Available online at www.sciencedirect.com

ScienceDirect

IFAC-PapersOnLine 49-7 (2016) 103–108

Smooth extremum-seeking control for fed-batch processes ⋆

Jamilis Martín * **Garelli Fabricio** * **De Battista Hernán** *

* *Group of Control Applications, LEICI, Faculty of Engineering, La Plata National University, CONICET, C.C.91 (1900), La Plata, Argentina (e-mail: martin.jamilis@ing.unlp.edu.ar).*

Abstract: Many biotechnological processes have optimal substrate concentrations where a maximum growth rate is achieved. In this work an extremum seeking controller and a gradient estimator are proposed to maximize the growth rate in fed-batch bioprocesses even when the substrate to growth rate map is unknown. Both the controller and estimator are obtained with high order sliding mode algorithms. Stability proofs are given, and tools to tune the algorithms in terms of bounds of the hessian of the map are derived. Simulation results that illustrate the performance of the controller are shown.

Keywords: extremum seeking, gradient estimation, high order sliding mode

1. INTRODUCTION

In the bioprocess industry is very common to find the necessity of performing a given conversion at the highest rate possible, i.e. with the highest productivity. For example, if it is desired to produce a large amount of biomass, the growth rate should be high. If the objective is to generate a given product, the production rate should be maximized. Fed-batch reactors (FBR) allow to obtain large amounts of biomass or products in short times, however its control is difficult when the microorganism being used gets inhibited by the excess of a substrate, giving place to optimal substrate concentrations where the reaction rate of interest is maximized. One of the most common methods to feed a FBR is with an open-loop exponential feeding of the substrate, in this way, when exponential growth takes place the substrate concentration is kept constant as well as the growth rate (in accordance to the exponential growth), Lee et al. (1999). However, any deviation from the modeled yields or assumed initial conditions makes the process work at a different growth rate than the desired one, existing the possibility of instability in non-monotonic kinetics, as explained in Smets et al. (2002). A closed loop version of the exponential feeding can be stated to obtain a given growth rate using an estimation of the rate as feedback signal, as in Dabros et al. (2010), Biener et al. (2012) and De Battista et al. (2012). Alternatively, the control objective can be to regulate the substrate concentration at a given value, and as a consequence to obtain a corresponding growth rate, Smets et al. (2002). In general growth rate feedback algorithms are inherently unstable in the optimal point, while substrate feedback algorithms are stable. However, the later ones require knowledge of the optimal substrate concentration, which can be uncertain and time varying. Moreover, substrate measurement is not possible in most cases, particularly at low concentrations.

Extremum seeking controllers allow to drive a system to a given operating point that maximizes (or minimizes) a given objective function. In the case of bioprocesses, this means that the algorithm searches for the maximum reaction rate value, possibly with partial or no knowledge at all of the kinetic model or the maximum location. For example, in Cougnon et al. (2011) an adaptive control law is proposed, where a dither signal added to the control action is used to estimate the maximum location. Dochain et al. (2011) gives a detailed explanation of dither based, model based and adaptive extremum seeking in bioprocesses. Other approaches , like Vargas et al. (2015) propose the use of a bank of super-twisting observers to estimate a virtual output which is later maximized with a switched control. For given design parameters there is guarantee that the output will oscillate close to its maximum value. In Lara-Cisneros et al. (2014) a different approach is taken combining first order sliding mode (FOSM) control techniques with a discrete time siding mode gradient estimator as the one presented by Fu and Ümit Özgüner (2011). The controller uses the gradient estimation to reach an operating point where the gradient is null, which is a necessary condition for an optimal point. The FOSM sliding mode controller is able to reach operating points very close the optimal ones. However, the gain choice is compromised between disturbance rejection and smoothness of reaction rate response. Also, the gradient estimation is delayed from the real value due to its discrete character. It is worth mentioning the work by Castanos and Kunusch (2015), who propose a super-twisting controller with a sliding mode gradient estimation scheme applied to hydrogen fuel cells, which can potentially be applied to bioprocesses. However, a time derivative of the growth rate is required, being that rate a variable which cannot be directly measured. The only way to obtain the derivative is to estimate it from a growth rate estimation or from some indirect measurement of the growth rate as could be the gas production rate.

⋆ This work was partially supported by ANPCyT-FONCyT, UNLP, CONICET.

