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A GAIN-SCHEDULING APPROACH FOR CONTROL OF DISSOLVED OXYGEN IN STIRRED BIOREACTORS

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Abstract: This paper discusses control of dissolved oxygen in a bioreactor when the stirrer speed is used as control signal. During batch and fed-batch cultivations the operating conditions change significantly which causes tuning problems, especially when performance requirements are high. A linearized process model reveals that the variations in the oxygen dynamics are mainly due to changes in the volumetric oxygen transfer coefficient $K_L a$. To account for the process variations, a control strategy based on PID control and gain scheduling from the stirrer speed is suggested. Controller parameters in different operating regions are obtained using auto-tuning experiments. The approach is easy to implement and does not require any exhaust-gas analysis. Experimental results from a laboratory reactor are presented. *Copyright © 1999 IFAC*

Keywords: Dissolved oxygen control, bioreactor, gain scheduling, auto-tuning.

1. INTRODUCTION

Today, many commercial products are produced using microorganisms. Living cells are grown to large numbers and made to produce a desired substance, often a protein. The cells are kept in a bioreactor where several control loops ensure that important process parameters, such as pH and temperature, stay within specified operating conditions. In aerobic processes, it is also important to provide the culture with oxygen. A simple way to supply enough oxygen is to keep a constant dissolved oxygen concentration. It is often sufficient to maintain the dissolved oxygen concentration above a certain level, and the performance demands on the dissolved oxygen control are then moderate. In some applications the performance requirements are higher, for instance when elevated oxygen levels are toxic for the microorganisms. High-performance control of dissolved oxygen is a key element in the substrate feeding strategy presented in

[Åkesson, 1998]. Tight control may also be beneficial for process supervision as the control input then can be used as an indicator of the biological activity, see for instance [Lee et al., 1996].

In a stirred bioreactor, dissolved oxygen can be controlled in many ways; by manipulating the air flow rate, the oxygen content in the incoming air, the reactor pressure, or the stirrer speed. We will here consider the case where the stirrer speed is used as control signal. The oxygen dynamics may vary significantly during cultivations in batch and fed-batch mode. This variation may cause tuning problems when controllers with fixed parameters are used and high performance is desired. To address this problem, a control strategy based on PID control and gain scheduling from the stirrer speed is suggested. The major advantages with the proposed approach is that no exhaust-gas analysis is required and that it is straightforward to implement in an industrial control system.

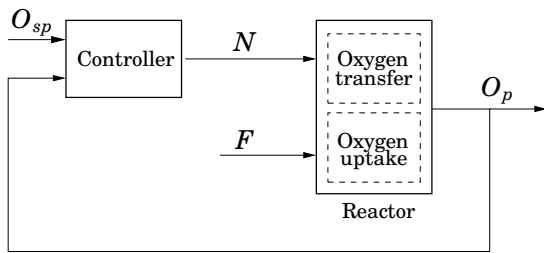


Fig. 1. Dissolved oxygen control loop where the dissolved oxygen signal O_p should be kept at the set-point O_{sp} . By manipulating the stirrer speed N the oxygen transfer to the reactor can be varied. In fed-batch and continuous cultivations, the oxygen consumption depends on the substrate feed rate F .

2. CONTROL PROBLEM

From a control point of view, dissolved oxygen control is a regulation problem where the main disturbance is the oxygen consumption due to cell metabolism, see Figure 1. In continuous and fed-batch cultivations, this disturbance is strongly correlated to the substrate feed rate. Apart from the microbial oxygen consumption, other disturbances affecting the process include temperature changes, foaming, and addition of surface active components. At low turbulence levels, gas bubbles at the surface of the dissolved oxygen sensor may give significant sensor noise [Heinzle et al., 1986]. Classification of different disturbances has been used to derive a rule-based control strategy [Yano et al., 1981].

Process variations

In continuous cultivations, the process is operated at steady-state and good performance can be expected using controllers with fixed parameters, see for instance [Clark et al., 1985]. When the reactor is run in batch or fed-batch mode, however, the process characteristics vary significantly with important process variables like cell mass, substrate concentration, and oxygen uptake. Many authors have reported tuning difficulties when controllers with fixed parameters are used, see [Court, 1988; Lee et al., 1991; Cardello and San, 1988]. Typical observations are stability problems for low oxygen uptake rates, that is, low stirrer speeds, and sluggish control at high oxygen uptake rates. Similar difficulties occur in dissolved oxygen control of activated sludge processes in wastewater treatment, where the air flow rate is used as control signal [Lindberg, 1997].

