Review Article

THE SCITECH JOURNAL ISSN 2347-7318 ISSN 2348-2311 Online

Bioreactors – Technology & Design Analysis

Jagriti Singh, Nirmala Kaushik* & Soumitra Biswas

Bioprocess & Bioproducts Programme, Technology Information, Forecasting & Assessment Council (TIFAC) 4th. Floor, 'A' Wing, Vishwakarma Bhavan, Shaheed Jeet Singh Marg, New Delhi – 110 016

Abstract

A bioreactor provides a controllable environment enabling the biological, biochemical and biomechanical requirements to manufacture engineered product. 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 analysing the other parameters such as oxygen, carbon dioxide, nutrient 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 modified cell systems. Understanding of the mass transfer behaviour in bioreactors would result in improved reactor designs, reactor operation, and modelling tools, which are important for maximizing reaction rates, optimizing throughput rates and minimising 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

Introduction

Bioreactors can broadly be defined as a vessel, deployed to utilize the activity of a biological catalyst to achieve a desired chemical transformation(ncsu.edu/biosuceed/courses/./BiorectorEngineering.pptx). Bioreactor generally provides a biomechanical and a biochemical environment that controls nutrient and oxygen transfer to the cells and metabolic products from the cells (Sharma K.R ,2012; El AJ Haj et. al, 2005; Bueno E.M et al, 2004). 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 animal or plants (Development of mathematical model, 1997) .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, cellulase 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 (Prezi.com).

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 favourable 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 (Gudin C et al, 1991). 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 (Williams, J.A, 2002).

The term bioreactor is often used synonymously with fermenter, 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 (Theresa P, Fermentation, biotech.about.com/od/glossary/g/ Fermentation.htm). Fermenters are made up of glass, glass exotic alloys, stainless steel, glass-lined steel, plastic tanks equipped with gauges. These are used for the growth of specialized pure cultures of bacteria, fungi and yeast, production of enzymes and a wide spectrum of fermented products.

The sizes of the bioreactor can vary widely from the microbial cell (few mm3) to shake flask (100-1000 ml) to laboratory scale fermenter (1 – 50 L) to pilot level (0.3 – 10 m3) to plant scale (2 – 500 m3) for large volume industrial applications (ncsu.edu/biosucceed/courses/). There are several aspects of biotechnological processes, which require special attention in designing a bioreactor. The reaction rate, cell growth, and process stability depend on the environmental conditions in the bioreactor. The bioreactor's conditions like gas (i.e. air, oxygen, nitrogen, carbon dioxide) flow rates, temperature, pH and dissolved oxygen levels and agitation speed/circulation rate, foam production, etc. need to be closely monitored and controlled (Chen H.C. et.al, 2006).

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 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, monoseptic conditions, optimal mixing with low, uniform shear rates should be maintained throughout the process. A culture can be

*Corresponding Author
E mail: nirmala.kaushik@gmail.com

aerated by one, or a combination, of the following methods: surface aeration, direct sparging, indirect and/or membrane aeration, medium perfusion, increasing the partial pressure of oxygen and increasing the atmospheric pressure (Eibl R et.al, 2008).

Adequate mass transfer (oxygen), heat transfer, clearly defined flow 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 (Sharma K.R, 2012)

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 (Alaghlavi, 2013). 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).

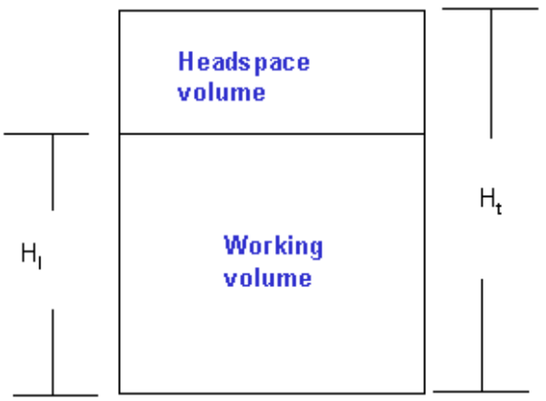


Figure 1. Headspace volume = Ht (Total volume of bioreactor) - Hl (Working volume)(Van't R et.al, 1991)

Agitator system consists of an external power drive, impeller and the baffles for intense mixing and increased mass transfer rates through the bulk liquid and bubble boundary layers. It provides enough shear conditions required for breaking up of bubbles (srmuni.ac.in). Most microbial fermentations use a Rushton turbine type impeller.

