Fluid Mixing Variables in the Optimisation of Fermentation Production*

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This paper explores the practicable possibilities that mixers have of enhancing the gas liquid oxygen transfer and what that means in terms of productivity of a given fermenter. The objective of the paper is to give some guidance to the rational evaluation of different mixer variables in a fermentation process.

Introduction

Aerobic fermentation is very sensitive to the role that fluid mixers play, since they are involved in a variety of important steps. One of these steps is the gas-liquid mass transfer step, since it supplies the basic respiratory mechanisms.

However, the additional effects of fluid mixing shear rates on the process involves its effect on the viability of the solid micro-organisms, and their ability to respirate and to use the oxygen efficiently in their growth process.

The basic premise of this paper is to explore the practical possibilities that mixers have of enhancing the gas-liquid oxygen transfer step and what that means in terms of productivity of a given fermenter, as well as affecting other features of the process.

Basic mass transfer premise

There is no way that the mixer can transfer oxygen from gas to liquid any faster than the solid micro-organisms can utilise the oxygen in their growth process. If the mixer is capable of supplying the oxygen faster than the organisms can use it, the main effect will be to increase the dissolved oxygen level, C, to balance out the mass transfer equation, $O.U.R. = K_L a\ (C^* - C) = K_s\ (C - C_s^*)$ and the dissolved oxygen level may or may not have an effect on the growth process. O.U.R. is the oxygen uptake rate of the organisms.

On the other hand, if the organism can utilise oxygen faster than the aerator can provide it, the dissolved oxygen will tend toward zero, although this may affect the resulting oxygen demand of the organism and bring the two rates even more closely into balance.

It is normally helpful to break the fermentation process down into several distinct steps and examine the role that mixing plays in these various steps. Then, we can examine the total effect on the process result from the combination of these different steps.

One of the first requirements is to get a measure of the effectiveness of the existing mixer in the process. This paper takes the perspective that there is an existing full scale fermenter that is carrying out a certain process. The basic questions covered here are: (1) what is the role of mixing in this particular process, (2) what are the possible advantages and disadvantages of increasing the mass transfer ability of the agitator to take advantage of the maximum potential of the present strain of micro-organism in the process, and (3) what is the potential advantage of providing a mixer that will provide adequate mass transfer for both an increased productive strain at the same cell concentration, or will provide proper oxygen mass transfer at an increased cell concentration.

In looking at the performance of a mixer in a tank with a particular starting concentration of micro-organisms, it is possible to determine the kinetics of the antibiotic production which produces the growth of the micro-organisms throughout the batch process.

Typical data, shown in Figs 1 and 2 show the change in dissolved oxygen, dissolved CO_2, and total yield of the desired antibiotic.

One factor that can add considerable confusion to the analysis is the observation that under-stimulation or over-stimulation of the growth rates of micro-organisms in their initial and log growth phase, can change their ability to produce antibiotic at the maximum yield point in the cycle and affect the ultimate total yield obtained at the end. It is entirely possible, that by increasing the mass transfer rate available to the fermentation, that it can have a detrimental effect on total yield because it changes the metabolic situation in the organisms during the first few hours of fermentation, which affects their ultimate potential for total yield.

This effect must be carefully distinguished in analysing the use of a higher mass transfer ability agitator, which can take advantage of increased respiration requirements of new improved strains or higher cell concentrations during the total cycle.

It is also common that fermentations made in different parts of the world, although supposedly somewhat similar, because of inherently different conditions of processing, can give different results in equipment that is quite similar.

The use of higher mixer mass transfer abilities can be examined in two ways:

(1) What effect does it have on a given type and concentration of starting seed, which includes bio-mass growth rates and total yield, and

(2) what effect does it have on production from a new, more productive strain or an increased initial seed concentration.

Fig. 3 shows that yields can be different from different fermenters and indeed, in different plants around the world at different mass transfer rates. Fig. 4 shows that the yield rate can also decrease if the increased mass transfer ability is used improperly.

