BUBBLE COLUMNS AND AIRLIFT BIOREACTORS

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Summary

Bubble columns and airlift loop bioreactors are attractive alternatives to stirred tank bioreactors for large-scale manufacturing of commodity products such as yeast, citric acid etc. Their most important advantage as compared to stirred tank bioreactors is that they allow oxygen mass transfer at considerably lower power input levels and, as they most often contain no moving parts, that their requirements concerning investment and maintenance costs are lower. Bubble columns and airlift loop reactors can be built with much larger working volumes than stirred tank reactors. Their advantages become effective predominantly at scales larger than 50-100 m³. Here we focus the attention on the dynamics of bubble columns and explain the fluid mixing in the turbulent flows in these multiphase reactors as well as reasons for their mass and heat transfer performance. The text is illustrated with a number of real examples from large-scale industrial applications.

1. Introduction

Many important bio-products are produced by means of fermentation where microbial, plant or animal cells are employed to produce them as their metabolites. These products include proteins for medical purposes, e.g., insulins, that are formed by genetically-modified yeasts or bacteria, or erythropoietin (EPO) produced by animal cells such as Chinese hamster ovary cells, or, on the other side of the spectrum, bulk chemicals such as 1,3-propanediol, produced with *Escherichia coli*, food additives

such as lysine by *Corynebacterium glutamicum* or just baker's yeast *Saccharomyces cerevisiae*.

Bioreactors are containments used to provide microbial, animal, or plant cells the environment for optimally producing the desired products. Experiences gained over many decades showed the cells' environment can best be kept under control when they are suspended in a liquid culture medium from which they receive all their nutrients. Particularly, temperature, pH, and the nutrient concentrations can easily be adjusted in a continuous liquid phase. Hence, in most bioreactors the cells are suspended in liquid media.

The only important component that cannot be fed to such a culture at an arbitrarily high rate is the oxygen that the cells need in most production processes. In nearly all practical cases oxygen is supplied by bubbling air through the liquid. In order to keep the cross section for the transfer of oxygen from the gas bubbles into the liquid phase high enough, a high gas throughput is necessary, preferentially using very small air bubbles.

In the classic catalytic chemistry, production processes are characterized by high space-time yields, i.e. in a reactor with a given culture volume, the formation of much product mass per production time. Chemists, however, often produce under high pressures and temperatures, frequently they need organic solvents, and many times they form toxic byproducts. Biotech production processes on the other hand use extremely specific catalysts, in most cases the enzymes active in living cells, and they work under comparably very mild conditions. However, the space-time-yields, are often considerably smaller. Hence, large reaction volumes and reactor sizes are commonplace in the biotechnological production of commodity products.

Since optimal conditions must be provided to all cells, homogenization of the culture medium is essential. In practice one tries to achieve this by intensively mixing the culture. This is the reason why most bioreactors from the smallest up to the production scale of 100 m³ and even larger are designed as stirred tank bioreactors. There an agitation system, consisting of one or more impellers mounted on a single central shaft driven by an electromotor, is used to induce turbulent motions in the culture in order to support both mixing and oxygen mass transfer. A clear advantage of aerated stirred tank reactors is that the power needed to maintain the turbulent motion in the culture can be adjusted independently (i) by the agitator and (ii) by means of the gas phase that is pressed into the culture by an air compressor.

Unfortunately, stirring at high power levels not only leads to high running costs but, at large scale equipment, also to high investment and maintenance costs. At culture volumes above 100 m³, where predominantly cheap bulk products are being produced, the energy cost factors have an important influence on the process economics. In some practical cases, the stirrer is thus shut down during cultivation phases where the broth viscosity is low and not too high oxygen transfer rates are required, in order to reduce the operation cost. Consequently, wherever possible in bulk product manufacturing, impellers are not installed at all and the tanks are operated as so-called bubble columns. Bubble columns find wide-spread applications, for instance in baker's yeast

production and even in systems that cultivate *Aspergillus niger*, a mold used, e.g., for the production of citric acid. At reactor dimensions larger than about 200-400 [m³] one will seldom find standard stirred tank reactors. Conversely, at smaller production scales lower than 50 [m³] one practically will not find bubble columns. In this article we will thus discuss bubble columns as alternatives to large aerated stirred tank bioreactors. We will not only mention the standard bubble columns but also airlift loop reactors that are variants which are obtained by modifications of the vessel geometry.

