Oscillatory reactors for biotechnological applications

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Introduction

Oscillatory flow has been studied since van Dijick (1935) proposed the reciprocating plate column (RPC) as a contactor for liquid-liquid extraction. The RPC has evolved significantly both in the extraction area and in some gas-liquid applications (Lo and Prochazka, 1983; Baird *et al*., 1994). Several plate designs have been reported but the Karr RPC (Karr, 1959) has been the most successful one. The principle of the Karr RPC is that an oscillatory drive was mechanically connected to a shaft linking a stack of multi-perforated plates with many circular perforations of several diameters.

Since the early 1990s, studies have shown that tubes containing periodically spaced orifice baffles where the fluid is oscillated by means of a piston or bellows while the plates remain stationery, can exhibit efficient fluid mixing and a narrow residence time distribution (Brunold *et al.*, 1989; Dickens *et al.*, 1989; Howes *et al.*, 1991; Mackley and Ni, 1991, 1993, Stonestreet and van der Veeken, 1995). The baffle edges promote the formation of eddies, which increase the radial mixing in the tube, leading to radial velocities of the same order of magnitude as the axial velocities (e.g. Mackley, 1991; Mackley and Ni, 1991; Ni and Pereira, 2000). These "oscillatory flow reactors" (OFR) can be operated continuously in horizontal or vertical tubes containing liquid or multiphase flows. The fluid is oscillated in the axial direction by means of diaphragms, bellows or pistons, at one or both ends of the tube, or by moving a set of baffles up and down from the top of the tube (Ni *et al.*, 2002).

The efficiency of the radial transport is affected by many variables, such as the oscillation frequency (f), amplitude (x_0), reactor internal diameter (d), baffle spacing (L), baffle internal diameter (d_0), baffle thickness (δ) and by the fluid's rheological properties (density, ρ, and viscosity, μ) and the net flow Reynolds number (Re_n). The intensity of mixing in an OFR is commonly described by the oscillatory Reynolds number, Re_o, and the Strouhal number St_r, which are defined as (Ni and Gough, 1997):

$$Re_o = (2\, p\, f\, x_0\, r\, d)/m \qquad (1)$$

$$St_r = d/(4 \pi x_0) \qquad (2)$$

From extensive studies, it is known that at Re_o values of 100-300, vortex rings are symmetrically generated within each baffle cavity during each oscillation of the fluid. At higher Re_o, the flow becomes more intensely mixed and chaotic, leading to increased axial mixing such that the OFR's mixing increasingly resembles that of a stirred tank (Ni *et al.*, 1999, 2002). The generation of vortices is no longer axi-symmetrical (Ni *et al*., 2002).

Experiments by Smith *et al* (1993) and flow visualization studies by Ni *et al.* (1995a) show that fluid oscillation in an OFR is an efficient method of uniformly suspending particles. The performance of the OFR as a heterogeneous catalytic reactor has been demonstrated for the suspension of titania particles acting as catalysts to oxidise waste water contaminants (Fabiyi and Skelton, 2000). The OFR has also been shown to be a good particle separator (Mackley *et al*, 1993).

The formation and dissipation of eddies in the OFR results in significant enhancement of processes such as heat transfer (Mackley *et al.*, 1990; Mackley and Stonestreet, 1995), mass transfer (Hewgill *et al.*, 1993; Ni *et al.*, 1995a, 1995b; Ni and Gao, 1996), particle mixing and separation (Mackley *et al.*, 1993), liquid-liquid reaction (Ni and Mackley, 1993), polymerization (Ni *et al*., 1998, 1999) and flocculation (Gao *et al.*, 1998). The OFR increases the holdup time of bubbles and particles, and is an effective method of controlling drop and bubble size distributions. Research also includes: fluid mechanics (Brunold *et al.*, 1989; Mackley and Ni, 1991, 1993), local velocity profiles and shear rate distribution (Ni *et al.*, 1995c), residence time distribution (Dickens *et al.*, 1989; Mackley and Ni, 1991, 1993; Ni, 1994), dispersion (Howes, 1988; Howes and Mackley, 1990), velocity profiles (Liu *et al.*, 1995) and scale-up correlations (Ni and Gao, 1996).