To overcome the problems with the varying process dynamics, various adaptive control schemes have been suggested. Approaches based on PID

control together with gain scheduling from the oxygen uptake rate and PID control combined with feed-forward from the oxygen uptake rate were presented in [Cardello and San, 1988]. On-line tuning of PID controllers based on output variance [Lee et al., 1992] and parameter estimation from off-gas analysis [Levisauskas, 1995] have also been suggested. Indirect adaptive control, that is, parameter estimation and subsequent controller design, have been tested in [Lee et al., 1991] and [Hsiao et al., 1992].

Feed forward

In fed-batch and continuous cultivations, the main disturbance is strongly correlated to the substrate feed rate. Feed-forward action from the feed rate could then be used to improve the control performance. A complication is that the dynamic relation between feed rate and stirrer speed often is poorly known, however, an approximate static relation can be obtained from recorded process data.

3. PROCESS MODEL

In this section a model of the dissolved oxygen dynamics in a laboratory scale bioreactor is derived. It is assumed that well-mixed conditions apply and that any mechanical or electrical dynamics from control signal to stirrer speed are negligible. The parameters in the model are adjusted using experimental data from a 3 liter reactor.

Mass-balance for the dissolved oxygen in the reactor yields the following differential equation

$$\frac{d(VC_o)}{dt} = K_L a(N) \cdot V(C_o^* - C_o) - q_o V X$$

where V , C_o , and X , denote liquid volume, dissolved oxygen concentration, and cell concentration, respectively. The first term models the oxygen transfer from gas phase (i.e. air bubbles) to liquid. Here, $K_L a$ is the volumetric oxygen transfer coefficient which is dependent on the stirrer speed, N , and C_o^* denotes the dissolved oxygen concentration in equilibrium with the gas phase. The second term describes the oxygen consumption due to the biological activity. The specific oxygen consumption rate q_o is a function of the substrate uptake rate and hence it will depend on the substrate feed rate.

Contributions from incoming and outgoing flows have been neglected because the oxygen solubility in water is very low. Concentration changes due to dilution effects can for the same reason

be neglected so that the oxygen equation can be rewritten as

$$\frac{dC_o}{dt} = K_L \alpha(N) \cdot (C_o^* - C_o) - q_o \cdot X$$

In practice, most sensors do not measure the oxygen concentration but the dissolved oxygen tension, a quantity proportional to the oxygen partial pressure. A dissolved oxygen tension of 100 % corresponds to a solution where the oxygen partial pressure is in equilibrium with air, that is, an oxygen saturated solution. The dissolved oxygen tension O is related to the dissolved oxygen concentration through Henry's law

$$O = H \cdot C_o$$

where the constant H depends on the oxygen solubility, see [Popović et al., 1979] and [Pirt, 1975]. In the sequel, the common literature value for water $H = 14000 \text{ \% l g}^{-1}$ will be used. In a laboratory reactor it is also reasonable to assume that O^* is close to 100 %. The oxygen dynamics can now be described as

$$\frac{dO}{dt} = K_L \alpha(N) \cdot (O^* - O) - \underbrace{q_o \cdot H X}_{=d}$$

From now on, the oxygen consumption term will be considered as a load disturbance d .

For a fixed air flow rate, the volumetric oxygen transfer coefficient, $K_L \alpha$, can be modeled as a function of the stirrer speed, N . Commonly used expressions are of the form $K_L \alpha \sim N^\gamma$, for instance $K_L \alpha \sim N^3$ as suggested in [Pirt, 1975]. To obtain good mixing, the stirrer speed is in practice never below a minimum value. In the working range, it is then reasonable to approximate the stirrer dependence with a linear expression

$$K_L \alpha(N) = \alpha \cdot (N - N_0)$$

For the 3 liter laboratory bioreactor, $\alpha = 0.92 \text{ h}^{-1} \text{ rpm}^{-1}$ and $N_0 = 323 \text{ rpm}$ give a good approximation for stirrer speeds between 400 rpm to 1200 rpm. These values were obtained using the $K_L \alpha$ -estimation technique suggested in [Van't Riet, 1979] using exhaust gas analysis. Except for air flow rate and stirrer speed, the oxygen transfer is also affected by viscosity, temperature, foaming etc., [Pirt, 1975]. Addition of antifoam chemicals also tend to give a temporary decrease in $K_L \alpha$.

