ON AUTOMATIC SEEKING OF OPTIMAL STEADY-STATES IN BIOCHEMICAL PROCESSES

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Abstract: It is discussed how the automatic seeking of optimal steady states in biochemical reactors can be achieved by using non-model based extremum-seeking control with semi-global practical stability and convergence properties. A special attention is paid to processes with multiple steady-states and multivalued cost functions. *Copyright ©IFAC 2007*

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1. INTRODUCTION

We are concerned with automatic seeking of optimal steady states in biochemical reactors when the process kinetics are unknown to the user. We want to examine how this objective can be achieved by using non-model based extremum-seeking control.

The goal of the paper is threefold :

1) To provide a clear characterization of the steady-states that achieve an optimal trade-off between yield and productivity maximization in biochemical processes.

2) To show how this optimization problem can be solved by using feedback extremum seeking (ES)

control with semi-global stability and convergence properties.

3) To show that the analysis can be extended to situations with multiple steady-states and a multivalued cost function by using generalized singular perturbation results as presented, for example, in Teel et al. (2003). Here the Aumann integral (Aumann (1965)) is used to define the average of all possible behaviors of the slow system and as a result the average of the slow system is a differential inclusion. We believe that viewing the problem in this manner is novel and could lead to solutions of various other problems not considered in this paper.

In this short communication, for the sake of simplicity and clarity, we limit ourselves to processes where a single monomolecular irreversible reaction takes place. However, even though we deal only with the simplest situation, the issues that emerge
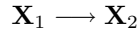
from our analysis are relevant for more general situations involving mutiple multimolecular reactions.

2. YIELD-PRODUCTIVITY TRADEOFF

We consider a single irreversible enzymatic reaction of the form:

$$\mathbf{X}_1 \longrightarrow \mathbf{X}_2$$

with $\mathbf{X}_1$ the substrate (or reactant) and $\mathbf{X}_2$ the product. The reaction takes place in liquid phase in a continuous stirred tank reactor. The substrate is fed into the reactor with a constant concentration c at a volumetric flow rate u. The reaction medium is withdrawn at the same volumetric flow rate u so that the liquid volume V is kept constant. The process dynamics are described by the following standard mass-balance state space model:

$$\dot{x}_1 = -r(x_1) + (u/V)(c - x_1) \tag{1a}$$
$$\dot{x}_2 = r(x_1) - (u/V)x_2 \tag{1b}$$

where x_1 is the substrate concentration, x_2 is the product concentration and $r(x_1)$ is the reaction rate (called *kinetics*). Obviously this system makes physical sense only in the non-negative orthant $x_1 \geqslant 0$, $x_2 \geqslant 0$. Moreover the flow rate u (which is the control input) is non-negative by definition and physically upper-bounded (by the feeding pump capacity):

$$0 \leqslant u \leqslant u^{max}. \tag{2}$$

In this paper we shall investigate two different cases depending on the form of the rate function $r(x_1)$. We begin with Michaelis-Menten kinetics which is the most basic model for enzymatic reactions:

$$r(x_1) = \frac{v_m x_1}{K_m + x_1}$$

with v_m the maximal reaction rate and K_m the half-saturation constant. To normalise the model we use $v_m V$ and v_m^{-1} as the units of u and time respectively. So the normalised model becomes

$$\dot{x}_1 = -\frac{x_1}{K_m + x_1} + u(c - x_1) \tag{3a}$$
$$\dot{x}_2 = \frac{x_1}{K_m + x_1} - ux_2. \tag{3b}$$

It can be readily verified that, for any positive constant input flow rate $\bar{u} \in (0, u^{max}]$, there is a unique steady-state $\bar{x}_1 = \varphi_1(\bar{u})$, $\bar{x}_2 = \varphi_2(\bar{u})$ solution of the following equations:

$$\bar{x}_1 + \bar{u}(c - \bar{x}_1)(K_m + \bar{x}_1) = 0 \tag{4a}$$
$$(c - \bar{x}_2) - \bar{u}\bar{x}_2(K_m + c - \bar{x}_2) = 0. \tag{4b}$$

