Insights from Mathematical Modelling into Process Control of Oxygen Transfer in Batch Stirred Tank Bioreactors for Reducing Energy Requirement

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Abstract: Significant energy savings can be made in aerobic stirred tank batch bioreactors by the manipulation of agitator power ($P_{ag}$) and air flowrate per unit working volume ($v_{vm}$). Control is often implemented to maintain the oxygen concentration in the bioreaction liquid ($CO_{L}$) at a constant value. This work used model simulations to show that controlling the $P_{ag}$ and $v_{vm}$ continuously over time, such that it is operated at or near the impeller flooding constraint results in the minimum energy requirement for oxygen transfer (strategy $C_{min}$); however, this might prove impractical to control and operate in practice. As an alternative, the work shows that dividing the bioreaction time into a small number of constant $P_{ag}$ time segments (5–10), where a PID controller is used to control $v_{vm}$ to maintain $CO_{L}$ constant in each segment, can achieve much of the energy saving that is associated with $C_{min}$. During each time segment, $v_{vm}$ is increased and a sudden decrease in $CO_{L}$ is used to detect the onset of flooding, after which there is a step increase in $P_{ag}$. This sequence of $P_{ag}$ step increases continues until the bioreaction is completed. This practical control approach was shown to save most of the energy that is associated with $C_{min}$.

Keywords: process control; energy efficiency; oxygen transfer; batch stirred tank bioreactor; mathematical modelling

1. Introduction

In aerobic bioreactors, oxygen is critical for microbial activity and it can easily become rate limiting, thus continuous supply is required [1]. In aerobic batch stirred tank bioreactors, the oxygen uptake rate ($OUR$) of the micro-organisms will vary over the batch bioreaction time and an aeration system is required to supply a sufficient oxygen transfer rate ($OTR$) to satisfy the $OUR$ of the micro-organisms. This typically consists of an air compressor to provide air that enters as bubbles and a mechanical agitator that greatly improves the oxygen transfer rate ($OTR$). Many studies have shown how agitation and air flowrate influence $OTR$ and, in turn, influence cell growth and the production of metabolites [2–9].

For stirred tank aerobic bioreactors, the aeration system is energy intensive with energy being required for the air compressor and mechanical agitator. This represents a significant cost in aerobic bioreactors [10] and contributes to the environmental impact that is associated with the consequential carbon footprint of the bioreactors. When considering this, it is becoming increasingly important to reduce cost [11] and carbon footprint by using energy more efficiently. Proper equipment selection, such as the selection of impeller type and impeller dimensions [12–14], can reduce aeration system energy and associated costs and carbon footprint. Hydrodynamics will strongly influence the rate of oxygen mass transfer [15–18] in a given stirred bioreactor. The agitator mechanical power input ($P_{ag}$) and air volumetric flowrate ($F_{v}$) are under direct operational control and can be manipulated to
produce a volumetric mass transfer coefficient \( k_{La} \) that can provide sufficient OTR to meet the OUR. Reducing aeration system energy requirement can be achieved by optimal operation of \( Pag \) and \( F_c \) [12,19–21].

Process control can improve the performance of bioreactors [22–26]. The control of \( Pag \) and \( F_c \) is used to control the oxygen transfer rate in aerobic bioreactors. A commonly used practical control strategy is to measure the oxygen concentration in the bioreaction liquid and use this information to vary \( F_c \) and/or \( Pag \) throughout the bioreaction, so as to maintain the oxygen concentration close to a constant value. Many combinations of the two can potentially deliver the same OTR that satisfies the OUR required in order to maintain a constant oxygen concentration [20]. When the total agitator and compressor energies are summed over the duration of the bioreaction, the total energy requirement that is associated with each combination will vary. Consequently, this presents an opportunity to reduce energy by manipulating and controlling \( Pag \) and/or \( F_c \) throughout the bioreaction to provide an OTR that satisfies the OUR requirement while using less total energy [19,20,27]. Furthermore, it represents an opportunity to minimise total energy by determining the combinations of \( Pag \) and \( F_c \) over the bioreaction time that minimises the total energy requirement.

Some studies have shown that operating at or close to the onset of flooding throughout the bioreaction can minimise the total energy requirement. Kreyenschulte et al. [28] developed a computation tool for assessing aeration system energy demand at the large-scale. For bioreactor volumes of 20 m\(^3\) and larger using conventional agitators, they showed that the minimum energy consumption was achieved by operating close to the onset of flooding. Fitzpatrick et al. [29] performed a mathematical modelling study, which showed that energy was minimised by operating at or close to the onset of flooding. Of course, this approach to energy reduction might be limited by other constraints, such as foaming and use of antifoams, the production of carbon dioxide, and damage to cells [18,30]. The shear sensitivity of mammalian cells will influence the selection of air spargers and impellers, and will limit air flowrates and the specific power input of agitators [18].

