) Metabolomics; data on the metabolite profiles inside the cells are obtained using different analytical techniques; and 5) Fluxomics; fluxes through all the cellular reactions are quantified. If there is a good fit between experimental data and model simulations the model is likely to be a good representation of the biological system, which can therefore be reconstructed from its essential parts. A poor fit shows that the model needs to be revised, and often the discrepancy between model simulations and the experimental data will point to where the model needs to be revised [Adapted from Nielsen and Olsson (2002)].

Table 1.1 Definition of research areas where biochemical engineers play an important role

Term	Definition
Bioprocess design	The overall design of a bioprocess. This involves both design of the equipment to be used in the process and quantitative evaluation of how the process is to be operated most efficiently. A key element in scale up of processes from laboratory scale to industrial scale.
Metabolic engineering	The use of directed genetic modification to improve the properties of a given cell, *e.g.* improved yield or productivity, expanded substrate range, and production of novel products. Quantitative analysis of cellular function plays an important role in this field.
Functional genomics	The qualitative assignment of function to open reading frames (ORFs). This includes assignment of function to ORFs that have been identified but have no known function as well as assignment of additional functions to ORFs with already assigned functions. With the interaction of many different processes it is necessary to consider interactions between the many different components, and this may require quantitative analysis
Systems biology	Description of overall cell function through a quantitative study of the interaction between all the individual components in the system (the cell), *e.g.* gene transcription, translation, protein-protein interaction, enzyme catalysis of biochemical reactions, and receptor-metabolite interaction. With a detailed description of the individual molecular events it is also possible to consider cell-cell interactions, and hereby whole cultures can be quantitatively described.

In the future it is expected that the distance will be very short between fundamental discoveries and process design, and biochemical engineers will play an important role in the different research fields mentioned above. Table 1.1 gives our definition of these different areas.

1.1 The Structure of the Book

The present text has been named *Bioreaction Engineering Principles*, and it is the second edition of a textbook that was first published in 1994. The text has been extensively rewritten and many new topics are included. The goal is the same as in the original text: To provide students and industrial researchers with some of the tools needed to analyze, and by analysis to improve the outcome of a bioreaction process. The book can by no means claim to present the desired integrated view of the whole bioprocess from selection of the strain to the downstream processing and further to the final marketable product (separation processes are entirely absent from the text). Our focus is on the central unit of the bioprocess, the bioreactor and the processes that occur in the reactor. Basically a bioreaction can be divided into two parts: operation of the cell factory and the interaction of the cell factories with each other and the environment imposed via operation of the bioreactor. With the

above mentioned developments in metabolic engineering and systems biology a fundamental understanding of the cell factory, i.e. how the cells function at different environmental conditions, has become even more important, not only for design of bioreactions but also to gain detailed insight into cellular function. Whether one wants to improve a bioprocess or to understand cellular function at a fundamental level the tools are to a large extent the same. However, as will be discussed in Chapter 7 the structure of the model used to describe cellular function depends on the purpose of the study.

What the text does – hopefully in a useful manner – is to integrate the concepts of mathematical modeling on reasonably general systems with some of the fundamental aspects of microbial physiology. The cell is the ultimate reactor, and everything that is going to come out of this reactor has to pass the boundary between the cell and the environment. But what happens inside the cell, in the *biotic phase*, is intimately coupled with the conditions in the environment, the *abiotic phase*. Therefore the coupling between cell and environment must be given a very serious treatment, although much idealization is necessary in order to obtain a model of reasonable complexity that can still be used to study certain general features of bioreactions. The real bioreaction system is an immensely complicated agglomerate of three phases – gas, liquid, and solid – with concentration gradients and time constants of greatly different magnitudes. This system is beyond the scope of any textbook; it is in fact hardly touched upon in front-line research papers. But the individual steps of a bioreaction, transport to or from the cells, and mixing in a vessel can be treated and will be illustrated with numerous examples, most of which are simple enough to be solved without recourse to a computer (and therefore perhaps better suited to impart the understanding of the underlying mechanisms).

The intended target group for this textbook is students who have studied both natural sciences and engineering sciences. This includes most students following a chemical engineering curriculum. Some knowledge of biology will be advantageous, but not mandatory for reading the book. The book divides the topic into several different themes, as illustrated in Fig. 1.2. It is of little use to investigate the kinetics of bioreactions without a certain appreciation of the biochemistry of living organisms. The ingestion of substrate components from the abiotic medium and the fate of a substrate as it is being converted through metabolic pathways must be known, and the widely different product distribution under varying environmental conditions must be recognized. Most chemical engineering students and all microbiologists and biochemists have a working knowledge of the major pathways of microorganisms. Still, a brief summary of the subject is given in Chapter 2, which at the same time gives an introduction to design of biotech processes. A cursory study of the many examples dispersed throughout the book may give the impression that *Escherichia coli*, *Saccharomyces cerevisiae*, lactic acid bacteria, and certain filamentous fungi are our favored microbial species, but it is important to emphasize that the concepts described in this textbook are equally well suited to analyze also other cellular systems, i.e. other microbes, cell cultures, plants, animal cells and even human cells.

It is often painful to analyze kinetic data from industrial (or, indeed, academic) research where the mass balances do not even approximately close. A microorganism grows and produces metabolites from substrates. Since all the input carbon and nitrogen must be found in one of the effluents from the bioreactor, the biomass, the remaining substrates or the metabolic products, it appears to be

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