The SPC tube

The problem with the previously mentioned designs, however, is that in either way sudden constrictions, bends and corners are used in the design of such vessels and this is not desirable when biological processes are involved due to the easy lodging of extraneous microorganisms in such places leading to difficulties of operation (e.g. complicated sterilisation procedures).
This has called for a new design where the baffles would be replaced by smooth periodic constrictions (SPC) a sequence of which would constitute the SPC tube – Figure 1. The energetic efficiency of such device is, at least theoretically, superior to its predecessors. In fact, such reactor is expected to have advantages in terms of flow as the flowing patterns will be definitely softer than those found in the devices quoted above – RPC and OFR – and their variations, leading to lower shear stresses that are advantageous in a number of situations (e.g. when living cells or enzymatic catalysts are present, which is always the case when biological processes are involved) (Sukan and Vardar-Sukan, 1987; Kennard and Janekeh, 1991).

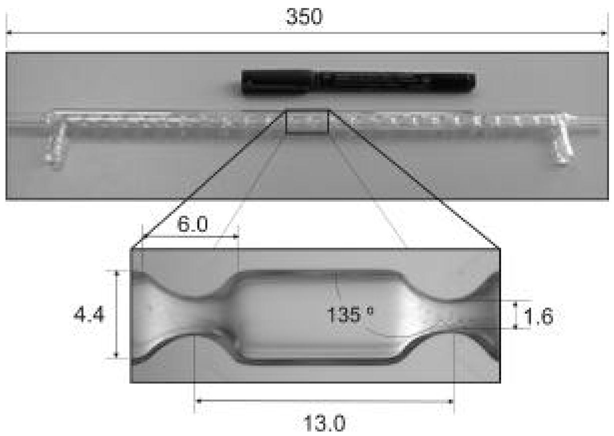

Figure 1: Geometry of a single SPC tube, with all distances in mm.

This SPC tube constitutes a new small scale technology for reaction engineering and particle suspension applications. Due to its small volume (about 4.5 ml) this reactor is envisaged for applications in specialist chemical manufacture and high throughput screening, being also suitable for multiphase applications at small-scale in the bioengineering field (e.g. fast parallel bio-processing tasks). The evaluation of this novel oscillatory flow screening reactor in terms of fluid micro-mixing and suspension of catalyst beads has been performed using Particle Image Velocimetry (PIV), combined with Computational Fluid Dynamics (CFD).

Particle Image Velocimetry

The instantaneous velocity vector maps in Figure 2 below, correspond to three different points of the oscillation cycle:
a) the point of maximum upward piston velocity;
b) point of zero piston velocity (before flow reverses downwards)
c) the point of minimum downward piston velocity, after flow reversing

