

FEDSM-ICNMM2010-' 0' **

MIXING CONSIDERATIONS IN STIRRED TANK BIOREACTORS WHEN USING FLUID PROPERTY ALTERING MICROORGANISMS

Enes Kadic and Theodore J. Heindel*
Department of Mechanical Engineering
Iowa State University
Ames, Iowa 50011

ABSTRACT

Stirred tank reactors are one of the standard reactors in the chemical industry and have been widely implemented for biological applications. They are used with viscous liquids, slurries, very low gas flow rates, and large liquid volumes. Stirred tank bioreactors are popular because a well-mixed state, required or preferred for numerous biological processes, is usually achieved in such situations; however, many production processes using microorganisms tend to experience fluid property alterations, which significantly impact mixing, operational parameters, and process results. The most troubling issues occur when a fluid gradually undergoes a viscosity change and/or slowly exhibits non-Newtonian behavior due to microorganism growth since these will alter the flow conditions and possibly limit the conversion rate or production scale. This paper provides an overview of the relevant mixing issues in stirred tank bioreactors when using a range of fluid viscosities, surface tensions, and/or non-Newtonian fluids.

INTRODUCTION

Stirred tank reactors (STRs) are standard reactors in the chemical industry and are easily implemented for biological applications [1]. Stirred tank bioreactors are also popular because a well-mixed state is easily achieved, which aids in providing necessary substrate contact, pH and temperature control, removal of toxic byproducts, uniform cell distribution, clog prevention, and particle size reduction [2, 3]. They are also used with viscous liquids and slurries, very low gas flow rates, and large liquid volumes.

Stirred tank reactors are widely applied in industry because of their low capital and operating costs [1]. Popular

applications are fermentation [3-8], carbonation, oxidation [7, 9], chlorination [6, 7, 9], hydrogenation [6, 7, 10, 11], dissolution, polymerization [11], chemical synthesis, and wastewater treatment [5, 11, 12]. Stirred tank reactors are preferred if high gas-liquid mass transfer coefficients are needed [13]. The fluid properties, which are important for microorganism processes, are the liquid viscosity, liquid surface tension, and Newtonian/non-Newtonian behavior/properties.

Superficial gas velocity, defined as the volumetric gas flow rate divided by the STR cross-sectional area, influences gas-liquid mass transfer through two mechanisms: gas-filled cavities and gas holdup. The sweeping action of the impeller creates a low pressure void that quickly fills the sparged gas. These gas-filled cavities are the mechanism for gas dispersion and gassed power reduction [14]. These cavities ultimately influence impeller loading, gas dispersion, and liquid circulation such that the impeller creates specific flow regimes which are of great importance for STR optimization.

Typical STR units (Figure 1) have a small height-to-diameter ratio relative to other reactor types [15]. The diameter T can vary from about 0.1 m for experimental units to 10 m for industrial applications [16]. 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 [15, 17], but certain exotic applications call for designs with aspect ratios up to 3 [17, 18]. Industrial multiple impeller designs are mostly limited to an aspect ratio of less than ~ 4 due to practical considerations [15].

* Corresponding Author: T.J. Heindel, theindel@iastate.edu

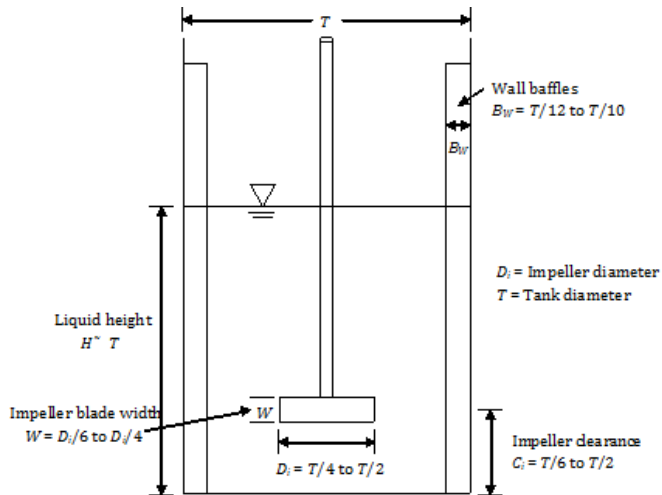


FIGURE 1: STANDARD SINGLE IMPELLER STIRRED TANK REACTOR DESIGN (ADOPTED FROM TATTERSON [17]).

Reactor shape, specifically the bottom, can vary greatly. The standard reactor design is cylindrical with a flat bottom [19], but dished, conical, or curved bottoms have also been used [16, 17]. 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 [9]. Other reactor shapes, such as spherical or semispherical, are in use [9] 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 [17].

VISCOSITY

Liquid properties affect gas-liquid mass transfer in STRs through their influence on impeller and reactor hydrodynamics and bubble coalescence. Impeller loading, flow patterns, and power dissipation rates depend on the viscosity of the fluid. The power draw is influenced by the dynamic viscosity during laminar operation while density is the main parameter during turbulent conditions. The transition regime encompasses a large Reynolds number range for STRs ($10 < Re < 20,000$) [20] during which the power draw is simultaneously influenced by both viscosity and density [21].

More importantly, however, is the viscosity's influence over coalescence and impeller loading. The liquid viscosity determines the degree to which the bubbles are deformable. As the viscosity increases, the bubbles become more deformable, coalescence occurs much easier and faster [22], and breakup is suppressed [23]. Deformable bubbles allow for the bubble interface to drain much easier and allow coalescence to occur in a shorter amount of time. Bubble breakup is suppressed because the higher viscosity tends to have a negative effect on turbulence. A second negative effect is that the larger bubbles

have a higher rise velocity and lead to a shorter residence time for the gas phase [23]. Hence, higher viscosity liquids are observed to have larger bubbles and smaller gas holdups and interfacial areas [23, 24].

Increased viscosity dampens turbulent eddies, and the viscosity gradients force gas towards the impeller zone [25]. If the fluid is highly viscous, it can lead to compartmentalization, dead zones, poor gas dispersion, and excessive gas accumulation in the impeller zone highlighted by large and stable gas cavities. Gas accumulation leads to impeller flooding at lower gas flow rates and may limit the amount of the gas that can be sparged. These events also effectively reduce the working volume, requiring large reactors for very viscous and/or non-Newtonian processes [12].

Liquid properties have a direct influence on gas-liquid mass transfer through liquid film behavior and bubble coalescence. Liquid properties influence the boundary layer thickness, surface tension, and surface pressure which determine the coalescence frequency, coalescence efficiency, mixing time, residence time, and liquid-phase mass transfer coefficient. Liquid viscosity influences the thickness of the boundary layer which affects eddy turbulence and diffusion at the gas-liquid interface [26]. As the turbulence is reduced, liquid surface renewal is dampened as well.

The thicker boundary layer also means that the mass transfer resistance offered by the liquid film increases. Boundary layer thickness, surface tension, and surface pressure influence surface rigidity. As the bubble surface becomes more rigid, eddy turbulence encounters a higher resistance to the diffusive sublayer penetration. These effects combine to decrease eddy diffusion, molecular diffusion, and, consequently, the liquid-phase mass transfer coefficient [27]. Surface mobility is also an important factor in determining residence time. As the surface rigidity increases, the drag force decreases allowing the bubble to rise faster than those with mobile surfaces [7].