Dissolved oxygen tension is measured with a probe in the reactor liquid. As will be seen, the probe dynamics cannot be neglected. For large deviations, the probe tends to respond faster for up responses than for down responses [Lee and Tsao, 1979] and the sensitivity of the probe also increases with temperature. In large reactors,

where mixing problems cannot be neglected, the probe placement may be important for the oxygen control performance [Belfares et al., 1989]. For non-viscous and well-mixed systems the probe may be modeled as a linear first order system and possibly a time delay

$$T_p \frac{dO_p}{dt} + O_p(t) = O(t - \tau)$$

with O_p denoting the measured dissolved oxygen tension. However, for viscous systems and for low stirrer speeds, it may be necessary to add a second time constant, see [Dang et al., 1977]. Within the considered range of stirrer speeds, T_p and τ are approximately constant. For the probe used in the laboratory reactor a time constant of $T_p \approx 20 \text{ s}$ was estimated. The time delay was less than the data logging period of 2 s. In the sequel $\tau = 2 \text{ s}$ will be used.

Linearized model

Around an equilibrium point, the equation for the dissolved oxygen dynamics may be linearized as

$$\frac{d\Delta O}{dt} + K_L \alpha \cdot \Delta O = b \cdot \Delta N - \Delta d$$

where the parameter b is given by

$$b = (O^* - O) \frac{\partial K_L \alpha}{\partial N}$$

The transfer function from the stirrer speed ΔN to the oxygen measurement ΔO_p becomes

$$G_{on}(s) = \frac{b}{s + K_L \alpha} \cdot \frac{e^{-s\tau}}{1 + sT_p}$$

Under the assumptions made, τ , T_p , and b are approximately constant during a cultivation. The major process variation can be seen in $K_L \alpha$, which may very well change one order of magnitude. In this case, the process model predicts that $K_L \alpha$ varies from 0.020 s^{-1} to 0.224 s^{-1} when the stirrer speed increases from 400 rpm to 1200 rpm. Note also that b depends on the linearization point in dissolved oxygen, i.e., the chosen set-point.

4. ANALYSIS AND CONTROL DESIGN

The linearized process model gives valuable insight into the reported tuning problems. In Figure 2, a Bode plot of G_{on} at two different stirrer speeds illustrate how the process dynamics is affected by changes in $K_L \alpha$. When $K_L \alpha$ increases with the stirrer speed, the low-frequency gain decreases and the phase lag in the low- and mid-frequency region decreases as well. This explains the tuning difficulties for a

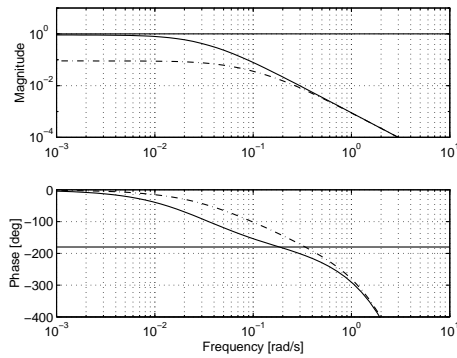


Fig. 2. Bode plot of the transfer function from stirrer speed to measured dissolved oxygen tension at 400 rpm (solid) and 1100 rpm (dash-dotted).

fixed controller, seen as stability problems at low stirrer speeds and sluggish behavior at high stirrer speeds.

It can also be seen that the high-frequency behavior is unaffected by the process variations. In principle a robust design can be obtained with a high-bandwidth controller, however, significant phase lead in the controller is then required. In practice such an approach would be prohibited by measurement noise. Hence, if a fixed controller is used there will be a trade-off between stability robustness at low stirrer speeds and achievable performance at high stirrer speeds. This can be illustrated by the following example.

Using the Kappa-Tau tuning method [Åström and Hägglund, 1995], two PID controllers are designed to work well at 400 and 1100 rpm respectively. Simulations of the closed-loop response to a step change in the substrate feed rate at 400 rpm and 1100 rpm are shown in Figures 3 and 4. The controller designed for 400 rpm behaves, as expected, well around 400 rpm but is unnecessarily slow at 1100 rpm. On the other hand, the controller designed for 1100 rpm gives an almost unstable closed-loop system when used at 400 rpm. Note also that it is possible to obtain a faster *and* more well-damped design at 1100 rpm where the process has less phase lag.

