

Mixing in bioreactor vessels

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2.07 Mixing in Bioreactor Vessels

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Glossary

characteristic time Reactor parameter characterizing the rate at which a (sub) process occurs in the reactor, such as heat production, oxygen mass transfer, and C-substrate consumption.

critical time The time value above which problems will occur due to variation in temperature, oxygen concentration, and C-substrate concentration.

degree of homogeneity The extent to which homogenization has progressed compared to the initial nonhomogeneous state.

ideally mixed The single-phase contents of a vessel are ideally mixed if the mixing process is much faster than the other relevant subprocesses (such as substrate conversion and residence time).

mixing time The time required to achieve a certain degree in the homogeneity of a considered volume of fluid in

batch at a certain scale of mixing, starting from a nonhomogeneous state.

mixing time number The dimensionless group consisting of mixing time, power dissipation, and characteristic length.

scale of mixing The smallest scale at which inhomogeneities are considered.

2.07.1 Introduction

The process of conversion of substances by microorganisms or by chemical reaction necessitates the transport of substrate and product toward and from the location of the conversion. One of the important possible limitations of the conversion process is the transport by mixing in each phase present. In a continuous process or fed batch process, the feed (substrate, wastewater) must be transported from the injection point through the bulk liquid to the organisms. The products of the conversion, at least those that may hinder the conversion process, must be removed from the microenvironment of the organisms. In a batchwise operated process, transport is needed to avoid local depletion of substrate, such as oxygen.

The way in which transport is desired to occur is dictated by the process type and realized by the choice of reactor type. The way in which the transport actually will happen is determined by technical and physical limitations in reaching the desired mixing behavior.

The two extremes in bulk liquid mixing behavior are the ideal stirred vessel (or ideal mixer) and the ideal plug flow. Ideal means that these cases can be described mathematically in a simple way, but that they cannot be realized in practice, only approached.

2.07.1.1 The Ideal Stirred Vessel

In the ideal stirred vessel, there are no concentration differences. The substance considered is homogeneously distributed in the vessel at all times. If there is a feed of concentrated substrate, then this substance is distributed instantly and completely at the moment of entry (Figure 1). Mathematically this means that the concentration c is independent of the location within the vessel. Consequently, the concentration of the outgoing flow is equal to the concentration within the vessel ($c_{\text{out}} = c$). Therefore, a macroscopic mass balance of a component over the vessel volume V is not a function of location.

$$\frac{dcV}{dt} = F_{\text{in}}c_{\text{in}} - F_{\text{out}}c + F_{\text{m, transfer}} - rV \quad [1]$$

accumulation = transport - conversion

The change in the amount of substance cV in time (accumulation) (mols^{-1} or kg s^{-1}) is the summation of inflow $F_{\text{in}}c_{\text{in}}$ (feed), outflow $-F_{\text{out}}c$, conversion (consumption $-rV$ or production $+rV$) of the substance, and possibly transfer ($F_{\text{m, transfer}}$) of the substance from (or to) another phase. In multiphase systems (e.g., aeration: air and water), a mass balance is needed for each phase (for air and water).

A special case of the ideal stirred vessel is when the vessel is operated batchwise ($F_{\text{in}} = 0$; $F_{\text{out}} = 0$) (single-phase system: $F_{\text{transfer}} = 0$, considered component is a substrate in solution):

$$\frac{dcV}{dt} = -rV \quad [2]$$

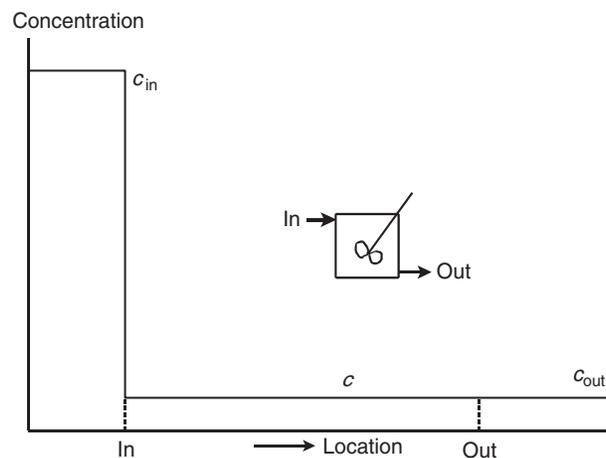


Figure 1 Example of the distribution of the concentration of a substance in the ideal stirred tank in steady state.

If the volume does not change as a result of the conversion or otherwise

$$\frac{dc}{dt} = -r \quad [3]$$

2.07.1.2 The Ideal Plug Flow

A vessel with ideal plug flow behavior is visualized as a flow in a tube (Figure 2). The velocity profile of the fluid in the tube is fully flat and there is totally no dispersion of the considered substance. Consider now a (very small) volume element of fluid that travels through the tube (the vessel) without exchange with its surroundings. The process in this volume is mathematically identical with that in the ideal stirred batch vessel, eqn 3. (The volume of the element considered is so small that diffusion is fast enough to maintain a homogeneous distribution within the element.) Since $dx = v dt$ eqn 3 gives

$$v \frac{dc}{dx} = -r \quad [4]$$

In a plug flow vessel, the amount of substance depends fully on location (Figure 2) and is only a function of time if the entry value is a function of time. Plug flow without conversion may be considered as a time 'delay', where the delay is equal to the residence time in the plug flow vessel.

The derivation of eqn 4 follows also from a mass balance of the component considered over a section located between x and $x + \Delta x$ (see Figure 3) for constant flow velocity (accumulation = transport - conversion)

$$(A \Delta x) \frac{dc}{dt} = Av c(x) - Av c(x + \Delta x) - A \Delta x r \quad [5]$$

or for $\Delta x \rightarrow 0$ (and v independent of x)

$$\frac{dc}{dt} = v \left(-\frac{dc}{dx} \right) - r \quad [6]$$

In steady state ($dc/dt = 0$, hence also the entry concentration is constant), eqn 4 results.

2.07.2 Characterization of Mixing

Although the ideal cases of mixing behavior discussed in the previous session cannot be realized in practice, special design can lead to reactors whose mixing behavior approximate the ideal case sufficiently to allow the ideal description. Small-scale laboratory fermenters with nonviscous medium and rigorously stirring may be considered to be ideally mixed. Slender packed columns may be

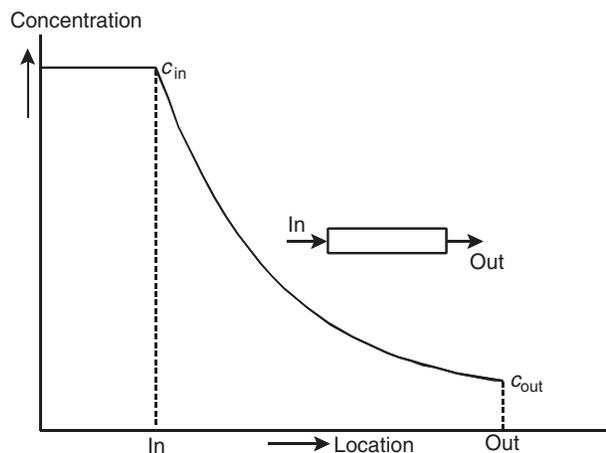


Figure 2 Example of the concentration distribution of a converted substance in an ideal plug flow reactor in steady state.

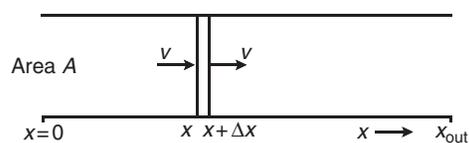


Figure 3 Control volume of ideal plug flow.

considered to be in ideal plug flow. Aeration tanks are generally considered to be well mixed; settlers are designed to approximate plug flow.

If the mixing process is much faster than the other relevant subprocesses (such as oxygen transfer, substrate conversion, and residence time), then the vessel may be considered to be ideally mixed. On the other hand, if mixing is much slower, nonbatch systems may be considered to be in ideal plug flow. Comparing subprocesses in this way is the subject of regime analysis. Here, it is sufficient to state that subprocesses may be characterized each by a time, a characteristic time, which is a measure of the rate at which the subprocesses run. For example, for oxygen transfer, this is the time it takes to saturate a depleted amount of liquid to a defined extent, given by $1/k_{l,a}$. For bulk liquid mixing, it is the time it takes to homogenize an added amount of substance in a given amount of liquid to a certain degree.

