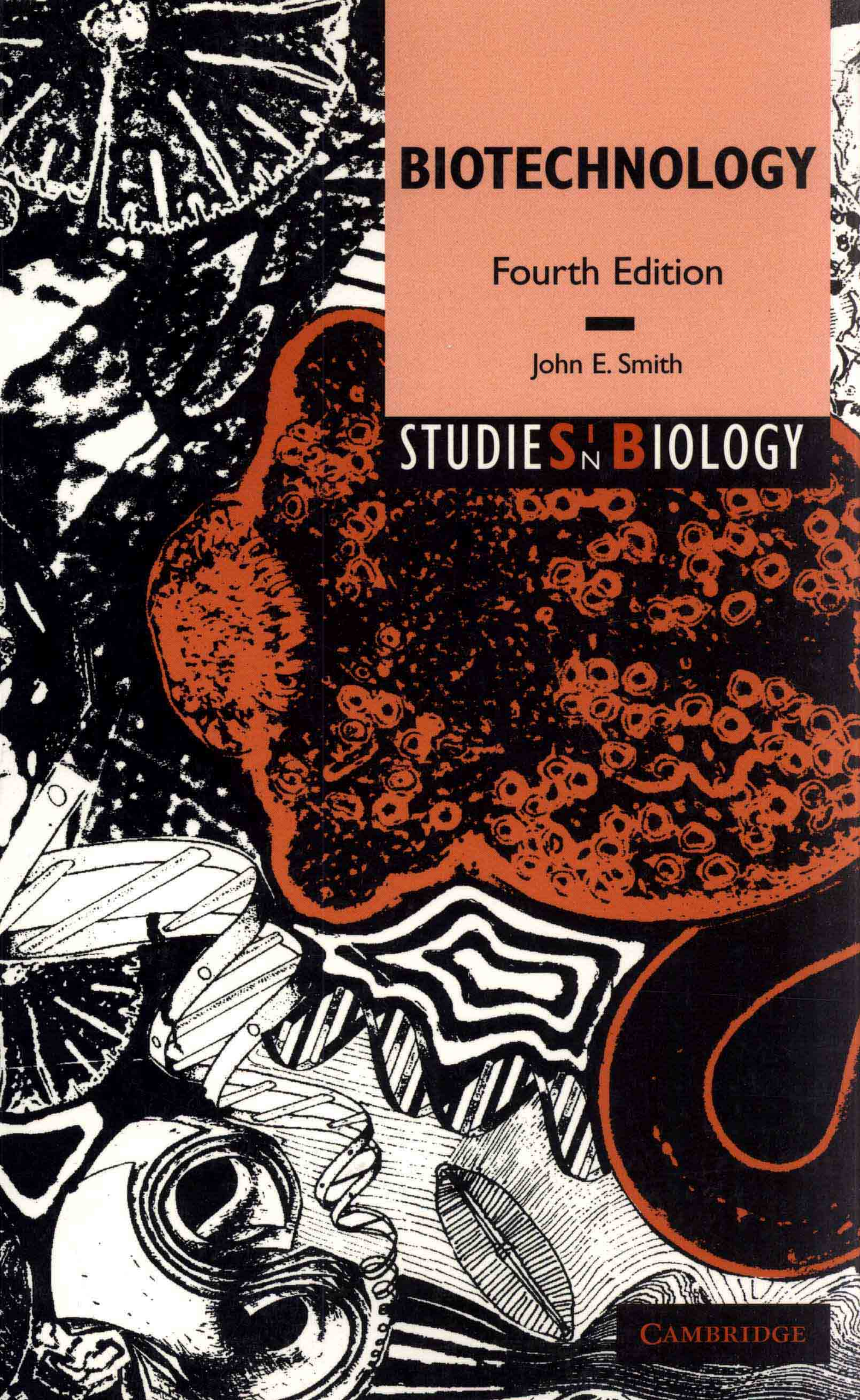
BIOTECHNOLOGY

Fourth Edition

John E. Smith

STUDIES IN BIOLOGY



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Preface

Biotechnology is, in essence, the deciphering and use of biological knowledge. It is highly multidisciplinary since it has its foundations in many disciplines, including biology, microbiology, biochemistry, molecular biology, genetics, chemistry and chemical and process engineering. It may also be viewed as a series of enabling technologies that involve the practical application of organisms (especially microorganisms) or their cellular components to manufacturing and service industries and environmental management. Historically, biotechnology was an artisanal skill rather than a science, exemplified by the manufacture of wines, beers, cheese, etc., where the techniques of manufacture were well worked out and reproducible, while the biological mechanisms were not understood. As the scientific basis of these biotechnology processes has developed, this has led to more efficient manufacturing of the traditional processes that still represent the major financial rewards of biotechnology. Modern biotechnological processes have generated a wide range of new and novel products, including antibiotics, recombinant proteins and vaccines, and monoclonal antibodies, the production of which has been optimised by improved fermentation practices. Biotechnology has been further revolutionised by a range of new molecular innovations, allowing unprecedented molecular changes to be made to living organisms. Genomics and proteomics are now heralding a new age of biotechnology, especially in the areas of human health and food production. In the environment, biotechnology innovations are creating major advances in water and land management and also remediating the pollution guaranteed by over-industrialisation.

Some of the new aspects of biotechnology, such as genetic engineering, have aroused certain social sensitivities of an ethical, moral and political character.

Regulatory authorities throughout the world are now examining the implications of these new and revolutionary techniques. It is hoped that common sense will prevail.

Undoubtedly, modern biotechnology can only maximise its full potential to benefit mankind through achieving a basis of public understanding and awareness and knowledge of the technologies. Participating scientists must learn to communicate openly with the public and attempt to demystify the complex nature of living systems. By doing so they will generate a greater level of confidence and trust between the scientific community and the public at large.

This expanded fourth edition of *Biotechnology* is again aimed at giving an integrated overview of its complex, multifaceted and often ill-judged subjects and, for some young readers, at pointing the way forward to exciting, satisfying and rewarding careers. Biotechnology will undoubtedly be the major technology of the twenty-first century.

I am again deeply indebted to Miss Elizabeth Clements for her skilful processing of the manuscript.

