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Nonlinear PI control of fed-batch processes for growth rate regulation

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ABSTRACT

This paper deals with the regulation of the biomass specific growth rate, which is an important goal in many fed-batch fermentation processes. The proposed control system is based on the minimal model paradigm, requiring only biomass and volume measurement along with some bounds on the reaction rate. The controller has the structure of a partial state feed-back with adjustable gain. An integral-proportional control algorithm is designed to adjust this gain. It is inspired in concepts of invariant control and system immersion. First, a nonlinear integral action that makes invariant a goal manifold defined by a reference model dynamics is developed. Then, a proportional output error feed-back is incorporated to the control law with the aim of fastening convergence. Stability is investigated in detail using Lyapunov functions. To implement the control law, an estimation of the growth rate is required like any other PI-like controller. Because of its strong convergence properties, a sliding observer that requires the same process information as the controller is used for this task, although conventional continuous observers can alternatively be used provided they are fast enough to preserve stability. Simulation results showing the transient response and robustness features of the controller under nominal and perturbed scenarios are presented.

1. Introduction

Fed-batch processes are extensively used in the expanding biotechnological industry, which is demanding for more efficient, reliable and safe processes to optimize production and improve power quality. For this reason, fed-batch processes are receiving great attention from the control research community. Fed-batch fermentation offers a large number of obstacles to control engineers. In fact, the control designer must deal with complex dynamic behavior of microorganisms, strong modeling approximations, external disturbances, nonlinear and even inherently unstable dynamics, scarce on-line measurements of most representative variables, etc. All these obstacles prevent control practitioners from using classic industrial controllers and force them to implement control algorithms specifically developed for bioprocesses. The survey papers [1–4] describe the history and state of the art in the field of fermentation fed-batch process control.

From a biological standpoint, the ideal control of a biotechnological process would achieve microorganisms to reach a (possibly time-varying) metabolic state at which their physiological behavior is appropriate for the desired goals: e.g. production of a given metabolite. To that end, control of fermentation processes makes use of available measured or estimated variables that somehow can implicit or explicitly be related to the cell metabolic state as a function of nutrients supply. In this respect, cell growth underlies many key cellular and developmental processes [5]. Thus, the desired microorganism metabolic states are usually strongly related to growth rate [6–12]. Consequently, in many cases control of growth rate, as key representative of the underlying metabolic processes, is the underlying main problem. For instance, control of growth rate is at the core of biomass and product model-based optimization during the singular phase [13,14], at that of some methods to avoid overflow metabolism [15], and can also be related to heterologous protein production and ATP consumption rate.

On the other hand, growth rate is related to substrate consumption rate. And this, in turn, can also be related to oxygen consumption rate. Thus, many control strategies exist aimed at tuning the feed rate so as to achieve either constant dissolved oxygen, constant substrate concentration in the broth or constant metabolite rate [16–21]. Probing strategies use dissolved oxygen measurement to control substrate feed rate taking into account the constraints of aerobic conditions and overfeeding [22]. In many of these cases the hidden goal is growth rate control [23] or can be related to it. Indeed, in industrial fermentation processes practical limits in available measurements and actuators will made some control strategies more feasible than others.

Growth rate control in fed-batch bioreactors implies the need of following an exponential feeding flow profile. Many papers found in the literature basically implement this control strategy in open-loop [24,25]. Of course, these conceptually simple controllers are

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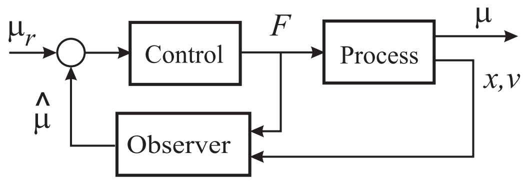

Fig. 1. Block diagram of process control systems using estimated output feed-back, where μ, $\hat{\mu}$ and μ_r are the real, estimated and reference specific growth rates, respectively, F is the feeding flow, x is the biomass concentration and v the liquid volume in the reactor.

however extremely sensitive to parameter uncertainties and external disturbances. Mismatches in biomass growth can be partially reduced by feeding the reactor in proportion to biomass population [14,26]. However, since the process is still open-loop in the sense that there is no error feed-back, the control is very sensitive to parameter uncertainties.

Yet, current availability of on-line reliable biomass and volume measurement devices allow direct control of specific growth rate. This is especially true for small and medium scale bioreactors used to produce enzymes and/or high-added values specialty metabolites. This has enabled a research line dedicated to develop generic and robust controllers based on the minimal model concept. This line exploits the integral relationship between the controlled variable and biomass population. In [27], a sliding mode controller applicable to the regulation of growth-linked fed-batch processes is presented. Because of the robustness properties of sliding modes, controller implementation requires minimum knowledge of the process. In fact, just on-line measurement of biomass concentration and volume, as well as an upper-bound on the growth rate are needed. On the pre-specified sliding surface, the sliding control effectively behaves as a nonlinear integral action without the need of estimating the unmeasurable controlled variable. The cost of robustness and implementation simplicity is the limited controller bandwidth. Other authors have incorporated an estimation of the controlled variable to the control algorithms, obtained from on-line measurement of biomass concentration [4,8,13,28]. Pioneering work in the field of growth rate observers was performed in [29]. With their variants, the estimated output feed-back controllers respond to the block diagram shown in Fig. 1. In this context, concepts of feed-back linearization have been applied with the aim of canceling the process nonlinearities and assigning linear dynamics by means of a proportional feed-back law [13]. In the same way, a globally stabilizing controller has been proposed inspired in passivation concepts [30]. This latter control law essentially differs from the previous one in the sense that the output error feed-back dominates the process dynamics instead of canceling it. This approach improves robustness and provides conditions for global stability even when kinetics show multiplicity. These control algorithms exhibit some implementation challenges associated to the output estimation feed-back. One of them is that the estimate is affected by measurement noise that propagates to the control action. Besides, continuous growth rate observers introduce a lag in the loop. The observer dynamics may interact with the controller, thus leading to undesirable behavior and even to instability. For these reasons, the gain of these proportional control laws cannot be chosen arbitrarily high to increase significantly the controller bandwidth and disturbance rejection.

The mentioned limitation of proportional control can be overcome by means of adding integral action to the control law [8]. Previously designed PI control algorithms follow a design strategy that could be defined as a natural extension of a linear PI, where a feed-forward term is added to cope with the continuous change of variables (biomass and volume) introduced by fed-batch operation (i.e. there is no equilibrium point), resulting in a two-degree-of-freedom control algorithm. Tuning of these algorithms tends to be a tough task, requiring good knowledge of the process parameters to set the feed-forward term, and elaborated tuning strategies to get a set of parameters for the PI-term good enough in the whole fed-batch range of operation. In this paper, we propose a different approach to design non-linear PI controllers which relies on geometric properties of the process and specification structures. Ideas and concepts of invariant control and passivity are combined to achieve PI controllers that outperform previous developments where some of these ideas were exploited separately [27,30]. The proposed approach exhibits three main features. First, it provides easy-to-tune controllers thus overcoming the main shortcomings of previous PI design methods. Second, global asymptotic stability, even for processes with non-monotonic kinetics, can be proved using insightful Lyapunov analysis. Finally, stability and performance are very robust to parameter uncertainties.