If the characteristic time of mixing, the mixing time of the mixing process in the whole reactor is much smaller than that of the other relevant subprocesses in that phase, then the simple model of the ideal stirred vessel may be used for the whole reactor. If the mixing time is much larger, then problems might arise, and for description of the process, a more complex model is needed.

2.07.2.1 Mixing Time

To arrive at a proper definition of the mixing time, first homogenization must be defined. Convective (bulk) mixing is effective to a certain scale. For smaller dimensions, diffusion (micromixing) takes over. Since the latter process cannot be influenced by the input of power, the corresponding scale may be used as the 'scale of mixing': the scale on which the inhomogeneities are considered. However, when mixing time is measured using a tracer, the scale of mixing is determined by the size of the probe. The probe size is generally larger than the scale of micromixing.

To what extent homogenization has progressed is indicated by the 'degree of homogeneity'

$$m = \left(1 - \left| \frac{c_{\infty} - c}{c_{\infty}} \right| \right) \times 100\% \quad [7]$$

After the concentration c of the substance considered has reached its final value c_{∞} , the degree of homogeneity is 100%.

The mixing time t_m is defined as the time required to achieve a certain degree in homogeneity of a considered volume of fluid in a batch vessel at a certain scale of mixing starting from a nonhomogeneous state. The mixing time is measured by following the concentration of an inert tracer in time at one or more locations within the vessel after adding a certain amount pulsewise. Practical mixing times are defined for degrees of homogeneity m between 50 and 95%, the latter being most common and used in this text ($0.95c_{\infty} < c < 1.05c_{\infty}$; see Figure 4).

2.07.3 Mixing Models

Mixing is caused by bulk flow and turbulent dispersion. Two main types of mixing models originate from this background: the bulk flow model, starting from the bulk flow path with dispersion superimposed on the average flow; and the turbulence model, starting from the mixing action of the energy-dissipating turbulent eddies.

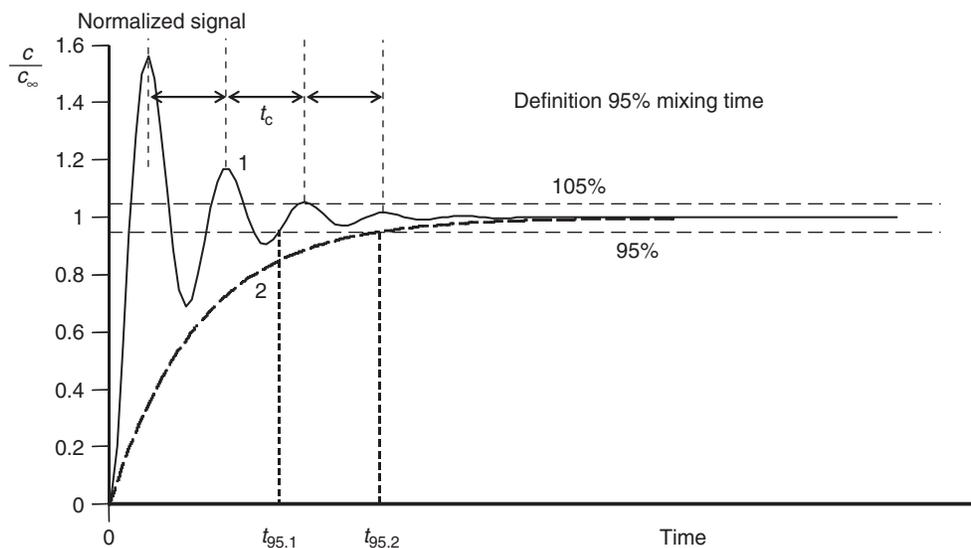


Figure 4 Mixing time: Visualization of the definition; 1 and 2 indicate two possible response curves after adding some substance to a batch vessel.

2.07.3.1 Bulk Flow Model

2.07.3.1.1 Stirred tank

The flow path in a one-phase stirred tank with a radial pumping stirrer is given in **Figure 5**. Each of these circulation loops can be modeled with a closed-loop reactor as shown in **Figure 6**. A probe (pH electrode, conductivity, etc.) can detect the recurrent tracer (acid, salt, etc.) concentration as shown in **Figure 4**. It is evident that a circulation loop exists in **Figure 6**. In the loop, a circulation time t_c can be defined (see **Figure 4**, curve 1) as the average time needed for the liquid to pass one circulation. Although less pregnant, a similar response curve can be found in a stirred tank after tracer addition in the stirrer region.

Based on stirrer pumping capacity and total volume, a mixing time relation can be derived for the fully turbulent case [2]:

$$t_m \propto \frac{1}{N} \left(\frac{T}{D} \right)^3 \left(\frac{H_L}{T} \right) \quad [8]$$

N_P = impeller power number defined by $P_s = N_P \rho_L N^3 D^5$, ρ_L = liquid density, D = stirrer diameter, T = tank diameter, H_L = liquid height, P_s = stirrer power consumption, N = stirrer speed.

Equation 8 predicts that for $Re > 5000$, for which N_P is constant, Nt_m has a constant value.

2.07.3.1.2 Bubble column

Following the same lines of Reference [2] with velocity data measured in bubble columns

$$t_m \propto (g v_{Gs}^c T^{-2})^{-0.33} \frac{H_L}{T} \quad [9]$$

g = gravitational acceleration, v_{Gs}^c = pressure-corrected superficial gas velocity.

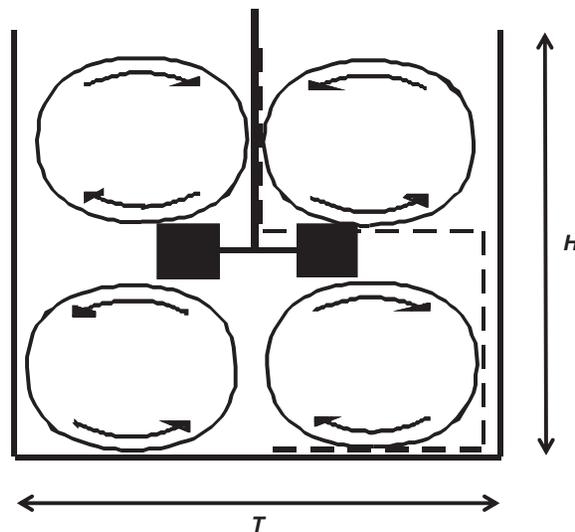


Figure 5 Schematic representation of the secondary flow path in a turbine stirred vessel [1].

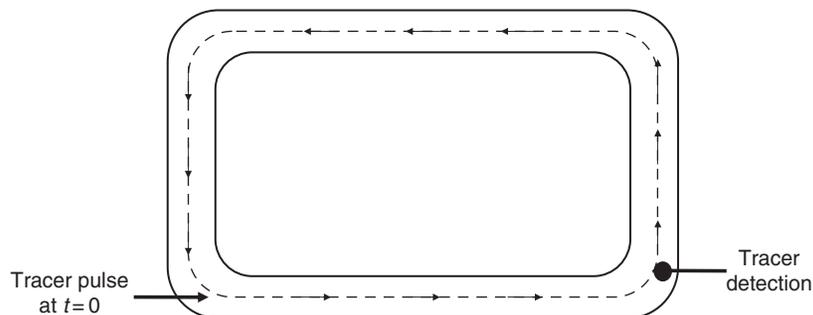


Figure 6 Modeled flow path for a turbine stirred tank.

2.07.3.1.3 Airlift

The airlift is a circulation loop in itself. The general formula for the flow velocity is given as [3, 4]

$$\int_0^{H_L} g \Delta \varepsilon(z) dz = 0.5 K_f (v_{Ls})^2 \quad [10]$$

K_f = friction coefficient, a value to be determined for each airlift, $\Delta \varepsilon(z)$ = holdup difference riser and downcomer, z = length coordinate.