It is also helpful to distinguish between the

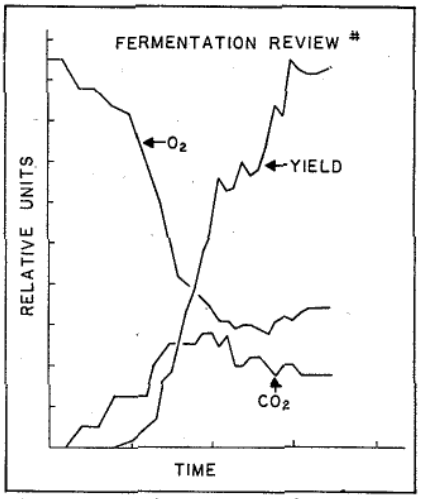

Figure 1. Typical path of batch fermentation.

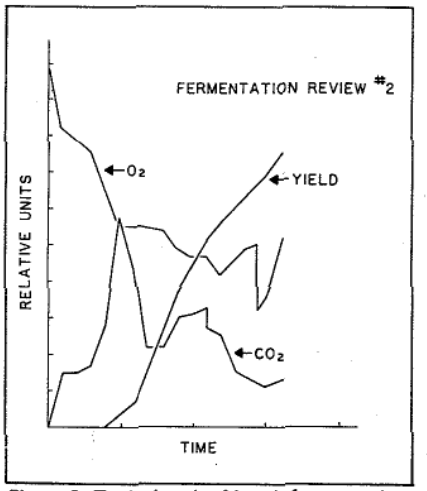

Figure 2. Typical path of batch fermentation.

Nomenclature

C^*	Equilibrium dissolved oxygen level corresponding to partial pressure in gas phase
C	Dissolved oxygen level
O.U.R.	Oxygen Uptake Rate
$K_L a$	Gas-liquid mass transfer rate
MJ	Mega Joule
D	Impeller diameter
T	Tank diameter

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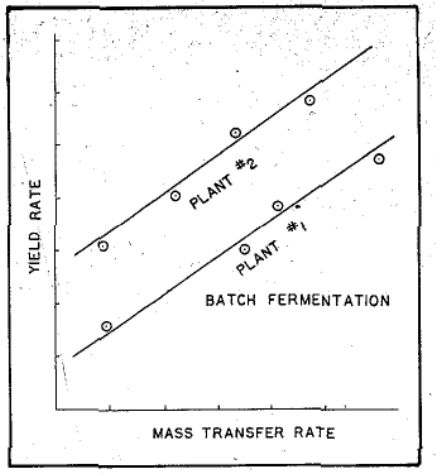

Figure 3. Fermentation yield rate for two different plant locations.

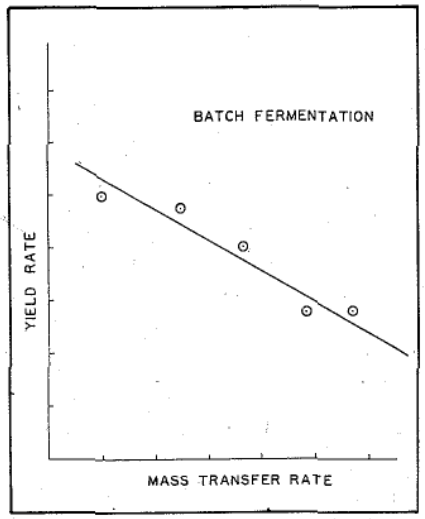

Figure 4. Illustration that mass transfer rate increase can sometimes decrease fermentation yield rate.

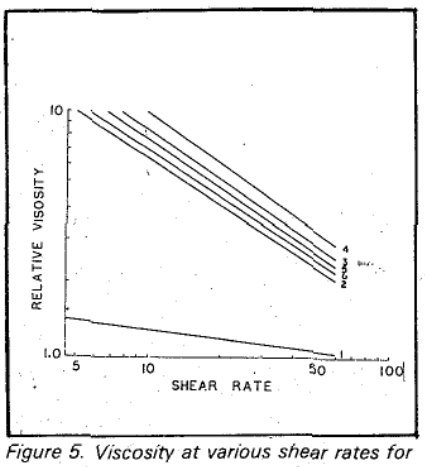

Figure 5. Viscosity at various shear rates for various days in fermentation cycle.

total yield of a process and the yield rates at various parts of the process.