The effect of liquid viscosity has been investigated by many authors by adding CMC (carboxymethyl cellulose) to water [28]. The solution viscosity increases with CMC concentration while providing a negligible influence on bubble coalescence [6] and bulk flow patterns [29]. The results show that the liquid-phase mass transfer rate (k_L) and the volumetric gas-liquid mass transfer coefficient ($k_L a$) decrease as viscosity increases [6, 15, 28, 30]. The gas-liquid interfacial area tends to decrease in these situations as well because the larger cavities and large cavity formations at lower gas flow rates induce a lower power draw [29] and larger average bubble diameters [5]. The power draw drop and flow pattern changes are more gradual such that torque and power draw oscillations are reduced. This behavior is attributed to more stable gas-filled cavities that form at lower gas flow rates in high viscosity liquids. The power draw drop, however, can be too smooth for some hydrofoil impellers such that it becomes difficult to identify the critical impeller speed required for complete dispersion, requiring purely visual identification [29].

Several options exist for highly viscous processes. The simplest is to live with the additional cost (higher power draw) and/or lower productivity. The harder choice to make is to adjust and invest in the bioreactor. Generally, stirred tank bioreactors are baffled, single shaft vessels with Rushton-type impellers (RT). The first potential change could be to address the impeller. A major weakness for radial flow impellers, such as the Rushton-type impeller, stems from one of the strengths: the high shear rates. The power dissipation (or shear) rates are concentrated at the blade tips [31] and are not uniformly distributed throughout the reactor [6, 32]. This unbalanced shear distribution can lead to stagnant zones in the outer reactor region [33] and higher mass transfer in the impeller stream relative to the working volume [34, 35]. According to Stenberg and Andersson [35], 50% of the energy is dissipated in the impeller stream, 20% in the immediate impeller vicinity, and 30% is dissipated through the rest of the reactor. This disparity

leads to radial flow impellers providing very poor top-to-bottom mixing [36], particularly in more viscous fluids.

A mixed configuration using a radial and axial flow impeller is assumed to be more efficient for gas dispersion and mixing in a low viscosity Newtonian fluid than a dual axial or radial configuration, even though the Rushton-type turbine combination provides better gas-liquid mass transfer performance. Efficiency, in this case, is defined as the capability to maximize gas-liquid mass transfer while minimizing power input [31]. It is often advantageous to use a Rushton-type or concave blade turbine as the bottom impeller. This impeller would provide optimal bubble breakage. The upper impeller can be a downward pumping axial flow impeller to enhance gas-liquid circulation [28]. This general conclusion stems from studies such as the one completed by Moucha et al. [37] and summarized in Figure 2.

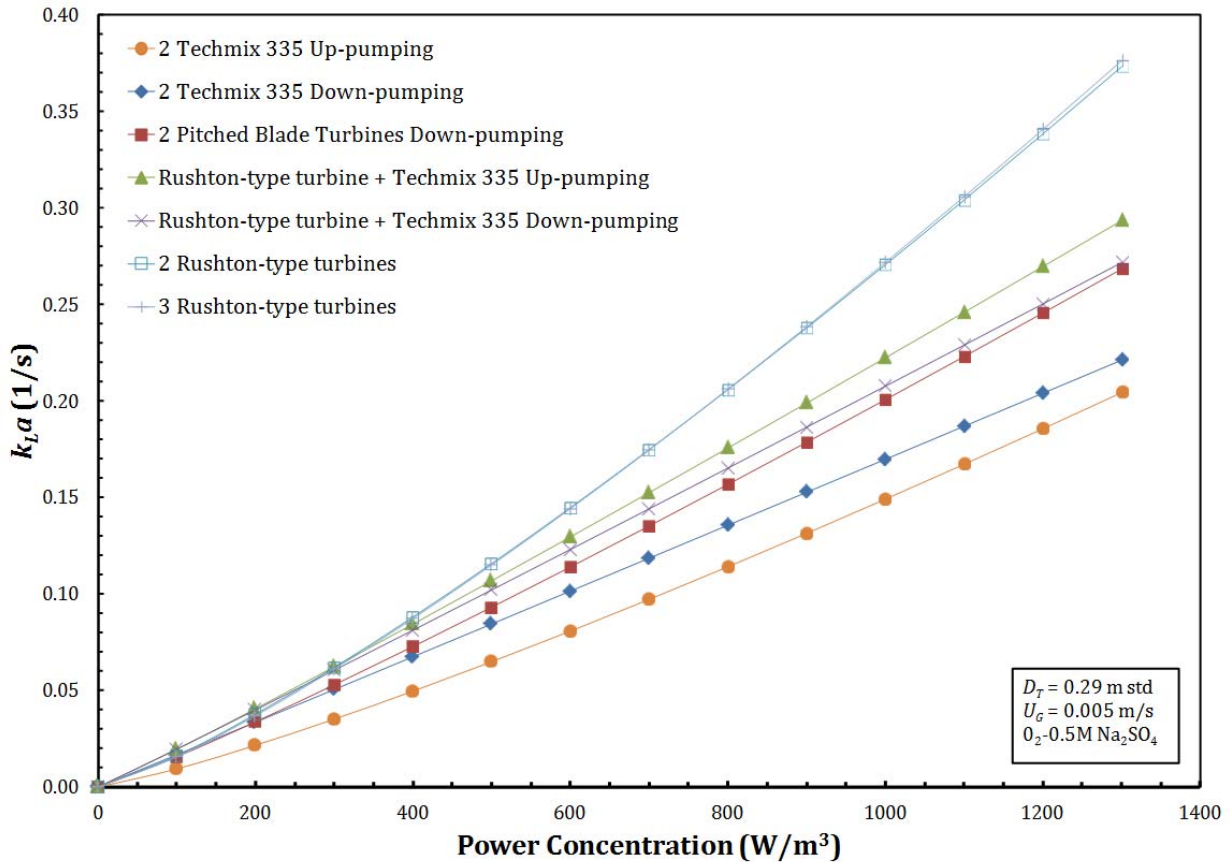


FIGURE 2: EFFECTS OF MULTIPLE IMPELLERS ON GAS-LIQUID MASS TRANSFER IN A STR (ADOPTED FROM MOUCHA ET AL. [37]).

The mixed configuration efficiency and the declining increase in the gas-liquid mass transfer coefficient ($k_L a$) with increasing number of turbines are determined by the impeller loading. The bottom impeller is loaded directly (by sparged gas) while the other impeller(s) are loaded indirectly (by impeller generated flow loops). Direct loading enhances gas dispersion capabilities of the Rushton-type turbine, while indirect loading puts more emphases on liquid mixing efficacy. Impeller loading is a more important consideration in experimental-scale reactors. Larger industrial-scale bioreactors and bioreactors using viscous media require more effective blending and top-to-bottom mixing than the Rushton-type turbine can provide [6, 38]. The Rushton-type turbine is oftentimes limited in this regard, and the conditions created in these impeller zones (cells) are more geared towards axial flow impellers [36].

Furthermore, the discharge from a radial flow impeller divides the reactor volume into well-mixed systems with minimal interchange [39]. As a result, radial flow impellers in large-scale systems may produce compartmentalization, caverns (impeller is encased by its flow field while most of the reactor is stagnant), higher gas recirculation, and low volumetric exchange zones [40]. For large STRs, the combination of a radial flow impeller on the bottom and a down-pumping axial flow impeller on the top enhances the reactor fluid mixing such that the reactor volume contact is maximized with minimal power input.

