Multi-scale Models for the Optimization of Batch Bioreactors

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Abstract: In this paper, we propose multi-scale models for a batch bioreactor, which are developed by expanding the so-called Herbert’s Microbial Kinetics (HMK) concept so that the effects of mixing conditions are incorporated via the inclusion of the aeration rate and stirrer speed into the microbial kinetics. By using the multi-scale models, we are able to optimize the batch bioreactor’s performances, i.e. yield and productivity, by adjusting the aeration rate and stirrer speed. Simulation and experimental studies on a batch (fermentation) bioreactor demonstrate the application of this approach, whereby the integration of the expanded HMK model with the Computational Fluid Dynamics (CFD) model of mixing, which we call it as a Kinetics Multi-Scale (KMS) model, is able to predict the experimental values of yield and productivity of the batch fermentation process accurately (with less than 5% errors).

Keywords: Batch; Fermentation; Modeling; Optimization; Performance

1. INTRODUCTION

Batch bioreactors are widely used in biotechnological applications, where biochemical reactions are taking place under controlled environments, i.e. temperature, oxygen, pH, nutrients and mixing conditions (Rahimi and Parvareh, 2005). In a fermentation process, the batch bioreactor’s performances are characterized by its transport capacities in order to optimally supply the microorganism with the required nutrients and oxygen so that the metabolism occurs to produce the desired products, i.e. ethanol, and/or by products, i.e. glycerol (Lübbert, 1992). The common approach in the optimization of batch bioreactors has always relied on the kinetics of fermentation, which assumes well-mixing behaviour. Our previous studies, for example Liew et al. (2009) showed that the mixing behaviour could lead to severe loss in yield and changes in microbial physiology. The integration of mixing phenomena into the bioreactor modelling is therefore vital, but it is not an easy task. The detailed description of the turbulent flow field, in combination with other transport equations, needs to be addressed (Jenne and Reuss, 1999).

Process models have been utilized as tools to improve the performance of a batch bioreactor via the improvement of the metabolic capabilities of microorganism by mean of genetic manipulations of the cell metabolism and the bioprocess conditions (Wiechert, 2002). The optimisation of bioreactors now implies the manipulation of both microbial culture and the environmental conditions (Konde and Modak, 2007). Model-based optimisation is employed for systematically determining the batch operating strategies (Hjersted and Henson, 2006). One of the fundamental aspects to the success of the model-based optimisation of the batch bioreactors is the adopted model of microbial kinetics, which should accurately capture the effects of environmental conditions, i.e. pH, temperature, aeration rate (AR) and stirrer speed (SS), on the rates of growth, substrate consumption and product formation. To date, most of the currently available models of microbial kinetics do not capture directly the effects of AR and SS on the growth rates. Therefore, the main contribution of this paper lies in the development of bioreactor models, where three approaches to incorporating the effects of AR and SS into the model of microbial kinetics based on the Herbert’s concepts are proposed. Two of the three developed models are referred to in this paper as the expanded Herbert’s Microbial Kinetics (HMK) models, which are multi-scale in nature. The proposed approaches of incorporating the mixing phenomena are not exclusively for the HMK concept. It can be extended to any other conventional model of microbial kinetics.

2. BIOREACTOR MODELING

The majority kinetics of ethanol fermentation utilize a formal macro-scale approach to describe the microbial growth, based on either Monod’s equation or on its numerous modifications which take into account the inhibition of microbial growth by a high concentration of product and/or substrate (Starzak et al., 1994). The models so far only explained the effect of ethanol inhibition via the mechanism of non-competitive inhibition of a simple reversible enzymatic reaction without taking into consideration the mixing conditions inside the batch bioreactor, i.e. the assumption of well-mixing behaviour is often applied. Deviation from the ideal mixing behaviour in practice could lead to severe loss in yield, change in microbial physiology, and affect on oxygen uptake rate. Thus, the integration of mixing phenomena, i.e. the effects of AR and SS, is necessary.
Three modelling approaches to incorporating the effects of mixing in a batch ethanolic fermentation process are proposed in this paper: (1) statistical data-based (SDB) model, (2) kinetics hybrid (KH) model and (3) kinetics multi-scale (KMS) model. The developed models are then validated against a series of experimental studies.