The yield rate allows us to examine in more detail on occasion the role of mixing in the actual situation at an actual point in time.

The role of cell concentration on *mass transfer rate*

Within a given batch run, the cell concentration changes as a function of time. In addition, the viscosity goes up with cell concentration at each point on the time curve of a fermenter. Figs 5 and 6 give typical data showing the change in viscosity as a function of the number of days of fermentation for different kinds of systems.

On the other hand, Fig. 7 shows the change in mass transfer rate with viscosity largely governed by a change in cell concentration of the total process. It is true that the costs of oxygen transferred per MJ go down as the cell concentration goes up. However, this cost must be balanced against the increasing productivity of a given dollar investment in the fermentation tank, piping and total plant cost. Analysis needs to be made of the role that mixer cost, including both capital and power, plays in the total productivity cost in order to evaluate desirability of going in this direction.

A previous paper by Ryu and Oldshue[4] treated an example where the final cell concentration was changed from 10 to 12 to 20g/ℓ, and the oxygen mass transfer dropped from 10 to 8.3 to 6.4 mols oxygen/MJ.

Looking at Table 1, we have listed the cost of electrical power and other essentials. We have used a capital cost of $900/kW of installed mixer capacity, including the associated blower and air supply, and including the installation of the equipment, including the electrical hookup. This is for a D/T ratio of 0.37.

Electrical power is assumed at 0.5c/MJ. Equipment energy efficiency is 0.9. Wire electrical cost is 0.7c/MJ. We are amortising the equipment, using present worth over a 5 year period, which results in a figure of 0.8c/MJ. Total cost of the equipment is therefore 1.5c/MJ. The cost of dissolving oxygen is 0.15c/mol/O_2 dissolved at 10g/ℓ. At 20g/ℓ, it is 0.23c/mol/O_2 dissolved cell concentration.

We have assumed that it takes 200 mols of oxygen to produce 1kg of product. We are also using a production cost of $60 total per kg of product. The percent cost of oxygen in the dilute system is approximately 0.7% of the total production cost. We are also assuming in this example that there is a fixed cost of $30/kg which does not change with the agitator, and that the variable fermentation cost goes down as the productivity of the particular tank in process increases (Table 2).

This is listed in Column A. Column D is given from the results of the paper by Ryu and Oldshue, which used a 500hp mixer operating at 20g/ℓ. While the percent of cost due to the mixer has increased, the total production cost per kg of product has gone down 25% to a value of approximately $45.2/kg.

Let's say that this higher power mixer, having a maximum impeller zone shear rate 30% higher than Case A, decreased the growth ability of the micro-organisms due to increased shear on these particles, changing the floc structure, etc. Let's say that this cut the production of penicillin to 90% of the

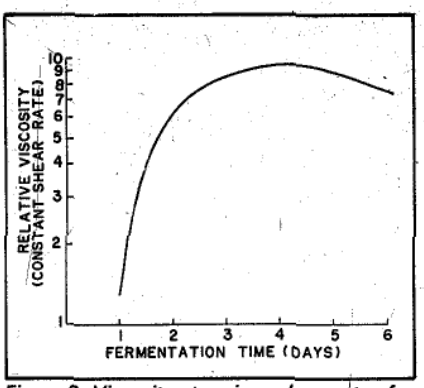

Figure 6. Viscosity at various shear rates for various days in fermentation cycle.

