KEYS TO BIOREACTOR SELECTIONS

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Traditionally, microbiologists have played the dominant role in bioreaction development, with assistance from those in multiple disciplines, including biochemists, geneticists and chemical engineers. And while the fermentation process — the precursor to modern bioreactions — has been used since prehistoric days, the major advancements of the last half century have had as much to do with technology as with biology. It is our objective to illustrate the relevance of established chemical engineering practices and processes as they apply to today's bioreaction engineering, as chemical engineers make further inroads into a field once thought to be the sole domain of biology-based scientists.

This article will discuss the key engineering issues in bioreactor design and operation, focusing on the similarities between traditional chemical reactor engineering and bioreaction engineering. Our objective is not to trivialize the field of biological-based processes; it is simply to demonstrate that strong parallels exist between the two fields. In fact, we will also discuss the key differences that must be taken into consideration for successful bioreactions. In so doing, we will provide chemical engineers with increased confidence in applying their knowledge and experience with chemi-

A handful of basic bioreactor designs is used to produce a wide range of products, from antibiotics to foods to fuels. Here's how to pick the best options for your application.

cal reactors to bear on the issues and opportunities available in bioreactor engineering.

The distant and recent past

Long before anyone understood the concept of bioreaction, humans were taking advantage of its results. Bread, cheese, wine and beer were all made possible through what was traditionally known as fermentation — a little-understood process, successful more by chance than design. It was, in fact, the failure and frustration of French vintners who found they were too often producing vinegar not wine, that led the famous French chemist and microbiologist Louis Pasteur to study the fermentation process at their request.

What Pasteur discovered was that fermentation occurred as a result of the biological activity of a microscopic plant called yeast. When unwanted microbes infiltrated the wine and "fed" on the alcohol produced by

the yeast, the microbes left behind distasteful and harmful wastes, which ruined the wine's flavor. Pasteur's work laid the foundation for bioreactors as we know them today, because once the process was identified and understood, it could be controlled. And it is the control of the process that concerns chemical engineers first and foremost. The scope of bioengineering has grown from simple wine-bottle microbiology to the industrialization of not only beer, wine, cheese and milk production, but also the production of biotechnology's newer products — antibiotics, enzymes, steroidal hormones, vitamins, sugars and organic acids.

Bioreactors vs. chemical reactors

By definition, a bioreactor is a system in which a biological conversion is effected. Although this definition can apply to any conversion involving enzymes, microorganisms, and animal or plant cells, for the purposes of this article, we will limit the definition. The bioreactors referred to here include only mechanical vessels in which (a) organisms are cultivated in a controlled manner and/or (b) materials are converted or transformed via specific reactions. Quite similar to conventional chemical reactors, bioreactors differ in that they are specifically designed to influence metabolic pathways. Traditional chemical reactor models and designs that may be used for bioreaction as well include: continuous stirred-tank reactors, continuous flow stirred-tank reactors, and plug-flow reactors, singularly or in series; ebullized-bed (*i.e.*, "bubbling and boiling") reactors; and fluidized-bed reactors. The term "bioreactor" is often used synonymously with "fermenter;" however, in the strictest definition, a fermenter is a system that provides an anaerobic process for producing alcohol from sugar.

Bioreactors differ from conventional chemical reactors in that they support and control biological entities. As such, bioreactor systems must be designed to provide a higher degree of control over process upsets and contaminations, since the organisms are more sensitive and less stable than chemicals. Biological organisms, by their nature, will mutate, which may alter the biochemistry of the bioreaction or the physical properties of the organism. Analogous to heterogeneous catalysis, deactivation or mortality occur and promoters or coenzymes influence the kinetics of the bioreaction. Although the majority of fundamental bioreactor engineering and design issues are similar, maintaining the desired biological activity and eliminating or minimizing undesired activities often presents a greater challenge than traditional chemical reactors typically require.