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The nature of biotechnology

1.1 Introduction

Major events in human history have, to a large extent, been driven by technology. Improved awareness of agriculture and metalworking brought mankind out of the Stone Age, while in the nineteenth century, the Industrial Revolution created a multitude of machinery together with ever-increasingly larger cities. The twentieth century was undoubtedly the age of chemistry and physics, spawning huge industrial activities such as petrochemicals, pharmaceuticals, fertilisers, the atom bomb, transmitters, the laser and microchips. However, there can be little doubt that the huge understanding of the fundamentals of life processes achieved in the latter part of the twentieth century will ensure that the twenty-first century will be dominated by biology and the associated technologies.

Societal changes are increasingly driven by science and technology. Currently, the impact of new biological developments must be absorbed not just by a minority (the scientists) but also by large numbers (the general public). If this does not happen the majority will be alienated. It is increasingly important to ensure a broad understanding of what bioscience and its related technologies will involve, and especially what the consequences will be of accepting or rejecting the new technical innovations.

The following chapters will examine how the new biotechnologists are: developing new therapies and cures for many human and animal diseases; designing diagnostic tests for increasing disease prevention and pollution control; improving many aspects of plant and animal agriculture; cleaning and improving the environment; and designing clean industrial manufacturing processes. Undoubtedly, biotechnology can be seen to be the most innovative technology that mankind has witnessed.

While biotechnology will undoubtedly offer major opportunities to human development (nutrition, medicine, industry), it cannot be denied that it is creating social/ethical apprehensions because of considered dangers to human rights that improper use could create. The advancement of genetic engineering, and especially the ramifications of the Human Genome Project, are achieving unique importance.

1.2 What is biotechnology?

There is little doubt that modern biology is the most diversified of all the natural sciences, exhibiting a bewildering array of subdisciplines: microbiology, plant and animal anatomy, biochemistry, immunology, cell biology, molecular biology, plant and animal physiology, morphogenesis, systematics, ecology, genetics and many others. The increasing diversity of modern biology has been derived primarily from the largely post-war introduction into biology of other scientific disciplines, such as physics, chemistry and mathematics, which have made possible the description of life processes at the cellular and molecular level. In the last two decades, well over 20 Nobel prizes have been awarded for discoveries in these fields of study.