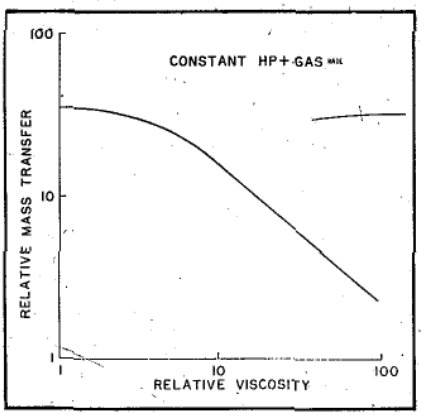

Figure 7. Decrease in mass transfer rate with viscosity for a given mixer and air rate.

value it could have had based on cell concentration only. This means that we now are producing less product than Column D would indicate, and the production costs have gone up to $46.7/kg (Case E), because we are not able to use all the additional capacity of the larger aerator. You notice that the aerator has given us the ability to transfer 1.1 mols/O_2/ℓ/hr, in contrast to the 200hp unit value of 0.7 mols O_2/ℓ/hr.

Assume that studies in the laboratory indicate that if we cut the shear rate down to where it is only 15% higher than case A, that the organism retains its growth potential. This mixer in case F has a D/T ratio 40% higher and therefore, instead of $900/kW, costs $1200/kW, including the associated blower. Putting this into the cost example, even though it changes drastically the initial cost of the equipment, the productivity is improved to the point that the actual production cost is approximately $45.2/kg as it was in case D.

If studies indicate that the shear rate has to be cut back to the same as it was in Case A, this means the mixer cost is now $1,575/kW because of the increased torque and D/T, and it does raise the production cost up to $45.3 (Case G), but is still a very small percentage of the total production cost, and

Table 1 Cost of mixing for production of antibiotics
(Based on Oxygen Transfer Rate)

Cost of electrical power:	0.7c/MJ
Equipment cost (expressed as power cost):	0.8c/MJ
Efficiency of oxygen mass transfer: Dilute system	10 Mols O_2/MJ
Power and equipment cost:	1.5c/MJ
Cost of dissolved oxygen: 20g/ℓ	0.23c/Mol O_2
Production cost of antibiotics	46c/kg Product
Fractional cost for mixing (antibiotics production):	0.6-1.6% of Production Cost
Production yield:	1kg/200 Mols O_2

Table 2

	Original Low Power Mixer (A)	(D)	New High Power Mixer (E)	(F)	(G)
Agitation Power (kW)	150	380	380	380	380
Aeration Power (kW)	37	95	95	95	95
Relative Product Yield (arbitrary units)	100	200	180	200	200
Cell Concentration (gram/litre)	10	20	20	20	20
Oxygen Uptake Rate (gram-O_2/litre/hr)	0.5	1.0	0.9	1.0	1.0
Maximum Available Oxygen Transfer Rate (gm-O_2/litre/hr)	0.7	1.1	1.1	1.1	1.1
Fixed Fermentation Cost ($/kg)	30	30	30	30	30
Variable Fermentation Cost ($/kg)	30	15.2	16.67	15.16	15.34
Total Production Cost ($/kg of Product)	60	45.2	46.7	45.16	45.34
Cost of Oxygen Transfer Operation (Mixing Equipment and Power) ($/kg)	0.42	0.52	0.57	0.58	0.72
Present Cost of Oxygen Transfer Operation	0.7	1.1	1.2	1.3	1.6
Present Cost Savings		25.0	22.0	25.0	24.5
Maximum Impeller Zone Shear Rate (Relative)	1.00	1.30	1.30	1.15	1.00

is a very small percentage in terms of mixer cost of the total production.

The main point here is that in this particular example, mixer horsepower and capital cost can effect tremendous changes in productivity because of their low cost in terms of the total cost.

Just how we assess the role of shear rate in the fermentation process is the subject of the next section.

Other typical cost examples can be worked out to evaluate performance of other products.

The role of fluid shear rate in micro-organism growth

There are a variety of shear rates in the mixing tank. We list only 4 out of an infinite possibility, and call attention to 2 different scales in which these 4 shear rates operate, Table 3.

Table 3 Impeller areas in the tank for shear rates

AVERAGE POINT VELOCITY

MAX IMP ZONE SHEAR RATE
AVE IMP ZONE SHEAR RATE
AVE TANK ZONE SHEAR RATE
MIN TANK ZONE SHEAR RATE

RMS VELOCITY FLUCTUATIONS

$$\sqrt{\overline{(u')^2}}$$

On a macro-scale, which is involved with the shear rate between the average point velocities in a fluid stream, we're concerned with the maximum impeller zone shear rate, the average impeller zone shear rate, the average tank zone shear rate, and the minimum tank zone shear rate.