If stability in the presence of process variations is the most important objective, fixed controllers should be tuned for the lowest K_{La} that is expected, that is, at the lowest stirrer speeds. This gives a robustly stable closed-loop system at the expense of a sluggish response at higher K_{La} values. As pointed out in the previous section, the chosen set-point O_{sp} also affects the process behavior. If a large span of set-points are to be used this may also have to be accounted for.

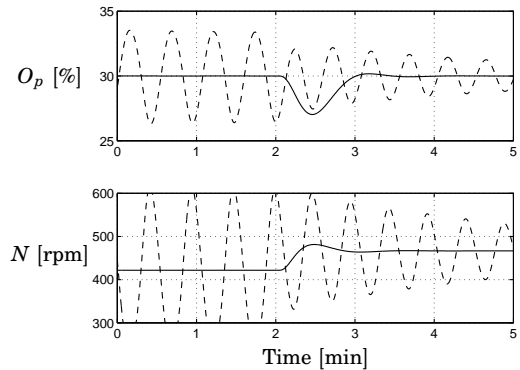


Fig. 3. Closed-loop simulation around 400 rpm. After two minutes, a load step change is made. Results with PID controller tuned for 400 rpm (solid) and 1100 rpm (dashed).

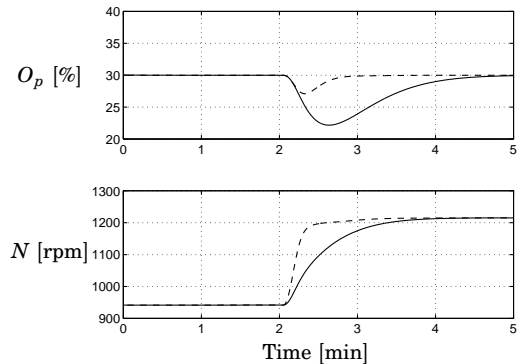


Fig. 4. Closed-loop simulation around 1100 rpm. After two minutes, a load step change is made. Results with PID controller tuned for 400 rpm (solid) and 1100 rpm (dashed).

5. A GAIN-SCHEDULING APPROACH

In order to obtain good performance at all operating points, without trading off robustness, the controller should depend on the operating conditions. The process dynamics changes with K_{La} , and this is a natural scheduling variable for adjustment of the controller parameters. However, this requires on-line estimation of K_{La} or a related quantity, for instance as in [Cardello and San, 1988]. As K_{La} is strongly correlated to the stirrer speed, a simpler approach is to use gain scheduling from the stirrer speed itself, a signal which is already available.

A direct way to obtain a suitable scheduling table is to first divide the working range for the stirrer speed into different operating regions, and then to obtain controller parameters in each region from automatic tuning experiments. This method is straightforward to implement in an industrial control system and it does not require any parameter estimation or exhaust-gas analysis. Furthermore, as automatic tuning is used, no *a priori* assumptions on the relation between K_{La} and the stirrer speed have to be made. A drawback is that changes in K_{La} due

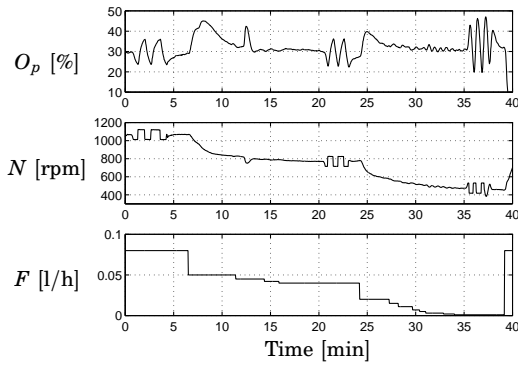


Fig. 5. Relay experiments at three different operating points. The load has been varied by changing the feed rate F .

to other sources than the stirrer speed, such as foaming and surface active compounds, are not captured. In processes where such effects are important, a method based on estimation of $K_L a$ would be preferable.