Air delivery system consists of a compressor, inlet air, sterilization system, air sparger and exit air sterilization system to avoid contamination.

Foam control system is an essential element of bioreactor as excessive foam formation leads to blocked air exit filters and builds up pressure in the reactor.

Temperature control system involves temperature probes, heat transfer system (jacket, coil). Heating is provided by electric heaters and steam generated in boilers and cooling is provided by cooling water produced by cooling towers or refrigerants such as ammonia.

pH control system uses neutralizing agents to control pH; these should be non- corrosive, non-toxic to cells when diluted in the medium. Sodium carbonate is commonly used in small scale bioreactor.

Sampling ports are used to inject nutrients, water, salts etc. in bioreactors and also for collecting samples .

Cleaning and sterilization system is important to avoid contamination. Thermal sterilisation by steam is preferred option for economical and large-scale sterilizations of equipment. Sterilization by chemical substances is generally preferred for heat-sensitive equipment. Sterilization is carried out by radiation by uv for surfaces and x-rays for liquids and also by membrane filters having uniform microspores and depth filters with glass wool (Van't R, 1991).

Charging & emptying lines are used for input of reactants and withdrawal of products in the bioreactor.

Bioreactors – An Insight into Mass Transfer

Mass transfer, referred as movement of molecules between phases controls or influences the conversion rate of the reactions. In a bioreactor, components for mass transfer may typically include oxygen, electron acceptor, total organic carbon (TOC), chemical oxygen demand (COD), biomass, ammonium and nitrate and macro nutrients (Agomuoh P.K, 2011).The transport of dissolved oxygen (DO) in a bioreactor occurs in three regions as (i) bulk fluid phase of the bioreactor (global mass transfer), (ii) from the bulk to the surface of the aggregated cells (internal mass transfer), (iii) through the aggregated cells (external mass transfer) (Salehi N et.al, 2013)

The mass transfer coefficient is evaluated by using an oxygen sorption method (Lau R et.al, 2012). The interfacial mass transfer area is determined on the basis of its measured bubble size distribution. The liquid-side mass transfer coefficient can be calculated from the volumetric mass transfer coefficient and the interfacial mass transfer area found. The liquid-side mass transfer varies with the superficial gas velocity as dictated by varying bubble rising parameters. (Raymond Lau & Tao Chen, 2012). Static liquid height improves gas-liquid mass transfer rate for increased interfacial mass transfer area. Bubble size due to type of gas distributor used also governs the mass transfer rate.

The two-film theory as proposed by Lewis and Whitman in 1924 attempts to quantity mass transfer from gas to liquid phase of the target compounds in biological systems. According to Henry's law, this model involves two phases with different concentrations , which are not in equilibrium. With the equilibrium existing only at the gas–liquid interface , the target compound moves towards or away from the inter-phase. Velocity of such movement depends on the properties and type of compounds of the two phases i.e. gas & liquid. Such velocities are expressed by the mass transfer rate coefficients. Overall mass transfer coefficient is a combination of mass transfer coefficients of gas phase, liquid phase and biofilm as given in the following equation:

$$1/_{k_{overall}} = 1/k_G + 1/k_L + 1/k_B$$

Where,

$K_{overall}$ - Overall mass transfer coefficient

k_G– Mass transfer rate coefficient of gas phase

k_L - Mass transfer rate coefficient of liquid phase

k_B - Mass transfer rate coefficient of the biofilm

The mass transfer coefficients depend on medium and physio–chemical properties, internal reactor system characteristics and the operating conditions. In suspended type reactors (e.g. airlift, bubble columns, and stirred tanks), the above equation can be applied considering kB as the resistance due to the water film around the cell. Considering resistance to mass transfer in the gas phase and the biofilm to be negligible, the overall volumetric mass transfer rate R from the gas phase to the aqueous phase may be defined in the following equation:

$R=k_{La}(C_G/H-C_L)+DAL/\delta_{film})a(C_G/H-_{CL})$ [Koch A.L, 1990]

where

D_{AL}- Gaseous pollutant diffusivity in the liquid (m2 s−1)

H - Henry coefficient (dimensionless)

δ_{film}- Liquid film thickness (m)

C_G -Pollutant concentrations in gas phase

C_L -Pollutant concentrations in liquid phase

k_{La} – Volumetric coefficient (s−1)

a - Specific interfacial area (m2 m−3) between the gas and liquid phase

Internal mass transfer rates depend on a combination of convection mechanisms, scaffold's structure and porosity, diffusion rate whereas external mass transfer rates depend on hydrodynamic conditions in a bioreactor (Went D et. al, 2008; Rolfe P, 2006).