Bouaifi and Roustan [38] found that the average bubble diameter was larger in the bottom section of the reactor than the upper section. They concluded that bubbles formed a distribution such that the larger bubbles were in a region outside the impeller stream and were up to four times larger than the bubbles entrained in the impeller stream. More specifically, gas in these setups would concentrate about the impeller shaft, impeller tip, and within the radial area between the impeller and reactor walls [29, 41]. These observations were made for an axial system, but are very similar to those made by Stenberg and Andersson [35] for a single Rushton-type turbine (1RT) setup, which produced a similar qualitative mass transfer behavior for these impeller types.

Bouaifi and Roustan [38] also observed that a “very heterogeneous bubble distribution” would form in a dual axial flow impeller system once the bottom impeller was flooded. If the impeller was properly loaded and complete dispersion occurred, 50-60% of the bubbles had a diameter of 1-3 mm. Thus, it was more effective to operate in the loaded and complete dispersion regime. These experiences confirm and explain the unbalanced mass transfer performance observed by Linek et al. [42, 43] and Gagnon et al. [31] in multiple impeller systems and by Bellgardt [33], Moilanen et al. [44], and Stenberg and Andersson [34, 35] in single impeller systems.

The impeller choice in multiple impeller reactors is therefore vital. A proper selection requires a minor power increase of ~15% to produce similar $k_L a$ of a Rushton-type setup but with a much friendlier environment for

microorganisms and larger scales [6]. The required radial and axial flow impeller often depends on the operational conditions. The simplest configuration includes a Rushton-type turbine for the lower impeller and a down-pumping pitched-blade turbine (PBT) for the upper turbine(s). Since these impellers tend to flood relatively early, it has been proposed to replace the Rushton-type turbine and down-pumping PBT to extend the operational use. For example, Pinelli et al. [45] did not find an advantage to using two Rushton-type turbines over two BT-6 impellers (asymmetric concave blade impellers designed by Chemineer). Gas holdup and macromixing were observed to be very similar, which would imply that the concave blade disc turbine could replace a Rushton-type turbine in a single or multiple impeller system without major hydrodynamic implications while providing more gas handling capacity [8]; something even more important in highly viscous fluids. While holding power concentration and superficial gas velocity constant, Chen and Chen [46] observed much higher mass transfer potential and smaller bubbles by replacing the RT with a comb and perforated blade disc turbine. The Lightnin A-315, which is a high efficiency hydrofoil impeller, could replace the down-pumping PBT if a higher gas capacity is necessary. A more homogeneous environment is also expected with this replacement at larger scales because the A-315 provides better recirculation exchange and interaction with the other impeller(s) [47].

Another option is to adjust the baffles and shaft position and configuration. Cabaret et al. [5] adjusted the shaft position, rotational direction, and baffles. The experience in a water system is that it is not helpful to introduce separate impeller shafts, off-centering of the impeller shaft, or the removal of baffles. Although counter-rotating, separate shafts had a similar effect to a baffled, centered shaft, the cost of having separate shafts would be considered a negative.

The effects in a higher viscosity solution were different. The changes may be observed in a solution with a viscosity of 15 mPa s (Figure 3). The counter-rotating shafts start to show an improvement over the standard shaft and baffle configuration. As the viscosity increases (Figure 4), the counter-rotating setup decreases slower than the standard configuration such that the gas-liquid mass transfer coefficient is 149% higher at a viscosity of 102 mPa s than in the standard configuration.

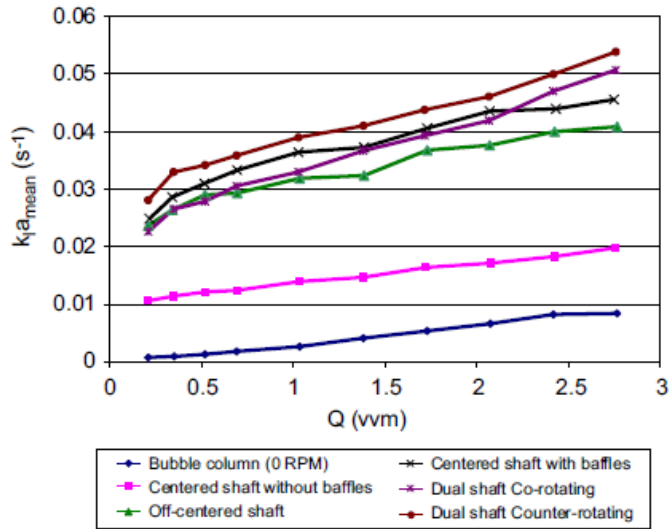


FIGURE 3: EFFECT OF GLUCOSE SOLUTION ($\mu = 15$ MPa-s) TO THE GAS-LIQUID MASS TRANSFER COEFFICIENT AT DIFFERENT GAS FLOW RATES AND CONFIGURATIONS [5].

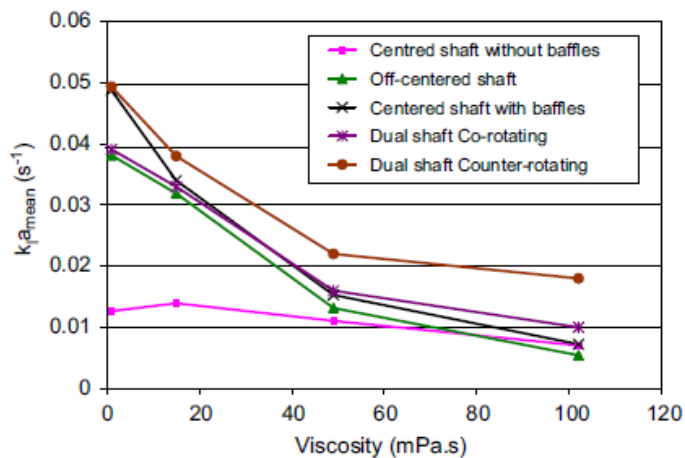


FIGURE 4: VISCOSITY EFFECT ON THE GAS-LIQUID MASS TRANSFER COEFFICIENT AT DIFFERENT CONFIGURATIONS ($Q = 1.03$ VVM) [5].

Figure 4 also confirms the expectation that baffles become less important as the viscosity increases beyond 50 mPa s. The turbulence is reduced to a level at which surface aeration is not expected to easily occur. Hence, viscous fluids may benefit from surface baffles, which are half baffles located in the upper half of the reactor. These baffles limit vortex formation while increasing surface turbulence [48]. Surface baffle design induces small vortices which entrain gas more effectively, increasing gas holdup and the gas-liquid mass transfer coefficient. The limitation of baffle usage in the lower portion of the reactor volume allows for higher turbulence and enhances sparged gas and power utilization [31]; however, Sivashanmugam and Prabhakaran [49] noted that such nonstandard baffles also lead to lower impeller power draw, which may decrease mass transfer in that portion of the tank. It

should be noted that such a setup may have limited applications for semi-batch operations.

SURFACTANTS AND ANTI-FOAMING AGENTS

The influence of various liquids on coalescence has led to their categorization into coalescing or non-coalescing liquids. Coalescing liquids, such as water or ocnol solution (anti-foaming agent), do not reduce, or may even enhance, bubble coalescence. The bubble film in these liquids tends to be relatively thin and provides minimal resistance to film drainage.