Furthermore each admissible steady-state belongs to the set

$$\Omega = \{(\bar{x}_1, \bar{x}_2) : \bar{x}_1 \geqslant 0, \bar{x}_2 \geqslant 0, \bar{x}_1 + \bar{x}_2 = c\}$$

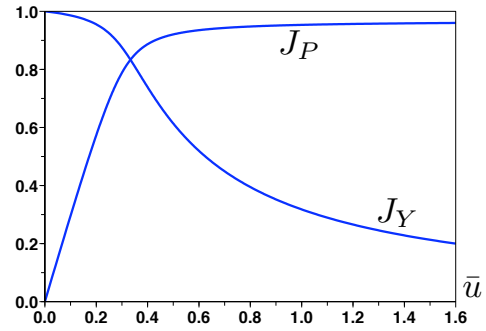and is globally asymptotically stable in the non-negative orthant.

Fig. 1. Productivity J_P and yield J_Y for system (3) with $c = 3$ and $K_m = 0.1$.

The industrial objective of the process is the production of the reaction product. For process optimization, two steady-state performance criteria are considered : the *productivity* J_P and the *yield* J_Y. The productivity is the amount of product harvested in the outflow per unit of time :

$$J_P = \bar{u}\bar{x}_2 = \bar{u}\varphi_2(\bar{u})$$

The yield is the amount of product made per unit of substrate fed to the reactor:

$$J_Y = \frac{\bar{x}_2}{c} = \frac{\varphi_2(\bar{u})}{c}$$

The sensitivity of J_P and J_Y with respect to $\bar{u}$ is illustrated in Fig. 1. A conflict between yield and productivity is clearly apparent: the productivity J_P is an increasing function (from 0 to 100%) of $\bar{u}$ while the yield J_Y is decreasing (from 100 to 0%). Operating the process at a yield J_Y close to 100% can result in a dramatic decrease of the productivity J_P (and vice-versa): it does not really make sense to optimize one of the criteria disregarding the other one. The process must be operated at a steady-state that achieves a trade-off between yield and productivity. This is typically a "multicriteria" optimization problem since the two criteria are antagonistic. A standard way to address the problem is to define an overall performance index as a convex combination of J_P and J_Y:

$$J_T = \lambda J_P + (1 - \lambda)J_Y \quad \lambda \in [0, 1].$$

This cost function is illustrated in Fig. 2 where it is readily seen that it has a unique global maximum u^*. The corresponding optimal steady-state is naturally defined as $x_1^* = \varphi_1(u^*)$, $x_2^* = \varphi_2(u^*)$.

3. EXTREMUM SEEKING CONTROL

As we have mentioned in the Introduction, we assume that neither the kinetic rate function $r(x_1)$ nor the index function $J_T(\bar{u})$ are known to the user. Our concern is to design a non-model based
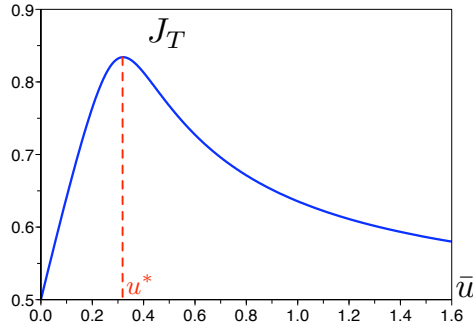
Fig. 2. Overall performance index J_T for system (3) with $c = 3$, $K_m = 0.1$ and $\lambda = 0.5$.

ES feedback controller able to automatically drive the process to the optimal operating point (x_1^*, x_2^*) that maximizes J_T without any precise knowledge of u^*. It is assumed that the process is equipped with an on-line sensor that measures the product concentration x_2 in the outflow. We then define a scalar ES scheme of the form proposed in Tan et al. (2006):