This work focusses on bioreactor process control to achieve energy reduction/minimisation for oxygen transfer in a batch stirred tank aerobic bioreactor. A bioreaction model is used to simulate a bioreaction and the only output variable that is used by the process controller is the oxygen concentration in the bioreaction liquid. The objective is to investigate the application of PID process control to manipulating \( F_c \) and/or \( Pag \), so that the energy for oxygen transfer is reduced or minimised, while also maintaining the oxygen concentration at a constant value.

2. Mathematical Modelling and Aeration System Control Strategies

2.1. Mathematical Modelling

The bioreactor simulated in this study had a working volume of 20 m\(^3\). A six bladed Rushton turbine impeller was used with a standard design configuration. The mathematical models, along with relevant parameter values, used for bioreaction kinetics, OUR, OTR, agitator, and compressor power requirements, phase equilibrium, and flooding constraints have already been presented in this journal by Fitzpatrick et al. [29], based on previous work that was conducted by the group.

2.2. Aeration System Control Strategies

A commonly used practical control strategy is to maintain the oxygen concentration in the bioreaction liquid (\( C_{O_2} \)) at a constant value, by controlling \( F_c \) (or \( vvm \)) and/or \( Pag \) throughout the bioreaction. This strategy is applied in this work (in this work, the parameter \( vvm \) is used instead of \( F_c \) because it is commonly used. \( vvm \) is defined as \( (vvm = F_c/V_L) \), where \( V_L \) is the bioreactor working volume. \( vvm \) is expressed in the units of minutes\(^{-1}\)).

A numerical method approach was applied, whereby the bioreaction kinetics and oxygen transfer modelling were used to simulate the bioreaction. In particular, it was applied to calculate \( C_{O_2} \) at each time step during the bioreaction, as illustrated in Figure 1, and to evaluate the agitator and compressor electrical power/energy requirements. A PID control algorithm was applied to vary the value of \( vvm \) (and \( Pag \)) throughout the fermentation to maintain \( C_{O_2} \) around a constant specified value.
(this is referred to as strategy **C**). The time step used in the numerical method approach was $10^{-4}$ h or 0.36 s. The computations were implemented in Matlab (MathWorks, Natick, MA, USA).

![Figure 1. General schematic of control strategy.](image)

There are a number of sub-strategies within strategy C which were investigated. Initially, $P_{ag}$ was kept constant and $v_{vm}$ was varied throughout the fermentation (this is referred to as strategy **C1**). Subsequently, from an oxygen transfer energy perspective, it is shown that dividing the bioreaction time up into two or more time segments with different constant $P_{ag}$ values, where $v_{vm}$ is varied in each time segment, might result in major energy savings (this is referred to as strategy **C1-N**, where $N$ is the number of time segments).

Further, it is shown that there is a $P_{ag}$-$v_{vm}$ combination profile over time that minimises the total electrical energy that is required for strategy C. This is referred to as strategy **Cmin**. It is shown that the optimal $P_{ag}$-$v_{vm}$ combinations often occur at the onset of the flooding constraint. Consequently, from a control perspective, it is important to able to detect the onset of flooding from the $C_{OL}$ data only. This is integrated into the C1-N control strategy, in particular, and it is referred to as strategy **C1F-N**.

### 3. Results and Discussion

**3.1. Bioreaction Progression**

Figure 2a presents the evolution of sugar, product and cell concentrations, and $OUR$ over the duration of the bioreaction. The bioreaction time is about 26.5 h when the oxygen concentration in the bioreaction liquid is maintained at 2 mg L$^{-1}$. The bioreaction progresses slowly over the first 10 h, after which there are significant changes in the concentrations, and the $OUR$ reaches a maximum of 4.7 g L$^{-1}$ h$^{-1}$ towards the end of the bioreaction. Figure 2b shows the influence of oxygen concentration in the bioreaction liquid on the specific growth rate. There is a progressive decrease in specific growth rate as the oxygen concentration is reduced below about 2 mg L$^{-1}$. 
3.2. Control of vvm in Strategy C1

For control strategy C1, $P_{ag}$ is assigned a constant value, such that flooding does not occur throughout the bioreaction. The lowest value of $P_{ag}$ for the bioreaction without flooding is approximately 38.5 kW. A PID control algorithm was developed to continuously vary vvm over time, so as to maintain $C_{ol}$ close to 2 mg L$^{-1}$. The PID controller continuously evaluates an error value $e(t)$ as the difference between a desired set point ($C_{ol} = 2$ mg L$^{-1}$) and the value of $C_{ol}$ evaluated from the model. It then calculates a value of the control variable vvm($t$) to minimise the error $e(t)$. The new value of vvm($t$) is based on the sum of proportional, integral, and derivative (PID) terms in Equation (1):

$$v_{vm}(t) = K_p e(t) + K_i \int_0^t e(t) \, dt + K_d \frac{de(t)}{dt}$$  \hspace{1cm} (1)