Many excellent professional surveys appeared in recent years on this topic (e.g. Heijnen & van't Riet 1984, Deckwer 1985, Chisti 1989, Schügerl 1997, Merchuk & Garcia Camacho 2010). Here we do not aim in copying them. Our focus is placed on insights into the dynamics of these reactors and not on the flood of engineering correlations derived for them.

2. First Characterization of Bubble Columns

Bubble columns are usually constructed as cylindrical vessels initially filled with liquid medium to which gas bubbles are continuously supplied at their bottoms. Apart from their length to diameter ratios, the only important construction detail is the gas-sparger forming the bubbles. The important point for understanding bubble columns is that the flow in these vessels is density-driven. Sparging bubbles in the liquid lowers the density of the culture locally which leads to convective flows within the entire column.

From the fluid mechanical point of view the bubble column fermenter is a two-phase gas-liquid flow system!
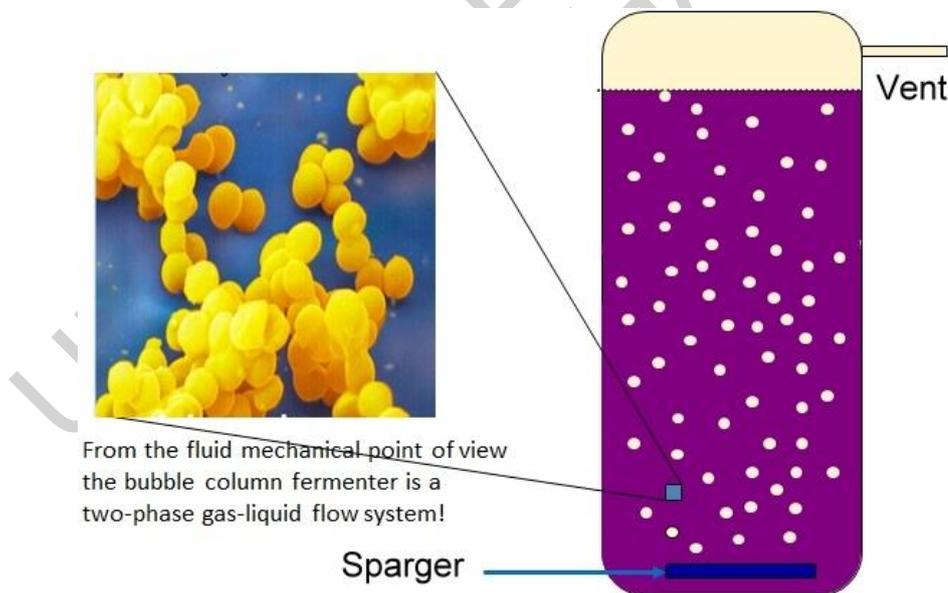
Vent

Sparger

Figure 1. Basic arrangement of a bubble column reactor

As depicted in Figure 1, the bubbles rise in the culture while exchanging volatile components with the liquid phase. The sizes of the bubbles are usually in the order of some millimeters and hence much larger than suspended microorganisms which are of diameters in the micron-range. The cells are even smaller than the smallest eddies in the turbulent liquid flow, which are in the order of magnitude of 0.1 mm. From the

fluid mechanical point of view, the bubble column bioreactor can thus be considered a two-phase gas-liquid flow system.

