Development of Sustainable Bioprocesses
Modeling and Assessment

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Dedicated To Our Families and Our Students
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Preface

This book is intended to provide a framework for the development of sustainable bioprocesses. It includes methods for assessing both the economic and environmental aspects of biotechnological processes and illustrates their application in a series of case studies covering a broad range of products. Bioprocesses have accompanied human development from very early times. Currently, bioprocesses are gaining increased attention because of their enormous potential for the production of high-value products, especially in human health care and because of their inherent attribute as sustainable processes. New bio-industries have potential as efficient processes based on renewable resources characterized by minimal pollution. Modern methods of enzyme optimization and metabolic engineering are powerful tools for the development of novel efficient biocatalysts. The development of new bioprocesses is enhanced by the application of modern process modeling and simulation techniques, combined with assessment methods that are applied systematically in the very early phases of process development. Future sustainability essentially depends on the ability of industry to develop new processes which are (i) short- and long-term commercially successful, which (ii) at the same time are environmentally friendly using minimal resources that are preferably renewable and constitute a minimal environmental burden, and which (iii) generally satisfy the needs of society.

This book attempts to provide integrating frameworks in a manner useful to both the student in chemical and biochemical engineering, and the scientist and engineer engaged in process development. As time-to-market is a criterion of ever increasing importance, methods are needed which can deliver superior results in a short time. This is of central importance for professionals working in industries applying bioprocesses. Such professionals may be biochemical, chemical, and process engineers, but also biologists, chemists, environmental managers, and business economists. This book may also assist graduate and postgraduate students of economics, as well as environmental sciences. The intent is to
assist both students and professionals by providing a condensed introduction into the basic theory of bioprocess modeling and sustainability assessment methods, combined with typical case studies. The book is intended to supplement more comprehensive texts on process economics, biochemical reaction engineering, and bioseparation processes. The case studies are supplemented with fully operational models, which are all supplied on the accompanying CD. The models are built using the software SuperPro Designer™ which is kindly supplied by Intelligen, Inc. (Scotch Plains, NJ, USA) in a version that allows running all examples. These case studies make the book particularly attractive to practitioners who would like to start modeling from an already well developed similar case to shorten development time. The only prerequisites required to be able to follow the book immediately is a basic understanding of bioprocesses and basic economic principles. The reader lacking this background is guided to literature filling these knowledge gaps.

We believe the book is unique in providing (i) an introduction to bioprocess modeling in combination with economic and environmental assessment methods, which both are important in a world with limited resources and increasing environmental pollution; (ii) the book cuts across multiple process industries, including pharmaceutical, biochemicals, chemicals, and food production. The methods presented are broadly applicable in all these fields; (iii) the book also addresses risk and uncertainty analysis, which are particularly important in early process and product development. These methods will help to efficiently direct research and development efforts, to reduce the risk of later stage failures, and to put decision-making on a fundamental basis; (iv) the unique set of case examples from various parts of biotechnology improves the understanding of this technology and provides a starting point for developing one’s own specific model.

**Organization of the Book**

The book consists of two parts. The first part presents the essential, necessary theory, and part two consists of 11 case studies covering a broad range of bio-industries.

Chapter 1 starts with a short introduction to bioprocesses, outlining the expected future potential of biotechnological processing. This chapter also highlights the importance of modeling and simulation for developing sustainable bioprocesses.

Chapter 2, characterizing the development of bioprocesses, describes types of bioprocesses, raw materials, and bioproducts. Then, essentials of bioreaction stoichiometry, thermodynamics, and kinetics are introduced. The elements of bioprocesses described comprise those of upstream processing, bioreaction, downstream processing, utilities, and also waste treatment and recycling. This chapter is concluded by the description of the development process including managerial issues.

Chapter 3 provides a hands-on approach on setting up a process model and simulating it. This starts with problem structuring, process analysis, and setting up a process scheme. Then the implementation into a computer model is illustrated. This chapter concludes with methods of uncertainty analysis comprising scenario analysis, sensitivity analysis, and Monte Carlo simulations.

An integral part of the book is sustainability assessment, and a problem-oriented approach to process development is described in Chapter 4. The economic assessment follows standard procedures, as already included in SuperPro Designer™. The environmental
assessment, which is primarily based on mass and energy balances of the process, uses an ABC method developed for such types of problems. Social assessment and safety are briefly addressed but not incorporated in the case studies.