Types of Bioreactor

There are mainly three types of reactions involved in fermentation process i.e. batch, continuous and semi-continuous or fed-batch depending on the feeding strategy of the culture and the medium into the bioreactor (Brian McNeil & Linda M Harvey, 2008). Traditional batch stirred tank reactors (STRs) and continuously stirred tank reactors (CSTRs) have existed for centuries and are still widely adopted in the chemical and bioprocessing industry for production due to their simplicity (Brian McNeil & Linda M Harvey, 2008). Other bioreactors, which have special design and operational attributes are photo-bioreactors, rotary drum reactors, mist bioreactor, membrane bioreactor, packed & fluidized bed bioreactors, bubble column & air lift bioreactors etc. These have been developed to cater to application specific processes.

Batch Process

In the batch process, after sterilisation, the sterile culture medium is inoculated with microorganisms. During this reaction period, cells, substrates including the nutrient salts, vitamins and concentrations of the products vary with time. The fermentation is allowed to run for a predetermined time and the product is harvested at the end (Carberry James J, 1976). To promote aerobic cultivation, the medium is aerated to provide a continuous flow of oxygen. Gaseous by-products such as CO_2 are removed; aeration and gas removal processes take place semi-continuously (Williams J.A, 2002).

Lag phase: The growth of microbial population when it is inoculated with a fresh medium starts after a certain period of time called lag phase.