10.1016/j.ifacol.2016.07.224

In this work we propose an extremum seeking controller based on the super-twisting algorithm (STA) and a high order sliding mode (HOSM) gradient estimator. The controller allows to reach the optimum in finite time and provides a smooth control action. The HOSM gradient estimator provides an estimation with finite time convergence and no additional dynamics are added to the system.

2. PROBLEM STATEMENT

This work is stated for bioprocesses in fed-batch reactors where there is a single limiting substrate. The microorganism specific growth rate and the single limiting substrate concentration are related by a static map. Due to an inhibiting effect of excess substrate on the growth rate, a maximum growth rate μ^* occurs at a given optimal substrate concentration s^*. An example of this are microorganisms with Haldane kinetics.

Table 1. Model parameters

Name	Description
x	biomass concentration
s	limiting substrate concentration
s_f	limiting substrate feeding concentration
v	volume
D	dilution rate
y_{xs}	biomass substrate yield
$\mu(s)$	reaction rate
$\omega(s)$	gradient of $\mu(s)$
$h(s)$	hessian of $\mu(s)$

The model for the fed-batch process in terms of concentrations is described as

$$\dot{x} = (\mu(s) - D)x \tag{1}$$

$$\dot{s} = -\frac{\mu(s)x}{y_{xs}} + D(s_f - s) \tag{2}$$

$$\dot{v} = Dv, \tag{3}$$

where all the parameters are described in Table 1. The static map is represented by $\mu(s)$, the specific growth rate, and its expression and parameters are considered unknown. For simplicity, from now on $\mu(s)$ is addressed as μ. Given the map, its gradient and hessian are defined as the first and second partial derivatives of μ with respect to s

$$\frac{\partial \mu(s)}{\partial s} = \omega(s) \tag{4}$$

$$\frac{\partial \omega(s)}{\partial s} = h(s). \tag{5}$$

Then, the gradient and hessian dynamics are obtained by means of the chain rule

$$\dot{\mu} = \omega \dot{s} = \omega \left(-\frac{\mu x}{y_{xs}} + D(s_f - s) \right) \tag{6}$$

$$\dot{\omega} = h \dot{s} = h \left(-\frac{\mu x}{y_{xs}} + D(s_f - s) \right). \tag{7}$$

The control objective is to reach an operation point where $\omega = 0$ (and $h < 0$). The susbtrate concentration corresponds to the optimal s^* and $\mu(s^*) = \mu^*$. As explained before, the point (s^*, μ^*) is unknown.

One of the main issues in bioprocess control is the scarcity of measurements in standard plants. For that reason in this work it is considered that the only measurements available are the biomass concentration x, and the dilution rate D which is obtained by dividing the input flow rate by the volume. Moreover, the dilution rate is bounded to $0 < D < D_{max}$.

3. CONTROLLER AND ESTIMATOR DESIGN

The control algorithm proposed in this work is composed by a feed-forward action, as the one proposed in Lara-Cisneros et al. (2014), and a HOSM controller based on the super-twisting algorithm (STA) originally proposed by Levant (1998). Both the feed-forward action and the STA controller require the knowledge of the substrate concentration, the growth rate and the gradient (s, μ and ω). As these variables are not being measured, their estimations are obtained with proper observers from the biomass measurement.

3.1 Control law

The proposed control law is

$$D = \left(\frac{\hat{\mu} x}{y_{xs}} + u_1 + u_2 \right) (s_f - \hat{s})^{-1} \tag{8}$$

$$u_1 = k_1 |\hat{\omega}|^{1/2} sign(\hat{\omega}) \tag{9}$$

$$\dot{u}_2 = k_2 sign(\hat{\omega}) \tag{10}$$

where $k_1 > 0$ and $k_2 > 0$ are the design gains and $\hat{\mu}$, $\hat{s}$ and $\hat{\omega}$ are the estimated growth rate, substrate concentration and gradient respectively. The sliding function is defined as the estimated gradient and the sliding surface is reached when $\hat{\omega}$ reaches zero.

Note that, replacing (8) in (2) yields

$$\dot{s} = u_1 + u_2 + \rho_1(\tilde{\mu}, \tilde{s}, \tilde{\omega}) \tag{11}$$

where $\rho_1(\tilde{\mu}, \tilde{s}, \tilde{\omega})$ is a disturbance term gathering the estimation errors made by the observers.

