A Model of Fed-batch Culture of Hybridoma Cells

A mathematical model for fed-batch culture of hybridoma cells [24] has been employed for generating simulation data in this study. The model is a seventh-order nonlinear model where both glucose and glutamine concentrations are used to describe the specific growth rate, $\mu$. The cell death rate, $k_d$, is governed by lactate, ammonia and glutamine concentrations. The specific $MAb$ production rate, $q_{MAb}$, is estimated using a variable yield coefficient model related to the physiological state of the culture through the specific growth rate. The mass balance equations for the system in fed-batch mode are:

$$\frac{dX_v}{dt} = (\mu - k_d)X_v - \frac{F}{V}X_v$$
$$\frac{dGlc}{dt} = (Glc_{in} - Glc)\frac{F}{V} - q_{glc}X_v$$
$$\frac{dGln}{dt} = (Gln_{in} - Gln)\frac{F}{V} - q_{gln}X_v$$
$$\frac{dLac}{dt} = q_{lac}X_v - \frac{F}{V}Lac$$
$$\frac{dAmm}{dt} = q_{amm}X_v - \frac{F}{V}Amm$$
$$\frac{dMAb}{dt} = q_{MAb}X_v - \frac{F}{V}MAb$$
$$\frac{dV}{dt} = F$$

(A.1)

with the following kinetic expressions:

$$\mu = \mu_{max} \left[ \frac{Glc}{K_{Glc} + Glc} \right] \left[ \frac{Gln}{K_{Gln} + Gln} \right]$$
$$k_d = k_{dmax}(\mu_{max} - k_{dalac}Lac)^{-1}(\mu_{max} - k_{damm}Amm)^{-1}k_{dglc}\frac{Gln}{K_{Gln} + Gln}$$
$$q_{gln} = \frac{\mu}{Y_{xv/gln}}$$
$$q_{glc} = \frac{\mu}{Y_{xv/glc}} + m_{glc} \left[ \frac{Glc}{K_{gln} + Glc} \right]$$
$$q_{lac} = Y_{lac/gl} q_{glc}$$
$$q_{amm} = Y_{amm/gl} q_{gln}$$
$$q_{MAb} = \alpha' \mu + \beta$$

where $X_v$, $Glc$, $Gln$, $Lac$, $Amm$ and $MAb$ are respectively the concentrations in viable cells, glucose, glutamine, lactate, ammonia and monoclonal antibodies; $V$ is the fermentor volume and $F$ the volumetric feed rate; $Glc_{in}$ and $Gln_{in}$ are the concentrations of glucose and glutamine in the feed stream,


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respectively; \( q_{\text{glc}} \), \( q_{\text{gln}} \), \( q_{\text{lac}} \), \( q_{\text{amm}} \) and \( q_{\text{MAb}} \) are the specific rates; \( Y_{xv/\text{glc}} \), \( Y_{xv/\text{gln}} \) and \( Y_{\text{lac/glc}} \) are yield coefficients. The parameter values are tabulated in Table A.1.

**Table A.1.** The parameter values of the kinetic model

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \mu_{\text{max}} )</td>
<td>1.09d(^{-1} )</td>
</tr>
<tr>
<td>( k_{d_{\text{max}}} )</td>
<td>0.69d(^{-1} )</td>
</tr>
<tr>
<td>( Y_{xv/\text{glc}} )</td>
<td>( 1.09 \times 10^8 \text{cells/mmol} )</td>
</tr>
<tr>
<td>( Y_{xv/\text{gln}} )</td>
<td>( 3.8 \times 10^8 \text{cells/mmol} )</td>
</tr>
<tr>
<td>( m_{\text{glc}} )</td>
<td>0.17mmol ( \cdot ) 10(^{-7} ) cells ( \cdot ) d(^{-1} )</td>
</tr>
<tr>
<td>( k_{\text{mglc}} )</td>
<td>19.0mM</td>
</tr>
<tr>
<td>( K_{\text{glc}} )</td>
<td>1.0mM</td>
</tr>
<tr>
<td>( K_{\text{gln}} )</td>
<td>0.3mM</td>
</tr>
<tr>
<td>( \alpha_0 )</td>
<td>2.57mg ( \cdot ) 10(^{-8} ) cells ( \cdot ) d(^{-1} )</td>
</tr>
<tr>
<td>( K_{\mu} )</td>
<td>0.02d(^{-1} )</td>
</tr>
<tr>
<td>( \beta )</td>
<td>0.35mg ( \cdot ) 10(^{-8} ) cells ( \cdot ) d(^{-1} )</td>
</tr>
<tr>
<td>( k_{\text{dlac}} )</td>
<td>0.01d(^{-1} )mM(^{-1} )</td>
</tr>
<tr>
<td>( k_{\text{damm}} )</td>
<td>0.06d(^{-1} )mM(^{-1} )</td>
</tr>
<tr>
<td>( k_{d_{\text{gln}}} )</td>
<td>0.02mM</td>
</tr>
<tr>
<td>( Y_{\text{lac/glc}} )</td>
<td>1.8mmol/mmol</td>
</tr>
<tr>
<td>( Y_{\text{amm/gln}} )</td>
<td>0.85mmol/mmol</td>
</tr>
</tbody>
</table>