This newly acquired biological knowledge has already made vastly important contributions to the health and welfare of mankind. Yet few people fully recognise that the life sciences affect over 30% of global economic turnover by way of health care, food and energy, agriculture and forestry, and that this economic impact will grow as biotechnology provides new ways of influencing raw material processing. Biotechnology will increasingly affect the efficiency of all fields involving the life sciences and it is now realistically accepted that, by the early twenty-first century, it will be contributing many trillions of pounds to world markets.

In the following chapters, biotechnology will be shown to cover a multitude of different applications, ranging from the very simple and traditional, such as the production of beers, wines and cheeses, to highly complex molecular processes such as the use of recombinant DNA technologies to yield new drugs or to introduce new traits into commercial crops and animals. The association of old traditional industries such as brewing with modern genetic engineering is gaining in momentum and it is not for nothing that industrial giants such as Guinness, Carlsberg and Bass are heavily involved in biotechnology research. Biotechnology is developing at a phenomenal pace and will increasingly be

Table 1.1. Some selected definitions of biotechnology

The application of biological organisms, systems or processes to manufacturing and service industries.
The integrated use of biochemistry, microbiology and engineering sciences in order to achieve technological (industrial) application capabilities of microorganisms, cultured tissue cells and parts thereof.
A technology using biological phenomena for copying and manufacturing various kinds of useful substances.
The application of scientific and engineering principles to the processing of materials by biological agents to provide goods and services.
The science of the production processes based on the action of microorganisms and their active components and of production processes involving the use of cells and tissues from higher organisms. Medical technology, agriculture and traditional crop breeding are not generally regarded as biotechnology.
Really no more than a name given to a set of techniques and processes.
The use of living organisms and their components in agriculture, food production and other industrial processes.
The deciphering and use of biological knowledge.
The application of our knowledge and understanding of biology to meet practical needs.

seen as a necessary part of the advance of modern life and not simply a way to make money!

While biotechnology has been defined in many forms (Table 1.1), in essence it implies the use of microbial, animal or plant cells or enzymes to synthesise, break down or transform materials.

The European Federation of Biotechnology (EFB) considers biotechnology as 'the integration of natural sciences and organisms, cells, parts thereof, and molecular analogues for products and services'. The aims of this Federation are:

(1) to advance biotechnology for the public benefit;
(2) to promote awareness, communication and collaboration in all fields of biotechnology;
(3) to provide governmental and supranational bodies with information and informed opinions on biotechnology;
(4) to promote public understanding of biotechnology.

The EFB definition is applicable to both 'traditional or old' and 'new or modern' biotechnology. Traditional biotechnology refers to the conventional

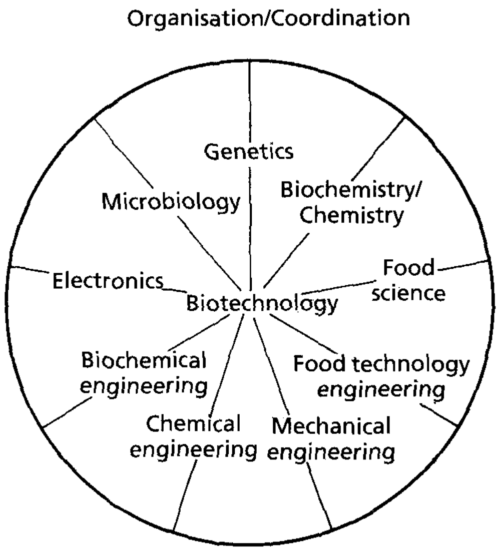

Fig. 1.1 The interdisciplinary nature of biotechnology (from Higgins *et al.*, 1985).

techniques which have been used for many centuries to produce beer, wine, cheese and many other foods, while 'new' biotechnology embraces all methods of genetic modification by recombinant DNA and cell fusion techniques together with the modern developments of 'traditional' biotechnological processes.

The difficulties of defining biotechnology and the resulting misunderstandings have led some to suggest the abandonment of the term 'biotechnology' as too general and the replacement of it by the precise term of whatever specific technology or application is being used.