$$y(t) = \lambda u(t)x_2(t) + (1 - \lambda)\frac{x_2(t)}{c} \tag{5a}$$

$$d(t) = a\sin(\omega t) \tag{5b}$$

$$\dot{\theta}_0(t) = k\omega y(t)d(t) \tag{5c}$$

$$\theta(t) = \theta_0(t) + d(t) \tag{5d}$$

$$u(t) = \alpha(\theta(t)) \tag{5e}$$

where $u = \alpha(\theta)$ is a smooth sigmoid function as depicted in Fig. 3 while (a, k, ω) are positive tuning parameters. In this feedback control law, the exogenous signal $d(t) = a\sin(\omega t)$ is a so-called *dither* that activates the extremum seeking.
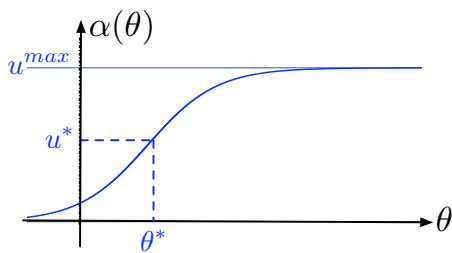

Fig. 3. Sigmoid function $\alpha(\theta)$.

The operation of the ES control algorithm (5) is illustrated in Fig. 4. There is a time scale separation between the system itself and the climbing mechanism. Starting from an initial condition $(x_1(0), x_2(0))$, there is first a fast convergence of the state to the nearest (stable) steady-state which is followed by a slow quasi-static climbing along the cost function up to the maximum. This behaviour is guaranteed from any initial condition so that we have the following semi-global convergence property.
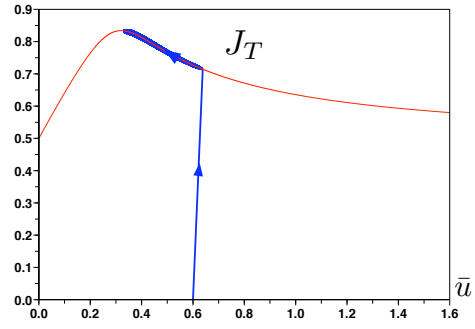

Fig. 4. Extremum seeking for system (3) with $a = 0.02$, $k = 1$, $\omega = 0.1$.

Property 1. For any initial condition $(x_1(0) \geqslant 0, x_2(0) \geqslant 0, \theta_0(0))$, the closed-loop system (3)-(5) has the following properties:

1) $x_1(t) \geqslant 0$, $x_2(t) \geqslant 0$, $\theta_0(t)$ bounded $\forall t$

2) For any $\nu > 0$, there exist parameters (a, k, ω) such that

$$\limsup_{t\to\infty} \left(|x_1(t) - x_1^*| + |x_2(t) - x_2^*| + |u(t) - u^*| \right) \leqslant \nu.$$

This property obviously implies that $\limsup_{t\to\infty} |y(t) - J_T(u^*)|$ can be made arbitrarily small: from any initial condition, the output $y(t)$ can be driven and regulated arbitrarily close to the optimal performance value $y^* = J_T(u^*)$.

Property 1 is a straightforward consequence of Theorem 1 in Tan et al. (2006) which notably involves a singular perturbation and an averaging Lyapunov stability analysis that can be summarized in the following way. From (4), for each $\theta \in \mathbb{R}$, the system (3) with input $\bar{u} = \alpha(\theta)$ has a single equilibrium $\bar{x}_1 = \varphi_1(\alpha(\theta))$, $\bar{x}_2 = \varphi_2(\alpha(\theta))$ which is globally asymptotically stable. The cost function J_T can then be viewed as a function of θ expressed as

$$J_T = Q(\theta) = \left[\lambda\alpha(\theta) + \frac{(1-\lambda)}{c} \right] \varphi_2(\alpha(\theta)).$$

This function has a unique global maximum at $\theta^* = \alpha^{-1}(u^*)$ such that

$$Q'(\theta^* + \zeta)\zeta < 0 \qquad \forall \zeta \neq 0. \tag{6}$$

The change of variables $\tilde{\theta} \triangleq \theta_0 - \theta^*$ and the change of time scale $\sigma \triangleq \omega t$ are introduced. Then, the "slow" θ_0-dynamics (5c) along the static characteristic $\bar{x}_1 = \varphi_1(\alpha(\theta))$, $\bar{x}_2 = \varphi_2(\alpha(\theta))$ are rewritten as

$$\frac{d\tilde{\theta}}{d\sigma} = kQ(\theta^* + \tilde{\theta} + a\sin\sigma)a\sin\sigma. \tag{7}$$

