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Bioreactors – Technology and Design Analysis

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Abstract: *A bioreactor provides a controllable environment enabling the biological, biochemical and biomechanical requirements to manufacture engineered products. As the bioreactor aims to create a desired biological product, it is important to closely monitor the reaction parameters like internal and external mass transfer, heat transfer, fluid velocity, shear stress etc. The effects of such reaction variables on biological cultures and analyzing the other parameters such as oxygen, carbon dioxide, nutrients and metabolism waste material transports have been addressed in the paper. Sophisticated and sound bioreactor design with unique performance characteristics is essential in production of useful biotechnological products from natural and genetically modeled cell systems. Understanding of the mass transfer behavior in bioreactors would result in improved reactor designs, reactor operation, and modeling tools, which are important for maximizing reaction rates, optimizing throughput rates and minimizing cost. The paper discusses the bioreactor design and various types of bioreactors, which are useful for industrial operations.*

Keywords: Bioreactor, batch & continuous reactors, fed-batch, CSTR, air-lift, bubble-column, plug flow

I. INTRODUCTION

Bioreactors can broadly be defined as a vessel, deployed to utilize the activity of a biological catalyst to achieve a desired chemical transformation. Bioreactor generally provides a biomechanical and a biochemical environment that controls nutrient and oxygen transfer to the cells and metabolic products from the. It could also be defined as an engineered device designed for optimal growth and metabolic activity of the organism through the action of biocatalyst, enzyme or microorganisms and cells of animals or plants .The raw material could be an organic or an inorganic chemical compound or even complex material. The product of conversion may include Baker's yeast, single cell protein, starter cultures, animal feed etc. or primary metabolites (e.g. amino acids, organic acids, vitamins,polysaccharides, ethanol, etc.) and secondary metabolites (e.g. antibiotics etc.). Bioreactors can be used for bioconversion or biotransformation products(steroid biotransformation, L-sorbitol etc.),enzymes (amylase, lipase, cellulose etc.), recombinant products (some vaccines, hormones such as insulin and growth hormones etc.). Varied Bioreactor designs have been developed to cater to a wide array of substrate products and biocatalysts.Bioreactors differ from conventional chemical reactors to the extent that they support and control biological entities. As the organisms are more sensitive and less stable than chemicals, bioreactor systems must be robust enough to provide a higher degree of control over process upsets and contaminations (Williams J.A., 2002).The bioreactor conditions should be favorable for the living microorganisms to exhibit their activity under defined conditions. This calls for a series of special features in the reaction engineering of biocatalytic processes . Maintaining the desired biological activity and minimizing undesired activities are certain challenges as biological organisms, by their nature, would mutate and hence alter biochemistry of the reaction or physical properties of the organism. The term bioreactor is often used synonymously with fermenters, which is a type of bioreactor using a living cell as the biocatalyst. Fermentation is referred to the
growth of microorganisms on food, under either aerobic or anaerobic conditions. Fermenters are made up of glass, glass exotic alloys, stainless steel, glass-lined steel, and plastic tanks equipped with gauges. These are used for the growth of products.

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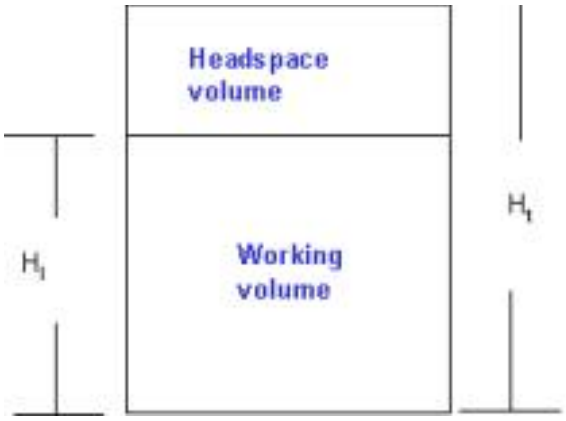
II. BIOREACTOR DESIGN AND OPERATIONS.

A good bioreactor design should address improved productivity, validation of desired parameters towards obtaining consistent and higher quality products in a cost effective manner. The design and mode of operation of a bioreactor depends on the production of the organism,optimum conditions required for desired product formation, product value and its scale of production. The effective bioreactor is to control and positively influence the biological reaction and must prevent foreign contamination. The capital investment and operating cost are also important factors to be considered in bioreactor design. During the fermentation, monostatic conditions, optimal mixing with low, uniforms heartrates should be maintained throughout the process.A culture can be aerated by one, or a combination, of the following methods: surface aeration, direct sparing, indirect and/or membrane aeration, medium perfusion, increasing the partial pressure of oxygen and increasing the atmospheric pressure.

Adequate mass transfer (oxygen), heat transfer, clearly defined low condition and appropriate feeding of substrate avoiding under or overdosing would need to be maintained in a bioreactor. Proper supply of suspension of solids, sufficient substrate, salts for nutrition, vitamins etc. should be ensured with water availability and oxygen (for aerobic processes). Gas evolution product and by-product removal need to be taken care of. The attributes of a bioreactor should comply with design requirements such as sterilization, simple construction and measuring, process control devices, regulating techniques, scale-up, flexibility in operations, compatibility with upstream and downstream processes, antifoaming measures etc. are essential factors.