Organisms, influenced by their morphology and the

■ Figure 1. Installation of a batch, 765-bbl beer fermenter made of stainless steel. (Courtesy of Paul Mueller Co.)

bioreaction medium, are shear-sensitive to varying degrees. A number of bacteria, yeast and fungi cultures that can be relatively tolerant of high-shear environments exhibit a robustness in high-energy mixing vessels. Animal, fish, insect and plant cells are delicate and usually require low-shear environments for viability. The viscosities of bioreaction masses may change during growth and production phases, and, often, the medium becomes non-Newtonian as a cycle progressed. Mixing within the bioreactor is integral to efficient heat and mass transfer during the production phases, which places additional constraints on the suitable agitation mechanism and rheology of the bioreaction medium.

Other key differences between chemical reactors and bioreactors are selectivity and rate. In bioreactors, higher selectivity — that is, the measure of the system's capability for producing the preferred product (over other outcomes) — is of primary importance. In fact, selectivity is especially important in the production of relatively complex molecules such as antibiotics, steroids, vitamins, proteins

and certain sugars and organic acids. Frequently, the activity and desired selectivity occur in a substantially smaller range of conditions than are present in conventional chemical reactors. Further, deactivation of the biomass often poses more severe consequences than a chemical upset.

Rate is of secondary importance. For many biological systems, an incubation period is needed to prepare a culture used to inoculate the bioreactor with the producing microbes or their precursors. Although a bioreaction can be brief, in systems where organism or biomass growth is necessary, the bioreaction can take 10–20 d for completion of the batch. Further, the bioreactor should not be regarded as an isolated unit, but as part of an integrated unit operation with both upstream (preparation) and downstream (recovery) unit operations.

Products of bioreactions

Bioreaction products are formed by three basic processes:

1. Processes in which the product is produced by the cells is either extracellular, e.g., alcohols or critic acid, or intracellular, e.g., a metabolite or enzyme. Production of cellular products is divided into two types, based on when they are produced within a biological cycle. Primary metabolites are produced during growth and are essential for continuing growth. Secondary metabolites are produced after growth has ceased. Primary metabolites include amino acids, nucleotides, nucleic acids, proteins, lipids and carbohydrates. Examples of primary products for industrial use include ethanol, citric acid, acetone, butanol, lysine, polysaccharides and vitamins.

Secondary cellular products are formed from the intermediates and products of primary metabolism, and tend to be specific to a species or group of organisms. Not all microorganisms produce secondary metabolites, but they are widespread among the filamentous fungi and plants. Many secondary products have toxic or antibiotic properties and are, as such, the basis of much of the antibiotic industry. Production of enzymes via bioreactions has displaced inefficient extraction techniques with mutation and genetic manipulation. Industrial enzymes find their home in baking, brewing, grain processing, dairy making, and in the production of detergents, juices, wines and other products.

2. Processes that produce a cell mass. Bakers' yeast, used in the baking industry, is an example of a produced cell mass. Others include single-cell proteins for food sources.

3. Processes that modify a compound that is added to the fermentation process are referred to as biotransformations. Biotransformations occur using the inherent enzymatic capability of most cells. Cells of all types can be employed to biocatalyze a transformation of certain compounds via dehydration, oxidation, hydroxylation, amination or isomerization. Enzymatic conversions frequently exhibit lower activation energies and higher selectivity than their chemical counterparts. Steroids, antibiotics and prostaglandins can all be produced via biotransformations.

Key issues in bioreactor design and operation

The goal of an effective bioreactor is to control, contain and positively influence the biological reaction. To accomplish this, the chemical engineer must take into consideration two areas. One is the suitable reactor parameters for the desired biological, chemical and physical (macrokinetic) system. The macrokinetic system includes microbial growth and metabolite production. Microbes can include bacteria, yeast, fungi, and animal, plant, fish and insect cells, as well as other biological materials.

The other area of major importance in bioreactor design involves the bioreaction parameters, including:
- controlled temperature
- optimum pH
- sufficient substrate (usually a carbon source), such as sugars, proteins and fats
- water availability
- salts for nutrition
- vitamins
- oxygen (for aerobic processes)
- gas evolution and
- product and byproduct removal.

In addition to controlling these, the bioreactor must be designed to both promote formation of the optimal morphology of the organism and to eliminate or reduce contamination by unwanted organisms or mutation of the organism.

