

# A simple positive state observer for multidimensional Goodwin’s oscillator

Anton V. Proskurnikov and Alexander Medvedev

**Abstract**—Periodic phenomena and oscillations are fundamental characteristics of the dynamics of living systems at all levels of organization, from a single cell to complex organisms. In spite of the recent progress in understanding biological oscillators and clocks, most of the aspects of their control, observation, and identification still remain nearly unexplored. In this paper, we address the problem of *observer* design for Goodwin’s oscillator that stands as a prototypic model of a biological rhythm and has been used to portray e.g. genetic oscillators, metabolic pathways, and hormonal axes. We show that, despite its nonlinear dynamics, Goodwin’s oscillator admits a simple Luenberger-type observer that preserves *positivity* of solutions and is free of many flaws of the standard high-gain state reconstruction, such as the peaking phenomenon and noise amplification. These improvements are achieved through exploiting the properties of the plant model rather than canceling the nonlinear dynamics by means of a high observer gain. The results are illustrated by numerical simulations for the third-order Goodwin model with a Hill nonlinearity.

## I. INTRODUCTION

The literature on nonlinear observers is extensive and virtually impossible to review in a brief format. We refer instead to popular books devoted to this important and compelling research area [1], [2]. Two recent special issues of IEEE Control Systems Magazine (June and July 2017) also cover applications of nonlinear observers to a number of timely engineering problems. Nonlinear observers specifically intended for use in chemical applications are reviewed in [3]. Unlike linear time-invariant systems theory, where observability and unobservability are *global* properties of the system and independent of a specific trajectory, the observability in nonlinear systems has usually to be addressed with respect to a particular solution. Systems with complex nonlinear dynamics can seldom be handled by a single observer design [?].

Periodical and non-periodical (i.e. chaotic and quasi-periodic) oscillators are used to model ubiquitous biological cycles across the whole scale of living systems from a single cell to complete organisms [4]. In practice, sustained oscillation is an inherently nonlinear phenomenon since linear oscillators do not produce orbitally stable solutions. A wide class of nonlinear oscillators relies on the mechanism of Andronov-Hopf bifurcation rendering the system equilibrium

unstable. This is in contrast with oscillators possessing locally stable equilibria and hidden attractors [5].

A standard strategy to deal with state observation in nonlinear systems is to linearize the plant model in a vicinity of an equilibrium to guarantee local stability of the state estimation error of a nonlinear observer. While this design principle works well for plants operating around an equilibrium, e.g. being controlled to it by a stabilizing feedback, periodic solutions of oscillators do not need to lie near an equilibrium and their location in the phase space is defined by the initial conditions on the plant. Therefore, the accuracy of linearization is compromised and a linear model cannot serve as a credible ground for observer design. Linearizing the plant dynamics along a trajectory is more accurate, but needs the knowledge of the complete plant solution which contradicts the very purpose of state reconstruction.

Goodwin’s oscillator [6] is an archetypal model of periodic phenomena in biology and has been mostly studied in context of biophysics and system biology [7]–[9]. Some consideration to stability properties of and positivity of solutions to Goodwin’s oscillator has been given in realm of automatic control [10]–[15]. Yet, control and state reconstruction in Goodwin’s oscillator have not so far been dealt with. The state reconstruction in an oscillator can be recast as a “master-slave” synchronization problem comprising the plant and the observer that incorporates an explicit plant model. This approach is, in principle, less restrictive in assuming observability of the plant solutions and has been successfully applied to the design of observers for a generalization of Goodwin’s oscillator to impulsive systems [16]. However, the existing works on synchronization of Goodwin’s oscillators [17]–[19] consider oscillators coupled over balanced graphs, remaining the state estimation problem uncovered.

