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Why use bubble-column bioreactors?

José C. Merchuk, Sigal Ben-Zvi (Yona) and Keshavan Niranjan

Among the plethora of bioreactors available for aerobic culture, bubble columns, which are composed of a cylindrical vessel fitted with a gas sparger, are gaining in use. The simple construction of bubble-column reactors makes them easy to maintain. In addition, it is possible to control the degree of shear, uniformly within the reactor, which is critical to the growth of plant and animal cells in particular. This article reviews in detail the hydrodynamic, heat and mass-transfer characteristics of bubble-column bioreactors – parameters that are important for industrial scale-up.

The introduction of submerged cultures for industrial aerobic bioprocesses was one of the most significant breakthroughs in the history of biotechnology. A dense culture has such a high oxygen demand that the dissolved oxygen is rapidly consumed: the only way to sustain the reaction is by the continuous addition of oxygen to the medium. The development of air-sparged, stirred reactors (fermenters) proved highly successful in this regard, and they were widely adopted. However, the increasing sophistication of the new industrial bioprocesses, and the use of a greater variety of host cells has created many specific requirements, and many alternative reactor designs are now available[1,2]. While the majority of recent bioreactor designs are quite sophisticated and rather complicated (to the extent that some of the systems appear to be quite difficult to build and operate on a large scale), 'bubble-column reactors' (BCRs) are gaining an important place in both chemical and biochemical industries[3].

Unlike mechanically agitated reactors, bubble columns are simple to construct and operate. They consist of vessels (usually cylindrical) in which gas is sparged into a liquid. They have no moving parts, as adequate levels of mixing can be achieved with the sparged gas. In BCRs, all the energy needed for

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Glossary

Nomenclature

A – Cross-sectional area (m^2)
a – Effective interfacial area (m^{-1})
a_b – Surface area of a gas bubble (m^2)
B – Constant in Eqn 1
Cp – Heat capacity ($J\,kg^{-1}\,K^{-1}$)
D – Diffusion coefficient ($m^2\,s^{-1}$)
D_c – Column diameter (m)
f – Function defined in Eqn 5, Box 2
g – Gravitational acceleration ($m\,s^{-2}$)
h – Heat-transfer coefficient ($W\,m^{-2}\,K^{-1}$)
I – Ionic strength ($g\text{-ion}\,l^{-1}$)
J_G – Superficial gas velocity ($m\,s^{-1}$)
k – Thermal conductivity ($W\,m^{-1}\,K^{-1}$)
k_L – Volumetric mass-transfer coefficient (s^{-1})
L_R – Aerated reactor height (m)
n – Flow-behaviour index
n' – Molar-flow rate ($mol\,s^{-1}$)
N_1 – First normal stress difference (Pa)
p – Pressure (Pa)
$p1$,$p2$ – Pressure at the bottom/top of the reactor (Pa)
R – Universal gas constant ($P\,a\,m^3\,M^{-1}\,K^{-1}$)
T – Temperature (K)
W – Work (J)

Greek characters

β – Exponent in Eqn 8, Box 2
ϵ_g – Gas holdup
γ – Shear rate (s^{-1})
γ' – Global shear-rate, as defined by Eqn 3 (s^{-1})
η – Generalized newtonian viscosity (Pa·s)
κ – Fluid consistency index ($Pa\,s^n$)
μ – Viscosity (Pa·s)
μ_{eff} – Effective viscosity (Pa·s)
ν_L – Kinematic viscosity of the liquid ($m^2\,s^{-1}$)
ρ_L – Density of the liquid ($kg\,m^{-3}$)
σ – Surface tension of the liquid ($kg\,s^{-2}$)
τ – Shear stress (Pa)

Dimensionless groups

Bo – Bond number ($gD_c^2\,\rho_L\,\sigma^{-1}$)
Ga – Galilei number ($gD_c^3\,\rho_L^2/\mu_{eff}^2$)
Fr – Froude number ($J_G\,g^{-0.5}\,D_c^{-0.5}$)
Nu – Nusselt number ($h\,D_c\,k^{-1}$)
Pr – Prandtl number ($Cp\,\mu\,k^{-1}$)
Pr* – Prandtl number of non-newtonian liquids (Eqn 8, Box 2)
Re – Reynolds number ($D_c\,J_G\,\nu^{-1}$)
Re* – Reynolds number of non-newtonian liquids (Eqn 8, Box 2)
Sc – Schmidt number ($\nu_L\,D^{-1}$)
Sh – Sherwood number ($k_L D_c D^{-1}$) or ($k_L D_c^2 D^{-1}$)
Wi – Weissenberg number (N_1/τ)

agitation, as well as the oxygen required for the culture, is provided by sparged air. Internal structures that modify the flow characteristics within the reactor can be installed; one such modification, which is gaining increasing industrial acceptance, is the air-lift reactor(ALR) (Ref. 4). In this article, we review the principal characteristics of simple bubble columns that do not have any internal structures.

Advantages

Mechanical simplicity

The most important advantages of bubble columns result from their simplicity. As there is no need to introduce energy by mechanical means, the sealing of the stirrer-shaft assembly, which is the most difficult problem to overcome in the mechanical design of a bioreactor, is eliminated. In addition, the absence of a shaft in the head space of the vessel gives more room for entry ports, an important factor in vessels with relatively small dimensions.

Mechanical simplicity is particularly important in biological processes, where sterility has to be maintained over extended periods. The absence of shafts eliminates a very expensive and equally vulnerable feature of mechanically stirred bioreactors, thereby increasing process reliability.

Mixing in viscous media

It is generally believed that bubble columns are less suited to processes involving highly viscous liquids. However, there is evidence to the contrary[5]. In the case of xanthan production, where the medium is highly non-newtonian in its rheological properties (see Box 1), mechanical agitation was only effective in a narrow zone around the impeller, leaving a large proportion of the bioreactor volume relatively unstirred and, consequently, anoxic. In an analogous situation, however, the use of a bubble column resulted in more-homogeneous mixing: the bubbles released at the sparger coalesced immediately to form very large bubbles (of similar diameter to that of the column) known as slugs, which rose rapidly along the axis of the column, setting the entire liquid into circulation, with upward movement near the cylinder axis and downward movement near the walls.