The paper is organized as follows. In Section 2 the problem is formulated and the control strategy is posed in terms of a goal manifold. The proposed control law and its analysis are considered in Section 3. Some examples highlighting the performance of the devised controllers are shown in Section 4. Finally, Section 5 outlines the conclusions of the work.

2. Problem statement

Many biotechnological processes are characterized by pure cultures with one limiting substrate and with the metabolite of interest being formed in parallel to the microbial growth. These growth-linked reactions may be inhibited when a substrate is in excess. In fed-batch mode, this sort of process accepts the following description in state-space [31,32]:

$$\Sigma = \begin{cases} \dot{x} = \mu(s)x - \dfrac{F}{v}x \\ \dot{s} = -y_s\mu(s)x - mx + \dfrac{F}{v}(s_i - s) \\ \dot{v} = F \end{cases} \tag{1}$$

where $x \in \mathcal{X} \subset \Re^+$ and $s \in \mathcal{S} = (0, s_i)$ are the biomass and substrate concentrations respectively; $s_i > 0$ is the influent substrate concentration; $v \in \Re^+$ is the liquid volume; $F \in \Re^+$ is the feeding flow; $y_s > 0$ is a yield coefficient; $m > 0$ is the maintenance constant. Finally, μ is the specific growth rate which is an either monotonic or non-monotonic function of substrate concentration taking values in the set $\mu \in (0, \mu_m)$.

The control objective is the regulation of this specific growth rate at a given value $\mu_r < \mu_m$ using F as control input. Control design is subject to the following constraints:

- The only on-line measurable variables are volume and biomass concentration.
- An estimation of μ, obtained from the on-line measurement of x and v, is available for feed-back.
- The control signal is nonnegative ($F \geq 0$).
- The yield coefficient y_s, the maintenance constant m, and the influent substrate concentration s_i are uncertain parameters that, moreover, may vary during the process.

2.1. Invariant control approach

Differing from continuous processes, the control specification in fed-batch bioreactors does not imply stabilization around an operating point. On the contrary, the state follows an unbounded trajectory. In fact, only substrate concentration stabilizes around a value s_r satisfying $\mu(s_r) = \mu_r$, whereas biomass concentration follows a bounded trajectory and volume goes to infinity. Let us define

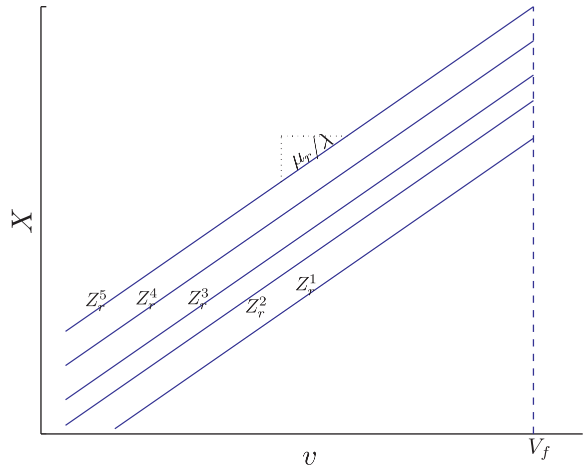

Fig. 2. Family of goal manifolds on the $X-v$ plane.

a reference model for Σ in accordance with the control objective, that is the (exponential) growth of biomass at the desired rate μ_r:

$$\Sigma_r \stackrel{\triangle}{=} \begin{cases} \dot{X} = \mu_r X, & X(t_0) = X_{r,0} \\ \dot{s} = 0, & s(t_0) = s_r \\ \dot{v} = \lambda X, & v(t_0) = v_{r,0} \end{cases} \tag{2}$$

where $X(t) = x(t)v(t)$ is the total biomass population in the bioreactor. The first equation in (2) represents the desired growth of biomass, which can be achieved by properly feeding the bioreactor in proportion to biomass population as established in the third equation.

This exosystem generates a goal manifold Z_r for Σ:

$$Z_r = Z_x \cap Z_s \tag{3}$$

$$Z_x = \left\{ (X, s, v) | z_x = X - X_{r,0} - \frac{\mu_r}{\lambda}(v - v_{r,0}) = 0 \right\} \tag{4}$$

$$Z_s = \{(X, s, v) | z_s = s - s_r = 0\} \tag{5}$$

where $X_{r,0}$ and $v_{r,0}$ are the initial total biomass and volume of the reference model, respectively. The manifold Z_x is obtained eliminating the time variable in (2) whereas Z_s results from $\mu(s_r) = \mu_r$. Actually, there is a family of goal manifolds Z_r since the initial values $(X_{r,0}, v_{r,0})$ of the reference model do not matter. Fig. 2 shows the projection of Z_r onto the $X-v$ plane for several initial conditions of the reference model. Note that the control objective of maintaining a constant growth rate μ_r is accomplished on any of these manifolds. The difference among all these manifolds lies on the amount of biomass obtained at the end of the process. Notice that in many cases it is the specific growth rate and not the amount of biomass that matters from the point of view of metabolic state [10].

The value of λ that makes any of these manifolds Z_r invariant is obtained from the second equation of (1). Thus,

$$\begin{aligned} &F(x, v) = \lambda x v \\ &\lambda = \lambda_r \stackrel{\triangle}{=} \frac{y_s \mu_r + m}{s_i - s_r} \end{aligned} \tag{6}$$

is an invariant control for Σ with respect to the reference manifold Z_r generated by Σ_r. In other words, once the system Σ is on Z_r, it remains there. Further, it can be shown that the control law (6) provides convergence from any process initial condition $(x(t_0), s(t_0), v(t_0))$ to a given Z_r with unknown initial conditions $(X_{r,0}, v_{r,0})$. Convergence rate is however rather poor because there is no feed-back of the off-the-manifold coordinates z_x and z_s. Additionally, the invariant gain λ_r depends on barely known and possibly time-varying parameters.

Observation: Feed-back laws similar to (6) have been previously investigated (see for instance [33,34]). However, this derivation based on invariance concepts is the key to the design of the adaptive control algorithm developed in the next section [35].