Non-coalescing liquids have surface tension reducing properties which, together with turbulence, determine the bubble diameter [50]. As surface tension decreases, the turbulent forces provided by impeller agitation are able to decrease the bubble diameter. The smaller bubbles provide more interfacial area increasing the gas-liquid mass transfer coefficient [15]. Impeller performance and bulk flow patterns are not retarded using non-coalescing liquids even if gas residence time and holdup are increased such that the qualitative interaction is analogous to an air-water system [29]. In other words, mixing is not significantly altered. Approximately the same amount of gas goes through the impeller region and impeller loading does not change significantly; however, gas-liquid mass transfer properties are quite different. It is this interaction which causes a significant effect on process efficiency.

Gas-liquid processes, especially in fermentation [29], utilize inputs and/or outputs which are surface active agents such as sugars, alcohols, or electrolytes. These surface active agents exhibit non-coalescing behavior while dampening bubble interface activity [35], potentially reducing the liquid-phase mass transfer coefficient by 75% [51]. As the bubble shrinks, the resistance offered by the liquid film changes significantly, further hindering surface velocity and turbulence [51]. The gas-liquid mass transfer is therefore determined by the balance of increased interfacial area and decreased liquid-phase mass transfer coefficient [4].

The exact effect on $k_L a$ depends on the particular surface active agent(s) and its concentration. Generally speaking, surface active agents increase mass transfer at low concentrations and decrease it at higher ones [6]. Electrolytes (like Na_2SO_4) can be used to describe the general behavior and are also representative of low-viscosity Newtonian fluids [47]. Na_2SO_4 causes an increase in $k_L a$ up to a certain concentration (0.2M), above which its coalescence-inhibiting effects are cancelled by k_L retardation. Increasing the concentration above 0.5M leads to a decrease in $k_L a$ [52].

Gas holdup may increase by up to 40% with the addition of electrolytes regardless of concentration [53], but the resulting increase in a (and $k_L a$) is offset by the potentially dominating decrease in k_L . These effects are unique to stirred tank reactors because dispersion and agitation are controlled by the impeller and its energy dissipation rate. Glycerol may be used to simulate viscous Newtonian liquids and has a non-

coalescing influence in concentration of 5-50% by weight. The maximum $k_L a$ is exhibited at 45% by weight [54]. Sokrat44, which has comparable viscosity properties to CMC TS.20 (produced by Lovochemie, Czech Republic), caused a reduction of 40-80% in $k_L a$ [30], but has been shown to behave qualitatively similar to electrolytes [6].

The chemical industry has developed two classes of special surface active agents which are of importance in biological gas-liquid processes: surfactants and anti-foaming agents. Surfactants are used in processes containing coalescence-prone liquids or requiring minimal bubble diameters. The name itself is derived from “surface active agents”, but is meant to distinguish the industrial products with coalescence inhibiting properties from other surface active agents which occur naturally, especially in fermentation broths [25, 55], or exhibit coalescence inciting properties. A common surfactant is soap. Common surfactants for research purposes are Tween 80 (polysorbate 80) and PEG 1000 (polyethylene glycol). They are nonionic surfactants, which make them less effective for non-coalescing duties, but they are fairly benign, safe, and quite common in the food industry.

Surfactants are amphiphilic and tend to accumulate at the gas-liquid interface, which provides the bubble with a stabilizing interface effect. The formation of these clusters, referred to as micelles, requires a critical micelle concentration, CMC (not to be confused with carboxymethyl cellulose which shares the same abbreviation). This shielding effect is achieved by the surfactant construction. Standard surfactants have a nonpolar hydrophobic tail and polar hydrophilic head. The charged nature of the hydrophilic head would repel two stabilized micelles (bubbles) and not allow enough contact time for the film to drain. Anionic surfactants, like detergents or soaps, have a negatively charged head. Cationic surfactants, like fabric softeners, have a positively charged head. Zwitterionic surfactants are somewhat rarer; these surfactants have a negative or positive charged head, which is often regulated by the acidity or pH of the liquid solution. Because the interface rigidity is increased, the bubbles are more likely to simply bounce off each other and not form a proper interface connection for drainage. The result is that surfactants typically lead to smaller bubbles and higher interfacial surface areas, which may lead to higher gas-liquid mass transfer coefficients [56].

Surfactants provide similar negative impacts on the liquid-phase mass transfer coefficient as other surface active agents with two exceptions. The first is that surfactants usually do not change surface tension relative to non-surfactant solutions, but the surface tension remains steady while stirring [57]. The second is that soluble surfactants do not impede diffusion of small molecules [51] and may not affect the film resistance (but this is rare). On the other hand, the polar group induces an energetic barrier for the turbulence to overcome and is usually seen as decreasing the surface renewal rate. The exact nature of the barrier depends on the polarity and molecular weight of the hydrophilic head, the length of the hydrophobic tail, and the

surfactant orientation at the gas-liquid interface [30]. An increase in the ionic strength, for example, would decrease coalescence frequency, decrease bubble diameter, and increase the interfacial surface area [15, 35]. The overall impact of surfactants on the interface is represented by a decrease of up to 75% in the liquid-phase mass transfer coefficient (k_L) [51] (Figure 5), but the increase in the interfacial area (Figure 6) is usually large enough so that the gas-liquid mass transfer coefficient is still larger with the use of surfactants [56]; however, the possibility that surfactants may decrease the gas-liquid mass transfer coefficient is feasible (Figure 7).

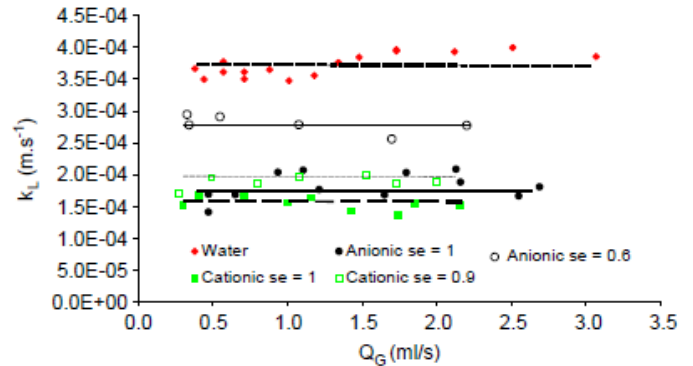


FIGURE 5: SURFACTANT EFFECTS ON LIQUID-SIDE MASS TRANSFER COEFFICIENT WITH GAS FLOW RATE [58].

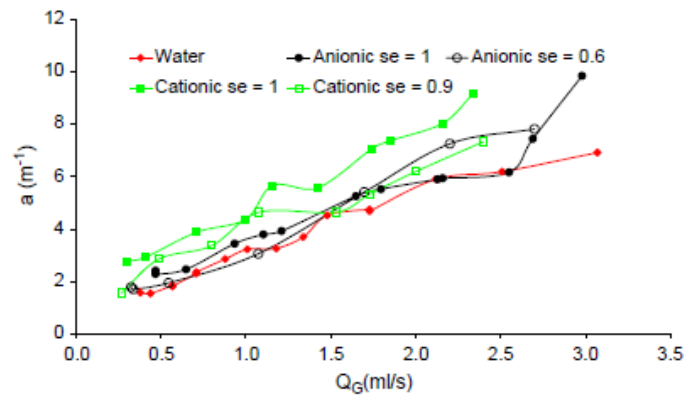


FIGURE 6: SURFACTANT EFFECTS ON INTERFACIAL AREA WITH GAS FLOW RATE [58].

