Chapter 1

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 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 its 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 by large numbers of people (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 and food production; cleaning-up and improving the environment; designing clean industrial manufacturing processes; exploring the potential for biological fuel generation; and unravelling the power of stem cell technology. Undoubtedly, biotechnology can be seen to be the most innovative technology that mankind has witnessed. The development of biotechnological products is knowledge and resource intensive.

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 healthcare, 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 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

Table 1.1 Some selected definitions of biotechnology

A collective noun for 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 and other industrial processes.
The deciphering and use of biological knowledge.
The application of our knowledge and understanding of biology to meet practical needs.

(3) to provide governmental and supranational bodies with information and informed opinions on biotechnology
(4) to promote public understanding of biotechnology.

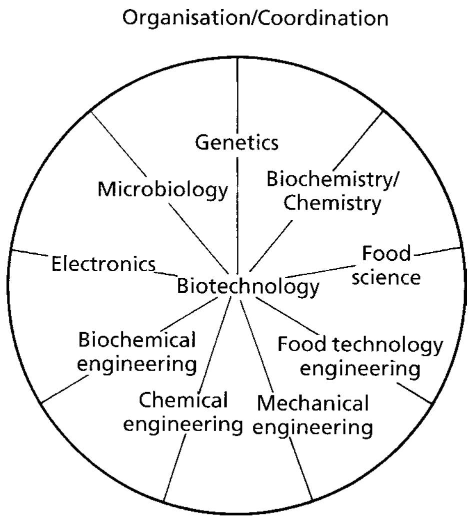
The EFB definition is applicable to both 'traditional or old' and 'new or modern' biotechnology. Traditional biotechnology refers to the conventional techniques that have been used for many centuries to produce beer, wine, cheese and many other foods, while 'new' biotechnology embraces all methods of genetic modification by recombinant DNA and cell fusion techniques together with the modern developments of 'traditional' biotechnological processes.

It is unfortunate that the term 'biotechnology' has become, in some quarters, a substitute for genetic modification or genetic engineering. This originated in the USA many years ago to offset the activists who were demonising these new genetic procedures to the lay public. Using the term biotechnology when describing trans-species genetic modifications was considered to be more friendly sounding and to arouse less anxiety! The term was then picked up by the media and by politicians, and subsequently found its way into government documents and legislation. A defining aim of this book is to re-establish the correct understanding of biotechnology.

In truth, genetic modification has been used by mankind for over 10 000 years to improve plants and animals by selective breeding. Only within the last 50 years has this process used new methods, such as polyploidisation, mutagenesis and X-rays, to achieve changes in genetic composition.

Genetic manipulation/modification/engineering is the modern method of selectively moving genes within the same species or between species, using modern molecular biology techniques.

Fig. 1.1 The interdisciplinary nature of biotechnology.



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 that will find significant application in many industrial sectors. As will be seen in later chapters, it is a technology in search of new applications and the main benefits lie in the future.

As stated by McCormick (1996), a former editor of the *Journal Bio/Technology*: 'There is no such thing as biotechnology, there are biotechnologies. 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 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, such as 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, cheese production, oriental foods (e.g. 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 possible, for modern scientifically based practices fully to 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 a profound impact on almost all areas of traditional biotechnology and further permitted breakthroughs in medicine and agriculture, in particular, that would be impossible by traditional

Table 1.2 Historical development of biotechnology

Biotechnological production of foods and beverages Sumarians and Babylonians were drinking beer by 6000 BC, they were the first to apply direct fermentation to product development; 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; 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 represents the largest fermentation capacity practised throughout the world.
Introduction of sterility to biotechnological processes In the 1940s complicated engineering techniques were introduced to the mass production of microorganisms to exclude contaminating microorganisms. Examples include the production 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.

breeding approaches. Some of the most exciting advances will be in new pharmaceutical drugs and therapies to improve the treatment of many diseases, and in the production of 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 are having 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 breadth of relevant biological and engineering knowledge and expertise is ready to be put to productive use; but 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.

Since the 1980s biotechnology has been recognised and accepted as a strategic technology by most industrialised nations. The economic returns from investing in strategic technologies accrue not just to the companies conducting research and development (R&D) but more importantly returns to society overall are estimated to be even higher!

The present industrial activities to be affected most 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 complex biological compounds rather than chemical compounds. Use will be made of proteins, hormones and related substances that occur in the living system or may even be created in vitro. The new techniques will also revolutionise many aspects of medicine, veterinary science and pharmaceutics. The recent mapping of the human genome must be recognised as one of the most significant breakthroughs in human history.