This article will provide a description and overview of a variety of bioreaction systems, including both bioreactors that are production-oriented and those used for environmental control. We will discuss the advantages and disadvantages of the various systems, with a brief mention of the typical applications for each. It is also worth noting here that there is a wide variety of bioreaction systems, and any attempt to categorize them by their various attributes will naturally result in some overlap of system characteristics.

We will *not* include all the various subtopics that may be relevant, since the study of bioreactions is so expansive that it would be impossible to include subtopics here in any detail. Those subtopics not covered include: microbiology, sterilization, rheology, mixing, agitator design, fluidization, heat transfer, mass transfer, surface phenomena and transport enhancements, kinetics, hydrodynamics, scaleup, modeling, instrumentation and process control. For the most part, an abundance of literature exists on these conventional chemical processes, and the treatment is frequently directly applicable to bioreactors with only slight modifications to accommodate for the living organisms involved in the process. For more in-depth reading on these topics, see the section on Further Reading at the end of this article.

Bioreaction/fermentation technologies

Now we will discuss the engineering aspects and applications for a variety of bioreaction/fermentation technologies, including the challenges of each and the advantages and disadvantages of the respective technologies. The various types

of bioreaction systems covered here include batch, continuous, semi-continuous, surface/tray, submerged, air-lift loop and trickle-bed setups. As stated before, there are overlapping characteristics in several of the technologies discussed.
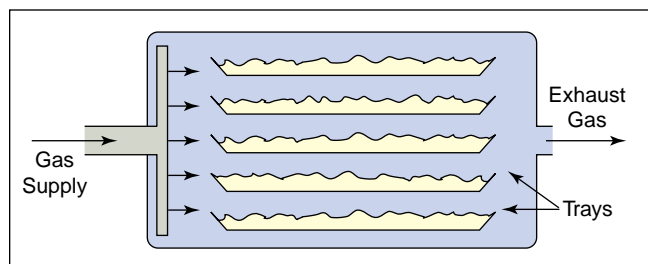
Batch bioreactions

The majority of bioreactions are batch-wise. The first phase of batch bioreaction is commonly sterilization, after which the sterile culture medium is inoculated with microorganisms that have been cultivated to achieve a specific result. During this dynamic reaction period, cells, substrates (including the nutrient salts and vitamins) and concentrations of the products vary with time. Proper mixing keeps the differences in composition and temperature at acceptable levels.

To promote aerobic cultivation, the medium is aerated to provide a continuous flow of oxygen. Gaseous byproducts formed, such as CO_2, are removed, and aeration and gas-removal processes take place semicontinuously.

Next, an acid or alkali is added if the pH needs to be controlled. To keep foaming to acceptable levels, antifoaming agents may be added when indicated by a foam sensor. A large, stainless steel batch fermenter for producing beer is shown in Figure 1. (A batch fermenter is similar to the bioreactor shown in Figure 3, but without the recycle loop.) One of the first types of batch systems is the tray fermenter (Figure 2), used in the early days of commercial aerobic bioreactions for products such as citric acid and penicillin. In this system, the trays are loaded with the culture medium and the organisms, and the airflow produces the bioreaction, during which exhaust gas is discharged. When the bioreaction is complete, end product is removed from the trays. Because this method is inefficient for producing large commercial quantities, it fell quickly to the wayside with the emergence of submerged tank systems, which are designed to handle significantly higher volumes.

Overall, batch bioreaction systems provide a number of advantages, including:
• Reduced risk of contamination or cell mutation, due to a relatively brief growth period.
• Lower capital investment when compared to continuous processes for the same bioreactor volume.
• More flexibility with varying product/biological systems.