2.1 Kinetics Herbert’s concept

To predict yield \( Y \) and productivity \( Pr \), a batch bioreactor can be modelled dynamically as follows:

\[
\dot{X} = \begin{bmatrix} X_v \\ S \\ P \\ r_s \\ r_p \end{bmatrix} = \begin{bmatrix} r_s \\ r_g \end{bmatrix},
\]

(1)

\[
\Phi = \begin{bmatrix} Y \\ Pr \end{bmatrix} = \begin{bmatrix} 100P(t_b)(S_c - S(t_b)) \\ \frac{P(t_b) - P_o}{t_b} \end{bmatrix}
\]

(2)

Where \( S_c = S(0) \) and \( P_o = P(0) \) is the initial substrate and ethanol concentrations (g/L) of the medium, \( t_b \) (hrs) is the batch time for the fermentation process. Other variables are the concentration profiles of substrate \( S \), product (ethanol) \( P \) and viable cell (biomass) \( X_v \). The microbial kinetics are:

1. rate of growth \( r_s \),
2. rate of product formation \( r_p \) and
3. rate of substrate consumption, \( r_g \).

In this work, the Herbert’s concept of endogenous metabolism is adopted. The by-product concentration is not included in this study because we only focus on the impacts of AR and SS on the concentration profiles of substrate \( S \), product (ethanol) \( P \) and viable cell (biomass) \( X_v \). This concept assumes that the observed rate of biomass formation \( r_c \) comprised of the growth rate \( (r_s) \) and the rate of endogenous metabolism \( (r_g) \) :

\[
r_c = (r_s) + (r_g)\end{end}

(3)

Where:

\[
(r_s) = [k_1 X_v S/(k_2 + S)] \exp(-k_3 P)
\]

(4)

\[
(r_g) = -k_4 X_v
\]

(5)

The rates of substrate consumption and product formation are assumed to be proportional to the biomass growth rate:

\[
r_g = -k_3 (r_s)
\]

(6)

\[
r_p = k_4 (r_s)
\]

(7)

Note that \( R_s = [r_s, r_g, r_p] \).

and the kinetics of ethanolic fermentation based on the Herbert’s concept, i.e. from (3) ro (7) consists of six kinetic parameters i.e. \( \kappa = [k_1, k_2, k_3, k_4, k_5, k_6] \) whereby the mixing effects in terms of AR and SS is to be included in each kinetic parameter.

2.2 Statistical Data-Based (SDB) Model

SDB model is developed by applying a regression analysis to a set of experimental data for different AR, SS, yield \( Y \) and productivity \( Pr \). The effect of mixing arising from different values of AR and SS are included in the regression model by treating AR and SS as inputs, or experimental variables \( X \) and \( Y \) as well as \( Pr \) as outputs, and response variables, \( \Phi \). AR is the rate of oxygen supplied into the bioreactor for the growth of microorganisms, whereas for SS is the speed of the impeller in the bioreactor for mixing the fermentation medium. After applying design experiments to the bioreactor, sets of experiment data for both inputs and outputs are obtained (see Table 1 in Section 2.5).

Let us consider the regression model as a quadratic model:

\[
\hat{\Phi} = A + BX + X^TDX + \epsilon
\]

(9)

where \( A, B, D \) are defined as model parameters, whereby \( A, B \) and \( D \) will be estimated in such a way that the sum of the squared errors between the predicted values \( \hat{\Phi} \) and experimental values \( \Phi \) of the responses are minimised. So, this problem can be mathematically stated as:

\[
P_i : \min_{A,B,D} \sum_{i=1}^{n} \left[ (\Phi_i - \Phi) \right]^T \left[ (\Phi_i - \Phi) \right]
\]

(10)

Where \( \Phi_i \) is the predicted values by (9) and the subscript \( i \) indicates the experimental number. Based on the full factorial design, the total number of experimental runs for \( n \) inputs is given by \( k = 2^n \); in our case \( n = 2 \) and hence \( k = 4 \). Note that different values of \( k \) result in different experimental designs. Some process constraints such as \( X_{min} < X < X_{max} \) where \( X_{min} \) and \( X_{max} \) denote the lower and upper limits of inputs, respectively can be included in the optimisation of \( P_i \).