The constants $K_p$, $K_i$ and $K_d$ were determined using the Ziegler-Nichols tuning method [31]. This is composed of the following steps:

1) Set a low $K_p$ value (1 or 10 for example) and set $K_i = K_d = 0$.
2) While $K_i = K_d = 0$, increase $K_p$ value until $C_{ol}$ sustained oscillations appear. The $K_p$ value where oscillations appear is called $K_{p,lim}$.
3) Measure oscillation period $T_0$.
4) Tune PID parameters using Equations (2) to (4).

$$K_p = 0.6 \ K_{p,lim}$$  \hspace{1cm} (2)

$$\tau_i = 0.5 \ T_0$$  \hspace{1cm} (3)

$$\tau_d = 0.125 \ T_0$$  \hspace{1cm} (4)

where $\tau_i = K_p/K_i$ and $\tau_d = K_d/K_p$.

$K_{p,lim}$ and $T_0$ were evaluated as 16 and 0.002 h, respectively, and the PID parameters were evaluated from Equations (2) to (4) as $K_p = 9.6$; $\tau_i = 0.001 \ h$; $\tau_d = 0.00025 \ h$, from which $K_i$ and $K_d$ were evaluated.

The control algorithm worked very well for the simulated bioreaction. After the initial part of the bioreaction, where the $C_{ol}$ is allowed decrease from 8 to 2 mg L$^{-1}$, the variation of $C_{ol}$ throughout the bioreaction was very small in the range of $2 \pm 0.03$ mg L$^{-1}$.

The duration of the time step in the simulation is $10^{-4}$ h or 0.36 s, thus the compressor air flowrate is being changed in the simulation at the end of each time step. This is a short period of time, thus the
impact of compressor change time (Δtc) or time interval between changing the compressor air flowrate was investigated. The simulations were performed with values of Δtc greater than 0.36 s. It was found that the PID controller worked well up to about Δtc = 5 s, but oscillations started to appear in the first half of the bioreaction at higher values of Δtc.

3.3. Energy Reduction and Minimisation

3.3.1. Energy Minimisation Using Strategy Cmin

OUR varies throughout the bioreaction time during batch operation, as illustrated in Figure 2a. At a specific time during the bioreaction, many different combinations of \(v_{vm}\) and \(P_{ag}\) can be determined in order to provide an OTR that satisfies the OUR at that time in order to maintain a constant \(C_{OL}\) value, subject to the constraints. Each of these combinations will have different power requirements. Consequently, for a specific value of OUR, there exists an optimum combination of \(P_{ag}\) and \(v_{vm}\) that minimises the oxygen transfer total power requirement, subject to constraints [29].

The simulations were performed (at a constant \(C_{OL}\) of 2 mg L\(^{-1}\)) during the bioreaction time to determine the combinations of \(v_{vm}\) and \(P_{ag}\) that minimise the total power requirement at each time increment during the bioreaction. Consequently, the minimum total energy requirement for the bioreactor is achieved by continuously controlling the bioreactor at these optimal combinations of \(P_{ag}\) and \(v_{vm}\) throughout the entire bioreaction, and this is referred to as strategy Cmin. This was simulated and Table 1 presents the electrical energy requirements for Cmin, along with the C1 energies for comparison. For the Cmin simulation, the minimum total power requirements throughout the bioreaction occurred at the onset of flooding.

| Control Strategy | Agitator \(E_{ag}\) | Compressor \(E_c\) | Total \(E_{tot}\) | Energy Savings (%) |
|------------------|---------------------|------------------|----------------|-------------------|
| C1               | 4104                | 459              | 4563           | -                 |
| Cmin             | 746                 | 706              | 1452           | 68.2              |
| C1-2             | 2174                | 463              | 2637           | 42.2              |
| C1-5             | 1221                | 529              | 1750           | 61.6              |
| C1-10            | 965                 | 590              | 1555           | 65.9              |

The power requirements will depend on the values of OUR, the \(k_{a}\) correlation, and the constraints. Fitzpatrick et al. [29] performed simulations for a typical range of OUR values, bioreactor working volumes, and for five \(k_{a}\) correlation equations. These simulations applied the same bioreaction kinetics as in this work. These simulations showed that the minimum total power requirement tended to be constrained by flooding for many of the scenarios, and it was close to the flooding value for those where the minimum was obtained before the occurrence of flooding. Overall, the simulations suggest that the scenario C minimum total energy can be achieved by the controlling \(v_{vm}\)–\(P_{ag}\) combinations at the onset of flooding throughout the bioreaction.