It must be stressed that the turbulent fluid motions needed in bioreactors for mixing the reaction system are energetically only supplied by the gas phase. From that point of view the gas flow rate or gas throughput v_g is the important quantity. Chemical and biochemical reaction engineers, however, prefer a slightly different key operational variable for bubble columns, namely the superficial gas velocity u_s defined as

$$u_s = \frac{v_g}{A} \quad [m/s] \tag{1}$$

where A [m²] is the cross sectional area of the column. The reason for this choice is that (i) nearly all important characteristics of the bubble column reactor are simple functions of the superficial gas velocity and (ii) it is directly proportional to the (scale-independent) specific power P_{aer}/V input into the column:

$$u_s = \frac{1}{\rho g} \frac{P_{aer}}{V} \quad [m/s] \tag{2}$$

ρ [kg/m³] is the liquid density, g [m/s²] the gravitational acceleration, $P_{aer}[W]$ the power input into the dispersion by the air compressor and V [m³] the culture volume. Not only g is constant, for a given system, ρ is considered practically constant as well.

At low superficial gas velocities or air throughputs, the bubble column depicts a quite homogeneous picture, which was termed the bubbly flow regime. The bubble sizes do not vary very much. With increasing u_s the flow becomes more and more turbulent and the bubble size distributions become broader. At high superficial gas velocities one gets a quite heterogeneous flow picture and then one speaks of the heterogeneous flow regime, often also referred to as the churn turbulent phase. The transition between both phases appears at about $u_s \approx 6$ [cm s^{-1}]. Figure 2 gives an impression of what is meant by these flow regimes.

Noteworthy, turbulence may also appear in the bubbly flow regime. Whether or not turbulence appears depends on the Reynolds number, Re, in fluid flow systems and in the liquids of lower viscosity present in most big production reactors, Re usually well exceeds its critical value for the appearance of turbulence even at quite low flow velocities which appear at superficial gas velocities which may be an order of magnitude smaller than 6 cm/s. Hence, the very big bubble columns need not be operated at $u_s > 6$ cm in order to obtain good turbulent mixing.
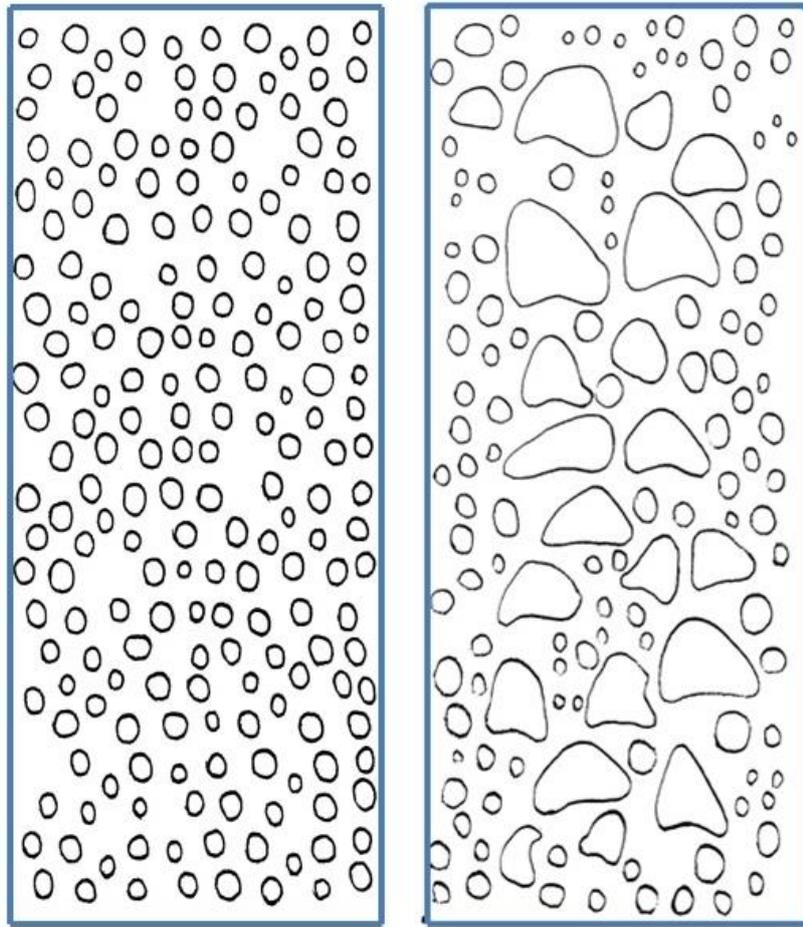
Figure 2. Main flow regimes that are important to biotechnological applications of large bubble columns: Left "bubbly flow", Right "churn turbulent flow" (Lübbert 2008)