In contrast, micro-scale shear rates involve the shear rates between the actual fluctuating velocities themselves, and operate on a scale from several hundred microns and lower.

In the paper by Oldshue[3], 'Spectrum of shear rates in a mixing tank', some of the ramifications of this situation are discussed. One way to evaluate their effect is to carry out a controlled series of experiments. We take a series of impellers and by varying the geometry of the impeller blades, thereby vary the relative proportion of the various kinds of shear rates in the process. Taking only 3 of these many kinds of shear rates, the maximum impeller zone shear rate (macro-scale), the average impeller zone shear rate (macro-scale), and the average tank zone shear rate (micro-scale), we evaluate those in a series of experiments shown in Table 4. By evaluating the effect of each of these different runs on the fermentation process, we can begin to get a feel for the effect of these three important shear rate levels in the process. It also is possible to look into other shear rate ratios, but this example will suffice to give the general idea.

The main point is that large fermenters tend to have higher shear rates and lower pumping capacities than do small scale models. Therefore, experiments done on small scale to evaluate the potentialities of large scale equipment must be very carefully designed so that they do not seriously modify the ratio of impeller blades to scale of the process under observation.

When this sort of data is used to evaluate the potential effect of 500 to 5,000hp mixers, there obviously has to be a degree of judgment and caution used. The larger the scale that these kinds of experiments can be conducted on, the better information given. This is one of the uses to which variable speed flexible geometry experimental fermenters in full scale tanks can be extremely useful in predicting performance of larger units full scale.

Some other mass transfer considerations

The desorption of CO_2 is an essential part of effective fermentation. The pressure and liquid depth that enhances absorption of oxygen discourages the desorption of CO_2. Tall, thin tanks with the same volume of air, yielding a higher superficial velocity, normally give more lbs of oxygen transfer per total horsepower of mixer in air than do short, squat tanks. There also is less absorption of CO_2 under the same conditions. Therefore, some idea of the role of CO_2 desorption rates, back pressure of CO_2 and other things must be obtained in order to evaluate this particular phenomenon. In addition, the fluid mixing pattern in the fermenter must be considered. As broth becomes more viscous, and tanks become taller, more impellers are used and there is a possibility of much longer top to bottom blending times being involved which do affect the dissolved CO_2 oxygen level throughout the entire system. In general, the dissolved CO_2 oxygen level will assume some value intermediate between the values that would be predicted based on concentration driving forces at the bottom and the top due to the gas stream.

Some mixing effects on gas-liquid mass transfer processes

In a paper published by Oldshue and Connelly[5], the effect of D/T ratio in mass transfer was explored. In general, it shows that the ratio of mixer power level to gas power level is extremely important. In addition, it is possible to have a gas controlled fluid regime in contrast to a mixer controlled fluid regime. Table 5 and Figs 8 and 9 illustrate the difference in flow pattern between low power level and high power level at a given gas rate. The main problem is

Table 4 A typical pilot plant program to evaluate various kinds of shear rates

Shear rate			Impeller		
Max	Avg	Floc	D	N	Dω/D
1.0	1.0	1.0	1	1	S
1.3	1.8	1.0	0.7	1.8	S
1.3	1.3	1.0	1	1.3	N
1.0	1.0	0.5	1	1	N
1.0	1.3	0.7	0.8	1.3	S

Table 5

DW	Blade Width
D	Impeller Diameter
MJ	Mega Joule
N	Speed
MAX	Maximum Impeller Zone Shear Rate
MIN	Minimum Impeller Zone Shear Rate
Fluc	Driving Turbulent Shear Rate

that the mass transfer correlations are different in these two areas.