3.3.2. Energy Reduction Using Strategy C1-N

Scenario Cmin might not be practical, because it involves trying to continuously control \(v_{vm}\) and \(P_{ag}\), so that they are at the onset of flooding throughout the bioreaction. In strategy C1, \(P_{ag}\) is kept constant and \(v_{vm}\) was varied throughout the fermentation. \(P_{ag}\) has a lower limiting value, whereby if \(P_{ag}\) is chosen below this limiting value, then the \(v_{vm}\) required at maximum OUR exceeds the flooding \(v_{vm}\) and \(C_{OL}\) cannot be maintained constant. Operating at this limiting value of \(P_{ag}\) throughout the bioreaction time results in relatively high total energy requirement due to the high agitator energy requirement.

Fitzpatrick et al. [29] suggests that this energy requirement can be greatly reduced by applying strategy C1-N, where the bioreaction time is divided up into \(N\) time segments (two or more time segments), where lower constant \(P_{ag}\) values are applied in each time segment without flooding the impeller. For the model bioreaction, the OUR progressively increases with time with the maximum
being near the end, as illustrated in Figure 2a. This bioreaction could be divided up into \( N \) time segments with \( P_{ag} \) progressively increasing from segment to segment, up until the limiting \( P_{ag} \) value in strategy C1 in the last time segment.

Figure 3 illustrates the variation in \( P_{ag} \), \( vvm \) and \( COL \) for a five-segment control strategy (C1-5) where the time duration of each segment is equal. Figure 3a shows the values of \( P_{ag} \) in each time segment. Within each time segment, the value of \( P_{ag} \) represents the lowest value without the occurrence of impeller flooding. The non-linear increase in \( P_{ag} \) from segment to segment is due to \( OUR \) increasing non-linearly, as illustrated in Figure 2a. Figure 3b shows how \( vvm \) is varied by the control algorithm. Within each time segment, \( vvm \) increases, as expected, and then decreases when there is a transition from one segment to the next with the step increase in \( P_{ag} \). This step increase in \( P_{ag} \) causes significant variation in \( COL \), as illustrated in Figure 3b; however, this is only for a short duration after the transition. Otherwise, the control algorithm works very well in controlling \( COL \). In fact, the variation at the transition can be greatly reduced by introducing a more gradual increase in \( P_{ag} \) at the end of each time segment, rather than a step increase.

Simulations were performed to compare the energy requirements of strategies C1-N with C1 and Cmin, and Table 1 presents the results. Increasing the number of time segments results in a major reduction in the total energy requirement for oxygen transfer. Dividing the bioreaction time into two time-segments results in a 42% energy reduction. Dividing the bioreaction time into 10 time-segments results in a 66% energy reduction. Consequently, there is a diminishing additional energy saving that is associated with each additional time segment. Increasing the number of time segments will progressively approach that of Cmin.

![Figure 3. Scenario C1-5: Effect of proportional, integral, and derivative (PID) control on (a) \( P_{ag} \) step increases and (b) \( COL \) and \( vvm \) (five equal time segments—non-flooding).](image)

3.4. Implementation of Strategy C1-N with Detection of Impeller Flooding using Oxygen Sensor Data (C1f-N)

Section 3.3 suggests that energy can be minimised by operating at or close to the onset of impeller flooding throughout the duration of the bioreaction; however, this might not be operable from a practical control perspective. Strategy C1-N, using a small number of time segments, is practically operable, and Section 3.3 suggests that this could obtain most of the energy savings that are associated with Cmin. For example, the data provided in Table 1 show that operating with 10 equal time segments (C1–10) provides 96.6% of the savings made by Cmin relative to strategy C1.

The problem with strategy C1-N, as outlined in Section 3.3, is that it inherently assumes that the relationship between the flooding \( vvm \) and \( P_{ag} \) is known. Such correlations do exist [32], however these are only approximations. Consequently, it would advantageous if the controller could detect the onset of flooding while using the measured \( COL \) data. With this, the controller could implement a step increase in \( P_{ag} \) once it detected flooding and automatically moved to the next time segment.