3. Proposed control algorithm

The issue faced here is to design a control algorithm with improved robustness and convergence features compared to (6) using minimal knowledge of reaction parameters. Let us consider the process Σ with a biomass-proportional feeding profile $F = \lambda_f(t)xv$:

$$\Sigma_f : \begin{cases} \dot{x} = \mu(s)x - \lambda_f x^2 \\ \dot{s} = -y_s \mu(s)x - mx + \lambda_f x(s_i - s) \\ \dot{v} = \lambda_f x v. \end{cases} \tag{7}$$

First, we will design an adaptation law for the invariant gain λ in (6) so that the process Σ_f with $\lambda_f = \lambda$ is effectively immersed into the reference dynamics Σ_r despite parameter uncertainties. Then, a proportional feed-back action will be included in λ_f to fasten convergence to the manifold Z_s while preserving the invariance property. At this stage of the control design it is assumed that an estimation of the growth rate is available for feed-back. We will justify this assumption in Section 3.4.

3.1. Adaptive integral control law

Recall that it does not matter to move along a given goal manifold but along any of them. All these manifolds are characterized by a given slope which is inversely proportional to the uncertain λ_r. The idea behind the control law design is to adapt this slope, i.e. λ, so that the state trajectory is always tangent to the manifold Z_x. This means that the following equality must hold:

$$\frac{\partial z_x}{\partial x}\dot{x} + \frac{\partial z_x}{\partial v}\dot{v} + \frac{\partial z_x}{\partial \lambda}\dot{\lambda} = 0. \tag{8}$$

Using (4) and (7), the following adaptation law for λ results:

$$\begin{aligned} &\dot{\lambda} = -\lambda^2 \psi(v) x \frac{\mu - \mu_r}{\mu_r} \\ &\lambda(t_0) = \hat{\lambda}_r \\ &\psi = \frac{v}{v - v_{r,0}} \end{aligned} \tag{9}$$

For technical reasons, the initial volume $v_{r,0}$ of the reference model must be lower than the process one: $v_{r,0} < v(t_0)$. So, $\psi(v)$ is a positive and decreasing function of v. Hence $\psi(v)$ is non-increasing in time. This means that the adaptation gain decreases with time as long as volume grows. This can be understood by observing in Fig. 2 that the manifold Z_x rotates around $(X_{r,0}, v_{r,0})$ as λ changes. Then, less variations of λ are necessary to keep the state trajectory on the manifold as the state moves away from the fixed point $(X_{r,0}, v_{r,0})$. So, λ converges rapidly to the unknown λ_r at the beginning of the process, but its capability to adapt to time-varying process parameters decreases with time. Anyway, note that the function $\psi(v)$ can be replaced by a constant gain. This is equivalent to moving the fixed point of the manifold in proportion to v as the state evolves rightwards in Fig. 2. Alternatively, other non-increasing functions of v can be also used as will be made clear later.

It is interesting to note that this adaptation based on invariance concepts is in practice equivalent to an (nonlinear) integral control of μ. The initial value $\hat{\lambda}_r$ is obtained from (6) using estimated values of the parameters.

In [27], the invariant control (6) is searched using a sliding mode algorithm on a prescribed manifold Z_x. The main feature of the approach used there is its robustness, since the sliding motion performs the adaptation (9) without using any estimation of μ. The cost paid is that the initial condition of the reference dynamics $(X_{r,0}, v_{r,0})$ must be specified beforehand. Since we are assuming here that an estimation of μ is available for feed-back, it has little sense to steer the state to a prescribed manifold rather than allowing it to evolve on any parallel manifold.

3.2. Proportional + integral feed-back

To improve convergence to the goal manifold Z_r, we propose including feed-back of the off-the-manifold coordinate z_s to the control action, always maintaining the biomass-proportional feeding profile. Since, we do not measure substrate concentration, we use instead $\mu(s)$ that can be estimated based on biomass and volume measurement. Thus, the proposed adaptive + proportional feed-back control law is

$$\begin{aligned} \lambda_f &= \lambda(1 - f(\mu - \mu_r)) \\ \dot{\lambda} &= -\lambda^2 \phi(\nu) x \frac{\mu - \mu_r}{\mu} \quad \lambda(t_0) = \hat{\lambda}_r \end{aligned} \tag{10}$$

where $\phi(\cdot)$ and $f(\cdot)$ are defined as follows.

Definition. Let $\phi : \mathcal{V} \triangleq [\nu_0, \infty) \mapsto [\phi_0, \phi_\infty] \subset \Re^+$ be a differentiable, positive and decreasing function satisfying

$$\lim_{\nu \to \infty} \phi(\nu) = \phi_\infty \tag{11}$$

Definition. Let $f : \Re \mapsto [-\bar{f}, 1]$ be a globally Lipschitz increasing function with Lipschitz constant k/μ_r satisfying $f(0) = 0$, with $\bar{f} \in \Re^+$.

Note that $f(\cdot)$ is an S-like bounded function. Its lower-bound assures that λ_f is bounded whenever λ is bounded whereas the upper-bound is compatible with the restriction on the feeding flow $F \geq 0$. The condition $f(0) = 0$ guarantees that the control is effectively invariant on the goal manifold Z_r.

Finally, note that, compared to(9), we have replaced μ_r with μ in the denominator of (10). This slight variation in the adaptation law allows to show global stability in a more elegant and simple fashion. Anyway, stability can also be demonstrated if λ is adapted like in (9) by considering that substrate may temporarily saturate at zero.

3.3. Stability analysis

This section is devoted to demonstrate that the process state converges to the goal dynamics generated by (2). This convergence is global for monotonic growth kinetics. In the case of non-monotonic kinetics, wash out may occur, particularly when the initial substrate concentration is very high. In this case, the domain of attraction can be estimated. We will show also that even in this case, global convergence can be achieved by suitably saturating the feed-back gain.

Replacing λ_f in (7) with (10), the following closed-loop process dynamics:

$$\Sigma_{cl} = \begin{cases} \dot{x} = \mu(s)x - \lambda(1 - f(\Delta\mu(s)))x^2 \\ \dot{s} = [-y_s\mu(s) - m + \lambda(1 - f(\Delta\mu(s)))(s_i - s)]x \\ \dot{\lambda} = -\lambda^2 \phi(\nu) x \dfrac{\Delta\mu(s)}{\mu(s)} \\ \dot{\nu} = \lambda(1 - f(\Delta\mu(s)))\nu x \end{cases} \tag{12}$$

where we have used

$$\Delta\mu(s) = \mu(s) - \mu_r \tag{13}$$

for the sake of brevity.

Recall that biomass concentration follows a bounded trajectory on $\Re^+$ imposed by the surface Z_x, and volume grows unboundedly. For this reason, we use concepts of partial stability in order to show convergence towards the goal manifold Z_r. Precisely, we show that substrate converges to the desired value s_r (i.e. the state converges to Z_s) whereas λ converges to the value λ_r at which the goal manifold Z_r is effectively invariant.

