

Summer School on Mathematical Control Theory

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Control of biological processes

Georges Bastin

CESAME
Center for Systems Engineering and Applied Mechanics
Bâtiment Euler
4, Avenue G. Lemaitre
B-1348 Louvain
Belgium

These are preliminary lecture notes, intended only for distribution to participants

CONTROL OF BIOLOGICAL PROCESSES

G. Bastin

1 Performance criteria

Let us consider a biological process where the objective is to produce the biomass or some metabolite of interest. In order to quantify the performance of the process, we shall introduce two criteria which are called **productivity** and **yield**.

Assume first that the goal is the production of a metabolite P . The **productivity** over a time period T is defined as the amount of P which is produced per unit of time during the period. It is denoted :

$$J_P = \frac{1}{T} \left[\int_0^T F_{out}(\tau)P(\tau)d\tau + V(T)P(T) - V(0)P(0) \right]$$

The amount, per unit of time, of a given limiting substrate which has been consumed during the same period for the production of P is given by :

$$J_S = \frac{1}{T} \left[\int_0^T (F_{in}(\tau)S^{in} - F_{out}(\tau)S(\tau))d\tau + V(0)S(0) - V(T)S(T) \right]$$

The **yield** of the process is then defined as the ratio between J_P and J_S , that is the amount of product P which has been made per unit of consumed substrate :

$$J_Y = \frac{J_P}{J_S}$$

In general, an explicit analytical computation of the performance criteria J_P and J_Y from the equations of the state-space model is not possible. In some simple cases however, such an analytical computation is possible and may bring interesting informations with a view to the development of optimization strategies we shall examine some of these simple examples.

Example 1. Production of a primary metabolite in a continuous reactor $S \rightarrow X + P$.

The state space model is written

$$\begin{aligned}\dot{X} &= r(S, X) - DX \\ \dot{S} &= -c_0r(S, X) + D(S^{in} - S) \\ \dot{P} &= c_1r(S, X) - DP\end{aligned}$$

We assume that the growth rate $r(S, X)$ is expressed as

$$r(S, X) = \mu(S)X$$

with $\mu(S)$ the specific growth rate.

In steady-state operation ($D = \text{constant}$), the equilibrium values \bar{X} , \bar{S} , \bar{P} of the state variables satisfy :

$$\begin{aligned}\mu(\bar{S}) &= D \\ \bar{X} &= \frac{1}{c_0}(S^{in} - \bar{S}) \\ \bar{P} &= \frac{c_1}{c_0}(S^{in} - \bar{S})\end{aligned}$$

Then, the steady state productivity may be expressed as a function of the substrate concentration :

$$J_P = D\bar{P} = \frac{c_1}{c_0}\mu(\bar{S})(S^{in} - \bar{S})$$

It is a non monotonic function of the substrate concentration \bar{S} as depicted in Fig. 1.

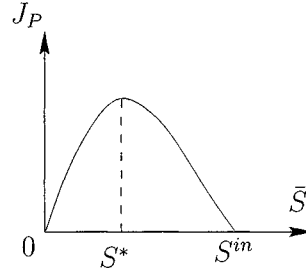


Fig. 1.

We observe that there is an optimal value S^* of the substrate concentration which maximizes the productivity.

On the other hand, the yield is constant, independently of the operating points :

$$J_Y = \frac{c_1}{c_0}$$

Example 2. Production of a secondary metabolite in a continuous reactor $S \rightarrow X$.
 $S \rightarrow P$.

The state space model is written :

$$\begin{aligned}\dot{X} &= \mu(S)X - DX \\ \dot{S} &= -c_0\mu(S)X - c_1\pi(S)X + D(S^{in} - S) \\ \dot{P} &= \pi(S)X - DP\end{aligned}$$

with $\mu(S)$ the specific growth rate and $\pi(S)$ the specific production rate.

In steady state operation ($D = \text{constant}$), the equilibrium values $\bar{X}, \bar{S}, \bar{P}$ of the state variables satisfy :

$$\begin{aligned}\mu(\bar{S}) &= D \\ \bar{X} &= \frac{\mu(\bar{S})}{c_0\mu(\bar{S}) + c_1\pi(\bar{S})}(S^{in} - \bar{S}) \\ \bar{P} &= \frac{\pi(\bar{S})}{c_0\mu(\bar{S}) + c_1\pi(\bar{S})}(S^{in} - \bar{S})\end{aligned}$$

In this case, the productivity and the yield are expressed as follows :

$$\begin{aligned}J_P &= D\bar{P} = \frac{\mu(\bar{S})\pi(\bar{S})}{c_0\mu(\bar{S}) + c_1\pi(\bar{S})}(S^{in} - \bar{S}) \\ J_Y &= \frac{\pi(\bar{S})}{c_0\mu(\bar{S}) + c_1\pi(\bar{S})}\end{aligned}$$

The shape of J_P and J_Y with respect to \bar{S} depends on the particular form of $\mu(S)$ and $\pi(S)$. It is however most often characterised by a conflict between yield and productivity maximization as illustrated in Fig. 2.