Experiments

The approach with gain scheduling from the stirrer speed was tested in a 3 liter laboratory bioreactor. The controller was implemented in the industrial control system SattLine (ABB Automation AB, Malmö, Sweden). A standard module for PID control with facilities for gain scheduling and relay auto-tuning was used. The control signal u is computed as

$$u = K(y_{sp} - y) + \frac{K}{T_i} \int^t (y_{sp} - y) dt - K T_d \frac{dy}{dt}$$

where y and y_{sp} are the process output and the set-point. The derivative term is low-pass filtered with a filter time constant of $T_d/6$ and a sampling time of 0.5 s was chosen. The working range for the stirrer was divided into three regions, and in each region controller parameters were obtained using the auto-tuner function during a fed-batch cultivation of recombinant *E. coli*, see Figure 5. The resulting controller parameters, see Table 1, confirm that a controller with lower gain and more phase lead is required at low stirrer speeds. They also indicate that the real process variation is more complicated than in the process model. In the mid region, the derivative time T_d was later changed to 1.0 s.

The obtained controller was tested in another *E. coli* cultivation and good disturbance rejection was achieved throughout the operating range. Load response experiments were made at the end of the cultivation, see Figures 6 and 7. At this stage, there was substantial foaming in the reactor and anti-foam chemicals, which affect the oxygen transfer, had to be added several times. The resulting disturbances were

Table 1. PID parameters for the laboratory reactor obtained from relay experiments.

Operating point	K	T_i	T_d
450 rpm	3.2 rpm/%	29.4 s	4.7 s
750 rpm	6.3 rpm/%	40.8 s	0.0 s
1050 rpm	6.8 rpm/%	61.2 s	0.0 s

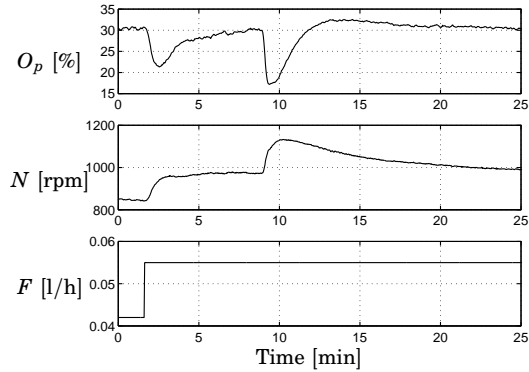


Fig. 6. Step load change followed by anti-foam addition at 9 min. At 920 rpm, the controller changed from mid to high operating region. The set-point O_{sp} was 30 %.

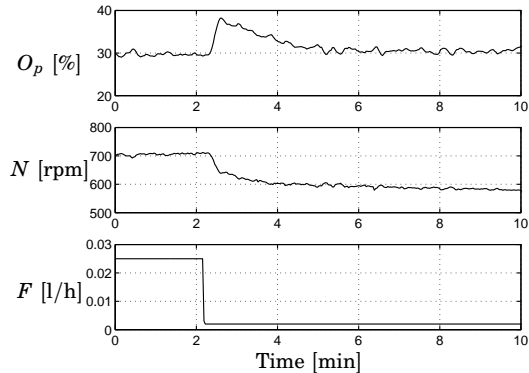


Fig. 7. Step load change in the lower part of the mid operating region. The low region was never entered. The set-point O_{sp} was 30 %.

also well handled but did take considerable time to eliminate completely, see Figure 6. At low stirrer speeds, excitation from sporadic disturbances, possibly due to air bubbles adhering to the sensor, was important, see Figure 7.

6. CONCLUSIONS

Control of dissolved oxygen in a bioreactor using the stirrer speed as control variable has been discussed. When high performance is required, process variations may cause tuning problems. A linearized process model reveals that the variations in the oxygen dynamics are due to changes in $K_L a$, the volumetric oxygen transfer coefficient. As $K_L a$ is strongly correlated to the stirrer speed, a control strategy based on PID control combined with gain scheduling from the

stirrer speed was suggested. No on-line parameter estimation or exhaust-gas analysis is required. A suitable gain schedule can be obtained in a straightforward way by dividing the working range for the stirrer into different operating regions, and then obtaining PID parameters in each region using auto-tuning experiments.

The control strategy was implemented using standard modules in an industrial control system and was tested during cultivations of *E. coli* bacteria. Good performance was achieved throughout the operating range — a substantial improvement compared to a fixed controller. Further improvements may be achieved by using more operating regions or changing the partitioning of the operating regions. The process model suggests that most of the process variation takes place at lower $K_L a$ values and that the partitioning of the operating regions should be denser in that range.