• Higher raw material conversion levels, resulting from a controlled growth period.
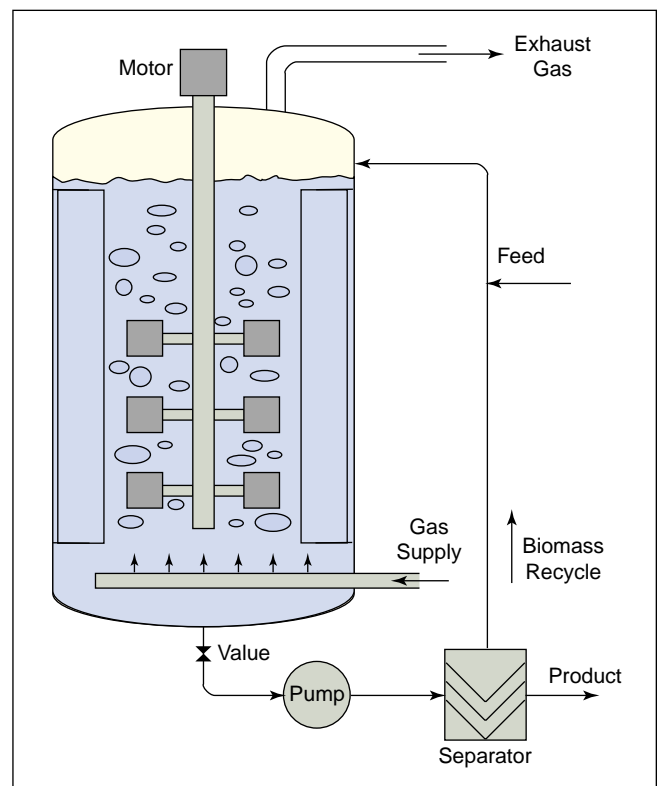The disadvantages include:
• Lower productivity levels due to time for filling, heating, sterilizing, cooling, emptying and cleaning the reactor.
• Increased focus on instrumentation due to frequent sterilization.
• Greater expense incurred in preparing several subcultures for inoculation.
• Higher costs for labor and/or process control for this non-stationary process.
• Larger industrial hygiene risks due to potential contact with pathogenic microorganisms or toxins.
Common applications for batch bioreactors include:
• Products that must be produced with minimal risk of contamination or organism mutation.
• Operations in which only small amounts of product are produced.
• Processes using one reactor to make various products.
• Processes in which batch or semicontinuous product separation is adequate.

Continuous bioreactions

The defining characteristic of continuous bioreaction is a perpetual feeding process. A culture medium that is ei-

■ Figure 2. A tray bioreactor is loaded with the culture medium and organisms, then airflow is started to initiate the reaction.

■ Figure 3. Stirred-tank bioreactor uses baffles and an agitator for optimal mixing, and recycles biomass.

ther sterile or comprised of microorganisms is continuously fed into the bioreactor to maintain the steady state. Of course, the product is also drawn continuously from the reactor. The reaction variables and control parameters remain consistent, establishing a time-constant state within the reactor. The result is continuous productivity and output. These systems provide a number of advantages, including:

• Increased potential for automating the process.
• Reduced labor expense, due to automation.
• Less non-productive time expended in emptying, filling and sterilizing the reactor.
• Consistent product quality due to invariable operating parameters.
• Decreased toxicity risks to staff, due to automation.
• Reduced stress on instruments due to sterilization.

The disadvantages of continuous bioreactors include:

• Minimal flexibility, since only slight variations in the process are possible (throughput, medium composition, oxygen concentration and temperature).
• Mandatory uniformity of raw material quality is necessary to ensure that the process remains continuous.
• Higher investment costs in control and automation equipment, and increased expenses for continuous sterilization of the medium.
• Greater processing costs with continuous replenishment of non-soluble, solid substrates such as straw.
• Higher risk of contamination and cell mutation, due to the relatively brief cultivation period.

Continuous bioreaction is frequently used for processes with high-volume production; for processes using gas, liquid or soluble solid substrates; and for processes involving microorganisms with high mutation-stability. Typical end products include vinegar, baker's yeast and treated wastewater.

Continuous vs. batch

There are several major advantages to using continuous bioreactions as opposed to the batch mode. First, continuous reactions offer increased opportunities for system investigation and analysis. Because the variables remain unchanged, a benchmark can be determined for the process results, and then the effects of even minor changes to physical or chemical variables can be evaluated. Also, by changing the growth-limiting nutrient, changes in cell composition and metabolic activity can be tracked. The constancy of continuous bioreaction also provides a more accurate picture of kinetic constants, maintenance energy and true growth yields.