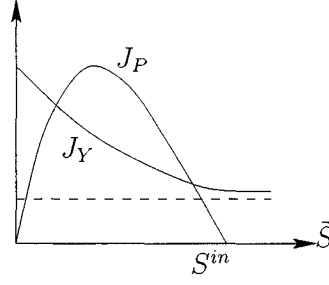


Fig. 2.

Example 3. Production of a primary metabolite in a fed-batch reactor $S \rightarrow X + P$.

The state space model is written as follows :

$$\begin{aligned}\frac{d}{dt}(XV) &= \mu(S)XV \\ \frac{dS}{dt} &= -c_0\mu(S)X + \frac{F_{in}}{V}(S^{in} - S) \\ \frac{d}{dt}(PV) &= c_1\mu(S)XV \\ \frac{dV}{dt} &= F_{in}\end{aligned}$$

We assume that the initial condition $P(0) = 0$ and that the substrate concentration S is exactly regulated at a constant value \bar{S} along the fed batch operation. Under these assumptions, the productivity and the yield can be shown to be expressed as :

$$\begin{aligned}J_P &= \frac{c_1X(0)V(0)}{T} \exp(\mu(\bar{S})T - 1) \\ J_Y &= \frac{c_1}{c_0} = \text{constant}\end{aligned}$$

Here the shape of J_P is similar of the shape of $\mu(\bar{S})$ as illustrated in Fig. 3.

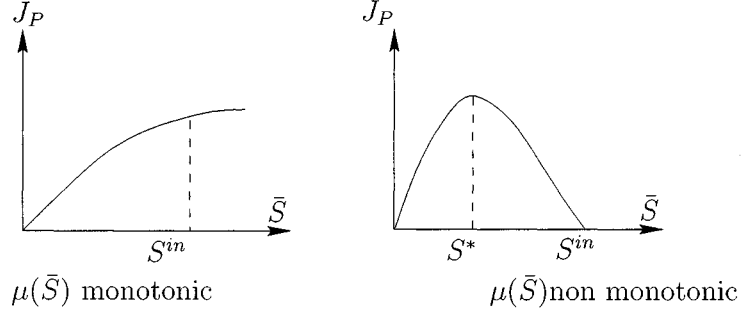


Fig. 3.

Example 4. Production of a secondary metabolite in a fed-batch reactor $S \rightarrow X$.
 $S \rightarrow P$.

The state space model is written as follows :

$$\begin{aligned} \frac{d}{dt}(XV) &= \mu(S)XV \\ \frac{dS}{dt} &= -c_0\mu(S)X - c_1\pi(S)X + \frac{F_{in}}{V}(S^{in} - S) \\ \frac{d}{dt}(PV) &= \pi(S)XV \\ \frac{dV}{dt} &= F_{in} \end{aligned}$$

We assume that the initial condition $P(0) = 0$ and that the substrate concentration S is exactly regulated at a constant value \bar{S} along the fed batch operation. Under these assumptions, the productivity and the yield are expressed as :

$$\begin{aligned} J_P &= \frac{\pi(\bar{S})}{\mu(\bar{S})} \exp(\mu(\bar{S})T) \\ J_Y &= \frac{V(T)P(T)}{c_0[V(T)X(T) - V(0)X(0)] + c_1V(T)P(T)} \\ &\simeq \frac{P(T)}{c_0X(T) + c_1P(T)} \\ &= \frac{\pi(\bar{S})(\exp(\mu(\bar{S})T) - 1)}{c_0\mu(\bar{S})\exp(\mu(\bar{S})T) + c_1\pi(\bar{S})(\exp(\mu(\bar{S})T) - 1)} \end{aligned}$$

As in example 2, there is most often a yield/productivity conflict.