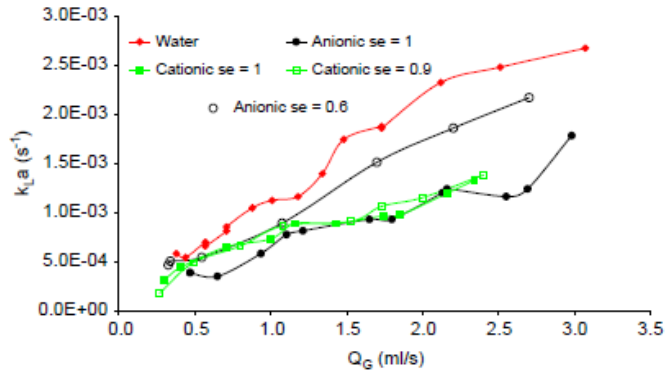


FIGURE 7: SURFACTANT EFFECTS ON THE GAS-LIQUID MASS TRANSFER COEFFICIENT WITH GAS FLOW RATE [58].

The downside of using surfactants is economical and practical in nature. Surfactants are sold by the chemical industry and would add to the product cost. Surfactants also have a tendency to attach to the product or microorganisms and wash out, which would require a surfactant separation and/or recovery system. The recovery system would minimize the surfactant cost, but would add a fixed cost element. Most separation or recovery units for gas-liquid processes use a charged filter, which cannot be reused, to attract the polar head [56]. If microorganisms are involved in gas-liquid processes, surfactants could suffocate or expose them to an unfriendly environment. For example, hand soap is designed to lyse bacteria. Other design options usually exist to increase gas-liquid mass transfer, which do not carry the added fixed or variable costs associated with surfactants.

The exception to the surface active agent rule is provided by anti-foaming agents, such as oconol. These surface active agents are used by the chemical industry in processes that create excessive foaming which limits gas disengagement at the reactor surface [59]. Anti-foaming agents are designed to induce bubble coalescence such that gas disengagement is maximized. This requires large bubbles and causes a rapid decline in $k_L a$ up to a certain concentration where the rate of decline stabilizes [30]. In addition to a lower gas-liquid mass transfer, anti-foaming agents require higher energy inputs and down-stream processing that is similar to surfactants. Anti-foaming agents also denaturize the biological components. Therefore, anti-foaming agents have limited application in most gas-liquid processes [59] and are usually avoided.

NON-NEWTONIAN LIQUIDS

Non-Newtonian fluids fall into two general categories: Shear thinning or shear thickening. Shear thinning non-Newtonian fluids are usually not challenging. Power management can be used to deal with any of the issues; however, shear thickening non-Newtonian fluids pose a real issue with economical and hydrodynamic constraints.

A more challenging situation is presented for viscous non-Newtonian liquids or, more commonly, processes which change a low viscous Newtonian fluid into a viscous non-Newtonian fluid with a complex rheology. Common non-Newtonian processes are encountered in fermentation due to mycelin growth and polymeric produced by the involved microorganisms [5, 29]. Mycelin growth is simulated using a material with similar macroscopic structure resembling fungal hyphae suspended in water, commonly achieved with paper-pulp suspensions. The polymeric effect on viscosity is simulated using CMC, Carbopol (carboxypolymethylene), or Xanthan gum [25, 29]. The viscosity of the solution is simulated by increasing the concentration of those additives over time.

Operations with these types of complex fluids proceed fairly efficiently while the fluid is Newtonian, even if it turns viscous; however, once the liquid becomes non-Newtonian, it adds an additional dampening effect that is very hard to overcome. It becomes very hard to provide proper mixing and dispersion and the reactor volume experiences a wide array of possible Reynolds numbers [60] and energy dissipation rates [12]. As a matter of fact, stagnant and transitional regions outside the impeller zone (shown in Figure 8) and cavern and channel formation are very common. Furthermore, the impeller is easily flooded due to the viscosity gradients which force the gas into the impeller zone [25]. Hence, the gas flow rate must be limited and increasing the impeller speed is a disadvantage [12].

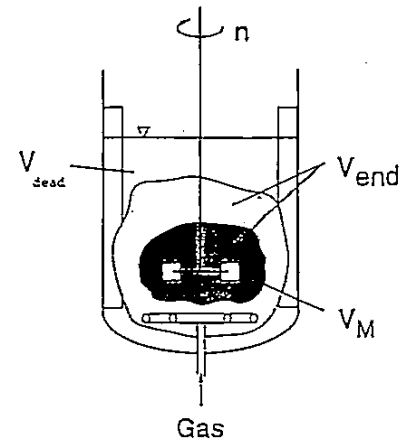


FIGURE 8: ENERGY DISSIPATION IN NON-NEWTONIAN LIQUIDS LEADING TO DEAD (V_{dead}) AND TRANSITIONAL (V_{end}) ZONES [61].

The effect of stagnant zones is of issue since it may interfere with variables used in hydrodynamic correlations. For example, the power concentration and superficial gas velocity are almost always used in gas holdup and gas-liquid mass transfer correlations. A stagnant region implies that the energy is being dissipated by a smaller liquid volume. As such, the actual power concentration experienced in the mixed region is actually larger than expected. In the same sense, the cross-sectional area through which the gas flows through may be

lower than the vessel cross-sectional area, which is used for the standard superficial gas velocity. Hence, the local velocities and turbulence are going to be underestimated with the use of superficial gas velocity in these cases. A solution to mitigate these events is to adjust the inputs and base them on the effective mixing volume (V_M shown in Figure 8) [61].

The mitigation of dead zones may be accomplished through two strategies. First, the user may increase the power input until the impeller overcomes the dampening properties of the liquid. CMC and Xanthan solutions experience thorough mixing at a gassed Reynolds number above 500 with 800-1000 being a good estimate for many processes. In order to achieve these turbulence levels, the impeller needs to impose a power concentration of at least 5 kW/m^3 . Solutions which show a higher dampening factor, such as polyacrylamide solutions, require higher turbulence levels corresponding to a gassed Reynolds number of more than 5000 and power concentration of at least 15 kW/m^3 [61]. The cost of these operations is naturally higher when compared to the usual power concentration for Newtonian liquids of $3\text{-}4 \text{ kW/m}^3$ [9, 51]. The other solution is to decrease the vessel size, which would have a similar effect to the previous strategy. It should be noted that pilot-scale vessels experience smaller turbulence issues due to the common scaleup procedure of keeping the power concentration constant relative to the experimental scale even though the Reynolds number increases exponentially with vessel diameter.

Correlations, which are often derived from an energy balance, are available such as:

$$\frac{P_G}{V_L} = \rho \left[\left(\frac{Ne Re_G^3}{d/T} \right)^{\frac{m+1}{2}} \left(\frac{K}{\rho} \right)^3 \right]^{\frac{1}{2-m}} \quad (1)$$

where P_G , V_G , ρ , Ne , Re_G , d , T , m , and K are the gassed impeller power draw, gassed liquid volume, liquid density, Newton number, gassed Reynolds number, stirrer diameter, vessel diameter, flow exponent, and consistency index, respectively. The consistency index and flow exponent are derived from apparent viscosity measurements such that

$$v_{app} = \frac{K}{\rho} \left(\frac{1}{K} \frac{P_{tot}}{V} \right)^{\frac{m-1}{m+1}} \quad (2)$$

where v_{app} and P_{tot} are the apparent viscosity and total (gassed and impeller) power, respectively [61].

