ADVANCES IN BIOTECHNOLOGICAL PROCESSES

Volume 3

Editors
Avshalom Mizrahi

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Preface

Rapid advances in the development of genetically engineered microorganisms have made new biological products not only available but also marketable. In many cases R & D has reached the point at which the manufacture of various products should be scaled-up.

A chapter in this volume of **Advances in Biotechnological Processes** deals with long-term storage of genetically unstable microorganisms—an important aspect of the commercialization of products from such cells—and two other chapters comprehensively describe instrumentation and control of fermentors and the industrial application of fermentation kinetics.

Among current approaches to fighting cancer are antitumor agents derived from microbial sources and antibody-toxin conjugates, both of which are also reviewed in this volume.

Interest in biotechnological processes and products extends both to "old" products like the ergot alkaloids and to such new processes as desulfurization of coal. Because coal is one of the fossil fuels that represents an abundant energy source, microbial methods of precombustion desulfurization, which are more promising than chemical and physical processes, are of great significance in our time.

Concern about chemical contamination of ecosystems has led to increasing production of bioinsecticides from microbial sources. Three chapters in this volume discuss the manufacture of such alternatives to hazardous chemical compounds.

The broad range of subjects that is comprehensively reviewed in this volume of **Advances in Biotechnological Processes**, indicates the ever-widening applications of biotechnology. We continue to encourage contributions to this series, for the state-of-the-art reviews of the many applications of biotechnology are of interest and value both to those engaged in the study and production of biologicals and to those who anticipate such involvement.

Avshalom Mizrahi
Antonius L. van Wezel

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Fermenter Instrumentation and Control

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I. INTRODUCTION

The development of the biotechnological process of fermentation has historically been highly empirical. With the emphasis on systematic screening of medium ingredients, process conditions, and new organisms, vessels commonly lacked feedback control of basic conditions such as air flow, pH, agitator speed, and pressure; few measurements were made other than of the product. The more modern philosphy of advance through understanding demands entirely different equipment. Modern highly instrumented pilot plant fermenters enable precise physical control of the microbial environment; linked supervisory computers give the computational power to implement any conceivable control strategy. However, as is well known, on-line biological measurement of biomass, substrates, and products is still difficult. The development of mathematical models of the fermentation process is important both to remedy this deficiency by providing methods of indirect estimation and for promoting faster development and better control of industrial fermentations. Much of the present article is concerned with biological measurement, estimation, and control.

Many reviews covering fermentation instrumentation and computer control have appeared (notably [1–16]). In addition, useful collections of articles can be found in conference and symposia publications (viz: [17–20]). It is not the intention of this article to cover the history of the subject nor to redigest previous reviews. We have focused on the more recent literature, referring to earlier work only where necessary for a perspective. Thus half the work reviewed has been published within two years before the time of writing.

The use of computers and microprocessors is now a well-established technology in fermentation development and industrial practice, and the industry is emerging from the era of needing to describe hardware installations, so much a feature of earlier publications.

We include in this work only a very brief discussion of computer and control configurations. However, we do believe that measurement hardware remains a cause for concern, and we have examined sensors rather more closely. Our viewpoint is unashamedly pragmatic: our aim throughout has been to ask what the usefulness of any device or technique is to the nonspecialist biotechnologist. We have included a major section on modeling and biological control with precisely this in mind, for it is our belief that models of processes will find an increasing role in fermentation development. We have attempted in that section particularly to demonstrate and explain rather than describe the work.

In the concluding section we illlustrate our arguments with some of our own experience at Beecham. The reader will be spared a more than cursory description of the equipment, but we have described the philosophy, financial justification, and the benefits actually achieved.

II. PHYSICAL MEASUREMENTS

The physical measurements (Table I) on a fermentation are generally straightforward—exceptions are noted in the table. The air-flow measurement (awkward to check on larger vessels) should be precise, because the values are used in conjunction with exit gas analysis for the determination of oxygen mass transfer coefficient and for mass balancing. Fermenter broth volume is similarly important—measurement of differential pressure between the vessel headspace and base is being superseded by load cells, which give better results (typically accurate to one part in 1,000). Load cells are expensive and also are difficult to fit on existing vessels; the pipework must be flexible to avoid anomalous readings.

A. Power and Viscosity

Power input would be a useful measurement but is often difficult to make. Small laboratory vessels can be rigged with dynamometers to measure torque