Definition. Let us call ζ the partial state $\zeta = \mathrm{col}(s, \lambda)$ and $\zeta_r = \mathrm{col}(s_r, \lambda_r)$. Let $\mathcal{M} = \mathcal{S} \times \Re^+$.

Consider now the continuously differentiable Lyapunov candidate function [36]

$$V(\zeta, \phi) = \phi \int_{s_r}^{s} \frac{\Delta\mu(\varsigma)}{\mu(\varsigma)(s_i - \varsigma)} d\varsigma + \left(\ln \frac{\lambda}{\lambda_r} + \frac{(\lambda_r - \lambda)}{\lambda} \right) \tag{14}$$

Clearly, this function satisfies $V(\zeta_r, \phi) = 0$. Further, since $\phi > 0$ and $\mu(s)$ is increasing (at least locally around s_r), the first term of the right hand side of (14) is positive in the neighborhood of s_r. On the other hand, it is easy to check that the second term of the right hand side of (14) is positive for all $\lambda \in \Re^+ - \{\lambda_r\}$. Thus, $V(\zeta, \phi)$ exhibits a minimum at ζ_r, $V(\zeta_r, \phi) = 0 \, \forall \phi$. This minimum is global for monotonic kinetic functions $\mu(s)$ and may be local for non-monotonic kinetics.

At least locally around ζ_r (globally for monotonic kinetic functions), $V(\zeta, \phi)$ is upper- and lower-bounded by the positive definite functions $\overline{V}(\zeta) \triangleq V(\zeta, \phi_0)$ and $\underline{V}(\zeta) \triangleq V(\zeta, \phi_\infty)$:

$$\underline{V}(\zeta) \leq V(\zeta, \phi) \leq \overline{V}(\zeta). \tag{15}$$

The time derivative of the Lyapunov function (14) is given by

$$\begin{aligned} \dot{V}(\zeta, \phi, x) = -\frac{\phi x}{\mu(s)(s_i - s)} \cdot \Bigg[& h(\phi)\lambda_f(\Delta\mu(s)) \\ & \int_{s_r}^{s} \Delta\mu(\varsigma) \frac{\mu(s)(s_i - s)}{\mu(\varsigma)(s_i - \varsigma)} d\varsigma + y_s(\Delta\mu(s))^2 \\ & + \lambda_r(s - s_r)\Delta\mu(s) + \lambda(s_i - s)\Delta\mu(s) f(\Delta\mu(s)) \Bigg] \end{aligned} \tag{16}$$

where $h(\phi) > 0$. For clarity of exposition, the sequence of operations to find (16) is given in Appendix A.

Since x follows a lower-bounded trajectory ($x(t) > \underline{x} \in \Re^+$), $\dot{V}(\zeta, \phi, x)$ is bounded by

$$\dot{V}(\zeta, \phi, x) \leq -Q(\zeta) \tag{17}$$

where

$$Q(\zeta) \triangleq -\dot{V}(\zeta, \phi_\infty, \underline{x}) \tag{18}$$

is nonnegative definite.

Then, Σ_{cl} is Lyapunov stable with respect to ζ uniformly in ν, and there exists $\mathcal{D} \subseteq \mathcal{M}$ ($\mathcal{D} \ni \zeta_r$) such that for all $(\zeta, \nu) \in \mathcal{D} \times \mathcal{V}$, $\zeta(t) \to \mathcal{E}(\mathcal{D}) \triangleq \{\zeta \in \mathcal{D} : Q(\zeta) = 0\}$ as $t \to \infty$ [36].

Note that $Q(\zeta)$ is not (locally) positive definite because $Q(s_r, \lambda) = 0$ independently of λ. Then, locally around ζ_r, i.e. for $\mathcal{D}$ small enough, $\mathcal{E}(\mathcal{D}) = \{\zeta \in \mathcal{D} | s = s_r\}$. Since $\mathcal{E}(\mathcal{D})$ is larger than ζ_r, we need to apply some invariance principle to prove asymptotic stability. Although it is not generally true for partially stable systems, an invariance principle can be derived for asymptotically autonomous partial systems [36,37] (Chapter 8). Fortunately, this is our case. In fact, $\phi \to \phi_\infty$ and $x \to \mu_r/\lambda_f$ as ν diverges. So, the partial system defined by the second and third equations of (12) asymptotically converges to the autonomous system

$$\Sigma_{cl}^{\infty} = \begin{cases} \dot{s} = \left(-\dfrac{y_s\mu(s) + m}{\lambda(1 - f(\Delta\mu(s)))} + \mu_r(s_i - s) \right) \mu_r \\ \dot{\lambda} = -\lambda\phi_\infty \dfrac{\mu_r}{\mu(s)} \dfrac{\Delta\mu(s)}{1 - f(\Delta\mu(s))} \end{cases} \tag{19}$$

Since $s = s_r$ in $\mathcal{E}(\mathcal{D})$, any invariant set in $\mathcal{E}(\mathcal{D})$ satisfies also $\dot{s} = 0$, i.e. $\lambda = \lambda_r$. Therefore, ζ_r is the largest invariant set for (19) in $\mathcal{E}(\mathcal{D})$. Consequently, Σ_{cl} is asymptotically stable with respect to ζ uniformly in ν.

Remark. The integral adaptive control (with $f \equiv 0$) also stabilizes the process around the goal trajectory Z_r. That is, the proportional feed-back term is not necessary for stability. However, its inclusion in λ_f improves convergence to the goal manifold. This is corroborated in (16) where the last term in the bracketed expression is always positive and proportional to $f(\Delta\mu(s))$.

3.3.1. Monotonic kinetic functions

For monotonic kinetic functions,

* $V(\zeta, \phi)$ verifies (15) for all $\zeta \in \mathcal{M}$, and $\underline{V}(\zeta)$ is radially unbounded in $\mathcal{M}$.
* $\dot{V}(\zeta, \phi)$ verifies (17) for all $\zeta \in \mathcal{M}$, and ζ_r is the largest invariant set for (19) in $\mathcal{E}(\mathcal{M})$.
* All biomass concentration trajectories are lower-bounded since neither s can go to zero nor λ can go to infinity.

Consequently, Σ_{cl} is globally asymptotically stable with respect to ζ_r uniformly in ν [36]. In other words, system Σ_{cl} globally asymptotically converges to the goal manifold Z_r defined by the reference model Σ_r.

This global stability result is valid also for weak non-monotonic kinetics for which the function $(\mu(s) - \mu_r)$ has only one root in $\mathcal{S}$.

