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

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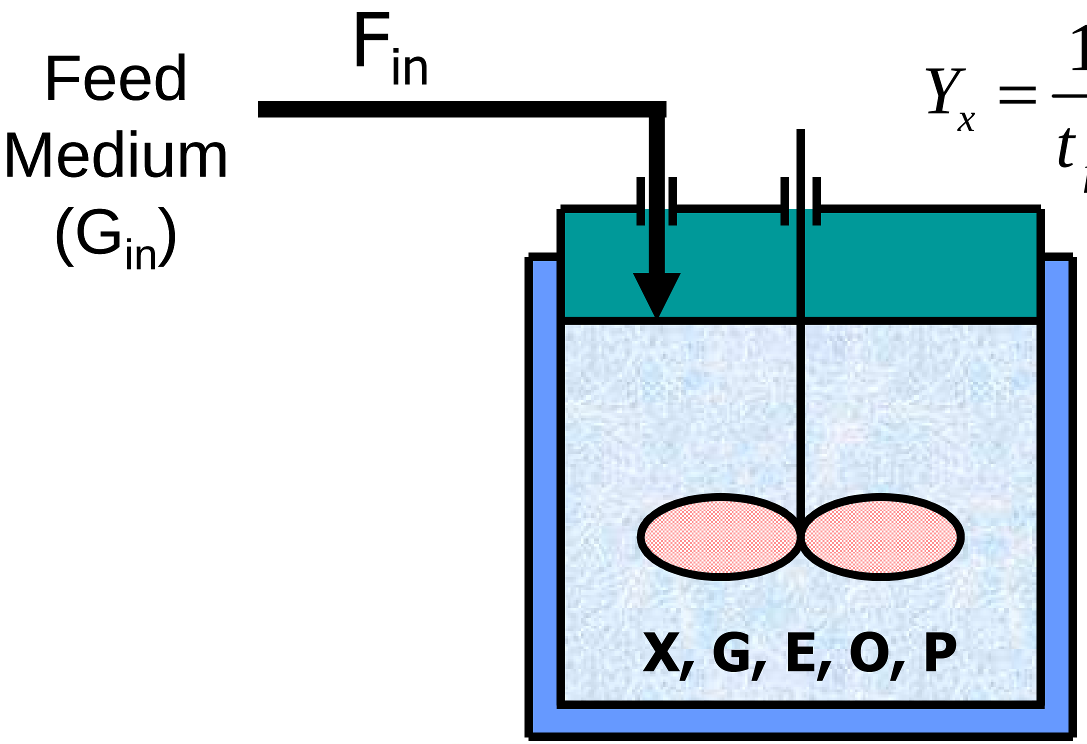
Introduction

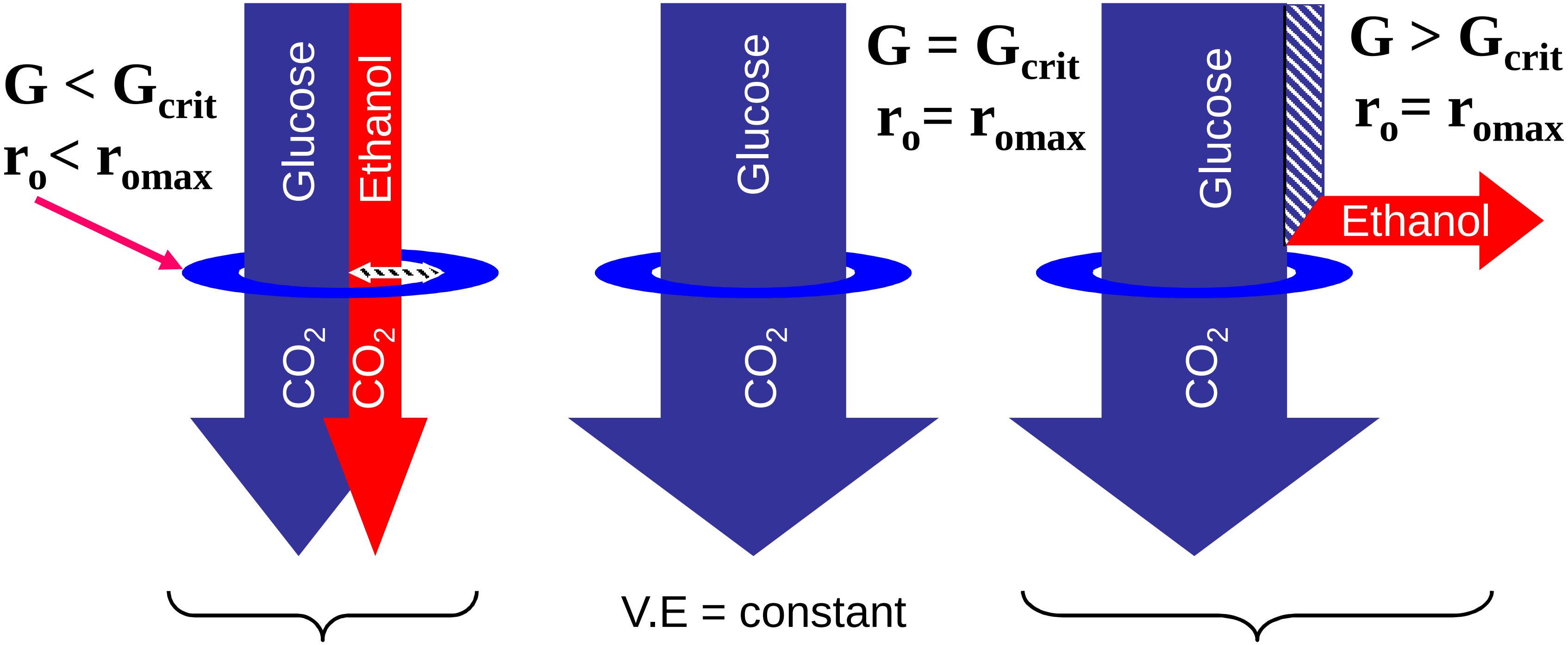
- **Process** : yeast fed-batch culture
- **Aim** : maximize biomass productivity



$$Y_x = \frac{1}{t_f} \frac{V(t_f)X(t_f) - V_0 X_0}{G_{in}(V(t_f) - V_0)}$$

Introduction

❑Yeast limited respiratory capacity



Respirative Regime
- Ethanol is consumed -

Optimal Operating Conditions

Respiro-Fermentative Regime
- Ethanol is produced -

Introduction

❑ Reaction scheme

- Glucose oxidation: $k_5 O + G \xrightarrow{r_1} k_1 X + k_7 P$
- Glucose fermentation: $S \xrightarrow{r_2} k_2 X + k_4 E + k_8 P$
- Ethanol oxidation: $k_6 O + E \xrightarrow{r_3} k_3 X + k_9 P$

$$\begin{bmatrix} \dot{X} \\ \dot{G} \\ \dot{E} \\ \dot{O} \\ \dot{P} \end{bmatrix} = \begin{bmatrix} k_1 & k_2 & k_3 \\ -1 & -1 & 0 \\ 0 & k_4 & -1 \\ -k_5 & 0 & -k_6 \\ k_7 & k_8 & k_9 \end{bmatrix} \cdot \begin{bmatrix} r_1 \cdot X \\ r_2 \cdot X \\ r_3 \cdot X \end{bmatrix} - D \cdot \begin{bmatrix} X \\ G \\ E \\ O \\ P \end{bmatrix} + \begin{bmatrix} 0 \\ G_{in} \cdot D \\ 0 \\ 0 \\ 0 \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ 0 \\ OTR \\ -CTR \end{bmatrix}$$

$S > S_{crit}$: respiro-fermentative regime ($r_3 = 0$)

$S < S_{crit}$: respirative regime ($r_2 = 0$)

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: $\begin{cases} \dfrac{d(VG)}{dt} \approx 0 \\ q_S = r_1 + r_2 \\ q_O = k_5 r_1 + k_6 r_3 \end{cases} \rightarrow X = \dfrac{F_{in} G_{in}}{q_S V}$

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: Fin*(t), V*(t) so that O*(t) = Oref

$\dfrac{q_O^*}{q_S^*} \approx k_5$ (considering only respiration on glucose so that r_2 and r_3 are equal to 0)

Model linearization
Feed-Oxygen Model

- Considering O*(t) = Oref:

$$D^* = \frac{F_{in}^*}{V^*} = \frac{OTR^*}{k_5 G_{in} + O^*}$$

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:

$$\frac{d\,\delta O}{dt} = -\left(\frac{k_5 G_{in} + O^*}{V^*}\right)\delta F_{in} - (k_L a + D^*)\delta O \qquad (*)$$