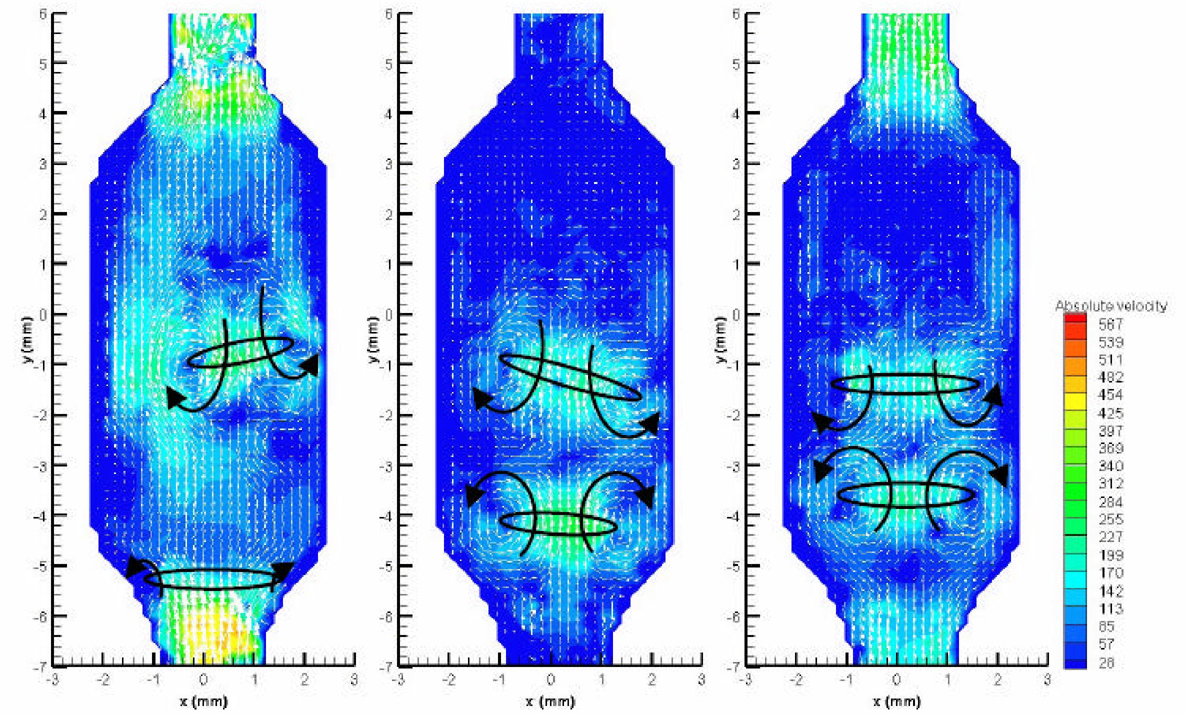

Figure 2: Instantaneous velocity vector maps at Re_o = 348, x_0 = 1.1 mm, f = 11.1 Hz coloured by absolute magnitude (mm/s) and different phase angles (black vortex rings and arrows added to aid visualization): *(a)* beginning of cycle; *(b)* 1/5th way through cycle, i.e. before flow reversing; *(c)* 3/10th way through cycle, i.e. after flow reversing.

At the lower constriction in 2a) there is flow separation, generating an upward-travelling vortex ring. The vortex ring emerges from the near-wall region and grows through figures 2b) and 2c) to occupy most of the cross-sectional area of the tube, before colliding with the previous vortex ring. It should be noted that the non-axisymmetry at the point of flow separation is related only to the non-axisymmetric separation near the expansion (which is difficult to avoid in the tube's manufacture). Maximum non-axisymmetry was observed in the velocity vector maps when *u(t)* was near its maximum value, but at lower axial velocities (e.g. in Figs. 2*b* and 2*c*), the vortex rings become more axisymmetric and more central.

Apart from the initial asymmetry during flow separation, due to the asymmetry of the tube at the constriction, the mixing patterns observed in this reactor are essentially the same as those observed for larger, sharp-baffled OFRs. Therefore we can expect to achieve the same uniformity and efficiency of mixing, as well as particle suspension and bubble hold-up as has been observed in those reactors.

Figure 3, below, shows that the flow structures become considerably more asymmetrical at higher Re_os, as is the case in conventional OFRs. At Re_o = 1350, it is clear that symmetry is completely broken: we can clearly see that there are two vortex rings travelling in the same direction in 3b), and in 3c), we can see that although the rings are travelling in opposite directions they are highly asymmetrical. Clearly the reactor should not be operated at such high Re_os, if plug flow is required, as the degree of axial mixing is high.