3.2 Gradient estimation

As it can be seen in (6), the dynamics of the reaction rate are linked to the gradient as

$$\dot{\mu} = \omega \dot{s} = \omega f(\mu, x, s) = \omega \left(-\frac{\mu x}{y_{xs}} + D(s_f - s) \right). \tag{12}$$

In order to obtain finite time convergence of the estimated gradient a HOSM observer is proposed. However, as the classical STA cannot handle the sign changes of $\dot{s} = f(\mu, x, s)$, a modified version is used, based on the one proposed in Moreno and Guzmán (2015)

$$\dot{\eta} = \hat{\omega} f(\hat{\mu}, x, \hat{s}) - \kappa_1 \left| f(\hat{\mu}, x, \hat{s}) \right| |\sigma|^{1/2} sign(\sigma) \tag{13}$$

$$\dot{\hat{\omega}} = -\kappa_2 f(\hat{\mu}, x, \hat{s}) sign(\sigma) \tag{14}$$

$$\sigma = \hat{\mu} - \eta \tag{15}$$

where κ_1 and κ_2 are design gains chosen with the criteria suggested in Moreno and Guzmán (2015), η is an auxiliary estimation of the specific growth rate μ which is only used in this observer, σ is the estimation error used as sliding coordinate. It must be noted that the growth rate and substrate estimations $\hat{\mu}$ and $\hat{s}$ are used because these variables are not measured. However, the same gradient estimator can be used in an scenario where these variables are measured, or at least a function of them, see Lara-Cisneros et al. (2014) for instance.

3.3 Observers

The growth rate estimation $\hat{\mu}$ is obtained using an exponential observer.The observer equations are

$$\dot{\hat{x}} = (\hat{\mu} - D)x - \gamma_1(x - \hat{x}) \quad (16)$$

$$\dot{\hat{\mu}} = \gamma_2(x - \hat{x})x. \quad (17)$$

The gains $\gamma_1 < 0$ and $\gamma_2 > 0$ can be adjusted to assign the eigenvalues of the error dynamics as

$$\lambda_1 + \lambda_2 = \gamma_1 x \quad (18)$$

$$\lambda_1 \lambda_2 = \gamma_2 x^2. \quad (19)$$

On the other hand, the substrate concentration estimation $\hat{s}$ is obtained with an asymptotic observer. The observer equations are

$$\dot{\hat{z}} = -D(\hat{z} - s_f) \quad (20)$$

$$\hat{s} = \hat{z} - \frac{x}{y_{xs}}. \quad (21)$$

where $\hat{z}$ is the estimation of $z = s + x/y_{xs}$, an auxiliary variable.

Both observers have been extensively treated in the literature Bastin and Dochain (1990); Dochain (2003). It is also possible to use discontinuous sliding mode observers which have finite time convergence and tracking without delays Jamilis et al. (2015); Nuñez et al. (2013); Picó et al. (2009). However, in this work it was avoided from a practical implementation point of view, not to have a chain of discontinuous observers. Nonetheless, discontinuous observers can be included in future versions of the controller.

4. STABILITY PROOF

In this section the stability proof of the proposed control algorithm (8)-(10) is given for the nominal case, i.e. with $\tilde{\mu} = \tilde{s} = \tilde{\omega} = 0$ and $\rho_1(\tilde{\mu}, \tilde{s}, \tilde{\omega}) = 0$. The results presented here are based on Moreno and Osorio (2008); Moreno (2012).

In the case without disturbances and considering that the gradient estimation reached the sliding surface, the substrate dynamic model is given by

$$\dot{s} = k_1|\omega|^{\frac{1}{2}} sign(\omega) + u_2. \quad (22)$$

Then, from (7) the dynamic model for the gradient is

$$\dot{\omega} = h\dot{s} = h\left(k_1|\omega|^{\frac{1}{2}} sign(\omega) + u_2\right) \quad (23)$$

