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HYDRODYNAMIC CONSIDERATIONS IN BIOREACTOR SELECTION AND DESIGN

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ABSTRACT

The biological production of renewable fuels and chemicals, medicines, and proteins is not possible without a properly functioning bioreactor. Bioreactors are expected to meet several basic requirements and create conditions favorable to the biological material such that the desired production is maximized. The basic requirements, which are strongly influenced by fluid mechanic principles, may include minimum damage to the biological material, maximum reactor volume utilization, optimized gas-liquid mass transfer, and/or enhanced mass transfer from the liquid to the biological species. Each of these goals may be achieved within any of the major bioreactor designs, which generally fall under the categories of stirred tank, bubble column, or airlift bioreactor. Yet, each of the bioreactor designs has strengths and weaknesses. This paper provides an overview of bioreactor hydrodynamic developments and the fluid mechanic issues that should to be considered when selecting a bioreactor for experimental and production purposes.

INTRODUCTION

Bioreactors are becoming more important in the production of biobased products such as proteins, medicines, and renewable fuels. The economic viability of these processes is dependent on the bioreactor's ability to aid the microorganism and provide a friendly environment. One of the important microorganism requirements is proper gas concentrations so that the microorganism has the necessary inputs for proper metabolism. These gas concentrations are obtained and maintained through optimized gas-liquid mass transfer and mixing, also known as hydrodynamics. Other bioreactor requirements include damage mitigation and bioreactor volume utilization. A proper bioreactor design should also maximize profitability through ease of use, maintenance, and construction.

MODES OF OPERATION

Batch, semi-batch, and continuous modes of operation are classified by the flow rates in and out of the system. Virtually all reactor types are capable of operating in these modes. The batch reactor is the oldest and most used bioreactor in industry [1, 2]. Batch bioreactors combine all the necessary ingredients and then operate until the desired product concentration is reached at which point the product is extracted. In well-known processes where the final product is relatively cheap, product concentration can be correlated to time, leading to some process automation, lower capital needs, and lower operational costs [1].

The need for more control over the biological process created the fed-batch (also known as the semi-batch) cultivation system, which is the most widely used variant of the batch reactor. This deviation is a variable volume process that introduces additives, gradually creating a more responsive and friendly growth environment [1]. In other words, the bacteria receives the right amount and type of nutrients at the appropriate growth stage, creating a more efficient and controllable process. The final result is a product that can be adjusted or extracted when it achieves the desired properties.

Continuous bioreactors have several intrinsic properties that differentiate them from batch bioreactors. The largest distinction is that substrate and product continuously flow in and out of the reactor, which does not allow for a cleaning or sterilization processes and extracts product regardless of identity or quality [1]. If output does not meet specifications, the resulting product has to be either discarded or separated and

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recycled back into the reactor. Either option creates a negative economic impact by increasing (i) initial investment due to the necessary installation of a recycling system and (ii) variable costs due to the discarded product and the associated inputs [3]. Product properties are controlled by substrate residence time which, by design, can only be controlled by material flow rate and reactor geometry.

In order to ensure a homogeneous product, the continuous process is assumed to be steady-state and conditions within the bioreactor are typically assumed to be independent of time [3]. Therefore, continuous bioreactors are agitated mechanically and/or by gas injection. Substrate input is not used for agitation so as to decouple it from reactor hydrodynamics. In order to make the steady-state conditions easier to achieve and maintain, most continuous bioreactors are run in a constant volume setting, which induces uniform volumetric substrate and product flow rates. Efficiency is enhanced using cell retention techniques such as fluidized beds, membrane reactors, or cell recycle [1].

The choice of the mode of operation can have a significant impact on the type of bioreactor available and the hydrodynamics experienced by the microorganisms. For example, a batch or semi-batch process will yield an environment which is constantly changing. The variations with time may cause the microbial production to vary significantly and may cause concentrations of a toxic substance to build up and reach critical levels. A continuous process, on the other hand, would yield a relatively consistent experience with time, but the process may require more capital.

A specific bioreactor may make the mode of operation harder or easier to implement. The stirred tank bioreactor (STR) has a significant amount of backmixing, and its flow pattern is not necessarily well-defined. Batch and semi-batch operation would be natural candidates for these bioreactors. The bubble column (BC) and airlift bioreactor (ALR) have a better and more defined flow direction even though backmixing may still occur. In general, it is harder for substrate and microorganisms to get stuck in a certain part of the bubble column or airlift bioreactor while this outcome is a real possibility with stirred tank bioreactors.

GAS-LIQUID MASS TRANSFER

Mass transfer operations in biological systems depend on a myriad of intermediate and parallel processes driven primarily by the system hydrodynamics. Reactors for gas-liquid applications fulfill two needs: dispersion and absorption [4]. Dispersion requires that the entire reactor volume be used to mix the gas into the liquid. This step, however, is usually easily achieved or is not the critical system constraint [4]. The low solubility of most gases limits gas absorption to the point that gas-liquid mass transfer becomes the rate limiting step for the overall reaction [4-11]. This limitation is even more severe in systems using very low solubility gases, such as carbon monoxide found in synthesis gas, some of which are very important in industrial applications [10]. Thus, the easiest way to increase the productivity for these processes is to increase the gas-liquid mass transfer [12].