An important characteristics of bubble columns with respect to the oxygen transfer between the gas bubbles and the liquid, is the relative volume of gas appearing in form of bubbles within the culture. This is referred to as the dimensionless relative gas holdup ε with $0 \le \varepsilon \le 1$. In a given liquid, ε primarily depends on the superficial gas velocity described by the engineering correlation:

$$\varepsilon = 0.6 u_{s'}^{0.7} \tag{3}$$

Where $u_{s'} = u_s / u_{us}$, with the unit velocity $u_{us} = 1$ [m s^{-1}], a quantity which is needed for dimensional correctness. This correlation gives a quite a coarse estimate but at least a hint to the fact that ε rises sub-proportionally with $u_{s'}$.

The main construction parameter of large bubble columns is the aspect ratio, i.e. the height H of the column in units of its tank diameter T. In practice both types of columns can be found, large aspect ratio columns and small aspect ratio columns. The

difference in their behavior, when they are employed as bioreactors, will be discussed later.

Figure 3 shows a typical example of slender bubble columns. These columns are operated at Citro-Misr Co. in Ramadan City, Egypt for citric acid production. In recent years, the citric acid industry replaced nearly all aerated stirred tank reactors that were formerly used by big bubble columns. Figure 3 shows the 600 [m³] reactors during the construction phase. The columns are about 30 [m] in height and 5 [m] in diameter. The plant was designed to produce 36.5 [t] citric acid monohydrate (CAM) per day.

Figure 3. Citric acid production reactors during their erection (Photo Courtesy of Vogelbusch Vienna)

3. Mass Transfer

One of the most important issues in bioprocess reaction engineering is, as already mentioned in the introduction, the gas-liquid mass transfer. The oxygen mass flux passes several steps from the interior of the air bubble via the physical gas-liquid interfacial area towards the bulk of the liquid phase. One of these steps, the transport

across the liquid side boundary layer at the gas-liquid interface, makes up by far the biggest influence on the transfer rates, hence it proved to be sufficient considering only this one.

The physical mechanism that dictates the flux across this resistance is molecular diffusion. Fick's first law thus applies. The simple graph in Figure 4 helps explaining the various quantities involved in this gas-liquid mass transfer law. The diffusive oxygen flux is driven by the concentration difference $\Delta O = O^* - O$ across the boundary layer, where O^* [mol/m³] is the solubility of oxygen in water, which is determined by Henry's law, and O the oxygen concentration dissolved in the bulk fluid. The volume-related oxygen transfer rate, OTR, in the case that no biochemical reactions influences the transfer, is expressed by the simple transport law

$$OTR = k_1 a \left(O^* - O \right) \ [\text{mol/m}^3/\text{h}] \tag{4}$$

The transport resistance is $R = 1/k_1 a = \delta / D / a$, where k_1 is the mass transfer coefficient, δ the strength of the boundary layer, and D the diffusion coefficient of oxygen in water. As k_1 and a most often cannot be determined separately, one focuses the attention to the product $k_1 a$ and takes it as the key transport coefficient.
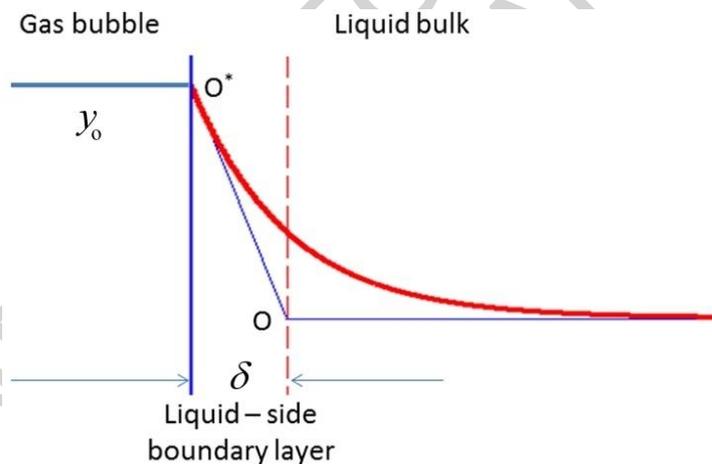

