# OUTPUT-FEEDBACK CONTROL FOR A CLASS OF BIOLOGICAL REACTORS \*

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**Abstract:** The problem of regulating the biomass growth rate at its maximum value in an open-loop unstable, continuous, non-monotonic biological reactor using biomass measurement and manipulation of substrate feed rate is considered. An Output-Feedback controller is designed exploiting the reactor open-loop stability and inherent observability properties and the relative degree structure to obtain robust and non-wasteful closed-loop performance. The resulting controller has a high degree of independency with respect to the kinetic growth rate expression, thus ensuring robustness against typical model uncertainties. A representative case example with non-monotonic Haldane kinetics is employed to test the proposed controller, in absence and presence of modeling and measurement errors.

Keywords: Non-monotonic Bioreactors, Output-Feedback Control, Observability.

### 1. INTRODUCTION

Process control plays an increasingly important role in the biotechnology industry, and the development of outputfeedback (OF) control systems that exploit advances in online measurement technology to achieve optimal productivity of continuous and fed-batch bioreactors is one of the most important challenges in biochemical manufacturing [Henson 2006]. With the additional requirements of low operation costs and robust performance, the OF control becomes a non-trivial and highly interdisciplinary engineering problem. Operation costs can be reduced by ensuring control wastefulness and simple (conventional-like) control strategies. Control wastefulness can be avoided by a proper open-loop motion and structural stability analysis which allows to identify the inherent (global) stabilizing mechanisms and to design the control exploiting them. The importance of structural stability (bifurcation) analysis in the biological reactor applications has already been pointed out by several authors (see e.g. [Pavlou and Kevrekidis 1992, Zhao and Skogestad 1997, Zhang and Henson 2001]) and in particular it should be mentioned that the question of what impact a close-to-bifurcation closed-loop operation has on the reactor performance can not be trivially answered. The robustness issue has to be addressed with the seek of designing a controller whose performance shows a reduced dependency on the kinetic function model, in the understanding that due to the lack of exact knowledge about the kinetic growth model [Bastin and Dochain 1990], only qualitative information is at hand for design purposes. The OF controller design becomes even more complicated if the reactor is not observable,

a typical situation for the case of non-monotonic growth kinetics [Schaum and Moreno 2007], such like the Haldane biomass growth dependency [Bastin and Dochain 1990].

According to advanced control strategies, the bioreactor control problem can be tackled with model-based OF control schemes which combine a nonlinear state-feedback (SF) controller with a nonlinear state observer [Hoo and Kantor 1986, Gouzé et al. 2000, Rapaport and Harmand 2002]. Even though these advanced control studies have provided valuable results, understanding and insight, the implementation of these nonlinear dynamic OF controllers still rise reliability and development-cost concerns among industrial practitioners, in a milieu where most of the control loops are of the conventional type. These considerations motivate the present study on the development of conventional-like control schemes that perform similar tasks than its advanced control counterparts. According to the constructive control approach [Sepulchre et al. 1997, Freeman and Kokotovic 1996], optimal nonlinear SF controllers are inherently robust, passive with respect to a certain output, non-wasteful with respect to control effort, and can be tractably constructed via inverse optimality by starting with a passive controller and verifying optimality with respect to a meaningful objective function.

In the present paper we consider the problem of stabilizing the equilibrium point of maximum production rate of a simple two state (turbidostat-type) continuous bioreactor for biomass production with non-monotonic biomass growth-rate dependency on the substrate. Different from previous related works where the substrate is the measured output, and taking advantage of recent advances in online measurement technology [Henson 2006] (such as spectrophotometry, flow injection analysis, chromatography,