2.3 Kinetics Hybrid (KH) Model

The basic assumption underlying the development of Kinetics Hybrid model is that the kinetic parameters are the function of the inputs \( X \) as:

\[
\kappa = h(X, \theta)
\]

(11)

Here \( \theta \in \mathbb{R}^{n_{pop}} \) is a matrix whose elements correspond to the parameters to be determined later. Substituting (11) into (3) to (7), the microbial kinetics of Herbert’s can be expressed as:

\[
R_s = g_m(Z, X, \theta)
\]

(12)

The advantage of expanded Kinetics Herbert’s model, i.e. (12), over the original microbial kinetic model, i.e. (3) to (7) is that the expanded one can be directly used to optimize \( Y \) and \( Pr \) with respect to AR and SS.

The development of Kinetics Hybrid model involves two main steps:

1. For experimental run \( i \), obtain the kinetics parameters \( \kappa_i \) using the original kinetics Herbert’s model based on (3) to (7) and batch reactor model based on (1) to (2).
2. For the obtained kinetic parameters \( \kappa_i, \forall i \in [1,2,...,k] \) and sets of aeration rates (AR) and stirrer speeds (SS), find \( \theta \) in (12) using regression method.

The combination of the batch bioreactor model which is denoted by (1) to (2), the Herbert’s kinetics model, denoted by (3) to (7) and the regression model of (11) constitutes the
so-called kinetics hybrid (KH) model of bioreactor. Clearly, in this approach, the effect of mixing is now embedded into the bioreactor model. In more details, the development of kinetics hybrid model follows the systematic procedure as:

**Step 1: Identification of Herbert’s Kinetic Parameters**
The Herbert’s kinetic parameters \((k, k_2, \ldots, k_s)\) are obtained via optimisation by solving the following quadratic problem:

\[
P_2: \min_{\kappa} \left\{ \sum_{j=1}^{s} \left[ \frac{\rho_j - \hat{Z}_j}{\hat{Z}_j} \right]^T \left[ \kappa_j - \hat{k}_j \right] \right\} \quad \forall \kappa_j \in \kappa
\]

(13)

Here \(\hat{Z}_j\) is the predicted value of \(Z\) using the bioreactor model of (1) to (2) at the \(j\)-sample time, and \(s\) is the number of samples taken during the course of batch experiments.

For the \(i\)-experimental run, the corresponding solution to problem \(P_2\) will yield \(\kappa_i = \hat{\kappa}_i\) that minimizes the sum of squared errors between the predicted values and experimental values of \(Z_j\). For a \(k + 1\) number of experimental runs, we will obtain a set of \(\kappa = \{\hat{\kappa}_1, \hat{\kappa}_2, \ldots, \hat{\kappa}_s\}\), which contains the solutions corresponding to all experimental runs including the base-line experimental run i.e. \(\hat{\kappa}_s\).

**Step 2: Determine the Regression Model of (11)**

This step is to find the regression model of \(\theta = \theta^*\) where the problem can be stated as:

\[
P_3: \min_{\theta} \left\{ \sum_{j=0}^{s} \left[ \kappa_j - \hat{\kappa}_j \right]^T [\kappa_j - \hat{\kappa}_j] \right\} \quad \forall \kappa_j \in \kappa
\]

(14)

where \(j\) is the number of experimental runs based on the design of experiment (i.e. \(j=4\) if factorial design is adopted). Here \(i=0\) indicates the experiment at the base-line conditions and \(\hat{\kappa}\) denotes the predicted value of \(\kappa\) based on a regression model, e.g. (9). As we have no a priori knowledge on the exact form of relationships \(h: \kappa \rightarrow \kappa\), we use the statistical approach, i.e. the technique used for the SDB model, thus assuming \(\kappa\) can be represented by a model equation of (9).

### 2.4 Kinetics Multi-Scale (KMS) Model

The kinetics multi-scale (KMS) model is developed based on the Kinetics Hybrid model but we use the general mass-energy balance over an element of reactor volume combined with a mixing model to replace the bioreactor model which is denoted by (1) to (2). The mixing model is implemented using Computational Fluid Dynamics (CFD) based on the \(k-\epsilon\) turbulence model (Dubey et al., 2006). This approach was used to describe the mixing mechanism in a bioreactor with sufficient accuracy (Ranade, 2002).