Two transfer coefficients may be considered at the gas-liquid interface. The liquid-phase mass transfer coefficient is represented by k_L, whereas the gas-phase mass transfer coefficient is identified by k_G. Since the gas-phase mass transfer resistance is typically much smaller than the liquid side, $k_G >> k_L$ and gas-liquid mass transfer is controlled by k_L [13]; this value is modulated by the specific (gas-liquid) interfacial area, a. The driving force for mass transfer is the gas concentration gradient between the gas phase, C^*, and the dissolved gas, C. The mass transfer rate is then determined by

$$\frac{dC}{dt} = k_L a\left(C^* - C\right) \tag{1}$$

The volumetric gas-liquid mass transfer coefficient, $k_L a$, is typically used when determining the mass transfer coefficient because it is difficult to measure k_L or a independently. Variances in volumetric mass transfer coefficient during operation are often thought to be a direct result of changes in the interfacial area [14, 15], which would imply that homogeneous (bubbly) operation is more desirable than heterogeneous flow [8]. However, according to Linek at al. [5], concise conclusions are often troublesome because the liquid-phase mass transfer coefficient is calculated using the gas-liquid mass transfer coefficient (k_L) and the specific interfacial area (a). Any measurement errors in either variable cause false conclusions or improper use of mass transfer models. This issue is more prevalent in stirred tank bioreactors, which may have high shear rates and turbulence levels, rather than in bubble column or airlift bioreactors.

STIRRED TANK BIOREACTOR CONSIDERATIONS

Typical stirred tank reactors (Figure 1) have a small height-to-diameter ratio relative to other reactor types [16]. The diameter T can vary from about 0.1 m for experimental units to 10 m for industrial applications [17]. As shown in Figure 1, the impeller and baffle dimensions, as well as the impeller clearance are typically a specified fraction of the tank diameter. The aspect ratio, defined as the liquid height-to-diameter ratio, is highly variable and depends on the number and arrangement of impellers and the reactor application. Single impeller systems typically have an aspect ratio of 1 [16, 18], but certain exotic applications call for designs with aspect ratios up to 3 [18, 19]. Industrial multiple impeller designs are mostly limited to an aspect ratio of less than ~4 due to practical considerations [16].

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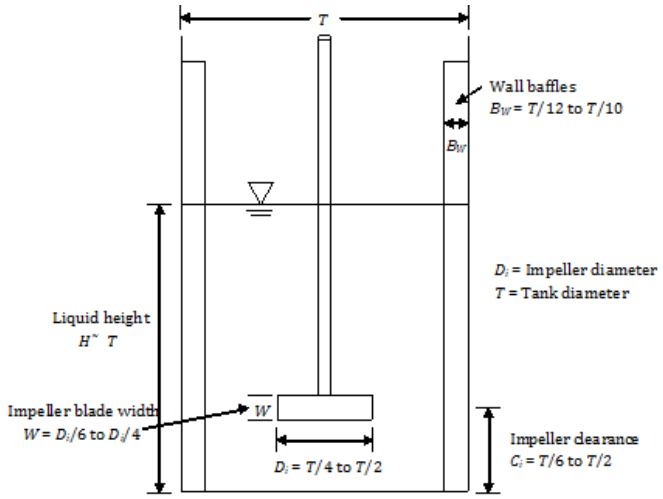

FIGURE 1: STANDARD SINGLE IMPELLER STIRRED TANK REACTOR DESIGN (ADOPTED FROM TATTERSON [18]).

Reactor shape, specifically the bottom, can vary greatly. The standard reactor design is cylindrical with a flat bottom [20], but dished, conical, or curved bottoms have also been used [17, 18]. The bottom shape does not seem to affect gas-liquid mass transfer or gas dispersion significantly, but the dished bottom is preferred for solid suspensions and mixing [4]. Other reactor shapes, such as spherical or semispherical, are in use [4] but the standard design is preferred for gas-liquid dispersion due to operational experience and cost. Even though standard reactor designs exist in the chemical industry for liquid-liquid processes, customized STR use for biological and gas-liquid applications preclude an optimized stirred tank reactor design for all applications [18].

Microbial cultures are used as catalysts in bioreactors. Bacteria are the most commonly used culture, but animal, plant, or insect cells have also been implemented [21]. STRs are popular for microorganism growth [11] because they enhance feedstock contact, provide pH and temperature uniformity, and maximize mixing [22]. Their impact on reactor hydrodynamics is mostly indirect. Occasionally, microorganisms retard turbulence if the organic volume fraction is above 11-15% depending on the species. The other possibility is that the microorganisms produce surface active agents [23]; however, their most common impact on hydrodynamics is that reaction kinetics may be limited by the environment such that the operational range (power concentration, superficial gas velocity, etc.) may be reduced. As such, it is more constructive to concentrate on the impact that hydrodynamics have on microorganisms.

