

# Part I

## Theoretical Introduction

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# 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

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**Table 1.1** Milestones in the history of biotechnology (data taken largely from [1.2] and [1.5])

Time	Event
4th/3rd mill. BC	Baking, brewing (Egypt)
2nd mill. BC	Ethanol distillation (China)
17th century	Invention of microscope (A. von Leeuwenhoek, Netherlands)
18th century	First vaccination in Europe (cowpox) (E. Jenner, UK). Heat sterilization of food and organic material (Spallanzani, Italy)
1860–1890	Most amino acids isolated, first tyrosine (J. von Liebig, Germany)
1890s	<i>In vivo</i> synthesis and extraction of hormones from animal tissue
1921	Insulin isolated from pig pancreas (Toronto, Canada)
1920s	Mutation of microorganisms by X-rays and chemicals (e.g. H.J. Mueller, USA)
1923	Commercial production of citric acid (Pfizer, USA)
1940s	Production of penicillin by fermentation (USA)
1950s	Design and scale-up of large aerated fermenters. Elucidation of principles of sterile air filtration
1953	Discovery of the double helix of DNA (J. Watson and F. Crick, USA)
1972	Restriction enzymes (W. Arber, Switzerland)
1973	First recombinant DNA organism (S. Cohen and H. Boyer, USA)
1975	Monoclonal antibodies (G.J.F. Köhler and C. Milstein, UK/Germany)
1976	Genentech first specialist biotech company
1980s	Polymerase chain reaction (PCR). Large-scale protein purification from recombinant microorganisms
1982/1983	First genetically engineered product: human insulin (Eli Lilly/Genentech)
1982	First rDNA vaccine approved in Europe
1986	Release of genetically engineered plant
1995	First bacterial genome sequenced ( <i>Haemophilus influenzae</i> )
1998	Isolation of human embryonic stem cells
2000/2001	Human genome sequenced

groups on these sales is shown in Table 1.3, where antibiotics and therapeutic proteins dominate due to their relatively high prices.

In 2000, there were 1270 bioscience companies in the U.S. and 1180 in the EU [1.5]. The six largest of them had revenues of \$8 billion and invested 20–37% of their revenues in research and development (R&D). The average investment spending for the pharmaceutical industries is 9–18%. The overall R&D spending in biotechnology was \$37 billion in 2000, with an expected growth rate of 30% per year [1.5].

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)

Industry	Scale	Downstream complexity	Biocatalyst	Products	Biotech market share
<b>Basic chemicals</b>	very large	low	MO/enzymes	organic small molecules	very low
<b>Fine chemicals</b>	medium	medium	MO/enzymes	organic small molecules	low
<b>Detergents</b>	large	low	MO	enzymes	medium
<b>Health care/cosmetics</b>	small–medium	medium–high	MO/enzymes/ mammalian cells	proteins and small molecules	medium
<b>Pharma</b>					
<b>conventional biopharma</b>	medium	medium–high	MO	organic small molecules	low–
	small	high	mammalian cells, MO	proteins	medium
<b>Food/feed</b>	very large	medium	MO/enzymes	proteins and others	medium
<b>Metal mining</b>	very large	low	MO	metals/metal compounds	very low
<b>Waste treatment</b>	very large	low	MO	Purified water, air, and soil	high

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**Table 1.3** Market volume of bioproduct groups. Estimated overall sales were \$60 billion in 2000 (= 100%) (Data from [1.4])

Bioproduct group	Share of bioproduct sales (%)	Typical products
Antibiotics	42	penicillins, cephalosporins
Therapeutic proteins	25	interferon, insulin, antibodies
Other pharma- and animal health products	17	steroids, alkaloids
Amino acids	8	lysine, glutamate
Enzymes	3	proteases, cellulases, amylases
Organic acids	3	lactic acid, citric acid
Vitamins	1	B2, B12, biotin
Polysaccharides	1	xanthan, dextran

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.

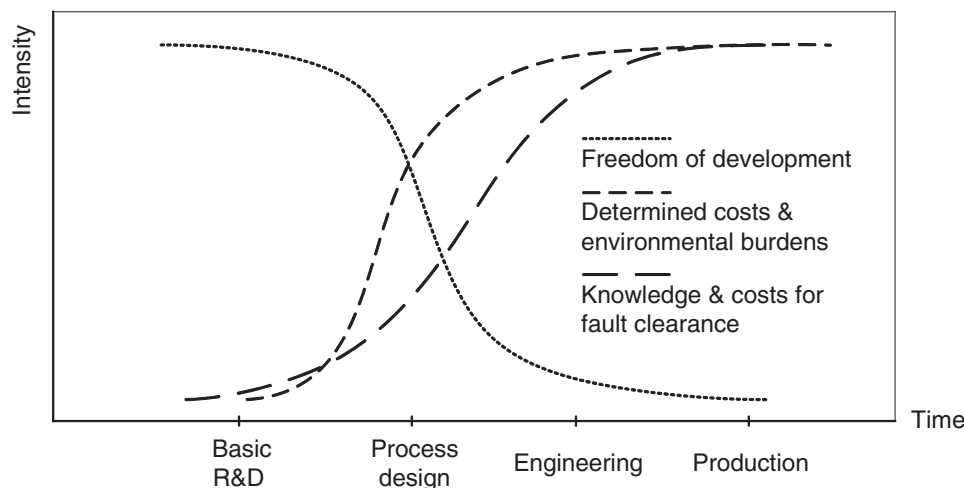
In the chemical industry it is expected that the sales from bioprocesses will rise to \$310 billion in 2010 and will then account for more than 20% of the overall sales of that industry [1.3]. Here, an increase is mainly expected for fine chemicals, especially chiral products. Compared with the chemical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

