ADVANCES IN BIOTECHNOLOGICAL PROCESSES

VOLUME 1

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Contents

Airlift Fermenters: Construction, Behavior, and Uses

U. Onken and P. Weiland

Concepts on the Biotransformation of Carbohydrates Into Fuel Ethanol
Carlos Rolz, Sheryl de Cabrera, Francisco Calzada, Ricardo García, Roberto de León, María del Carmen de Arriola, Fabiola de Micheo, and Edna Morales

Methane Production by Fermentation of Agricultural Residues
Edgar C. Clausen and James L. Gaddy

The New β-Lactam Antibiotics

D. Butterworth, J D. Hood, and M.S. Verrall

Single-Cell Protein Production: Review of Alternatives
Nissim S. Samuelov

Advances in Biotechnological Processes 1, pages 1–30

Bioreactors for Submerged Culture

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INTRODUCTION AND STATEMENT OF THE PROBLEM

Biotechnology is the modern interdisciplinary endeavor *par excellence*, combining the biological sciences and engineering technology. From an industrial point of view, its aim is to transform the biological functions of cells into processes that are applicable to industry [1]. In one sense, biotech-

nology means the application in the laboratory of techniques arising from progress in the biological sciences, with the objective, at least in the industrial context, of designing and producing organisms capable of elaborating products of economic value. In another sense biotechnology denotes application of the appropriate technology to exploit the laboratory-derived organisms on a large scale, rendering the processes economically attractive.

Of these two meanings, the former pertains to the devising and application of technical laboratory manipulations, and while this is certainly engineering, the latter meaning relates more directly to the commonly held notions of engineering. It is to the second meaning that this paper is addressed, and more specifically, to the actual equipment used for such work.

In a production plant, the central process of biotechnology is fermentation. Accordingly, the central apparatus is the bioreactor, or fermentor. The bulk of this paper is concerned with the fermentor: What should be the basic "philosophy," or more accurately, the rationale, for a fermentor design? What constitutes a good design? How can an optimum configuration be approached?

We shall find that, for a great many cases, a majority, in fact, one basic configuration seems to be most adaptable. In recent years a number of new designs have been proposed and in some cases reduced to practice, and we shall make some effort to introduce these to the reader.

This paper is not intended to be exhaustive; neither will it be in any sense a handbook for the design expert. It is, rather, intended for those who must use fermentation processes on an industrial scale, and who must make choices about which type of fermentation reactor to employ or to investigate for their particular processes. It is our intent to help such practitioners by pointing the way.

On a basic level, fermentation—or rather industrial fermentation—involves the use of microorganisms, which are microscopic, single-celled, biologically active entities. These microorganisms must be manipulated so as to transform a set of substrates into a set of desired products. It is possible to manipulate these organisms because they possess catalytic biological activity, or enzymes.

This principle can be reduced to its essentials in certain very special cases by discarding the microorganism itself and using only the catalyst, the isolated, purified, and usually immobilized enzymes. Usually, because of a combination of thermodynamic, chemical, and biological factors, such an approach is not economically sound with today's technology, so the number of applications has been very limited. One possible way of circumventing at least some of the problems is to immobilize whole cells, taking a cue from waste treatment technology. Again, applications are so far relatively few.

This paper deals primarily with techniques for submerged culture of free-floating organisms.

The intact cell is an exquisitely balanced Eulerian (or open) thermodynamic and chemical system, which is capable not only of carrying out many thousands of simple and complex reactions in a coordinated way but also of reproducing itself. Thus the cell is autocatalytic.

Assume that we are dealing with fully functional, living systems of microorganisms and that they are being used for the transformation of substrates into useful or desirable products. The objective is to achieve the transformation at the lowest possible unit cost, subject to various constraints, which may be limiting. These constraints might be availability of capital for the physical plant, or operating constraints such as availability of cooling water, electric power, or raw materials. The impact of recovery and purification costs must also be considered. Clearly, a process that yields a dilute product solution might be cheap to run as a fermentation, but recovery costs will ordinarily be high.

We seek to accomplish our objective by adjustment of the physical and chemical environment in the apparatus—that is, the fermentor—so as to direct the balance of the cellular system in a desirable way.

We can now state the fundamental problem of fermentor design. Given a set of physical and chemical manipulations resulting in a set of physical and chemical, and biological conditions, what configuration of apparatus and equipment is best suited to carrying out those manipulations, subject to a set of possibly limiting constraints? The answer to that question constitutes the basic fermentor design for the process.