This paper proposes a simple state observer for an  $n$ -dimensional Goodwin’s oscillator that guarantees positivity of the state estimates. The states of Goodwin’s oscillator are often interpreted as concentrations of chemical substances and negative transients in the state estimates have to therefore be avoided. Also, measuring concentrations in medical applications is costly and often impossible for ethical reasons. Thus reconstructing unavailable concentrations from the measurable ones offers an attractive and inexpensive alternative. Another conceivable application of the proposed observer is fault detection in biomedical applications.

The observer structure is akin to that of the Luenberger observer and exploits the nonlinear dynamics of Goodwin’s oscillator for achieving positivity of the state estimates as well as an effective filtering of the output estimation error instead of canceling the nonlinear dynamics, as in conven-

A.V. Proskurnikov is with Department of Electronics and Telecommunications, Politecnico di Torino, Turin, Italy. He is also with Institute for Problems of Mechanical Engineering of the Russian Academy of Sciences (IPME RAS), St. Petersburg, Russia; [anton.p.1982@ieee.org](mailto:anton.p.1982@ieee.org)

Alexander Medvedev is with Information Technology, Uppsala University, Uppsala, Sweden; [alexander.medvedev@it.uu.se](mailto:alexander.medvedev@it.uu.se)

A. Medvedev was in part financed by Grant 2015-05256 from the Swedish Research Council. A. Proskurnikov acknowledges the support of RFBR under grant 18-38-20037.

tional high-gain observers. A price to pay for that is a limited control of the state estimate convergence rate.

The rest of the paper is organized as follows. After some preliminaries in Section II, the equations of Goodwin's oscillator are recapitulated in Section III. The state estimation problem in Goodwin's oscillator is formulated and a particular observer for solving it is introduced. Positivity and convergence properties of the proposed observer are studied, with and without measurement disturbance. The obtained results are illustrated by a numerical example in Section IV. Section V, concluding the paper, is followed by an appendix with technical proofs.

## II. PRELIMINARIES AND NOTATION

Unless otherwise stated, all vectors in this paper belong to the vector space  $\mathbb{R}^n = \{x = (x_1, \dots, x_n)^\top\}$ . The Euclidean norm of a vector  $x$  is denoted  $|x| \triangleq \sqrt{x^\top x}$  and  $|x|_\infty \triangleq \max_i |x_i|$ . The operator norms of a matrix  $A$ , induced by  $|\cdot|$  and  $|\cdot|_\infty$ , are  $\|A\|$  and  $\|A\|_\infty$ , respectively. We use  $\mathbb{R}_+^n$  to denote the non-negative orthant of this space  $\mathbb{R}_+^n \triangleq \{x : x_i \geq 0, \forall i\}$ .  $\mathbb{R}^{k \times m}$  denotes the set of real  $k \times m$  matrices. We also introduce the coordinate basis of  $\mathbb{R}^n$ , i.e. vectors  $\mathbf{e}_1 = (1, 0, \dots, 0)^\top, \dots, \mathbf{e}_n = (0, 0, \dots, 1)^\top$ . The set  $\{1, \dots, n\}$  is denoted  $\overline{1, n}$  for brevity.

## III. GOODWIN'S OSCILLATOR AND ITS OBSERVER

The classical Goodwin's model describes a simple reaction network involving three chemicals (e.g. a gene, a protein, and an intermediate enzyme [6]). Henceforth, we consider a more general system with  $n \geq 3$  chemicals, whose concentrations obey the cyclic feedback system as follows

$$\begin{cases} \dot{x}_1(t) = h(x_n(t)) - b_1 x_1(t), \\ \dot{x}_2(t) = g_1 x_1(t) - b_2 x_2(t), \\ \vdots \\ \dot{x}_n(t) = g_{n-1} x_{n-1}(t) - b_n x_n(t), \end{cases} \quad (1)$$

$$\begin{aligned} & \Downarrow \\ \dot{x}(t) &= f(x(t)), \quad f(x) \triangleq Ax + h(x_n)\mathbf{e}_1, \end{aligned} \quad (2)$$

where  $b_i, g_i > 0, \forall i$ . Therefore,

$$A \triangleq \begin{bmatrix} -b_1 & 0 & \dots & \dots & 0 \\ g_1 & -b_2 & & & \vdots \\ \vdots & & \ddots & & \vdots \\ 0 & & & g_{n-1} & -b_n \end{bmatrix} \in \mathbb{R}^{n \times n} \quad (3)$$

is a two-diagonal matrix that is both *Hurwitz* and *Metzler*.