$$\dot{u}_2 = k_2 sign(\omega) \quad (24)$$

Applying the following variable change

$$\xi_1 = |\omega|^{\frac{1}{2}} sign(\omega) \quad (25)$$

$$\xi_2 = u_2 \quad (26)$$

a new system can be obtained

$$\dot{\xi}_1 = \frac{1}{2|\xi_1|}(k_1\xi_1 + \xi_2)h \quad (27)$$

$$\dot{\xi}_2 = \frac{1}{2|\xi_1|}(2k_2\xi_1). \quad (28)$$

Which can be written in matrix form as

$$\dot{\xi} = \frac{1}{2|\xi_1|}A\xi \quad (29)$$

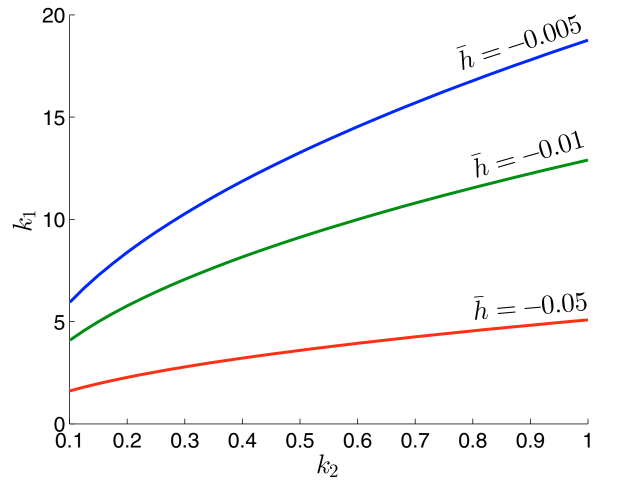


Fig. 1. Set of feasible gains for nominal stability when $\underline{h} = -1.3$ and for different cases of $\bar{h}$

where

$$A = \begin{bmatrix} hk_1 & h \\ 2k_2 & 0 \end{bmatrix}. \quad (30)$$

From (30) becomes clear that $\mu(s)$ needs to be convex ($h < 0$) so that the trajectories of ξ are stable. Although this condition is not met with Haldane kinetics, an upper bound for the substrate concentration $\bar{s}$ can be given so that if $0 < s < \bar{s}$ then $\underline{h} < h < \bar{h} < 0$, being $\underline{h}$ and $\bar{h}$ the lower and upper bounds for the hessian in that interval. Then, the map is convex in the given interval.

System (29) is a linear differential inclusion (LDI)

$$\dot{\xi} = \frac{1}{2|\xi_1|}\mathcal{A}\xi \quad (31)$$

where

$$\mathcal{A} = conv(A_1, A_2) \quad (32)$$

$$A_1 = \begin{bmatrix} \bar{h}k_1 & \bar{h} \\ 2k_2 & 0 \end{bmatrix} A_2 = \begin{bmatrix} \underline{h}k_1 & \underline{h} \\ 2k_2 & 0 \end{bmatrix}. \quad (33)$$

To see that A_1 and A_2 define a convex set which includes all the matrices of the family A, take the scalar $0 < \theta < 1$

$$\theta A_1 + (1-\theta)A_2 = \quad (34)$$

$$\begin{bmatrix} (\theta\bar{h} + (1-\theta)\underline{h})k_1 & (\theta\bar{h} + (1-\theta)\underline{h}) \\ 2k_2 & 0 \end{bmatrix} \quad (35)$$