BASIC FERMENTOR CONFIGURATIONS

Control Variables in a Fermentation Process

We have stated that there is a set of manipulations that can be performed in a fermentation to allow us to arrive at a desired result. Those manipulations are generally of two types: those that can be continually adjusted or controlled and those that cannot. For example, once a particular ingredient has been added to a fermentor, we ordinarily cannot remove or alter the level of that ingredient other than by adding more of it. Other manipulations can be changed at will, for example pH, or temperature.

Of the many fermentor variables that can be listed, only a few are important in making the basic choices of fermentor configuration. These are the fermentor volume, the heat-removal requirement, the oxygen requirement, the CO_2 ventilation requirement, the viscosity developed during the fermentation, the sensitivity of the microbial culture to shear stresses, and

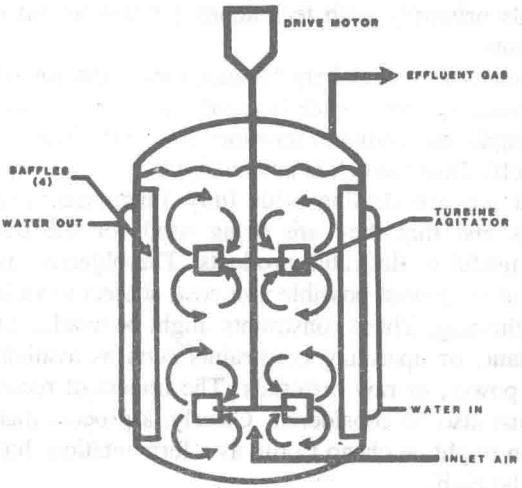

Fig. 1. Schematic diagram of the stirred tank reactor (STR). Arrows show fluid circulation pattern.

the degree of asepsis required. These variables can, in turn, be related to the physical constraints such as cooling water, air, electric power, and steam availability. All other variables are, for the most part, unrelated to the particular fermentor design. The methods of manipulation and control are essentially the same no matter what fermentor configuration is employed.

Basic Fermentor Configurations

Many different fermentor layouts have been proposed, and some have been tested experimentally. However, for processes involving dispersions of free-floating organisms, the reactors can generally be classified into one of three major groups. Fiechter [2], Kristiansen [3], and, more recently, Sittig [4] have listed these with some of their basic characteristics. Consolidating their lists, the three groups are:

1) Reactors with mechanical internal agitation, lacking a loop (Fig. 1). This group includes the traditional stirred tank, and also multi-stage column contactors [eg, ref. 5].
2) Bubble columns (Fig. 2). These are the simplest bioreactors, consisting of a long tube with some sort of sparging device at the bottom. Modified bubble columns are possible, which are fitted with one or more sieve plates or other devices at intermediate positions in the column. These provide redispersion of the gas phase.

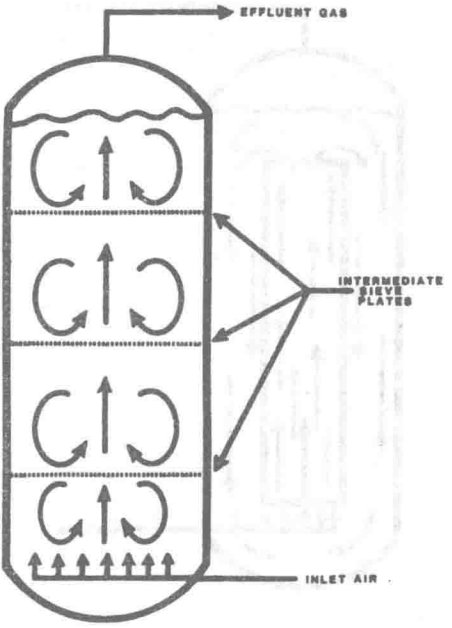

Fig. 2. Bubble column bioreactor. Arrows show fluid circulation pattern.

3) Loop reactors. These are column (or tower) reactors in which mixing and circulation of the liquid contents of the tower are induced by one of three principal means:

a) Air lift loop reactors. In such reactors, circulation is caused by the motion of injected gas through a central tube with fluid recirculating through the annulus between the tube and the tower proper [6] (Fig. 3). Clearly, the gas could flow up through the annulus and return through the central tube as well.

Another well known air lift loop fermentor employs an external circulation loop, as exemplified by the "pressure cycle fermentor" [7–9].

b) Propeller loop reactors [10] (Fig. 4). In this configuration, loop circulation is promoted by a propeller, which acts as a pump to force fluid either up or down through a central draft tube. This configuration includes the Waldhof fermentor as a special case.

c) The jet loop reactor [10] (Fig. 5). Here, an external circulation loop is employed, with a mechanical pump to move the liquid. Gas and recirculated liquid are injected into the tower through a nozzle. Intense shear fields are set up at the nozzle, which disperses the injected gas and redisperses coalesced gas bubbles in the recirculating fluid. A variant of the jet loop reactor