Shear damage

Many commercially important bioprocesses involve shear-sensitive cultures of, for example, animal cells. Shearing action in biological media is necessary for mixing, mass transfer and heat elimination: its importance increases with scale-up. However, excessive shear can damage the cells. Mechanically stirred bioreactors are prone to producing high-shear regions in certain areas of the medium (particularly in the vicinity of the impeller, where most of the energy introduced is dissipated), but little mixing elsewhere. However, in bubble columns, the turbulence is distributed more evenly.

In practice, ALRs are usually recommended for growing shear-sensitive cells, because of their reputed lower shear compared with BCRs. However, Onken *et al.*[8] found no perceptible differences in the doubling time of animal cells cultured in BCRs and ALRs under the same growth conditions. They also highlighted the importance of sparger design, and discussed the reduction in animal-cell damage caused by the addition of bovine serum albumin (BSA).

Box 1. Rheology

Rheology is the study of flow and deformation of matter. Fluids tends to deform, more or less continuously, when subjected to shearing forces. The rate at which fluids deform is characterized by the shear rate (γ), and the shearing force per unit area is known as shear stress (τ). The viscosity of a fluid (μ) is given by the shear stress divided by the shear rate (i.e. $\mu = \tau/\gamma$). For a newtonian fluid at a given temperature, pressure and composition, the viscosity is constant, independent of applied shear, i.e. for newtonian flow:

$$\tau = \mu\gamma \qquad \text{(Eqn 1)}$$

where μ is a constant. In other words, $\tau \propto \gamma$. However, there is another group of fluids, called non-newtonian fluids, for which the viscosity can change by a factor of 10 or even 1000 on application of shear. Obviously, such an enormous change cannot be ignored. For such cases, it is useful to define a modified viscosity (η) that varies with shear rate. The rheological characterization of a 'generalized newtonian fluid' can then be described mathematically as:

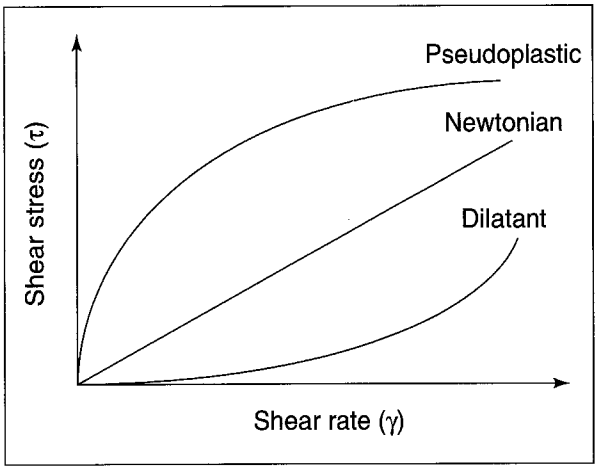
$$\tau = \eta\gamma \qquad \text{(Eqn 2)}$$

The behaviour of different non-newtonian fluids is shown in the figure. The pseudoplastic fluids, which fit the behaviour of polymers and therefore also describe biological exopolymer systems, are of interest in biotechnology. As can be seen in the Fig., the viscosity of the pseudoplastic fluid decreases with increasing shear rate; such liquids are therefore called 'shear thinning'. Ostwald[6], and de Waele[7] suggested a model that describes the shear-rate-dependent viscosity by a 'power law':

$$\eta = \kappa\gamma^{n-1} \qquad \text{(Eqn 3)}$$

where the constants κ and n are known as the fluid-consistency index and the flow-behaviour index, respectively.

The power-law constants can be determined in suitable viscometric apparatus, and should be carried out over the range of shear experienced by the liquids during the process.



Rheology curves of newtonian and non-newtonian fluids.

This effect was also observed by Croughan *et al.*[9] on addition of dextran.

There is evidence to suggest that one of the main causes of cell damage in sparged bioreactors is related to the bursting of bubbles that disengage from the liquid at the top of the column. This phenomenon generates rapid, surface-tension-driven motion of the liquid (A. Handa, PhD Thesis, University of Birmingham, Birmingham, UK, 1978). In addition, rupture of the film around the bursting bubble generates small droplets (30–300 μm) that are ejected at high velocities[10]. The addition of Pluronic F-68, a polymeric additive, to BCR cultures suppressed this effect remarkably. This is attributed to the strong elastic relaxation effect of the additive. (The use of additives to reduce shear damage is reviewed in Ref. 11.)

Plant cells, which are also shear sensitive, have been grown successfully in BCRs (Refs 12,13). Experimental observations showed that the growth of plant-cell cultures in BCRs, stirred-tank reactors (STRs) and shake flasks was similar. By contrast, Tanaka[14] reported that BCRs gave better results than STRs and ALRs at concentrations of cellular material up to 5 g l^{-1}.

It appears, therefore, that the use of BCRs for shear-sensitive cultures may be a practical alternative to other bioreactor configurations, provided that an appropriate protective agent (such as Pluronic F-68, BSA or dextran) is employed.

Disadvantages

The main disadvantage of bubble columns is that agitation is coupled with the aeration rate, so aeration cannot be altered without changing the level of agitation, and *vice versa*. (The rate of oxygenation of the culture could, however, be changed by modifying the composition of the aeration gas supply.) Another disadvantage is that it is difficult to use small-scale experiments to model industrial processes: as the characteristics of the hydrodynamics are, to some extent, scale-dependent, it may be difficult to extrapolate from the results of small-scale experiments. Finally, the range of gas-flow rate in the bioreactor has a clear upper limit, determined by the phenomenon of droplet entrainment. This problem increases very sharply at very-high gas-flow rates, when the liquid may be almost 'blown-out' of the reactor.