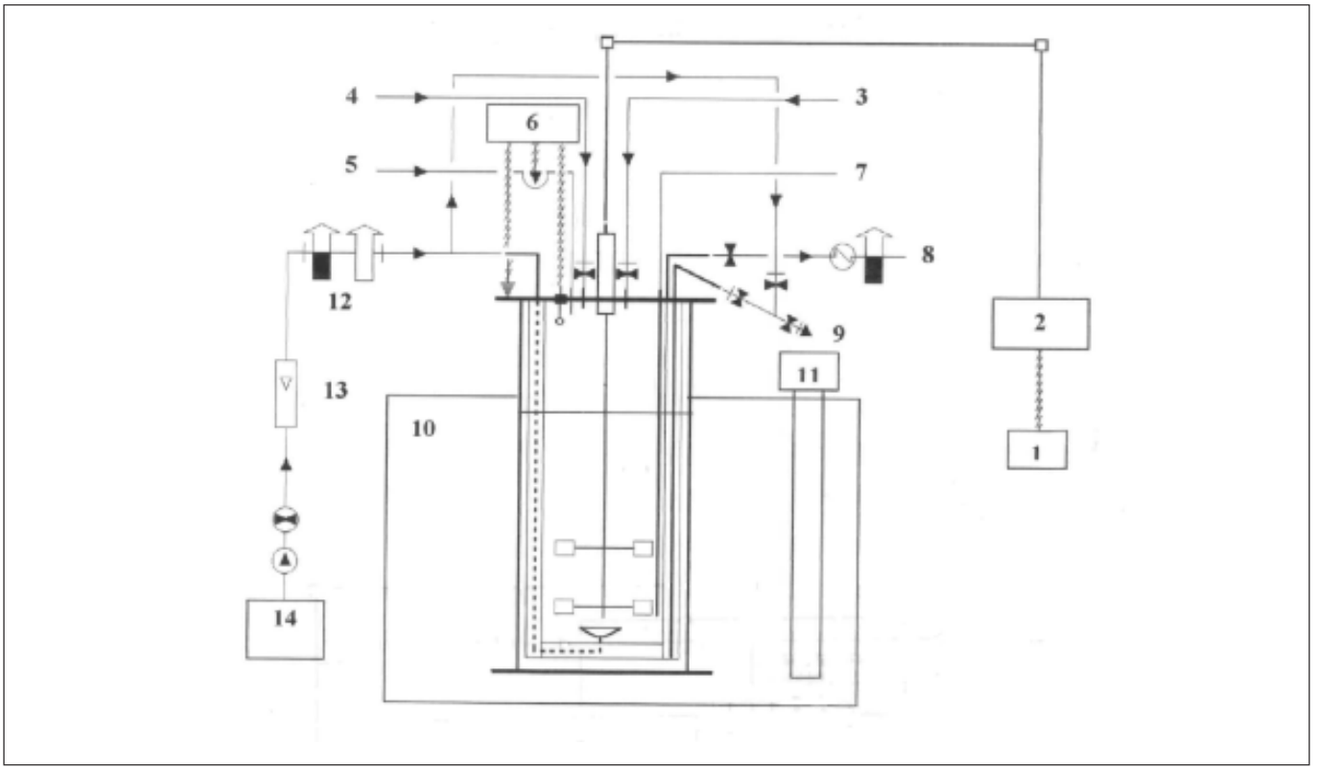


Figure 2. Schematic Representation of Bioreactor-1.Engine regulator 2.engine 3.inoculum 4.carbon source 5.anti-foam 6.anti-foam controller 7.thermometer 8.air exhaust system with filter and condenser 9.sampling 10.water bath 11.temperature controller 12.air filters

THE SCITECH JOURNAL ISSN 2347-7318 ISSN 2348-2311 Online

Log or Exponential phase: In this phase, the microbial cell numbers double per unit time period. When the cell number from such a reaction is plotted on logarithmic scale as function of elapsed time, a curve is obtained with a constantly increasing slope.

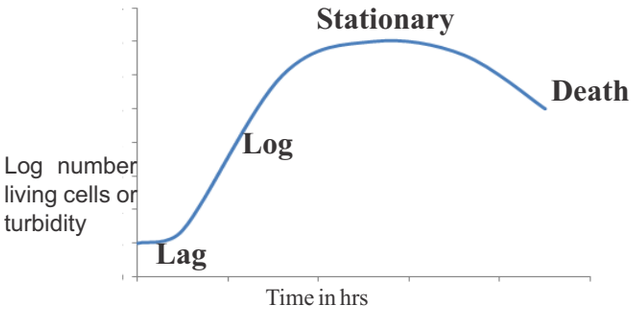


Figure 3. Growth Curve (Nanda S, 2008)

Stationary phase: In stationary phase there is no net increase or reduction in cell number. The cell functions such as energy metabolism and some biosynthetic processes go on.

Death phase: The cells may start dying if the incubation is continued after the bacterial population attains the stationary phase. Cells may die due to cell lysis, which is a much slower process than the growth phase.

Batch Bioreactor Design

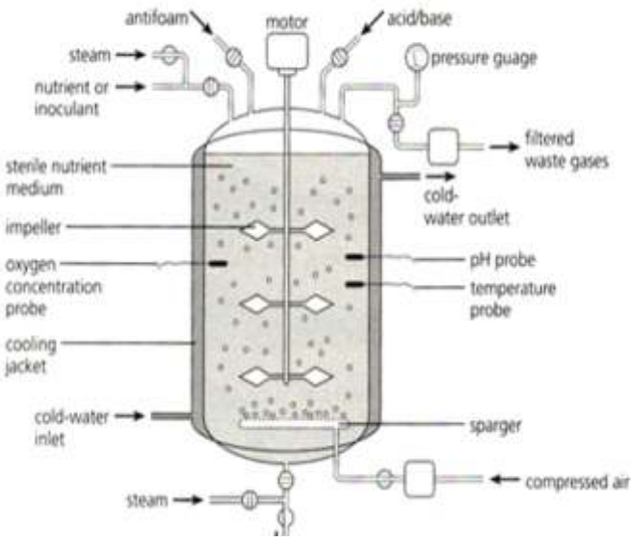


Figure 4. Bioreactor (Shuler & Kargi, 1982)

Batch bioreactors comprise of single tank capable of carrying out sequence of reactions and are easy to operate. The tank is equipped with an agitator (stirred tank reactor – STR) to mix the reactants along with 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 litre to more than 15,000 litres. Liquids and solids are usually charged via inlets in the top cover of the reactor. Vapours and gases also discharge through connections in the top. Usually liquids are removed from the bottom. (Tsuneo & Shoichi, 1984). STRs generally jacketed for steam heating or cooling requirements and are equipped with baffles and round sparger for aeration.

