Productivity optimization of cultures of *Saccharomyces cerevisiae* using a simple robust control strategy

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Introduction

- **Process**: yeast fed-batch culture
- **Aim**: maximize biomass productivity

\[ Y_x = \frac{1}{t_f} \frac{V(t_f)X(t_f) - V_0X_0}{G_{in}(V(t_f) - V_0)} \]
Introduction

Yeast limited respiratory capacity

\[ G < G_{\text{crit}} \]
\[ r_0 < r_{\text{omax}} \]

- **Respirative Regime**
  - Ethanol is consumed

- **Optimal Operating Conditions**

\[ G = G_{\text{crit}} \]
\[ r_0 = r_{\text{omax}} \]

- **Respiro-Fermentative Regime**
  - Ethanol is produced

\[ G > G_{\text{crit}} \]
Introduction

Reaction scheme

- Glucose oxidation:
  \[ k_5O + G \xrightarrow{r_1} k_1X + k_7P \]

- Glucose fermentation:
  \[ S \xrightarrow{r_2} k_2X + k_4E + k_8P \]

- Ethanol oxidation:
  \[ k_6O + E \xrightarrow{r_3} k_3X + k_9P \]
Outline

- Model linearization
  - Feed-Oxygen transfer
  - Feed-Ethanol transfer
- Simple design of two adaptive robust controllers
- Comparison of the two control strategies
- Experimental results
- Conclusions
Model linearization
Feed-Oxygen Model

Main assumption:

\[ \begin{align*}
\frac{d(VG)}{dt} & \approx 0 \\
q_s &= r_1 + r_2 \\
q_o &= k_5 r_1 + k_6 r_3
\end{align*} \]

\[ \rightarrow X = \frac{F_{in} G_{in}}{q_s V} \]

and

\[ \frac{dO}{dt} = -\left( \frac{q_o}{q_s} G_{in} + O \right) \frac{F_{in}}{V} + k_L a (O_{sat} - O) \]

Defining a nominal trajectory around which the system is linearized: \( \text{Fin}^*(t), V^*(t) \) so that \( O^*(t) = O_{ref} \)

\[ \frac{q_o^*}{q_s^*} \approx k_5 \] (considering only respiration on glucose so that \( r_2 \) and \( r_3 \) are equal to 0)
Model linearization
Feed-Oxygen Model

- Considering $O^*(t) = O_{ref}$:

$$D^* = \frac{F_{in}^*}{V^*} = \frac{OTR^*}{k \_5 G_{in} + O^*}$$

which is constant.

If the variation of $V$ is neglected, a Taylor series expansion limited to the first order around the nominal trajectory allows to write:

$$\frac{d \delta O}{dt} = -\left( \frac{k \_5 G_{in} + O^*}{V^*} \right) \delta F_{in} - (k \_L a + D^*) \delta O \quad (*)$$

$$\delta O = O - O^*$$

$$\delta F_{in} = F_{in} - F_{in}^*$$

and, assuming that $D$ is negligible in comparison with $k \_L a$, (*) becomes:

$$\frac{d \delta O}{dt} = -\left( \frac{k \_5 G_{in} + O^*}{V^*} \right) \delta F_{in} - k \_L a \ \delta O \quad (5)$$
Model linearization
Feed-Oxygen Model

- As the principal variation of the volume is due to the added feed-rate:
  \[
  \frac{dV}{dt} = F_{in}^*
  \]
  
  the solution of this differential equation is:
  \[
  F_{in}^*(t) = D^*V_0 \exp(D^*t)
  \]

Putting all together

\[
\frac{d (O - O^*)}{dt} = -\left( \frac{k_5 G_{in} + O^*}{V^*} \right) [ F_{in} - D^*V_0 \exp(D^*t) ] - k_L a (O - O^*)
\]

whose Laplace transform is given by:

\[
O(p) = -\frac{1}{k_L a} \left( \frac{k_5 G_{in} + O^*}{V^*} \right) \left[ \frac{F_{in}(p) - D^*V_0}{p - D^*} \right]
\]
Finally, the discrete-time linear model is given by:

\[
O(k) = \frac{b}{1-a} \frac{q^{-1}}{q^{-1}} \left[ F_{in}(k) - d_i(k) \right]
\]

\[
d_i(k) = \frac{c}{1-\gamma} \frac{q^{-1}}{q^{-1}} \delta(k)
\]

An equivalent Feed-ethanol model can be obtained considering another optimal trajectory \(E^*(t)=E_{ref}\) and assuming again that:

\[
\frac{d(VG)}{dt} \approx 0 \iff r_2 XV = F_{in} G_{in} - r_1 XV
\]