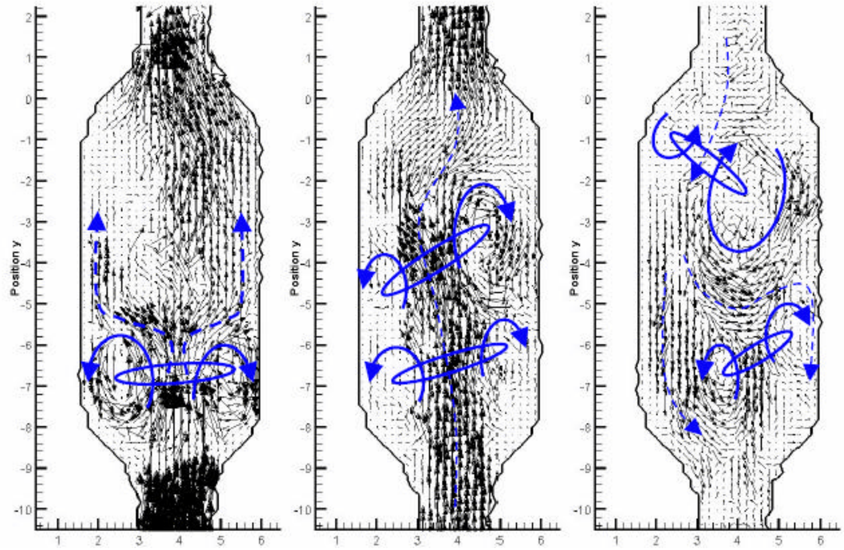

Figure 3: Instantaneous velocity vector maps at Re_o = 1,350, x_0 =0 4 mm, f = 12.1 Hz and different phase angles (vortex rings and arrows added to aid visualization): *(a)* start of a new cycle *(b)* 1/5th way through cycle, i.e. before flow reversing *(c)* 3/10th way through cycle, i.e. after flow reversing.

Suspension of high concentrations of catalyst particles requires that intensive eddy structures are present at all phase angles. This state is most easily assured by operating the meso-reactor at high oscillation frequencies.

CFD simulations

To allow non-axisymmetry to be simulated it was necessary to move to a 3D mesh. It was possible to simulate asymmetric flows using a laminar model, provided there were enough cells in the mesh, although simulation by large eddy simulation required less computational time, as it required fewer cells. The laminar simulations below again exhibit good agreement with experimentally observed phenomena but are now able to generate non-axisymmetrical vortices (Fig. 4).

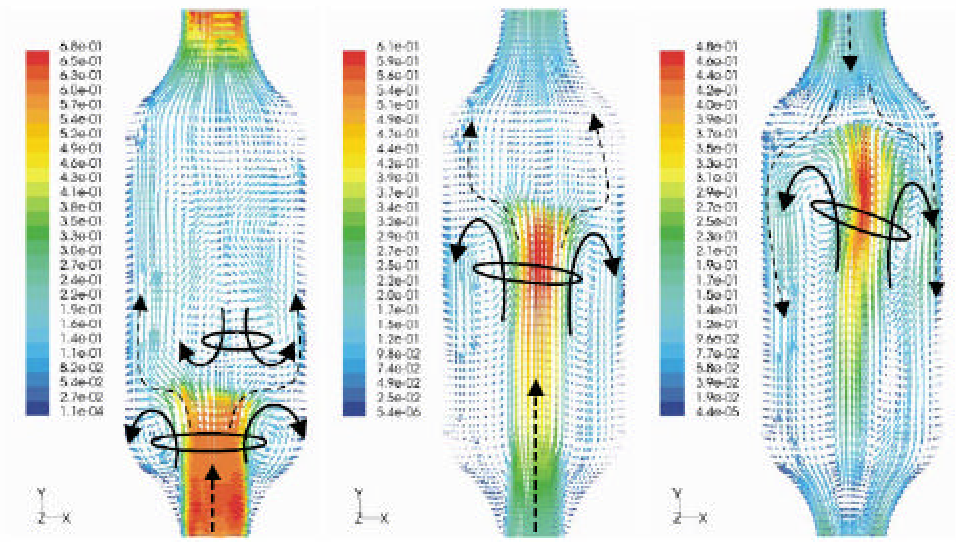

Figure 4: Simulated flow patterns for Re_o = 348, x_0 = 1.1 mm, f = 11.1 Hz, using 3D laminar model, after 26 simulation cycles. Velocity vectors coloured by velocity magnitude (m/s), on plane z = 0, (black arrows added to aid visualization) at: *(a)* start of cycle, i.e. maximum upward velocity; *(b)* 1/5th of an oscillation cycle, i.e. before flow reversing *(c)* 3/10th of an oscillation cycle, i.e. after flow reversing.

Effect of Reactor Orientation on Particle and Bubble Suspensions

In Figure 5, below, the suspension of silica particles is shown for different angles of reactor tube. The oscillation conditions presented correspond to the minimum necessary oscillation amplitude, at 12.1 Hz, to keep all the particles suspended. Silica particles were used as they are relatively easy to observe, due to their relatively large particle diameter.