The \(k-\epsilon\) turbulence model is normally used in order to describe the mixing behaviour and to compute the turbulence in the bioreactor. The energy dissipation is expressed as:

\[
\epsilon = \frac{(\Delta Pf_u)/m}{m} = \frac{(\Delta Pu)/(\rho p)}
\]

(15)

Where \(\Delta P\) denotes the pressure drop, \(m\) is the mass, \(u\) is the velocity of the fluid, \(F\) is the tube cross-section, \(x\) is the axial coordinate and \(\rho\) is the density of the fluid. The fluid flow equations need to be solved for a constant density fluid (Bode, 1994). These consist of the continuity equation:

\[
div(\rho u) = 0
\]

and the transport equations:

\[
div(\rho u_k) = div\left(\frac{\mu_{eff}}{\sigma_j} \nabla k\right) + G - \rho \epsilon
\]

\[
div(\rho u_k) = div\left(\frac{\mu_{eff}}{\sigma_j} \nabla \epsilon\right) + (C_1 G - C_2 \rho \epsilon)(\epsilon/\kappa)
\]

(16)

Where \(\nabla k\) and \(\nabla \epsilon\) denote the gradient of \(k\) and \(\epsilon\), respectively. \(k\) is the kinetic energy of turbulence at the point of interest.

The Eddy Viscosity is given by:

\[
\mu = C_{mu} \kappa^2 / \epsilon
\]

(19)

Note that \(G\) is the scalar dissipation function \((G = \tau_{ij} \tau_{ij} / 2 \mu_{eff})\) and the scalar values: \(C_{mu} = 0.09, C_1 = 1.44, C_2 = 1.92, \sigma_2 = 1\) and \(\sigma_3 = 1.3\). The Navier-Stokes equation is used for flow equations to describe the instantaneous behaviour of the turbulent liquid flow in ethanolic fermentation process, as shown below:

\[
\frac{\partial (\rho u_i)}{\partial t} + \frac{\partial (\rho u_i u_j)}{\partial x_j} = -\frac{\partial \tau_{ij}}{\partial x_j} + \frac{\partial p}{\partial x_i} + \rho g_i
\]

\[
\frac{\partial \rho}{\partial t} + \frac{\partial (\rho u_i)}{\partial x_i} = 0
\]

(20)

(21)

For model accuracy and computational expense, a reasonable eddy viscosity models relating the individual Reynolds stresses to mean flow gradients are adopted:

\[
\rho u_i u_j = -\rho_{turb} \left( \frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right) + \frac{2}{3} \rho \partial_{ij} \kappa
\]

(22)

Where \(\rho_{turb}\) is the turbulent eddy viscosity. The transport of momentum is thought of as turbulent eddies, which like molecules, collide and exchange momentum.

The general balance over an element of reactor volume is given by:

\[
\partial (\rho \phi)/\partial t + \partial (\rho u_i \phi)/\partial x_i = \partial (\Gamma_{\phi} \partial \phi/\partial x_i)/\partial x_i + S_{\phi}
\]

(23)

Where \(\phi\) is the density of fluid, \(\phi\) is the concentration of any component, \(U_i\) is the local velocity in the \(x_i\)-direction, \(\Gamma_{\phi}\) is the effective diffusivity of \(\phi\) and \(S_{\phi}\) is the volumetric source term (rate of production of \(\phi\) per unit volume). The reaction rates described by (12) are embedded into the source term \(S_{\phi}\).

Also note that the notation \(\phi = Z\) denotes the output variables i.e. biomass, substrate and ethanol concentrations. Using the KMS model, we can compute the mass of substrate and mass of product at the end of batch time over the total reactor volume, i.e.:

\[
MS_{sb} = \sum_{i=1}^{h} (S_i \Delta V_i)
\]

(24)

\[
MP_{sb} = \sum_{i=1}^{h} (P_i \Delta V_i)
\]

(25)

where the volume of medium in the reactor \(V_R\) is given by:
Here $h$ is the number of discretizations (i.e. finite volume). Then, we can calculate as follows:

$$\Phi_3 = \left[ \frac{Y}{Pr} \right] = \frac{100(MP_{\text{o}} - MP_{\text{o}}) / (MS_{\text{o}} - MS_{\text{o}})}{(MP_{\text{o}} - MP_{\text{o}}) / h}$$  \hspace{1cm} (27)

Here $MS_{\text{o}}$ and $MP_{\text{o}}$ correspond to the initial mass of substrate and mass of product (ethanol) in the fermentation medium, respectively.