The impeller in STRs 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 (Abbott M.S.R et.al, 2013). 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 (Garcia-Ochoa F& Gomez E, 2009; Martin M et. al, 2008). 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 (William J.A, 2002). STRs are used for homogenization, suspension of solids, dispersion of gas-liquid mixtures, aeration of liquid and heat exchange. They are most common types of aerobic bioreactors in use today; they may feature a specific internal configuration designed to provide 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 (slideshare.net/signtoxic/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.

Mass Balance for Batch Reactors

The batch reactor is assumed well stirred with uniform concentration distribution across the reactor (slideshare.net/signtoxic/bioreactors). Hence,

$d(VC)/dt = Q_{in}.C_{in} - Q_{out}.C_{out} + R.V$

Where $d(VC)/dt$ = Rate of mass accumulation in control volume

Q_{in} = flow rate into the system

Q_{out} = flow rate out of the system

C = Concentration of stream/substrate

R = Rate of reaction

V = Volume of the stream/substrate

The inflow and outflow stream rates are zero

$Q_{in} - Q_{out} = 0$

Hence,

(VC)/dt = RV (if reactant volume changes significantly) or

d(C)/dt = R (if reactant volume remains constant)

R= k. C where k = rate constant, C= concentration

Continuous Process

For a bioreactor on continuous mode operations, fresh medium is continuously added and the products, along with the culture are removed at the same rate, thus maintaining constant concentrations of nutrients and cells throughout the process (Acharya T, 2013; Abbott M.S.R et.al., 2013). Continuous process is frequently used for high-volume production; for reactions 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. Chemostat is a common example of continuous process reactor.

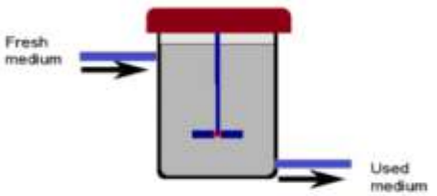


Figure 5. Continuous reactor (Soccol C.R, 2013)

Continuous Bioreactor Design

The reactants are well mixed in a continuous stirred-tank reactor . They are also known as vat- or backmix reactor. The characteristic feature of continuous bioreactor is a perpetual feeding process. Liquid or slurry stream is continuously introduced and liquid contents are continuously removed from the reactor. In practice, mechanical or hydraulic agitation is required to achieve uniform composition and temperature (Martin M, Montes F.J et. al, 2008). A culture medium that is either sterile or comprises of microorganisms is continuously fed into the bioreactor to maintain the steady state. The reaction variables and control parameters remain consistent, establishing a time constant state within the reactor. The result is continuous productivity and output (Brian McNeil & Linda M. Harvey, 2008).

.CSTR requires large volume reactors to obtain desired conversions.Configuration of such reactors is widely used in industrial applications and in wastewater treatment units (i.e. activated sludge reactors) (slideshare.net/signtoxic/bioreactors). By automating the process, there could be reduced labour expense and time saving in filling, emptying and sterilizing the reactor with reduced toxicity risks. CSTRs can yield consistent product quality to invariable operating parameters. However, CSTRs are more energy consuming due to the presence of mechanical pumps.

Mass Balance for CSTR

The material balance for this reactor gives:

d(VC)/dt = Qin.Cin - Qout.Cout + R.V

If the reactor volume is constant and flow rates of the inflow and outflow streams are the same, then

d(C)/dt = 1/τ (Cin - Cout + R)

This parameter τ = V/Q in it is called the mean residence time of the CSTR.

The steady state of the CSTR is described by setting the time derivative in the expression, d(VC)/dt = 0

Q in . C in - Qout . Cout + R.V= 0

Conversion of reactant 'X' is defined for a steady-state CSTR as follows:

X = (Qin. C in - Qout. Cout) / Q in .C in

Fed-batch Process

The process uses a combination of batch and continuous reactions. In this process additional nutrients are added progressively to the reactor as the bioreactions are underway so as to obtain better yields and higher selectivity along with controlling the reaction temperature (slideshare.net/signtoxic/bioreactors). The products are harvested at the end of the production cycle as in a batch bioreactor (Abbott M.S.R et.al, 2013). Semi-batch reactors are stabler and perform safer operations than in a batch reactor.