3.4.1. Detection of Impeller Flooding Using Oxygen Sensor Data and Implementation of Strategy C1f-N
Considering the above, work was undertaken to develop an algorithm that could detect the onset of flooding. Before doing this, a \( k_{La} \) model for the flooding region had to be developed, so that \( k_{La} \) in the simulated bioreaction would decrease in the flooded region. As a first attempt, a simplified model for estimating \( k_{La} \) in the flooded region was constructed. This essentially consisted of applying the \( k_{La} \) correlation Equation (5), such that it is symmetrical around the flooding air superficial velocity \( (v_{SF}) \), as presented in Equation (6), where air superficial velocity \( (v_{a}) \) is defined as air volumetric flowrate per unit cross-sectional area of bioreactor [29]. Figure 4 illustrates how \( vvm \) and \( Pag \) influence \( k_{La} \) in the non-flooded and flooded regions for two values of \( Pag \).

\[
\text{Region 1:} \quad \begin{align*}
    v_a &\leq v_{SF} \\
    k_{La} &= K \left( \frac{Pag}{V_L} \right)^{n_1} (v_a)^{n_2} 
\end{align*}
\]

\[
\text{Region 2:} \quad \begin{align*}
    v_{SF} &< v_a \geq 2 v_{SF} \\
    k_{La} &= K \left( \frac{Pag}{V_L} \right)^{n_1} (v_{SF} - (v_a - v_{SF}))^{n_2} 
\end{align*}
\]

\[
\text{Region 3:} \quad \begin{align*}
    v_a &> 2 v_{SF} \\
    k_{La} &= 0 
\end{align*}
\]

The work on developing a flooding detection algorithm first looked at how the model behaved when the simulated flooding occurred. This is presented in Figure 5 for a strategy C1 case where flooding occurs during the bioreaction. \( Pag \) was assigned a constant value of 3.8 kW, which is well below the value of \( Pag \) where the onset of flooding occurs at the maximum OUR for the non-flooded case (~38.5 kW). The flooding occurred at about 15.51 h into the bioreaction, as can be seen in Figure 5 by the rapid decrease in \( Col \), which took approximately 45 s to decrease from the set-point of 2 mg L\(^{-1}\) down to 0. This is because as \( Col \) decreases due to the increase in OUR, the controller responds by increasing \( vvm \) to increase the OTR. However, this is counterproductive once \( vvm \) is in the flooded

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Figure 4. Effect of \( vvm \) and \( Pag \) on \( k_{La} \) in the non-flooded and flooded regions using a symmetrical \( k_{La} \) model.
region and it causes $k_{la}$ (and OTR) to decrease rather than increase, which, in turn, causes $Col$ to decrease rapidly. This rapid continuous decrease in $Col$ was used to detect the onset of flooding. Flooding was detected when $Col$ decreased below a certain value (referred to as $Col_{FLD}$), which was below the 2 mg L$^{-1}$ control set-point. Simulations were first performed at a value of $Col_{FLD}$ that was equal to 1.9 mg L$^{-1}$ and this worked well. However, significant fluctuations in $Col$ occur after the subsequent increase in $Pag$, thus flooding detection had to be suspended for a short time period after the $Pag$ transition.

![Figure 5. Effect of flooding on control strategy C1. ($Pag = 3.8$ kW and flooding occurs at 15.51 h).](image)

The flooding detection was then integrated into the C1-N control strategy and it is referred to as strategy C1-N. To implement the C1-N strategy, it is first necessary to estimate a high enough value of $Pag$ ($Pag_{max}$), such that flooding does not occur at maximum OUR. This is, in essence, sizing the mechanical power requirement of the agitator. One approach to doing this is to experimentally measure the maximum OUR at a small scale for the bioreaction. Subsequently, the modelling equations that were presented by Fitzpatrick et al. [29], including a relevant $k_{la}$ correlation, were be applied to gain an estimate of $Pag$ at the onset of flooding for the maximum OUR value, as was carried out for Figure 3. This can also be used to provide an estimate on the maximum vvm requirement ($vvm_{max}$), which essentially sizes the air compressor and prevents any excessive airflow response by the PID controller.

Once $Pag_{max}$ is estimated, the C1-N control strategy is implemented, as follows:

A step increase in $Pag$ from time segment to time segment ($\Delta Pag$) is defined in Equation (7).

$$\Delta Pag = \frac{Pag_{max}}{N}$$  \hspace{1cm} (7)

Subsequently, the $Pag$ in each time segment ($Pag_i$) (where $i$ is an integer starting at 1) is given in Equation (8).

$$Pag_i = i \times \Delta Pag$$  \hspace{1cm} (8)

This is a little different to the previous implementation of C1-N where the time segments were of equal duration, but the step increases in $Pag$ varied in magnitude, as illustrated in Figure 3. Currently, the durations are different, but the step increases in $Pag$ are the same. This is illustrated in Figure 6 for five time segments (C1-F-5). This is more practical, because it is not known exactly what the flooding $Pag$ is at the end of each time segment for the case of using equal time segment durations.
Further simulations were performed for two and 10 segments and Table 2 presents the energy requirements, and these can be compared with C1-N presented in Table 1, where there was no flooding detection. The energy requirements and energy savings are similar, but they are a little greater for the cases while using flood detection. This is most likely because the segment time durations and $P_{ag}$ values in each time segment are different.