The second part describes 11 case studies which originate from our own work and from various persons around the world who used modeling tools for bioprocesses and who kindly accepted our invitation to contribute to this book. All process model examples are implemented into SuperPro Designer™. An attached CD-ROM contains the process models described in the book. The models are selected such that characteristic examples of each application area covered are comprized. These major areas of bioprocess industries covered include bulk biochemicals, fine chemicals, enzymes, and low- and high-molecular-weight pharmaceuticals. These elaborate examples are of inestimable value in providing a quick hands-on approach, which will be highly welcomed both by students and professionals already working in bioprocess industries.

The authors’ different backgrounds help to cover the broad field. Prof. Charles L. Cooney from the Chemical Engineering Department at MIT in Cambridge, Massachusetts, USA has extended experience in chemical and biochemical engineering. He initiated the creation of SuperPro Designer™ during the PhD work of Demetri Petrides, who is now chief executive of Intelligen, Inc. Throughout his career he closely cooperated with firms actively engaged in biochemical process development. Prof. Elmar Heinzle from the Biochemical Engineering Institute of the Saarland University, Germany studied Applied Chemistry at the Technical University of Graz, Austria and specialized in Biochemical Engineering. During his time at the Swiss Federal Institute of Technology (ETH), Zurich, Switzerland and at the Saarland University he also closely cooperated with various chemical and biochemical industries and was involved in process modeling and assessment. He was also engaged with modeling biochemical kinetics and reactors throughout his carrier and published two books with Drs I.J. Dunn, J. Ingham and J.E. Prenosil [Ingham, J., Dunn, I.J., Heinzle, E., Prenosil, J.E. (2000): Chemical Engineering Dynamics. An Introduction to Modelling and Computer Simulation, 2nd Edition, Wiley-VCH; Weinheim; Dunn, I.J., Heinzle, E., Ingham, J., Prenosil, J.E. (2003): Biological Reaction Engineering. Dynamic Modelling Fundamentals with Simulation Exercises. Wiley-VCH; Weinheim]. These books stimulated the organization of this book combining 50% basic theory with 50% case studies supplied as executable computer programs on an attached CD. Dr Arno Biwer studied biogeography at the Saarland University, where he made his PhD in the field of modeling and assessment of biotechnological processes. After a postdoctoral stay at MIT with Prof. C.L. Cooney, he moved back to the Saarland University to put together the book presented here.

The authors hope that they can contribute to the establishment of sustainable bioprocesses, which have a great potential to serve human needs and at the same time help to efficiently use renewable resources and to prevent pollution of our limited natural environment. The authors would be very grateful for any comments on the book. Please, use the corresponding web site http://www.uni-saarland.de/dsbp.
Acknowledgments

We greatly appreciate the financial support from the Deutsche Bundesstiftung Umwelt (DBU). This substantial support allowed Dr Biwer to fully dedicate his energy to this project for half a year. We are especially grateful to Prof. Stephanie Heiden from DBU, who was fascinated by this project from the very beginning and whose support was essential to complete this book. We are particularly grateful to all authors who contributed with most valuable case studies. We think that these case studies contain an invaluable wealth of information and support for students and experts setting up relevant process models. We thank Dr Demetri Petrides from Intelligen, Inc. who contributed a running version of SuperPro Designer™, a necessary platform to permit running the book’s process models. We are very grateful to Dr Irving Dunn from ETH Zurich for reading the manuscript and making many very useful suggestions for improvement. We thank Dr Urs Saner from Roche for useful advice concerning aspects of economic assessment. We thank Erik Geibel who did a great job putting all figures in a perfect shape. We also appreciate the support from John Wiley & Sons, Ltd., particularly Lyn Roberts who helped initiate this project and Lynette James who accompanied and supported our work in the second phase.
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Part I

Theoretical Introduction
1

Introduction

1.1 Bioprocesses

1.1.1 History of Biotechnology and Today’s Situation

Biotechnological processes have been essential for human survival and for satisfying various needs throughout human culture. Table 1.1 gives a short overview of the history of biotechnology. Early biotechnological processes that use microorganisms to produce a certain product have been used for several thousand years. The Egyptians brewed beer and baked bread in the 4th millennium BC. A basic purification step, the distillation of ethanol, was applied in the 2nd millennium BC in China. Modern biotechnology was started in the 19th century when general knowledge about biological systems, their components, and interactions between them grew [1.1]. In the first half of the 20th century the first large-scale fermentation processes, namely citric acid and penicillin, were realized. The progress of recombinant gene technology then led to a substantial increase in the number of bioprocesses and their production volume starting with insulin, the first product manufactured with recombinant technology, in the early 1980s.

While the first bioprocesses exclusively used fungi, bacteria and yeasts, the industrial production was later extended with the application of enzymes and mammalian cells. Other biocatalysts like plant and insect cells, and transgenic plants and animals were added to the available platform of technologies but are much less used in production so far. In parallel, fermentation and downstream technologies were further developed and the engineering knowledge about designing bioprocesses grew significantly.