The most influential factor is shear gradients that may hinder productivity regardless of the mass transfer situation [21, 22, 24]. Shear gradients damage microorganisms through several mechanisms. The simplest one is cell wall (physical) damage. This mechanism also separates animal and plant cell applications from bacterial ones. Bacteria are usually smaller and have stronger cell walls relative to their size than animal or plant cells such that bacterial processes use a power range of 1-5 W/kg (comparable to chemical processes) while cellular processes use 0.0005-0.1 W/kg [21]. In other words, smaller cells are usually able to withstand higher shear gradients because the most damaging eddies have to be on the order of the cell size. As such, animal cell growth rate has been found to be reduced with eddies smaller than 130 μm [24].

Shear gradients may also interfere with cell-to-cell interaction, cell-to-substrate adhesion, and microbial competition. Additionally, certain microorganisms prefer to flocculate. Hoffmann et al. [22][‡] concluded that bacteria, which tended to form elongated filaments, were more prone to shear induced damage than those which formed cocci (spherical formations). Although the elongated filaments were more advantageous for food collection during calmer operation, the introduction of strong turbulence provided a competitive advantage for cocci forming bacteria such that those dominated the population at the end of the experiment.

The bacteria's spatial juxtaposition (awareness relative to other bacteria) may also be hindered by turbulence. In the worst case scenario, the bacteria are not able to make significant contact and are not able to achieve the necessary cell density for optimal operation [24] or are not able to make syntropic relationships with other bacterial cultures [22]. The result is that startup performance is very poor with minimal or insignificant conversion while long term performance is not hindered in a bacterial mixture that allows competition and has at least one shear tolerant species. Conditioning with feast and famine cycles improved recovery time and tolerance to feed and shear shocks [22].

Thus, STRs using shear sensitive microorganisms have to minimize cellular damage, maximize feedstock transfer to microorganisms, and maximize mixing. The latter requirements are important because the bacterial structure may change during starvation mode to make the culture even more susceptible to cell wall degradation. This situation is true for mycelia (fungi) and may be applicable to other branching bacteria. A healthy specimen, shown in Figure 2A, has relatively thick branches without vacuoles (empty pockets). As the bacteria starves (Figure 2B), it reduces the number of branches and starts to consume its internal reserves, which leads to the formation of vacuoles. As the number and size of vacuoles increases, the cell wall strength and its ability to resist environmental stresses decreases. As starvation is extended, the specimen will consume as much of its own mass as it can (which depends on the species) and vacuoles will dominate its structure, as can be seen in Figure 2C. At this point, the

[‡] The conclusions are based on a particular set of microbial species and have not been verified by other researchers. According to their published article, Hoffmann et al. [17] experimented with different sized vessels at the same impeller speed. Since turbulence is more intense and power concentration higher with scale, their results and conclusions may not be universally applicable.

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microorganism is easily and significantly damaged by shear gradients [22]. Energy and mass is diverted to the tip, as pointed out in Figure 2C, in order to search for a food source. This tip is of solid construction relative to the main body. Insufficient mixing can have similar effects in that the reactor volume may have localized pockets in starvation mode and not producing an optimal amount (if any) of product in those regions [25].

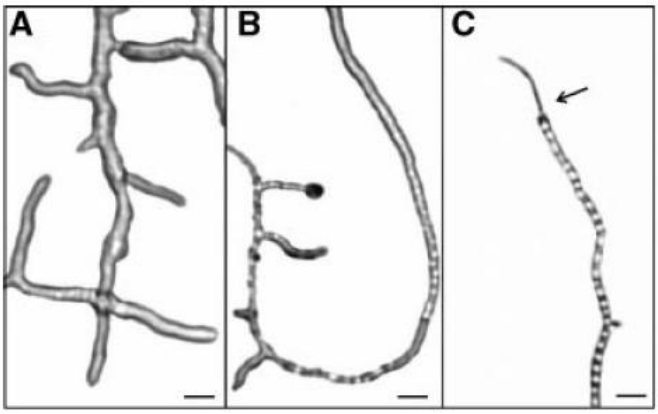

FIGURE 2: BACTERIA STARVATION: (A) A HEALTHY SPECIMEN, (B) A BACTERIUM UNDER STARVATION CONDITIONS, AND (C) EXTENSIVE STARVATION WITH THE FORMATION OF MANY VACUOLES (EMPTY POCKETS) [22].