In Fig. 10, the optimum D/T ratio is shown for various combinations of mixer power and gas power, and has placed in it the typical D/T range for large scale industrial fermentations. This illustrates another fact, that we don't always design a mixer with the optimum of any one particular variable. In other words, the optimum geometry for gas-liquid mass transfer would probably turn out to be disastrous in terms of shear rate and blending for relatively fragile mycelial type solids. On the other hand, if we have a bacterial fermentation which shear rate does not seem to be a particularly important factor, then we can design more closely toward the optimum ratio for gas-liquid mass transfer.

Physical appearance of the surface of the tank is often the only thing that can be seen. Two different criteria were used, one the geysering of gas bubbles escaping to the surface, and the other, the diameter of the swell of a gas controlled flow pattern. Figures from this article show the kind of data that is typical, and also show that a high shear low pumping capacity impeller is inferior to high flow low shear rates for this particular

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phenomenon. This is completely independent of the optimum criteria for gas-liquid mass transfer, and it is necessary to distinguish carefully between those processes and those effects which are governed by fluid shear rates, compared to those processes which cover other types of mixing phenomena.

Summary

The main objective of this paper is to give some guidelines to the rational evaluation of different mixer variables in a fermentation process. Gas-liquid mass transfer is only important if the process needs more of it. Fluid shear rates and pumping capacities are only important if they have effect on the growth potential of the system.

Oxygen transfer to organisms in their initial growth phase as compared to their mature growth phase can have peculiar effects and must be carefully evaluated to determine the optimum total performance. Seemingly small differences in the details of a process, such as equipment, water quality, food supply, and other variables in different parts of the world can make seemingly identical fermenters behave differently.

Normally, the investment in mixer power and capital can pay large dividends in optimising the productivity of a given fermentation plant with a given set of tanks and other conditions.

Pilot planting can be done to determine the basic level of oxygen mass transfer performances while setting up the overall effect of shear rates and pumping capacities in the system.

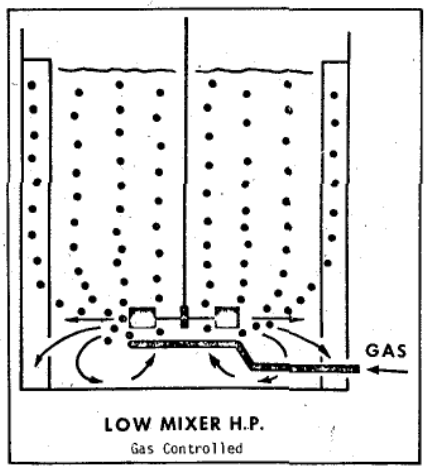

Fig. 8. Illustration of gas controlled flow pattern.

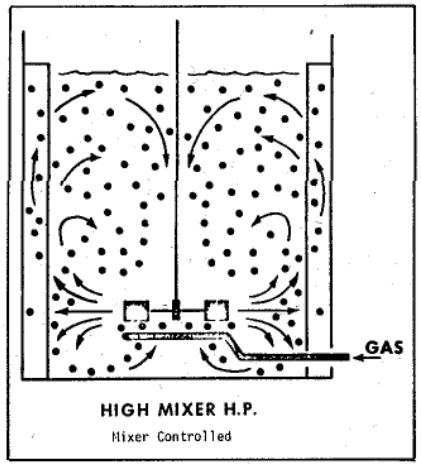

Fig. 9. Illustration of mixer controlled flow pattern.

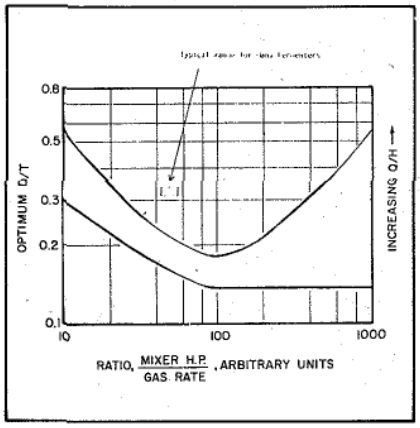

Fig. 10. Optimum D/T ratio of gas-liquid mass transfer, including typical aerator for mycellial fermentation.

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