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etc.), here the biomass is considered as the measuredcontrolled output, with the dilution rate being the manipulated control input. An important feature is that the reactor is globally detectable but not observable [Schaum and Moreno 2007]. Solutions for similar problems have been reported based on feedback linearization control [Hoo and Kantor 1986] using a Kalman-Filter for the reconstruction of the unmeasured state and assuming complete knowledge of the growth rate, while in [Gouzé et al. 2000] and [Rapaport and Harmand 2002] an interval observer was proposed assuming a partial knowledge of the growth rate. Adaptive control techniques have been applied in [Mailleret et al. 2004], [Marcos et al. 2004], and an event-driven optimal control strategy in the context of a fed-batch reactor e.g. in [Betancur et al. 2004]. A flatness based predictive controller was designed in [Mahadevan et al. 2001] for a fed-batch reactor. In the present paper, based on the characterization of the open-loop reactor behavior and the reactor inherent relative degree and observability properties a constructive-like interlaced controller-estimator design [Gonzalez and Alvarez 2005, Diaz-Salgado et al. 2007] is applied to the bioreactor case, yielding a robust PI biomass controller that recovers the behavior of a nonlinear passive SF controller with optimality-based robustness and control non-wastefulness features (cp. [Alvarez and Gonzalez 2007, Schaum et al. 2008). A representative case example with Haldane kinetics is considered as an application example through simulations, including functioning tests in the presence of measurement and optimal biomass set-point errors.

#### 2. CONTROL PROBLEM

Consider a bioreactor where substrate is fed and converted into biomass, according to the following conservationbased dynamics (see e.g. [Bailey and Ollis 1986, Bastin and Dochain 1990])

$$\dot{s} = -\alpha\mu(s)b + \theta(s_e - s)$$
  
$$\dot{b} = \mu(s)b - \theta b, \quad y = b.$$
(1)

Here, s and b are the substrate and biomass concentration, respectively,  $\mu(s)$  is the non-monotonic growth rate function,  $\mu(s)b$  is the biomass production by bioreaction,  $\theta = q/V$  is the dilution rate, i.e. the ratio of flow rate q and volume V,  $\alpha$  is the inverse yield coefficient,  $s_e$  is the substrate inlet concentration, and y is the biomass measurement signal. In compact vector notation the reactor model (1) is written as

$$\dot{x} = f(x), \ x = [s, b]^T, \ f = [f_s, f_b]^T, \ y = Cx, \ C = [0, 1]^T.$$
(2)

The objective of the maximum-productivity closed-loop (CL) reactor operation amounts to the regulation of the substrate concentration s at the set-point  $s^*$  where the growth rate function  $\mu(s^*)$  reaches its maximum. Thus, our control problem consists in designing a biomass controller so that  $(s^*, b^*)$  is a global attractor for the closed-loop reactor, in the understanding that  $s^*$  is off-line determined from modeling  $(\mu)$  and/or experimentation and on-line calibrated according to the substrate measurements taken for monitoring and/or supervisory control purposes.

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Thus, our control problem consists in manipulating the dilution rate  $\theta$  in such a way that  $(s^*, b^*)$  is a global attractor for the CL reactor.

#### 3. REACTOR ANALYSIS

Here, the reactor dynamics, observability properties and relative degree structure are characterized.

#### 3.1 Open-Loop stability analysis

In this section, an open-loop dynamical characterization is performed, yielding: (i) the equilibrium point and bifurcation structure of the open-loop reactor, and (ii) a feedforward-like component which assigns a biomass set-point  $b^*$  to the substrate one  $s^*$  which maximizes the growth rate  $\mu(s)$ .

The equilibrium points of the reactor (1) correspond to the solutions of f(s,b) = 0. Correspondingly, the undesired washout point  $(b^*, s^*) = (0, s_e)$  is always an equilibrium. The existence of other steady states (SS) depends on the relation between  $\mu(s)$  and  $\theta$ . In the case of a non-monotonic growth rate  $\mu(s)$ , one finds a saddle-node-type bifurcation [Guckenheimer and Holmes 1983], depending on the dilution rate value  $\theta$  according to

$$\begin{aligned} \theta &< \max_{s} \mu(s) \Rightarrow \exists \ 3 \ \text{SSs} \\ \theta &= \max_{s} \mu(s) \Rightarrow \exists \ 2 \ \text{SSs} \\ \theta &> \max \mu(s) \Rightarrow \exists \ 1 \ \text{SS.} \end{aligned}$$
(3)