The basic features of a bioreactor include headspace volume, agitator system, oxygen delivery system, foam control, temperature & pH control system, sampling ports, cleaning and sterilization system and lines for charging & emptying the reactor .These are briefly described as follows:

Headspace Volume: The working volume of a bioreactor is the fraction of its total volume taken up by the medium, microbes, and gas bubbles and remaining volume is called the headspace. Generally, the working volume will be ~70-80% of the total reactor volume. This, however, depends on the rate of foam formation during the reactor(Van't R, 1991).



III. LITERATURE

To assess the exhibition of various arrangement strategies reasonably, it is prudent to utilize a bunch of contextual analyses as benchmark issues. In this segment, we propose a bunch of four issues which have been very much recorded in the writing. Besides, these chose issues have been now tackled by various explores utilizing generally unique methods, so

1. Fed-batch reactor for ethanol production: this case study considers the dynamic optimization of a fed-batch reactor involving the production of ethanol by Saccharomyces cerevisiae, as studied by Chen and Hwang ,Luus , Banga et al. Balsa-Canto et al and Jayaraman et al . The (free terminal time) optimal control problem is to maximize the yield of ethanol using the feed rate as the control variable.

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2. Fed-batch reactor for penicillin production: this problem considers the dynamic optimization of a fed-batch reactor for the production of penicillin. It was studied by Lim et al. and revised by Cuthrell and Biegler . The same problem was also studied by Luus using Iterative Dynamic Programming, and by Banga and co-workers using a CVP scheme and stochastic optimization methods. The optimal control problem is to maximize the total amount of penicillin produced (performance index) using the feed rate of substrate as the control variable.

3. Park-Ramirez fed-batch bioreactor: this problem deals with the optimal production of secreted protein in a fed-batch reactor, as originally formulated by Park and Ramirez . It has also been considered by other researchers as an example of a challenging singular optimal control problem . The objective is to maximize the secreted heterogonous protein by a yeast strain in a fed-batch culture. The dynamic model accounts for host-cell growth, gene expression, and the secretion of expressed polypeptides.

4. Lee-Ramirez fed-batch bioreactor: this problem was first presented by Lee and Ramirez and deals with the optimal fed-batch control of induced foreign protein production by recombinant bacteria. The nutrient and inducer feeding rates to the fed batch bioreactor are the control variables. The objective is to maximize the profitability of the process (i.e. the difference between the value of the product and the cost of the inducer) for a specified final time of fed-batch operation. The same problem was studied by Tholudur and Ramirez using neural network parameter function models, and by Carrasco and Banga , who used adaptive stochastic algorithms to obtain better results. These authors indicated that in the original formulation the performance index exhibited a very low sensitivity with respect to the controls. Recently, Tholudur and Ramirez presented a modified parameter function set for this problem in order to increase the sensitivity to the controls.

IV. METHODOLOGY

The complexity of modern vaccines breeds manufacturing challenges for pharmaceutical companies working to meet a growing demand. “Vaccine manufacturing is challenging; and the larger the scale, the greater the challenge,” says William Reed, PhD, vice president, industrial operations, USA, sanofi pasteur, Swiftwater, Pa. In part, the challenge arises from the nature of vaccines, which are produced by biological processes. Instead of simply mixing chemicals to make a small molecule, pharmaceutical companies grow vaccines in a series of steps, including fermentation. As Reed says, “These are biological processes that are very difficult to characterize and control. Therefore, they are part science and part art.

1. In chemical processes, conditions are fixed and well-researched With the biological processes involved in vaccine production, the variables are magnitudes greater because of using living organisms. As a result, vaccine production does not always scale geometrically. To a point, you can scale that way, but processes must be specific to the scale you are operating at. For example, very small changes in the reagents can produce large changes in the efficacy of the resulting vaccine and the efficiency of producing it. “There are many minor components present in any number of media reagents at levels below the level of detection of existing analytical methodologies. Some of them could increase several fold before they could be detected. These changes in minor components of raw materials can result in significant changes in the vaccine-manufacturing process.” If such changes decrease the quality of the product, scientists at sanofi pasteur create a “process excellence team” to determine what caused the change. Then the analytical teams attempt to determine specifically what has changed. At the same time, the procurement teams attempt to identify specific lots of raw materials whose introduction matches up with the event.

2. To some extent, how a vaccine gets manufactured depends on its intended use. All vaccines we manufacture are produced with the highest regard for safety for both the patient and the manufacturing personnel. And that can change a company’s approach.