Today, the bioindustries have reached a critical size and are additionally based on a broad understanding of genomics, proteomics, bioinformatics, genetic transformation, and molecular breeding. Table 1.2 shows the industries where bioprocesses are applied today. These different industries are reflected in the case studies in the second part of the book. The present worldwide sales of bioprocess products are reported to range between 13 and 60 billion dollars, depending on the source [1.2–1.4]. The share of the different product
### Table 1.1: Milestones in the History of Biotechnology (data taken largely from [1.2] and [1.5])

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>4th/3rd mill. BC</td>
<td>Baking, brewing (Egypt)</td>
</tr>
<tr>
<td>2nd mill. BC</td>
<td>Ethanol distillation (China)</td>
</tr>
<tr>
<td>17th century</td>
<td>Invention of microscope (A. von Leeuwenhoek, Netherlands)</td>
</tr>
<tr>
<td>18th century</td>
<td>First vaccination in Europe (cowpox) (E. Jenner, UK). Heat sterilization of food and organic material (Spallanzani, Italy)</td>
</tr>
<tr>
<td>1860–1890</td>
<td>Most amino acids isolated, first tyrosine (J. von Liebig, Germany)</td>
</tr>
<tr>
<td>1890s</td>
<td>In vivo synthesis and extraction of hormones from animal tissue</td>
</tr>
<tr>
<td>1921</td>
<td>Insulin isolated from pig pancreas (Toronto, Canada)</td>
</tr>
<tr>
<td>1920s</td>
<td>Mutation of microorganisms by X-rays and chemicals (e.g. H.J. Mueller, USA)</td>
</tr>
<tr>
<td>1923</td>
<td>Commercial production of citric acid (Pfizer, USA)</td>
</tr>
<tr>
<td>1940s</td>
<td>Production of penicillin by fermentation (USA)</td>
</tr>
<tr>
<td>1950s</td>
<td>Design and scale-up of large aerated fermenters. Elucidation of principles of sterile air filtration</td>
</tr>
<tr>
<td>1953</td>
<td>Discovery of the double helix of DNA (J. Watson and F. Crick, USA)</td>
</tr>
<tr>
<td>1972</td>
<td>Restriction enzymes (W. Arber, Switzerland)</td>
</tr>
<tr>
<td>1973</td>
<td>First recombinant DNA organism (S. Cohen and H. Boyer, USA)</td>
</tr>
<tr>
<td>1975</td>
<td>Monoclonal antibodies (G.J.F. Köhler and C. Milstein, UK/Germany)</td>
</tr>
<tr>
<td>1976</td>
<td>Genentech first specialist biotech company</td>
</tr>
<tr>
<td>1980s</td>
<td>Polymerase chain reaction (PCR). Large-scale protein purification from recombinant microorganisms</td>
</tr>
<tr>
<td>1982</td>
<td>First rDNA vaccine approved in Europe</td>
</tr>
<tr>
<td>1986</td>
<td>Release of genetically engineered plant</td>
</tr>
<tr>
<td>1995</td>
<td>First bacterial genome sequenced (<em>Haemophilus influenzae</em>)</td>
</tr>
<tr>
<td>1998</td>
<td>Isolation of human embryonic stem cells</td>
</tr>
<tr>
<td>2000/2001</td>
<td>Human genome sequenced</td>
</tr>
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</table>

The share of bioproducts differs from industry to industry. Some products are provided almost exclusively by bioprocesses, e.g. amino acids like lysine and glutamate, carboxylic acids, e.g. citric and lactic acid, and vitamins, e.g. vitamin B2 and vitamin C. One focus of bioprocesses is the pharmaceutical industry. Since the introduction of the centralized European drug-approval system in 1995, recombinant proteins count for 36% of all new drug approvals [1.6]. More than 100 new drugs and vaccines produced by bioprocesses have been brought to market since the mid 1970s and more than 400 are in clinical trials—the highest number ever [1.2, 1.5]. The average process development from laboratory to final...
Table 1.2  Process industries versus process types. MO = microorganisms (bacteria, yeasts, fungi)