### 2.5 Model Analysis and Validation

In this section, we develop the models using the proposed approaches. Then the models are analysed using ANOVA and validated against the experimental data (Noordin et al., 2004). The SDB model was developed using the input and output data as shown in Table 1, and the regression method results in the following quadratic model where the ANOVA analysis is presented in Tables 2 and 3:

$$\begin{align*}
Y &= 33.098 + \frac{-18.785 - 0.143}{0.234} AR + \frac{0 - 9.9 \times 10^{-4}}{1.02 \times 10^{-3}} SS + 0.147 AR \times SS \\
\end{align*}$$ \hspace{1cm} (28)

**Table 1: Experiment data**

<table>
<thead>
<tr>
<th>Std Order</th>
<th>Run Order</th>
<th>Black</th>
<th>C: Aeration Rate, AR (LPM)</th>
<th>E: Stirrer Speed, SS (rpm)</th>
<th>X: Yield, Y (%)</th>
<th>F: Productivity, Pr (g/L.hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1.25</td>
<td>200</td>
<td>21.50</td>
<td>0.180</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>1.0</td>
<td>150</td>
<td>14.788</td>
<td>0.999</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>1.25</td>
<td>200</td>
<td>21.050</td>
<td>0.176</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>1.0</td>
<td>250</td>
<td>15.105</td>
<td>0.102</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>1.5</td>
<td>250</td>
<td>24.040</td>
<td>0.160</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>1.5</td>
<td>150</td>
<td>16.392</td>
<td>0.106</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>1.25</td>
<td>200</td>
<td>24.000</td>
<td>0.230</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>1.25</td>
<td>200</td>
<td>23.500</td>
<td>0.280</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>9</td>
<td>1.25</td>
<td>200</td>
<td>22.250</td>
<td>0.190</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>1.25</td>
<td>129.29</td>
<td>18.511</td>
<td>0.115</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>11</td>
<td>1.25</td>
<td>200</td>
<td>23.500</td>
<td>0.210</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>12</td>
<td>0.90</td>
<td>200</td>
<td>20.500</td>
<td>0.165</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2: ANOVA Results for Yield**

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum of Squares</th>
<th>Degree of Freedom</th>
<th>Mean Square</th>
<th>F Value</th>
<th>P-value Prob &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>90.10</td>
<td>5</td>
<td>18.02</td>
<td>9.73</td>
<td>0.0047 Sig.</td>
</tr>
<tr>
<td>A – AR</td>
<td>21.17</td>
<td>1</td>
<td>21.17</td>
<td>11.44</td>
<td>0.0117</td>
</tr>
<tr>
<td>B – SS</td>
<td>28.20</td>
<td>1</td>
<td>28.20</td>
<td>15.24</td>
<td>0.0059</td>
</tr>
<tr>
<td>AB</td>
<td>13.44</td>
<td>1</td>
<td>13.44</td>
<td>7.26</td>
<td>0.0309</td>
</tr>
<tr>
<td>A²</td>
<td>12.76</td>
<td>1</td>
<td>12.76</td>
<td>6.90</td>
<td>0.0341</td>
</tr>
<tr>
<td>B²</td>
<td>16.60</td>
<td>1</td>
<td>16.60</td>
<td>8.97</td>
<td>0.0201</td>
</tr>
<tr>
<td>Residual</td>
<td>10.64</td>
<td>3</td>
<td>3.55</td>
<td>6.12</td>
<td>0.0563 Not Sig.</td>
</tr>
<tr>
<td>Lack of Fit</td>
<td>2.32</td>
<td>4</td>
<td>0.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>132.31</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The ANOVA results demonstrate that the model is highly significant, as indicated by the Fisher’s $F$ test ($F_{\text{model}} = 9.73$ and 9.3) and a low “Prob $> F$” value ($P_{\text{model}} > 0.0047$ and $> 0.0054$). Additionally, the goodness of the fit of the model is also checked by the determination coefficient ($R^2$). In this case, the values of the determination coefficient ($R^2 = 0.8743$ and $R^2 = 0.8691$) indicate that 87% of the sample variation in yield and productivity are well explained by the model. Thus, the SDB model is statistically adequate to predict the yield and productivity within the range of experimental setting.