A Phase 1 clinical program may involve hundreds of vaccine doses, and a Phase 2 study can involve thousands. As we make the first few hundred doses at a small scale, it is important to do this in a process that can easily be increased in scale. Once a company brings a vaccine to commercial scale, it is already well-characterized and validated. The objective then becomes to maintain and monitor the process to avoid any process drift and deliver a product that is consistent with that which was used in the clinical trials and ultimately approved by the regulators. So, in general, companies keep manufacturing consistent across clinical trials, especially late-stage ones, and commercial-scale

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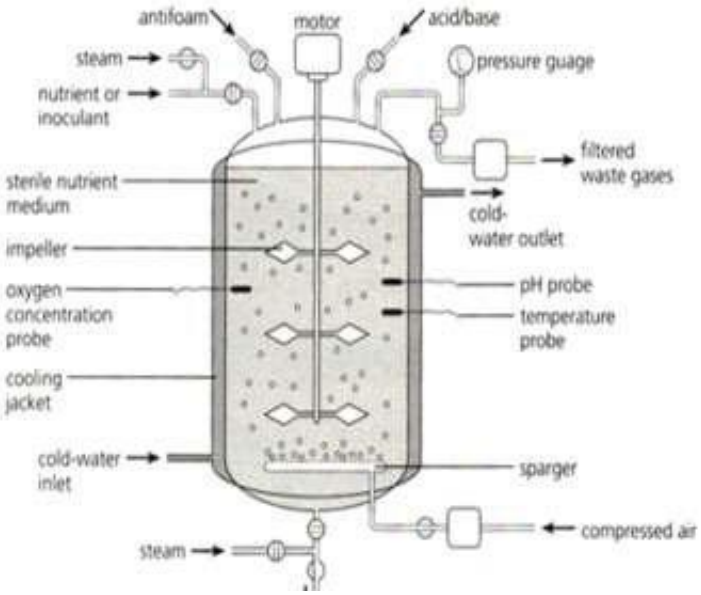
production. You want to be certain that throughout the development, scale-up, and product-manufacture phase that you have similar and consistent product characteristics.

V. BATCH BIOREACTOR DESIGN



Batch bioreactors consist of a single tank capable of carrying out sequences of reactions and are easy to operate. The tank is equipped with an agitator (stirred tank reactor – STR) to mix the reactants along with an integral heating and cooling system. Buffer solution or pH controller is used to control pH of the reactant. These vessels may vary in capacity
from less than 1 liters to more than 15,000 liters. Liquids and solids are usually charged via inlets in the top cover of the reactor. Vapors and gasses also discharge through connections in the top.Usually liquids are removed from the bottom. .STRs are generally jacketed for steam heating or cooling requirements and are equipped with baffles and round sparger for aeration.The impeller in STRs is is connected to an external motor, which drives the stirrer system. The agitator assembly, including the seal, is a route of contamination and hence the shaft has to pass into the bioreactor through a set of aseptic seals.The impellers contribute to mixing and dissolution of the required atmospheric oxygen into the aqueous phase, and maximize the interfacial area between the gaseous and aqueous phase. The design of the impeller blades,speed of agitation and the depth of liquid determines the effectiveness of agitation. The important variables, which affect mixing and mass transfer rates are number and types of stirrer, speed of stirrer and the flow rate of gas used. These reactors are preferred for low-volume & high-value products, particularly if many sequential operations are employed to obtain product yields. These reactors are also used when multiple products are produced in the same equipment or when continuous flow is difficult, as in case of highly viscous or sticky solids-laden liquids. STRs are used for homogenization, suspension of solids, dispersion of gas-liquid mixtures, aeration of liquid and heat exchange. They are the most common types of aerobic bioreactors in use today; they may feature a specific internal configuration designed to provide a specific circulation pattern. They can be used with a variety of microbial species and widely adopted for microorganisms, fermentation and plant cell culture. Nutrient concentration pH and amount of dissolved oxygen can be controlled within this type of bioreactors. Advantages of batch reactors include more flexibility with varying product systems and with reduced risk of contamination or cell mutation, due to a relatively brief growth period with lower capital investment as compared to
continuous processes for the same bioreactor volume.

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VI. CONCLUSION

Bioreactors have been used for decades to produce a range of therapeutic bimolecular and other high-value products. They provide the opportunity to monitor and control environmental conditions continuously throughout the culture/reaction period along with the added benefit of maintaining a closed system. They are a critical and integral part of the development of many new processes.The proper selection and design of the bioreactor addressing high process efficiencies would determine the economic viability of bioprocess and its corresponding capital investment. Suitable process engineering calculation methods have been developed to give a quantitative understanding of mass transfer. Innovative methodologies for gas transfer, maintenance of pH, sensors and actuators detectin temperature, optimal feeding. As Bioreactors are highly dependent on temperature control, it is essential to select the suitable temperature control device based on the specific requirements of each application by calculating the heat load. The type of bioreactor would depend upon the morphology of cells, shear tolerance, growth and production behavior of the culture. In the Indian context, developing various bioprocesses with detailed studies on reaction kinetics; mass transfer etc. assumes critical importance especially towards scaling up the process by designing and fabricating suitable bioreactors. The specialization in process & mechanical design and fabrication of bio-processing equipment at the post-graduate biotechnology engineering studies would go a long way in developing indigenous capability of the country.

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