Figure 4. Definition of the variables involved in gas-liquid mass transfer

$k_1 a$ mainly depends on the superficial gas velocity u_s and to a smaller extend on the broth viscosity μ.

$$k_1 a = K u_s^{\beta} \mu^{\chi} \qquad \left[1/\text{h} \right] \tag{5}$$

The general behavior of the oxygen mass transfer as described by these equations is not doubted; however, the parameters K, β, and χ are neither independent of the scale nor of the position in the reactor. In big reactors, the assumption of a constant O^* along the axis of the column cannot be justified as the bubbles lose oxygen when they

rise through a tall reactor and the hydrostatic pressure becomes smaller on their way. This leads to an expansion of the bubble volume and thus to an increase of the transport cross section for the gas-liquid mass transfer. Simple models assume a logarithmic decay of the oxygen volume fraction in the bubbles and take the logarithmic mean for the corresponding O^* values determined with Henry's law. This however needs additional information about the oxygen volume fraction in the bubbles when they disengage from the culture. Another point is the dependency of k_1 from the interfacial properties. Much disputation about that question can be found in the open literature. van't Riet and Tramper (1991) state that most data support Higbie's approach (1935), where k_1 is dependent on the square root of the diffusion constant of the solute in the solvent, here D_{ow}, the diffusion coefficient of oxygen in water:

$$k_1 = \sqrt{\frac{4D_{ow}u_B}{pd_B}} \tag{6}$$

Further key influence parameters are the representative bubble diameter d_B and bubble rise velocity u_B as well as the total pressure p.

With respect to the gas-liquid mass transfer, the second important factor of the product k_1a is the specific interfacial area a [m² m^{-3}], i.e. the transport cross section presented by the bubbles per culture volume. Bubble diameter d_B and thus, a, may change due to coalescence and redispersion processes. Most often not sufficiently recognized is the coalescence behavior of the bubbles in the two-phase flow system. Usually, culture broths are coalescence repressing (!) two phase systems. We thus must often add antifoam agents to promote coalescence in order to avoid foam formation! The practical consequence is that in bubble columns the bubble size is less influenced by secondary coalescence/redispersion processes, e.g., by eddies in the turbulent flow. Hence, as opposed to aerated stirred tank bioreactors, the primary gas sparger is of considerable importance to bubble column reactors.

Spargers are often constructed as big wheels made from stainless steel tubes. The air supply goes to the hub and is dispersed into the surrounding liquid through small bores distributed across the entire tube system. Generally, the aim is generating small bubbles at the bottom of the reactors. The bubble sizes depend on the pressure difference Δp between gas and liquid and the bore diameter, d_h, the equivalent bubble diameter d_B is known to become smaller with smaller bores and higher Δp. Small hole-diameters at the sparger should thus be of advantage. However, in biotechnology practice, the hole must not be too small, since then practical problems with clogging may lead to severe disadvantages. Hence, in practice one often finds simple sparger constructions based on ring tubes or tree-like tube arrangements with bores in the millimeter range.