All the steady-states (SSs) are located on the curve

$$b^*(s) = \theta(s_e - s) / [\alpha \mu(s)], \tag{4}$$

which will always be of finite value as long as  $s_e > 0$ , because in this case there exists a minimum concentration  $s_{\min} > 0$  such that  $\dot{s} > 0$  for all  $s \ge s_{min}$ . Furthermore, for all values of b larger than the corresponding value  $b^*$ , the function  $f_s$  attains negative values (and thus the substrate concentration will decrease), while for biomass values less than  $b^*$ , the function  $f_s$  is positive (and swill grow). Consequently, the set defined by  $s = b^{*-1}(b)$ represents a family of global attractors for the substrate concentration. The biomass flow direction is determined by the relation between  $\mu(s)$  and  $\theta$ . Figure 1 shows the corresponding bifurcation and Fig. 2 the associated phase plane (flow) diagrams. This analysis shows that the



Fig. 1. Bifurcation diagram over the dilution rate  $\theta$ .

point of maximum biomass production corresponds to a structurally unstable equilibrium and is semi-stable, in the sense that the corresponding Taylor linearization has a zero eigenvalue corresponding to the biomass dynamics.



Fig. 2. Phase plane diagrams for the three possible cases: (A)  $\theta < \mu(s^*)$ , (B)  $\theta = \mu(s^*)$  and (C)  $\theta > \mu(s^*)$ .

Thus, the substrate dynamics naturally converges to a manifold which contains the desired equilibrium point, and, in an open-loop application, for slight perturbations the reactor trajectories will tend to the undesired washout SS.

#### 3.2 Observability Properties

The next analysis enables the delimitation of outputfeedback performance possibilities on the basis of the underlying observability property. Global nonlinear observability is defined as the absence of indistinguishable trajectories [Hermann and Krener 1977] which correspond to different initial values but generate identical measurements. Accordingly, the reactor observability property can be characterized as follows:

(A) The substrate concentration s is not globally observable and not locally observable around the steady state of maximum reaction rate  $s^*$ , but is globally detectable (cp. [Schaum and Moreno 2007]).

The lack of observability implies that the reconstruction of the substrate concentration can not be speeded up for arbitrary trajectories, in the understanding that for indistinguishable trajectories the convergence time is fixed by the dilution rate.

(B) Based on the notion of instantaneous observability [Hermann and Krener 1977], which underlies the geometric observer design [Alvarez and Fernandez 2009], in a way that is similar to the calorimetric determination of polymerization rates [Alvarez and Gonzalez 2007], we have that the value m of  $\mu(s)$  is uniquely determined by the measurement y and its time derivative, meaning that it can be quickly reconstructed with a reduced order observer.

Recalling the fact that, actually, the growth rate is an uncertain function, only approximate reconstruction is possible using any kind of observer which requires the functional dependence on the substrate concentration. On the other hand, the actual value of the growth rate can be arbitrarily fast reconstructed for substrate estimation with an open-loop-type observer with speed fixed by the dilution rate [Bastin and Dochain 1990].

#### 3.3 Relative-Degree Structure

Denoting the relative degree rd(u, z) between a regulated output z and the corresponding input u by the number of times z has to be derived to yield an explicit and well-defined relation of the type  $z^{(rd(z,u)-1)} = \varphi(x) +$   $g(x)u,\,g(x)\neq 0,$  the reactor has the following relative degree structure

$$rd(\theta, b) = 1 \Leftrightarrow b \neq 0 \text{ and } rd(\theta, s) = 1 \Leftrightarrow s_e \neq s,$$
 (5)

meaning that either the biomass dynamics or the substrate dynamics can be linearized by state feedback and consequently either of each dynamics can be controlled via passive state-feedback, if the corresponding zero dynamics is asymptotically stable [Isidori 1999].