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

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

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:

$$O(p) = -\frac{\frac{1}{k_L a}\frac{k_5 G_{in} + O^{*}}{V^{*}}}{1 + \frac{1}{k_L a} p}\left[F_{in}(p) - \frac{D^{*}V_0}{p - D^{*}}\right]$$

Model linearization
Feed-Oxygen Model

- Finally, the discrete-time linear model is given by:

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

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

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

$$\frac{d(VG)}{dt} \approx 0 \quad \Leftrightarrow r_2 XV = F_{in} G_{in} - r_1 XV$$

Simple manipulations lead to:

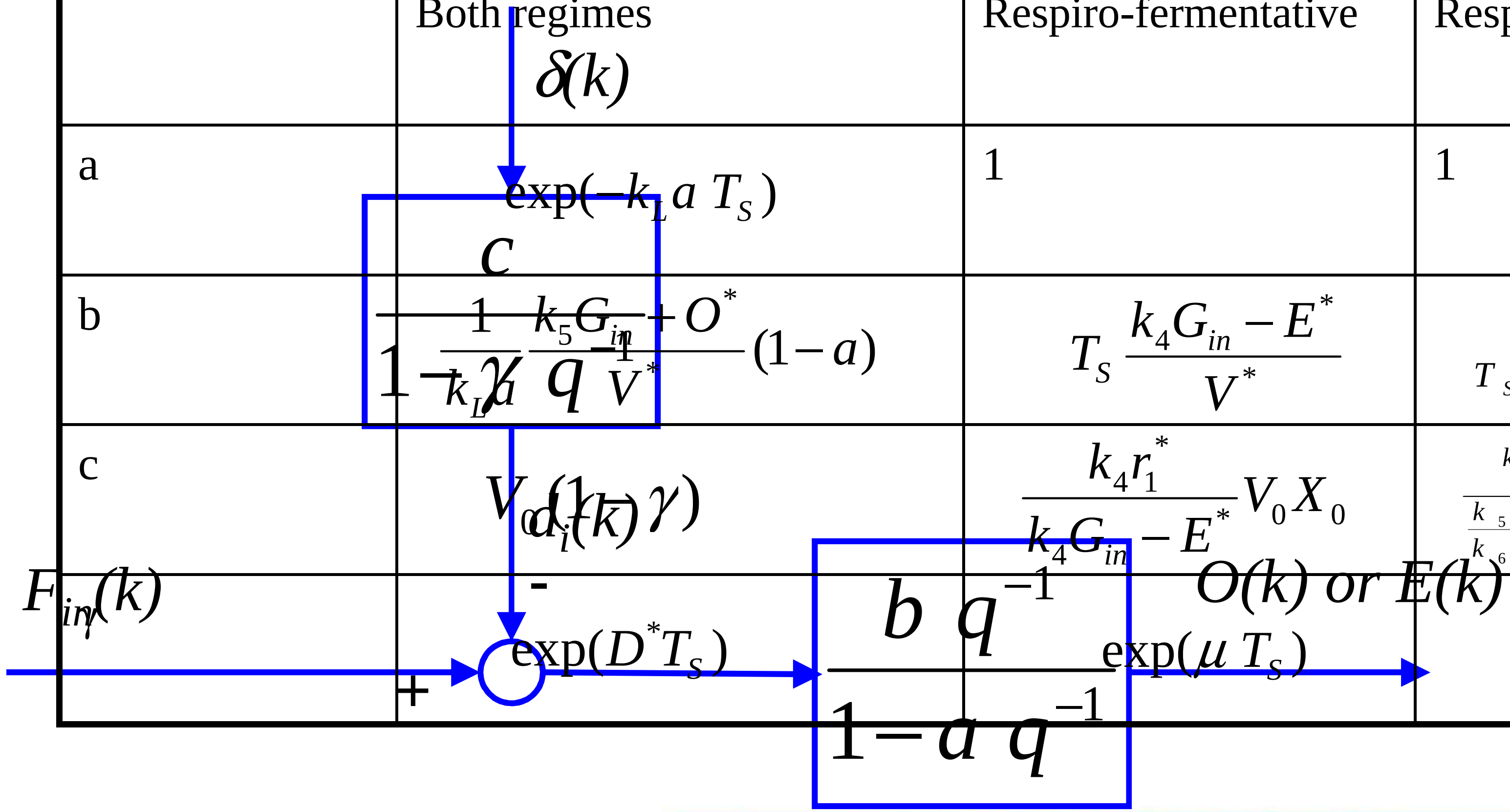
$$E(k) = \frac{b\ q^{-1}}{1 - a\ q^{-1}} \left[F_{in}(k) - d_i(k) \right]$$

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

Model linearization

Feed-Ethanol and feed-oxygen models

- Linear model:



Parameters	Oxygen model	Ethanol model	
	Both regimes	Respiro-fermentative	Respirative
a	$\exp(-k_L a\, T_S)$	1	1
b	$\frac{1}{k_L a}\frac{k_5 G_{in}+O^*}{V^*}(1-a)$	$T_S\frac{k_4 G_{in}-E^*}{V^*}$	$T_S\frac{\frac{k_5}{k_6}G_{in}-E^*}{V^*}$
c	$V_0(1-\gamma)$	$\frac{k_4 r_1^*}{k_4 G_{in}-E^*}V_0 X_0$	$\frac{k_4\frac{r_{O\max}^*}{k_6}}{\frac{k_5}{k_6}G_{in}-E^*}V_0 X_0$
γ	$\exp(D^* T_S)$	$\exp(\mu\, T_S)$	$\exp(\mu\, T_S)$

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

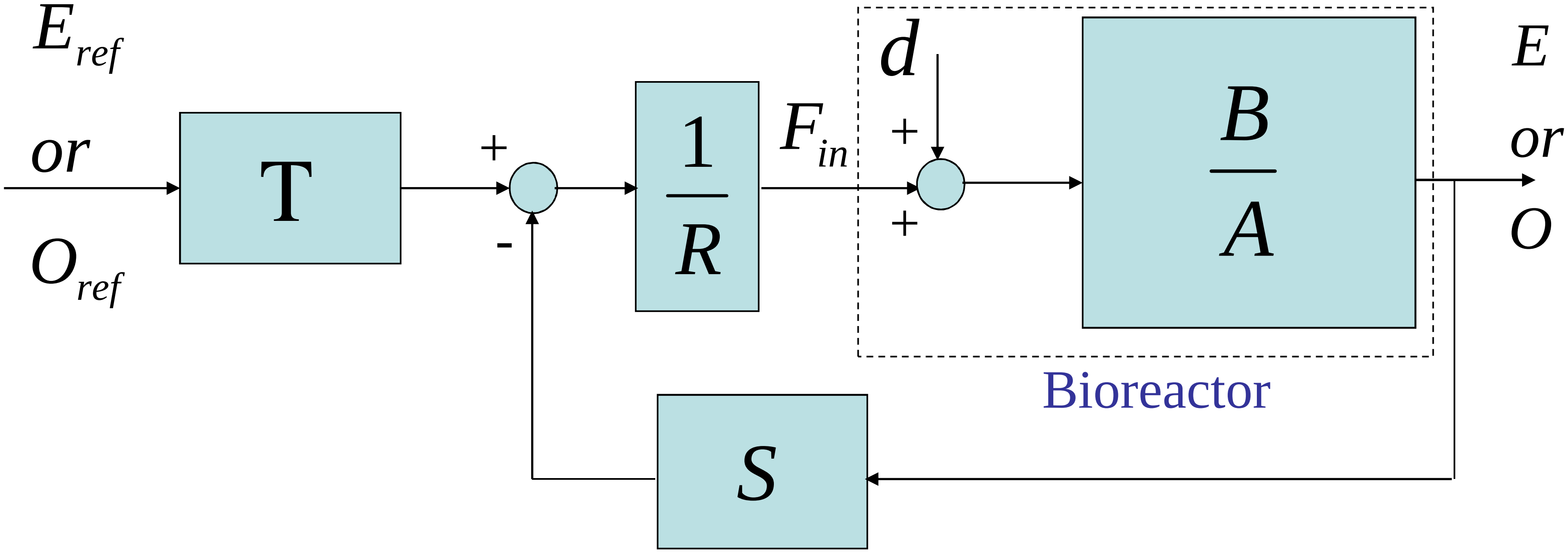
- Exponential disturbance.
- Variation of the kinetic parameter:

$$\gamma = \exp(\mu\, T_S) \;\; or \;\; \exp(D^{*} T_S)$$

- 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 γ and b.