Unlike a single scientific discipline, biotechnology can draw upon a wide array of relevant fields, such as microbiology, biochemistry, molecular biology, cell biology, immunology, protein engineering, enzymology, classified breeding techniques, and the full range of bioprocess technologies (Fig. 1.1). Biotechnology is not itself a product or range of products like microelectronics: rather it should be regarded as a range of enabling technologies which will find significant application in many industrial sectors. As will be seen in later sections, it is a technology in search of new applications, and the main benefits lie in the future. New biotechnological processes will, in many instances, function at low temperature, will consume little energy, and will rely mainly on inexpensive substrates for biosynthesis.

As stated by McCormick (1996), a former editor of the *Journal of Bio/Technology*, 'There is no such thing as biotechnology, there are biotechnologies.

Table 1.2. Historical development of biotechnology

Biotechnological production of foods and beverages
Sumerians and Babylonians were drinking beer by 6000 BC; Egyptians were baking leavened bread by 4000 BC; wine was known in the Near East by the time of the book of Genesis. Microorganisms were first seen in the seventeenth century by Anton van Leeuwenhoek, who developed the simple microscope, and the fermentative ability of microorganisms was demonstrated between 1857 and 1876 by Pasteur – **the father of biotechnology**. Cheese production has ancient origins, as does mushroom cultivation.

Biotechnological processes initially developed under non-sterile conditions
Ethanol, acetic acid, butanol and acetone were produced by the end of the nineteenth century by open microbial fermentation processes. Waste-water treatment and municipal composting of solid wastes created the largest fermentation capacity practised throughout the world.

Introduction of sterility to biotechnological processes
In the 1940s, complicated engineering techniques were applied to the mass cultivation of microorganisms to exclude contaminating microorganisms, e.g. in the cultivation of antibiotics, amino acids, organic acids, enzymes, steroids, polysaccharides, vaccines and monoclonal antibodies.

Applied genetics and recombinant DNA technology
Traditional strain improvement of important industrial organisms has long been practised; recombinant DNA techniques, together with protoplast fusion, allow new programming of the biological properties of organisms.

There is no biotechnology industry; there are industries that depend on biotechnologies for new products and competitive advantage.'

It should be recognised that biotechnology is not something new but something which represents a developing and expanding series of technologies dating back (in many cases) thousands of years, when humans first began unwittingly to use microbes to produce foods and beverages like bread and beer and to modify plants and animals through progressive selection for desired traits. Biotechnology encompasses many traditional processes such as brewing, baking, winemaking, production of cheese and oriental foods such as soy sauce and tempeh, and sewage treatment, where the use of microorganisms has been developed somewhat empirically over countless years (Table 1.2). It is only relatively recently that these processes have been subjected to rigorous scientific scrutiny and analysis; even so it will surely take some time, if at all, for modern scientifically based practices to fully replace traditional empiricism.

The new biotechnology revolution began in the 1970s and early 1980s when scientists learned to alter precisely the genetic constitution of living organisms by processes outside of traditional breeding practices. This 'genetic engineering' has had profound impact on almost all areas of traditional biotechnology and has further permitted breakthroughs in medicine and agriculture, in particular, that would be impossible by traditional breeding approaches. Some of the most exciting advances will be in the development of new pharmaceutical drugs and therapies aimed at improving treatments to many diseases, and in producing healthier foods, selective pesticides, and innovative environmental technologies.

There is also a considerable danger that biotechnology will be viewed as a coherent, unified body of scientific and engineering knowledge and thinking to be applied in a coherent and logical manner. This is not so; the range of biological, chemical and engineering disciplines that are involved have varying degrees of application to the industrial scene.

Traditional biotechnology has established a huge and expanding world market and, in monetary terms, represents a major part of *all* biotechnology financial profits. 'New' aspects of biotechnology founded in recent advances in molecular biology, genetic engineering and fermentation process technology are now increasingly finding wide industrial application. A width of relevant biological and engineering knowledge and expertise is ready to be put to productive use; however, the rate at which it will be applied will depend less on scientific or technical considerations and more on such factors as adequate investment by the relevant industries, improved systems of biological patenting, marketing skills, the economics of the new methods in relation to currently employed technologies, and – possibly of most importance – public perception and acceptance.