### 4. NONLINEAR PASSIVE SF CONTROL

According to the reactor properties discussed above, it follows that for the regulation of the substrate to its nominal value  $s^*$ , which corresponds to maximal biomass production rate, one can manipulate the dilution rate either based on a substrate estimate to implement a SF controller which linearizes the substrate dynamics (see e.g. Hoo and Kantor [1986]), or based on the biomass measurement to implement a SF controller to linearize the biomass dynamics using an estimate of the (quickly reconstructible) growth rate. Taking into account that the set  $b^{*-1}(s)$  is globally attractive for all s, here a biomass concentration controller is designed to ensure that the SS  $(b^*, s^*)$  is a global attractor for the CL system. From a feed-forward (FF) point of view, the point  $b = b^*(s^*)$  of maximum biomass production is an equilibrium b, if the following FF control is applied

$$\theta^* = \mu(s^*). \tag{6}$$

Hence, the relation (4) becomes  $b^*(s^*) = \bar{b} = (s_e - s^*)/\alpha$ . On the other hand, the enforcement of the linear output error dynamics

$$\dot{b} = -k(b - b^*) \tag{7}$$

yields the globally stabilizing nonlinear passive SF

$$\theta = k(b - \bar{b})/b + \mu(s). \tag{8}$$

The corresponding zero dynamics (i.e. the substrate dynamics on the invariant  $b = \bar{b}$ ) are given by

$$\dot{s} = -\alpha \mu(s) \bar{b} + \mu(s)(s_e - s) = -\mu(s) [s - s^*].$$
(9)

These zero dynamics are asymptotically stable, the substrate concentration converges to the steady state  $\bar{s} = s^*$ with convergence rate fixed by the growth rate  $\mu(s)$ , and the reactor system is passive. Thus, the controller (8) is a nonlinear passive controller, meaning that it is inherently robust due to the relative degree one feature [Sepulchre et al. 1997, Freeman and Kokotovic 1996].

## 5. OUTPUT FEEDBACK CONTROLLER

The aim of the OF controller is the recovery of the behavior with the nonlinear passive SF controller (8), in a robust (with least possible model dependency), simple, and conventional-like (PI) control framework. For this purpose, the above characterized observability properties are exploited for OF control design purposes.

#### 5.1 Model for Control

Following the constructive control idea that the model is an important design degree of freedom (cp. [Alvarez and Gonzalez 2007]), depending on the relative degree and observability structures, an adequate model is tailored for the design, with the least possible model dependency, of an OF controller which recovers sufficiently well the theoretically achievable performance of the nonlinear passive SF controller (8).

Note that, according to the preceding characterization, the substrate can be regulated to the concentration  $s^*$  with maximum biomass growth rate, without having explicit knowledge about the actual substrate concentration s, because the reactor inherent stabilizing mechanisms take the substrate automatically to the value  $s = b^{*-1}(b)$  (4). On the other hand, the growth rate value  $m = \mu(s)$  can be reconstructed arbitrarily fast. Having in mind that the kinetic growth expression is uncertain, the following model (in deviation form, referred to the nominal SS) with minimal dependence on the particular kinetic approximation is chosen for OF control [Alvarez and Gonzalez 2007]:

$$\dot{e}_s = -\alpha\mu(s)b + \theta(s_e - s) 
\dot{e}_b = a\theta + \delta, \quad \dot{\delta} \approx 0, \quad y = b, 
e_b := b - b^*, \quad e_s := s - s^*,$$
(10)

where the load input  $\delta$ , which (theoretically) corresponds to the combined biomass growth and dilution action

$$\delta = \mu(s)b - [b+a]\theta := \gamma(b, s, \theta), \tag{11}$$

is viewed as an unknown input, and  $\boldsymbol{a}$  is given according to

$$a \approx \partial f_b / \partial \theta \Big|_{(\bar{b},\bar{s})=(b^*,s^*)} = -\bar{b} = -b^*(s^*).$$
(12)

According to the observability property of the reactor (1), the estimation model (10) is strongly observable with respect to the unknown input  $\delta$ , meaning that it can be arbitrarily fast reconstructed from the biomass measurement.

In terms of the reconstructible load  $\delta$ , the nonlinear, passive, globally stabilizing SF controller is written as follows

$$\theta = -\left[k(b-\bar{b})+\delta\right]/a, \quad \delta = \gamma(b,s,\theta), \tag{13}$$

where b is measured and  $\delta$  is quickly reconstructible.