The multi-feed case, which involves two separate feeds \( F_1 \) and \( F_2 \) for glucose and glutamine respectively, is reformulated as follows:

\[
\frac{dX_v}{dt} = (\mu - k_d)X_v - \frac{F_1 + F_2}{V} X_v \\
\frac{dGlc}{dt} = (Glc_{in} - Glc) \frac{F_1 + F_2}{V} - q_{\text{glc}} X_v \\
\frac{dGln}{dt} = (Gln_{in} - Gln) \frac{F_1 + F_2}{V} - q_{\text{gln}} X_v \\
\frac{dLac}{dt} = q_{\text{lac}} X_v - \frac{F_1 + F_2}{V} Lac \\
\frac{dAmm}{dt} = q_{\text{amm}} X_v - \frac{F_1 + F_2}{V} Amm \\
\frac{dMAb}{dt} = q_{\text{MAb}} X_v - \frac{F_1 + F_2}{V} MAb \\
\frac{dV}{dt} = F_1 + F_2 \tag{A.3}
\]

The following initial culture conditions and feed concentrations are used in the work:

\[
X_v(0) = 2.0 \times 10^8 \text{cells/L} \\
Glc(0) = 25mM \\
Gln(0) = 4mM \\
Lac(0) = Amm(0) = MAb(0) = 0 \\
Clc_{in} = 25mM \\
Glnin = 4mM \\
V(0) = 0.79L \tag{A.4}
\]

The above mathematical models and initial conditions have been used to generate a ‘reality’ for testing the schemes proposed in the work.
An Industrial Baker’s Yeast Fermentation Model

A mathematical model of an industry fed-batch fermentation process, which was given in [19], is used to describe the system. The kinetics of yeast metabolism that is considered in the model is based on the bottleneck hypothesis [18]. The model is governed by a set of differential equations derived from mass balances in the system. It comprises the following equations:

Balance equations:

$\frac{d(V \cdot C_s)}{dt} = F \cdot S_0 - \left( \frac{\mu}{Y_{ox/s}} + \frac{Q_{e,pr}}{Y_{e/s}} + m \right) \cdot V \cdot X$ (B.1)

$\frac{d(V \cdot C_o)}{dt} = -Q_o \cdot V \cdot X + k_{L,a_o} \cdot (C_o^* - C_o) \cdot V$ (B.2)

$\frac{d(V \cdot C_c)}{dt} = Q_c \cdot V \cdot X + k_{L,a_c} \cdot (C_c^* - C_c) \cdot V$ (B.3)

$\frac{d(V \cdot C_e)}{dt} = (Q_{e,pr} - Q_{e,ox}) \cdot V \cdot X$ (B.4)

$\frac{d(V \cdot X)}{dt} = \mu \cdot V \cdot X$ (B.5)

$\frac{dV}{dt} = F$ (B.6)

where, $C_s$, $C_o$, $C_c$, $C_e$, $X$, and $V$ are state variables which denote concentrations of glucose, dissolved oxygen, carbon dioxide, ethanol, and biomass, respectively; $V$ is the liquid volume of the fermentation; $F$ is the feed rate which is the input of the system; $m$ is the glucose consumption rate for the maintenance energy; $Y_{e/s}$ and $Y_{ox/s}$ are yield coefficients; $k_{L,a_o}$ and $k_{L,a_c}$ are volumetric mass transfer coefficients; $S_0$ is the concentration of feed.