Goodwin-type model (1) naturally arises in modeling of endocrine regulation [20]–[22], metabolic pathways [23], [24], and genetic oscillators (e.g. circadian clocks) [7], [25]. The decreasing nonlinear function  $h(y)$ , characterizing the feedback loop, is often chosen to be the *Hill* nonlinearity [8]

$$h(y) = \frac{a}{1 + Ky^m}, \quad a, K, m > 0. \quad (4)$$

We do not restrict here the feedback function  $h(\cdot)$  to be a Hill function, adopting however the following assumption.

*Assumption 1:* The function  $h(\cdot)$  is non-negative, non-increasing, and Lipschitz with the constant  $H > 0$  on the interval  $[0, \infty)$ . In particular,  $h(0) \geq h(y) \geq 0, \forall y \geq 0$ .

Assumption 1 is satisfied by e.g. Hill function (4) with  $H = \max_{y \geq 0} (-h'(y))$ . It also allows various piecewise-smooth functions that arise as approximations of the feedback nonlinearities in Goodwin-like models [20], [26], [27].

Since  $A$  is Metzler and  $h(y) \geq 0, \forall y \geq 0$  by Assumption 1, it can be easily shown that the positive orthant  $\mathbb{R}_+^n$  is invariant, i.e. Goodwin's oscillator is a *positive* system. We are interested only in such nonnegative solutions. Since for any nonnegative solution one has  $h(y(t)) \leq h(0)$  and the matrix  $A$  is Hurwitz, all such solutions are bounded.

In this paper, we are concerned with the problem of *observer* design for Goodwin's oscillator (1). This problem is sensible since some of the concentrations  $x_i$  cannot typically be measured for physiological or ethical reasons. For instance, some endocrine regulation loops ("axes") are controlled by dedicated centers in the hypothalamus that release special neurohormones, serving as messengers between the hypothalamus and the pituitary gland (e.g. the gonadotropin or the cortisol-releasing hormone). Their half-life times are short, which implies the necessity of fast sampling, and measuring the releasing hormone concentrations is troublesome due to the poor accessibility of the anatomic location.

Assume that the only available measurement is the concentration  $x_r(t)$  (with  $1 \leq r \leq m$ ) corrupted by a disturbance

$$z(t) = x_r(t) + \eta(t). \quad (5)$$

We assume that the disturbance signal  $\eta(t)$  is bounded and does not lead to negative values of  $z(t)$  (otherwise, the measurement can be saturated at 0).

*Assumption 2:* There exists a constant  $M_\eta \geq 0$  such that

$$\max(-x_r(t), -M_\eta) \leq \eta(t) \leq M_\eta.$$

Our goal is to design an *observer*, that is, a non-anticipatory operator  $z(\cdot) \mapsto \hat{x}(\cdot)$  reconstructing the state vector from the output measurements  $z(t)$ . In the absence of disturbances, it should asymptotically eliminate the observation error

$$\delta(t) = x(t) - \hat{x}(t) \xrightarrow[t \rightarrow \infty]{} 0. \quad (6)$$

### A. The proposed observer's structure

In this paper, we advocate the following simple high-gain observer structure

$$\dot{\hat{x}}(t) = f(\hat{x}(t)) + \gamma(z(t) - \hat{x}_r(t))\mathbf{e}_r, \quad (7)$$

where  $f(\cdot)$  is defined in (2) and  $\gamma > 0$  is the *observer gain*, which has to be chosen sufficiently large. Equivalently, Eq. (7) can be rewritten as

$$\dot{\hat{x}}(t) = (A - \gamma\mathbf{e}_r\mathbf{e}_r^\top)\hat{x}(t) + \gamma z(t)\mathbf{e}_r + h(\hat{x}_n(t))\mathbf{e}_1. \quad (8)$$