### 5.2 Reduced Order load observer

For the estimation of the unknown load input  $\delta$  a reduced order observer [Luenberger 1971] is designed, following the ideas of [Alvarez and Gonzalez 2007]. For this purpose consider as measurement

$$\psi = \dot{e}_y, \quad e_y = y - b^*. \tag{14}$$

According to the slow-varying regime assumption with respect to the system dynamics (i.e.  $\dot{\delta} \approx 0$  (10)), the following observer is set

$$\hat{\delta} = \omega(\psi - \hat{\psi}), \tag{15}$$

where  $\hat{\psi}$  is given by the estimated value  $\hat{\psi} = a\theta + \hat{\delta}$  and  $\omega$  is the observer gain. Introducing the variable

$$\chi \triangleq \hat{\delta} - \omega e_y, \tag{16}$$

one obtains the following dynamics which does not depend on the unknown value of  $\psi = \dot{e}_y$ 

$$\dot{\chi} = -\omega\chi - a\omega\theta - \omega^2 e_y, \qquad (17)$$

and can be implemented on-line. In the absence of measurement errors, this observer reconstructs  $\delta$  arbitrarily fast.

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### 5.3 Dynamic Output Feedback Controller

The combination of the nonlinear passive SF controller (13) with the reduced order observer (15), yields the OF dynamic controller

$$\begin{aligned} \dot{\chi} &= -\omega\chi - a\omega\theta - \omega^2 e_y \\ \hat{\delta} &= \chi + \omega e_y \\ \theta &= -\left[k(b - b^*) + \hat{\delta}\right]/a. \end{aligned}$$
(18)

This controller depends in a reduced way on the particular approximation of  $\mu(s)$ . Actually, the only dependence on this uncertain value appears in the value of  $\bar{b} = b^*(s^*)$  (4). Due to the strong observability property of the model for control (10) with respect to  $\delta$  (11), the nonlinear passive SF controller performance with inherent robustness features against model uncertainties and bounded disturbances in the sense of practical stability [Sepulchre et al. 1997, Freeman and Kokotovic 1996], can be arbitrarily well recovered.

In PI form, the preceding controller is written as follows

$$\theta = \kappa \left[ e_b + \frac{1}{\tau} \int_0^{\tau} e_b(\tau) d\tau \right], \ e_b = b - b^*, \qquad (19)$$
  
$$\kappa = -(k+\omega)/a, \quad \tau = (k+\omega)/(k\omega).$$

This feature enables an easy implementation of the proposed controller design in an industrial-like framework using standard control elements. The tuning of the PI controller gains  $\kappa, \tau$  can be carried out based on the original OF gains  $k_b, \omega$  in accordance to simple guidelines based on the closed-loop stability criterion presented next.

#### 6. CLOSED-LOOP STABILITY AND TUNING

Introducing the load estimation error  $\epsilon_{\delta} := \hat{\delta} - \delta$ , one obtains, by combining the approximation error stemming from the assumption  $\dot{\delta} \approx 0$  in (10), the dynamic controller (18) and the system dynamics (1), and after some algebraic manipulations, the following error dynamics

$$\begin{aligned} \dot{e}_{b} &= -ke_{b} - \epsilon_{\delta} \\ \dot{e}_{s} &= -\mu(s)e_{s} + \left(k\frac{s_{e} - s}{b} - \alpha\mu(s)\right)e_{b} + \frac{(s_{e} - s)}{b}\epsilon_{\delta} \\ \dot{\epsilon}_{\delta} &= -\left(\omega + \mu'(s)(s_{e} - s) + \frac{ke_{b}}{b} + \frac{\epsilon_{\delta}}{b} + \frac{\omega - k}{a}\right)\epsilon_{\delta} + \\ &+ \left(\alpha\mu(s)b - k\left[\frac{ke_{b} + \epsilon_{\delta}}{b} + s_{e} - s\right] + (a + b)\frac{k^{2}}{a}\right)e_{b} \\ &+ \mu'(s)\mu(s)be_{s}. \end{aligned}$$

$$(20)$$

Notice that each one of the three error states is inputto-state stable [Sontag 2000] with respect to the other two ones, if the biomass does not vanish (cp. the relative degree one condition (5)). Accordingly the following convergence result is obtained.