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REFERENCES

- ÅKESSON, M. (1998): "A probing strategy for substrate feeding in *Escherichia coli* cultivations." Licentiate Thesis ISRN LUTFD2/TFRT-3220--SE. Department of Automatic Control, Lund Institute of Technology, Sweden.
- ÅSTRÖM, K. J. and T. HÄGGLUND (1995): *PID Controllers: Theory, Design, and Tuning*, second edition. Instrument Society of America, Research Triangle Park, NC.
- BELFARES, L., M. N. PONS, and J. M. ENGASSER (1989): "Study of dissolved oxygen control parameters in multiturbine fermentors." In *Proceedings of the 1989 American Control Conference*, pp. 2430–2435. Green Valley, AZ, USA.
- CARDELLO, R. J. and K.-Y. SAN (1988): "The design of controllers for bioreactors." *Biotechnology and Bioengineering*, **32**, pp. 519–526.
- CLARK, T. A., T. HESKETH, and T. SEDDON (1985): "Automatic control of dissolved oxygen tension via fermenter agitation speed." *Biotechnology and Bioengineering*, **17**, pp. 1507–1511.
- COURT, J. R. (1988): "Computers in fermentation control: Laboratory applications." In BUSHHELL, Ed., *Progress in Industrial Microbiology*, pp. 1–45.
- DANG, N. D. P., D. A. KARRER, and I. J. DUNN (1977): "Oxygen transfer coefficients by dynamic model moment analysis." *Biotechnology and Bioengineering*, **19**, pp. 853–865.
- HEINZLE, E., J. MOES, M. GRIOT, E. SANDMEIER, I. J. DUNN, and R. BUCHER (1986): "Measurement and control of dissolved oxygen below 100 ppb." *Annals New York Academy of Sciences*, **469**, pp. 178–189.
- HSIAO, J., M. AHLUWALIA, J. B. KAUFMAN, T. R. CLEM, and J. SHILOACH (1992): "Adaptive control strategy for maintaining dissolved oxygen concentration in high density growth of recombinant *E. coli*." *Annals New York Academy of Sciences*, **665**, pp. 320–333.
- LEE, S. C., H. N. CHUNG, and Y. K. CHANG (1991): "Adaptive control of dissolved oxygen concentration in a bioreactor." *Biotechnology and Bioengineering*, **37**, pp. 597–607.
- LEE, S. C., C. G. KIM, Y. K. CHANG, and H. N. CHANG (1992): "Dissolved oxygen concentration and growth rate control in fed-batch fermentation process." In *Proceedings of 2nd IFAC Symposium on Modelling and Control of Biotechnical Processes*. Keystone, Colorado, USA.
- LEE, T. H., Y. K. CHANG, and B. H. CHUNG (1996): "Estimation of specific growth rate from agitation speed in DO-stat culture." *Biotechnology Techniques*, **10:5**, pp. 303–308.
- LEE, Y. H. and G. T. TSAO (1979): "Dissolved oxygen electrodes." In GHOSE ET AL., Eds., *Advances in Biochemical Engineering*, vol. 13, pp. 35–86.
- LEVISASKAS, D. (1995): "An algorithm for adaptive control of dissolved oxygen concentration in batch culture." *Biotechnology Techniques*, **9:2**.
- LINDBERG, C.-F. (1997): *Control and estimation strategies applied to the activated sludge process*. PhD thesis, Uppsala University, Systems and Control Group.
- PIRT, S. J. (1975): *Principles of Microbe Cell Cultivation*. Blackwell Scientific Publications.
- POPOVIĆ, M., H. NIEBELSCHÜTZ, and M. REUSS (1979): "Oxygen solubilities in fermentation fluids." *European Journal of Applied Microbiology and Biotechnology*, **8**, pp. 1–15.
- VAN'T RIET, K. (1979): "Review of measuring methods and results in nonviscous gas-liquid mass transfer in stirred vessels." *Ind. Eng. Chem. Process Des. Dev.*, **18:3**, pp. 357–364.
- YANO, T., T. KOBAYASHI, and S. SHIMIZU (1981): "Control system of dissolved oxygen concentration employing a microcomputer." *Journal of Fermentation Technology*, **59:4**, pp. 295–301.