<table>
<thead>
<tr>
<th>Run Order</th>
<th>$k_1$</th>
<th>$k_2$</th>
<th>$k_3$</th>
<th>$k_4$</th>
<th>$k_5$</th>
<th>$k_6$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.4085</td>
<td>0.0010</td>
<td>0.6631</td>
<td>0.1040</td>
<td>0.7558</td>
<td>0.0143</td>
</tr>
<tr>
<td>2</td>
<td>1.3245</td>
<td>0.0010</td>
<td>0.6559</td>
<td>0.0770</td>
<td>0.8788</td>
<td>0.0163</td>
</tr>
<tr>
<td>3</td>
<td>1.1257</td>
<td>0.0010</td>
<td>0.6333</td>
<td>0.0989</td>
<td>0.7292</td>
<td>0.0173</td>
</tr>
<tr>
<td>4</td>
<td>1.2594</td>
<td>0.0010</td>
<td>0.6731</td>
<td>0.0879</td>
<td>0.7127</td>
<td>0.0179</td>
</tr>
<tr>
<td>5</td>
<td>2.5629</td>
<td>0.0010</td>
<td>0.6999</td>
<td>0.1026</td>
<td>0.8366</td>
<td>0.0125</td>
</tr>
<tr>
<td>6</td>
<td>1.4925</td>
<td>0.0010</td>
<td>0.6703</td>
<td>0.1310</td>
<td>0.6328</td>
<td>0.0123</td>
</tr>
</tbody>
</table>

For the kinetics hybrid model, solving the optimisation problem of $P_2$ gives the predicted Herbert’s kinetic parameters as shown in Table 4. This set of data is then used to obtain the following regressed linear model by solving the optimisation problem of $P_3$:

$$\begin{align*}
1.4085 &- 0.2852X_1 + 0.3692X_2 \\
\end{align*}$$ \hspace{1cm} (29)

By combining the linear model of (29) with the macro scale bioreactor of (1) to (7), the kinetics hybrid model was obtained. This model is validated against another set of experimental data of AR and SS, which were chosen within the experimental range, i.e. 1.2LPM AR and 175rpm SS. Fig. 1 shows the example results of model validation. Similar results were obtained for both actual glucose and biomass concentrations. Due to the space limitation, we do not show the results in this paper.
The ANOVA results of the fitness of the KMS model are shown in Table 5. We do not show the ANOVA results for the productivity due to the space limitation.

Table 5: ANOVA results on yield for the KMS model

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum of Squares</th>
<th>Degree of Freedom</th>
<th>Mean Square</th>
<th>F Value</th>
<th>p-value</th>
<th>Prob &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>52.65</td>
<td>5</td>
<td>10.53</td>
<td>7.10</td>
<td>0.0115</td>
<td>Sig.</td>
</tr>
<tr>
<td>Residual</td>
<td>10.38</td>
<td>7</td>
<td>1.48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of Fit</td>
<td>6.75</td>
<td>3</td>
<td>2.25</td>
<td>2.48</td>
<td>0.2003</td>
<td>Not Sig.</td>
</tr>
<tr>
<td>Pure Error</td>
<td>3.63</td>
<td>4</td>
<td>0.91</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The determination coefficients of the KMS model are $R^2 = 0.8353$ and $R^2 = 0.8021$, respectively for the yield and productivity. This result shows that more than 80% of the sample variation in yield and productivity are well explained by the model. Thus, statistically the model is sufficiently accurate in terms of the prediction for yield and productivity within the experimental range.

3. OPTIMIZATION OF THE BIOREACTOR

Our objective is to find the optimum AR and SS by maximizing the yield and productivity using the developed models, i.e. SDB, KH and KMS models. The optimization problem is formulated as follows:

$$P_o : \max_{x_{\text{min}} \leq x \leq x_{\text{max}}} \{ \phi(\vec{X}) \}$$

Subject to: the model (i.e. SDB, KH or KMS Model).