Flow configurations in bubble columns

With few exceptions, the discussion of flow regimes and heat and mass transfer in the published literature are generally applicable to liquids with a viscosity, or an effective viscosity, <50 mPa·s. The behaviour of bubbly dispersions in highly viscous liquids is quite different. Bubbles in such liquids coalesce readily, and very large bubbles (some as large as the column diameter) form in tall columns. In addition, the coalescence of bubbles in the bulk volume of such liquids, and the

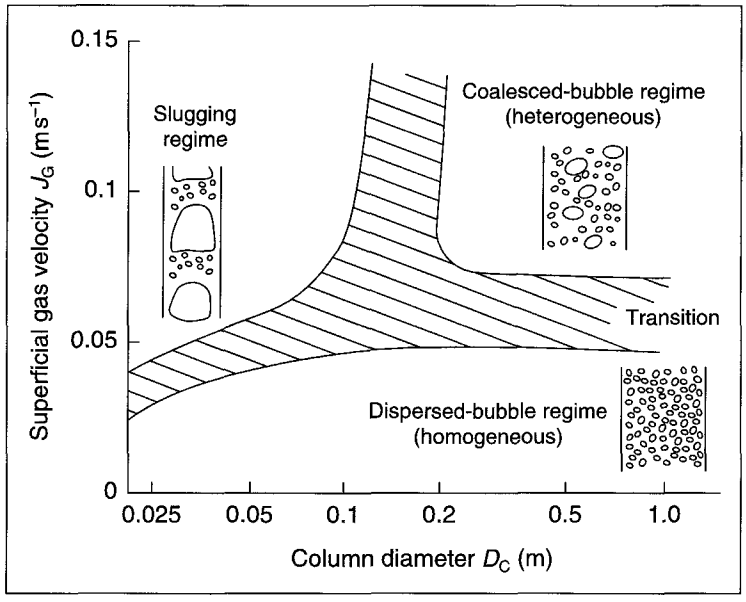


Figure 1

Flow regimes in bubble columns (from Ref. 21). The dispersed-bubble regime, characterized by bubbles that have more or less the same size as those produced by the sparger, is observed in all columns, regardless of their diameter, when the superficial gas velocity is low (<0.04 m s^{-1}). The coalesced-bubble regime, characterized by bubble coalescence and bulk-liquid circulation, is observed in columns with a diameter of 0.2 m or more at higher superficial gas velocities (>0.075 m s^{-1}). Finally, slugging regime, characterized by the cylindrical bubbles bridging the column, is observed in columns with smaller diameters (≤0.1 m), at superficial gas velocities >0.04 m s^{-1}.

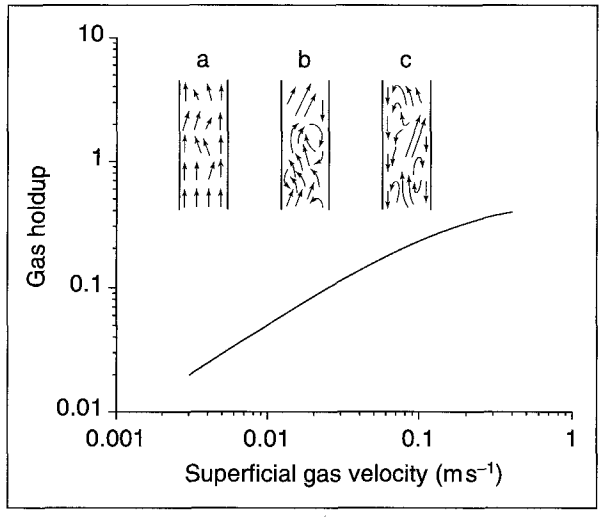


Figure 2

Recirculation patterns in bubble columns (from Merchuk[22]). **(a)** This pattern is observed at low supercritical gas velocities. The bubbles gently ascend through the liquid more or less along straight lines. **(b)** At higher gas velocities, the bubbles, which are now larger in size, begin to deviate from straight trajectories and follow a wavy path. **(c)** With a further increase in gas velocity, the bubbles are seen to recirculate with the liquid. Turbulence levels are markedly higher, and the bubbles tend to coalesce and break. The gas velocities at which these transitions are observed depend on the diameter of the column.

break up of bubbles at the surface, generates very tiny bubbles, resulting in an apparently bimodal distribution of bubble size. Hydrodynamics and mass transfer in these highly viscous newtonian and non-newtonian liquids is an important area of current research activity[15–18].

Although about a dozen different gas–liquid flow configurations have been recognized[19], only two of them are of interest in the operation of bubble columns[20,21]: (1) homogeneous bubbly flow regime, where bubbles are relatively small and of uniform diameter, and the turbulence level is low; and (2) churn-turbulent regime, where a wide range of bubble sizes coexists within a very turbulent liquid. As shown in Fig. 1, this flow regime can be reached from the homogeneous bubbly flow by increasing the gas-flow rate. Another way of obtaining churn-turbulent flow is by starting from slug flow and increasing the column diameter. Slug flow arises at high gas-flow rates and in relatively small column diameters; it is characterized by large bubbles bridging over most of the diameter of the column. Slug flow is a phenomenon that is best avoided, as large bubbles provide a relatively low interfacial area for mass transfer. However, very viscous liquids may be an exception. The criteria for flow-regime transition have been reviewed by Barnea and Taitel[19].

During batch operation of a bubble column, where there is very little, if any, net liquid flow, the following conditions usually hold: at low gas superficial velocity (volumetric flow divided by cross-sectional area), the bubbles generated by the gas sparger rise without much coalescence or breakup occurring; the bubble diameter is constant if changes in hydrostatic pressure and mass-transfer effects are assumed to be negligible. As the gas superficial velocity increases, bubble size, bubble oscillations and liquid turbulence levels increase; coalescence and breakup of bubbles is visible, but the general behaviour does not change very much. The gas holdup increases linearly with superficial velocity. With a further increase in superficial velocity, bulk circulation of the liquid commences; a central ascending and oscillating liquid path develops, with recirculation cells on either side (Fig. 2). These patterns can easily be seen in a two-dimensional bubble column built for the visualization of fluid-dynamic phenomena.