In order to enhance the specific interfacial area, a, several construction details were considered. The first was to reduce the bore diameters and increase the air pressure within the sparger in order to form small gas jets from each bore. This is shown in

Figure 5, where the gas is pressed in form of jets through small orifices at the end of the spokes. It depicts the jet sparger for the big bubble column reactors such as the one shown in Figure 3. These jets quickly decay to a series of small bubbles.
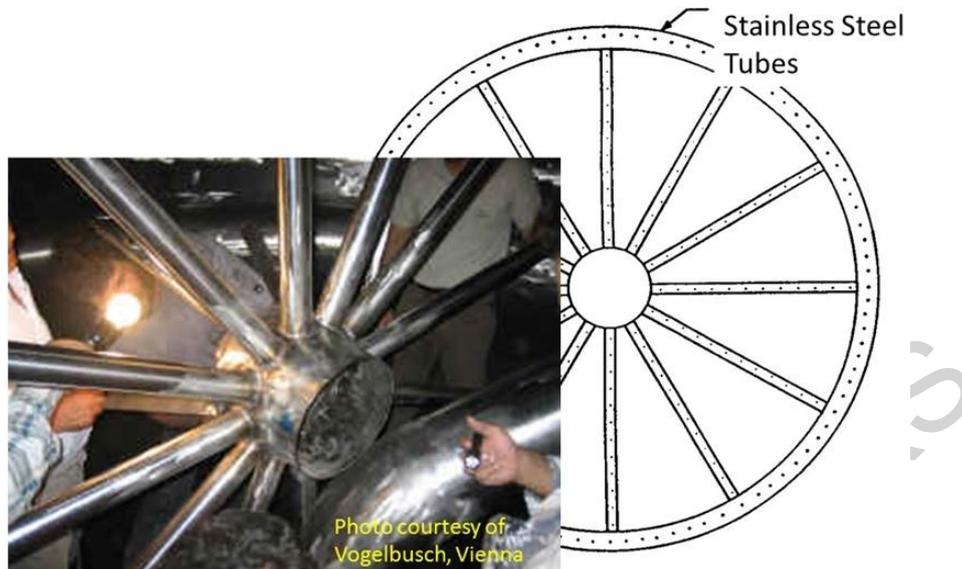

Figure 5. Examples of gas spargers for large citric acid production bioreactors
(Courtesy of Vogelbusch, Vienna).

An extreme version of gas-jet-type bubble formation was developed by DSM in Holland (Groen et al. 2005). They applied such high pressures and used such narrow nozzles that supersonic conditions appeared at the nozzle exits. In this way very small bubbles were generated. Such an arrangement is shown in Figure 6. Then, however, it must be guaranteed that air is continuously pressed at high pressure levels through these nozzles in order to avoid clogging.
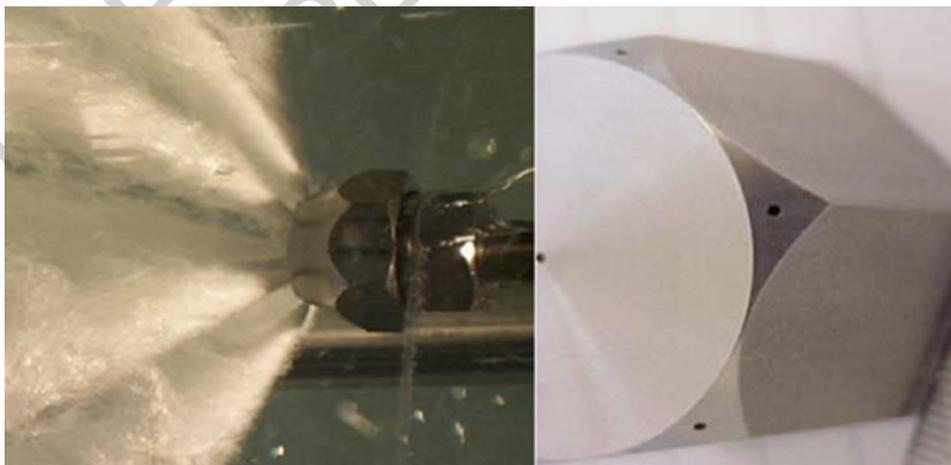

Figure 6. Dispersion by a supersonic air jet expanding into the liquid phase. Right the geometry of the nozzle arrangement showing that there are seven narrow bores in the stainless steel nozzle screwed onto an air pressure tube (Courtesy of DSM).