The situation, in other words, can be managed from an engineering point of view; however, two major practical problems still exist, especially for industrial processes. First, mixing difficulties result in a poor gas and nutrient distribution and reduced productivity [31], which in turn causes the process time to be governed by the final 10-20% conversion [62] and requires greater vessel size relative to Newtonian processes

[12], potentially acting counter to the strategy of decreasing the vessel size to limit power concentration necessary for the achievement of a well-mixed volume. The second problem is that many processes may be economically not profitable with higher energy usage. Manufacturers' solution has been to simply stop the process once the viscosity or elasticity reaches certain levels [12, 61].

It is also important to note that the definition for a well-mixed state with non-Newtonian vessels may be ambiguous. Newtonian systems often define a well-mixed state in terms of a tracer experiment such that the time required to disperse the tracer is short relative to the process time or some other time definition. The more viscous non-Newtonian systems are occasionally simply satisfied to have some sort of liquid movement in the reactor periphery and a more turbulent core. Hence, we arrive at the process being limited by the final 10-20% conversion.

A potentially better approach would be to base the power concentration and residence time partially on the Damköhler number, which may be defined as the ratio of the characteristic fluid time (the residence time in this case) to the characteristic (bio)chemical reaction time. The reaction time may be derived based on knowledge or estimates of the biochemical reaction order and kinetics. The Damköhler number would then be derived based on the required or desired conversion rate. As a rule of thumb, a 10% conversion rate leads to a Damköhler number smaller than 0.1 while a 90% conversion requires a Damköhler number greater than 10 [63]; however, this rule of thumb has been derived based on experiences in chemical engineering and an assumption that the reaction has first-order kinetics.

Biochemical processes, especially those using microorganisms, are limited by transport phenomena such as gas-liquid mass transfer, which would imply a lower-bound Damköhler requirement of at least 1 while Damköhler numbers larger than 10 in viscous non-Newtonian processes would probably be economically restrictive due to the power requirements. A further simplification could be made by introducing a dimensionless time, defined as the ratio of tracer concentration equalization time to the calculated residence time. The goal would be to design the vessel power concentration to provide a dimensionless time of unity or less. Economic restraint might not make that possible, but at least the user could be somewhat certain that conversion targets will be in the desired neighborhood. The natural problems with such a method would be the estimates for biochemical reaction terms and economic and operational constraints, but it could potentially make the design and scaleup procedure easier and more consistent when combined with predictive mixing models such as Eqn. (1)

A few other options exist to mitigate mixing problems. The reactor design could abandon the Rushton-type impeller and implement shear normalizing setups using traditional axial or nontraditional helical impellers which produce a lower apparent

viscosity solution [60] and, hence, require lower turbulence levels to reach a well-mixed state.

Another solution is to alter the type and number of impellers with non-Newtonian liquids or rheology. These processes are operated in the laminar regime which puts more emphases on the viscous behavior of the fluid. Multiple impellers have been determined to produce better gas-liquid mass transfer in viscous fluids than the commonly used helical ribbon impeller. Most researchers, however, spend time investigating low viscosity impeller combinations for viscous non-Newtonian applications [60]. These low clearance impellers can require large amounts of power, making their operation impractical, especially for very viscous non-Newtonian liquids [31]. In these cases, the operation is simply shut down if the impellers are not capable of providing proper conditions [12]. A process using non-Newtonian and low viscosity fluids can be enhanced by increasing the number of blades in a paddle or turbine impeller; however, the turbine impeller is still more effective for gas-liquid mass transfer purposes [4].

Cabaret et al. [5] and Gagnon et al. [31] concluded that better mixing and higher product conversion can be achieved if a close clearance impeller, such as the helical ribbon, is used in conjunction with a radial flow impeller such as the RT in a highly viscous system. The Rushton-type turbine provides proper gas dispersion, while the close clearance impeller attempts to contact most of the reactor volume and provides proper bulk mixing, shear distribution, lower apparent viscosity, and minimal stagnant zones [60]. These effects also lead to higher reactor utilization and can decrease power requirements.

Several authors have suggested the inclusion of a viscosity term to the standard $k_L a$ correlation in order to account for viscous and non-Newtonian effects [4, 12, 30, 50, 60]:

$$k_L a = C \left(\frac{P_G}{V_L} \right)^A U_g^B \mu_a^C \quad (3)$$

where A , B , C , and D are fitted constants, and $k_L a$, P_g , V_L , and U_g are the gas-liquid mass transfer coefficient, gassed impeller power draw, liquid volume, and the superficial gas velocity, respectively. The viscosity (μ_a) is the apparent viscosity based on the Ostwald-de Waele model. A Casson viscosity [4, 50] and a liquid-to-water viscosity ratio [54] have also been used successfully.

Extensive attempts have been made in modeling gas-liquid processes involving non-Newtonian liquids in stirred tank bioreactors using dimensionless groups since the standard correlation form for STRs is seen as inadequate for these specific conditions. These correlations tend to be more complicated and require numerous static, but only few dynamic, inputs. One of the simplest correlations is presented by Ogut and Hatch [12] which involves four dimensionless groups and requires six inputs. One of the more complicated forms, proposed by Nishikawa et al. [64], uses 12 dimensionless groups because the model tries to explain

operation during low power input leading to the stirred tank reactor behaving like a bubble column. A general word of warning would be that if a correlation is based on statistical fitting, it runs the risk that the fit is achieved by probability rather than causality. The result could be that the correlation predicts improbable outcomes when extended beyond the operating range [35].

CONCLUSIONS

Industrial biological processes experience a change in liquid properties as the process progresses to completion. These changes can include variations in the liquid viscosity and surface tension. Furthermore, the liquid may become non-Newtonian in nature with the production of certain byproducts such as proteins. Stirred tank bioreactors are expected to perform better under lower viscosity and surface tension while operating with Newtonian liquids. If, however, such operation is not an option, the stirred tank bioreactor may employ different hydrodynamic strategies to maximize operation such as the use of low-clearance impellers, increasing the number of impeller blades, multiple impeller systems (combining low and higher shear impellers), surfactants, and an early termination option. The costs associated with these alternatives are higher with a rheologically complex system, but they are not insurmountable, and a system-specific optimization is possible.

ACKNOWLEDGMENTS

Support for the work described in this paper from the ConocoPhillips Company is acknowledged.

NOMENCLATURE

a	gas-liquid interfacial area (per unit liquid volume)
B_W	baffle width
C_i	impeller clearance
d, D_i	impeller diameter
H	liquid height
K	consistency index
k_L	liquid-phase mass transfer coefficient
$k_L a$	volumetric gas-liquid mass transfer coefficient
m	flow exponent
Ne	Newton number
PBT	pitched-blade turbine
P_G	gassed impeller power draw
P_G/V_L	power concentration per unit volume
Q, Q_G	gas flow rate
Re_G	gassed Reynolds number
RT	Rushton-type impeller
STR	stirred tank reactor
t	time
T	stirred tank reactor diameter
U_g	superficial gas velocity
W	baffle width
V_{dead}	dead-zone liquid volume
V_{end}	transitional liquid volume
V_L	liquid (gassed) volume

V_M	well-mixed liquid volume
vvm	gas volume per liquid volume per minute
ρ	liquid density
v_{app}	apparent viscosity