In this formula, ε and v_{Ls} depend on each other. (Iteration procedures are shown by Verlaan *et al.* [4] to calculate the values of, $\Delta \varepsilon$ and v_{Ls})

2.07.3.2 Turbulence Models

2.07.3.2.1 Stirred tank

The basis for calculation of mixing time is the relation [5]

$$t_m \propto \left(\frac{e_t}{L_c^2} \right)^{-1/3} \quad [11]$$

e_t = local energy dissipation rate, L_c = integral scale of turbulence.

The problem that is included in this formula is the uneven distribution of the energy dissipation throughout the vessel being much larger near the stirrer than, for instance, near the vessel wall. Mixing is complete only when all parts of the vessel are mixed. The position of the lowest energy dissipation rate therewith determines the mixing time [5].

Groen [1] also used energy dissipation as a starting point. He regards the stirrer dimension as the characteristic length scale of the turbulent eddies and includes also the energy provided by the gas flow. He derives with flow paths as given in Figure 7,

$$t_m \propto \frac{T^{2/3}}{e^{1/3}} \left(\frac{H_s}{T} \right)^{4/3} \left(\frac{H_L}{T} \right)^2 \quad [12]$$

e = total, stirrer plus air, specific energy dissipation

For a one-phase stirred tank and a given ratio of stirrer diameter and stirrer height, this may be transformed into

$$t_m \propto \frac{1}{N} \frac{\left(\frac{T}{D} \right)^{5/3}}{N_p^{1/3}} \left(\frac{H_L}{T} \right)^2 \quad [13]$$

2.07.3.2.2 Bubble column

Groen [1] could also apply his model straightforwardly to a bubble column:

$$t_m \propto \frac{T^{2/3}}{e^{1/3}} \left(\frac{H_L}{T} \right)^2 \quad [14]$$

wherein

$$e = g v_{Gs}^c$$

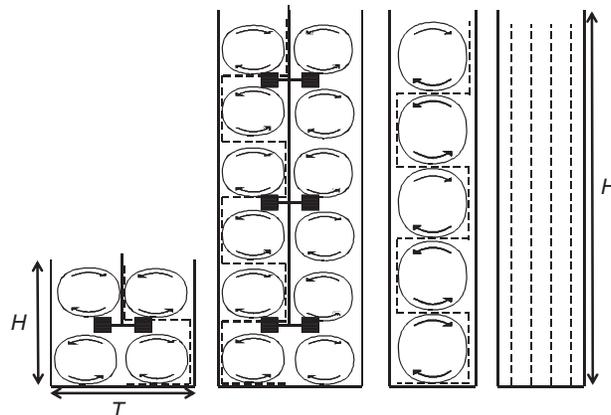


Figure 7 Schematic representation of the flow paths in stirred vessels (single- and multi-impeller) and bubble columns (heterogeneous and homogeneous regime) [1].

2.07.3.2.3 Airlift

Energy dissipation models for an airlift are less useful because bulk circulation flow models provide the opportunity to calculate the circulating velocities. Dispersion then can be included by the relation between circulation time and mixing time, which is assumed to be

$$t_m = (\text{from 4-7}) t_c \quad [15]$$

2.07.3.3 Mixing Time Number

The mixing time relations shown in the previous sections contain either factor $e^{1/3}$ or $N_p^{1/3}$. At given stirrer speed and diameter, $N_p^{1/3}$ is equivalent to $e^{1/3}$. A dimensionless mixing number N_{mix} including scale effects, can be defined as [1]

$$N_{\text{mix}} = \frac{t_m e^{1/3}}{T^{2/3}} \quad [16]$$

The mixing number should be dependent on geometric data of the vessels only, because the dependence on stirrer speed and power number for stirred tanks and on dissipated energy for bubble columns is included in the mixing number itself.

With eqn 16 the mixing time relations for both a stirred tank and a bubble column [1] transform to

$$N_{\text{mix}} \propto \left(\frac{H_L}{T} \right)^2 \quad [17]$$

2.07.4 Experimental Verification

2.07.4.1 Inherent Variations in Measured Mixing Times

It is stated already that the actual value of the mixing time depends on the required homogeneity. Usually 95% is taken. Given this criterion, the reproducibility of the experiments can be within 10%. However, another criterion, and another measurement scale, leads to another, and again reproducible, mixing time value.

An even much more important cause for the large differences in measured mixing times is the dependence on the position of the tracer addition and the measurement point. For a single turbine stirred tank, addition of the tracer at the top of the vessel and measurement near the vessel bottom makes considerably longer measured mixing time values compared to the case of a tracer added in the stirrer region. For a bubble column or a stirred tank with multiple stirrers, halfway the bubble column or stirred tank makes considerably shorter mixing times. As an example, **Figure 8** shows that the measured mixing time can differ by a factor of 2 depending on the positions of tracer addition and measurement point. The lesson learned is that we cannot expect exactly the same mixing time values when comparing measured values of different authors in the same vessel geometry; too many (reproducible) possibilities for differences do exist.

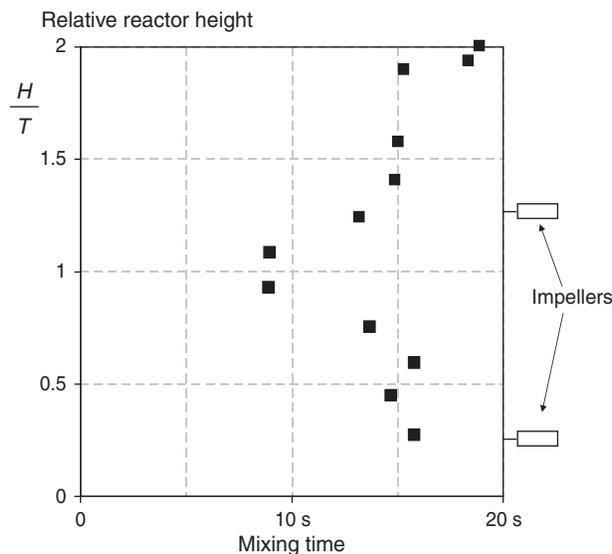


Figure 8 Effect of position of addition on the mixing time in a nonaerated stirred vessel ($T=0.72$ m) with two Rushton type impellers ($N=110 \text{ min}^{-1}$, $D=T/2$). Adapted from Cronin DG, Nienow AW, and Moody GW (1994) An experimental study of mixing in a protofermenter agitated by dual Rushton turbines. *Transactions of the Institute of Chemical Engineers, Food and Bioproducts Proceedings* 72(C1): 35–40.

2.07.4.2 Single-Phase Stirred Tanks

2.07.4.2.1 Influence of T/D value

Voncken *et al.* [7], already in 1964, had thoroughly researched the influence of T/D . They measured the $(T/D)^2$ relation. Many authors [5] have found relations around the value of 2. All these data together can be summarized within the variations possible as

$$t_m \propto \left(\frac{T}{D}\right)^2 \quad [18]$$

The relation comes very near to the relation predicted by using flow patterns and turbulence theory [1].

2.07.4.2.2 Influence of $H_L/T > 1$ and the number of stirrers

Groen [1] measured the $(H_L/T)^2$ relation for a large variety of scales. Several authors reported relation values of 1.5 up to 2.5. Within the accuracy of mixing time measurements, we assume

$$t_m \propto \left(\frac{H_L}{T}\right)^2 \quad [19]$$

2.07.4.2.2.(i) Single phase mixing time equation

Nienow [5] has worked out eqn 19. Correcting the data of Nienow [5] with a factor of 2, assuming that to be the difference between tracer addition near the stirrer and at the top of the vessel, and combining the T/D relation and the H_L/T relation with his data and the data of Groen [1] gives

$$t_m = \frac{10}{N} \frac{\left(\frac{T}{D}\right)^2}{N_p^{1/3}} \left(\frac{H_L}{T}\right)^2 \quad [20]$$

or, rewritten as a function of the dimensionless mixing time number

$$N_{\text{mix}} = \frac{t_m e^{1/3}}{T^{2/3}} = 11 \left(\frac{T}{D}\right)^{1/3} \left(\frac{H_L}{T}\right)^2 \quad [21]$$

Single phase, turbulent
Tracer added on top

Figure 9 shows N_{mix} calculated with eqn 21 for a large variety of scales. This describes the experimental results very well.