RST controller



- 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:

$$H_m = \frac{B_m(q^{-1}) A_m(1)}{B_m(1) A_m(q^{-1})}$$

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

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:

$$A\ D\ R' + BS = A_0 A_m$$

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, μ varies during the culture and must be adapted (RLS algorithm):

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

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

$$\Rightarrow$$

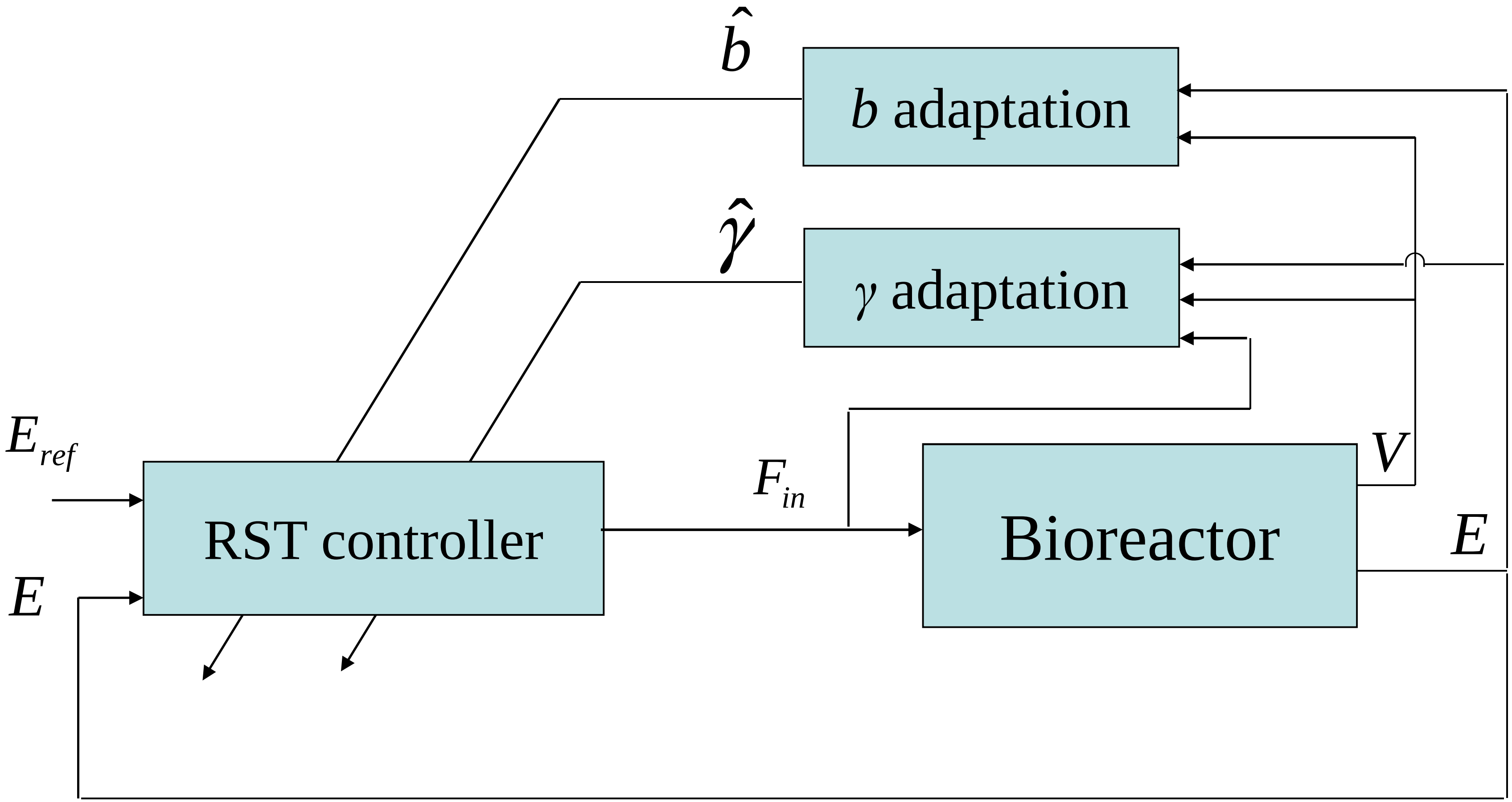
$$\hat{d}(k) = \hat{d}(k-1)\ \gamma$$

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

- 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



Case study: ethanol regulation

- Initial and operating conditions:
  - $X_0 = 0.4$ g/l
  - $E_0 = 0.5$ g/l
  - $G_0 = 0.0125$ g/l
  - $V_0 = 5$ l
  - $G_{in} = 500$ g/l
  - $E_{in} = 0.1$ g/l
  - $E_{ref} = 1$ g/l
- Controller parameters:
  - $a_1 = 0.7$
  - $b_0 = (k_4 G_{in} - E_0)/V_0$