3.3.2. Non-monotonic kinetic functions

If the kinetic function exhibits multiplicity, i.e. there are two substrate concentrations satisfying $\mu(s) - \mu_r = 0$, the previous results about stability are only local. In fact, the reactor may be washed out, particularly when the fed-batch process begins with a large initial substrate concentration. Wash-out occurs when the feeding flow increases in an attempt to rise the growth rate that evolves in the opposite direction because of inhibition. Thus, a way of avoiding it is limiting the dilution rate.

Consider a non-monotonic kinetic function having its maximum at s_m, and satisfying $\mu(s_r) = \mu(s_r^*) = \mu_r$ for $s_r < s_m$, and $s_m < s_r^* < s_i$. Locally around s_r, the kinetic function is increasing. Then, Σ_{cl} locally asymptotically stabilizes (partially) around ζ_r uniformly in ν and x. Furthermore, if the kinetic function $\mu(s)$ is known, a domain of attraction could be derived from (16) using invariance set theorems [38].

On the other hand, if s exceeds s_r^*, stability is not guaranteed (see (14) and (16)). However, it is easy to see in the second equation of (12) that if λ_f is suitably bounded, substrate concentration cannot exceed s_r^* or, at least, cannot remain above it. Then, one can include in the adaptation law (9) a saturation term to prevent λ from exceeding a bound $\bar{\lambda}$ satisfying

$$\begin{aligned} &\bar{\lambda} > \lambda_r \\ &\bar{\lambda}(1+\bar{f}) < \min_{s \geq s_r^*}\left(\frac{\mu(s)y_s + m}{s_i - s}\right) \end{aligned} \tag{20}$$

Just a model for the reaction kinetics and a lower-bound for the yield coefficient y_s are needed to compute this bound. This can be done off-line before running the process.

Suppose that the initial substrate is $s(0) > s_r^*$. Then, λ increases according to (9) until it saturates at (20). Then, substrate concentration drops because consumption exceeds the feed rate. Note that the Lyapunov function (14) decreases while λ is saturated. Immediately after substrate falls below s_r^*, λ leaves saturation and the Lyapunov function decreases further. From then on, the state evolves to the goal manifold without any possibility of wash-out. This situation is illustrated in Section 4.3.

3.4. Effects of the growth rate observer

It is well known in linear system theory that stability of an output feed-back control system can be assessed by analyzing separately stability of the controller and that of the observer. It is well known also that the application of this separation principle cannot be directly extended to nonlinear systems. So, in general, checking stability of the whole nonlinear control system is usually a very involved problem.

An estimate of the growth rate is needed to implement the controller developed in this paper (as well as any other specific growth rate controller found in the literature). There are a variety of continuous biomass-based growth rate observers useful for this task. However, these observers do not exhibit uniform exponential convergence to time varying signals. For instance, the observer proposed in [29] introduces a second-order dynamics into the loop. Stability analysis of the controller plus observer can still be realized, although it will be by far much more complicated than the one presented here. Additionally, the results will be valid only for a particular observer. Although there are not guarantees, it is expected that the controller stability is not affected by the observer provided it is fast enough.[1]

Alternatively, a new family of growth rate observers has been introduced in [39]. There, a super-twisting sliding observer having the form

$$\mathcal{O} : \begin{cases} \dot{\hat{x}} = (\hat{\mu} - \lambda_f(t)x + 2\beta(|(x-\hat{x})|)^{1/2}\mathrm{sign}(x-\hat{x}))x \\ \dot{\hat{\mu}} = (\alpha\,\mathrm{sign}(x-\hat{x}))x \end{cases} \tag{21}$$

has been presented where, like in continuous observers, an upper-bound for $|\dot{\mu}|$ is used for tuning the gains α and β (see the details in [39]). It is proved there that this observer converges in finite time to the time-varying real growth rate. After convergence, the estimate perfectly tracks the real growth rate up to a noise signal. The main consequence of this property is that the separation principle can be applied in a straightforward way because the observer does not add dynamics to the loop. In other words, the observer does not alter the stability property of the controller. So, the stability analysis made above keeps valid for the whole controller plus observer system. The only precaution to take is that the observer should converge before the process state leaves the domain of attraction (if it is not global). Anyway, in the practical industrial operation, there is always a batch open-loop phase previous to switching the fed-batch phase on. The observer will converge (in the strong sense mentioned above) during this phase.

4. Numerical results

Simulation results for fed-batch processes with non-monotonic kinetics are presented to illustrate the performance of the control strategy under different scenarios. The model of the process built in simulations is (7), where $\mu(s)$ is the Haldane function

$$\mu(s) = \mu_m \frac{1 + 2\sqrt{k_s/k_i}}{(k_s/s) + 1 + (s/k_i)} \tag{22}$$

Responses obtained using three different control actions are evaluated

$$\lambda_f = \hat{\lambda}_r \tag{23}$$

$$\lambda_f = \hat{\lambda}_r(1 - f(\hat{\mu} - \mu_r)) \tag{24}$$

[1] This is typically assumed in the literature to avoid a complete stability analysis.