Microorganisms and their reaction kinetics may start out being gas-liquid mass transfer limited, but the process and changing environment may change the limiting factor to temperature or pH level. Bacteria are classified by their temperature preference into mesophilic or thermophilic families. Mesophilic bacteria operate optimally at about 30°C with a sharp drop-off in efficiency as temperature approaches 50°C. These cultures are used more widely because they are easier to control and produce a more consistent product, but are generally able to convert only 40% of the biological matter in 30 to 40 days. Thermophilic bacteria, on the other hand, prefer temperatures of about 60°C and have proven conversion rates up to 48% in just 10 days [26, 27]. Acidity is quite variable (although not for a specific bacterial culture) and can range from pH 4.3 to pH 7.9 for anaerobic bacteria [27]. Output can be maximized for acid sensitive processes using syntropic relationships (i.e., volatile fatty acids oxidizing bacteria and hydrogen utilizing methanogens) [22].

Furthermore, the production and conversion process often introduces unwanted byproducts or creates products which negatively affect bioreactor operation. For example, protein producing microorganisms, which are often used in pharmacokinetics, produce a mixture over time that is damaging to the bacteria aside from the surface active agent properties of the protein. Shear is tolerated by the microorganisms in this mixture, but air-liquid interfaces, which are naturally very common in gas-liquid processes, can lead to denaturation [28].

Batch and semi-batch STRs are also influenced by the accumulation of products in the volume, which can significantly change liquid phase properties. Although the production is certainly welcome, it can lead to the process being tail dominated (process time controlled by last 20%, for example) or creating an extremely viscous liquid phase, which, in most cases, forces the operation to cease.

Many industries in which the stirred tank bioreactors are being implemented require production to be very consistent and/or the design phase to be completed quickly. For example, it is common in the biopharmaceutical industry to start the design phase once approval of a drug has been secured; however, the design process requires a significant amount of time during which the patent clock is ticking. Hence, costly delays are very common [28].

The need for better results has led to the implementation of process and genetic engineering. The goal of process engineering is to optimize the conditions such that production and/or conversion are increased; however, it can be difficult to predict hydrodynamic effects on microorganisms. The answer has been to carefully test microorganisms on the bench-scale (experimental) and implement genetic engineering techniques to create more shear resistant strains [29]. Process engineering, however, prevails in practice as genetic engineering has not been able to produce very resistive strains (although productivity has been increased) such that stirred tank bioreactors are limited in their power dissipation rates, thus limiting reactor shear rates.

BUBBLE COLUMN AND AIRLIFT BIOREACTOR CONSIDERATIONS

Bubble column (BC) and airlift bioreactors (ALR) can often be thought of in a similar fashion when it comes to microorganisms mainly because the shear rates within these vessels are often similar. The airlift bioreactors may achieve much higher gas and liquid velocities (Figure 3), which lead to larger shear rates and turbulence, particularly in the reactor base or gas-liquid separator. Fortunately, the base and separator can be designed to limit the turbulence in these areas and improve airlift bioreactor performance with shear sensitive microorganisms.

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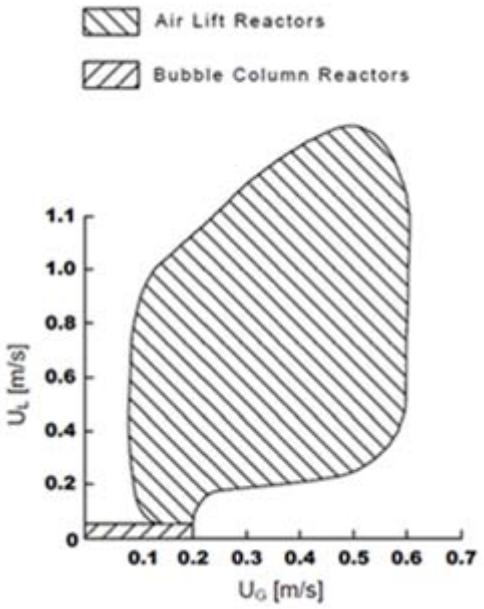

FIGURE 3: COMPARISON BETWEEN SUPERFICIAL LIQUID AND GAS VELOCITIES IN BUBBLE COLUMNS AND AIRLIFT REACTORS [30].

Bubble columns (BC) belong to a family of pneumatic bioreactors. The concept, in which compressed air is injected into the base of a cylindrical vessel, is a cheap and simple method to contact and mix different phases [31]. The liquid phase is delivered in batch or continuous mode, which can be either counter- or cocurrent. The batch bubble column is the more common form, but the cocurrent version, shown in Figure 4, is also encountered. Countercurrent liquid flow is rarely used in industry as it provides minor, if any, advantages and multiple complications [32], with separation by evaporation being one of the few exceptions [33].