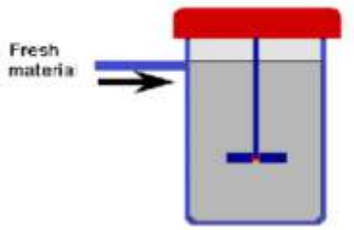


Figure 6. Fed-batch bioreactor (Abbott M.S.R. et.al, 2013)

Special Purpose Bioreactors

Plug Flow Reactor

Plug flow reactors are also referred to as a tubular or piston- flow reactor. It is a vessel, through which the flow is continuous and unidirectional in a steady state. In ideal tubular reactor, the fluids flow as if they were solid plugs or pistons, and reaction time is the same for all flowing material at any given tube cross section. The fluid is hypothesized to flow as plugs or pistons in a tubular reactor with identical reaction time over the reactor cross-section. The concentration of substrates and microorganisms vary throughout the reactor. Tubular reactors are functionally similar to batch reactor as they provide high driving force initially; this reduces as the reaction continues along the tubes. (National Technical University of Athens, 2008).

Fluid flow in small diameter tubes could be laminar for highly viscous liquids and turbulent for gases. Turbulent flow regime for its positive

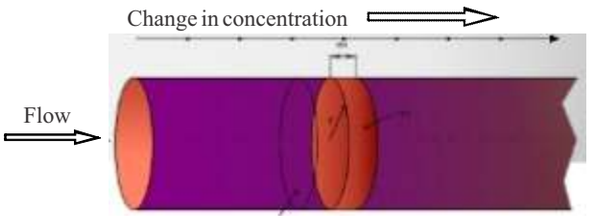
influence on mixing and heat transfer is a preferred choice. The heat transfer rate can be optimised using tubes with larger or smaller diameter arranged in parallel. However, the control of temperature and heat can result in undesirable temperature gradients and which is expensive to maintain (Purohit S, 2013).

Table: 1 Comparison on basis of Mode of Operation (Baron G.V, Willaert R.G et. al, 1996)

Mode of Operation	Advantages	Disadvantages
Batch	Simple equipment; suitable for small production volumes along with multi-product flexibility	Downtime for loading and cleaning; reaction conditions change with time
Continuous	High productivity; better product quality due to constant conditions; good for kinetic Studies	Requires flow control, longevity of catalyst necessary, stability of organisms
Semi-batch or Fed-batch operation	Control of environmental conditions e.g. substrate concentration (inhibition), induction of product formation; most flexible for selecting optimal conditions; most frequently used in biotechnological processes and in fine chemical industry	Requires feeding strategy e.g. to keep constant temperature or substrate concentration

Mass Balance for Plug Flow Reactor

Plug flow in a tube is an ideal-flow assumption in which the fluid is well mixed in the radial directions. The fluid velocity is assumed to be a function of only the axial position in the tube.



Thin disk of area, Ac and length, dz

Figure 7. Plug flow reactor – graphical representation (Agomuoh P.K, 2011)

Considering the reactor cross sectional areas as 'A c' and a thin disk with infinitesimal thickness 'Δz' for the reactor volume element, the material balance for the volume element is as follows:

$d(VC)/dt = Q\,in\,z.\,C\,in - Qout\,z+\Delta z.\,C\,out + R.\,\Delta V$

Where $d(VC)/dt$ = Rate of mass accumulation in control volume

Q in (flow rate into the system) = Q out (flow rate out of the system) = Q

Cin = Concentration of stream at disk inlet (z); Cout = Conc. of stream at disk outlet ($z + \Delta z$)

R = Rate of reaction

V = Reactor volume

Dividing the above equation by ΔV and taking the limit as ΔV goes to zero yields,

$d(C)/dt = - dC.Q/dV + R$

If the tube has constant cross section, 'Ac', then velocity, 'v' is related to volumetric flow rate by $v = Q/Ac$, axial length is related to tube volume by $z = V/Ac$,

The equation can be rearranged as

$dC/dt = -d(C\,v)/ d\,z + R$ or $R = dC/dt - d(Cv)/dz$

Bubble Column Reactor

The bubble column reactor is one of the simplest types of reactors, which is easy to scale-up (Kantarci N, *et al* 2005).The reactor comprises of a cylindrical vessel provided with a gas sparger, which pushes gas bubbles into a liquid phase or a liquid-solid suspension. For rectors handling a solid phase, the reactors are termed as slurry bubble column reactors. (Borakb & Kutlu O. Ulgena, 2005; Henzler H.J & Kauling, 1985). The reactors can be deployed to manufacture environmentally benign synthetic fuels such as methanol.(Kawase Y & Kumagi T, 1991; afrodita.rcub.bg.ac.rs). The bubbles create less shear stress compared to other reactors with agitators (Kantarci N, *et al* 2005).