Simple manipulations lead to:

\[
E(k) = \frac{b}{1-a} \frac{q^{-1}}{q^{-1}} \left[ F_{in}(k) - d_i(k) \right]
\]

\[
d_i(k) = \frac{c}{1-\gamma} \frac{q^{-1}}{q^{-1}} \delta(k)
\]
## Model linearization

### Feed-Ethanol and feed-oxygen models

<table>
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<tr>
<th>Parameters</th>
<th>Oxygen model</th>
<th>Ethanol model</th>
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<td>Both regimes</td>
<td>Respiro-fermentative</td>
<td>Respirative</td>
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<tr>
<td>$\delta(k)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$a$</td>
<td>$\exp(-k_a T_S)$</td>
<td>1</td>
</tr>
<tr>
<td>$c_1$</td>
<td>$\frac{k_S}{k_T} \frac{O^*}{Q V}$</td>
<td></td>
</tr>
<tr>
<td>$b$</td>
<td>$\frac{1}{1 - k_T \frac{Q}{V}}$</td>
<td>$T_S \frac{k_4 G_{in} - E^<em>}{V^</em>}$</td>
</tr>
<tr>
<td>$c$</td>
<td>$V_{a(k)} \gamma$</td>
<td>$\frac{k_4 r_1^<em>}{k_4 G_{in} - E^</em>} V_0 X_0$</td>
</tr>
<tr>
<td>$F_{in}(k)$</td>
<td>$- \exp(D^* T_S)$</td>
<td>$b q^{-1} \exp(\mu T_S)$</td>
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### Linear model:

$\delta(k)$
Outline

- Model linearization
  - Simple design of an adaptive robust controller
    - RST controller
    - Adaptation scheme
    - Some simulation results
    - Model improvements
- Comparison of the two control strategies
- Experimental results
- Conclusions
Simple design of an adaptive robust controller

- Exponential disturbance.
- Variation of the kinetic parameter:

\[ \gamma = \exp(\mu T_s) \text{ or } \exp(D^* T_s) \]

- Variation of the gain \( b \) according to the operating regime.

- The controller must be able to:
  - Reject an exponential disturbance (Internal model principle).
  - Robustify the system against uncertainties on \( \gamma \) and \( b \).
**Controller:**

\[
R(q^{-1})F_{in}(k) = -S(q^{-1})E(k) + T(q^{-1})E_{ref}(k)
\]
Simple design of an adaptive robust controller

- Polynomials $R, S, T$ computed by a pole-placement procedure.
- Unstable pole in the polynomial $D = 1 - \gamma q^{-1}$ → must be included in the $R$ polynomial.

- Closed loop:
  \[ E = \frac{BT}{AR + BS} E_{ref} + \frac{BR}{AR + BS} d \]

- Reference model:
  \[ H_m = \frac{B_m(q^{-1})A_m(1)}{B_m(1)A_m(q^{-1})} \]

Robustness

Tracking behaviour

Tracking behaviour
Simple design of an adaptive robust controller

1) Choose the tracking dynamics by choosing the $A_m$ zeros.

2) Tune the robust behaviour by choosing the $A_0$ zeros.

3) Solve the diophantine equation:

$$ A \ D \ R' + B S = A_0 A_m $$

so as to obtain the $R'$ and $S$ polynomials.

4) $T$ is given by:

$$ T = A_0 \frac{A_m(1)}{B(1)} $$
Adaptation scheme

Sometimes, $\mu$ varies during the culture and must be adapted (RLS algorithm):

$$\hat{d}(k) = Ay(k) - Bu(k)$$

$$D(q^{-1})\hat{d}(k) = 0$$

$$\hat{d}(k) = \hat{d}(k-1) \gamma$$

$$\gamma = \exp(\mu T_s)$$

The gain $b$ is updated with the volume $V$ and the ethanol concentration $E$ measurements:

$$b(k) = \frac{k_4 G_{in} - E(k)}{V(k)} T_s$$
Adaptation scheme

RST controller

$E_{\text{ref}}$

$E$

$F_{\text{in}}$

Bioreactor

$V$

$E$

$b$ adaptation

$\gamma$ adaptation

$\hat{b}$

$\hat{\gamma}$
Case study: ethanol regulation

- **Initial and operating conditions:**
  - $X_0 = 0.4 \text{ g/l}$
  - $E_0 = 0.5 \text{ g/l}$
  - $G_0 = 0.0125 \text{ g/l}$
  - $V_0 = 5 \text{ l}$
  - $G_{\text{in}} = 500 \text{ g/l}$
  - $E_{\text{in}} = 0.1 \text{ g/l}$
  - $E_{\text{ref}} = 1 \text{ g/l}$

- **Controller parameters:**
  - $a_1 = 0.7$
  - $b_0 = (k_4 G_{\text{in}} - E_0) / V_0$
Controller design