Applying a Taylor series expansion, this equation is rewritten as

$$\frac{d\tilde{\theta}}{d\sigma} = ka\left[f(\sigma, \tilde{\theta}) + a^2 R \right]$$

whith $f(\sigma, \tilde{\theta}) \triangleq Q(\theta^* + \tilde{\theta}) \sin \sigma + aQ'(\theta^* + \tilde{\theta}) \sin^2 \sigma$ and R contains higher order terms in $\sin \sigma$. The function $f(\sigma, \tilde{\theta})$ being 2π-periodic in σ, if the parameter a is taken small enough, we can neglect the higher order terms and we have for the averaged system

$$\frac{d\theta_{av}}{d\sigma} = ka\frac{1}{2\pi}\int_0^{2\pi} f(\sigma, \theta_{av})d\sigma \triangleq \frac{ka^2}{2}Q'(\theta^* + \theta_{av}).$$

This system is globally asymptotically stable as can be seen from the Lyapunov function $V = (1/2)\theta_{av}^2$, since

$$\frac{dV}{d\sigma} = \frac{ka^2}{2}Q'(\theta^* + \theta_{av})\theta_{av} < 0 \quad \forall \theta_{av} \neq 0$$

because of condition (6).

The case-study that we have presented so far is representative of a large class of biochemical processes that exhibit some yield-productivity decoupling as observed in many practical applications (see e.g. Jadot et al. (1998)). However it must be emphasized that Proposition 1 is restricted to situations where the two following conditions hold:

C1. For each admissible value of the flow rate $\bar{u}$ the system must have a single globally asymptotically stable equilibrium.

C2. The performance cost function must be single-valued and "well-shaped" in the sense that, for the admissible range of flow rate values $0 \leqslant \bar{u} \leqslant u^{max}$, it must have a single maximum value $J_T(u^*)$ without any other local extrema.

There are situations where these conditions are not satisfied: the system may have multiple (stable and unstable) equilibria for some input values $\bar{u}$ and the yield or productivity criteria may be multivalued functions. As we shall discuss in the next section, the problem may happen even with simple monomolecular reactions when the kinetics are subject to substrate inhibition or auto-catalytic effects (e.g. Wang et al. (1999)).

4. MULTIVALUED PERFORMANCE COST FUNCTION

We consider again the simple model (1) but we now assume that, in addition to the Michaelis-Menten kinetics, the reaction rate is subject to exponential substrate inhibition. The rate function is as follows:

$$r(x_1) = \frac{v_m x_1}{K_m + x_1}e^{-bx_1^p}$$

where b and p are two positive constant parameters. The dynamical model is written:

$$\dot{x}_1 = -\frac{v_m x_1}{K_m + x_1}e^{-bx_1^p} + u(c - x_1) \qquad (8a)$$

$$\dot{x}_2 = \frac{v_m x_1}{K_m + x_1}e^{-bx_1^p} - ux_2 \qquad (8b)$$

Depending on the value of $\bar{u} \in (0, u^{max}]$, the system may have one, two or three steady-states $(\bar{x}_1, \bar{x}_2)$ with $\bar{x}_1$ solution of:

$$\frac{v_m \bar{x}_1}{K_m + \bar{x}_1}e^{-b\bar{x}_1^p} = \bar{u}(c - \bar{x}_1)$$

and $\bar{x}_2 = c - \bar{x}_1$.