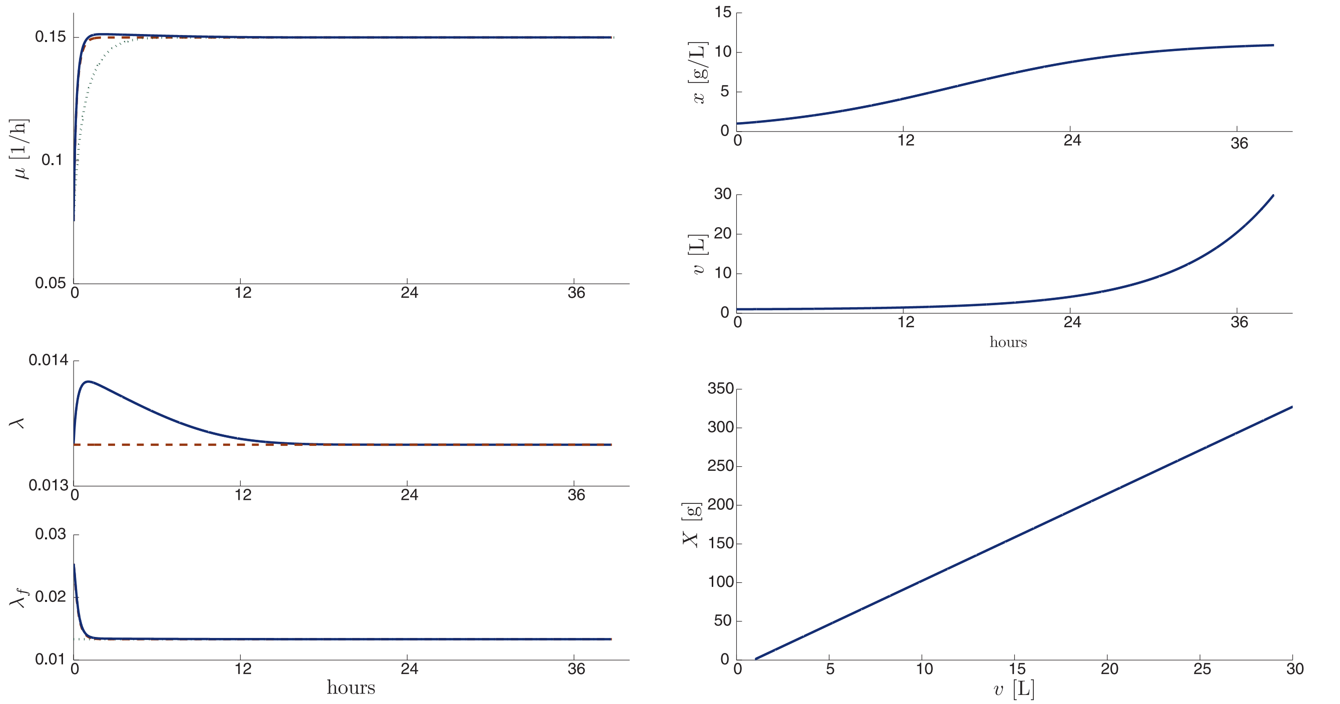

Fig. 3. (Example 1) Responses from a low initial substrate concentration under nominal conditions, i.e. invariant gain λ_r is known. Solid, PI control; dashed, proportional control; dotted, open-loop control.

Table 1
Parameters and test conditions.

μ_m [1/h]	0.22	$x(t_0)$ [g/L]	1
k_s [g/L]	0.14	$s(t_0)$ [g/L]	[0.05,0.05,6]
k_i [g/L]	6	$V(t_0)$ [L]	1
y_s	1.43[a]	μ_r [1/h]	0.15
m [1/h]	0.05	k	3
s_i [g/L]	20	ϕ	30
V_f [L]	30	$\hat{\lambda}_r$	$[1, 0.7, 1]\cdot\lambda_r$

[a] Parameter y_s in Example 2 grows at 2% per hour since $t = 30$ h.

and

$$\lambda_f = \lambda(1 - f(\hat{\mu} - \mu_r)) \tag{25}$$

$$\dot{\lambda} = -\phi\lambda^2 x \frac{(\hat{\mu} - \mu_r)}{\hat{\mu}}, \lambda(t_0) = \hat{\lambda}_r$$

with

$$f = tanh\left(\frac{k}{\mu_r}(\hat{\mu} - \mu_r)\right) \tag{26}$$

This $tanh(\cdot)$ function provides unit gain around the origin, and smooth saturation that guarantees positiveness and boundedness of λ_f. Anyway, any other function with these properties can be used.

Biomass concentration was measured using the sensor described in [40]. Sampling was carried out each 12 s, and a filtered value over a window of 2 min was provided. The estimation $\hat{\mu}$ was obtained using the super-twisting observer (21), tuned following the guidelines in [39]. Noise sensitivity and tracking properties of this observer have been assessed experimentally in that paper.

The process and controller parameters used in simulations are listed in Table 1. As mentioned above, the proportional control action improves stability and speeds up the response of the process. However, the proportional channel is a direct path for noise from the sensors to the feeding flow. Then, there is a trade-off among speed of response and noise in the selection of the proportional gain k. On the other hand, the gain ϕ determines the speed of adaptation of λ and, consequently, how fast model uncertainties and perturbations are compensated for. A too high value of ϕ may cause undesirable overshoots during the transient response. Therefore, ϕ is selected as a trade-off between robustness and transient response.[2]

The control strategies (23)–(25) are hereinafter referred to as open-loop, proportional and PI control, respectively.

4.1. Example 1

This example is aimed at showing the performance of the controller from a low initial substrate concentration under nominal conditions. That is, the invariant gain λ_r is supposed to be known.

The results are presented in Fig. 3. It is observed that the control (23) converges to μ_r more slowly than the feed-back controllers. There is little difference between the tracking responses of the proportional (24) and the proportional-integral (25) control laws. This is because λ is practically not adjusted by the integral control during the transient. The trajectories followed by biomass concentration and volume almost coincide for all three control actions. The bottom-right plot shows how the process state evolves on the goal manifold.

4.2. Example 2

In this second example we evaluate the robustness of the proposed control with respect to parameter uncertainty. The invariant gain λ_r in (23)–(25) is underestimated in a 30%. Further, after $t = 30$ h, the yield coefficient y_s is increased at the rate of 2% per hour. The evolution of the process variables is shown in Fig. 4. See that, in the presence of the uncertain and time varying parameter, the constant-gain control law (23) leads to a 37% error in the controlled variable that even grows linearly after $t = 30$ h. The proportional control (24) reduces the tracking error by a factor of four.

[2] Note that, if a decreasing function ψ as defined in (9) was used, its capability to reject disturbances would reduce with time.