Secondly, continuous bioreaction provides a higher degree of control than does batch. Growth rates can be regulated and maintained for extended periods. By varying the dilution rate, biomass concentration can be controlled. Secondary metabolite production can be sustained simultaneously along with growth. In steady-state continuous bioreaction, mixed cultures can be maintained using chemostat cultures — unlike in batch bioreaction, where one organism usually outgrows another. Chemostats are continuous-flow stirred-tank bioreactors (CFSTRs) in an idealized steady-state, i.e., the feed- and outlet-stream compositions and flows are constant, and perfect mixing occurs within the CFSTR vessel. In chemostats, the outlet stream composition is considered to be the same as within the bioreactor. Bioreactors operated as chemostats can be used to enhance the selectivity for thermophiles, osmotolerant strains, or mutant organisms with high growth rates. Also, the medium composition can be optimized for biomass and product formation, using a pulse-and-shift method that injects nutrients directly into the chemostat. As changes are observed, the nutrient is added to the medium supply reservoir and a new steady state is established.

A third advantage is the quality of the product. Because of the steady-state of continuous bioreaction, the results are not only more reliable, but also more easily reproducible. This process also results in higher productivity per unit volume, because time-consuming tasks, such as cleaning and sterilization, are unnecessary. The ability to automate the process also renders it less labor-intensive, and, therefore, more cost-efficient and less sensitive to the impact of human error.

Along with the strengths of continuous bioreaction, there are inherent disadvantages that may make this process unsuitable for some types of bioreaction. For example, one challenge lies in controlling the production of some non-growth-related products. For this reason, the continuous process often requires feed-batch culturing, and a continuous nutrient supply. Wall growth and cell aggregation can also cause wash-out or prevent optimum steady-state growth.

Another problem is that the original product strain can be lost over time, if it is overtaken by a faster-growing one. The viscosity and heterogenous nature of the mixture can also make it difficult to maintain filamentous organisms. Long growth periods not only increase the risk of contamination, but also dictate that the bioreactor must be extremely reliable and consistent, incurring a potentially larger initial expenditure in higher-quality equipment.

Semicontinuous bioreactions

This hybrid of batch and continuous operations is found in many types of processes. One of the more frequently used is initiating the bioreaction in the batch mode, until the growth-limiting substrate has been consumed. Then, the substrate is fed to the reactor as specified (batch) or is maintained by an extended culture period (continuous). For secondary metabolite production, in which cell growth and product formation often occur in separate phases, the substrate is typically added at a specified rate. Like batch reactors, semicontinuous reactors are non-stationary. These systems provide a number of advantages, including:

• Higher yield, resulting from a well-defined cultivation period during which no cells are added or removed.
• Increased opportunity for optimizing environmental

conditions of the microorganisms in regard to the phase of growth or production and age of the culture.

• Nearly stationary operation, important with slightly mutating microorganisms and those at risk for contamination.

The disadvantages include:

• Lower productivity levels due to time-consuming procedures for filling, heating, sterilizing, cooling, emptying and cleaning the reactor.

• Greater expenses in labor and/or dynamic process control for the process.

Semicontinuous bioreactors are typically used when continuous methods are not feasible, for example, those in which slight mutation or contamination of the microorganism occurs. Such bioreactors are also used when batch methods do not offer the desired productivity levels.

Submerged bioreactors — stirred tank

The most common type of aerobic bioreactor in use today is the stirred-tank reactor, which may feature a specific internal configuration designed to provide a specific circulation pattern. Ideal for industrial applications, this unit offers manufacturers both low capital and operating costs. For laboratory experiments with smaller volumes, the mixing vessel is typically made of glass. Stainless steel tank construction is the standard for industrial applications involving larger volumes. The height-to-diameter ratio of the vessel can vary, depending on heat removal requirements.