Figure 6. Control strategy C1r-5 (with automatic detection of flooding; $Col_{FLD} = 1.9 \text{ mg L}^{-1}$): (a) $P_{ag}$ step increases; and, (b) $Col$ and $vvm$.

Table 2. Comparison of energy requirements (MJ) for the strategies with onset of flooding detection (C1r-N) (set-point $Col = 2 \text{ mg L}^{-1}$). The % energy savings are relative to strategy C1.

| Control Strategy | Agitator $E_{ag}$ | Compressor $E_{c}$ | Total $E_{tot}$ | Energy Savings (%) |
|------------------|------------------|--------------------|----------------|-------------------|
| C1               | 4104             | 459                | 4563           | -                 |
| Cmin             | 746              | 706                | 1452           | 68.2              |
| Strategy C1r-N   |                  |                    |                |                   |
| C1r-2            | 2303             | 520                | 2823           | 38.1              |
| C1r-5            | 1305             | 596                | 1901           | 58.3              |
| C1r-10           | 1001             | 635                | 1637           | 64.1              |

In the results shown above, the simulations were performed at $Col_{FLD} = 1.9 \text{ mg L}^{-1}$, which is only 0.1 mg L$^{-1}$ below the control set-point of 2 mg L$^{-1}$. The PID controller performed well in controlling $Col$ in the simulated bioreactions; however, random fluctuations in real oxygen sensor measurements could cause the measured $Col$ to be below 1.9 mg L$^{-1}$ and cause unwanted step increases in $P_{ag}$ and greatly reduce the energy saving potential. Consequently, the influence of random fluctuations in the oxygen sensor measurements are investigated in the next section.

3.4.2. Dealing with Random Fluctuations in the Oxygen Sensor Measurements and Unwanted $P_{ag}$ Step Increases

Random fluctuations in real oxygen sensor measurements could cause unwanted step increases in $P_{ag}$, which would greatly reduce the energy saving potential. This is highly undesirable. A number of factors could cause the random fluctuations, including the medium being two-phase consisting of air bubbles in aqueous liquid and variations in oxygen concentrations due to non-ideal mixing. This section examines the impact of these fluctuations and how they can be overcome. The impact of random fluctuations is included in the modelling through Equation (9).

$$Col_{sensor} = Col \left(1 + x \cdot Y\right)$$  \(9\)

where $Col_{sensor}$ is the simulated oxygen sensor measurement, $Y$ is the maximum fluctuation amplitude (mg L$^{-1}$), and $x$ is a random number generated between $-1$ and $+1$. The error value $e(t)$ is now calculated as the difference between a desired set point ($Col = 2 \text{ mg L}^{-1}$) and the value of $Col_{sensor}$, and this is used in the PID controller equation (1) in order to evaluate $vvm$.

This was initially applied for $Y = 0.2$ and $Col_{FLD} = 1.9 \text{ mg L}^{-1}$. Figure 7a shows the random fluctuation in sensor oxygen concentration in the liquid ($Col_{sensor}$), and Figure 7b shows its effect on
When compared to Figure 6a, this shows the $P_{ag}$ step increases occurring much earlier than desired and, consequently, the energy saving potential is lost. This simply occurs because the random fluctuations (with $Y = 0.2$) causes $C_{OL, sensor}$ to randomly decrease below $C_{OL,FLD}$ activating unwanted step increases in $P_{ag}$. This causes a fluctuation in $vvm$, which causes the real value of the oxygen concentration in the liquid ($C_{OL}$) to also vary, as illustrated in Figure 7c.

One approach for trying to prevent the random fluctuations causing unwanted $P_{ag}$ step increases is to reduce the value of $C_{OL,FLD}$. From Equation (9) and considering that $C_{OL}$ is fluctuating around its set-point ($C_{OL,sp}$), then unwanted $P_{ag}$ step increases will occur if the condition in Equation (10) is met.

$$C_{OL,sp}(1 - Y) < C_{OL,FLD}$$

When considering this, simulations were run for combinations of $Y (= 0.1, 0.3, 0.5)$ and $C_{OL,FLD} (= 1.9, 1.7, 1.5, 1.2, 0.8)$ to evaluate whether unwanted $P_{ag}$ step increases occurred or not, and Table 3 presents the results. The results show that an unwanted $P_{ag}$ step increase did occur when the condition in Equation (10) was met. Furthermore, Table 3 shows some unwanted $P_{ag}$ step increases
occurring for some $\text{COL}_{\text{F,LD}}$ lower than in the condition, and this is due to the random fluctuation in the $\text{COL}$ value below the set-point value (Figure 7c).