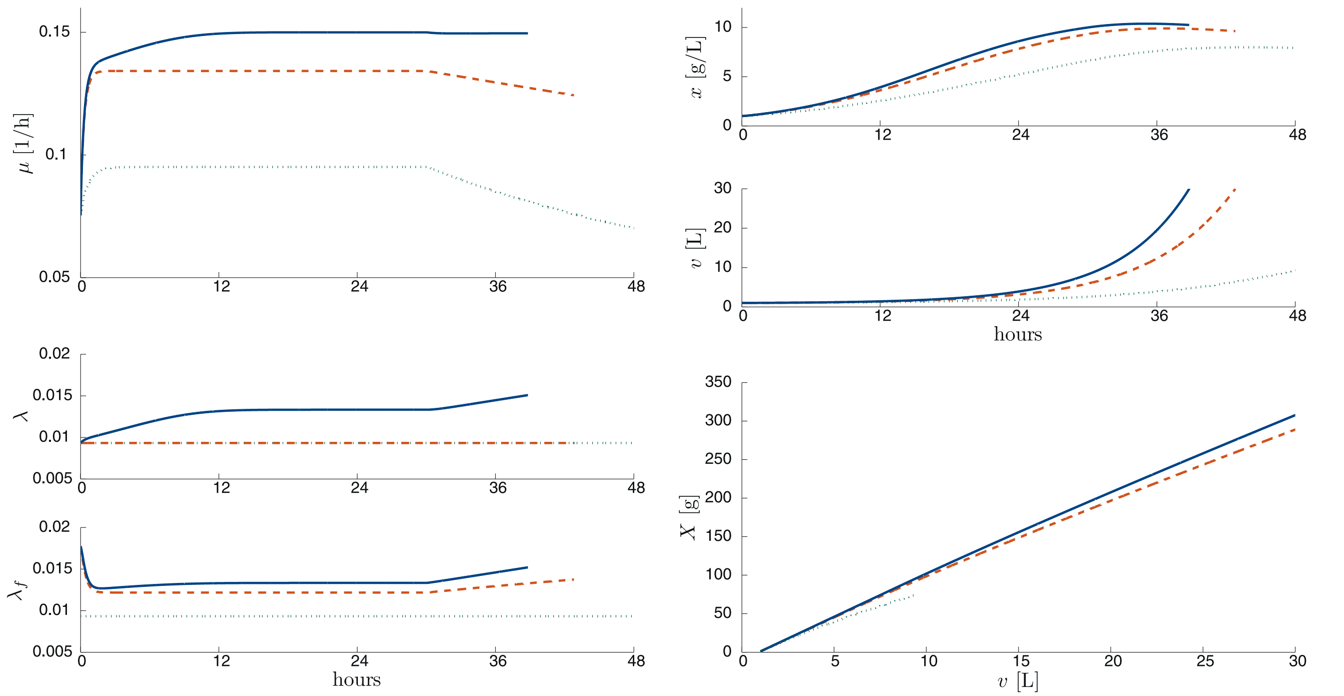

Fig. 4. (Example 2) Responses from a low initial substrate concentration under uncertain conditions. Solid, PI control; dashed, proportional control; dotted, open-loop control.

On the contrary, the integral action of the adaptive controller (25) cancels the tracking error while y_s is constant. Further, tracking error is negligible even when y_s begins to grow linearly. It can be observed how λ is smoothly adapted during the first 12 h and after y_s drift begins at $t = 30$ h. Biomass concentration and volume follow now substantially different trajectories. The bottom plot clearly shows that the process state traces different curves on the plane $X - v$. In particular, it is interesting to see how the integral control blends the manifold as y_s (and thus λ_r) rises. The process with control (23) is interrupted at $t = 48$ h before the reactor is filled out.

4.3. Example 3

The third example is aimed at showing the convergence property of the proposed controller from a large initial substrate concentration. The initial condition is selected beyond the high-substrate root s_r^* of the Haldane function. This is an inherently

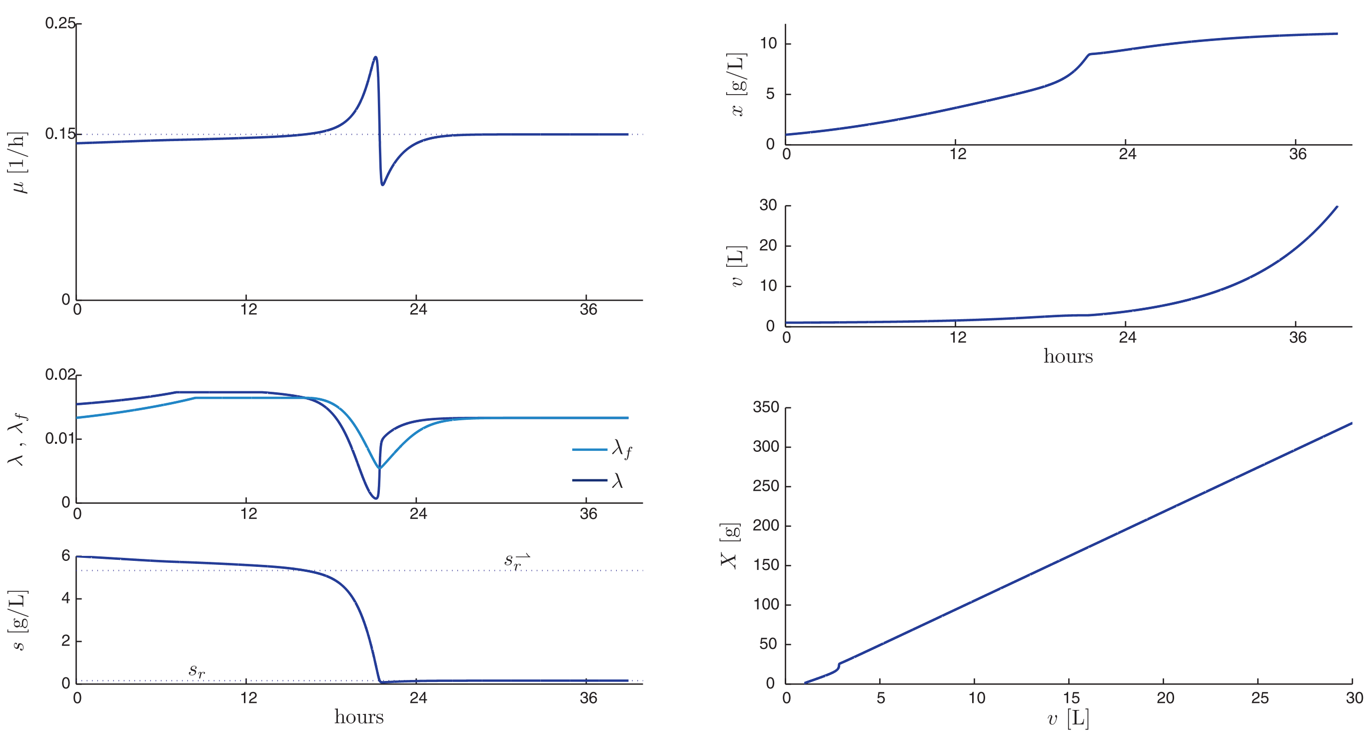

Fig. 5. (Example 3) Tracking response from a very high initial substrate concentration under nominal conditions.