<table>
<thead>
<tr>
<th>Industry</th>
<th>Scale</th>
<th>Downstream complexity</th>
<th>Biocatalyst</th>
<th>Products</th>
<th>Biotech market share</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic chemicals</td>
<td>very large</td>
<td>low</td>
<td>MO/enzymes</td>
<td>organic small molecules</td>
<td>very low</td>
</tr>
<tr>
<td>Fine chemicals</td>
<td>medium</td>
<td>medium</td>
<td>MO/enzymes</td>
<td>organic small molecules</td>
<td>low</td>
</tr>
<tr>
<td>Detergents</td>
<td>large</td>
<td>low</td>
<td>MO</td>
<td>enzymes</td>
<td>medium</td>
</tr>
<tr>
<td>Health care/cosmetics</td>
<td>small–medium</td>
<td>medium–high</td>
<td>MO/enzymes/mammalian cells</td>
<td>proteins and small molecules</td>
<td>medium</td>
</tr>
<tr>
<td>Pharma</td>
<td>medium</td>
<td>high</td>
<td>MO/mammalian cells, MO</td>
<td>organic small molecules proteins</td>
<td>low–medium</td>
</tr>
<tr>
<td>conventional biopharma</td>
<td>small</td>
<td>high</td>
<td>MO/mammalian cells, MO</td>
<td>proteins</td>
<td>medium high</td>
</tr>
<tr>
<td>Food/feed</td>
<td>very large</td>
<td>medium</td>
<td>MO/enzymes</td>
<td>proteins and others</td>
<td>medium</td>
</tr>
<tr>
<td>Metal mining</td>
<td>very large</td>
<td>low</td>
<td>MO</td>
<td>metals/metal compounds</td>
<td>very low</td>
</tr>
<tr>
<td>Waste treatment</td>
<td>very large</td>
<td>low</td>
<td>MO</td>
<td>Purified water, air, and soil</td>
<td>high</td>
</tr>
</tbody>
</table>
Table 1.3 Market volume of bioproduct groups. Estimated overall sales were $60 billion in 2000 (\(\approx\) 100\%) (Data from [1.4])

<table>
<thead>
<tr>
<th>Bioproduct group</th>
<th>Share of bioproduct sales (%)</th>
<th>Typical products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>42</td>
<td>penicillins, cephalosporins</td>
</tr>
<tr>
<td>Therapeutic proteins</td>
<td>25</td>
<td>interferon, insulin, antibodies</td>
</tr>
<tr>
<td>Other pharma- and animal</td>
<td></td>
<td>steroids, alkaloids</td>
</tr>
<tr>
<td>health products</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amino acids</td>
<td>8</td>
<td>lysine, glutamate</td>
</tr>
<tr>
<td>Enzymes</td>
<td>3</td>
<td>proteases, cellulases, amylases</td>
</tr>
<tr>
<td>Organic acids</td>
<td>3</td>
<td>lactic acid, citric acid</td>
</tr>
<tr>
<td>Vitamins</td>
<td>1</td>
<td>B2, B12, biotin</td>
</tr>
<tr>
<td>Polysaccharides</td>
<td>1</td>
<td>xanthan, dextran</td>
</tr>
</tbody>
</table>

Approval takes 10–15 years and costs $300–800 million [1.5]. A short but comprehensive overview of present biotechnological production is provided in the book of R. Schmid [1.7].

1.1.2 Future Perspectives

The last decade brought an enormous stimulation from biological sciences combined with informatics, e.g. the genome sequences of man, plants, and microorganisms or the isolation of human stem cells. However, this knowledge waits to be transformed to technology and market products. The knowledge of molecular breeding, stem cell technology and pharmagenomics might lead to strongly personalized therapies and therapeutics.

It can be expected that biocatalysts such as insect and plant cells and transgenic plants and animals sooner or later will reach a much broader applicability, although this might not happen in the next decade. The increased use of extremophiles and their enzymes and biocatalysis in non-aqueous solution will broaden the technology platform for bioprocesses. Apart from the recombinant technology, the naturally occurring organisms also provide a huge reservoir of new products, e.g. the almost endless variety of plants, insects, and microorganisms in the tropical rain forests.

The share of bioprocesses in the different industries will rise substantially during the next decades. Additionally, bioprocesses will be used in industries where they are not used today or where only lab-scale processes are developed, e.g. the production of new materials with new properties that mimic natural materials. It is expected that the combination of biotechnology, nanotechnology, and information technology will lead to a substantial rate of progress and expansion [1.2]. The use of information technology has already led to improvements in the screening and development of new drugs and in the understanding of biological systems (bioinformatics). It might also lead to bio-chips for computers that replace silicon-based chips.

In the chemical industry it is expected that the sales from bioprocesses will rise to $310 billion in 2010 and will than account for more than 20\% of the overall sales of that industry [1.3]. Here, an increase is mainly expected for fine chemicals, especially chiral products. Compared with the chemical industry the bioindustries are still immature and production costs are relatively high. Therefore, not only do the strains and fermentations