Particularly in biological wastewater plants where the aeration cost is dominant, many alternative air dispersion systems where investigated and used in real practice. All of them were led by the idea that the total power needed to finely disperse the air must be reduced. So two-phase flow arrangements were constructed where the liquid phase and the gas phase where brought together within narrow momentum exchange spaces from where the dispersions are then expanded into the culture broth. An important example is the development of Bayer AG Leverkusen in the 1980s. This is shown in Figure 7.
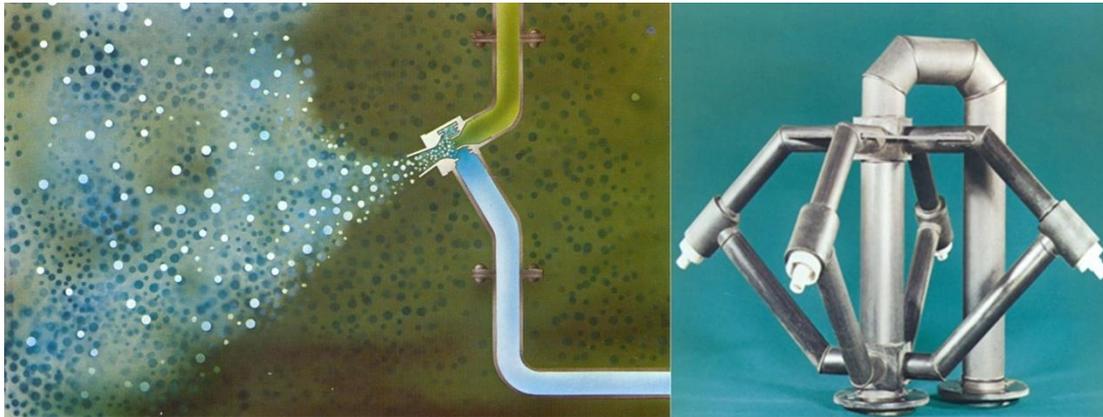

Figure 7. Momentum exchange two-phase gas liquid aeration nozzles developed by Bayer in the 1970s (Courtesy of Bayer AG)

Here, as the Figure shows, energy supplied with the liquid flow is used to cut down the gas fluid elements into many small bubbles. On the right of the Figure it is shown that 4 such two-phase nozzles are arranged in one aeration block. Many such blocks were installed on the flat bottom of a waste water treatment tower. Similar systems were developed at all big chemical companies at that time, e.g. Hoechst AG, BASF AG, ICI Inc. etc. Their common idea was using an auxiliary local (!) energy source to support air dispersion.

Further alternatives are widely distributed in the yeast manufacturing industries. These are mechanically supported air dispersion systems. An example is shown in Figure 8. The aerator looks like an impeller with 13 long narrow blades. They rotate and are driven from below. What looks like an impeller shaft is a tube that allows sucking air from the reactor's head space to the low pressure regions behind the rotating hollow blades of this sparger. The horizontal metal bars above this dynamic sparger are flow baffles that prevent rotation of the entire liquid in the column. Again, this is a dynamically aerated bubble column, not a stirred tank reactor. The arrangement shown serves for both, aeration (sucking air from the head space) and gas dispersion.

Similar constructions were developed by Frings GmbH in Bonn, Germany. Here a rotor/stator system generates high shear rates in the area where the gas is to be dispersed. A graph is shown in Figure 9. Again the air is sucked from the head space into the low pressure region behind the rotor blades where it is dispersed in the high shear flow between the tips of the rotor blades and the stator.

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Biography Sketch

Andreas Lübbert studied Physics at the Technical University Hannover, Germany. His doctoral theses he wrote at the same University under the guidance of Professor Karl Schügerl about elementary chemical reactions. He received his *venia legendi* for the subject 'Technical Chemistry' at the University

of Hannover, Germany. Since 1980 he worked on biochemical engineering subjects. In 1995 he followed a call on the Chair of Bioprocess Engineering at the Martin-Luther-University Halle-Wittenberg, Germany