have to be optimized and production scales increased, but also a substantial progress in downstream technologies is necessary. Modeling, simulation, and accompanying sustainability assessment will play a crucial role in achieving a full exploitation of the potential of bioprocessing.

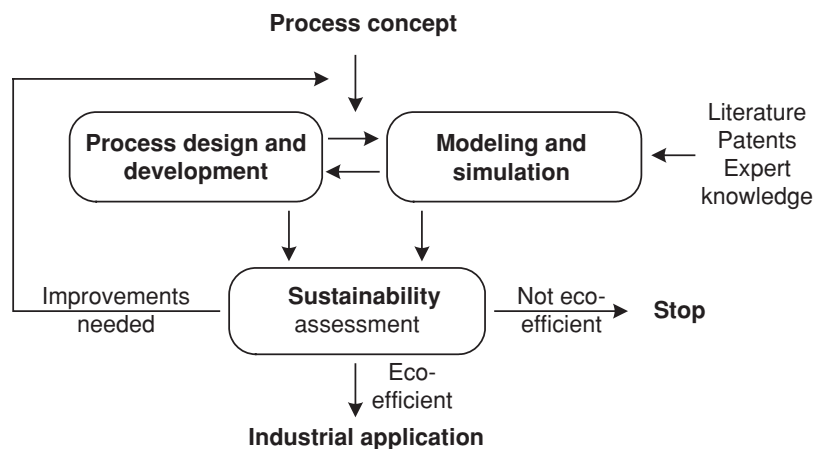
However, in some areas the expected positive development will reach its full potential only if the public acceptance of biotechnology can be improved considerably (see Section 4.4 and 4.5). The expanding development of biofuel is an important example. Here, an open and constructive dialogue based on a sound sustainability assessment (see Chapter 4) is crucial, and scientists can make a valuable contribution to this discussion (see e.g. [1.8–1.10]). Furthermore, well-trained bioengineers are essential for the existing potential of biotechnology to be realized. A more detailed discussion of the future perspectives is given in the literature [1.2, 1.3, 1.5].

## 1.2 Modeling and Assessment in Process Development

In process development we want to gain an understanding of the actual future production process as early and as detailed as possible. The modeling of the process under development and a thorough assessment helps to improve this knowledge. Here an iterative assessment is essential in order to realize competitive industrial processes. Decisions have to be made based on sound estimates of costs and potentials of a process and the ‘hot spots’ in the process schedule have to be identified. The assessment should include economic and environmental evaluation; this is known as integrated development. Figure 1.1 illustrates the importance of an early evaluation. The more advanced the process design, the more the final production process with its cost structure and environmental burdens is already determined. The additional cost for redesign to solve a problem that was previously overlooked rises with the development stage. For environmental problems often only end-of-pipe technologies that cause additional cost are possible in a later stage of the development.



**Figure 1.1** Process knowledge and freedom of decision in the process development [1.11]

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**Figure 1.2** *Integrated development of bioprocesses*

In development gaps and uncertainty in data cause an incomplete picture of the expected production-scale process. The use of process modeling can fill this gap and provide a sound evaluation basis [1.11]. Figure 1.2 shows the iterative approach of modeling and assessment. The models should be developed in close collaboration with the process design, and additional information is taken from patents, literature, and other external sources. The simulation results are used to evaluate the process and to guide the R&D effort to the most promising directions and the most urgent problems. Thereby, it is important to look at the whole process and not only to optimize single parts, such as the fermentation step isolated from the whole process. The most competitive and sustainable process is the overall aim. The modeling and assessment process is repeated iteratively and demands an interdisciplinary effort. Using this approach, crucial problems that might impede a successful transformation to an industrial application can be identified earlier, thus avoiding the waste of R&D spending. Naturally, the created models and the assessment based on these models include a certain inherent uncertainty. This uncertainty has to be considered and quantified.