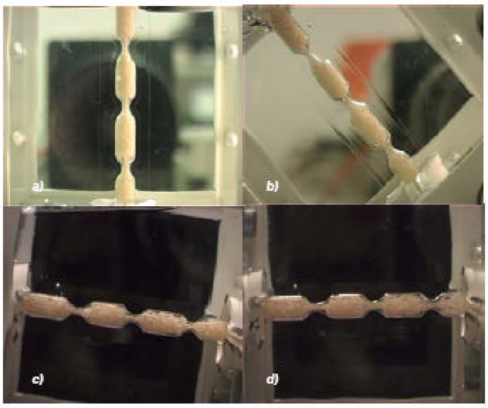

Figure 5: Complete suspension of 40 % (v/v) of silica particles at varying angles and similar oscillation conditions: *(a)* vertical position, f = 12.1 Hz, x_0 = 4 mm; *(b)* 45º, f = 12.1 Hz, x_0 = 4 mm; *(c)* 10º, f = 12.1 Hz, x_0 = 3 mm; *(d)* horizontal position, f = 12.1 Hz, x_0 = 3 mm. In *b), c)* and *d),* the right hand side corresponds to the bottom of the tube.

Residence times and mixing in the novel oscillatory flow screening reactor

This section is concerned with the fluid mechanics and mixing performance of the novel oscillatory flow screening reactor. Using fibre optic probes (Fig. 6) an empirical mixing coefficient k_m is determined for the system as a function of the applied fluid oscillating frequency and amplitude (Fig. 7). A mass balance performed to the tracer concentration x in the cavity of the bottom of the tube (the cavity which is at farthest distance from the injection point) yields, after integration along the experiment time t:

$$ln\left(\frac{1/x_{inf}-1/x_i}{1/x_{inf}-1/x_{ini}}\right)=-k_m t \qquad (3)$$

where x_{inf} is the concentration at infinite time, x_{ini} is the initial concentration and x_i is tracer concentration at time t_i. Equation (3) allows the determination of k_m directly from the experimental data.

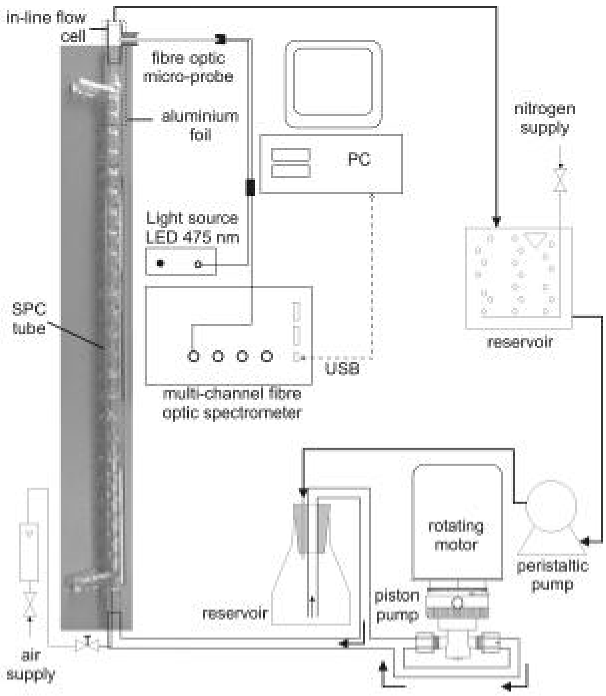

Figure 6: Experimental setup for RTD and k_La studies.