The use of microorganisms to replace certain existing procedures could make many industries more efficient and environmentally friendly and greatly contribute towards industrial sustainability. Waste will be reduced, energy consumption and greenhouse gas emissions will be lowered, and greater use of renewable raw materials will be made. In the European Union (EU) this has been termed ‘white biotechnology’, while healthcare and agricultural-related biotechnologies have respectively been termed ‘red’ and ‘green’ biotechnologies.

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. Can biotechnology contribute to real-world challenges such as climate change, bioenergy, healthier ageing and agricultural sustainability? This question will be answered in later chapters.

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 that 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 that occur during multidisciplinary cooperation leads to the crystallisation of a new disciplinary area with its own concepts and methodologies. In

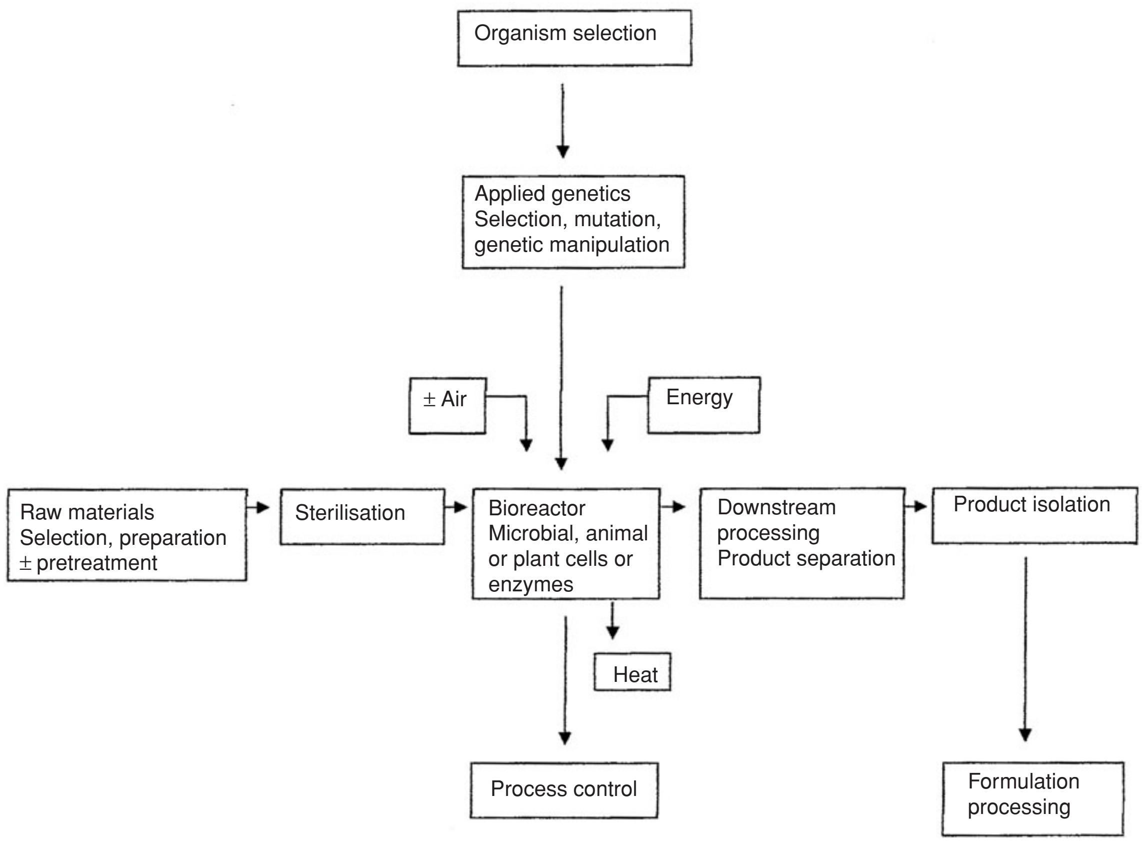


Fig. 1.2 Schematic overview of a biotechnological process.

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. Biotechnology has two clear features: its connections with practical applications and interdisciplinary cooperation.

The industrial application of biotechnology will increasingly rest upon each of the contributing disciplines to understand the technical language of the others and, above all, to understand the potential as well as the limitations of the other areas. For instance, for the fermentation bioindustries 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 complete retraining is required (Fig. 1.2).

Table 1.3 Types of companies involved with biotechnology

Therapeutics	Pharmaceutical products for the cure or control of human diseases, including antibiotics, vaccines, 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, speciality chemicals.
Equipment	Hardware, bioreactors, software and consumables supporting biotechnology.

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 that created the greatest advances in fermentation technology. Since then we have witnessed a phenomenal development in this technology, not only in the production of antibiotics but in many other useful, simple or complex biochemical products, for example organic acids, polysaccharides, enzymes, vaccines, hormones, etc. (Table 1.4). Inherent in the development of fermentation processes is the growing close relationship between the biochemist, the microbiologist and the chemical engineer. Thus, biotechnology is not a sudden discovery but rather a coming of age of a technology that was initiated several decades ago. Looking to the future, the *Economist*, when reporting on this new technology, stated that it may launch 'an industry as characteristic of the twenty-first century as those based on physics and chemistry have been of the twentieth century'.