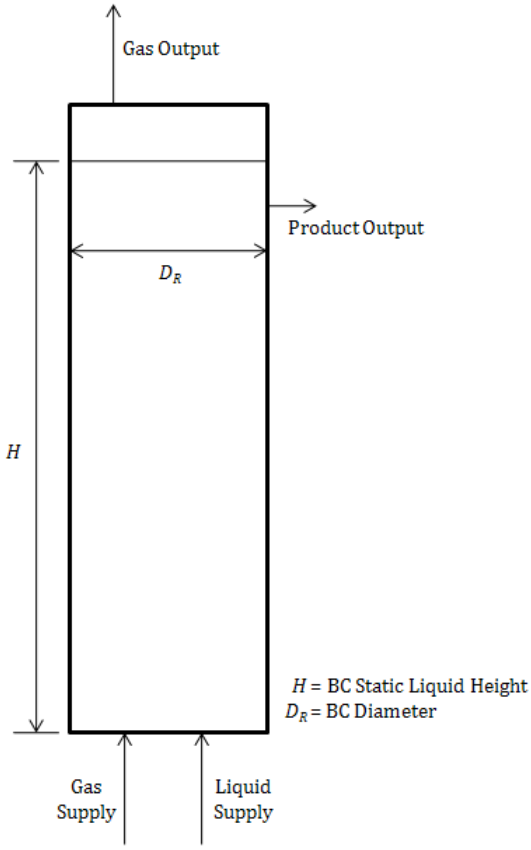

FIGURE 4: BUBBLE COLUMN SCHEMATIC; IF THE LIQUID IS ALSO FLOWING CONTINUOUSLY, THE BUBBLE COLUMN WOULD BE IDENTIFIED AS COCURRENT.

Bubble columns tend to be tall vessels with a large aspect ratio (H/D_R) because the height is a controlling factor for the process and residence time, especially for batch and semi-batch operations [34]. Biochemical processes require an aspect ratio between 2 to 5, even for experimental work. Industrial applications require much taller vessels with an aspect ratio of at least 5 [35], but it is fairly common to have vessels with an aspect ratio greater than 10 [1]. An aspect ratio greater than 5 is also preferred because it does not influence bubble column hydrodynamics [36].

The airlift reactor (ALR) is a pneumetic device which attempts to reconcile bubble column shortcomings and provide more control to the operator. Two general families of airlift reactors exist: internal- and external-loop airlift reactors (ILALRs and ELALRs, respectively). The internal-loop variant is sectioned by a baffle (Figure 5a) or draught tube (Figure 5b). The external-loop airlift reactor (Figure 6) connects the up- and down-flowing regions with additional piping. These basic designs can be modified extensively to create a wide array of application specific requirements [37-42].

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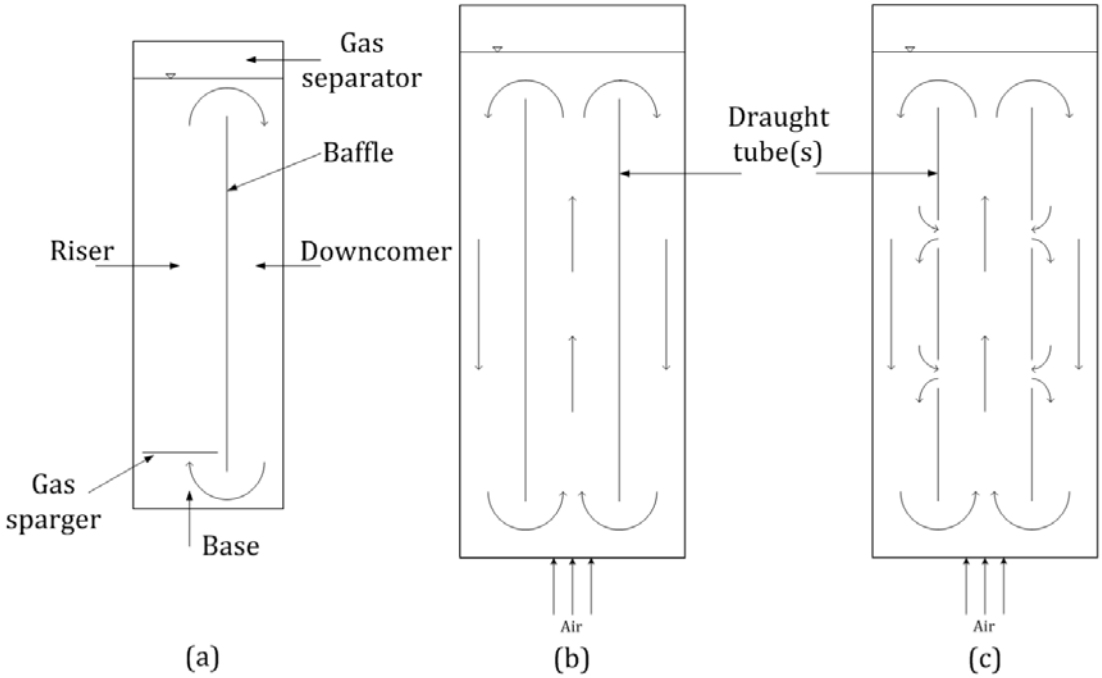

FIGURE 5: INTERNAL-LOOP AIRLIFT REACTOR WITH (A) A BAFFLE SEPARATING THE RISER AND DOWNCOMER, (B) A CONTINUOUS DRAUGHT TUBE SEPARATING THE RISER AND DOWNCOMER, AND (C) A SECTIONED DRAUGHT TUBE SEPARATING THE RISER AND DOWNCOMER.