When operating at low gas velocities, bubbles ascend in straight lines, particularly in the lower half of the column (Fig. 2a). In the top half of the column, they follow a wavy trajectory, apparently as a result of the increase in bubble diameter, caused by the decrease in hydrostatic pressure and some degree of coalescence. However, as the gas velocity increases, the wavy trajectory increases in amplitude and a main stream is generated, characterized by high local velocity and larger bubbles (Fig. 2b). Recirculation cells with small bubbles entrained within the main-stream flow appear adjacent to the column walls. With a further increase in gas velocity, the frequency of the waves in the bubble trajectory increases sharply, while the amplitude remains constant or increases only slightly. This leads to a sharp increase in turbulence. The recirculation flow rate in the regions close to the vessel walls

increases at the expense of the central path which, under these conditions, consists of the largest bubbles. A clear downward flow of liquid develops, bringing the smallest bubbles to the bottom of the column. At higher values of superficial gas velocity, the wavy flow along the column axis is damped, and most of the gas passes rapidly through the centre. At the same time, the loop on either side becomes even more turbulent, and the downward flow of recirculating liquid is clearly visible along the column walls (Fig. 2c).

The change in flow pattern (depicted by the transition from Fig. 2b to Fig. 2c) corresponds to the 'transition regime', a phenomenon reported in bubble columns with a sparge hole <0.01 m (Ref. 16). One of the characteristics of this regime is an increase in the gas holdup. A critical superficial velocity has been defined[23,24] as the superficial gas velocity at maximum holdup, and is the point where liquid recirculation begins.

The modelling of the recirculation regime is very important for predicting the mixing characteristics of bubble columns. One of the more widely accepted models for the hydrodynamics of bubble columns is the circulation-cell model proposed by Joshi and Sharma[25]. It assumes that the liquid flow can be depicted as closed circulation cells. The model predicts that the height of the circulation cell is equal to the column diameter, for any given diameter. The number of circulation cells is therefore equal to the total dispersion height divided by the diameter (Fig. 3a). This model does not concur with the observations made on two-dimensional bubble columns[22], particularly because the circulation cells that have liquid circulating in opposing directions are assumed to be lateral on either side of the column axis. The axial component at the wall would change direction on passing from one cell to another. This contradicts the widely accepted view that, in the recirculation regime, flow at the wall is downwards along the length of the column.

The recirculation model has been extended to a three-dimensional version[26], which assumes that cylindrical eddies are piled up at 90° to one another in the column (Fig. 3b). This arrangement solves the problem of the interference between eddies, if one accepts the view that flow at the wall occurs in a downward direction.

An alternative approach to depicting the fluid dynamics of bubble columns in recirculating turbulent flow is the description of a single internal loop near the walls of the column. This has been done starting with the equation of motion, which represents the conservation of momentum within the system[27,28]. Mathematical expressions were obtained for the profile of liquid velocity along the radius of the column. This profile shows an ascending central core and a descending annulus of liquid near the walls. This means that, at some point within the radius, the liquid velocity is zero. This point is, in fact, a characteristic feature of the model. Menzel *et al.*[29] found it experimentally, and used this approach to describe flow and shear fields in a bubble column.

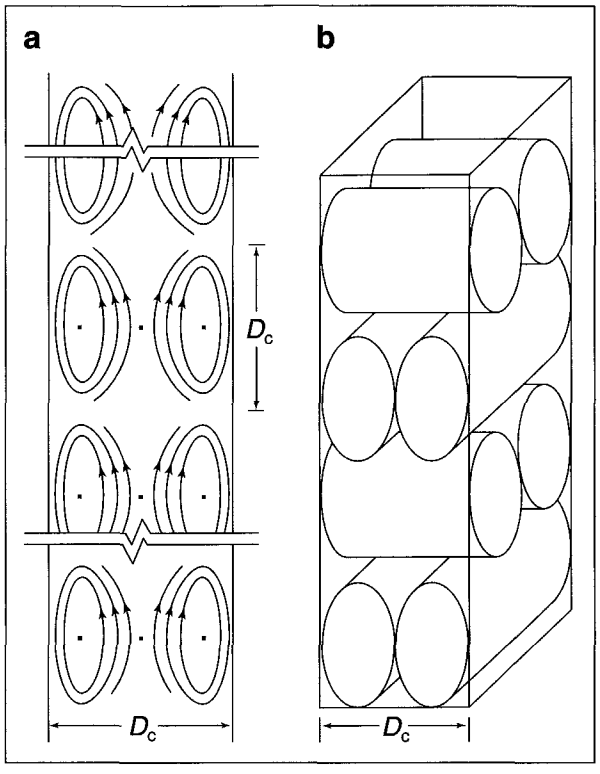


Figure 3
(**a**) Multiple circulation cells in a bubble column (from Ref. 25). These cells are arranged in axial alignment and the height of each cell is equal to the column diameter. (**b**) Cylindrical eddies model (from Ref. 26) assume the formation of superimposed rotating vortices, which are piled up transverse to one another along the column. As with (**a**), the height of the vortex is taken to be equal to the column diameter.

Mass transfer rate

The volumetric mass-transfer coefficient (k_La) is an important parameter used to characterize bioprocesses. It is the product of two terms: (1) the mass-transfer coefficient (k_L), which depends on the physical properties of the liquid and fluid dynamics near the interface; and (2) the interfacial area per unit volume of the aerated reactor (a). The coefficient k_L depends only weakly on the fluid dynamics, which are, in turn, influenced by power input[30,31], while the interfacial area depends strongly on the physical properties of the medium, bioreactor design and hydrodynamics.

In aerobic processes, chemical reactions can enhance the oxygen-uptake rate[32]. Similarly, biochemical reactions may enhance the oxygen-uptake rate in small, laboratory-scale reactors such as shake flasks, etc., where k_La is generally low, but not in industrial-scale equipment[33]. It is extremely difficult to determine k_L and a separately in any system. The product (k_La) can, however, be readily measured and used in characterizing bioreactor performance.