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

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

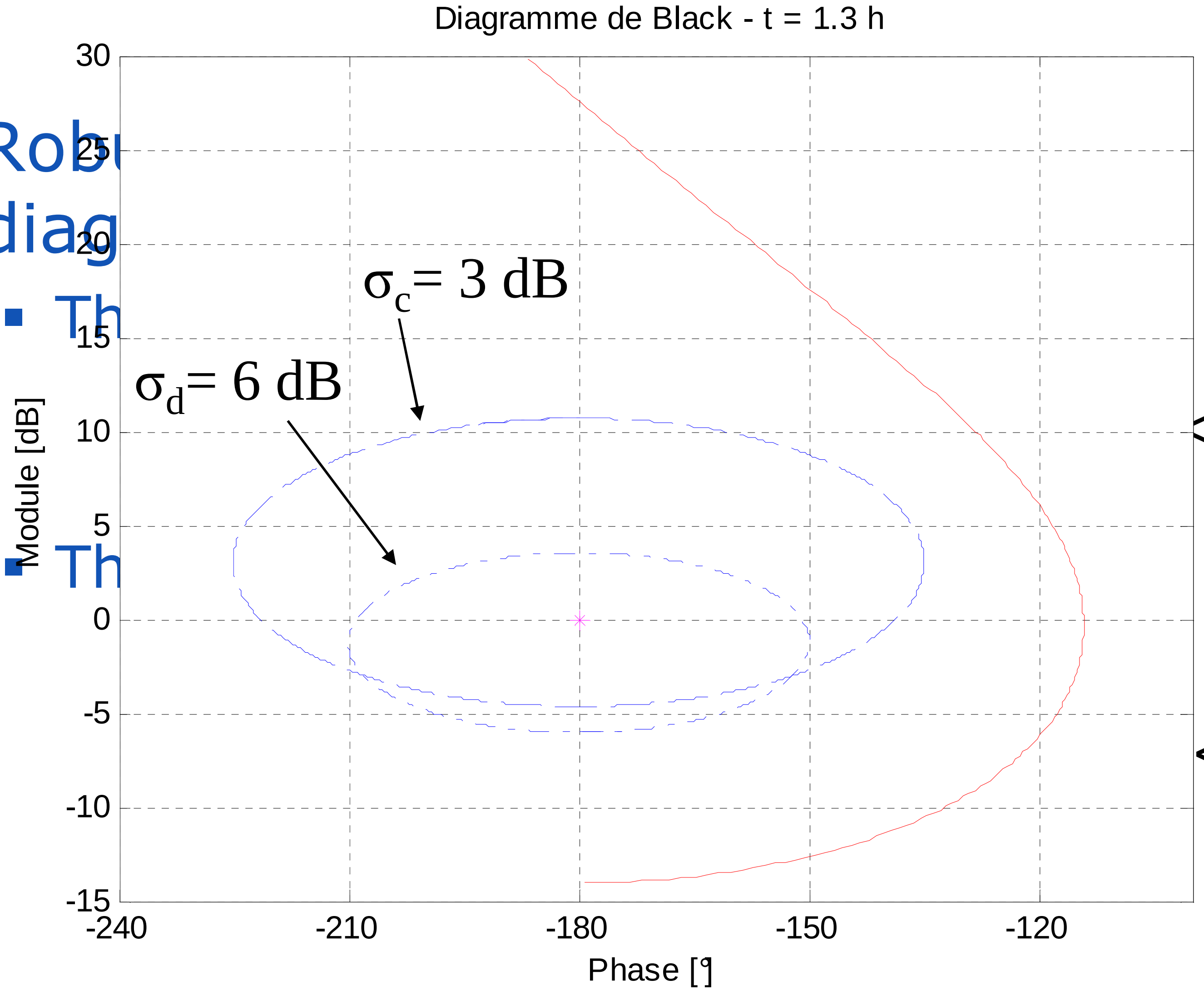
4) $T = (1 - 0.7\, q^{-1})\, A_m(1)/b$

Controller design

❑ Rob… diag…

- Th…

- Th…



$< 6\ dB$

$< 3\ dB$

Controller design

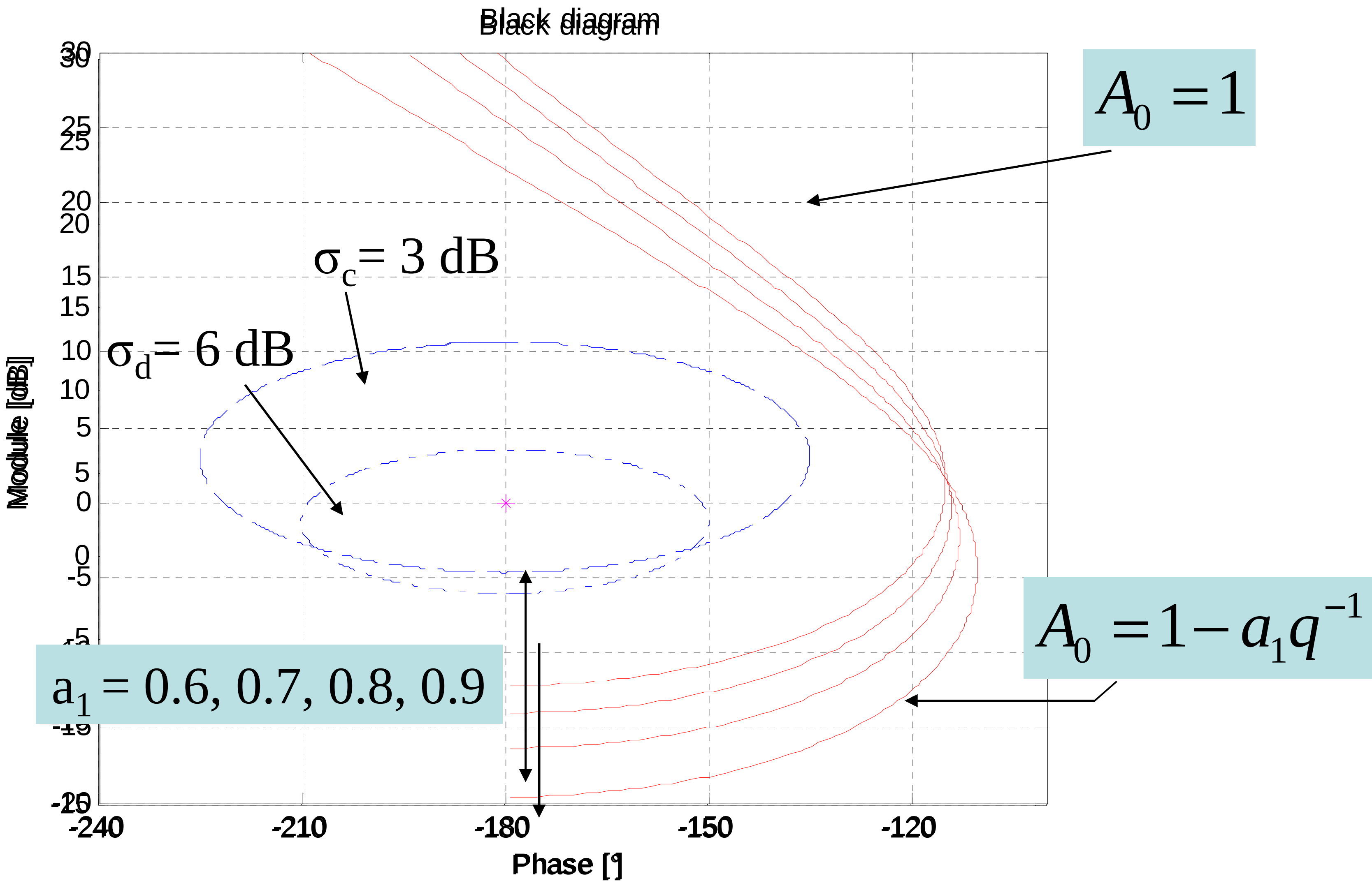
- Robustness insured by the a_1 parameter:

$$a_1 = 0.7$$

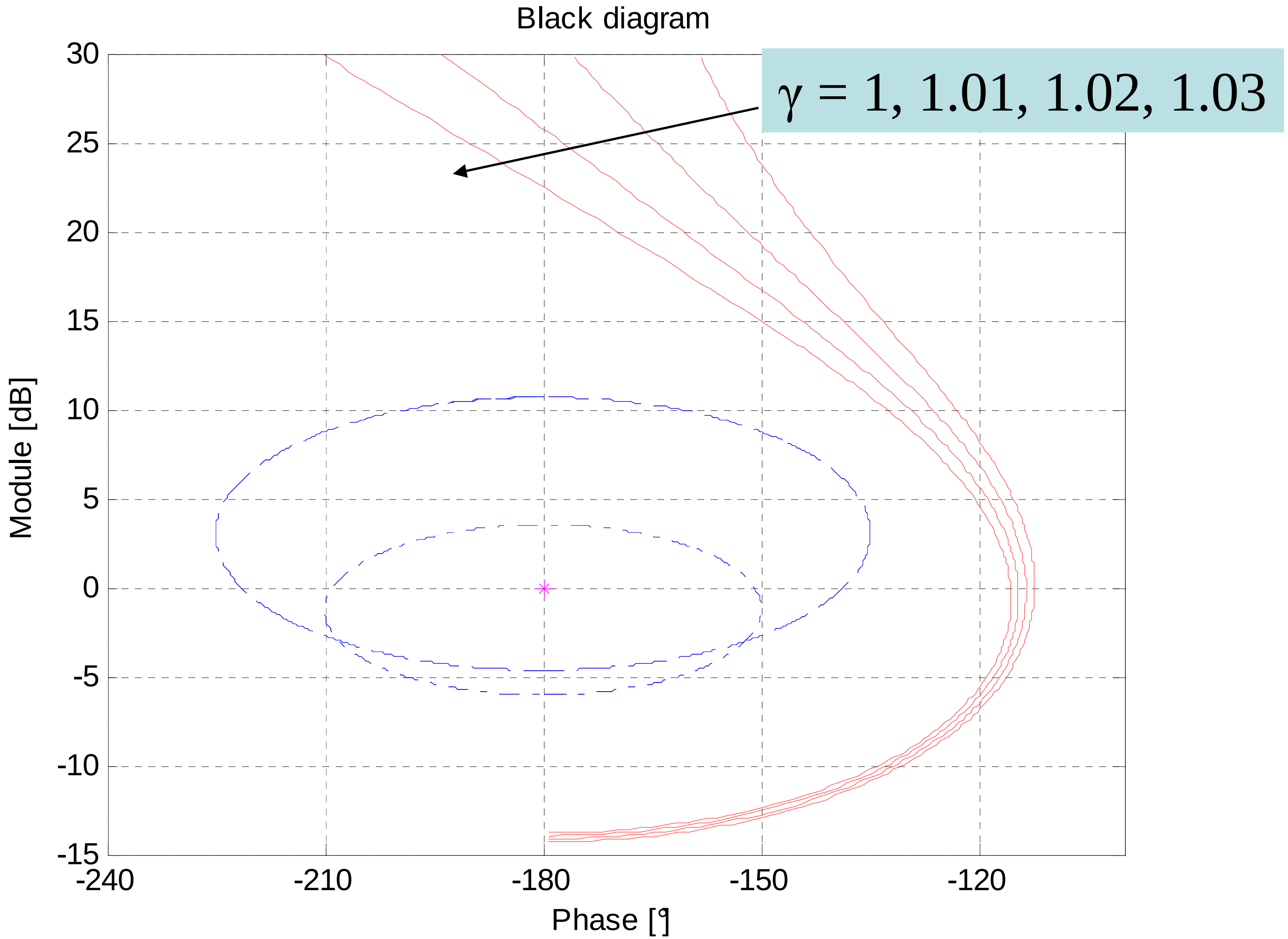
- Good disturbance rejection when γ is well adapted:

$$\gamma \approx 1.023$$

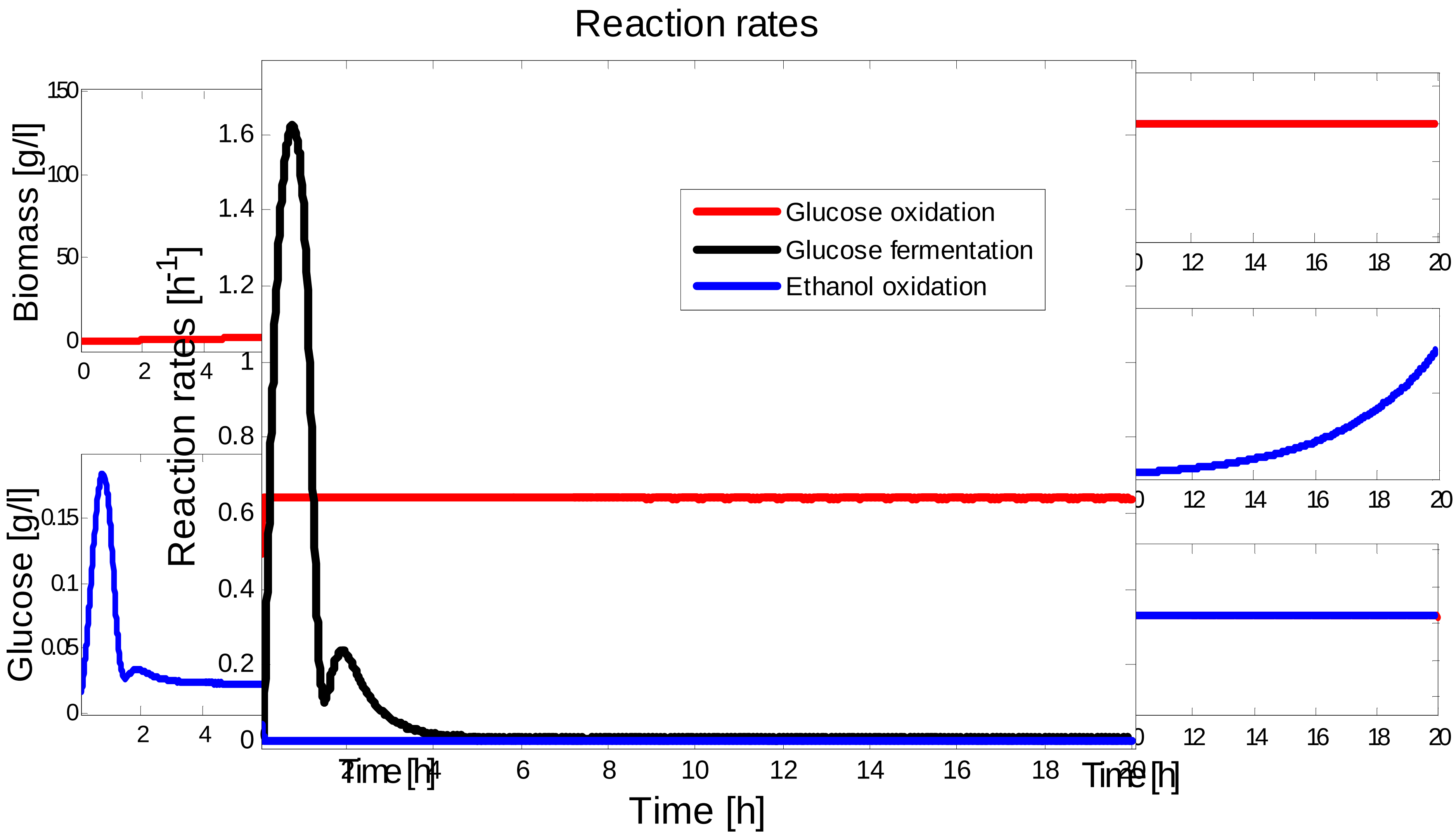
Robustness analysis



Controller design



Simulation results

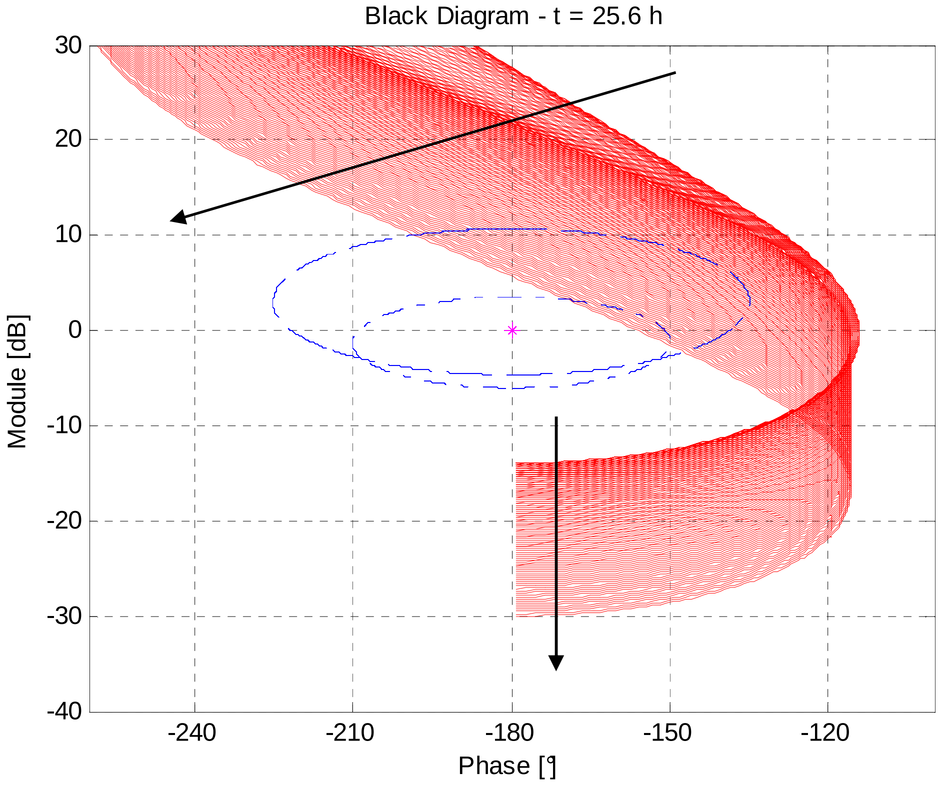


Adaptation

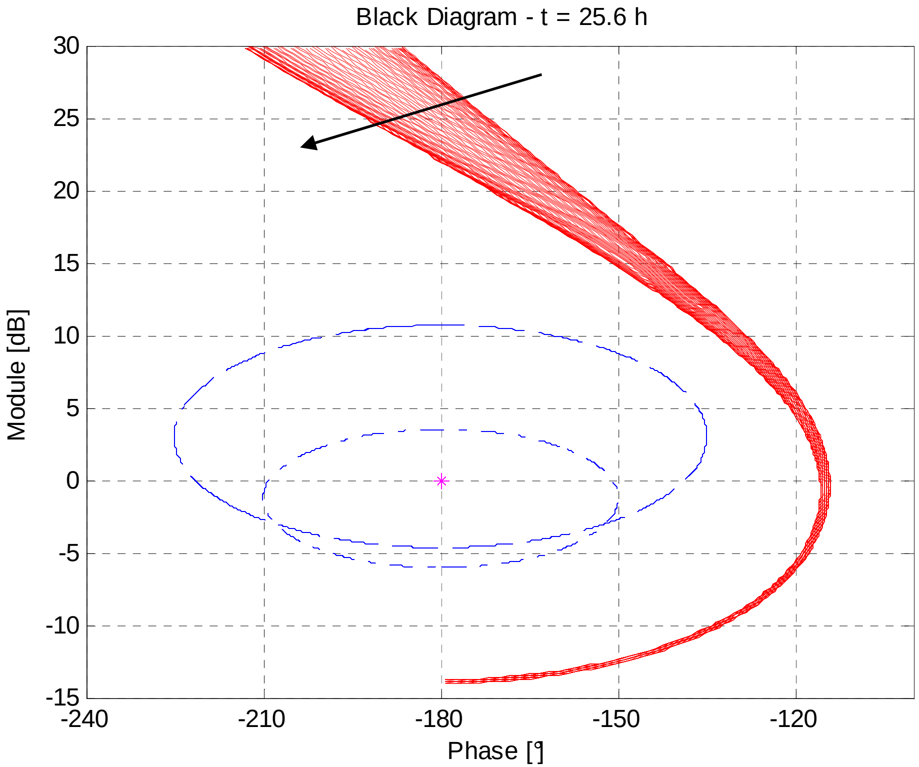
If b is not adapted the gain margin increases but the phase margin decreases when V grows