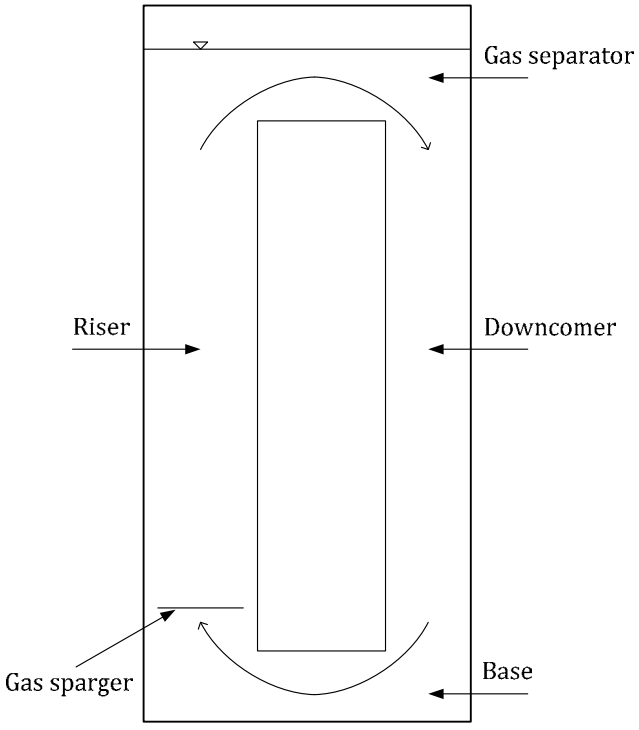

FIGURE 6: EXTERNAL-LOOP AIRLIFT REACTOR SCHEMATIC.

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Airlift reactor construction is very simple and similar to that of a bubble column [43, 44]. There are four basic sections: riser, gas separator, downcomer, and base. The riser is the up-flowing section of the airlift reactor. The gas sparger is oriented such that gas is injected into the riser. The gas sparger location may be within the riser or the base, which is simply the region that connects the downcomer to the riser. The gas separator is at the top of the reactor. As the name implies, gas disengages from the liquid phase (or slurry) in the gas separator. The downcomer is defined as the region in which down-flowing phases are present.

Airlift reactors can be viewed in two different lights. One is that the ALRs are variations of the bubble column. The bubble-bubble interactions, forces, construction, and reactor applications in ALRs are very similar with those of the bubble column. On the other hand, ALR hydrodynamics are based on interactions between the riser and downcomer gas holdup. The gas separator in conjunction with gas injection in the riser section generally leads to the gas holdup in the riser section being larger than in the downcomer. This effect creates a hydrodynamic pressure difference, which leads to the liquid and/or gas phases circulating in a fairly controlled manner. This mechanism is a source of many advantages unique to the airlift reactor.

The main advantages of the bubble column and airlift bioreactor are economic. They require very little maintenance or floor space and have low operating costs [36]. The low operating and maintenance costs are mainly due to the lack of moving parts. Compressed gas is capable of producing a friendlier and uniform environment, which is important for processes involving shear sensitive microorganisms [35]. Compressed gas is also a more effective power source for very large reactor volumes (up to 500 m^3) [1].

The pneumatic power source typically produces lower energy dissipation rates compared to stirred tank bioreactors. This property is a positive feature for shear sensitive microorganisms, but may be a hindrance for gas-liquid mass transfer. A lower energy dissipation rate also implies that the possible average bubble diameter is expected to be larger, which, in turn, causes a smaller interfacial area and gas-liquid mass transfer coefficient. Furthermore, bubble column and airlift bioreactor designs allow for online modification of microorganism concentrations [35].

An additional advantage of bubble column and airlift bioreactors is that they are able to sustain much larger solids loading ratios than stirred tank bioreactors. The price one needs to pay for this option is a decrease in gas holdup. In the case of low solids loading (less than 5% by volume), the slurry phase does not significantly change the solution properties. As the solids loading increases, the behavior of the slurry starts to deviate. For solids loading up to 25% by volume, the gas holdup decreases significantly. Beyond this concentration, gas holdup increases slightly as small bubbles start to accumulate because of the decrease the bubble rise velocity [35, 45]. This observation is often attributed to a significant increase in the apparent viscosity once the solid holdup increases beyond 20% [45]. This experience is reflected in airlift reactor studies, with some minor differences. Small amounts of drag-reducing polymers could actually enhance fluidization and recirculation, especially in airlift reactors [13]. Airlift reactors tend to have less phase backmixing, and an increase in solid holdup often results in an increase phase buildup in the reactor base and wall regions [46, 47].

The external-loop airlift reactor (ELALR) has a wide array of variants ranging from the fairly simple to quite complex multistage designs. The ELALR is typically limited for use with shear sensitive cells, photosynthetic microorganisms like algae, or processes requiring fluid recirculation. For example, mammalian cell structure can usually tolerate shear stresses in the range of 0.05-500 N/m^2 [13], but the sensitivity is highly variable with cell structure and density such that cells could be highly shear sensitive at low cell density and somewhat resistant at higher densities [48]. Hence, the reactor operating conditions need to be flexible enough to adjust from very low shear conditions and still potentially operate with a high degree of turbulence (high shear stress).