Glucose uptake rate:

$Q_s = Q_{s,max} \frac{C_s}{K_s + C_s}$ (B.7)

Oxidation capacity:

An Industrial Baker’s Yeast Fermentation Model

\[ Q_{o,lim} = Q_{o,max} \frac{C_o}{K_o + C_o} \quad (B.8) \]

Specific growth rate limit:

\[ Q_{s,lim} = \frac{\mu_{s,lim}}{Y_{x/s} C_s} \quad (B.9) \]

Oxidative glucose metabolism:

\[ Q_{s,ox} = \min \left( \frac{Q_s}{Q_{s,lim}}, \frac{Y_{s/o} Q_{o,lim}}{Y_{x/o} Q_{s,lim}} \right) \quad (B.10) \]

Reductive glucose metabolism:

\[ Q_{s,red} = Q_s - Q_{s,ox} \quad (B.11) \]

Ethanol uptake rate:

\[ Q_{e,up} = Q_{e,max} \frac{C_e}{K_e + C_e} \frac{K_i}{K_i + C_i} \quad (B.12) \]

Oxidative ethanol metabolism:

\[ Q_{e,ox} = \min \left( \frac{Q_{e,up}}{(Q_{o,lim} - Q_{s,ox} Y_{x/o}) Y_{e/o}} \right) \quad (B.13) \]

Ethanol production rate:

\[ Q_{e,pr} = Y_{e/s} Q_{s,red} \quad (B.14) \]

Total specific growth rate:

\[ \mu = \mu_{oz} + \mu_{red} + \mu_e \quad \text{or} \quad \mu = Y_{x/s} Q_{s,ox} + Y_{x/e} Q_{s,red} + Y_{z/e} Q_{e,ox} \quad (B.15) \]

Carbon dioxide production rate:

\[ Q_c = Y_{x/s} Q_{s,ox} + Y_{x/e} Q_{s,red} + Y_{z/e} Q_{e,ox} \quad (B.16) \]

Oxygen consumption rate:

\[ Q_o = Y_{o/s} Q_{s,ox} + Y_{o/e} Q_{e,ox} \quad (B.17) \]

Respiratory Quotient:

\[ RQ = \frac{Q_c}{Q_o} \quad (B.18) \]

The model parameters and initial conditions that are used for dynamic simulations are listed in Table B.1 and Table B.2.
Table B.1. The parameter values of the industrial model.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
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<tr>
<td>$m$</td>
<td>0.00321</td>
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<tr>
<td>$K_{La_0}$</td>
<td>600</td>
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<tr>
<td>$K_e$</td>
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<tr>
<td>$Y_{c/e}$</td>
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<td>$K_l$</td>
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<td>$Y_{o/e}$</td>
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<tr>
<td>$K_s$</td>
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<tr>
<td>$Y_{ox}$</td>
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<tr>
<td>$Q_{e,max}$</td>
<td>0.70805</td>
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<tr>
<td>$Y_{c/s}$</td>
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</tr>
<tr>
<td>$Q_{s,max}$</td>
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<tr>
<td>$Y_{c/s}$</td>
<td>1.9</td>
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<tr>
<td>$Q_{o,max}$</td>
<td>0.2</td>
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<tr>
<td>$Y_{o/s}$</td>
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<tr>
<td>$\mu_{cr}$</td>
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<tr>
<td>$C^*_{o}$</td>
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<tr>
<td>$Y_{x/e}$</td>
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<td>$C^*_c$</td>
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<td>$Y_{ox}$</td>
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<tr>
<td>$K_{La_c}$</td>
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<tr>
<td>$Y_{red}$</td>
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<tr>
<td>$Y_{x/s}$</td>
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<tr>
<td>$K_o$</td>
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Table B.2. Initial conditions for dynamic simulation.

<table>
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<tr>
<th>State variables</th>
<th>Values</th>
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<tr>
<td>$C_s$</td>
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<tr>
<td>$V$</td>
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<tr>
<td>$C_c$</td>
<td>0</td>
</tr>
<tr>
<td>$C_o$</td>
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<tr>
<td>$C_c$</td>
<td>0</td>
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<tr>
<td>$X$</td>
<td>0.54</td>
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References

References