Adaptation

b is constant

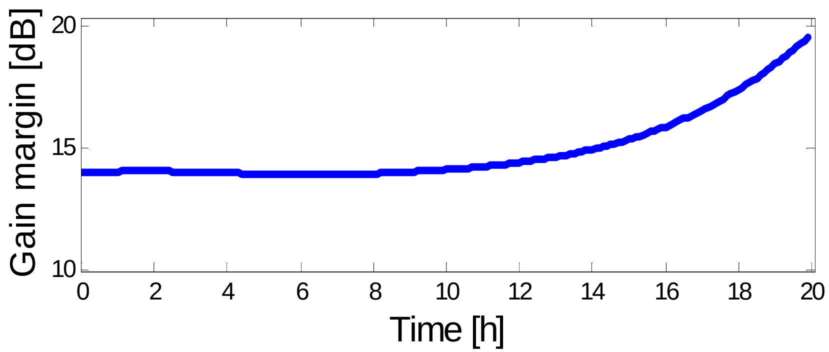


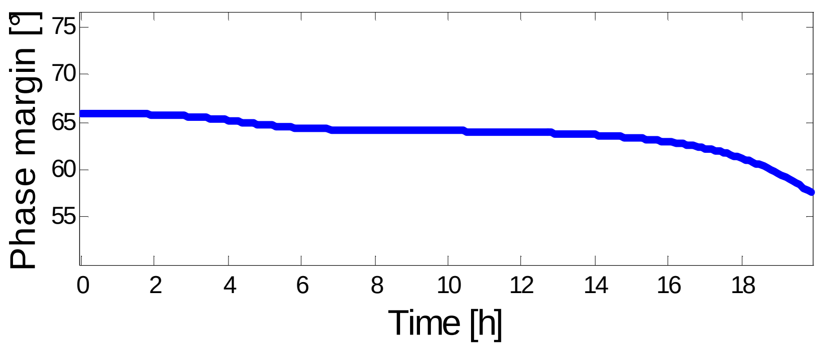
b is adapted



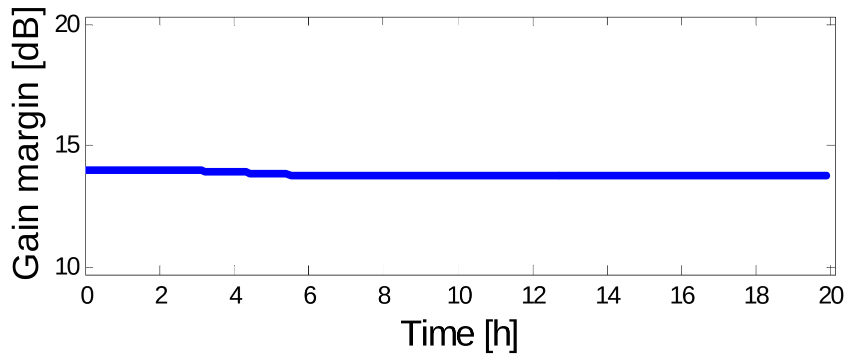
Adaptation

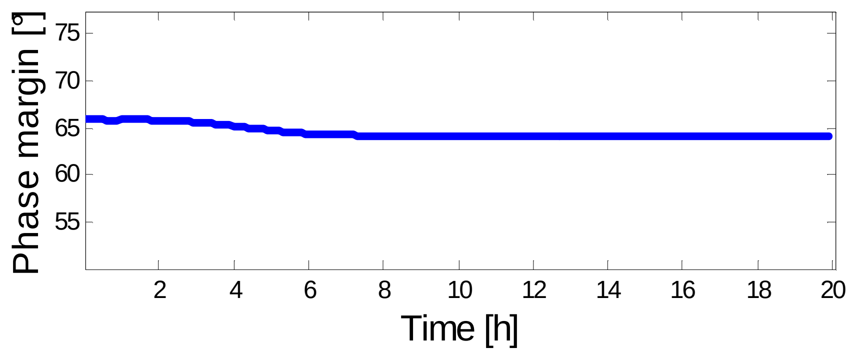
b is constant





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:

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

$$\nu = e^{\left(\frac{T_s}{T_{mes}}\right)}$$

Outline

- ❑ Model linearization
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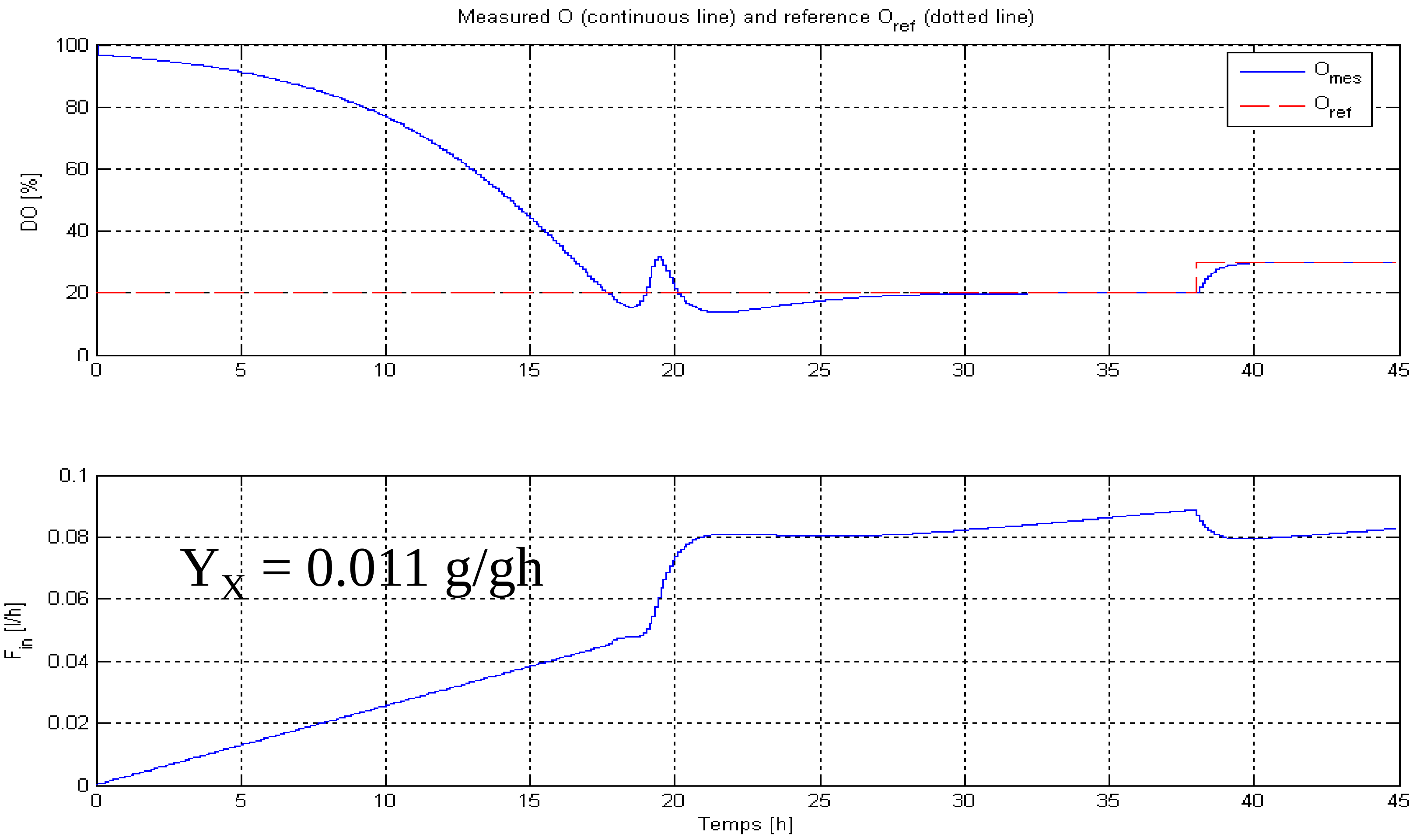
Simulations