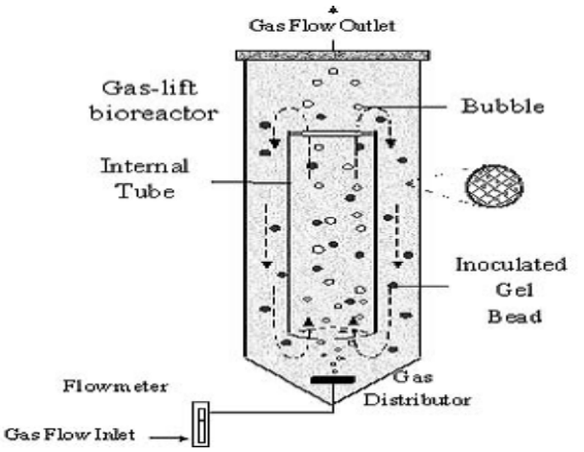


Figure 8. Bubble column bioreactor (Wilkinson P.M et.al, 1992).

Bubble column reactors have excellent heat and mass transfer characteristics. They call for little maintenance and low operating costs due to lack of moving parts and compactness. Bubble column reactors are preferred choice for high durability of the catalyst or other packing material, online catalyst addition and withdrawal ability (Soccol CR et.al, 2013). Bubble columns reactors are used in biochemical processes such as fermentation and biological wastewater treatment (Thorat B.N et.al, 1998). These reactors are also used in methanol synthesis, and manufacture of

other synthetic fuels which are environmentally much more advantageous over petroleum-derived fuels (Soccol C.R et.al, 2013). These are particularly useful for hairy root culture of the plant cells. Although the construction of bubble columns is simple, efficient design and scale-up require an improved understanding of multiphase fluid dynamics and its influences. Their design depends on the three main phenomena i.e. heat, mass transfer & mixing characteristics and chemical kinetics of the reacting system (Borakh K.O.U, 2004) Industrial bubble columns usually operate with a length-to-diameter ratio of at least 5. In biochemical applications this value usually varies between 2 and 5 (Borakh K.O.U, 2004)

Airlift Bioreactor (ALB)

Airlift bioreactor, also known as a tower reactor uses the expansion of compressed gas for mixing. ALBs can be used for both free and immobilized cells and are suitable for bacteria, yeast, fungi, plant, and animal cell. In these reactors, the fluid volume is divided by providing an inner draft tube for improving circulation & oxygen transfer and equalizing shear forces in the reactor (Veera U.P & Joshi J.B, 1999). Air flows up the riser tube, forming bubbles, and exhaust gas is released from the top of the column. The degassed liquid then flows through downcomer and the product is emptied from the bottom of the tank. The downcomer tube can be designed to serve as an internal heat exchanger, or a heat exchanger can be added to an internal circulation loop (Christi M.Y, 1989). Sparging is done either inside or outside the draft tube. In absence of agitation, the reactor requires low energy making it an energy efficient system. ALBs have increased mass-transfer as enhanced oxygen solubility is achieved in large tanks with controlled flow and efficient mixing with good residence time (Bailey & Olis, 1986).

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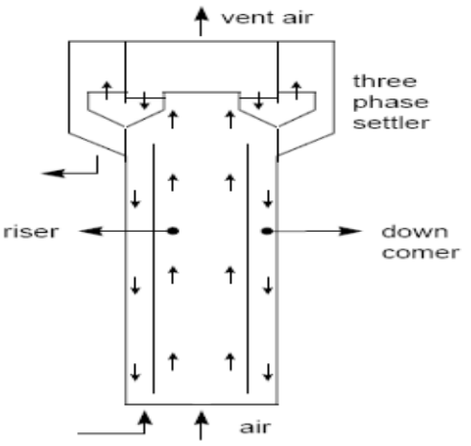

Figure 9. Airlift reactor (Siegel M.H & Robinson C.W, 1992).