**Table 3.** Effect of $Y$ and $\text{COL}_{\text{F,LD}}$ on whether or not unwanted $\text{Pag}$ step increases occurred (Yes/No) (set-point $\text{COL} = 2 \text{ mg L}^{-1}$).

| $\text{COL}_{\text{F,LD}}$ (mg L$^{-1}$) | $Y = 0.1$ | $Y = 0.3$ | $Y = 0.5$ |
|---------------------------------------|------------|------------|------------|
| 0.8                                  | No         | No         | Yes        |
| 1.2                                  | No         | Yes        | No         |
| 1.5                                  | No         | Yes        | Yes        |
| 1.7                                  | Yes        | Yes        | Yes        |
| 1.9                                  | Yes        | Yes        | Yes        |

Colour signifies that constraint in Equation (10) was met.

Reducing the effect of the fluctuations by applying a moving average to fluctuation in $\text{COL}_{\text{sensor}}$ (i.e., $\text{COL}_{\text{senMA}}$) is another approach for trying to prevent the random fluctuations causing unwanted $\text{Pag}$ step increases. This was implemented in the model by evaluating the average of $\text{COL}_{\text{sensor}}$ over the last ten time steps. Figure 8 illustrates the effect of using moving average to reduce the fluctuations. This had a beneficial impact on reducing unwanted step increases in $\text{Pag}$, as the first “Yes” in Table 3 became a “No” for each of the values of $Y$. Care has to be taken not to have too long a time duration over which a moving average is calculated as it introduces a time delay.

![Figure 8](image)

**Figure 8.** Comparison of the sensor oxygen concentration in liquid ($\text{COL}_{\text{sensor}}$) and its moving average ($\text{COL}_{\text{senMA}}$).

### 3.4.3. Impact of Operating at Lower Values of $\text{COL}_{\text{F,LD}}$

To avoid the effect of random fluctuations in the oxygen sensor measurements ($\text{COL}_{\text{sensor}}$) causing unwanted $\text{Pag}$ step increases, it may be necessary to operate at lower values of $\text{COL}_{\text{F,LD}}$, as outlined in the previous section. Some of the C1=5 simulations that were run at lower values of $\text{COL}_{\text{F,LD}}$ (typically below 0.8 mg L$^{-1}$) showed an unusual behaviour. This occurred in simulations both with and without random fluctuations, thus the root cause of this behaviour was not the presence of the random fluctuations. Figure 9 illustrates the behaviour, where there was a lower number of $\text{Pag}$ step increases (one less in Figure 9a) and an unusual $\text{COL}$ profile towards the end of the bioreaction (Figure 9b). This behaviour did not have a major influence on bioreaction time or total energy requirement, even at a very low $\text{COL}_{\text{F,LD}}$ of 0.1 mg L$^{-1}$, where the bioreaction time increased by 0.2 h and the total energy increased by 3.7%.
The rationale for the behaviour is somewhat complex. Before a Pag step increase, Col decreases towards Col fld due to the onset of flooding and the PID controller correspondingly causes an increase in vvm, as illustrated in Figure 9b. This moves the system further into the flooding zone, which reduces kla and causes Col to rapidly decrease. This usually results in a Pag step increase when Col decreases to Col fld. However, in the latter part of the bioreaction (Figure 9b), the rate of decrease of Col suddenly changed to a slower rate and Col decreased more slowly towards Col fld. This sudden transition corresponded to, or was triggered by, vvm attaining its maximum value (vvm max). This is a specified value in the model that equals the value of vvm at the onset of flooding at the final value of Pag. Once vvm becomes constant, kla also attains a constant value, and a complex interplay between variables occurs, which causes Col to decrease at a much slower rate. This slower decrease in Col results in Col not being reduced to Col fld before the end of the bioreaction (as illustrated in Figure 9b) and, thus, the final Pag step was not triggered (Figure 9a).

![Figure 9](image)

**Figure 9.** Effect of Col fld = 0.5 mg L⁻¹ on control strategy C1r-5 (with automatic detection of flooding; Y = 0): (a) Pag step increases; and, (b) Col and vvm (Note: time starts at 17 h).

An initial suggestion to overcome this might be to increase the value of vvm max, because limiting this value caused the slowing of the decreases in Col that resulted in the final Pag step increase not being triggered. This was simulated; however, the modelling showed that this worked for some simulations, but not for other simulations, especially those at low values of Col fld. The reason for this approach not working is because increasing vvm beyond the original specified vvm max does trigger the Pag step increase as desired; however, the higher vvm is in the flooding zone at the higher final Pag value. How far it is into the flooding zone has a major influence on kla and OTR. If too far into the flooding zone, insufficient OTR is developed and Col will continue to decrease towards zero, slowing the bioreaction and significantly increasing the bioreaction time.