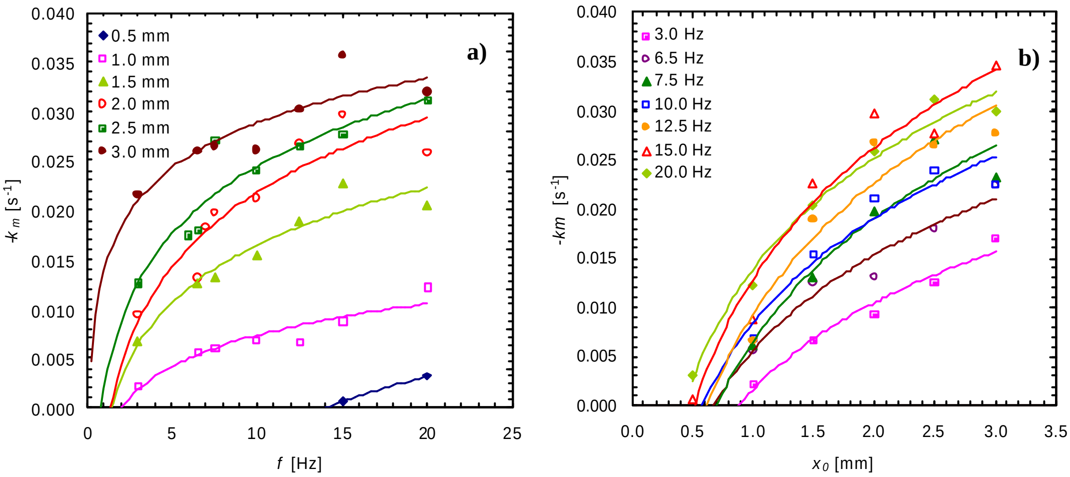

Figure 7: Variation of the mean values of mixing coefficient k_m with fluid oscillation (a) frequency and (b) amplitude at different oscillation conditions.

In a continuous mode of operation the mean residence time of the tracer was determined as in Equation 4 and the results are shown in Fig. 8 as a function of the oscillation conditions.

$$\bar{t} \cong \frac{\sum_{i=1}^{\infty}\left\{\frac{1}{2}[t_i + t_{i-1}][x_i - x_{i-1}]\right\}}{\sum_{i=1}^{\infty}\{x_i - x_{i-1}\}} \tag{4}$$

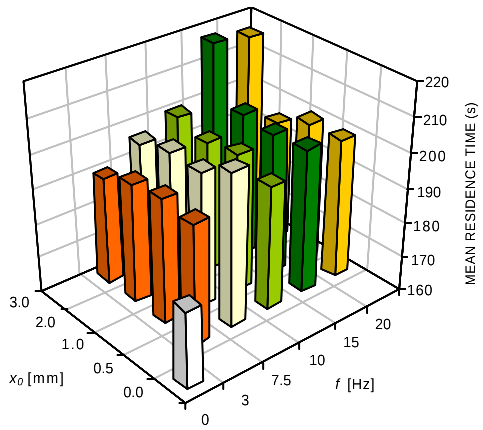

Figure 8: Mean residence time of the tracer, measured at the outlet of the screening reactor for various oscillation amplitudes, x_0, and frequencies, f, at a fluid flow rate of 1.94 ml/min.

The screening reactor presented an intermediate mixing behaviour at all the studied range of oscillation amplitudes (0 to 3 mm centre-to-peak) and frequencies (0 to 20 Hz).

Determination of k_La in the novel oscillatory flow screening reactor

In order to complete the characterisation of the screening reactor the air-water oxygen mass transfer rates were determined. A state-of-the-art fibre-optical micro-probe (oxygen micro-optrode) was applied for on-line monitoring of oxygen saturation levels (Fig. 6). The main objective of this work was to demonstrate that this novel reactor is able to support growth of oxygen-dependent biological cultures, therefore being able to support applications as a screening device for fast parallel bioprocessing. Volumetric oxygen mass transfer rates of up to 0.05 s^{-1} were obtained in the range of fluid oscillation amplitudes from 0 to 3 mm (centre-to-peak) and frequencies from 0 to 20 Hz (Fig. 9).

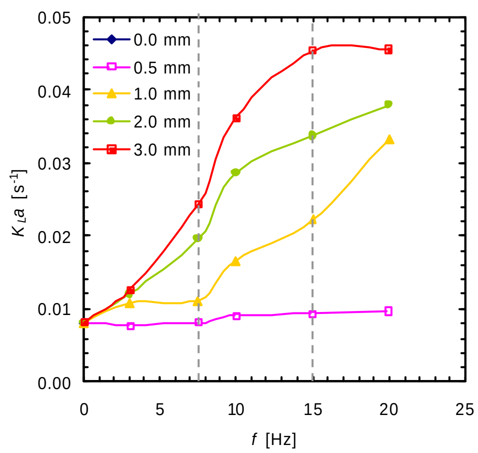

Figure 9: Effect of fluid oscillation frequency over the mean values of k_La, at constant values of fluid oscillation amplitudes. In all cases, v = 1.58 ml min^{-1} and v_{gas} = 0.28 ml min^{-1} (i.e. 0.064 vvm).