1) \( A_m = 1 - 0.9 \ q^{-1} \)
2) \( A_0 = 1 - 0.7 \ q^{-1} \)
3) Solving the diophantine equation:

\[
A \ D \ R' + BS = A_0 A_m
\]

We obtain \( R' = 1 \)

\[
S = s_0(\gamma,b) + s_1(\gamma,b) \ q^{-1}
\]

4) \( T = (1 - 0.7 \ q^{-1}) \ A_m(1)/b \)
Controller design

Robustness evaluation on the Black diagram:

The direct sensibility:

\[ \sigma_c = 3 \text{ dB} \]
\[ \sigma_d = 6 \text{ dB} \]

The complementary sensibility:

\[ < 6 \text{ dB} \]
\[ < 3 \text{ dB} \]
Controller design

- Robustness insured by the $a_1$ parameter:

  $$a_1 = 0.7$$

- Good disturbance rejection when $\gamma$ is well adapted:

  $$\gamma \approx 1.023$$
Robustness analysis

\[ A_0 = 1 \]

\[ \sigma_c = 3 \, \text{dB} \]

\[ \sigma_d = 6 \, \text{dB} \]

\[ a_1 = 0.6, 0.7, 0.8, 0.9 \]

\[ A_0 = 1 - a_1 q^{-1} \]
Controller design

Black diagram

\[ \gamma = 1, 1.01, 1.02, 1.03 \]
Simulation results

Reaction rates

- **Biomass [g/l]**
  - Biomass levels are plotted against time [h].

- **Glucose [g/l]**
  - Glucose consumption is shown with time.

- **Ethanol oxidation**
  - Ethanol oxidation rates are depicted with time.

- **Glucose oxidation**
  - Glucose oxidation rates are illustrated with time.

- **Glucose fermentation**
  - Glucose fermentation rates are shown with time.
Adaptation

If $b$ is not adapted the gain margin increases but the phase margin decreases when $V$ grows
Adaptation

b is constant

b is adapted
Adaptation

b is constant

b is adapted
Model improvements

- Ethanol response to feed variations is delayed (≈12 min).
- Delay = 2 sampling periods.
- Ethanol probe dynamics generally neglected (1-3min).
- New model:

\[
H(q^{-1}) = \frac{b \ q^{-3} \left[ (T_s + T_{mes} (\nu - 1)) + (T_{mes} - \nu (T_s + T_{mes})) \right] q^{-1}}{(1-q^{-1})(1-\nu \ q^{-1})}
\]

\[
\nu = e^{-\frac{T_s}{T_{mes}}}
\]
Outline

- Model linearization
- Simple design of an adaptive robust controller
- Comparison of the two control strategies
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- Conclusions
Simulations

- **Initial and operating conditions:**
  - $X_0 = 0.4 \text{ g/l}$
  - $E_0 = 0.9 \text{ g/l}$
  - $G_0 = 0.012 \text{ g/l}$
  - $O_0 = 100\%$
  - $V_0 = 6.8 \text{ l}$
  - $G_{in} = 350 \text{ g/l}$
  - $E_{ref} = 1 \text{ g/l}$ or $O_{ref} = 20\%$

- **Controller parameters:**
  - $A_0 = 1 - 0.7q^{-1}$ for Oxygen regulation
  - $A_0 = (1 - 0.9q^{-1})(1 - 0.95q^{-1})$ for Ethanol regulation
  - $b_0 = (k_4 G_{in} - E_0)/V_0$
Simulation results
PO2-Feed regulation

Measured $O_2$ (continuous line) and reference $O_{\text{ref}}$ (dotted line)

$Y_X = 0.011 \text{ g/gh}$
Simulation results
Ethanol-Feed regulation

Measurements E (continuous line) and reference E_{ref} (dotted line)

Y_{X} = 0.024 g/gh
Experimental results
Conclusions

- 2 simple linear models with the same structure.
- Linear framework is well-adapted to stability and robustness analysis.
- Only one measured concentration: O or E.
- Improvements of the model based on experimental observations.
- 40% improvement in productivity compared to conventional bioprocesses.
Some extensions

$E_{in} > E_{ref}$:
- Imposes the consumption of ethanol (respirative regime).

$E_{in} < E_{ref}$:
- Imposes the production of ethanol (respiro-fermentative).

Interesting in some applications.
Biological interpretation

Yeasts’ limited respiratory capacity

Respirative Regime - Ethanol is consumed -

V.E = constant

Optimal Operating Conditions

Respiro-Fermentative Regime - Ethanol is produced -

\[ E_{in} > E_{ref} \]

\[ E_{in} < E_{ref} \]
Forced respirative regime:

\[ E_{\text{in}} > E_{\text{ref}} \]

- Ethanol consumption
- Only in respirative regime
Forced respiro-fermentative regime: $E_{\text{in}} < E_{\text{ref}}$

Ethanol production

Only in respiro-fermentative regime