The productvity $J_P = \bar{u}\bar{x}_2$ is represented in Fig. 5 as a function of $\bar{u}$. In this example, J_P is clearly a multivalued function of $\bar{u}$. However it can be seen that it has a unique global maximum for $\bar{u} = u^*$. Moreover, the graph of Fig. 5 can also
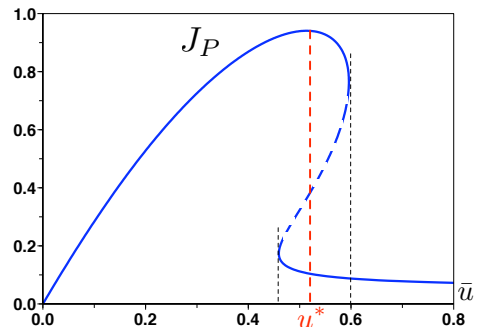

Fig. 5. Productivity J_P for system (8) with $c = 3$, $v_m = 2$, $K_m = 1$, $b = 0.08$, $p = 3.4$.

be regarded as a bifurcation diagram with respect to the parameter $\bar{u}$ where the solid branches correspond to stable equilibria and the dashed branch to unstable equilibria. Hence it can be seen that the maximum point is located on a stable branch.

Here we assume that the industrial objective is to achieve the maximization of the productivity J_P. Although conditions C1 and C2 are not satisfied in this case, a fully satisfactory operation of the ES control law (5) (with $y(t) = u(t)x_2(t)$) can nevertheless be observed in Fig. 6 and Fig. 7.
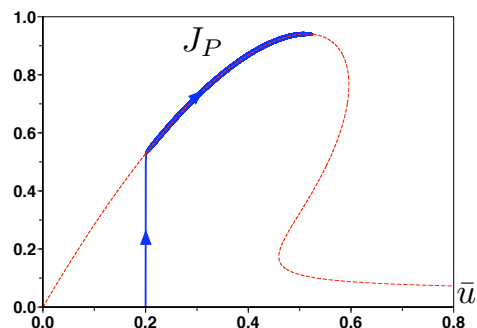

Fig. 6. Extremum seeking for system (8) with $a = 0.003$, $k = 10$, $\omega = 0.01$.

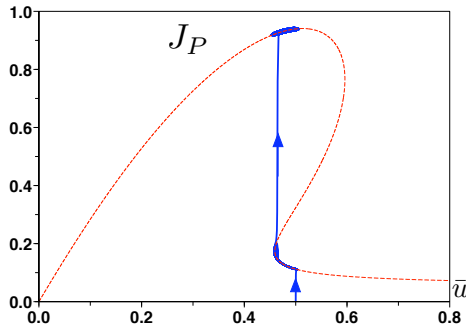The result of Fig.6 is expected since we are in conditions quite similar to the previous case of

Fig. 7. Extremum seeking for system (8) with $a = 0.003$, $k = 6$, $\omega = 0.01$.

Section 3. The result of Fig. 8 is more informative since here the convergence towards the maximum of the cost function is operated in two successive stages. In a first stage, there is a fast convergence to the nearest stable state which is located *on the lower stable branch* followed by a quasi-steady-state progression along that branch. Then, when the state reaches the bifurcation point, there is a fast jump up to the *good upper branch* and a final climbing up to the maximum point. It is very important to emphasize here that, in order to get the result of Fig.7, the amplitude a of the dither signal must be large enough. Otherwise, the trajectory of the closed loop system definitely remains stuck on the lower branch at the bifurcation point as shown in Fig.8. On the other side, too
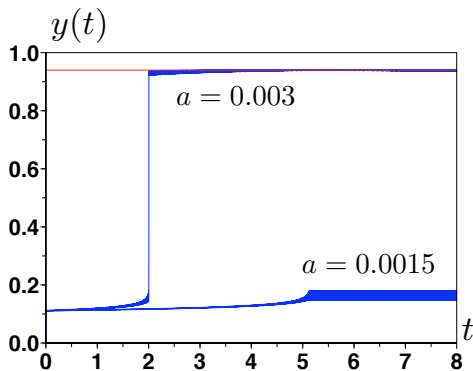

Fig. 8. Output signal $y(t)$: when a is too small, the trajectory is stuck on the lower branch.

large values of the dither amplitude are also prohibited because they produce cyclic trajectories as shown in Fig.9. From all these observations, we can conclude that by tuning the amplitude of the dither signal properly, it is possible to pass through the discontinuities of the stable branches of the cost function and to converge to the global maximum.