The observation error  $\delta(t)$  defined in (6) evolves as

$$\begin{aligned} \dot{\delta}(t) &= (A - \gamma\mathbf{e}_r\mathbf{e}_r^\top)\delta(t) - \gamma\eta(t)\mathbf{e}_r + \\ &+ [h(x_n(t)) - h(\hat{x}_n(t))]\mathbf{e}_1. \end{aligned} \quad (9)$$

## B. Main Results

It may seem that the presence of a high gain  $\gamma$  inevitably leads to large “peaks” in some components of the state estimation error vector  $\delta_i(t)$  (see the discussion below). The principal difference of (7) from the conventional high-gain observers is that such peaks are, however, not only uniformly bounded, but, in fact, keep the state estimate  $\hat{x}(t)$  in the positive orthant. We formulate the following lemma.

*Lemma 1:* For any<sup>1</sup>  $\gamma \geq 0$ , the algorithm (7) provides the following properties:

- (a) *Positivity.* If  $\hat{x}(0) \in \mathbb{R}_+^n$ , then  $\hat{x}(t) \in \mathbb{R}_+^n, \forall t \geq 0$ ;
- (b) *Uniform boundedness.* The estimation error and the estimated state satisfy the inequalities

$$|\delta(t)|_\infty \leq c_1 e^{-\alpha t} |\delta(0)|_\infty + c_2 M_\eta + c_3 h(0), \quad (10)$$

where the constants  $c_i, \alpha > 0$  are independent of  $\gamma$ .

To formulate the main result of the paper, establishing the robust convergence of the state estimate for large gains, we introduce the gain threshold

$$\gamma_* \triangleq -b_r + \frac{g_1 g_2 \dots g_{n-1} H}{b_1 \dots b_{r-1} b_{r+1} \dots b_n} \left( \cos \frac{\pi}{n+1} \right)^{n+1}. \quad (11)$$

Here  $H$  is the Lipschitz constant from Assumption 1.

The following theorem establishes the properties of observer (7).

*Theorem 1:* Suppose that  $\gamma > \gamma_*$ . Then, in the absence of disturbance (i.e.  $M_\eta = 0, \eta \equiv 0$ ), the state estimation error  $\delta(t)$  vanishes asymptotically, c.f. (6). In general, when  $\eta \neq 0$ , the stationary state estimation error is bounded by

$$\overline{\lim}_{t \rightarrow \infty} |\delta(t)| \leq \min(c_4 \gamma M_\eta, c_2 M_\eta + c_3 h(0)), \quad (12)$$

where  $c_4 > 0$  is independent of  $\gamma$  and  $c_2, c_3$  are the same as in (10).

Proofs of Lemma 1 and Theorem 1 are provided in Appendix. One way to prove Theorem 1 is to use the idea of feedback incremental passivity, elaborated in [18], [19] to cope with network of diffusively coupled oscillators. We give a simpler proof, based on the “secant criterion” for stability of cyclic matrices [15], [28].

## C. Observer (7) vs. classical observers

Note that Theorem 1 formally resembles many existing results on observers for nonlinear systems; at the same time, it is different in several important ways:

- Unlike the existing high-gain and LMI-based observers for nonlinear systems [29]–[35], our algorithm enjoys the *positivity* property. Positive observers are known only for very special types of nonlinear systems [36];
- Our observer inherits the structure of the classical Luenberger’s observer, however, its design does not require solving LMIs as in [32], [33];
- The standard drawback of high-gain observers is the presence of peaks in the estimate  $\hat{x}(t)$  and amplification of noises [2]; these effects can be visibly mitigated [31],

<sup>1</sup>Formally, for  $\gamma = 0$ , (7) is not an observer, since it uses no information about the measurements and the estimate does not converge.