The data in Figure 9 are all measured for a stirrer in each $H=T$ compartment. The situation for other geometries is more complicated. Groen measured for instance a distinct influence of the number of stirrers. The mixing time in a tall vessel equipped with one stirrer is lower than that in the same vessel with a stirrer in each $H=T$ compartment. In Figure 10, the diamonds show measured t_m values for a large-scale fermenter dependent on height, with a clearance between impellers of $2D$ (5.4 m^3 per impeller) at constant P/V . As expected, the mixing time increases quadratically with height (line confirming quadratic relation of eq 21) and also a large number of impellers increase the mixing time at constant volume (diamonds have a higher mixing time than squares at the same volume). This means that, at the same stirrer speed, doubling the power input (by doubling the number of stirrers per volume) increases the mixing time instead of decreasing. This elucidates that the effect of compartmentalization with more impellers is stronger than the effect of power input. The type of stirrers (three turbines

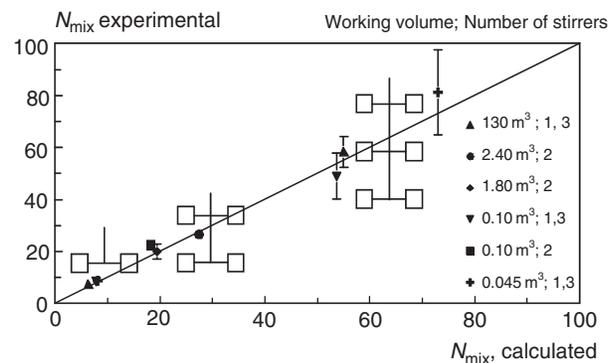


Figure 9 Mixing time number model verification for nongassed vessels and Rushton impeller(s). Measurements were done at several scales and geometries as indicated. In the case of reduced number of impellers, the working volume was adapted accordingly. $T/D=2$ ($130 \text{ m}^3/45 \text{ m}^3$); 2.5 (2.4 m^3); 2.9 (1.8 m^3); 2.27 (all others). Blade height is $0.25D$, but $0.30D$ (2.4 m^3) or $0.33D$ (1.8 m^3). Volumes are water volumes [1].

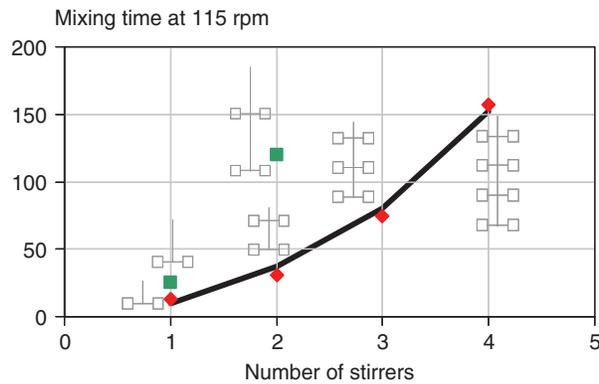


Figure 10 Mixing times in multi-impeller systems. $V_L = 22 \text{ m}^3$ reactor with four Rushton turbine impellers with clearance $2D$ ($H = 6.55 \text{ m}$, $T = 2.07 \text{ m}$, $D = 0.7 \text{ m}$, 4 baffles, water). Diamonds: mixing time for 1 impeller per 5.5 m^3 ; squares: mixing time for 1 (lower) impeller per 11 m^3 . Data for the same tank at lower liquid volumes ($V_L = 16.5, 11$, and 5.5 m^3) are indicated by the length of the stirrer axis. Unpublished data and Enfors SO, Jahic M, Rozkov A, *et al.* (2001) Physiological responses to mixing in large scale bioreactors. *Journal of Biotechnology* 85: 175–185.

versus two Scaba and one turbine or multiple stirrers) also influences the mixing time [9, 10]. In general, compartmentalization is considerably less, but not fully absent when using axial pumping impellers. Yet, it is difficult to give definite answers. The lower stirrer is nearly always of the radial pumping type, and with axially downward pumping stirrers at the higher positions maybe the mixing time is decreased.

One should realize that the type(s) of stirrer(s) at $H_L > T$, the mixing intensity and scale criteria, and the position of the tracer addition/measurement points all influence the mixing time, with an estimated range of about 0.5 up to 2 times the value of eqns 20 and 21.

Table 1 shows mixing time values for a range of volumes from 1 l up to 1000 m^3 and for different geometries. A general value of stirrer power $P/V = 2000 \text{ W m}^{-3}$ and $T/D = 2.5$ is used.

It is clear that scale-up inevitably leads to larger mixing time values. Large-scale mixing times of the order of 100 s are found. To bring back 100 s to 10 s, a factor of 10^3 increase in the required power value is needed or a power of 2 MW m^{-3} due to the $1/3$ power for e in the N_{mix} formula. In particular, tall vessels (with multiple stirrers) lead to extreme mixing time values. The data of Table 1 also show that the scale of operation and H_L / T values are overpowering all other effects such as the earlier mentioned possible variations of a factor of 0.5 up to 2.

The mixing time can easily become larger than the characteristic time for mass transfer (order of 10 s) or substrate uptake. The consequences of this will be discussed later.

2.07.4.2.3 Influence of viscosity

Viscosity can have a dramatic effect on the mixing time. The effect is dependent on the stirrer Reynolds number:

$$Re_{\text{st}} = \frac{\rho N D^2}{\eta}$$

Figure 11 shows that above a value of 5000, the Nt_m value is constant. However, below a value of 1000, the Nt_m value can increase easily a factor of 10 or more. This will certainly lead to complications because in that case nearly all characteristic times will be lower than the mixing time.

The Reynolds number will increase at scale-up for the usual criteria such as constant P_s/V_L values or constant tip speed. This has a positive effect. In the case of viscosity limitations at a small scale of, for instance at 1 liter scale and Re_{st} around 1000, it might be possible that at a large scale the Re_{st} number increases to a value above 5000 where no viscosity problems occur anymore.

In the case of high-viscosity and pseudoplastic liquids, the liquid in the top of a tall vessel can come to a complete standstill. Mixing in the stirrer region is not that bad in that case, but the mixing time for the vessel as a whole is infinite.

Table 1 Calculated mixing times for a stirred tank for different scales and aspect ratios $\frac{T}{D} = 2.5$, $e = 2 \text{ W kg}^{-1}$

$V_L \text{ (m}^3\text{)}$	0.01	10	100	1000
H_L				
5T	79	364	607	1011
2T	15	71	119	198
T	4	21	35	58

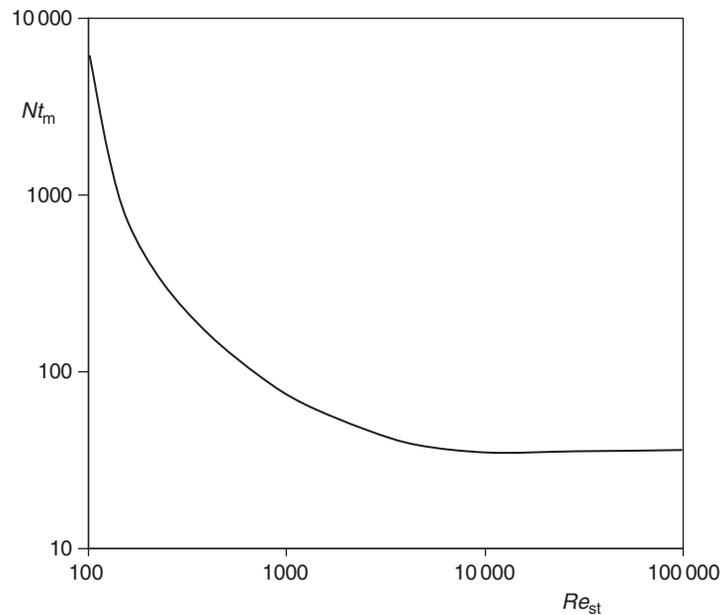


Figure 11 Nt_m values for a Rushton type turbine impeller.

