# ADVANCES IN BIOPROCESS ENGINEERING

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Edited by

Enrique Galindo

and

Octavio T. Ramírez

*Instituto de Biotecnología,*
*Universidad Nacional Autonoma de Mexico,*
*Cuernavaca, Morelos, Mexico*

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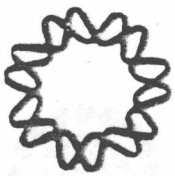

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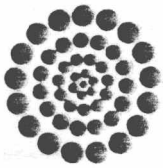

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## PREFACE

The exigent and rapidly growing markets of biotechnological products are demanding new and highly efficient bioprocesses. Molecular biology and immunology techniques have been crucial for achieving the important progress that the so called new biotechnology has made. However, improvements in actual process and industrialization of new ones depend more on how well a laboratory scheme is translated to production scale. In this activity, bioprocess engineering plays a key role.

Motivated by the belief that increased participation of engineering is needed in nowadays biotechnology, biochemical engineers at the Institute of Biotechnology of the National University of Mexico in Cuernavaca, Morelos, Mexico, organized the *First International Symposium on Bioprocess Engineering*. The Symposium aimed to be an International forum to present and discuss Bioprocess Engineering issues.

The Symposium consisted of invited and referred papers. Thirteen distinguished biochemical engineers were invited to give lectures at the Symposium. In addition, the response from the international community was very enthusiastic. About 120 abstracts were submitted for consideration. From the former, 80 were selected to submit full manuscripts, which then were sent to referees for reviewing. Finally, 55 papers were accepted for presentation in the Symposium and most of them are published in this book. The Symposium was truly international, 33 countries were represented from all over the world.

The papers address several topics of bioprocess engineering, namely: fundamentals of biochemical engineering, process development and optimization, control and automation of bioprocesses, design and scale up of bioreactors, enzyme engineering, waste treatment and downstream operations.

Basic bioengineering aspects such as transport mechanisms, models for mycelial growth, oxygen transport and structured models for bioreactors, rheology and mixing in fermentations and the utility of image analysis were addressed in some of the papers. Bioprocesses for the production of ethanol, gibberellic acid, lactic acid, proteases, β-galactosidase anakinra, streptokinase, penicillin-amidase, and lipases, as well as a bioleaching process, were described in various papers. Traditional and new processes (recombinant fermentations, plant and animal cell culture, and transgenic animals) are represented. Solid, liquid and gaseous substrates were considered in a variety of bioprocesses. The bioreactor modes studied included stirred tanks, air-lifts, percolation columns and packed and fluidized beds with immobilized cells. Interesting control problems are discussed for various model systems such as fermentors, enzymatic reactors and downstream operation systems. Authors from industry have also shared some of their experiences in process development and scale-up techniques. A good number of papers dealt with the treatment of solid, liquid or gaseous wastes using aerobic and anaerobic processes. Enzymatic engineering was well represented with examples of immobilized enzyme reactors, peptide synthesis and non-aqueous biocatalysis. Downstream operations papers dealt with the recovery of therapeutic bioproducts produced by recombinant microorganisms and transgenic animals.

The Symposium and the book would have been impossible to make without the participation of many people in various stages and aspects. We want to thank the invited speakers, the authors, the Scientific Committee and the referees for their enthusiastic response, their time and work in making this Symposium a valuable one. Our gratitude to our sponsors, who made possible the Symposium and the book. We thank the National University of

Mexico and particularly the Institute of Biotechnology for their support and encouragement in organizing this event. Many thanks to all the Organizing Committee for helping us in taking care of endless organization details and to our wives for their patience and support.

We hope this book can contribute to the development of Bioprocess Engineering, a key profession in turning biotechnology possibilities into biotechnology realities.

Enrique Galindo
Octavio R. Ramírez

Symposium Organizers and Editors
Institute of Biotechnology, National University of Mexico,
Cuernavaca, Mexico, 1994

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* *denotes corresponding author.*

Invited paper

# Bioreactor Engineering

N.W.F. Kossen

Gist-brocades B.V., Research & Development, P.O. Box 1, 2600 MA Delft,
THE NETHERLANDS

*This paper is not about formal design rules for bioreactors as such. There is plenty of literature available about this subject: Bailey and Ollis [1] ; Schügerl [2]; Van't Riet [3], Kossen [4]; as well as about its limitations: Zlokarnik [5]. The continuous thread through this paper is that the kind of product to be made in the bioreactor has a direct influence upon the time and the money that is available for the design of a new reactor, or the adaptation of an existing one. Time and money determine to a large extent the rules and methods that should be used. Designs with a built-in flexibility will appear to be essential. Finally the consequences for the education of those involved in bioprocess engineering (including bioreactor design) will be discussed.*

## THE DEVELOPMENT OF A BIOREACTOR AS A PART OF A PRODUCT/PROCESS DEVELOPMENT CHAIN (PDC)

The development of a bioreactor is an integrated part of a chain of events, the product/process development chain (PDC) (fig.1). A number of remarks can be made regarding this PDC:

First of all the environment of the micro-organisms is different in every part of the chain. The greatest difference is between the environment during screening and production (any resemblance between these environments is a lucky coincidence). Due to the flexibility of biotechnology this problem can be overcome further down stream the PDC.