### Theorem 1. (Proof in Appendix A)

For all initial conditions with  $b(0) \neq 0$ , the reactor state (b, s) converges asymptotically to the prescribed maximum rate SS  $(\bar{b}, \bar{s}) = (b^*(s^*), s^*)$  if the estimator-controller gain pair  $(\omega, k)$  is chosen such that

$$(i)\lambda_{\delta}(\omega,k) - L_{\delta}^{\delta} > 0, (ii)\lambda_{s} - L_{s}^{s} > 0$$
  

$$(iii)k(\lambda_{\delta}(\omega,k) - L_{\delta}^{\delta}) > L_{\delta}^{\delta}(k)$$
  

$$(iv)\lambda_{c}(\omega,k)\min_{s \in [s_{min},s_{e}]} \mu(s) > L_{s}^{c}L_{c}^{s}(k),$$

$$(21)$$

with  $L_{\xi}^{a}$  being the Lipschitz constant of the *a*-dynamics with respect to the state  $\xi$ ,  $\lambda_{\xi}$  the effective (smallest) eigenvalue of the  $\xi$  dynamics, and *c* representing the coupled  $(e_{b}, \epsilon_{\delta})$ -dynamics. All constants are given in Appendix A. In the presence of parameter and measurement errors, practical convergence is ensured.

This result ensures practical convergence to a neighborhood of the prescribed optimal operation point  $(s^*, b^*)$ . The radius of this neighborhood can be further improved by off-line calibration according to periodic product quality analysis.

The qualitative conditions (i) to (iv) of Theorem 1, show that the biomass can be rapidly driven to its nominal value, if the estimator-controller gain pair  $(\omega, k)$  is chosen adequately. According to the tuning guidelines adapted from [Gonzalez and Alvarez 2005], set  $k, \omega$  conservatively, increase  $\omega$  until there is oscillatory behavior, back-off  $\omega$ and increase k until there is oscillatory behavior, back-off k and, if necessary, repeat these steps.

### 7. APPLICATION EXAMPLE

In order to illustrate the performance of the designed OF controller, a representative non-monotonic case example is considered using the (re-parametrized) Haldane law (see e.g. [Bastin and Dochain 1990])

$$\mu(s) = \frac{\kappa s}{(1 + \sigma s)^2},\tag{22}$$

where  $\kappa = \sigma$ ,  $\sigma =$ , The parameters used for the simulation are given by  $\kappa = 10s^{-1}, \sigma = 3, \alpha = 2/3, s_e = 1$ . For these parameters the desired point of maximum biomass production is given by  $(\bar{s}, \bar{b}) = (1/3, 1)$ , and the undesired washout equilibrium point is given by (s,b) = (1,0). The controller and estimator gains have been tuned according to the qualitative condition of Theorem 1 considering two cases: (I) nominal behavior, without modeling and measurement errors, and (II) robust behavior, with modeling errors  $(\sigma_{est}, \kappa_{est}) = (2, 12)$ , periodic feed substrate concentration, and measurement errors of 4% amplitude and noise-like oscillations with frequency about 13-times the natural frequency are considered. The afore stated tuning procedure led to  $\omega = 35$ , and k = 3. Figures 3 and 4 show the respective closed-loop behavior. As it can be seen, in OL operation, the reactor does not reach the desired maximum production steady state but reaches the undesired washout point in a time around 40 residence times  $t_R = 1/\theta^* = 1.2$ , while in CL operation, the growth rate converges to the desired maximum production steady state in about 2-3 residence times. The growth rate estimation (the dash-dotted line in each first plot respectively) of the CL system is very fast, and that the control action is coordinated. The same basic functioning is obtained for the robust behavior test with an asymptotic production rate offset (here  $\mu(s^*) = 1.5$ ) of about 4%. As mentioned above this offset can be made smaller by adjusting the rate function kinetic parameters according to periodic substrate measurements used for product quality controls.