The operating principles of the stirred-tank bioreactor are relatively simple. As shown in Figure 3, the sterile medium and inoculum are introduced into a sterilized tank, and the air supply typically enters at the bottom. For optimal mixing, the tank features not only an agitator system but also baffles, which help prevent a whirlpool effect that could impede proper mixing. In the early stages of the process, warm water may be circulated through the baffles to heat up the system; later, cool water may be circulated inside of them to keep the process from overheating. The number of baffles typically ranges from four to eight.

As the bioreaction progresses, the bubbles produced by the air supply are broken up by the agitator as they travel upward. Many types of agitators are currently used, with the most common one being the four-bladed disk turbine. Newer designs featuring 12 or 18 blades, or concave ones, have also been shown to improve the hydrodynamics. At the top of the tank, exhaust gas is discharged and the product flows back down, where it is drained from the tank.

In a continuous flow stirred-tank reactor, the substrate is continuously fed into the system and the product is continually drawn out and separated, with the producing organism recycled back into the tank for reuse. As with conventional chemical reactors, bioreactors can be placed in series or parallel with controlled recycle streams.

Airlift reactor systems

Also known as a tower reactor, an airlift bioreactor can be described as a bubble column containing a draught tube.

Many types of airlift bioreactors are currently in use today. Air is typically fed through a sparger ring into the bottom of a central draught tube that controls the circulation of air and the medium (Figure 4). Air flows up the tube, forming bubbles, and exhaust gas disengages at the top of the column. The degassed liquid then flows downward and the product is drained from the tank. The tube can be designed to serve as an internal heat exchanger, or a heat exchanger can be added to an internal circulation loop.

Airlift systems provide some advantages vs. more conventional bioreactors, such as the standard fermenter:

• Simple design with no moving parts or agitator shaft seals, for less maintenance, less risk of defects and easier sterilization.

• Lower shear rate, for greater flexibility — the system can be used for growing both plant and animal cells.

• Efficient gas-phase disengagement.

• Large, specific interfacial contact-area with low-energy input.

• Well-controlled flow and efficient mixing.
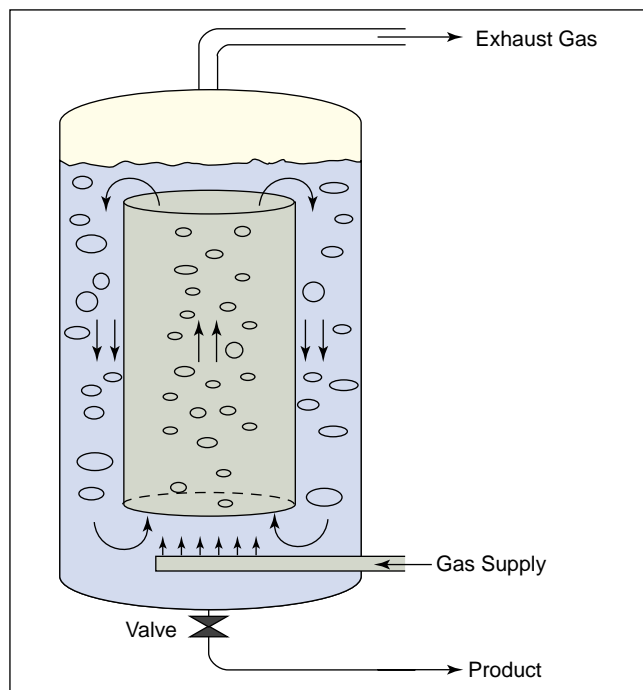
• Well-defined residence time for all phases.

• Increased mass-transfer due to enhanced oxygen solubility achieved in large tanks with greater pressures.