2.07.4.3 Two-Phase Stirred Tanks

2.07.4.3.1 Influence of aeration

Aeration influences the bulk flow field and the behavior of the stirrer. **Figure 12** shows the different bulk flow patterns. At low gas flow rates and high stirrer speeds, the flow pattern resembles largely the flow pattern of the unaerated case resulting in total gas recirculation. Increasing the gas flow rate changes the flow pattern. The increasing energy content of the gas pushes the flow from the stirrer upward. Here, we get a situation of limited gas recirculation. Finally, a situation can occur where the gas is not flown out anymore and the circulation loop is totally reversed, with the gas and liquid rising up along the shaft. This is called flooding.

A second effect of aeration is the formation of cavities behind the stirrer blades [2, 11]. **Figure 13** shows three distinct types. Vortex clinging cavities appear with a gas recirculating bulk flow. Large cavities are coupled to only partial gas recirculation. Stirrer power consumption and pumping capacity decrease at cavity formation and they might also influence the flow and mixing time.

Altogether, mixing time determination in gassed stirred tanks might be complicated. A fine example is shown in **Figure 14**. The unaerated data fulfill the $Nt_m = \text{constant}$ criterion. However, a number of data show a distinct deviation from this curve. A careful observation of the flow conditions and the use of the total energy dissipation by means of the mixing number give the solution as shown in **Figure 15**. Flooding leads to lower mixing times. The bulk flow is reversed at flooding and will be more similar to gulf

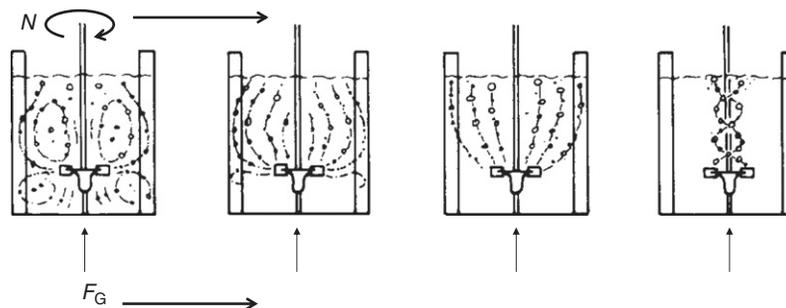


Figure 12 Flow patterns in an aerated stirred vessel with Rushton type impeller. Left to right: increasing gas flow rate or decreasing stirring speed. Adapted from Gogate PR, Beenackers AACM, and Pandit AB (2000) Multi impeller systems with a special emphasis on bioreactors: A critical review. *Biochemical Engineering Journal* 6: 109–144.

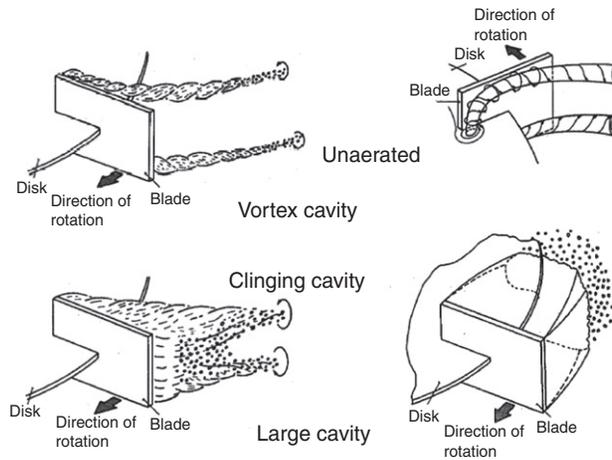


Figure 13 Cavity shapes. Warmoeskerken MMCG (1986) Gas-Liquid Dispersion Characteristics of Turbine Agitators. PhD Thesis, Delft University of Technology. <http://repository.tudelft.nl/view/ir/uuid%3A2bc4c2fc-f89e-497a-ab7a-ed8a7a2d15df/>.

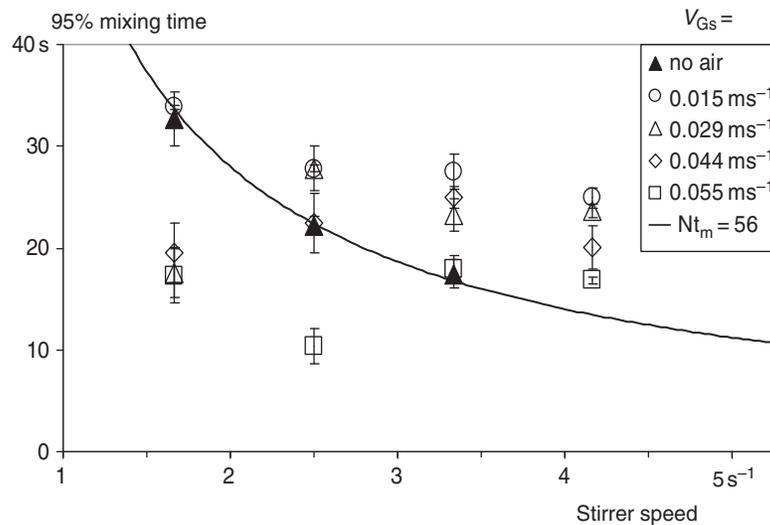


Figure 14 Mixing times influenced by gas superficial velocity in a 4 m³ stirred tank with two impellers. Groen DJ (1994) Macromixing in Bioreactors. PhD Thesis, Delft University of Technology. <http://repository.tudelft.nl/view/ir/uuid%3A3ac019f1-d19a-4853-9a29-554f1149bd5b/>.

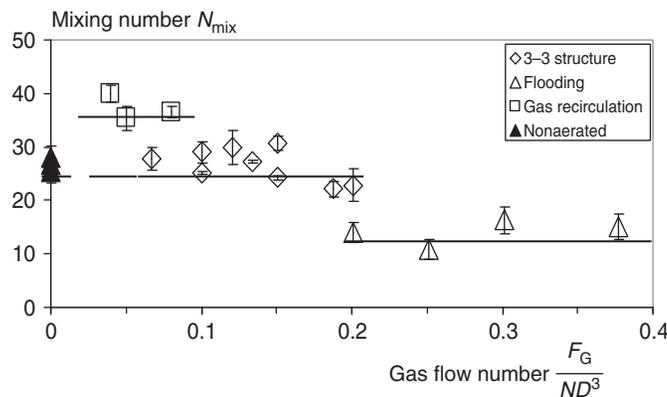


Figure 15 The effect of aeration and cavity structures on the mixing number. Four regimes emerge: nonaerated; complete gas recirculation; impeller loading conform 3–3 structure; flooding. The mixing time in the 3–3 structure regime is equal to that of the unaerated case at equal total power input. Groen DJ (1994) Macromixing in Bioreactors. PhD Thesis, Delft University of Technology. <http://repository.tudelft.nl/view/ir/uuid:3ac019f1-d19a-4853-9a29-554f1149bd5b/>.

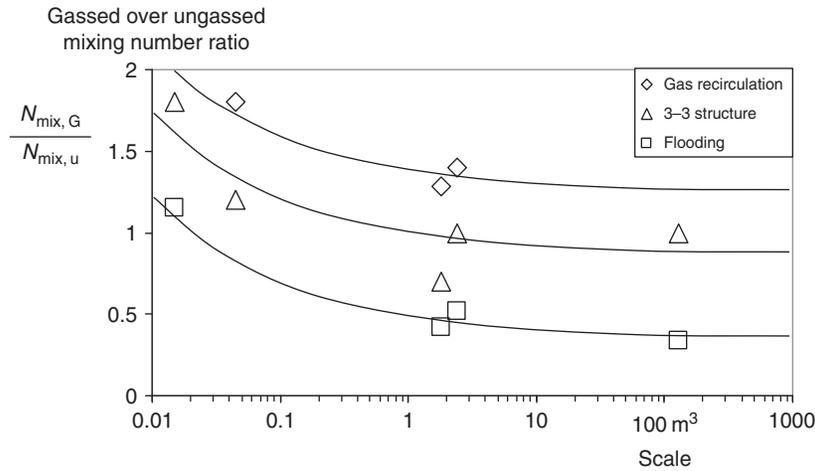


Figure 16 The influence of scale and flow regime on the mixing number. Groen DJ (1994) Macromixing in Bioreactors. PhD Thesis, Delft University of Technology. <http://repository.tudelft.nl/view/ir/uuid%3A3ac019f1-d19a-4853-9a29-554f1149bd5b/>.

stream flow. Intensive aeration (3–3 structure) leads to mixing numbers of the same value as in the unaerated case. Figure 15 shows that limited aeration leads to higher N_{mix} values.