Fig. 3. Comparison of OL and OF responses with  $k = 3, \omega = 35$ . Solid line: OF response, dashed line: OL response, dash-dotted line: reaction rate estimate.



Fig. 4. Perturbed OF response for  $k = 3, \omega = 35$  and errors as given in the text. Solid line: OF response, dash-dotted line: reaction rate estimate, dashed line: set point value

### 8. CONCLUSION

The problem of regulating the biomass growth rate to its maximal production rate for an open-loop unstable, continuous, non-monotonic biological reactor using biomass measurement and manipulation of substrate exchange rate was considered. An Output-Feedback linear PI controller was designed exploiting the reactors open-loop stability and inherent observability and the relative degree one structure, to obtain a robust and non-wasteful closedloop performance. The designed controller is rather independent of the kinetic growth model, meaning robustness with respect to modeling errors, and quickly recovers the behavior of a nonlinear passive SF controller. The model dependency of the biomass set-point has been transferred to the a priori and/ or off-line model calibration stage. A bioreactor example with Haldane kinetics was employed to illustrate the closed-loop performance.

### REFERENCES

- Alvarez, J. and Fernandez, C. (2009). Geometric observation of nonlinear process systems. *Journal of Process Control*, (19) 2, 247–260.
- Alvarez, J. and Gonzalez, P. (2007). Constructive control of continuous polymer reactors. J Proc. C, 17, 463–476.
- Bailey, J. and Ollis, D. (1986). Biochemical Engineering Fundamentals. McGraw-Hill.
- Bastin, G. and Dochain, D. (1990). On-Line Estimation and Adaptive Control of Bioreactors. Elsevier.
- Betancur, M., Titica, M., Moreno, J., Dochain, D., and Guay, M. (2004). Event software sensor and adaptive extremum seeking alternatives for optimizing a class of fedbatch bioreactors. In Proceedings of 7th (IFAC) International Symposium on Dynamics and Control of Process Systems (DYCOPS), Cambridge, Massachusetts, USA.
- Diaz-Salgado, J., Schaum, A., Moreno, J., and Alvarez, J. (2007). Interlaced estimator-control design for continuous exothermic reactors with non-monotonic kinetics. In Eighth International IFAC Symposium on Dynamics and Control of Process Systems, Cancun, Mexico.
- Freeman, R. and Kokotovic, P. (1996). Robust Nonlinear Control Design: State-Space and Lyapunov Techniques. Birkhäuser, Boston.
- Gonzalez, P. and Alvarez, J. (2005). Combined piinventory control of solution homopolymerization reactors. Ind. Eng. Chem. Res. J., 7147–7163.
- Gouzé, J., Rapaport, A., and Hadj-Sadok, Z. (2000). Intervall observers for incertain biological systems. *Ecological* modelling, 133, 45–56.
- Guckenheimer, J. and Holmes, P. (1983). Nonlinear Oscillations, , Dynamical Systems and Bifurcations of Vector Fileds. Springer-Verlag.
- Henson, M. (2006). Exploiting cellular biology to manufacture high-value products. *IEEE Control Systems Magazine*, August 2006, 54–62.
- Hermann, R. and Krener, A. (1977). Nonlinear controllability and observability. *IEEE Tr. Aut. Cont.*, 728–740.
- Hoo, K. and Kantor, J. (1986). Linear feedback equivalence and control of an unstable biological reactor. *Chem. Eng. Comm.*, 46, 385–389.
- Isidori, A. (1999). Nonlinear Control Systems II. Springer.
- Luenberger, D. (1971). An introduction to observers. IEEE Trans. Autom. Cont., 16(5), 596-602.
- Mahadevan, R., Agrawal, S., and Doyle, F. (2001). Differential flatness based nonlinear predictive control of fed-batch bioreactors. *Control Engineering Practice*, 9, 889–899.
- Mailleret, L., Bernard, O., and Steyer, J. (2004). Nonlinear adaptive control for bioreactors with unknown kinetics. *Automatica*, 40, 1379–1385.
- Marcos, N., Guay, M., Dochain, D., and Zhang, T. (2004). Apaptive extremum seeking control of a continuous stirred tank bioreactor with haldnae kinetics. *Journal* of Process Control, 14, 317–328.
- Pavlou, S. and Kevrekidis, I. (1992). Microbial predation in a periodically operated chemostat: A global study of

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the interaction between natural and externally imposed frequencies. *Mathematical Biosciences*, (108) 1, 1–55.