Variables affecting k_La

The volumetric mass-transfer coefficient (k_La) is affected primarily by superficial gas velocity, sparger design, characteristics of the medium, and the interaction of these three factors. In the bubbly flow regime,

Box 2. Dimensionless correlations

Dimensionless correlations are a standard tool used in chemical engineering to generalize and correlate results over a wide range of geometric dimensions and physicochemical variables. When the relationship between the process variables is clearly understood, it is possible to derive, from first principles, an equation or a set of equations relating these variables, which are dimensionally consistent. Division by one of the terms will then generate a series of dimensionless groups, each with a clearly understood physical meaning. However, in practice, we do not understand how different process variables are related. Indeed, we seldom know little more than the fact that the variables under consideration are related. In such situations, where limited knowledge of the phenomenon studied does not allow explicit dimensionally consistent equations to be deduced, the principles of dimensional analysis, established by Rayleigh and Buckingham, are used (see Ref. 38). Dimensionless groups usually represent the ratio of two competing phenomena. A high value of the exponent of the dimensionless group in the correlation indicates that the relevant phenomena are of considerable significance in the process.

It has become customary to name the dimensionless groups after the scientist who made the most significant contribution to the development of the related field of science and technology. For example, mass-transfer coefficients are usually expressed in terms of Sherwood numbers, honouring the American scientist Thomas K. Sherwood:

$$\mathrm{Sh} = \frac{k_L D_c}{D} \qquad \text{(Eqn 1)}$$

As k_L cannot be determined explicitly in practice, it is prudent to use the volumetric mass-transfer coefficient, $k_L a$, and consequently modify the Sherwood number as:

$$\mathrm{Sh}^* = \frac{k_L a D_c^{\,2}}{D} \qquad \text{(Eqn 2)}$$

The Sherwood number evidently represents the ratio of mass-transfer rate to molecular diffusivity, and it has proven very useful in the correlation of experimental results in mass transfer.

Correlations for mass-transfer coefficient

(1) Akita and Yoshida's correlation[39]

$$\frac{k_L a D_c^{\,2}}{D} = 0.6\left(\frac{\nu_L}{D}\right)^{0.5}\left(\frac{gD_c^{\,2}\rho_L}{\sigma}\right)^{0.62}\left(\frac{gD_c^{\,3}}{\nu_L^2}\right)^{0.31}\varepsilon_g^{\,1.1}$$

or in terms of dimensionless groups:

$$\mathrm{Sh} = 0.6\,\mathrm{Sc}^{0.5}\,\mathrm{Bo}^{0.62}\,\mathrm{Ga}^{0.31}\,\epsilon_g^{\,1.1} \qquad \text{(Eqn 3)}$$

where the gas holdup was correlated for pure liquids and non-electrolyte solutions as:

$$\frac{\epsilon_g}{(1-\epsilon_g)^4} = 0.2\left(\frac{gD_c^{\,2}\rho_L}{\sigma}\right)^{1/8}\left(\frac{gD_c^{\,3}}{\nu_L^2}\right)^{1/12}\left(\frac{J_G}{\sqrt{gD_c}}\right)^{1.0}$$

or:

$$\frac{\epsilon}{(1-\epsilon)^4} = 0.2\,\mathrm{Bo}^{1/8}\,\mathrm{Ga}^{1/12}\,\mathrm{Fr}^{1} \qquad \text{(Eqn 4)}$$

For salt solutions, the coefficient 0.2 is replaced by 0.25.

(2) Hikita *et al.* correlation[40]

$$k_L a = \frac{14.9gf}{J_G}\left(\frac{J_G\mu_L}{\sigma}\right)^{1.76}\left(\frac{\mu_L^4 g}{\rho_L\sigma^3}\right)^{-0.284}\left(\frac{\mu_G}{\mu_L}\right)^{0.243}\left(\frac{\mu_L}{\rho_L D}\right)^{-0.604} \qquad \text{(Eqn 5)}$$

where the value of f changes according to the ionic strength of the electrolyte solution. For non-electrolyte solutions, $f = 1.0$, and for electrolyte solutions, f depends on the ionic strength as follows:

For $0 < I < 1.0$ g-ion l^{-1}, $f = 10^{0.068\,I}$

For $I > 1.0$ g-ion l^{-1}, $f = 1.114 \cdot 10^{0.021\,I}$

(3) Suh *et al.* correlation[5]

For non-newtonian liquids with effective viscosities higher than 4 mPa·s, Suh *et al.*[5] proposed the following correlation:

$$\mathrm{Sh} = 0.018\,\mathrm{Sc}^{0.5}\,\mathrm{Bo}^{0.2}\,\mathrm{Ga}^{0.62}\,\mathrm{Fr}^{0.51}\,[1+0.12\mathrm{Wi}]^{-1} \qquad \text{(Eqn 6)}$$

the effective viscosity is calculated from Eqn 3, Box 1, and γ is obtained from Eqn 1 taking B = 2800.

Box 2. Dimensionless correlations (continued)

Heat-transfer correlations

For the correlation of the heat-transfer coefficients, the dimensionless group used most frequently has been named after the German scientist Ernst Kraft Wilhelm Nusselt (1882–1957). The Nusselt number is defined as:

$$Nu = \frac{hD_c}{k} \qquad \text{(Eqn 7)}$$

and it signifies the ratio of turbulent heat transfer to pure heat conductivity. It is, therefore, analogous to the Sherwood number (which is also called the Nusselt number for mass transfer).