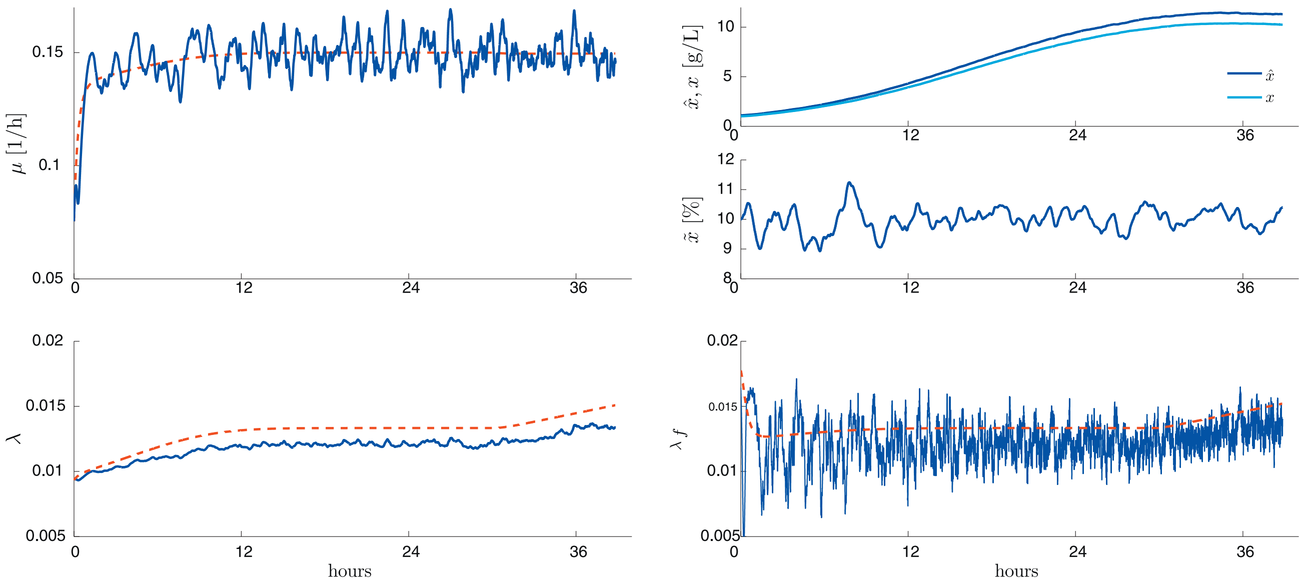

Fig. 6. (Example 4) Response of the PI control for the same setting as in Example 2. Measurement noise and offsets are considered.

unstable region. In fact, the control has the opposite effect to what is expected, thus producing a positive feed-back. To avoid wash-out, λ_f and λ are bounded, so that the substrate concentration inevitably falls below s_r^*. Once in this region, the controller stabilizes the process around the goal trajectory. It is observed in Fig. 5 how the control action saturates during the initial phase of the process. When substrate concentration falls below s_r^*, the saturation region is left and substrate rapidly converges to s_r.

4.4. Example 4

Simulation results for the same setting as in Example 2 but considering noise and offsets of the biomass sensor are presented in Fig. 6. Noise level corrupting the biomass measure $\hat{x}$ is compatible with the sensor used (see [27,39,40]). Also, an offset $\tilde{x} = +10\%$ in the measurement of biomass concentration is considered to assess robustness against sensor uncertainty. For clarity of presentation, only the results obtained with the proposed nonlinear PI controller are presented. The results for the PI control in Example 2 are repeated with dashed line.

It is observed that the controller achieves good regulation despite noise and sensor offset. See that λ is much smoother than λ_f, showing that noise is mainly amplified by the proportional term of the control action. Note also how the integral control compensates for the offset in the biomass sensor.

5. Conclusions

In this work a nonlinear proportional-integral control of the specific growth rate for fed-batch processes is proposed. A biomass-proportional feeding profile is followed, being the feeding gain continuously adapted by the controller. The integral action makes a goal manifold invariant despite parameter uncertainties, so that steady-state errors are cancelled. On the other hand, the proportional control action speeds the transient response up. Therefore, by combining invariant with proportional control laws, the achievements of previous developments [27,30] are outperformed. The design approach followed in this paper, based on geometric properties of the process dynamics, leads to easy-to-tune PI controllers in contrast with previous PI algorithms characterized by tuning difficulties and parameter sensitivity. Another key advantage of our proposal is that global asymptotic stability is guaranteed without restrictions for monotonic growth kinetics, whereas the feeding flow should be suitable bounded for non-monotonic kinetics. The implementation of the control law only requires on-line measurement of biomass concentration and volume, being the controlled variable estimated using an observer. Robustness to model uncertainties and disturbances is one of the main attractive features of the controller.

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Appendix A.

In this section the expression of the time derivative (16) of the Lyapunov function (14), repeated below for the sake of clarity, is derived.

Differentiating

$$V(\zeta,\phi) = \phi \int_{s_r}^{s} \frac{\Delta\mu(\varsigma)}{\mu(\varsigma)(s_i-\varsigma)} \mathrm{d}\varsigma + \left(\ln\frac{\lambda}{\lambda_r} + \frac{(\lambda_r-\lambda)}{\lambda}\right) \tag{27}$$

with respect to time yields

$$\dot{V}(\zeta,\phi) = \dot{\phi} \int_{s_r}^{s} \frac{\Delta\mu(\varsigma)}{\mu(\varsigma)(s_i-\varsigma)} \mathrm{d}\varsigma + \phi\frac{\Delta\mu(s)}{\mu(s)(s_i-s)}\dot{s} + \frac{(\lambda-\lambda_r)}{\lambda^2}\dot{\lambda} \tag{28}$$

Let us now define

$$h(\phi) \triangleq -\frac{v}{\phi}\left.\frac{\partial\phi}{\partial v}\right|_{v=\phi^{-1}} \tag{29}$$

with ϕ^{-1} the inverse function of ϕ.

Recall that ϕ is a decreasing function of v. Then, $h(\phi) > 0$ and

$$\dot{\phi} = -h(\phi)\phi\lambda_f x \leq 0\,\forall t \tag{30}$$

Now, replacing $\dot{\phi}$, $\dot{s}$ and $\dot{\lambda}$ in (28) with (30) and (12) yields

$$\dot{V}(\zeta,\phi,x) = -\frac{\phi x}{\mu(s_i-s)}\cdot\left[h(\phi)\lambda_f\int_{s_r}^{s}\Delta\mu(\varsigma)\frac{\mu(s)(s_i-s)}{\mu(\varsigma)(s_i-\varsigma)}d\varsigma + \Delta\mu(y_s\mu+m)+\Delta\mu(-\lambda_f+\lambda-\lambda_r)(s_i-s)\right] \quad (31)$$

The term $\Delta\mu\lambda_r(s_i-s_r)-\Delta\mu(y_s\mu_r+m)$, which equals 0 from (6), can be added to the right-hand side of (31). Taking into consideration that, from (24), $\lambda-\lambda_f=\lambda\cdot f(\Delta\mu)$ and regrouping terms it follows that

$$\dot{V}(\zeta,\phi,x) = -\frac{\phi x}{\mu(s)(s_i-s)}\cdot\left[h(\phi)\lambda_f(\Delta\mu(s))\int_{s_r}^{s}\Delta\mu(\varsigma)\frac{\mu(s)(s_i-s)}{\mu(\varsigma)(s_i-\varsigma)}d\varsigma + y_s(\Delta\mu(s))^2 + \lambda_r(s-s_r)\Delta\mu(s)+\lambda(s_i-s)\Delta\mu(s)f(\Delta\mu(s))\right] \quad (32)$$

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