Piloting Bioreactors for Agitation Scale-Up

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This article offers guidance on
how to design appropriate experiments
to measure scalable data for agitation
in both aerobic and anaerobic bioreactors.

Laboratory and pilot-plant fermenters are typically operated with the primary purposes of evaluating the microbiology and biochemistry to determine such things as optimum temperature, pH, nutrient composition, biomass loading and feeding strategy. Often, agitation is not considered to be a critical part of the study, other than to make sure that it is adequate. The result is that the pilot-scale agitation conditions are usually quite different from those at full scale. In addition, not enough independent study is done to provide scalable relationships between agitation and results. This article addresses these issues and describes methods for gaining scalable data and relationships, both for aerobic and anaerobic bioreactors.

Aerobic bioreactors

In these reactors, the primary agitation criterion is generally the mass transfer capability. Liquid mixing can also become important in larger bioreactors (working volume greater than 20,000 L). The chief determinants of the mass-transfer coefficient ($k_l a$) in a mechanically agitated, aerobic bioreactor are the agitator specific power (power/volume, P/V) and the superficial gas velocity (U_s), which is the gas flow divided by the tank cross-sectional area.

In most pilot reactors, the operating conditions have a much higher P/V and much lower U_s than is typical of full-scale equipment. Table 1 illustrates a sample set of variables as a function of scale, for a nominal oxygen transfer rate (OTR) of 200 mmol/L-h. This table is not designed to represent a specific set of experimental data. Instead, it is calculated based on "average" air-water correlations, and is intended to show how the P/V and U_s will tend to vary upon scale-up if effort is not made to control this variation. The correlation used is shown later as Eq. 1.

Most full-scale fermenters have a P/V level of about 1–3 W/L, while many pilot fermenters have a P/V in the range of 5–10 W/L. Mass-transfer relationships are generally only accurate to within ±30%, and only within the range of variables studied. It is not usually safe to extrapolate by much.

Likewise, there are differences in U_s. Many full-scale fermenters fall in the range of 0.03–0.09 m/s, while the pilot-scale value is usually below 0.02. In Table 1, some values are much less.

Although many think of airflow in terms of volume of air under standard conditions per volume of liquid per minute (VVM), it is not the proper scaling parameter for $k_l a$. Most production bioreactors have a VVM rate in the 0.5–1.5 range. However, to match full-scale U_s, the pilot VVM may need to be more than 10.

Table 2 illustrates the pilot conditions necessary to model the 150,000-L unit in Table 1. Since $k_l a$ depends on P/V and U_s, we would scale down keeping these the same to model $k_l a$ at the pilot scale. The result is a required VVM rate ranging from about 5 to 30, depending on the pilot scale. These observations lead to certain principles for piloting aerobic bioreactors.

Correct piloting principles

Because of the need to avoid extrapolation, the pilot studies for mass transfer should employ runs with the same range of P/V and U_s as full scale. This means lower agitator shaft speed and higher airflow than typical pilot studies. Combinations of high airflow and low rpm may pose a danger of flooding the impeller, so this should be checked. The pilot air supply and sparge system may need to be modified for the higher-than-normal airflow.

Steps to good pilot protocol

The principles can be organized into four steps:
Step 1. Start with an estimated $k_l a$ correlation.
If any pilot data are available and sufficient to fit a mass-transfer correlation to them, use these for the preliminary full-scale design, even if the variable values are differ-

ent from full scale. It at least is a place to start. If no such data are available, use data or correlations for similar systems, either from published sources or available internally.

One such correlation for an ionic air/water system is:

$$k_l a = 0.95(P/V)^{0.6}(U_S)^{0.6} \qquad (1)$$

Step 2. Estimate a reasonable full-scale design by calculating airflow and power at the full scale to give the required OTR.

a. Start with the peak oxygen-uptake-rate (OUR) requirement and assume that the OTR must match it.

b. Set the airflow based on 50% oxygen transfer. This is based on the author's experience that the lowest total power consumption (agitator plus compressor) occurs roughly at this condition. 1 ft^3 of air at 60°F and 1 atm pressure contains 1.2 g-mol of gas or 0.25 g-mol of oxygen. Similarly, 1 normal m^3 contains 44.06 g-mol of gas.

c. Calculate a mass balance and determine the mass-transfer driving force.

d. Solve the $k_l a$ correlation for agitator power.

e. Now an approximate full-scale P/V and U_s are known.