Kawase and Moo-Young's correlation for heat transfer coefficient[41]

$$Nu = 0.075\,(10.3\,n^{-0.63})^{\beta}\,n^{1/3}\,(Pr^*)^{1/3}\,Fr^{-\beta}\,(Re^*)^{\beta+3(n+1)} \qquad \text{(Eqn 8)}$$

where:

$$\beta = (4-n)/[6(n+1)];\ Pr^* = (\kappa\, D^{1-n}Cp)/(k\, J_G^{1-n});\ \text{and}\ Re^* = (\rho\, D_c^{\,n} J_G^{2-n})/\kappa$$

This equation reduces for newtonian liquids to:

$$Nu = 0.134\,Pr^{1/3}\,Fr^{-1/4}\,Re^{3/4} \qquad \text{(Eqn 9)}$$

the volumetric mass-transfer coefficient increases linearly with increasing superficial gas velocity. The increase in gas-flow rate increases the number of bubbles, but not their shape as, under these conditions, there are no interactions between bubbles. Further increases in the superficial gas velocity results in a less-than-linear increase in the volumetric mass-transfer coefficient, as a result of coalescence, which changes the interfacial area per unit volume of gas.

The sparger determines the initial bubble size and shape in a given liquid. A sparger with small diameter holes, such as a perforated or sintered plate, will generate smaller bubbles than a single orifice sparger, and will therefore provide a higher interfacial gas–liquid contact area in the vicinity of the sparger.

The mean bubble size in the column as a whole is determined by the equilibrium between bubble coalescence and breakup, which depends both on the physicochemical properties of the liquid and the turbulence levels. There is a critical bubble size that can exist in a given liquid under given fluid-dynamic conditions, such that any bubble larger than this size will tend to break down. In noncoalescing liquids, the bubbles released by the sparger, if smaller than the critical size, will determine the mean size. If, on the other hand, the released bubbles are larger than the critical size, they will break, and the mean size will be close to the critical value. By contrast, for coalescing liquids, the mean bubble size will be close to the critical bubble size, regardless of the initial size distribution.

Properties of the liquid medium, such as viscosity and surface tension, affect $k_L a$. As gas is sparged, liquid movement is initiated and a gas–liquid interface is created. The nature of the operation of pneumatically agitated reactors such as bubble columns does not permit the aeration process to be separated from the mixing process. Changes in the superficial gas velocity will therefore alter both liquid-phase momentum and mass transfer. The viscosity of the liquid, which is a property affecting the liquid-phase momentum, will also have a strong effect on volumetric mass transfer. Although k_L is affected by viscosity to some extent, the effective interfacial area (a) is much more sensitive to it. In addition, the surface tension affects bubble coalescence and breakup, and therefore also affects the interfacial area, although the mechanism by which this occurs is still not clear. In the case of small bubbles ($d < 10$mm), the presence of surface-active agents will also affect k_L by controlling the rigidity of the bubble surface[34].

The actual mechanism of mass transfer from a bubble into liquid has not yet been elucidated fully. Early work by Baird and Davidson[35] assumed that the mass transfer from a spherical, cap-shaped bubble (the shape commonly observed in biological media) takes place through the boundary layer surrounding the bubble; this does not include the rear of the bubble interfacing with the wake, and the contribution of the wake region to mass transfer is thus ignored. By contrast, Coppus and Rietima[36] showed that the contribution of the wake region cannot be neglected entirely. They concluded that mass transfer occurs simultaneously from the front and rear, and the contribution of the rear to the total mass transfer can be as high as 20–30% in certain cases. Recent investigations by Schmidt and Lubbert[37] also suggest that the wake behind the bubble plays a more important role in mass transfer than previously thought. They observed that the mass transferred across the bubble boundary layer almost invariably found its way into the wake, from where it was dissipated into the bulk. If this is established conclusively, then we can visualize mass transfer as taking place in two stages: transfer across the bubble interface into the wakes; and

subsequent dissipation into the bulk. This would lead to significant modification of current, well-established theories of mass transfer.

Scale-up

The problems encountered in the scale-up of bioreactors can be categorized into two groups. One covers the cases where a high power input per unit volume is used at the laboratory scale, but cannot be attained at an industrial scale, because of economic or mechanical limitations. Obviously, this group does not include plant or animal cultures, where high specific power input cannot be tolerated because of cell fragility. The other group comprises problems relating to a lack of knowledge of hydrodynamics in large-volume vessels.

In general, bioprocesses involve several steps: mass or heat transfer by convection; transfer by diffusion mechanisms (facilitated or otherwise); and catalytic reactions. In the case of catalytic reactions, heat and mass transfer are integral to the process, as molecules must encounter each other in order to react, and energy (heat) transfer will accompany the reaction. Depending on whether these steps are in parallel, or in series, and on their relative velocities, the overall rate of the process may be limited by a single step. The equilibrium between the individual component rates can be (and usually is) altered by a change in the scale of the system: although a change in scale does not change the physicochemical or kinetic parameters (scale-independent variables), it does affect the overall convective mass- and heat-transfer rates (scale-dependent variables). Thus, for the same system, on a different scale, a new equilibrium between the rates of the many steps occurring may be established, and the interplay of all the parameters may lead to a regime where a different step is controlling the process rate.

Knowledge of the mixing, heat- and mass-transfer rates, and their dependence on the dimensions of the bioreactor are therefore basic requirements for process scale-up. This information, as well as the energy requirements for a given operation, is available in the form of correlations that can be used in design equations.

Mass-transfer correlations

The volumetric mass-transfer rate (k_La) is, perhaps, the key parameter to consider in the design and scale-up of a reactor. This parameter may be evaluated using correlations that are available in the technical literature (see Box 2), or by extrapolating from experimental data. It is, however, not uncommon to find that different correlations predict different values for k_La. These differences are sometimes related to the experimental methods used to determine them. Mass-transfer coefficients can be determined for either laboratory- or industrial-scale equipment using any of several experimental methods (for details, see Box 3).

Newtonian liquids

Akita and Yoshida[39] reported a correlation for k_La deduced from experimental data obtained using water, various aqueous ionic solutions, and methanol and glycol solutions in bubble columns of different sizes (see Box 2). This is the most reliable and widely used correlation to date, and it is recommended for a conservative estimate of k_La. This correlation permits the evaluation of k_La in a column of diameter D_c, for a gas whose molecular diffusivity in the liquid is D. These three variables are combined into a single dimensionless group, the Sherwood number, whose value can be calculated as a function of the superficial gas velocity in the column, the column diameter, and the physical properties of the liquid – viscosity, diffusivity, density and surface tension.