To solve this optimization problem, we can use a nonlinear programming technique, but in this study, we employ RSM technique to find the optimum AR and SS.

From Fig. 2, we observe that there is a significant (quadratic) effect of AR and SS on the response surface. In general, the response of yield increases as the SS increases from 150rpm to its peak value at 242rpm. Additionally, the yield shows a significant increase with the increase in AR. Overall, the SDB model demonstrates a reasonable prediction of the impacts of AR and SS on the values of yield. For the KH model, the effects of AR and SS on the yield are shown in Fig. 3. The surface responses show that the yield and productivity increase with the increase of AR and SS. Thus, this suggests that the KH model was able to capture the effect of both AR and SS on the yield. Just like the SDB model, the KH model is able to predict the impacts of AR and SS on the yield reasonably well.
productivity using different models. The KMS model exhibits the best prediction of maximum experimental yield and productivity. This means that by including the CFD model in the macro bioreactor model, the effect of mixing arising from the AR and SS can reasonably be captured by the KMS model – provide the most accurate prediction of yield and productivity. Despite its simplicity, the SDB model predictions are relatively better than the KH model predictions. The fact that KH model resulted in the largest error in the predictions of maximum experimental yield and productivity suggested that there was a significant deviation from ideal mixing inside the bioreactor. Interestingly, despite this significant deviation from the ideal mixing condition, the SDB model was shown to be capable of predicting the maximum yield and productivity with a sufficient accuracy i.e. less than 5% error.

Table 6: Comparisons of Model Predictions and Experimental Results for Yield

<table>
<thead>
<tr>
<th>ℓ- Model</th>
<th>Optimum Aeration Rate (LPM)</th>
<th>Optimum Stirrer Speed (rpm)</th>
<th>Model Predicted Maximum Yield (%)</th>
<th>Experimentally Verified Maximum Yield (%)</th>
<th>Error Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDB</td>
<td>1.47</td>
<td>242</td>
<td>24.49</td>
<td>23.72</td>
<td>3.46</td>
</tr>
<tr>
<td>KH</td>
<td>1.43</td>
<td>250</td>
<td>21.15</td>
<td>20.95</td>
<td>14.73</td>
</tr>
<tr>
<td>KMS</td>
<td>1.45</td>
<td>240</td>
<td>24.12</td>
<td>24.57</td>
<td>1.80</td>
</tr>
</tbody>
</table>

The yield obtained by using the AR and SS values from the KMS model is adopted as the experimentally maximum value, with respect to which the error is calculated.

Table 7: Comparisons of Model Predictions and Experimental Results for Productivity

<table>
<thead>
<tr>
<th>ℓ- Model</th>
<th>Optimum Aeration Rate (LPM)</th>
<th>Optimum Stirrer Speed (rpm)</th>
<th>Model Predicted Maximum Prod. (g.L/hr)</th>
<th>Experimentally Verified Maximum Prod. (g.L/hr)</th>
<th>Error Prod. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDB</td>
<td>1.47</td>
<td>242</td>
<td>0.198</td>
<td>0.185</td>
<td>11.90</td>
</tr>
<tr>
<td>KH</td>
<td>1.43</td>
<td>250</td>
<td>0.150</td>
<td>0.148</td>
<td>29.52</td>
</tr>
<tr>
<td>KMS</td>
<td>1.45</td>
<td>240</td>
<td>0.207</td>
<td>0.210</td>
<td>1.43</td>
</tr>
</tbody>
</table>

The productivity obtained by using the AR and SS values from the KMS model is adopted as the experimentally maximum value, with respect to which the error is calculated.

4. CONCLUSIONS

In this paper, we have proposed three multi-scale models of a batch bioreactor by expanding the Herbert’s kinetics concept to incorporate the mixing conditions. It was shown that the models could be used to optimize the bioreactor’s performances. Furthermore, it was found from this study that the incorporation of mixing CFD model into the KH model of microbial kinetics (i.e. KMS modelling approach) could predict reasonably well the optimum yield and productivity by adjusting the aeriation rate and stirrer speed. As the results, the developed models could be used for studying the effects of AR and SS on the rates of growth, substrate consumption and product formation, which is not possible using the conventional models.

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REFERENCES