In the next section, we shall examine how the averaging Lyapunov stability analysis can be extended
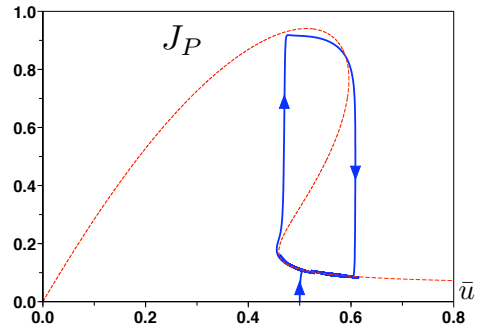

Fig. 9. Extremum seeking for system (8) with $a = 0.015$, $k = 6$, $\omega = 0.01$.

to the case of a multivalued (or "set-valued") cost function, by using the notion of "Integral of a set-valued function" (Aumann (1965)). This analysis will explain why, in contrast with the previous case, it may be required to increase the parameter a for guaranteeing the convergence of the averaged system.

5. AVERAGING STABILITY ANALYSIS

In this section, we are concerned with the analysis of a dynamical system

$$\dot{x} = f(x, u) \tag{9a}$$
$$y = h(x, u) \tag{9b}$$

under the ES control law (5) whith a set-valued cost function having a form similar to Fig.5 (obviously we have system (8) in mind). Since only the stable branches of the static characteristic matter, the set-valued cost function $Q(\theta)$ is defined as a set of two continuous single-valued functions:

$$Q(\theta) = \{Q_1(\theta), Q_2(\theta)\}$$

with the following conditions:

(1) $Q_1 : [\theta_1, +\infty) \rightarrow \mathbb{R}$ and $Q_2 : (-\infty, \theta_2] \rightarrow \mathbb{R}$ with $\theta_1 < \theta_2$;
(2) For each value of $\theta \in [\theta_1, +\infty)$, there is a LAS equilibrium $x = \ell_1(\theta)$ of system (9) such that $Q_1(\theta) = h(\ell_1(\theta), \alpha(\theta))$;
(3) For each value of $\theta \in (-\infty, \theta_2]$, there is a LAS equilibrium $x = \ell_2(\theta)$ of system (9) such that $Q_2(\theta) = h(\ell_2(\theta), \alpha(\theta))$;
(4) $\forall \theta \in [\theta_1, \theta_2]$, $Q_2(\theta) > Q_1(\theta)$;
(5) $\forall \theta \in [\theta_1, +\infty)$, $Q'_1(\theta) < 0$;
(6) The function Q_2 has a unique global maximum at $\theta_1 < \theta^* < \theta_2$.

We can then state the following qualitative observations.

(a) Under the above conditions, it is clear that the singular perturbation analysis of Tan et al. (2006) applies : if, at some time, the trajectory is not in the vicinity of Q, it will quickly converge

to this set. Thus we can consider, as illustrated by the simulations, that the trajectories are sequences of alternative fast jumps and quasi-static motions. Furthermore *if the parameter a is chosen sufficiently small*, the quasi-static trajectories along Q_2 converge to a small neighborhood of the optimal steady-state.

(b) But the simulations also show that, *if the parameter a is too small*, the trajectories on Q_1 may be stuck at the local maximum corresponding to the bifurcation point. Furthermore, when stuck on Q_1, condition (5) implies that θ_0 is automatically prevented to increase (in order to approach θ^*) since climbing along Q_1 is enforced by the ES control algorithm.

(c) Hence, although it is necessary to keep the parameter a rather small, it may also be necessary to increase a to pass through the bifurcation point and force a jump from Q_1 to Q_2 as in Fig.7. But, unfortunately, if a is too large, a cyclic behaviour as in Fig.9 is also possible.

The set-valued averaging analysis presented below gives a more technical justification of the fact that increasing a may lead to passing through the bifurcation point. The definition of the averaged system makes use of the notion of Aumann integral in order to capture the complex trajectories that can occur in $[\theta_1, \theta_2]$.