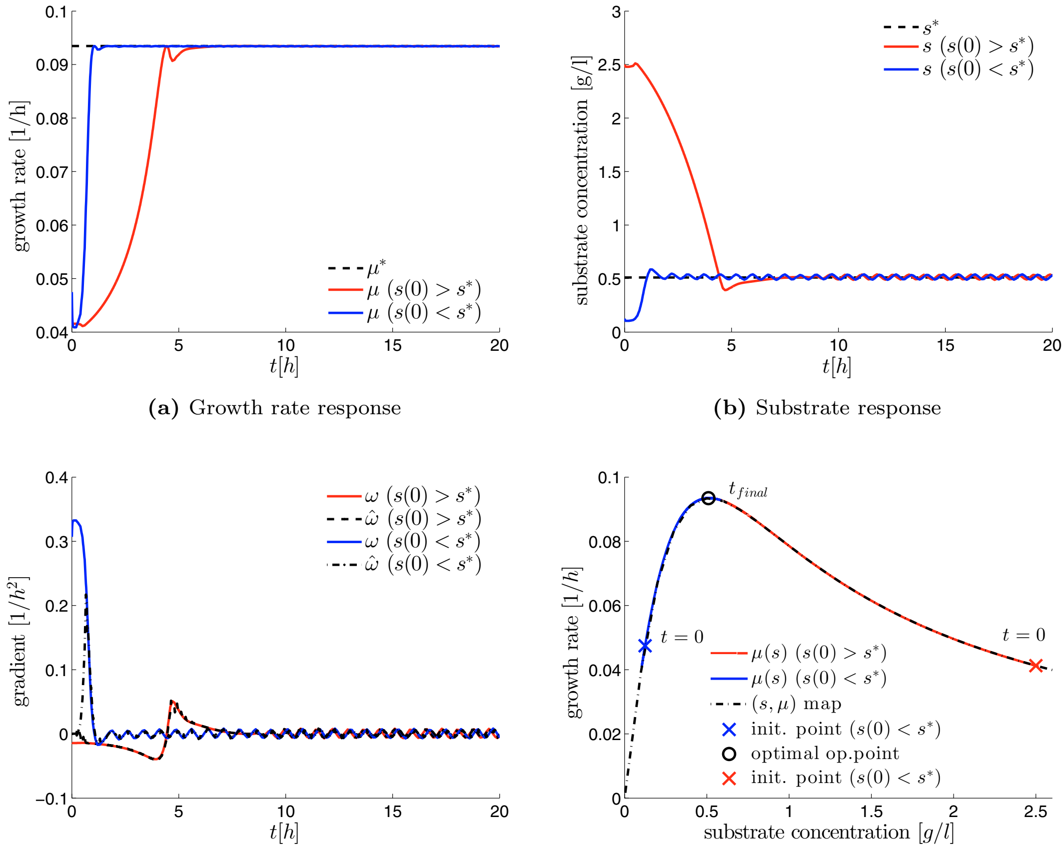
Any h (which is scalar) in the range $(\underline{h}, \bar{h})$ can be represented as $\theta\bar{h} + (1-\theta)\underline{h}$ with $0 < \theta < 1$, see Boyd and Vandenberghe (2004), then (35) equals (30).

Finally, from Boyd et al. (1994), defining a Lyapunov quadratic function $V(\xi) = \xi^T P \xi$ where $P > 0$ and symmetric, system (31) is stable as long as

$$A_1^T P + PA_1 < 0 \quad (36)$$

$$A_2^T P + PA_2 < 0 \quad (37)$$

To illustrate this result take the following example: given the bounds $(\underline{h}, \bar{h})$ and the gain k_2, find the smallest value of k_1 for which problem (37) is feasible and (31) is stable. This problem can be solved numerically using YALMIP (Löfberg (2004)). In Figure 1 the set of gains



(a) Growth rate response

(b) Substrate response

(c) Gradient and estimations

(d) Growth rate vs. substrate concentration. Marks: Crosses for initial conditions. Circle for optimal operating point. Dash and dots line for static map.

Fig. 2. Simulation results: Case with two different initial substrate concentrations. In red the case when $s(0) > s^*$, in blue the case when $s(0) < s^*$. Gradient estimations are drawn in dashed lines.

that guarantee stability for different bounds of the hessian is shown. The lower bound is fixed at $\underline{h} = -1.3$ and the upper bound took the values $\bar{h} = -0.005, -0.01, -0.05$. These values where taken from the kinetic model used for the simulation results, the lower bound corresponds to the minimum value of the hessian.

The implemented controller uses estimations of the specific growth rate, substrate concentration and gradient. Although their effect on stability is not analysed in this work, it is worth mentioning that the gradient estimator has finite time convergence, which means that ideally the estimation error remains zero after reaching that value. On the other hand, the growth rate and substrate observers are continuous and introduce additional dynamics to the closed loop. However, due to the slow nature of the process, the control algorithm can be executed at a substantially lower frequency than the observers, so that the observers dynamic effect on the closed loop is minimized via frequency decoupling.