Overall, a thirteen-fold increase was obtained when compared with the gas sparging in a conventional bubble column at the same gas superficial velocity (0.37 mm s^{-1}), according to the correlation of Deckwer et al. (1974). An averaged seventy percent increasing was also obtained when compared with the conventional oscillatory flow reactor (Oliveira and Ni, 2004) operating in the same range of fluid oscillation conditions (oscillation amplitude and frequency). It was concluded that coupling of oscillatory flow in the presence of periodic constrictions effectively enhances the volumetric oxygen mass transfer coefficient both with the increase of oscillation amplitude and frequency, by means of two main factors: 1) the small internal diameter of constricted tubes composing the screening reactor (< 1.6 mm) and 2) the fluid flow patterns generated within the reactor, which controlled the mean bubble residence time and the mixing intensity. A schematic summary of the main processes involved in k_La enhancement in this novel reactor is presented in Fig. 10.

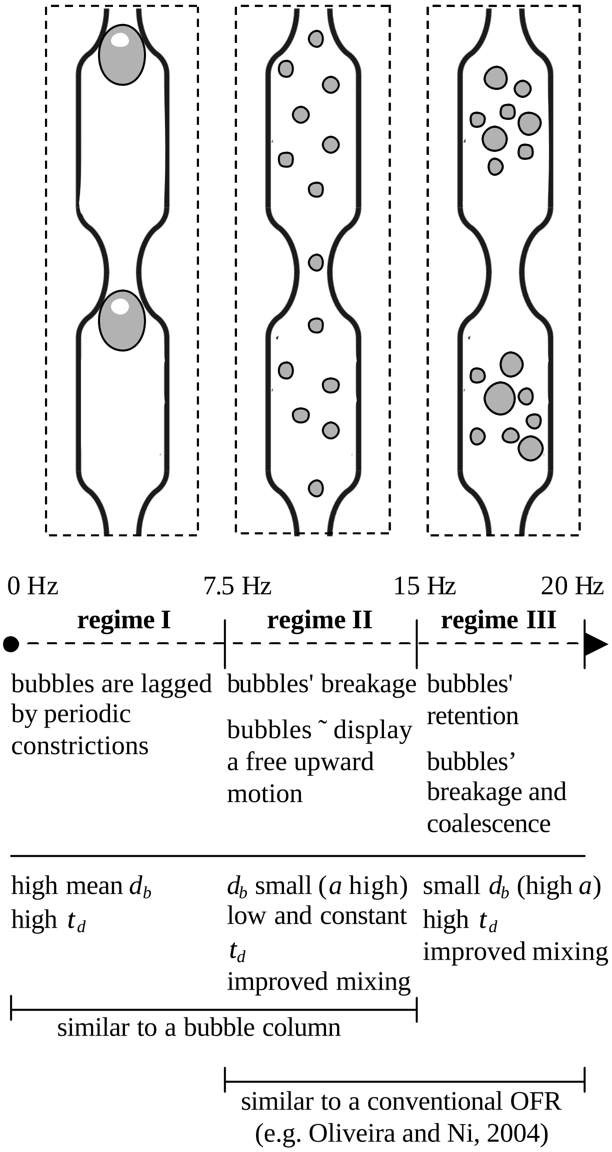

Figure 10: Schematic representation of bubbles behaviour in the three identified regimes, in the studied range of fluid oscillation frequencies. The first row summarises the general bubbles behaviour while the second row summarises the main consequences and the phenomenon leading to the general k_La enhancement.

Multiphase reactors have been extensively used in chemical industries on gas-liquid-solid catalytic processes. Also in pharmaceutical/biochemical industries and in wastewater treatment plants (Siegel *et al.*, 1988, Vicente *et al.*, 2001) those systems are receiving increasing attention.
Looking at the rapid progress of biotechnology over the last two decades and the corresponding development of companies producing biotechnology-based products, the development of new bioreactors meeting the need for process enhancement is certainly an up-to-date task that needs to be continued.

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