REFERENCES

- Williams, J.A., "Keys to bioreactor selection," *Chemical Engineering Progress*, 2002. 98(3): p. 34-41.
- Branyik, T., A.A. Vicente, P. Dostalek, and J.A. Teixeira, "Continuous beer fermentation using immobilized yeast cell bioreactor systems," *Biotechnology Progress*, 2005. 21(3): p. 653-663.
- Hoffmann, R.A., M.L. Garcia, M. Veskiar, K. Karim, M.H. Al-Dahhan, and L.T. Angenent, "Effect of shear on performance and microbial ecology of continuously stirred anaerobic digesters treating animal manure," *Biotechnology and Bioengineering*, 2008. 100(1): p. 38-48.
- Garcia-Ochoa, F.F. and E. Gomez, "Mass transfer coefficient in stirred tank reactors for xanthan gum solutions," *Biochemical Engineering Journal*, 1998. 1(1): p. 1-10.
- Cabaret, F., L. Fradette, and P.A. Tanguy, "Gas-liquid mass transfer in unbaffled dual-impeller mixers," *Chemical Engineering Science*, 2008. 63(6): p. 1636-1647.
- Fujasova, M., V. Linek, and T. Moucha, "Mass transfer correlations for multiple-impeller gas-liquid contactors. Analysis of the effect of axial dispersion in gas and liquid phases on "local" k_{La} values measured by the dynamic pressure method in individual stages of the vessel," *Chemical Engineering Science*, 2007. 62(6): p. 1650-1669.
- Scargiali, F., A. D'Orazio, F. Grisafi, and A. Brucato, "Modelling and simulation of gas-liquid hydrodynamics in mechanically stirred tanks," *Chemical Engineering Research & Design*, 2007. 85(5): p. 637-646.
- Vasconcelos, J.M.T., S.C.P. Orvalho, A.M.A.F. Rodrigues, and S.S. Alves, "Effect of blade shape on the performance of six-bladed disk turbine impellers," *Industrial & Engineering Chemistry Research*, 2000. 39(1): p. 203-213.
- Oldshue, J.Y., "Fluid mixing technology." 1983, New York, NY: McGraw-Hill Publications Co.
- Murthy, B.N., R.S. Ghadge, and J.B. Joshi, "CFD simulations of gas-liquid-solid stirred reactor: Prediction of critical impeller speed for solid suspension," *Chemical Engineering Science*, 2007. 62(24): p. 7184-7195.
- Shewale, S.D. and A.B. Pandit, "Studies in multiple impeller agitated gas-liquid contactors," *Chemical Engineering Science*, 2006. 61(2): p. 489-504.
- Ogut, A. and R.T. Hatch, "Oxygen transfer into Newtonian and non-Newtonian fluids in mechanically agitated vessels," *Canadian Journal of Chemical Engineering*, 1988. 66(1): p. 79-85.
- Bredwell, M.D., P. Srivastava, and R.M. Worden, "Reactor design issues for synthesis-gas fermentations," *Biotechnology Progress*, 1999. 15(5): p. 834-844.
- McFarlane, C.M., X.-M. Zhao, and A.W. Nienow, "Studies of high solidity ratio hydrofoil impellers for aerated bioreactors. 2. Air-water studies," *Biotechnology Progress*, 1995. 11(6): p. 608-618.
- Charpentier, J.-C., *Mass-transfer rates in gas-liquid absorbers and reactors*, in *Advances in Chemical Engineering*, T.B. Drew, G.E. Cokelet, J.W. Hoopes, Jr., and T. Vermeulen, Editors. 1981, Academic Press: New York City, New York. p. 1-133.
- Harnby, N., M.F. Edwards, and A.W. Nienow, "Mixing in the process industry," 2nd ed. 1992, Boston: Butterworth-Heinemann Ltd.
- Tatterson, G.B., "Fluid Mixing and Gas Dispersion in Agitated Tanks." 1991, New York: McGraw-Hill, Inc.
- Nielsen, J. and J. Volladsen, *Description and modelling*, in *Bioprocessing*, H.-J. Rehm, G. Reed, A. Puehler, and P. Stadler, Editors. 1993, VCH: New York, NY. p. 79-102.
- Ulbrecht, J.J. and G.K. Patterson, "Mixing of liquids by mechanical agitation. Chemical Engineering: Concepts and Review," ed. J.J. Ulbrecht. Vol. 1. 1985, New York: Gordon and Breach Science Publishers.
- Nienow, A.W., "Hydrodynamics of stirred bioreactors," *Applied Mechanics Reviews*, 1998. 51(1): p. 3-32.
- Tatterson, G.B., "Scaleup and Design of Industrial Mixing Processes. 1994, New York: McGraw-Hill, Inc.
- Martín, M., J.M. García, F.J. Montes, and M.A. Galán, "On the effect of the orifice configuration on the coalescence of growing bubbles," *Chemical Engineering and Processing: Process Intensification*, 2008. 47(9-10): p. 1799-1809.
- Zahradnik, J., M. Fialová, M. Ruzicka, J. Drahos, F. Kastánek, and N.H. Thomas, "Duality of the gas-liquid flow regimes in bubble column reactors," *Chemical Engineering Science*, 1997. 52(21-22): p. 3811-3826.
- Li, H. and A. Prakash, "Heat transfer and hydrodynamics in a three-phase slurry bubble column," *Industrial & Engineering Chemistry Research*, 1997. 36(11): p. 4688-4694.
- Kawase, Y. and M. Moo-Young, "Volumetric mass transfer coefficients in aerated stirred tank reactors with Newtonian and non-Newtonian media," *Chemical Engineering Research & Design*, 1988. 66(3): p. 284-288.
- Worden, R.M. and M.D. Bredwell, "Mass transfer properties of microbubbles: II. Analysis using a dynamic model," *Biotechnology Progress*, 1998. 14(1): p. 39-46.
- Azbel, D., "Two-phase flows in chemical engineering." 1981, New York: Cambridge University Press.
- Puthli, M.S., V.K. Rathod, and A.B. Pandit, "Gas-liquid mass transfer studies with triple impeller system on a laboratory scale bioreactor," *Biochemical Engineering Journal*, 2005. 23(1): p. 25-30.