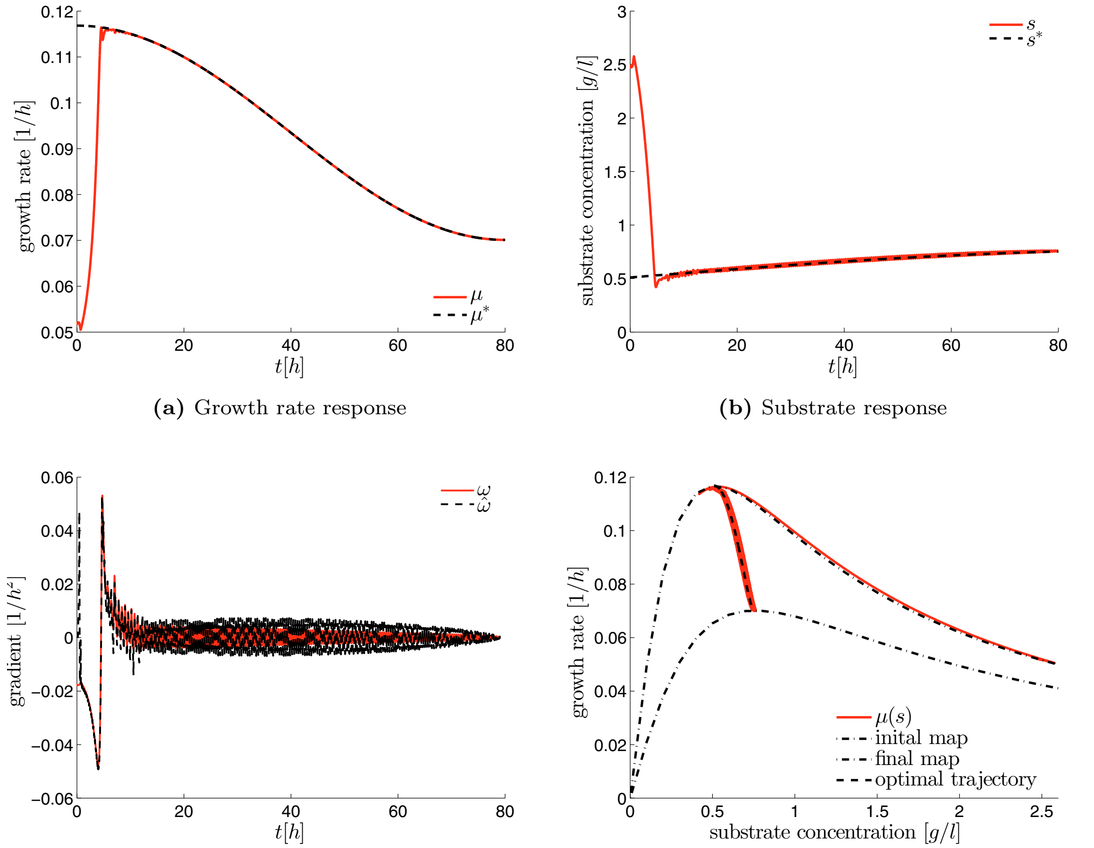
5. SIMULATION RESULTS

In this section simulation results are shown for the growth rate maximization in a fed-batch process with Haldane kinetics as the one in Lara-Cisneros et al. (2014). The given process is described as in (1), (2) and (3), with $y_{xs} = 2.5g/g$ and $s_f = 20g/L$. An expression for the growth rate is given to perform the simulations

$$\mu = \frac{\mu_{max} s}{K_S + s + \dfrac{s^2}{K_I}} \tag{38}$$

where $K_S = 1.2g/L$, $K_I = 0.22g/L$, $\mu_{max} = 0.531/h$. The optimal substrate concentration and growth rate for this kinetic model are $s^* = 0.51g/L$ and $\mu^* = 0.0931/h$. The control algorithm is run with period of $0.1h$ which is reasonable considering the bandwidth of a real bioprocess. The observers and gradient estimator are run with a much higher frequency, $T = 1 \times 10^{-4}h$.

Figure 2 shows the growth rate, substrate concentration, gradient and trajectory in the μ, s map for two different initial substrate concentrations, one lower than the optimal and the other one higher. The initial condition for the gradient is also different in both cases, in sign and modulus. In both cases the optimal substrate concentration is reached in finite time, although it is faster in the case with $s(0) < s^*$ due to the magnitude of the gradient, which can be seen in Figure 2(c). Some oscillations around the optimal substrate concentration can be observed in Figure 2(b) due to the discretization of the controller and its amplitude can be diminished decreasing the period of execution. However, these oscillations end up acting as a



(a) Growth rate response

(b) Substrate response

(c) Gradient and estimations

(d) Growth rate vs. substrate concentration and optimal trajectory

Fig. 3. Simulation results: Case with varying optimums

dither signal which allows to evaluate if the operating point is the optimum. It must be noticed that the oscillations are negligible in the growth rate. Figure 2(c) also shows the gradient estimations, that after an initial transient reach the real gradient value and track it without delay. At some points some small errors show up, which are related to the delays in the exponential growth rate observer. Nevertheless, this errors are not relevant in the final control action.