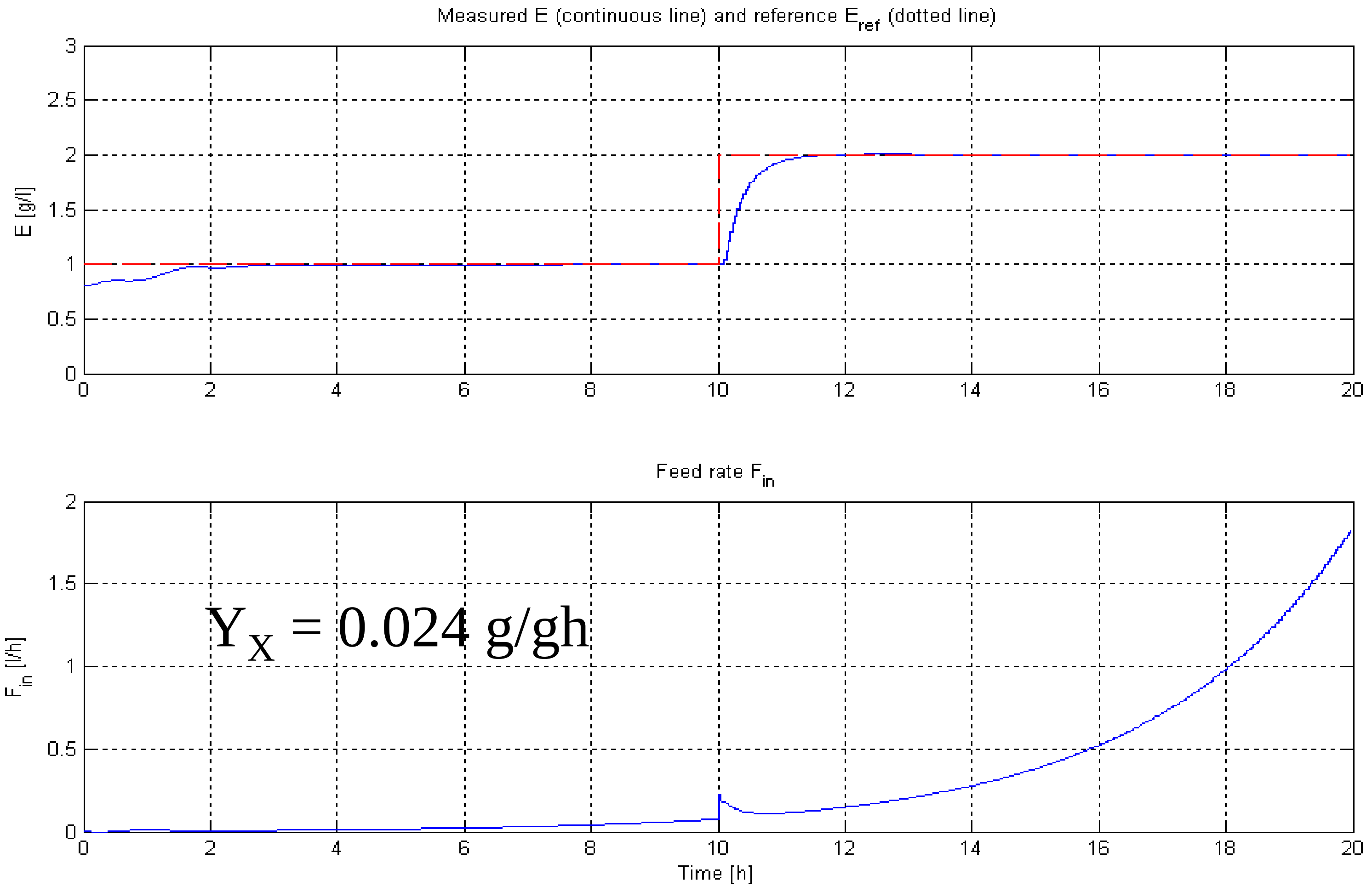
- Initial and operating conditions:
  - $X_0 = 0.4$ g/l
  - $E_0 = 0.9$ g/l
  - $G_0 = 0.012$ g/l
  - $O_0 = 100\%$
  - $V_0 = 6.8$ l
  - $G_{in} = 350$ g/l
  - $E_{ref} = 1$ g/l or $O_{ref} = 20\%$
- Controller parameters:
  - $A_0 = 1 - 0.7q^{-1}$ for Oxygen regulation
  - $A_0 = (1 - 0.9q^{-1})(1 - 0.95q^{-1})$ for Ethanol regulation
  - $b_0 = (k_4 G_{in} - E_0)/V_0$

Simulation results
PO2-Feed regulation

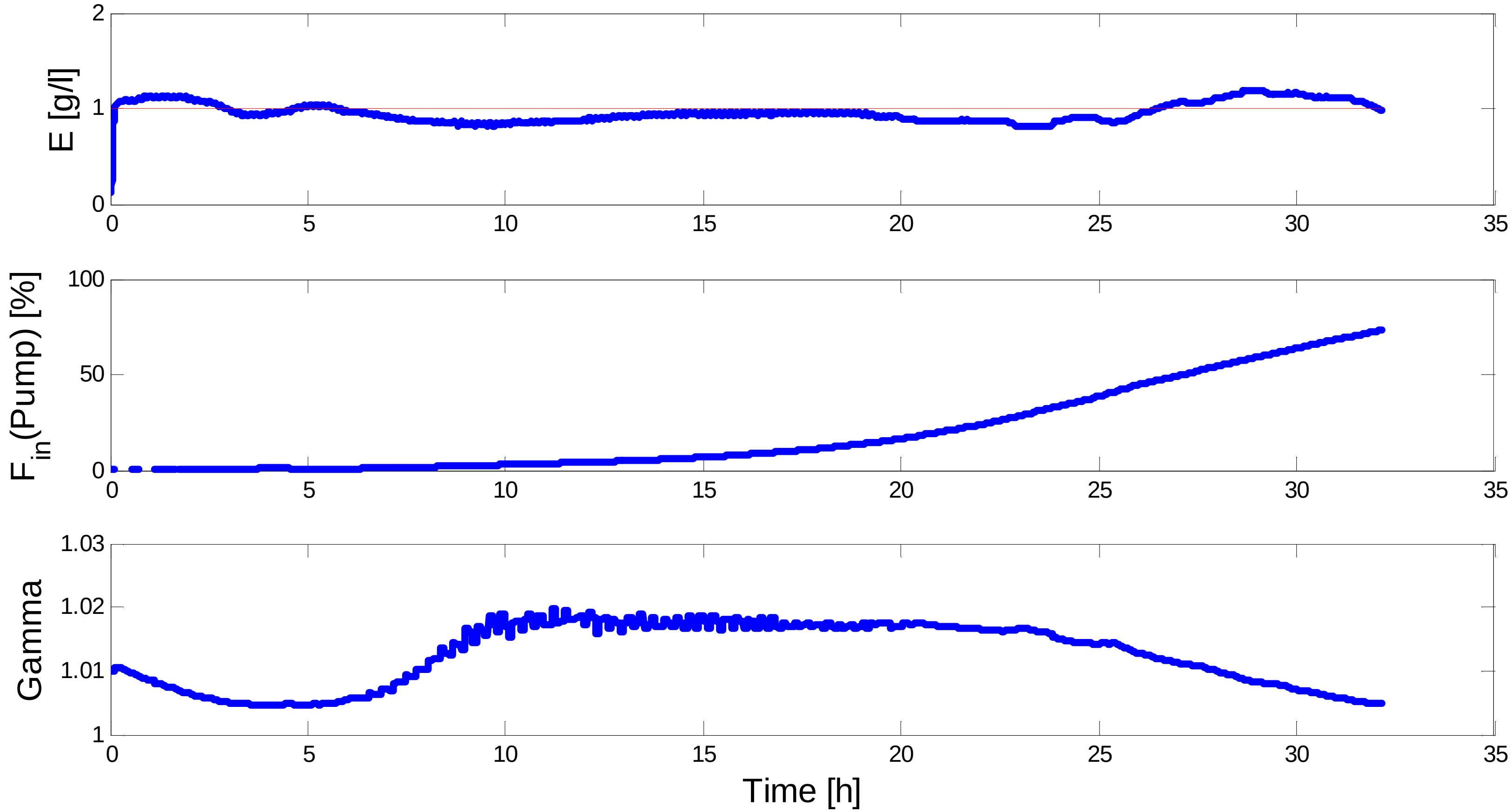


$Y_X = 0.011$ g/gh

Simulation results
Ethanol-Feed regulation



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.