Conclusions

We have shown above that the productivity J_P and the yield J_Y can be explicitly computed in simple cases. These examples have shown that some process optimization

may be achieved by an appropriate regulation of the substrate concentration at an optimal set point S^* . In case of yield/productivity the selection of the set point S^* may be a tool for achieving an optimal trade-off between yield and productivity.

2 Substrate regulation

Let us consider the general state space model of a biological process :

$$\dot{\xi} = Cr(\xi) - (m(\xi) + Q(\xi)) + D(\xi^{in} - \xi) \quad \xi(0) \in \Delta$$

The dynamics of some substrate S is in particular written as :

$$\dot{S} = -\sigma(\xi)S + u(S^{in} - S)$$

where $\sigma(\xi)$ is the specific consumption rate.

The control objective is to regulate the substrate concentration S at the set point S^* by using the dilution rate D as control input u . There is obviously a physical saturation constraint on the control input :

$$0 \leq u(t) \leq u^{\max}$$

Under these constraints, we have seen that the following boundedness properties are guaranteed :

- The state $\xi(t)$ is bounded and belongs to the simplex Δ .
- In particular, the substrate concentration S is bounded as :

$$0 < S(t) < S^{in} \quad \forall t$$

- The specific consumption rate $\sigma(\xi)$ is bounded as :

$$0 \leq \sigma(\xi) \leq \sigma^{\max}$$

with $\sigma^{\max} = \sup_{\xi \in \Delta} \sigma(\xi)$

In order to solve the above regulation problem, a saturated feedback linearizing control is considered :

$$u = \text{sat} \left(\frac{\sigma(\xi)S + k_P(S^* - S)}{S^{in} - S} \right)$$

where the “sat” function means $0 \leq u \leq u^{\max}$.

This control law is parametrized by a proportionnal gain k_P which can be tuned in order to assign the closed loop dynamics.

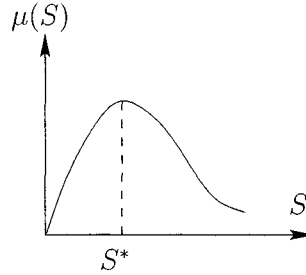
Since this control law is an input-output feedback linearization, the stability of the zero-dynamics should be investigated. We observe however that the stability of the zero dynamics is not really an issue for fed-batch processes which do not need to be globally stabilised since they are operated on a fixed finite time interval. In contrast the stability of the zero dynamics must be checked for continuous reactors.

Example. Stability of zero dynamics for a simple microbial growth in a continuous reactor $S \rightarrow X$.

The state space model is written as :

$$\begin{aligned}\dot{X} &= \mu(S)X - uX \\ \dot{S} &= -c_0\mu(S)X + u(S^{in} - S)\end{aligned}$$

It is assumed that the specific growth rate $\mu(S)$ is a non-monotonic function of the substrate concentration S and that the set point S^* is selected such as maximizing $\mu(S)$, see the following figure.



The control law is written :

$$u = \text{Sat} \left[\frac{c_0\mu(S)X + k_P(S^* - S)}{S^{in} - S} \right]$$

There a single closed-loop equilibrium :

$$\begin{aligned}\bar{S} &= S^* \\ \bar{X} &= \frac{S^{in} - S^*}{c_0}\end{aligned}$$

which is easily shown to be open-loop unstable. At the closed loop equilibrium, the control is :

$$u = \frac{c_0\mu(S^*)X}{S^{in}S^*}$$

This implies that the zero dynamics are :

$$\dot{X} = \mu(S^*)X \left(1 - \frac{c_0X}{S^{in} - S} \right)$$

The Jacobian at the equilibrium is $-\mu(S^*) < 0$ which implies that the closed loop equilibrium is asymptotically stable.

Adaptive implementation to cope with modelling uncertainty.

In practice, there is often an important modelling uncertainty regarding the reaction rates. In particular, if a reliable model of the specific uptake rate $\sigma(\xi)$ is not available, it becomes impossible to apply the control law just as it has been defined above. A standard

solution to that problem is to use an adaptive implementation where the unknown function $\sigma(\xi)$ is replaced by an on-line estimate $\hat{\sigma}$ as follows :

$$\begin{aligned}u &= \text{sat}_{[0, u^{\max}]} \frac{\hat{\sigma}S + k_P(S^* - S)}{S^{in} - S} \\ \dot{\hat{\sigma}} &= \text{sat}_{[0, \sigma^{\max}]} (k_i S(S^* - S))\end{aligned}$$

The stability of this adaptive control scheme may be analysed with a classical Lyapunov approach.