Figure 3 shows results for the case where the optimum substrate concentration and growth rate are time varying. The variation can be produced by the unmodeled effect of another substrate, compound of the medium or product. Figure 3(d) shows the initial and final kinetic models for the growth rate, where the transition from one to another is smooth. The change in the optimal substrate and growth rate gives places to an optimal trajectory also shown in Figure 3(d). As it can be observed, the controller is able to reach the optimal trajectory and stay on it for the rest of the process. This is also depicted in Figure 3(a), where the growth rate is always tracking the optimum growth rate. Equivalently, in Figure 3(c) it can be observed that after convergence the controller keeps in a neighbourhood of the sliding surface for the rest of the process, that means, the gradient stays equal to zero.

6. DISCUSSION AND CONCLUSIONS

The HOSM extremum seeking controller is able to reach the optimal substrate concentration and growth rate in finite time. After convergence, the tracking of the optimal operating point is done without delays as expected from the STA, even if the optimal point is changing. To do so, no previous knowledge of the kinetic model is required, what constitutes an advantage. The obtained control action (dilution) is continuous and smooth, which makes it suitable for plants where adjustable pumps or valves are used. This also allows to finally obtain a smoother response in the growth rate, without oscillations. For cases where the available actuators are of discontinuous nature , it is advisable to use a similar scheme with a first order sliding mode control instead, as the one in Lara-Cisneros et al. (2014). The control and gradient estimation scheme is based on the use of a biomass concentration measurement only. Considering that this variable is easier to measure than substrate concentration, either by optical density methods or with dielectric spectroscopy probes, this scheme is easier to apply or adapt to many different bioprocesses.

With respect to the gradient estimation, the use of the HOSM observer allows to obtain an accurate estimation in finite time and without delays, contributing to a better regulation of the growth rate. Some degradation of the estimated gradient shows up because the data is obtained from observers. However, this has little effect on the controlled output.

Future work includes the stability proofs for the disturbed case and the experimental validation. Also, the inclusion of discontinuous observers and design of an extremum seeking controller for a multi-substrate case.

REFERENCES

Bastin, G. and Dochain, D. (eds.) (1990). *On-line Estimation and Adaptive Control of Bioreactors*. Process Measurement and Control. Elsevier, Amsterdam. doi:http://dx.doi.org/10.1016/B978-0-444-88430-5.50001-3.

Biener, R., Steinkämper, A., and Horn, T. (2012). Calorimetric control of the specific growth rate during fed-batch cultures of saccharomyces cerevisiae. *Journal of Biotechnology*, 160(3–4), 195 – 201. doi: http://dx.doi.org/10.1016/j.jbiotec.2012.03.006.

Boyd, S., El Ghaoui, L., Feron, E., and Balakrishnan, V. (1994). *Linear Matrix Inequalities in System and Control Theory*, volume 15 of *Studies in Applied Mathematics*. SIAM, Philadelphia, PA.

Boyd, S. and Vandenberghe, L. (2004). *Convex Optimization*. Cambridge University Press, New York, NY, USA.

Castanos, F. and Kunusch, C. (2015). Ditherless extremum seeking for hydrogen minimization in pem fuel cells. *Industrial Electronics, IEEE Transactions on*, 62(8), 5218–5226. doi:10.1109/TIE.2015.2426143.

Cougnon, P., Dochain, D., Guay, M., and Perrier, M. (2011). On-line optimization of fedbatch bioreactors by adaptive extremum seeking control. *Journal of Process Control*, 21(10), 1526 – 1532. doi: http://dx.doi.org/10.1016/j.jprocont.2011.05.004. Special Issue:Selected Papers From Two Joint {IFAC} Conferences: 9th International Symposium on Dynamics and Control of Process Systems and the 11th International Symposium on Computer Applications in Biotechnology, Leuven, Belgium, July 5-9, 2010.

Dabros, M., Schuler, M., and Marison, I. (2010). Simple control of specific growth rate in biotechnological fed-batch processes based on enhanced online measurements of biomass. *Bioprocess and Biosystems Engineering*, 33(9), 1109–1118. doi:10.1007/s00449-010-0438-2. URL `http://dx.doi.org/10.1007/s00449-010-0438-2`.