29. McFarlane, C.M. and A.W. Nienow, "Studies of high solidity ratio hydrofoil impellers for aerated bioreactors. 3. Fluids of enhanced viscosity and exhibiting coalescence repression," *Biotechnology Progress*, 1996. 12(1): p. 1-8.
30. Linek, V., M. Kordac, and T. Moucha, "Mechanism of mass transfer from bubbles in dispersions: Part II. Mass transfer coefficients in stirred gas-liquid reactor and bubble column," *Chemical Engineering and Processing*, 2005. 44(1): p. 121-130.
31. Gagnon, H., M. Lounes, and J. Thibault, "Power consumption and mass transfer in agitated gas-liquid columns: A comparative study," *Canadian Journal of Chemical Engineering*, 1998. 76(3): p. 379-389.
32. Ungerman, A.J. and T.J. Heindel, "Carbon monoxide mass transfer for syngas fermentation in a stirred tank reactor with dual impeller configurations," *Biotechnology Progress*, 2007. 23(3): p. 613-620.
33. Bellgardt, K.-H., "Bioreaction engineering: Modeling and control." 2000, New York City, New York: Springer. 18.
34. Stenberg, O. and B. Andersson, "Gas-liquid mass transfer in agitated vessels--I. Evaluation of the gas-liquid mass transfer coefficient from transient-response measurements," *Chemical Engineering Science*, 1988. 43(3): p. 719-724.
35. Stenberg, O. and B. Andersson, "Gas-liquid mass transfer in agitated vessels--II. Modelling of gas-liquid mass transfer," *Chemical Engineering Science*, 1988. 43(3): p. 725-730.
36. McFarlane, C.M. and A.W. Nienow, "Studies of high solidity ratio hydrofoil impellers for aerated bioreactors. 1. Review," *Biotechnology Progress*, 1995. 11(6): p. 601-607.
37. Moucha, T., V. Linek, and E. Prokopova, "Gas hold-up, mixing time and gas-liquid volumetric mass transfer coefficient of various multiple-impeller configurations: Rushton turbine, pitched blade and Techmix impeller and their combinations," *Chemical Engineering Science*, 2003. 58(9): p. 1839-1846.
38. Bouaifi, M. and M. Roustan, "Power consumption, mixing time and homogenisation energy in dual-impeller agitated gas-liquid reactors," *Chemical Engineering and Processing*, 2001. 40(2): p. 87-95.
39. Nienow, A.W., "Gas-liquid mixing studies: A comparison of Rushton turbines with some modern impellers," *Chemical Engineering Research & Design*, 1996. 74(A4): p. 417-423.
40. Nocentini, M., D. Pinelli, and F. Magelli, "Analysis of the gas behavior in sparged reactors stirred with multiple Rushton turbines: Tentative model validation and scale-up," *Industrial & Engineering Chemistry Research*, 1998. 37(4): p. 1528-1535.
41. Boden, S., M. Bieberle, and U. Hampel, "Quantitative measurement of gas hold-up distribution in a stirred chemical reactor using X-ray cone-beam computed tomography," *Chemical Engineering Journal*, 2008. 139(2): p. 351-362.
42. Linek, V., T. Moucha, and J. Sinkule, "Gas-liquid mass transfer in vessels stirred with multiple impellers--I. Gas-liquid mass transfer characteristics in individual stages," *Chemical Engineering Science*, 1996. 51(12): p. 3203-3212.
43. Linek, V., T. Moucha, and J. Sinkule, "Gas-liquid mass transfer in vessels stirred with multiple impellers--II. Modelling of gas-liquid mass transfer," *Chemical Engineering Science*, 1996. 51(15): p. 3875-3879.
44. Moilanen, P., M. Laakkonen, O. Visuri, V. Alopaeus, and J. Aittamaa, "Modelling mass transfer in an aerated 0.2 m³ vessel agitated by Rushton, Phasejet and Combijet impellers," *Chemical Engineering Journal*, 2008. 142(1): p. 95-108.
45. Pinelli, D., A. Bakker, K.J. Myers, M.F. Reeder, J. Fasano, and F. Magelli, "Some features of a novel gas dispersion impeller in a dual-impeller configuration," *Chemical Engineering Research & Design*, 2003. 81(A4): p. 448-454.
46. Chen, Z.D. and J.J.J. Chen, "Comparison of mass transfer performance for various single and twin impellers," *Chemical Engineering Research & Design*, 1999. 77(2): p. 104-109.
47. Bouaifi, M., G. Hebrard, D. Bastoul, and M. Roustan, "A comparative study of gas hold-up, bubble size, interfacial area, and mass transfer coefficients in stirred gas-liquid reactors and bubble columns," *Chemical Engineering and Processing*, 2001. 40(2): p. 97-111.
48. Patwardhan, A.W. and J.B. Joshi, "Design of stirred vessels with gas entrained from free liquid surface," *Canadian Journal of Chemical Engineering*, 1998. 76(3): p. 339-364.
49. Sivashanmugam, P. and S. Prabhakaran, "Simulation of an effect of a baffle length on the power consumption in an agitated vessel," *International Journal of Food Engineering*, 2008. 4(2): p. Article 3.
50. Garcia-Ochoa, F.F. and E. Gomez, "Theoretical prediction of gas-liquid mass transfer coefficient, specific area and hold-up in sparged stirred tanks," *Chemical Engineering Science*, 2004. 59(12): p. 2489-2501.
51. Bredwell, M.D. and R.M. Worden, "Mass-transfer properties of microbubbles: I. Experimental studies," *Biotechnology Progress*, 1998. 14(1): p. 31-38.
52. Linek, V., M. Kordac, M. Fugasova, and T. Moucha, "Gas-liquid mass transfer coefficient in stirred tanks interpreted through models of idealized eddy structure of turbulence in the bubble vicinity," *Chemical Engineering and Processing*, 2004. 43(12): p. 1511-1517.
53. Majirova, H., D. Pinelli, V. Machon, and F. Magelli, "Gas flow behavior in a two-phase reactor stirred with triple turbines," *Chemical Engineering & Technology*, 2004. 27(3): p. 304-309.

54. Nocentini, M., D. Fajner, G. Pasquali, and F. Magelli, "Gas-liquid mass transfer and holdup in vessels stirred with multiple Rushton turbines: Water and water-glycerol solutions," *Industrial & Engineering Chemistry Research*, 1993. 32(1): p. 19-26.
55. van der Meer, A.B., A.A.C.M. Beenackers, R. Burghard, N.H. Mulder, and J.J. Fok, "Gas/liquid mass transfer in a four-phase stirred fermentor: Effects of organic phase hold-up and surfactant concentration," *Chemical Engineering Science*, 1992. 47(9-11): p. 2369-2374.
56. Cheng, H. and D.A. Sabatini, "Separation of organic compounds from surfactant solutions: A review," *Separation Science and Technology*, 2007. 42(3): p. 453 - 475.
57. Vazquez, G., M.A. Cancela, R. Varela, E. Alvarez, and J.M. Navaza, "Influence of surfactants on absorption of CO₂ in a stirred tank with and without bubbling," *Chemical Engineering Journal*, 1997. 67(2): p. 131-137.
58. Painmanakul, P., K. Loubiere, G. Hebrard, M. Mietton-Peuchot, and M. Roustan, "Effect of surfactants on liquid-side mass transfer coefficients," *Chemical Engineering Science*, 2005. 60(22): p. 6480-6491.
59. Bliem, R. and H. Katinger, "Scale-up engineering in animal cell technology: Part II," *Trends in Biotechnology*, 1988. 6(9): p. 224-230.
60. Tecante, A. and L. Choplin, "Gas-liquid mass transfer in non-Newtonian fluids in a tank stirred with a helical ribbon screw impeller," *Canadian Journal of Chemical Engineering*, 1993. 71(6): p. 859-865.
61. Henzler, H.-J. and G. Obernosterer, "Effect of mixing behaviour on gas-liquid mass transfer in highly viscous, stirred non-newtonian liquids," *Chemical Engineering & Technology*, 1991. 14(1): p. 1-10.
62. Lines, P.C., "Gas-liquid mass transfer using surface-aeration in stirred vessels, with dual impellers," *Chemical Engineering Research & Design*, 2000. 78(3): p. 342-347.
63. Fogler, H.S., "Elements of chemical reaction engineering," 4th ed. Prentice Hall PTR International Series in the Physical and Chemical Engineering Science, ed. N.R. Amundson. Vol. 11. 2005, Upper Saddle River, NJ: Prentice Hall. 1080.
64. Nishikawa, M., M. Nakamura, and K. Hashimoto, "Gas absorption in aerated mixing vessels with non-Newtonian liquid," *Journal of Chemical Engineering of Japan*, 1981. 14(3): p. 227-232.