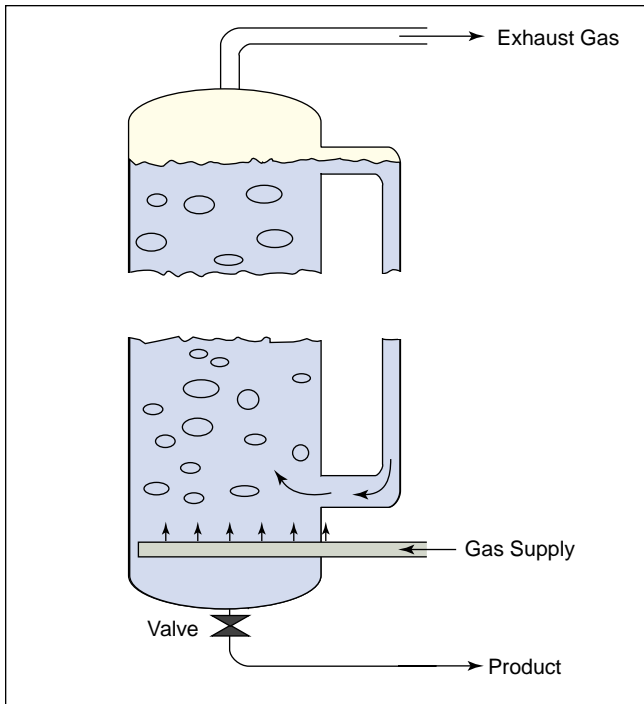• Large-volume tanks possible, increasing the output.

• Greater heat-removal vs. conventional stirred tanks.
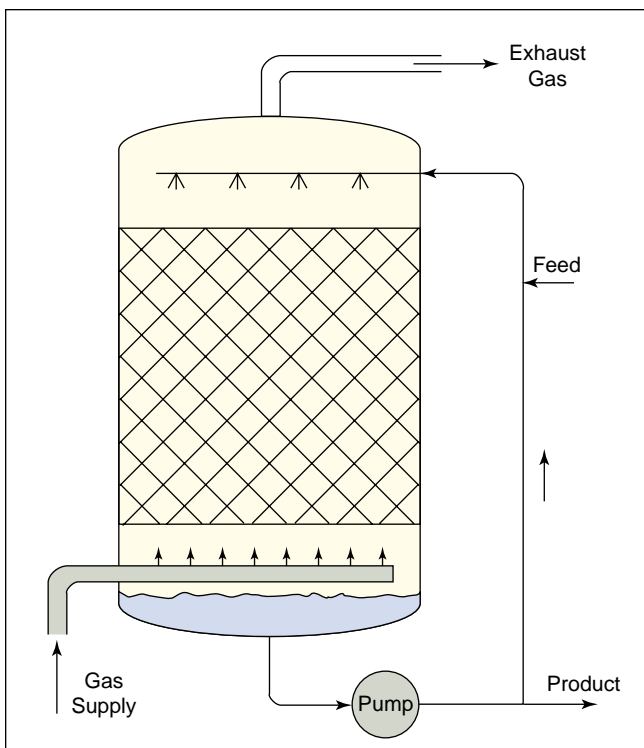
The main disadvantages are:

• Higher initial capital investments due to large-scale processes.

■ Figure 4. The simple design of a concentric draught-tube bioreactor with annular liquid downflow results in less maintenance.

■ Figure 5. An airlift external-loop reactor has induced circulation that directs air/liquid throughout vessel.

■ Figure 6. A trickle-bed employs adhered, immobilized enzymes to accomplish a reaction.

• Greater air throughput and higher pressures needed, particularly for large-scale operation.

• Low friction with an optimal hydraulic diameter for the riser and downcomer.

• Lower efficiency of gas compression.

• Inherently impossible to maintain consistent levels of substrate, nutrients and oxygen with the organisms circulating through the bioreactor and conditions changing.

• Inefficient gas/liquid separation when foaming occurs.

However, these disadvantages can and must be minimized in designing airlift systems. For example, if only one location serves as the feed source, the organism would experience continuous cycles of high growth, followed by starvation, resulting in the production of undesirable byproducts, low yields and high mortality rates. A design with multiple feed points eliminates this risk, especially for large-scale operations. The same risks are inherent in a single entry point for oxygen, which must be delivered at various places within the vessel, with the majority of the air entering at the bottom to circulate the fluid through the reactor.