De Battista, H., Picó, J., and Picó-Marco, E. (2012). Nonlinear {PI} control of fed-batch processes for growth rate regulation. *Journal of Process Control*, 22(4), 789 – 797. doi:http://dx.doi.org/10.1016/j.jprocont.2012.02.011.

Dochain, D. (2003). State and parameter estimation in chemical and biochemical processes: a tutorial. *Journal of Process Control*, 13(8), 801 – 818. doi: http://dx.doi.org/10.1016/S0959-1524(03)00026-X.

Dochain, D., Perrier, M., and Guay, M. (2011). Extremum seeking control and its application to process and reaction systems: A survey. *Mathematics and Computers in Simulation*, 82(3), 369 – 380. doi: http://dx.doi.org/10.1016/j.matcom.2010.10.022. 6th Vienna International Conference on Mathematical Modelling.

Fu, L. and Ümit Özgüner (2011). Extremum seeking with sliding mode gradient estimation and asymptotic regulation for a class of nonlinear systems. *Automatica*, 47(12), 2595 – 2603. doi: http://dx.doi.org/10.1016/j.automatica.2011.09.031.

Jamilis, M., Garelli, F., Mozumder, M., Castañeda, T., and De Battista, H. (2015). Modeling and estimation of production rate for the production phase of non-growth-associated high cell density processes. *Bioprocess and Biosystems Engineering*, 38(10), 1903–1914. doi:10.1007/s00449-015-1430-7.

Lara-Cisneros, G., Femat, R., and Dochain, D. (2014). An extremum seeking approach via variable-structure control for fed-batch bioreactors with uncertain growth rate. *Journal of Process Control*, 24(5), 663 – 671. doi: 10.1016/j.jprocont.2014.03.011.

Lee, J., Lee, S.Y., Park, S., and Middelberg, A.P. (1999). Control of fed-batch fermentations. *Biotechnology Advances*, 17(1), 29 – 48. doi: http://dx.doi.org/10.1016/S0734-9750(98)00015-9.

Levant, A. (1998). Robust exact differentiation via sliding mode technique. *Automatica*, 34(3), 379–384.

Löfberg, J. (2004). Yalmip : A toolbox for modeling and optimization in MATLAB. In *Proceedings of the CACSD Conference*. Taipei, Taiwan. URL `http://users.isy.liu.se/johanl/yalmip`.

Moreno, J. and Osorio, M. (2008). A lyapunov approach to second-order sliding mode controllers and observers. In *Decision and Control, 2008. CDC 2008. 47th IEEE Conference on*, 2856–2861. doi: 10.1109/CDC.2008.4739356.

Moreno, J. and Guzmán, E. (2015). Super-twisting observer for second-order systems with time-varying coefficient. *IET Control Theory & Applications*, 9(4), 553–562. doi:10.1049/iet-cta.2014.0348.

Moreno, J. (2012). Lyapunov approach for analysis and design of second order sliding mode algorithms. In L. Fridman, J. Moreno, and R. Iriarte (eds.), *Sliding Modes after the First Decade of the 21st Century*, volume 412 of *Lecture Notes in Control and Information Sciences*, 113–149. Springer Berlin Heidelberg. doi:10.1007/978-3-642-22164-4 4.

Nuñez, S., Battista, H.D., Garelli, F., Vignoni, A., and Picó, J. (2013). Second-order sliding mode observer for multiple kinetic rates estimation in bioprocesses. *Control Engineering Practice*, 21(9), 1259 – 1265.

Picó, J., De Battista, H., and Garelli, F. (2009). Smooth sliding-mode observers for specific growth rate and substrate from biomass measurement. *Journal of Process Control*, 19(8), 1314–1323.

Smets, I.Y., Bastin, G.P., and Van Impe, J.F. (2002). Feedback stabilization of fed-batch bioreactors: Non-monotonic growth kinetics. *Biotechnology Progress*, 18(5), 1116–1125. doi:10.1021/bp010191p. URL `http://dx.doi.org/10.1021/bp010191p`.

Vargas, A., Moreno, J., and Wouwer, A.V. (2015). Super-twisting estimation of a virtual output for extremum-seeking output feedback control of bioreactors. *Journal of Process Control*, 35, 41 – 49. doi: http://dx.doi.org/10.1016/j.jprocont.2015.08.003.