If it is accepted that biotechnology has its roots in distant history and has large, successful industrial outlets, why then has there been such increased public awareness of this subject in recent years? Undoubtedly, the main dominating reason must derive from the rapid advances in molecular biology, in particular recombinant DNA technology, which are giving humans dominance over nature. By these new techniques (to be discussed in later chapters) it is possible to manipulate directly the heritable material (DNA)

Table 1.4 World markets for biological products in 1981

Product	Sales (US$ millions)
Alcoholic beverages	23 000
Cheese	14 000
Antibiotics	4500
Penicillins	500
Tetracyclines	500
Cephalosporins	450
Diagnostic tests	2000
Immunoassay	400
Monoclonal	5
Seeds	1400
High fructose syrups	800
Amino acids	750
Baker's yeast	540
Steroids	500
Vitamins, all	330
Vitamin C	200
Vitamin B_{12}	14
Citric acid	210
Enzymes	200
Vaccines	150
Human serum albumin	125
Insulin	100
Urokinase	50
Human factor VIII protein	40
Human growth hormone	35
Microbial pesticides	12

of cells between different types of organisms in vitro creating new hybrid DNA molecules not previously known to exist in nature. The potential of this series of techniques first developed in academic laboratories is now being rapidly exploited in industry, agriculture and medicine. While the benefits are immense, the inherent dangers of tampering with nature must always be appreciated and respected.

While in theory the technology is available to transfer a particular gene from any organism into any other organism, microorganism, plant or animal, in actual practice there are numerous constraining factors, such as which genes are to be cloned and how they can be selected. The single, most limiting factor in the application of genetic engineering is the dearth of basic scientific knowledge of gene structure and function.

The developments of biotechnology are proceeding at a speed similar to that of microelectronics in the mid-l970s. Although the analogy is tempting, any expectations that biotechnology will develop commercially at the same spectacular rate should be tempered with considerable caution. While the potential of 'new' biotechnology cannot be doubted, a meaningful commercial realisation is now only slowly occurring and will accelerate throughout the twenty-first century. New biotechnology will have a considerable impact across all industrial uses of the life sciences. In each case the relative merits of competing means of production will influence the economics of a biotechnological route. Biotechnology will undoubtedly have great benefits in the long term in all sectors and, above all, will save countless lives.

The growth in awareness of modern biotechnology parallels the serious worldwide changes in the economic climate arising from the escalation of oil prices since 1973. There is a growing realisation that fossil fuels (although at present in a production glut period) and other non-renewable resources will one day be in limited supply. This will result in the requirement for cheaper and more secure energy sources and chemical feedstocks, which biotechnology could perhaps fulfil. Countries with climatic conditions suitable for rapid biomass production could well have major economic advantages over less climatically suitable parts of the world. In particular, the tropics must hold high future potential in this respect.

Another contributory factor to the growing interest in biotechnology has been the current recession in the Western world, in particular the depression of the chemical and engineering sections, in part due to the increased energy costs. Biotechnology has been considered as one important means of restimulating the economy, whether on a local, regional, national or even global basis, using new biotechnological methods and new raw materials. In part, the industrial boom of the 1950–1960s was due to cheap oil; while the information technology advances in the 1970s and 1980s resulted from developments in microelectronics. It is quite feasible that the twenty-first century will increasingly be seen as the era of biotechnology. There is undoubtedly a worldwide increase in molecular biological research, the formation of new biotechnological companies, large investments by nations, companies and individuals, and the rapid expansion of databases, information sources and, above all, extensive media coverage.

It is perhaps unfortunate that there has been an over-concentration on the new implications of biotechnology, and less identification of the very large traditional biotechnological industrial bases that already function throughout the world and contribute considerably to most nations' gross national profits. Indeed, many of the innovations in biotechnology will not appear a priori as new products, but rather as improvements to organisms and processes in long-established biotechnological industries, e.g. brewing and antibiotics production.

New applications are likely to be seen earliest in the areas of healthcare and medicine, followed by agriculture and food technology. Exciting new medical treatments and drugs based on biotechnology are appearing with ever-increasing regularity. Prior to 1982, insulin for diabetics was derived from beef and pork pancreases. The gene for human insulin was then isolated and cloned into microorganisms that were then mass-produced by fermentation. This genetically engineered human insulin, identical to the natural human hormone, was the first commercial pharmaceutical product of recombinant DNA technology and now supplies millions of insulin users worldwide with a safe, reliable and unlimited source of this vital hormone. Biotechnology has also made it easier to detect and diagnose