Hikita *et al.*[40] measured the volumetric mass-transfer coefficient in bubble columns with electrolyte and nonelectrolyte solutions, using various gases (Box 2). They introduced a term for the gas density into the expression. However, gas-phase properties are generally deemed not to be of critical concern in the design of bioreactors, unlike in certain chemical reactors, although interest in the role of gas properties on the performance of bubble columns has recently been revived[44].

Non-newtonian liquids

Biological media are often viscous and non-newtonian, and thus complicate the mathematical treatment of mass transfer, because of the variation of viscosity with shear-rate (see Box 1). An approach that is frequently used to predict k_La in non-newtonian liquids was proposed by Nishikawa *et al.*[45]. They studied the problem of heat transfer in bubble columns and correlated the shear rate with the superficial gas velocity for $J_G > 0.04\,m\,s^{-1}$ as:

$$\gamma = B\,J_G \qquad \text{(Eqn 1)}$$

where γ is the shear rate in s^{-1}, J_G is the superficial gas velocity in $m\,s^{-1}$, and B is a constant estimated as 5000. This shear rate is then used in the power law (see Box 1 for definition) to calculate a mean value of apparent viscosity for the whole reactor (see Box 1). Henzler *et al.*[46], Kawase and Moo-Young[41], Schumpe and Deckwer[47], Zaidi *et al.*[48], Deckwer *et al.*[49] and Godbole *et al.*[50] have all applied Eqn 1 to develop their respective correlations for k_La, by taking various values of B in the range $D_c < B < 3000$ for calculating the apparent viscosity. Similar correlations for viscoelastic non-newtonian liquids include the relaxation time of the liquid in terms of the Deborah number[51], or the 'first normal stress' derived from the equation of conservation of momentum in the form of the Weissenberg number[5] (see Box 2).

The constancy of B in Eqn 1 is questionable, as it predicts that liquids that have different rheological properties have the same shear rate at a given superficial gas velocity. Hence, shear rates calculated from Eqn 1 should only be used in relevant equations to calculate k_La, and should not be used to describe hydrodynamics.

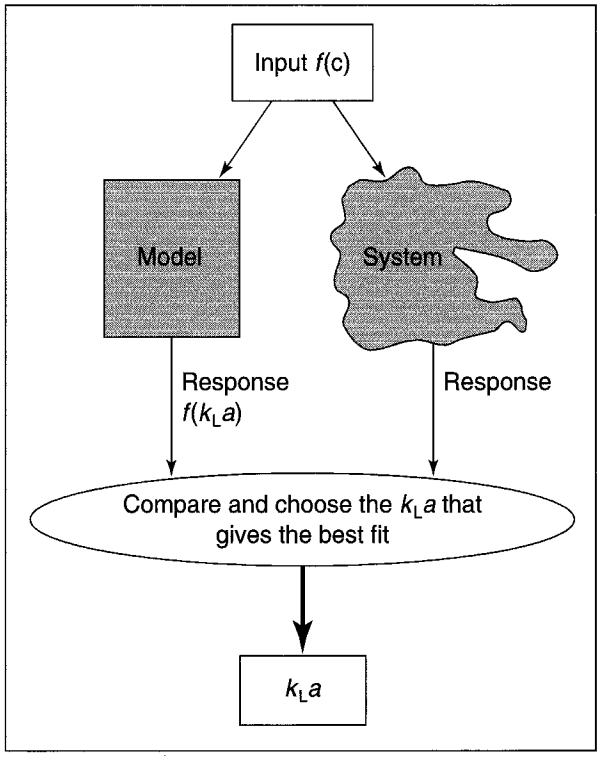
A novel approach was suggested by Merchuk and Ben-Zvi[52], which involved the evaluation of a mean

Box 3. Measurement of the mass-transfer coefficient

The figure shows the methods used to determine the mass-transfer coefficient k_La. It shows that: (1) all the methods compare the performance of the real system with that expected from a mathematical model; (2) models represent a simplified (amenable to mathematical treatment) description of the system; and (3) k_La is not a real property of the system, such as temperature, pressure or surface tension, but is a parameter of the model.

Models for gas–liquid mass transfer do not only consider the microscopic description of gas–liquid interface where mass transfer takes place, but also the macroscopic description of the reactor, including the level of mixing in both the gas and liquid phases (i.e. whether these phases have a uniform composition or not). If a method to determine the mass-transfer coefficient is being sought for a given bioreactor, it is extremely important to consider the assumptions underpinning the method and to check their applicability to the situation under consideration.

Regardless of the assumptions underlying the model, the methods used to determine mass-transfer coefficients can be classified into those based on steady-state measurements and those based on transient responses. Detailed descriptions of various methods are given by Atkinson and Mavituna[42].



The steps involved in the determination of the mass-transfer coefficient, k_La.

In bubble-column bioreactors, the gas phase (i.e. air) is always continuous, while the liquid phase may either be continuous or (more often) batch. Transient methods are based on applying a change in the concentration of the oxygen in the gas phase, and continuously recording the concentration of dissolved oxygen in the liquid phase. The results predicted by the model relating dissolved oxygen with time are then compared with those obtained experimentally and, as shown in the Fig. above, the value of the model parameter, k_La, that gives the best fit is selected.

One of the main problems with the transient method is the lag time of the oxygen electrodes used to determine the level of dissolved oxygen. The distortion in the measured values, resulting from probe-response dynamics, tends to complicate the unsteady-state methods used to determine k_La. Parameters that describe the probe-response dynamics will become an influential factor in the calculation of k_La, particularly when the value of k_La is approximately equal to or greater than the inverse of the probe-response time. It has been suggested[43] that this can be solved in some cases by truncating the initial portion of the electrode response.