The net effect of the above is that reducing Col fld to low values, e.g., <0.8 mg L⁻¹ in the simulations, can result in complex dynamics occurring, as highlighted above. However, it might not be necessary to operate at such low values of Col fld and, consequently, the issue will not manifest itself. Furthermore, the behaviour that is illustrated in Figure 9 resulted in a minor reduction in bioreactor performance, with only small increases in energy requirement and bioreaction time.

4. Conclusions

A PID controller was used to control vvm, so as to maintain Col at a constant value of 2 mg L⁻¹ throughout a simulated bioreaction whose OUR progressively increased over time. When Pag is kept constant throughout the bioreaction, this leads to excessive oxygen transfer energy requirement, because a high value of Pag is required at maximum OUR to prevent flooding. Operating at or near the impeller flooding constraint throughout the bioreaction results in the minimum energy requirement for oxygen transfer (strategy Cmin); however, this might prove impractical to control and operate in practice. It was shown that most of the energy saving that is associated with Cmin could be achieved by dividing the bioreaction time into a small number of time segments (e.g., 5) with lower constant Pag values. The onset of flooding occurs at the end of each time segment and this
initiates a $P_{\text{ag}}$ step increase for the next time segment. To implement this, the onset of flooding needs to be detected in order to signal the increase in $P_{\text{ag}}$. This was achieved while using the simulated $C_{\text{OL}}$ vs. time data, where there was a rapid decrease in $C_{\text{OL}}$ when flooding occurred, and this was used to detect the onset of flooding and initiate the step increase in $P_{\text{ag}}$ for the next time segment. Random fluctuations in the oxygen sensor readings can cause unwanted $P_{\text{ag}}$ step increases, which could reduce the energy saving potential; however, the incorporation of lower values of $C_{\text{OL,FLD}}$ and moving averages can overcome this problem. The insights developed in this paper are coming from mathematical modelling simulations and some practical insights (such as sensor measurement fluctuations); consequently, practical experimental and pilot scale work is required to test and further develop the presented ideas. Furthermore, there might be other practical constraints that may influence the determination of $v_{\text{vvm}}$ and $P_{\text{ag}}$ and impact on the energy reduction potential, such as foaming and the shear sensitivity of cells. Finally, the control of oxygen transfer coupled with reducing the energy requirement is complex, as there are many variables that can interact with each other, which sometimes might result in unusual non-intuitive behaviours. The implementation of modelling simulations and interrogating the resulting data can help to explain these behaviours.

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**List of Symbols**

- $C_{\text{OL}}$: oxygen concentration in the bioreaction liquid (mg L$^{-1}$)
- $C_{\text{OL,FLD}}$: oxygen concentration at which $P_{\text{ag}}$ step increase occurs (mg L$^{-1}$)
- $C_{\text{OL,sensor}}$: simulated oxygen sensor measurement (mg L$^{-1}$)
- $C_{\text{OL,senMA}}$: moving average of $C_{\text{OL,sensor}}$ values (mg L$^{-1}$)
- $C_{\text{OL,sp}}$: oxygen concentration controller set-point (mg L$^{-1}$)
- $E_{ag}$: agitator electrical energy (GJ)
- $E_{c}$: compressor electrical energy (GJ)
- $E_{\text{tot}}$: sum of agitator and compressor electrical energy (GJ)
- $e(t)$: difference between $O_{2}$ concentration set-point and simulated value (mg L$^{-1}$)
- $F_{i}$: inlet air volumetric flowrate (m$^{3}$ h$^{-1}$)
- $k_{\text{La}}$: volumetric oxygen mass transfer coefficient (h$^{-1}$)
- $K_{d}$, $K_{i}$, $K_{p}$: PID controller constants
- $N$: number of time increments
- $O_{\text{U}}$: oxygen uptake rate (g L$^{-1}$ h$^{-1}$)
- $O_{\text{TR}}$: oxygen transfer rate (g L$^{-1}$ h$^{-1}$)
- $P$: product concentration (g L$^{-1}$)
- $P_{\text{ag}}$: agitator mechanical power input (kW)
- $S$: sugar concentration (g L$^{-1}$)
- $t$: time (hours)
- $T_{0}$: oscillation period PID controller (h)
- $V_{L}$: bioreactor working volume (m$^{3}$)
- $v_{\text{vvm}}$: volume of air per minute per unit bioreactor working volume (min$^{-1}$)
- $v_{s}$: air superficial velocity (m h$^{-1}$)
\[ v_0 \text{ air superficial velocity at onset of flooding (m h}^{-1}) \]
\[ X \text{ cell concentration (g L}^{-1}) \]
\[ Y \text{ maximum random fluctuation amplitude in oxygen concentration (mg L}^{-1}) \]
\[ \mu \text{ specific growth rate (h}^{-1}) \]
\[ \mu_{\text{max}} \text{ maximum specific growth rate (h}^{-1}) \]
\[ \tau \text{ PID controller parameters (h)} \]

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