Second, the over all success of the development of a process in biotechnology depends on all the steps of this chain. Contrary to ordinary chains, however, weak links of this chain can be compensated by the contribution of other links.

If e.g. the productivity of a bioreactor is below standard this problem can be solved by a number of methods:

a. selection of a new strain
b. genetic improvement of the strain by either classical or molecular genetics
c. physiological improvements like changing the composition or the rate of addition of the substrate
d. improving the bioreactor as such
e. improving the yield of the down stream processing.

There is a definite difference between the methods mentioned in this list. The first three, a, b, and c, are "upstream" solutions (relative to the bioreactor). Furthermore they are "software" solutions (no investments in nuts and bolds are needed). Finally results in this area can often be obtained rapidly and with relatively few investments (2 or 3 man years of work and often much less). Solution d is a typical "hardware" solution, and the investments needed can be quite substantial.

Conclusions. The conclusions of this paragraph are that there is not just one solution to a problem. It even shows, "horribile dictu," that the solution can be achieved by disciplines different from your own, and that there is no "a priori"



*E. Galindo and O.T. Ramírez (eds.), Advances in Bioprocess Engineering, 1-11.*

argument why the contribution of one discipline is better than that of another.

## THE RELATION BETWEEN THE DESIGN OF A BIOREACTOR AND THE PRODUCT.

There are a number of relations between the design of a bioreactor and the product:

a. Via the sequence: product ----> micro organism ----> reaction conditions (the "environment") ----> reactor design. This is the approach of the PDC and is mainly used for the design of a new process for a new product.
b. Via the influence of the process on the product:
   - yield
   - properties (composition, structure of enzymes etc.)

   This approach is often used when an existing process has to be optimized.
c. Commodities vs specialties:

| commodities | specialties |
|---|---|
| -cost leader | -differentiation |
| -long life cycle (>10y) | -short life cycle (<5y) |
| -large market share (economy of scale) | -first to the market (economy of time) |
| -optimization | -"quickies" |
| -"hard/software" sol. | -"software" solutions |
| -patents an issue | -patents a big issue |

The relations a and b are well known, and are well integrated in the teaching programs of the universities. This is not the case for relation c.
The focus will from now on be on the similarities and the differences between the development of bioreactors for commodities and specialties.

### Commodities

The main point here is to realize a lower cost price than your competitors. This usually asks for economy of scale (for production and marketing). We will restrict our attention to the influence on the design of bioreactors.

A low cost price usually means (among others) a very sophisticated design of a reactor (low fixed and variable costs). This often results in a design where the process fits in the installation as a hand in a glove. If this fit is not proper, costly adaptations are necessary (as an example the adaptations in the ICI bioreactor for the production of "pruteen" to increase the mixing performance can be mentioned). Furthermore the collection of all the necessary data (especially those on kinetics) can be extremely elaborate. For the production of commodities in biotechnology this close fit is not necessarily the right philosophy as will be shown in the next paragraph.

Quite often the successes of the "software" solutions (improvements of strains or substrates) allow for the continuous increase of the productivity of bioreactors to such an extend that there is hardly any need for new bioreactors. The increase in productivity can often keep up with the increase in demand of the product. If the demand does not increase, the increased productivity often results in the availability of one or more of the existing reactors for new products. Often the main necessary changes in hardware are adaptations to the needs of the new strains (cooling and aeration capacity) to extend the "limits of growth".

When a company has decided to produce a new product in a new bioreactor the design of this reactor is often caught up by strain improvement: when the reactor is ready the strain is, as a result of ongoing improvements, already much more productive than the one used for the design calculations.

Also the quality of the substrate can vary enormously as a function of time (fluctuations due to changing seasons, geographical origin, or supplier).

The need for methods to improve the output of bioreactors increases when the product becomes a commodity and/or when it is at the end of its life cycle (cost cutting). The cost/benefit ratio for R&D for this purpose must be checked carefully and frequently (small margins).