Most large-scale bioreactors operate in the range of high gas load because of efficient mass transfer [2] and the mixing time in that case will be about the same as that for the unaerated case. Figure 16 shows this for measurements at different scales. In particular, this is true at large scales. At a small scale (below 50 l), the effect of aeration seems to become negative, and the mixing time increases up to a factor of about 2. Altogether, the mixing time in aerated stirred tanks has the same value as for the unaerated case, considering that depending on aeration rate, stirrer speed, and scale, a variation of a factor in the range of 0.5 up to 2 can occur.

2.07.4.3.2 Influence of $H_L / T > 1$ and the number and type of stirrers

Groen [1] and Vrabel *et al.* [9] have shown that, in general, the quadratic relation works out well. From the same sources, it is clear that differences up to a factor of 2 occur when certain combinations of stirrers are used, in particular, downward pumping stirrers in the upper compartments and a turbine in the lower compartment.

2.07.4.3.3 Conclusion

The mixing time in aerated stirred tanks has about the same value as for the unaerated case, considering that depending on aeration rate a variation of a factor in the range of 0.5 up to 2 can occur. As shown earlier in Table 1, scale of operation and H/T values are overpowering this effect.

$$t_m = \frac{10}{N} \frac{\left(\frac{T}{D}\right)^2}{N_p^{1/3}} \left(\frac{H_L}{T}\right)^2 \quad [20]$$

with N_p = unaerated power number
or

Stirred tank

$$N_{\text{mix}} = \frac{t_m e_u^{1/3}}{T^{1/3}} = 11 \left(\frac{T}{D}\right)^{1/3} \left(\frac{H_L}{T}\right)^2 \quad [21]$$

Single and two phase, turbulent
Tracer added on top

with e_u = unaerated power dissipation

2.07.4.4 Bubble Column

Measurements at different scales including commercial-scale bubble columns are shown in Figure 17. Till $H_L/T = 3$ the mixing number is about 16, independent of the height of the column, with a scatter of a factor of 0.5 up to 2.

At $H/T > 3$, the situation changes considerably; here a relation with H/T^2 appears.

Thus the conclusion for a bubble column should be

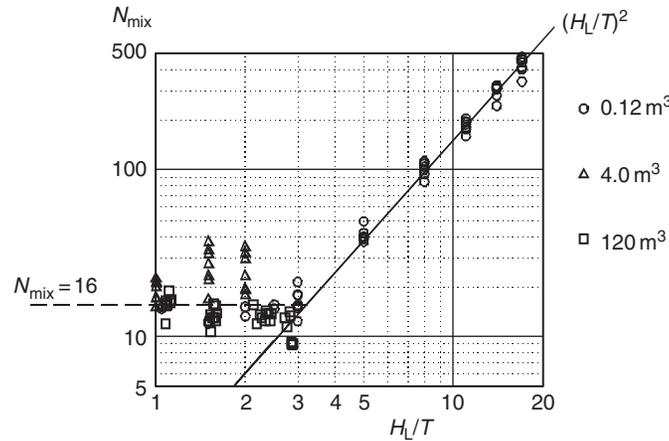


Figure 17 Measured mixing numbers in bubble columns: aspect ratio and scale. Data from Groen DJ (1994) Macromixing in Bioreactors. PhD Thesis, Delft University of Technology. <http://repository.tudelft.nl/view/ir/uuid:3ac019f1-d19a-4853-9a29-554f1149bd5b/>.

$$t_m = 16 \frac{T^{\frac{2}{3}}}{(g v_{Gs}^c)^{1/3}} \frac{H_L}{T} < 3 \quad [22]$$

$$N_{mix} = \frac{t_m e^{1/3}}{T^{2/3}} = 16 \frac{H_L}{T} < 3 \quad [23]$$

and

$$t_m = 1.6 \frac{T^{\frac{2}{3}}}{(g v_{Gs}^c)^{1/3}} \left(\frac{H_L}{T}\right)^2 \frac{H_L}{T} > 3 \quad [24]$$

$$N_{mix} = \frac{t_m e^{1/3}}{T^{2/3}} = 1.6 \left(\frac{H_L}{T}\right)^2 \frac{H_L}{T} > 3 \quad \text{Bubble Column} \quad [25]$$

These equations are in accordance with those predicted by the bulk flow as well as the turbulence theories. However, the $(H/T)^1$ relation in eqn 9 certainly does not hold and should be replaced by the relations given above.

As can be expected, mixing time increases inevitably with scale, at a constant pressure-corrected superficial gas velocity (pneumatic power input) with a factor of $T^{\frac{2}{3}}$.

All data until now are for the heterogeneous flow regime. The homogeneous flow regime leads to larger mixing times [1, 2]. As this regime will hardly be present in any commercial fermenter, this will not be discussed here and the interested reader can refer the literature on this.

Table 2 shows calculated values dependent on scale and H/T for a v_{Gs}^c value of 0.05 m s^{-1} . As for the stirred tanks, scale and H/T overrule any other effect. The increase from $H = T$ compared to $H = 2T$ follows from the formula, due to the larger diameter at $H = T$ at a given volume.

2.07.5 The Airlift

The airlift reactor is developed from the viewpoint of controlled flow and intensified circulation caused by the density difference between the riser column filled with air bubbles and a downcomer column filled with liquid only or less air.

Table 2 Calculated mixing times for bubble columns (eqns 23 and 25) at different scales and H_L/T values $v_{Gs}^c = 0.05 \text{ m s}^{-1}$

$V_L \text{ (m}^3\text{)}$	0.01	10	100	1000
H_L				
$5T$	13	62	103	172
$2T$	7	30	51	84
T	8	35	59	98

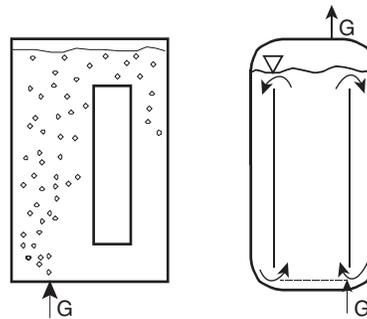


Figure 18 Schematic representation of external and internal airlift loop reactor.

A schematic representation of airlift types (external and internal) is given in [Figure 18](#). Controlling the flow is interesting in particular on very large scales. Extensive reviews of airlift type reactors are given by [Merchuk \[12\]](#) and [Gumery *et al.* \[13\]](#).

The flow velocity can be calculated for the reactors of [Figure 17](#) starting from eqn 10 [3, 4]. Flow velocities are dependent of the friction factor that is dependent on the construction data of each air lift and therefore no general relation can be derived. The riser velocity values found are in the range of 0.1 up to more than 1 m s⁻¹ for pilot plant (10l) up to commercial scale (>1000 m³) reactors [14].

From the circulation velocity, the circulation time could be calculated and the mixing time measured. [Verlaan *et al.* \[4\]](#) reported that for an airlift reactor $t_m = (4-7)t_c$.

Downcomers with a relatively small cross section can hinder the circulation too much. In that case, the velocity in the riser becomes very low and the riser will start to behave as a bubble column. Nothing can be said in that case for velocities from calculations. A comparable effect may occur at high air entrainment into the downcomer [15].

2.07.6 Comparison of the Reactor Types

Relations are given in the previous sections for the bulk liquid mixing time based on equations similar to that derived from theories and modified on the basis of experimental results.