- Rapaport, A. and Harmand, J. (2002). Robust regulation of a class of partially observed nonlinear continuous bioreactors. *Journal of Process Control*, 12, 291–302.
- Schaum, A. and Moreno, J. (2007). Dynamical analysis of global obseravbility properties for class of biological reactors. In 10th International IFAC Symp. Computer Applications in Biotechnology 2007, Cancun, Mexico.
- Schaum, A., Moreno, J., Alvarez, J., and Diaz-Salgado, J. (2008). Dissipativity-based observer and feedback control design for a class of chemical reactors. *Journal* of Process Control, 18(9), 896–905.
- Sepulchre, R., Jankovic, M., and Kokotovic, P. (1997). Constructive Nonlinear Control. Springer.
- Sontag, E.D. (2000). Nonlinear Control in the Year 2000, volume 2 of Lecture Notes in Control and Information Sciences, chapter The ISS Philosophy as a unifying Framework for Stability-like Behavior. Springer.
- Zhang, Y. and Henson, M.A. (2001). Bifurcation analysis of continuous biochemical reactor models. *Biotechnol. Prog.*, 17, 647–660.
- Zhao, Y. and Skogestad, S. (1997). Comparison of various control configurations for continuous bioreactors. *Ind. Eng. Chem. Res.*, 36, 697–705.

#### Appendix A. PROOF OF THEOREM 1

*Proof*: Write the error dynamics (20) as follows

$$\dot{e} = -\operatorname{diag}_{i=b,\delta,s} (\lambda_i) e + \varphi(e), e = [e_b, \epsilon_\delta, e_s]^T, \qquad (A.1)$$

with  $\lambda_b = k, \lambda_{\delta} = \omega + \mu'(s)(s_e - s^*) + \frac{\omega - k}{a}, \lambda_s = \mu(s)$ , and  $\varphi$  chosen accordingly. The errors are bounded in norm by positive scalars  $\sigma_i, i = b, \delta, s$  such that

$$\dot{\sigma}_i = -(\lambda_i - L_i^i)\sigma_i + \sum_{j \neq i} L_j^i \sigma_j, i = b, \delta, s, \qquad (A.2)$$

with  $L_i^b = 0, i = b, s$  and  $L_{\delta}^b = 1$ . Accordingly  $e_b$  is individually stable and conditions (i) and (ii) of Theorem 1 ensure individual stability of  $\epsilon_{\delta}$  and  $e_s$ . Following the small-gain theorem as stated in [Gonzalez and Alvarez 2005], the error pair  $(e_b, \epsilon_{\delta})$  is stable if condition (iii) holds. Let correspondingly  $\lambda_c$  be the effective, dominant eigenvalue of the (Hurwitz) matrix

$$A_c = \begin{bmatrix} -k & 1\\ L_b^{\delta} & -(\lambda_{\delta} - L_{\delta}^{\delta}) \end{bmatrix}, \qquad (A.3)$$

so that one can find a positive scalar function  $\sigma_c \geq ||[e_b, \epsilon_\delta]^T||$  such that

$$\dot{\sigma}_c = -\lambda_c \sigma_c + L_s^c \sigma_s, \, \dot{\sigma}_s = -\mu(s)\sigma_s + L_c^s \sigma_c, \qquad (A.4)$$

with  $L_s^c = L_s^{\delta}$  and  $L_c^{\delta} = \max\{L_b^s, L_{\delta}^s\}$ . Correspondingly, if in addition to conditions (i) to (iii), condition (iv) holds, then the CL error dynamics is stable. According to [Freeman and Kokotovic 1996] practical stability follows is obtained for bounded errors and disturbances.  $\Box$