As in Section 3, we introduce the change of coordinates $\tilde{\theta} = \theta_0 - \theta^*$ and the change of time scale $\sigma = \omega t$. But here, the $\tilde{\theta}$-dynamics become a *differential inclusion* (see e.g. (Clarke, 1983, Chap.3)):

$$\frac{d\tilde{\theta}}{d\sigma} \in kQ(\theta^* + \tilde{\theta} + a\sin\sigma)a\sin\sigma. \quad (10)$$

where the right hand side is a set-valued 2π-periodic function. Then the average of system (10) is defined as the differential inclusion

$$\frac{d\theta_{av}}{d\sigma} \in kaf_{av}(a, \theta_{av}) \quad (11)$$

with $f_{av}(\sigma, \theta_{av})$ being the set-valued function defined as

$$f_{av}(a, \theta_{av}) \triangleq \frac{1}{2\pi}\int_0^{2\pi} Q(\theta^* + \theta_{av} + a\sin\sigma)\sin\sigma d\sigma$$

whith an Aumann integral on the right hand side (see Aumann (1965)). (Given a set-valued map $F(.)$, the Aumann integral of F is defined as the set of integrals of all measurable selections from F.)

Let us now define the following single-valued function $Q_0(\theta)$ which is a selection from $Q(\theta)$:

$$Q_0(\theta) = \begin{cases} Q_1(\theta) & \theta_2 < \theta < +\infty \\ Q_2(\theta) & -\infty < \theta \leqslant \theta_2 \end{cases}.$$

Then we can write:

$$f_{av}(a, \theta_{av}) = \hat{f}_{av}(a, \theta_{av}) + g(a, \theta_{av})$$

with

$$\hat{f}_{av}(a, \theta_{av}) \triangleq \frac{1}{2\pi}\int_0^{2\pi} Q_0(\theta^* + \theta_{av} + a\sin\sigma)\sin\sigma d\sigma.$$

Under conditions (1)-(4), it can be shown that the set $g(a, \theta_{av})$ is upper bounded independently of a:

$$\max_{w \in g(a,\theta_{av})} |w| \leqslant M.$$

Then, a sufficient condition to avoid that the trajectory is stuck on Q_1 is obviously that $\theta_1 - \theta^*$ be not a fixed point of the average system :

$$0 \notin f(a, \theta_1 - \theta^*) = \hat{f}_{av}(a, \theta_1 - \theta^*) + g(a, \theta_1 - \theta^*)$$

We observe that $\hat{f}(0, \theta) = 0$ and therefore, by continuity, that we may have $0 \in f(a, \theta_1 - \theta^*)$ for small values of a. Hence it appears clearly that a sufficient condition for having $0 \notin f(a, \theta_1 - \theta^*)$ is that a be sufficiently large to get $|\hat{f}_{av}(a, \theta_1 - \theta^*)| > M$. This allows to understand why increasing the parameter a may prevent the trajectory to remain stuck on the lower equilibrium branch Q_1.

In conclusion, our analysis shows that global extremum seeking is possible for systems with multivalued discontinuous cost functions, but there are competing requirements on the value of the dither amplitude parameter a which are impossible to quantify a priori since we are in a context where neither the plant model nor the cost function are known a priori. This means that, in practical applications, ES control is certainly a relevant procedure for automatic seeking of optimal steadystates but experimenting with different values of the dither amplitude may lead to significant performance improvements.

REFERENCES

R.J. Aumann. Integrals of set-valued functions. *Journal of Mathematical Analysis and Applications*, 12(1):1–12, 1965.

F.H. Clarke. *Optimization and nonsmooth analysis*. Wiley, New York, 1983.

F. Jadot, G. Bastin, and J.F. Van Impe. Optimal adaptive control of a bioprocess with yielproductivity conflict. *Journal of Biotechnology*, 65:61–68, 1998.

Y. Tan, D. Nesic, and I. Mareels. On nonlocal stability properties of extremum seeking control. *Automatica*, 42:889–903, 2006.

A.R. Teel, L. Moreau, and D. Nesic. A unification of time-scale methods for systems with disturbances. *IEEE Transactions on Automatic Control*, 48:1526–1544, 2003.

H-H. Wang, M. Krstic, and G. Bastin. Optimizing bioreactors by extremum seeking. *International Journal of Adaptive Control and Signal Processing*, 13:651–669, 1999.