Mixing time values can differ from that given by the relations shown. As discussed, this is mainly due to tracer injection position and number, and type and position of the stirrers (in the case of multiple stirrers).

These differences are limited when compared to differences that occur when different scales and different types of reactors are compared. As an example, calculated mixing times are shown in [Table 3](#).

This simple table shows trends that go far beyond differences of 0.5 up to 2 times the value of the formula at given conditions. All rows in the table show the increase of mixing time with scale. At very large scales, times of several minutes are inevitable. For mixing time-sensitive fermentations, we always have to solve problems at scale-up.

Table 3 Mixing time values calculated for a stirred tank (eqn 21), a bubble column (eqns 22 and 24), and an airlift reactor (based on References 2 and 4,) $e_u = 2W \text{ kg}^{-1}$

		$V_L(\text{m}^3)$		$v_{Gs}^c(\text{m}^{-1})$					
		0.01	10	0.01	0.10	0.01	0.10	0.01	0.10
H_L/T									
10	Airlift	49	19	220	96	420	180	730	320
10	BC	78	36	363	168	604	281	1000	468
10	STR	270	270	1200	1200	2000	2000	3500	3500
5	Airlift	47	18	198	78	360	150	610	260
5	BC	23	11	106	50	176	82	294	136
5	STR	79	79	364	364	606	606	1000	1000
2	Airlift	46	18	192	72	340	140	570	240
2	BC	11	5	52	24	86	40	144	67
2	STR	15	15	71	71	119	119	198	198

The first group of data at an aspect ratio of 10 shows that the airlift has a mixing time about half of that of the bubble column. However, the second group of data shows that already at an aspect ratio of 5 instead of 10, the mixing time in the bubble column becomes smaller when compared to the airlift. This difference increases further at an aspect ratio of 2. It is highly questionable to prefer the mechanically more complicated airlift for mixing reasons only.

The group of data at an aspect ratio of 5 shows that the bubble column is to be preferred when compared to the stirred tank, even though the stirred tank has an additional energy dissipation of 2 W kg^{-1} due to the stirrer. Bubble columns are much more efficient for mixing at these aspect ratios. The stirred tank is even more unacceptable at an aspect ratio of 10. This can be expected with a high aspect ratio reactor known from the chemical industry in mind, the Rotating Disc Contactor that is used in those cases where plug flow is desired.

The third group of $H_L = 2T$ shows that at low aspect ratios the mixing time of a bubble column and that of a stirred tank become more comparable, yet the bubble column is still better and uses much less power.

The table also shows a stirred tank of 1000 m^3 with a dissipated power of 2 W kg^{-1} , amounting to a total of 2 MW. Such vessels did not exist until now, because of mechanical limitations. From the viewpoint of mixing also, these reactors are not to be preferred.

When one considers mixing, the conclusion is that bubble columns are by far to be preferred in most cases because of lower mixing time, lower power consumption, and simple mechanics.

However, it is known that oxygen mass transfer in viscous systems is limited or even very low in bubble columns and airlift reactors [2]. Stirred tanks can handle viscous broths better. The mixing time will not change very much at large scales and at not too high viscosity values for all type of reactors because of the high Re_{st} number. Mass transfer is not Re_{st} dependent but only viscosity dependent, and this explains largely why stirred tanks are preferably used for a number of fermentations up to a volume of about 300 m^3 . Also, the use of stirred tanks in multipurpose (pilot) plants can be explained by this fact as it provides flexibility.

Another reason to use stirred tanks might be that the volumetric productivity of a stirred tank can be higher than that of a bubble column. Volumetric productivity for aerobic fermentations is nearly always limited by mass transfer rate. This is directly related to power consumption, which can be higher in a stirred tank.

2.07.7 Gas-Phase Mixing

Gas-phase mixing data are scarce. This is despite the fact that the measurements are relatively easy to do by means of residence time measurements. This is not a real problem because in most cases the gas-phase mixing is hardly relevant for the process in the bioreactor. And when the gas phase is in plug flow, it is even an opportunity for mass transfer because of the optimal driving force, in contrast to the liquid mixing where bad mixing can easily lead to problems.

2.07.7.1 Stirred Tank

Gas-phase mixing in a stirred tank will be largely dependent on the flow regime. Only in the case of full recirculation and $T = H_L$, intensive mixing of the gas phase will occur. Recirculating gas will mix, immediately after entering the vessel, with the gas entering the tank by coalescence in the cavities behind the stirrer blade. This is also the case for the so-called noncoalescing systems. At these conditions, the gas phase can be regarded as ideally mixed [2].

Without full recirculation, mixing will be much less. In addition, recirculation downward to a lower compartment will hardly occur at $H_L > T$. At these conditions, the gas phase can be regarded as near to plug flow.

Gas-phase recirculation will also be dependent on bubble size. Smaller bubbles will more easily recirculate than larger ones due to their lower rise velocity.

2.07.7.2 Bubble Column

Nearly all commercial-scale bubble columns are of the type with $H_L > T$ or $H_L \gg T$. Most of the published experiments are done at diameters smaller than those of commercial-scale bubble columns and at high aspect ratios. The results show that the gas phase can be regarded as near to plug flow. It can be expected that this will not be different for commercial-scale reactors. The relation in the review of Heijnen and Van 't Riet [16] also should lead to the conclusion that this will be the case. In large-scale low aspect ratio bubble columns, circulation velocities can easily be much higher than the bubble rise velocity and air will be entrained downward. Nevertheless, most air will be in upflow and the effect is limited.

2.07.7.3 Airlift

The riser of an airlift reactor can be described with the number of mixers or Peclet number at least the same and probably much more than that of a bubble column. This means that the gas can be regarded as plug flow. However, in the case of an internal airlift reactor in the recirculating gas regime, a considerable amount of air may be recirculated.

2.07.8 The Meaning of Mixing

2.07.8.1 Characteristic Times

It is the purpose of the mixing process to get a homogeneous distribution of those molecules or conditions that are important for the functioning of the microorganisms. As such, mixing time is not interesting as long as the distribution is even or even enough. Microorganisms do not know about mixing time, their only experience is their own microenvironment, which they may prefer not to be too variable. However, in some cases where microorganisms produce a product due to stress conditions, we prefer to exert stress conditions.

To get an insight into the consequences of mixing, the principle of characteristic times is a useful tool. Characteristic times are reactor parameters and can be determined for a number of processes. Here, we will determine the values for heat production, oxygen mass transfer, and C-substrate consumption.

For heat production, a characteristic time can be defined as the time needed to heat up the vessel content by 1 °C, adding up all heat sources. Most of the heat is due to the metabolic activity, and for an aerobic fermentation at an oxygen uptake rate (OUR) of 100 mol m⁻³ h⁻¹ this time is of the order of 1 h. For oxygen mass transfer, the value of 1/k_la is the characteristic time for saturation by mass transfer. For a fully loaded commercial fermentation, this value can be around 10 or 20 s. Another characteristic time is that of oxygen depletion of the broth, which is the time value of the actual oxygen concentration in the liquid divided by the OUR. For C-substrate consumption, the characteristic time can be defined as the ratio between the concentration in the liquid divided by the rate of C-substrate consumption (C-substrate depletion). Assuming Monod kinetics, the concentration in the microenvironment at half of the maximum growth rate is equal to the Monod constant K_m. The value of K_m is different for each substrate and microorganism. It can be less than 1 up to 10 g m⁻³. For instance for a glucose consumption rate of 1 kg m⁻³ h⁻¹, the characteristic time becomes less than 1 s up to around 10 s.

Table 4 gives these characteristic time values. Mixing time is dependent on scale as already discussed. The other three values appear to be independent of scale. What are the consequences? To determine this, we again consider the microorganism and its microenvironment. We have defined characteristic times as reactor parameters. For the microorganism, we define critical times, the time at which problems occur due to variations in the microenvironment of the microorganisms [2].