Whatever the method used to calculate k_La, the basis of the technique is the comparison of the measured variable with the value (or values) that a mathematical model of the process predicts. It has been pointed out that the choice of the model is very important and poor assumptions on flow characteristics and mixing levels in gas or liquid phases may lead to significant errors[3].

shear-rate, also known as the global shear-rate, over the entire volume of the bubble column, based on k_La measurements. Taking this approach, a surprisingly simple equation was found to correlate the volumetric mass-transfer coefficient with the global shear-rate for both newtonian and non-newtonian liquids:

$$k_La = 1.4 \times 10^{-6}\ \gamma'^{1.70} \qquad \text{(Eqn 2)}$$

where the global shear rate is given by:

$$\gamma' = \left(\frac{p_1 J_g \ln\left(p_1 / p_2\right)}{aL_R^2 \kappa} \right)^{1/n} \qquad \text{(Eqn 3)}$$

A comparison of the predictions of Eqn 2 with several sets of experimental data is shown in Fig. 4. Even though some of the data, particularly those of Nakanoh and Yoshida[51], deviate considerably from the model, the variation of k_La with the global shear-rate shows the same trend for all the data sets; this includes newtonian as well as non-newtonian systems. It is evident that this approach can lead to the development of a general correlation for the mass-transfer coefficient in terms of the global shear-rate, applicable to any liquid, regardless of whether it is newtonian or non-newtonian. Additional data are required to strengthen this promising approach, in order to expand its range of applicability.

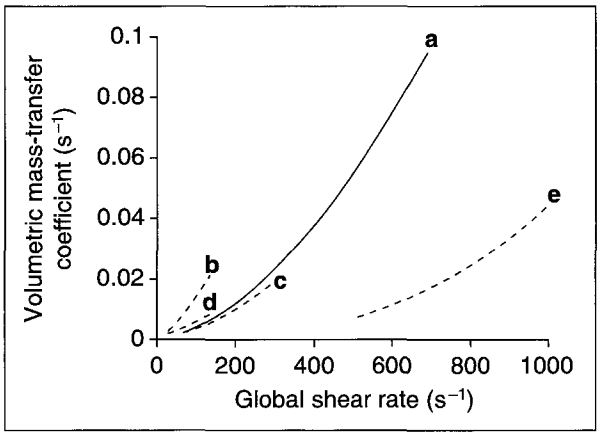


Figure 4

Volumetric mass-transfer coefficient for newtonian and non-newtonian liquids as a function of shear-rate in bubble columns. (**a**) The global approach; (**b**), (**c**), (**d**) and (**e**) are curves deduced from the correlations of Godbole *et al.*[50], Schumpe and Deckwer[47], Deckwer *et al.*[49] and Nakanoh and Yoshida[51], respectively. In each case, the shear rate under given experimental conditions was calculated from Eqn 3 (in text). Experimental data reported in the literature vary considerably, depending on: (1) the physicochemical properties of the test liquids used; (2) the methods employed to determine the rates of mass transfer; and (3) the assumptions made with regard to the pattern of mixing in the gas and liquid phases. When any correlation is used for design purposes, it must be ascertained that the conditions expected in practice are as close as possible to the ones under which the correlation was deduced. The global approach (**a**) attempts to reconcile data published by various authors. While all the reported data do not collapse into a simple correlation of the form shown in Eqn 2 in text, the advantage of using global shear-rate as the primary correlating factor is evident: the variation of volumetric mass-transfer coefficient with this shear rate shows the same trend for all data sets.

Heat-transfer correlations

The heat-transfer rates achievable in bubble columns are much higher than those achieved in single-phase flow[53]. This is because of the bubble-driven turbulence and liquid recirculation, which are characteristics of the flow in bubble columns. Several correlations have been proposed for the prediction of the heat-transfer coefficient in these reactors; the one deduced by Kawase and Moo-Young[54] is shown in Box 2. The model, which appears to fit most published data, can take non-newtonian behaviour of liquids into consideration, and it predicts the enhancement in heat transfer resulting from shear-thinning effects. Kawase–Moo-Young's correlation also enables the heat-transfer coefficient to be estimated as a function of the physical properties of the liquid, the column dimensions and the operative variables.

Power input

From a commercial point of view, the required power input is a key consideration in the design of a new process. In the case of high-value products, the contribution of power input to the total cost of product manufacture is usually negligible. However, for low-value bulk products, the cost of power input can be critical.

A comparison of power-input requirements in mechanically and pneumatically agitated reactors was carried out by Sigurdson and Robinson[55]. Their results suggest that in order to achieve k_La values up to $0.07\,s^{-1}$, the total power consumed by a bubble column is less than that consumed by a stirred tank reactor for industrial-scale operation. For k_La values ranging from 0.07 to $0.10\,s^{-1}$, the power consumed by both types of reactor was comparable. If higher values of k_La are required, a stirred-tank configuration would be preferable, despite the high energy costs because of practical considerations: to achieve such high k_La values in a bubble column, the gas velocity would have to be so high that there would be the possibility of liquid entrainment into the outgoing gas.

Concluding remarks

Bubble columns have many advantageous characteristics that make them an attractive choice for the scaling-up of biological processes. Their mechanical simplicity enables a more sterile operation. Perhaps more importantly, it is possible to control levels of shear within the reactor – a crucial factor for the growth of plant and animal cells in particular. Reliable design correlations are also available for momentum, mass and heat transfer, making it possible to construct large reactors rationally.

Even though the effectiveness of simple bubble columns for highly viscous liquids (viscosity ~1 Pa·s) has been questioned, recent evidence indicating that this type of reactor has certain advantages in the high viscosity range is encouraging[5,56]. The mass-transfer rate in such liquids is, however, adversely affected. Most of the mass transfer occurs in the vicinity of the gas sparger where bubbles are relatively small; the upper sections containing very large bubbles offer negligible interfacial area. Notwithstanding some disadvantages, bubble columns will continue to find new applications in bioprocessing.

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