Step 3. Design a series of pilot runs using shaft speeds and airflow rates to bracket the values of P/V and U_s calculated for the full-scale design of Step 2.

a. Calculate the pilot airflow based on using the same U_s as full scale.

b. Calculate the agitator speed to give the same P/V as full scale.

c. Prepare an experimental plan or grid of values that go above and below the values calculated in Step 2 by at least factors of 0.5–2 for airflow and 0.75–1.3 for agitator speed. This will give a 4:1 range on both U_s and P/V.

d. Check for impeller flooding and eliminate flooded runs. To avoid flooding, limit the maximum aeration number, Qg/ND^3, to $K(N^2D/g)(D/T)^{3.5}$, where the correlation

constant, K, is 30 for a Rushton turbine, 70 for a 180-deg. concave turbine (such as the Chemineer CD-6), and 170 for the Chemineer BT-6.

Several incomplete studies have suggested that the maximum aeration number for concave turbines increases faster than linearly as a function of the Froude number, N^2D/g, so the above flooding relationship may be conservative for such turbines in some cases. This article does not address the effect of viscosity on flooding. If the viscosity exceeds 100 cP, consult other sources or visually check for flooding.

Some runs with combinations of low rpm and low gas flow may not provide sufficient OTR for the organisms to thrive at full biomass concentration. Yet, data are needed for full-scale design. There are several tactics to cope with this problem. One is to reduce the biomass. Sometimes this can be done by taking the data for such runs in the early stages of a fermentation, while the organism growth is just beginning. Another method is to increase the back-pressure at equal actual airflow. This provides higher mass transfer for a given superficial gas velocity. However, it also increases the concentration of CO_2 in the liquid and the off-gas, which may be a problem for some organisms. A third method is to use an oxygen-enriched feed gas. While expensive, it may be useful if the other methods do not work.

Step 4. Fit a correlation to the new data.

With good measurements of driving force, OTR and other parameters, it is now possible to correlate the data. The most common correlation takes the form:

$$k_l a = A(P/V)B(U_s)C \qquad (2)$$

although other forms may also be used. Typically, the data fit is ±30%. This new model may be used for full-scale design and optimization. However, a reasonable safety factor should be applied both to P/V and U_s to allow for experimental error and possible process changes in the future.

Anaerobic bioreactors

In aerobic bioreactors, the effect of agitation is obvious due to the effect on bubble size and holdup. In anaerobic fermentation, however, the reason the effects of agitation extend

Table 1. Pilot/full-scale variable range for an OTR of approximately 200 mmol/L-h.

Scale	Volume, L	U_S, m/s	P/V, W/L	VVM
Pilot	1	0.0065	9.8	3
	5	0.009	7.1	2.5
	20	0.011	6.1	2
	100	0.015	4.5	1.6
	300	0.019	3.9	1.4
Production	5,000	0.032	2.4	0.96
	20,000	0.044	1.8	0.85
	150,000	0.064	1.3	0.68
	350,000	0.074	1.1	0.62
	1,000,000	0.091	0.88	0.57

Table 2. Pilot conditions to model a 150,000-L bioreactor.

Volume, L	U_S, m/s	P/V, W/L	VVM
1	0.064	1.3	30
5	0.064	1.3	17.8
20	0.064	1.3	11.3
100	0.064	1.3	6.7
300	0.064	1.3	4.67

beyond those on solids suspension is not fully clear. Yet, it certainly does. For example, one study found that agitation affected the rate of production, yield and maximum product titer in an ethanol fermentation using sugar and *Saccharomyces Cervisiae*. When the results were plotted against. *P/V*, the improvement did not level off until *P/V* exceeded 1.6 W/L, which is a very high value for ethanol fermentation.

It would be preferable to scale up agitation from anaerobic processes based on a fundamental understanding of the mechanism by which agitation affects results. Lacking this, we must resort to empirical studies.

One way to do this is to conduct experiments at two scales, using geometric similarity for the vessels and the agitator impellers. The only thing that can be varied is the agitator speed, which can be varied until the results are matched at both scales. Then, a scaling rule can be created using $N_2/N_1 = (1/R)^n$, where R is the geometric scale ratio and n is the scaling exponent. Sometimes the value of n corresponds to a derivable physical relationship. For example, a value of 1 corresponds to equal tip speed, equal torque/volume and equal fluid velocity. A value of 2/3 corresponds to equal *P/V*.

If two scales are not available, the scaling method can sometimes be inferred by using impellers of two different sizes or even two different types in subsequent tests in the same vessel. The different impellers should be operated to give equal results; for example, it may be found that equal results are obtained at equal impeller tip speed, equal *P/V*, equal average fluid velocity or equal blend time. The parameter that gives equal results in one scale can then be used as the basis for scale-up.

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