2.07.8.2 Heat Production

For heat production, a characteristic time is derived on the basis of a temperature increase of 1 °C. Let us assume that the metabolism of a given microorganism does not show a relevant change in production characteristics, growth rate, or unwanted product formation at temperature differences less than 0.1 °C. From this value, a critical time for heating (defined for the given organism, not as a reactor parameter such as the characteristic time) at which the metabolism is influenced of 360 s can be calculated. The question to be answered is: is the microenvironment of the microorganism ever able to heat up 0.1 °C. To get the answer, the mixing time as characteristic time for smoothing out temperature differences and the calculated critical time for heating have to be compared. Mixing times are of the order of 10–100 s, and the critical time is much larger. Thus, heat will not accumulate to problematic values. From the viewpoint of temperature differences in the vessel content, no (for the microorganism) relevant temperature differences due to heat production will exist across the vessel. The same is true for the bulk temperature differences due to cooling. Although heat production occurs everywhere in the vessel, heat removal occurs only at cooling surfaces. This causes temperature differences in the heat transfer layer at the cooling surface. Mixing hardly influences this.

2.07.8.3 C-Substrate

The Monod equation states a fixed relation between growth rate and bulk substrate concentration. Assuming that the critical time for C-substrate can be defined on the basis of a small change in concentration for which the growth rate will change according to Monod, this critical time value will be an order of magnitude smaller than the C-substrate characteristic time given in Table 4. Thus the critical time based on the Monod equation will be orders of magnitude smaller than the mixing time, in particular on large scales. Applying a

Table 4 Order of magnitude of characteristic time values^a

	<i>Small scale</i> 0.1 m ³	<i>Large scale</i> 100 m ³
Mixing time	10	100
Oxygen depletion	10	10
Mass transfer	20	20
Heating	3600	3600
C-substrate (1)	<1	<1
C-substrate (2)	20	20

^aMass transfer (1/k_lA) at OUR = 100 mol m⁻³ h⁻¹. Oxygen depletion at atmospheric saturated conditions and OUR = 100 mol m⁻³ h⁻¹. Heating, time to heat up 1 °C at OUR = 100 mol m⁻³ h⁻¹. C-substrate glucose at half of the maximum growth rate and a feed rate of 2 kg m⁻³ h⁻¹ and (1) K_m = 0.1 g m⁻³ and (2) K_m = 10 g m⁻³.

circulation loop model, one could state that the circulation time ($t_m = (4-7)t_c$) is the relevant time for concentration changes in the microenvironment of the substrate that is added at a given position. The same conclusion can be drawn for the circulation time. It can be concluded that it is totally impossible, in particular and surely on a larger scale, to have a substrate concentration throughout the vessel homogeneous enough to get a constant growth rate according to the Monod equation. Apparently, the growth rate relation with concentration is much more complex and the critical time is much larger than the Monod-based value. However, somewhere at scale-up, due to the increase of mixing time with scale, this mechanism can be expected to start to fail. Usually this will cause a decrease in production yield or result in the production of unwished products. As an example Enfors *et al.* [8] show this to be the case.

In those cases where the substrate becomes a problem, possible solutions are rather straightforward. The first one is to optimize the substrate addition position. A change from the top of the vessel to halfway between the stirrers in the case of multiple stirrers, or halfway the vessel in a slender bubble column, is to be preferred because it decreases the mixing time up to a factor of 2. In case this is not sufficient to get the yield to the original level, multiple and carefully positioned addition points are a possible solution. Mixing and circulation times of the reactor do not change; however, the microenvironment of the microorganism circulating around in the vessel is fed several times during the circulation loop, and the characteristic time for 'circulation' is therefore the real characteristic time divided by the number of addition points.

Reactor configuration, type, H_1/T , and scale are of essential relevance as shown in Table 3.

2.07.8.4 Oxygen Mass Transfer

The characteristic time for mass transfer is a reactor parameter. It is a time characteristic for the decrease in oxygen concentration once the aeration is halted. As we do not expect this to be the case, this characteristic time is not related to a critical time for the microorganism.

2.07.8.5 Oxygen Depletion in Stirred Tank

A stirred tank can reach higher oxygen transfer values than a bubble column. However, the main part of the transfer takes place in the stirrer region. This will lead to problems as the dissolved oxygen has to be transported by circulation to other parts of the vessel. The characteristic time for depletion is the relevant value for the critical time for depletion when it is assumed that all oxygen is transferred near the stirrer and the characteristic time is based on the C_{oL} value in the stirrer region. Applying the circulation time model, the critical time for depletion is of the order of the circulation time ($t_m = (4-7)t_c$) at smaller scales but certainly lower than the mixing time at larger scales, and thus problems can be expected. It is indeed common knowledge that local oxygen depletion can occur in large-scale stirred tanks. In those cases where problems do occur, the possible solutions are as follows:

- increase of the top pressure, thus increasing the liquid oxygen concentration near the stirrer (if possible without too high carbon dioxide concentrations);
- increase of oxygen mass transfer ($k_L a$ or enrichment of gas phase), thus increasing the liquid oxygen concentration near the stirrer;
- a decrease of OUR; and
- prevention of design of tall, slender large-scale stirred tanks as shown in Table 3.

The use of multiple stirrers is highly questionable. Due to the static pressure, the mass transfer due to the higher driving force is highest at the lower stirrer, and last but not the least, multiple stirrers do have a negative influence on mixing.

Some microorganisms and cell cultures are sensitive to CO_2 concentrations. A critical time for CO_2 can be defined in the same way as done for oxygen. The solutions are almost the same, with the inclusion of

- increase of the air flow rate (ventilation).

2.07.8.6 Oxygen Depletion in Bubble Column

Oxygen is transferred at all positions in a bubble column, although the transfer near the sparger can be much higher. The characteristic time for depletion is based on C_{oL} outside the immediate region of the sparger. This starting point added to the fact of transfer anywhere in the vessel makes the critical time for broth depletion much larger than for the stirred tank case. Then the mixing time will be smaller than the critical time and no problems will arise. Problems might occur only at extreme OUR conditions and corresponding low dissolved oxygen concentration values. Above a larger transfer near the sparger, oxygen transfer in a bubble column is higher in the lower part due to a higher (static) pressure and less gas-phase oxygen depletion. This may be compensated by a larger interfacial area in the upper part due to gas expansion. Also, in that case, bulk liquid mixing in large-scale bubble columns (as long as $H/T < 3$ for which $N_{mix} = 16$) will decrease these differences. Altogether not much problems can be expected.

In those cases where problems do occur, possible solutions are as follows:

- increase of top pressure leveling up the liquid oxygen concentration in the whole column;
- increase of oxygen mass transfer by increasing the gas flow rate (also favorable for ventilation);
- decrease of OUR;
- prevention of design of slender, tall large-scale columns as shown in Table 3.

2.07.9 Conclusions

Mixing is a well described and researched phenomenon. Experimental data are also available for commercial-scale reactors. Measurements are reproducible and data found with different methods are in-line with each other. Although measurements are reproducible, values can differ easily within a range of 0.5 up to 2. The reason behind this is not a difference in measurement method or data interpretation. Mixing time (at a given intensity and scale) depends on the position of the measurement probe and on the position of addition of the tracer. Lowest mixing times are measured when tracer addition and measurement are done halfway the bubble column, or halfway between stirrers in a stirred tank in case of multiple stirrers. Much longer mixing times are found at tracer addition at the top of the vessel or at the lowest stirrer for the case of multiple stirrers. For multiple stirrers, a radial pumping stirrer in the lower compartment combined with axial pumping stirrers is a better configuration than radial pumping stirrers only.

Several conclusions can be drawn for the relevance of mixing time by comparing the characteristic times for the vessel with the critical times for the microorganism. Substrate mixing for bubble column and stirred tank can be problematic as does dissolved oxygen depletion for stirred tanks. Temperature distribution and dissolved oxygen depletion for a bubble column will be less problematic.

A main line is an inherent increase of mixing time (and possible problems) with scale and a drastic increase of mixing time with slenderness. The bubble column generally shows a lower mixing time than the stirred tank. The airlift shows a larger mixing time for not too slender columns when compared to the bubble column of the same volume.

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Relevant Website

<http://www.bakker.org> – Presents a lot of data about mixing. Also gives sites of all important mixing companies and university mixing research groups.