Stirred tank reactors usually create shear stresses much larger than those that can be tolerated by mammalian cells, and bubble column and internal-loop airlift bioreactors (ILALRs) may reach the high end of the spectrum at best. Bubble-bubble interactions, especially bubble bursts or breakup, create high local shear stresses, which have a negative impact on mammalian cell growth. ELALRs, on the other hand, can maintain low shear rates while still providing a respectable oxygen transfer of 0.6-1.0 mmol/L-min [13], which is sufficient even for human skin (0.0011 mmol/L-min at 10^6 cells/ml) and liver cells (0.005 mmol/L-min at 10^6 cells/ml) [48]. This is doable using minimal circulation in the downcomer, and cell suspension on packed material in the lower portion of the downcomer. The cells have minimal bubble-bubble interactions and usually have enough oxygen for growth and liquid flow for waste disposal.

Nonetheless, cell density can become a major problem. For example, mammalian cells are usually 100 μm within a blood capillary for oxygen transfer. Therefore, nature has provided a design limitation. Cells can only be 150-200 μm away from an oxygen source, such as dissolved oxygen in a liquid, because oxygen has a maximum diffusion depth of about 240 μm for cellular material. This may limit the cell density and, in turn, the operational gas flow or local shear rate. Some production problems of critical cells are mitigated by cellular design. Connective tissue cells are elongated and form low density cell structures, while some critical ones, such as liver or kidney cells, operate at high density, but also form many more blood capillaries [48]. In other words, the ELALR provides the possible production of a wide array of mammalian cell structures as well as shear sensitive microorganism byproducts.

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BUBBLE COLUMN AND AIRLIFT BIOREACTOR DIFFERENCES

Differences between the bubble column and airlift bioreactor are important. For example, even though both bioreactors have similar bubble behavior, the mixing and hydrodynamics occur in a slightly different manner. It should be noted that both bioreactors are expected to operate in the heterogeneous flow regime at a large scale.

This fact implies that bubble columns experience descending flow, vortical flow, fast bubble flow, and central plume flow (Figure 7). The central region of the bubble column is made up of a central plume through which relatively small bubbles ascend. This central plume is surrounded by a fast bubble flow that is made of larger bubbles. At the edge of this motion, vortices form that trap bubbles and liquid, forming the vortical flow region. These vortices direct bubbles near the column wall to descend (descending flow region). The fast and descending bubble streams flow in a spiral pattern. As such, the general mixing in the bubble column is strong and not easily defined.

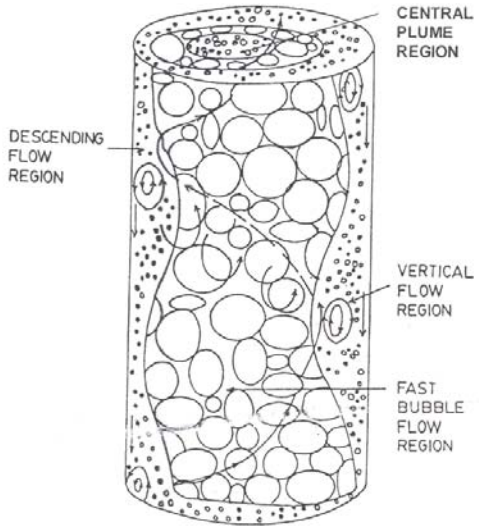

FIGURE 7: MACROSCOPIC FLOW STRUCTURE IN THE HETEROGENEOUS FLOW REGIME [49].

The airlift bioreactor, on the other hand, has better defined flow patterns (Figure 8). ALR circulation can be sectioned into three general regimes. At very low gas flow rates, which correspond to U_{Gr} < 0.012 m/s, the induced liquid circulation velocity is not strong enough to entrain gas bubbles into the downcomer. Note that U_{Gr} is the superficial gas velocity in the riser. The gas phase is able to almost completely disengage from the liquid phase (regime 1). This regime, referred to as the bubble free regime, is usually not significantly influenced by the liquid properties simply because the amount of gas present in the system is still fairly low. In order for the liquid properties to become more important, a higher degree of bubble-bubble interaction is needed. The liquid is capable of entraining only very small bubbles (d_B < 1 mm) in regime 1. The resulting downcomer gas holdup is usually small with a maximum of about 3%. The bubble free regime is only used when shear sensitive microorganisms need to be protected, which may be accomplished with suspension in the downcomer.