The present industrial activities to be most affected will include human and animal food production, provision of chemical feedstocks to replace petrochemical sources, alternative energy sources, waste recycling, pollution control, agriculture, aquaculture and forestry. From a medical dimension, biotechnology will focus on the development of biological compounds rather than on chemical compounds. Use will be made of proteins, hormones and related substances that occur in the living system or even in those that are created *in vitro*. The new techniques will also revolutionise many aspects of medicine, veterinary sciences, and pharmaceutics. The recent mapping of the human genome must be recognised as one of the most significant breakthroughs in human history.

Many biotechnological industries will be based largely on renewable and recyclable materials and so can be adapted to the needs of a society in which energy is ever increasingly expensive and scarce. In many ways, biotechnology is a series of embryonic technologies and will require much skilful control of its development, but the potentials are vast and diverse, and undoubtedly will play an increasingly important part in many future industrial processes.

1.3 Biotechnology: an interdisciplinary pursuit

Biotechnology is a priori an interdisciplinary pursuit. In recent decades a characteristic feature of the development of science and technology has been the increasing resort to multidisciplinary strategies for the solution of various problems. This has led to the emergence of new interdisciplinary areas of study, with the eventual crystallisation of new disciplines with identifiable characteristic concepts and methodologies.

Chemical engineering and biochemistry are two well-recognised examples of disciplines that have done much to clarify our understanding of chemical processes and the biochemical bases of biological systems.

The term '*multidisciplinary*' describes a quantitative extension of approaches to problems which commonly occur within a given area. It involves the marshalling of concepts and methodologies from a number of separate disciplines and applying them to a specific problem in another area. In contrast, '*interdisciplinary*' application occurs when the blending of ideas which occur during multidisciplinary cooperation leads to the crystallisation of a new disciplinary area with its own concepts and methodologies. In practice, multidisciplinary enterprises are almost invariably mission-orientated. However, when true interdisciplinary synthesis occurs, the new area will open up a novel spectrum of investigations. Many aspects of biotechnology have arisen through the interaction between various parts of biology and engineering.

A biotechnologist can utilise techniques derived from chemistry, microbiology, biochemistry, chemical engineering and computer science (Fig. 1.1). The main objectives will be the innovation, development and optimal operation of processes in which biochemical catalysis has a fundamental and irreplaceable role. Biotechnologists must also aim to achieve a close working cooperation with experts from other related fields such as medicine, nutrition, the pharmaceutical and chemical industries, environmental protection and waste process technology.

The industrial application of biotechnology will increasingly rest upon each of the contributing disciplines in order to understand the technical language

Table 1.3. Types of companies involved with biotechnology

Category	Biotechnology involvement
Therapeutics	Pharmaceutical products for the cure or control of human diseases, including antibiotics, vaccines and gene therapy.
Diagnostics	Clinical testing and diagnosis, food, environment, agriculture.
Agriculture/forestry/ horticulture	Novel crops or animal varieties, pesticides.
Food	Wide range of food products, fertilisers, beverages, ingredients.
Environment	Waste treatment, bioremediation, energy production.
Chemical intermediates	Reagents including enzymes, DNA/RNA and speciality chemicals.
Equipment	Hardware, bioreactors, software and consumables supporting biotechnology.

of the others and, above all, to understand the potential as well as the limitations of the other areas. For instance, for the fermentation bio-industries the traditional education for chemical engineers and industrial plant designers has not normally included biological processes. The nature of the materials required, the reactor vessels (bioreactors) and the operating conditions are so different that it requires complete retraining.

Biotechnology is a demanding industry that requires a skilled workforce and a supportive public to ensure continued growth. Economies that encourage public understanding and provide a competent labour force should achieve long-term benefits from biotechnology. The main types of companies involved with biotechnology can be placed in seven categories (Table 1.3).

A key factor in the distinction between biology and biotechnology is their scale of operation. The biologist usually works in the range between nanograms and milligrams. The biotechnologist working on the production of vaccines may be satisfied with milligram yields, but in many other projects aims are at kilograms or tonnes. Thus, one of the main aspects of biotechnology consists of scaling-up biological processes.

Many present-day biotechnological processes have their origins in ancient and traditional fermentations such as the brewing of beer and the manufacture of bread, cheese, yoghurt, wine and vinegar. However, it was the discovery of antibiotics in 1929 and their subsequent large-scale production in the 1940s