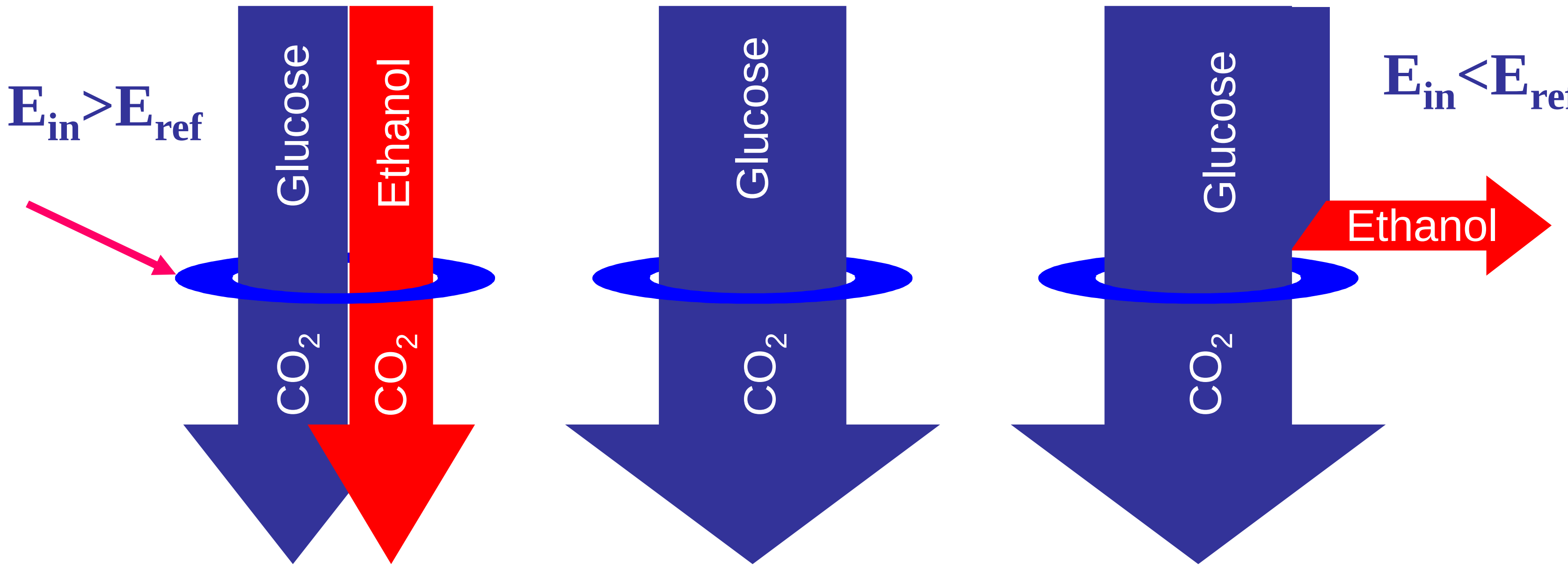
Some extensions

- $E_{in} > E_{ref}$:
  - 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



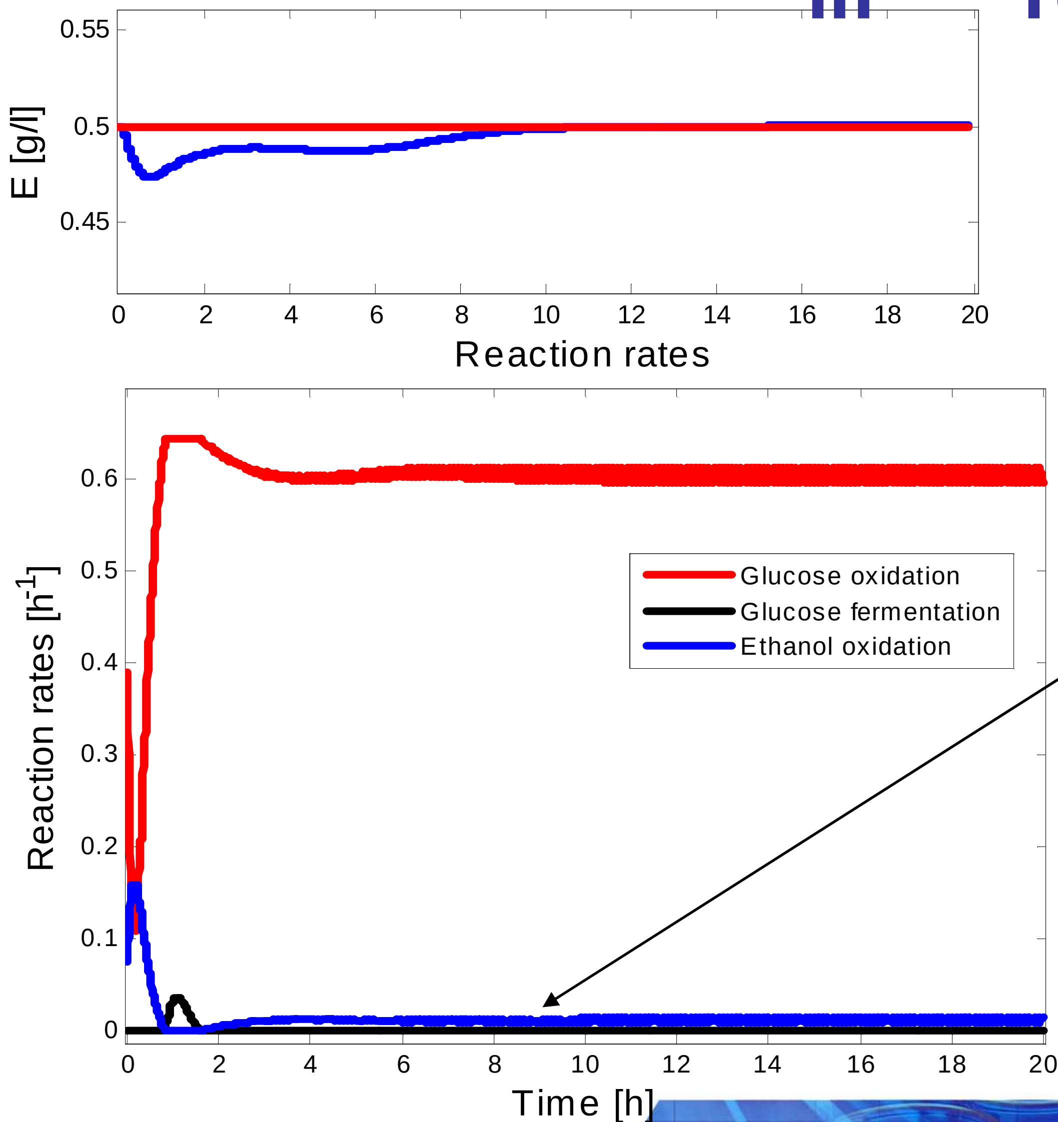
Respirative Regime
- Ethanol is consumed -

V.E = constant

Optimal Operating Conditions

Respiro-Fermentative Regime
- Ethanol is produced -

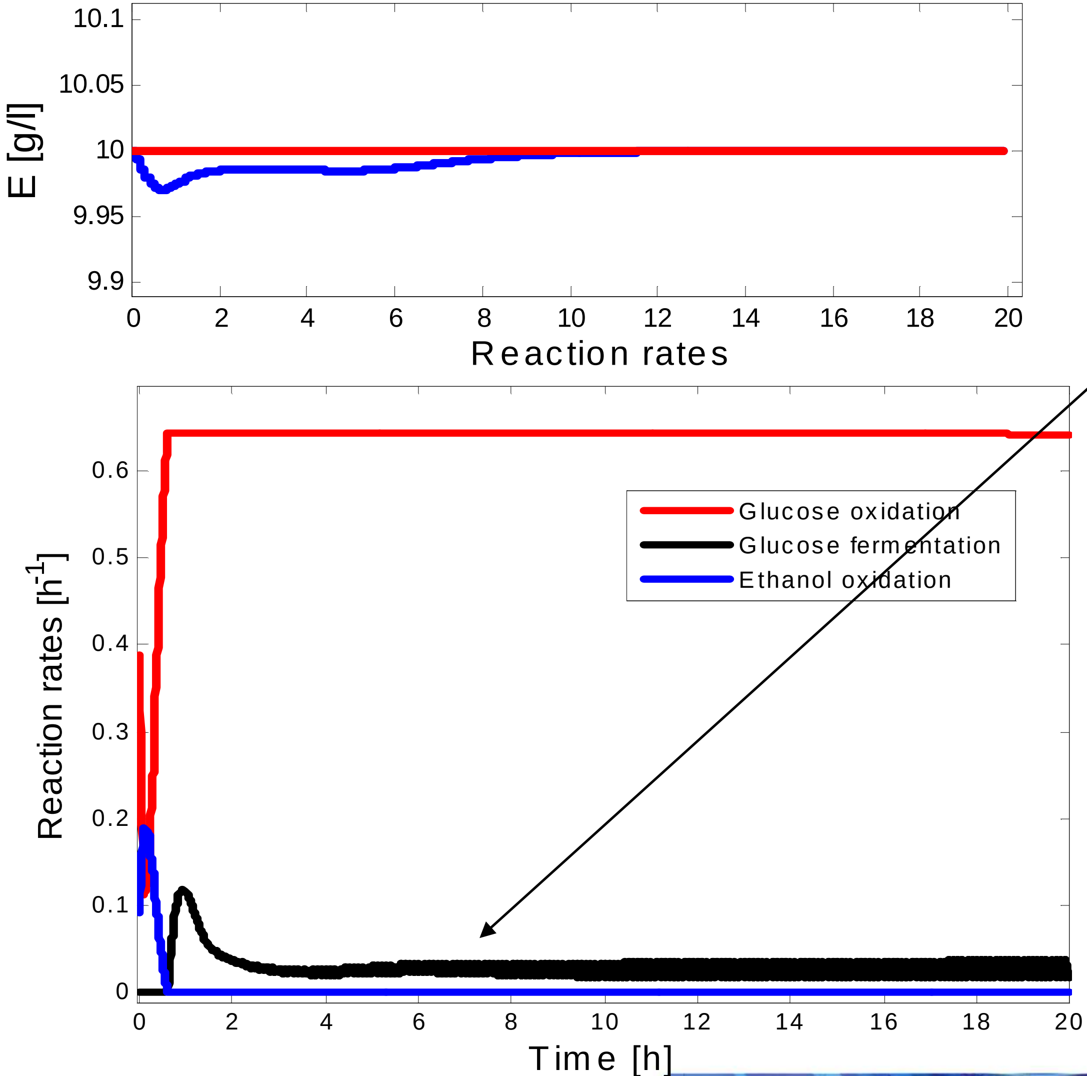
Forced respirative regime : $E_{in} > E_{ref}$



Ethanol consumption

Only in respirative regime

Forced respiro-fermentative regime : $E_{in} < E_{ref}$



Ethanol production

Only in respiro-fermentative regime