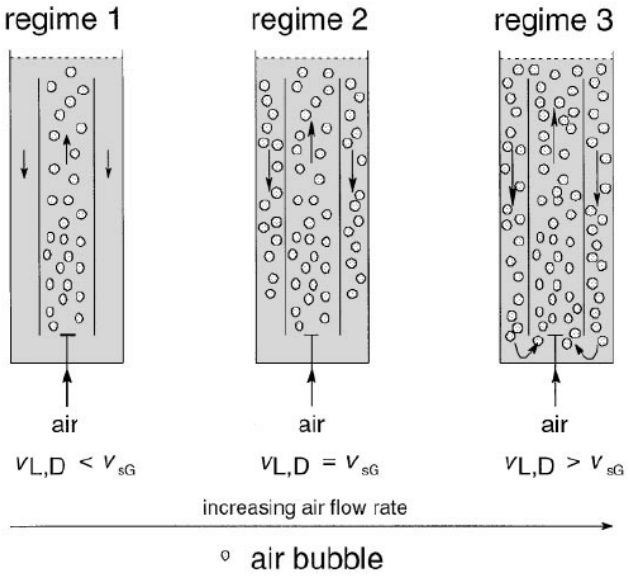

FIGURE 8: CIRCULATION REGIME PROGRESSION IN A DRAUGHT TUBE INTERNAL-LOOP AIRLIFT REACTOR [50] WHERE $V_{L,D}$ IS THE DOWNCOMER LIQUID VELOCITY AND V_{SG} IS THE GAS SLIP VELOCITY.

Once the gas is in the downcomer, the liquid has to flow even faster to cause circulation. Gas bubbles are still lighter than the liquid and have a buoyant force, which propels them to rise against the flow. The liquid phase momentum has to provide the power to overcome the buoyant force and create a net downward force in order to cause forward motion and eventual circulation. In effect, a superficial liquid velocity exists at which gas bubbles can be suspended or are stagnant in the downcomer (regime 2). Hence, this circulation regime is referred to as the transition regime. A practical use for this regime does not exist since the gas phase would not recirculate.

If the downcomer liquid velocity is larger in magnitude than the bubble rise velocity, the bubble will circulate with the liquid [51]. This minimum superficial liquid velocity usually occurs at U_{Gr} = 3.5-5.0 cm/s [52, 53] and is described by thorough gas bubble circulation (complete bubble circulation regime – regime 3). It should be noted that regime 3 is by far the most commonly encountered circulation regime. Since the gas flow rate for pilot and industrial scale reactors is high, the superficial gas velocity is also very high, which all but guarantees circulation [13, 43]. Bubble free (regime 1) and transition (regime 2) regimes are usually avoided because they have poor phase contacting, mixing, and selectivity [53]. In addition, special attention and effort are required to keep the flow in the bubble free and transition regimes for an industrial-scale reactor.

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Complications arise when/if the gas disengagement leads to a smaller riser gas holdup, such that the driving force is not heavily influenced. The gas disengagement process has some geometric influences which cause the transition to regime 3 to occur relatively early in the transition flow regime or well into the heterogeneous flow regime. A second complication is that the recirculated gas can lead to more frequent bubble collisions and coalescence so that the riser gas holdup may decrease early in regime 3 until the flow structure stabilizes. Interestingly, the transition to regime 3 occurs at a gas holdup of 10-12% regardless of the bubble flow regime, and for reasons and through mechanisms which are not well understood at this time [50].

In general, the maximum downcomer gas holdup is about 20% in the external-loop airlift reactor [50] while the internal-loop airlift reactor has a maximum gas holdup of 80-95% of the riser value [50, 54]. Hence, the maximum downcomer gas holdup introduces a significant limitation to the external-loop airlift bioreactor while the hydrodynamic performance of the internal-loop airlift and bubble column bioreactor are similar. This connection lies behind the line of reasoning in extending bubble column bioreactor behavior and studies onto the airlift bioreactors.

CONCLUSIONS

Bioreactor hydrodynamics govern mixing and gas-liquid mass transfer. The stirred tank bioreactor is a good choice for semi-batch and shear resistive microorganisms while the bubble column and airlift bioreactor are better choices for continuous processes and shear sensitive microorganisms. The limitation of the stirred tank bioreactor is mainly due to its highly turbulent environment, which may experience compartmentalization, and expensive operation and maintenance, especially if the scale is large. The bubble column and airlift bioreactors, on the other hand, are inexpensive alternatives, which may be limited by gas holdup, mixing, or power dissipation rate.

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NOMENCLATURE

a	gas-liquid interfacial area (per unit liquid volume)
ALR	airlift reactor
BC	bubble column
B_W	baffle width
C	concentration
C_i	impeller clearance
D_i	impeller diameter
D_R	bubble column diameter
ELALR	external-loop airlift reactor
H	liquid height
ILALR	internal-loop airlift reactor
k_L	liquid-phase mass transfer coefficient
k_La	volumetric gas-liquid mass transfer coefficient
STR	stirred tank reactor
t	time
T	stirred tank reactor diameter
U_G	superficial gas velocity
U_L	superficial liquid velocity
$V_{L,D}$	superficial liquid velocity in airlift reactor's downcomer
V_{sG}	gas slip velocity
W	impeller blade width

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