We live in a world of limited resources, with a fast growing population and a limited carrying capacity of our planet. Therefore, besides the economic structure of a process, environmental and social aspects should be considered (see e.g. [1.12–1.15]). The concept of sustainability connects these three aspects that interact in many ways with each other. As we will discuss in Chapter 4, the development of a more sustainable process improves the long-term success and leaves it usually well prepared for future regulatory demands.

In this book, we look at one specific product that might be produced in one or several processes. This product provides a certain human benefit or service. We do not discuss the general question whether it is sustainable to supply this service or not. We also do not discuss other ways that might meet this benefit and whether they are more sustainable. These aspects can be very relevant. However, the required product is usually determined before the process development starts and the discussion of these aspects goes far beyond the scope of this book. Looking only at one specific product, different processes that provide the same product are compared. However, if the product is the same, it can be assumed that

its behaviour during use and disposal is identical. Therefore, once the product is defined, one can concentrate on the production process itself, the supply chain of the raw materials, and the environmental impact of the wastes produced during manufacturing, and one does not have to look at the use and disposal of the product itself. This substantially reduces the necessary effort for modeling and assessment.

It is widely expected that the use of bioprocesses can contribute considerably to a more sustainable development. Biotechnology is seen as a 'powerful enabling technology for achieving clean industrial products and processes that can provide a basis for industrial sustainability' [1.16]. Bioprocesses are economically competitive in a growing number of industries and have advantages concerning several local and global environmental challenges. Bioprocesses are usually based on renewable resources and thus reduce the depletion of limited fossil raw materials. The mild reaction conditions with regard to temperature, pressure, and pH reduce the risk of accidents. Since bioprocesses work with biological systems, the by-products and other wastes have normally a low pollution potential. Nevertheless, the environmental performance has to be optimized and aligned with the economic performance during the development. Here, relatively low product concentrations and productivities are generally the major limitations. The use of agricultural raw materials puts bioprocesses in competition with food production. Furthermore, the aspects of bio-risks and related public acceptance have to be discussed.

The Rio conference and, more recently, the Kyoto Protocol [1.17], identified global warming as one of the most urgent environmental problems. The greenhouse effect is essentially determined by the carbon balance between the different carbon reservoirs. By using renewable carbon sources, bioprocesses usually have an equalized carbon balance. This is an important environmental asset and, with the starting trade of carbon dioxide emission allowances, also an economic advantage. However, in this context the energy requirements of a bioprocess have to be assessed critically.

## References

- [1.1] Fiechter, A. (2000): History of modern biotechnology I. Springer, Berlin.
- [1.2] Sager, B. (2001): Scenarios on the future of biotechnology. *Technol. Forecasting Social Change*, **68**, 109–129.
- [1.3] Festel, G., Knoell, J., Goetz, H., Zinke, H. (2004): Der Einfluss der Biotechnologie auf Produktionsverfahren in der Chemieindustrie. *Chem.-Ing.-Tech.*, **76**, 307–312.
- [1.4] Storhas, W. (2003): Bioverfahrensentwicklung. Wiley-VCH, Weinheim.
- [1.5] Hulse, J. (2004): Biotechnologies: past history, present state and future prospects. *Trends Food Sci. Technol.*, **15**, 3–18.
- [1.6] Walsh G. (2003): Pharmaceutical biotechnology products approved within the European Union. *Eur. J. Pharm. Biopharm.*, **55**, 3–10.
- [1.7] Schmid, R. (2003): Pocket guide to biotechnology and genetic engineering, Wiley-VCH, Weinheim.
- [1.8] Young, A. (2004): The future of biotechnology in support of bio-based industries. *Environ. Sci. Pollut. Res.*, **11**, 71–72.
- [1.9] Gaugitsch, H. (2004): The future of biotechnology in support of bio-based industries – a differentiated assessment of the future of biotechnology. *Environ. Sci. Pollut. Res.*, **11**, 141–142.

## 10 Development of Sustainable Bioprocesses Modeling and Assessment

- [1.10] Braun R., Moses V. (2004): A public policy on biotechnology education: What might be relevant and effective? *Curr. Opin. Biotechnol.*, **15**, 246–249.
- [1.11] Heinzle, A., Hungerbühler, K. (1997). Integrated process development: The key to future production of chemicals. *Chimia*, **51**, 176–183.
- [1.12] El-Halwagi, M. (1997): Pollution prevention through process integration – systematic design tools, Academic Press, London.
- [1.13] Verfaillie, H., Bidwell, R. (2000): Measuring Eco-efficiency: A Guide to Reporting Company Performance, World Business Council for Sustainable Development, Geneva.
- [1.14] OECD (1995): The life cycle approach: An overview of product/process analysis OECD, Paris.
- [1.15] OECD (2001): OECD Environmental indicators: Towards sustainable development OECD, Paris.
- [1.16] OECD (1998): Biotechnology for clean industrial products and processes – Towards industrial sustainability OECD, Paris.
- [1.17] UNFCCC (1997): The Kyoto Protocol; United Nations Framework Convention on Climate Change, Bonn.