Airlift external-loop reactors

Another type of airlift system is the airlift external-loop reactor system (AELR; Figure 5), used primarily for batch operation. Figure 5 shows a cut-away view, that is, the vessel and downcomer are actually taller than shown for the particular diameter drawn. A variation of the airlift system, the AELR uses induced circulation to direct air and liquid throughout the vessel. This system consists of a riser and an external downcomer, which are connected at the bottom and the top, respectively. As the injected air at the bottom of the riser creates gas bubbles that begin to rise through the main tank, exhaust gas disengages at the top and the resulting heavier solution descends through the downcomer.

The AELR has some advantages over standard airlifts:

• Effective heat-transfer and efficient temperature control.

• Low friction with an optimal hydraulic diameter for both the riser and downcomer.

• Well-defined residence time in the individual section of the AELR.

• Increased opportunity for measurement and control in the riser and the downcomer.

• Independent control of the gas input-rate and liquid velocity by a throttling device between riser and downcomer.

Anaerobic bioreactions

Anaerobic bioreactions are used in applications such as ethanol production, winemaking, beer brewing and wastewater treatment. Technologies are well established in wine, ethanol and beer production, with improvements resulting from product improvements and manufacturing cost reductions. Continuous bioreactors for beer have been commercialized, however, batch fermenters continue to receive capital investments. Waste treatment is a field largely considered to have matured with fully functional technolo-

gy in place, therefore, not as much attention has been paid to developing newer wastewater treatment processes.

Technologies under development

A number of new processes are being developed. One involves the use of isolated enzymes rather than whole cells to carry out a chemical change. The advantage is that this process does not require catering to the special requirements of living cells. However, enzymes, too, can undergo changes and, therefore, require determining the optimal conditions to express their catalytic activity. An additional problem is that using isolated enzymes is frequently an expensive undertaking for a single use application.

Consequently, long reaction times may be necessary if cost factors necessitate that expensive enzymes must be used only in low concentrations. There are other disadvantages to their use, too, such as the need to remove the enzyme from the product once the desired bioreaction has taken place.

Immobilized enzyme technology is now successfully solving some of these difficulties. With the enzyme immobilized in a bed or tube, the solution of substrate for conversion is then passed through for conversion to product. The product is continuously collected as effluent from the bioreactor. The design and operation of an immobilized system is similar to that of processes employing heterogeneous catalysis. Heterogeneous systems enable product recovery at lower separation costs than do corresponding homogeneous systems.

Gas-liquid-solid contacting bioreactors have been investigated with a number of immobilized enzyme systems. Enzyme immobilization can take a variety of different forms and it has been studied on a range of supports. The method used in a particular application depends on the characteristics of the enzyme, its system, the substrate and the bioreactor fluid. Enzymes may be supported on a mesh-type or conventional mass-transfer structure, encapsulated in a film, supported by gel or silica-derived systems, on macroporous ion-exchange resins, or on other polymeric supports.

One system that currently employs this technology is the trickle bed bioreactor (Figure 6). Not unlike certain types of biofilters traditionally used for emission control, this system features a screen onto which the enzyme is adhered and immobilized, and through which the substrate solution is passed for conversion.

Membranes and hollow fibers have been tried for immobilized bioreaction systems. An example is hollow fibers with enzymes incorporated into their walls. The diffusion of the substrate through the tube wall allows contact with the gelled enzyme and conversion into product. Subsequent diffusion of the product provides the separation necessary for its recovery. Under the influence of the differential pressure across the tube wall, the product flows through to the inside of the tube, eventually to be collected at a multitube header. Ethanol production has been achieved in the laboratory with immobilized enzymes in fixed-bed and membrane reactors. Enzymes have already been successfully tested for sugar conversion to ethanol.

Glucose isomerization to fructose is a well-established, high-volume commercial process for the production of high-fructose corn syrup (HFCS). Technologies using immobilized glucose isomerase in fixed-bed and fluidized bioreactor continue to be developed.

Summary

Bioreactors will be integral to the development of many new high-value products and the replacement of existing chemical-based commodity processes. The proper selection and design of the bioreactor will determine the optimal commercial bioprocess and the corresponding capital investment. The bioreactor should not be regarded as an isolated unit, but as part of an integrated unit operation with both upstream (preparation) and downstream (separations) unit operations.   **CEP**

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