Packed Bed Bioreactors

The reactors necessarily constitute a bed of packings, made of polymer, ceramic, glass, natural material, and available in a variety of shapes and sizes that allows fluids to flow from one end to the other. The immobilized biocatalyst is packed in the column and fed with nutrients either from top or from bottom. Fluid comprising of dissolved nutrient and substrate flows through the solid bed. The fluid flow rate and residence time are controlled to increase or decrease substrate contact with the bed. The packed-bed compartment located either external to, or within, the reservoir of the medium (metal.ntua.gr/).

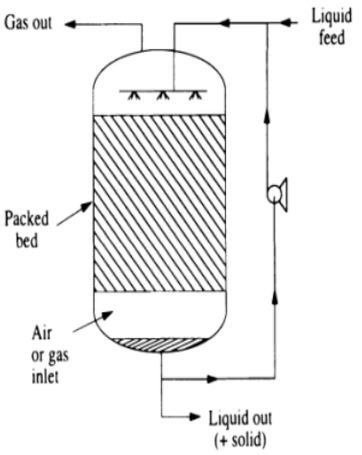

Figure 10. Packed bed reactor (Siegel M.H & Robinson C.W, 1992)

Packed beds can either be run in the submerged mode (with or without aeration) or in the trickle flow mode. The flow velocities in the channels can be high to eliminate external mass transfer limitation in the adjacent liquid film. Simultaneously, plugging can be avoided, although at the cost of high pressure drop (Wang G et.al, 1992). Undesired properties of these reactors include poor temperature control, heat gradients, unwanted side reactions and difficulty in replacing catalyst. They also suffer from blockages and poor oxygen transfer. Changes in the bed porosity during operation alter the flow characteristics of these reactors. These are generally used in waste water engineering.

Fluidized Bed Reactor

Fluidized bed reactors (FBRs) constitute packed bed with smaller size particles. Thus the problems of clogging, high liquid pressure drop, channelling and bed compaction are prevented as compared to packed bed reactors. These reactors operate in a continuous state with uniform particle mixing and temperature gradients. In these reactors, the cells are immobilized small particles which move with the fluid. The smaller particle size facilitates higher rate of mass transfer, oxygen transfer and nutrients to the cells. The biocatalyst concentration can significantly be higher and washout limitations of free cell systems can be overcome (Gibilaro L.G, 2001). In this reactor, the cross-section area is expanded near the top to reduce superficial velocity of fluidizing liquid to a value below the terminal velocity of the particles to prevent elutriation. The efficiency of fluidized bed reactor depends on the attachment of particles that are maintained in suspension by an upward flow rate of the fluid to be treated. The particles are often called biofilm carriers and either they are inert core on which the biomass is created by cell attachment; or porous particles in which the biocatalyst is entrapped (self-immobilization).

The fluidized reactors are operated in co-current up flow with liquid as continuous phase. Usually fluidization is obtained either by external liquid re-circulation or by gas fed to the reactor .Some undesirable properties of FBRs includes increased reactor vessel size, pumping requirements and pressure drop, particle entrainment, erosion of internal components, pressure loss etc.

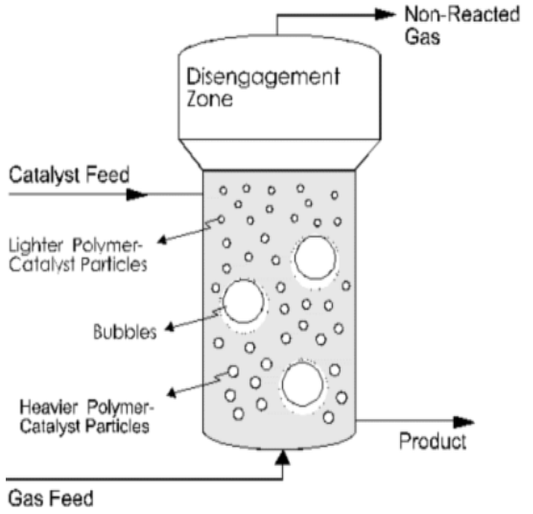

Figure 11. Fluidized bed reactor (Kwong W.H, 2000).

Conclusion

Bioreactors have been used for decades to produce a range of therapeutic biomolecules 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 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 detecting temperature, optimal feeding and cell quantification etc. are important tools for process engineering. 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 behaviour of the culture.

In 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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Citation : Jagriti Singh, Nirmala Kaushik & Soumitra Biswas 2014. Bioreactors – Technology & Design Analysis.
The Scitech Journal: Vol 01 (6):28-36