[33] but not avoided completely. Observer (7) is “self-saturating” and the peaks (inevitable in high-gain observation schemes) cannot grow infinitely as  $\gamma \rightarrow \infty$ ;

- The price to pay for the appealing properties above is a limitation in assigning an arbitrary convergence rate, which is in contrast enabled by the high-gain observers [29]).

## D. Extensions

We briefly mention two ways to extend the main result.

1) *The case of uncertain nonlinearity:* Identification of nonlinear interactions between hormones (or other chemicals) is an independent problem that is not considered here. For this reason, assuming exact knowledge of the feedback nonlinearity  $h(y)$  may seem restrictive. However, if an approximation for this function  $\hat{h}(\cdot)$  is known such that  $\hat{h}(y) \geq 0$  and the deviation  $\varkappa(y) = h(y) - \hat{h}(y)$  is bounded  $|\varkappa(y)| \leq M_\varkappa \forall y \geq 0$ , one may replace the observer (7) by

$$\begin{aligned} \dot{\hat{x}}(t) &= \hat{f}(\hat{x}(t)) + \gamma(z(t) - \hat{x}_r(t))\mathbf{e}_r, \\ \hat{f}(x) &\triangleq Ax + \hat{h}(x_m)\mathbf{e}_1. \end{aligned} \quad (13)$$

The equation for the observation error becomes

$$\begin{aligned} \dot{\delta}(t) &= (A - \gamma\mathbf{e}_r\mathbf{e}_r^\top)\delta(t) + \gamma\eta(t)\mathbf{e}_r + \varkappa(t)\mathbf{e}_1 \\ &\quad + [h(x_n(t)) - \hat{h}(\hat{x}_n(t))]\mathbf{e}_1. \end{aligned} \quad (14)$$

Here, with some abuse of notation,  $\varkappa(t) \triangleq \varkappa(\hat{x}_m(t))$ , which function can be considered as another bounded disturbance in the system. Examining the proof of Theorem 1 in Appendix, it can be noticed that the error  $\delta(t)$  is robust against this uncertainty, i.e., for  $\gamma > \gamma_*$ , one has

$$\overline{\lim}_{t \rightarrow \infty} |\delta(t)| \leq \min(c_4 \gamma M_\eta + c'_4 M_\varkappa, c_2 M_\eta + c'_2 M_\varkappa + c_3 h(0)).$$

In other words, replacing the nonlinearity  $h(y)$  by a sufficiently close approximation (by e.g. polynomial functions [37]), the observation performance is preserved.

2) *Towards reduction of the conservatism:* It can be noted that the derivative’s maximal value  $H$  in (17) can be replaced by a smaller constant, using asymptotic properties of the Goodwin system. It can be easily shown that Goodwin’s oscillator has a compact invariant set, attracting all non-negative solutions. An elegant approximation of this set was found in [38], [39]. As shown in these papers, there exist constants  $\underline{x}_r, \bar{x}_r$  (depending on the system’s parameters, namely, the properties of the mapping  $\Psi(y) = g_1 \dots g_{n-1} h(y)/(b_1 \dots b_n)$ ) such that

$$\underline{x}_r \leq \underline{\lim}_{t \rightarrow \infty} x_r(t) \leq \overline{\lim}_{t \rightarrow \infty} x_r(t) \leq \bar{x}_r.$$

A simple modification of the techniques from [38], [39] allows to get a similar estimate for the observer’s solution

$$\underline{\hat{x}}_r \leq \underline{\lim}_{t \rightarrow \infty} \hat{x}_r(t) \leq \overline{\lim}_{t \rightarrow \infty} \hat{x}_r(t) \leq \bar{\hat{x}}_r.$$

Using these refined estimates, one shows that, as  $t \rightarrow \infty$  the estimate  $|h(x_n) - h(\hat{x}_n)| \leq \bar{H}|x_n - \hat{x}_n|$  holds, where  $\bar{H}$  is the maximum of  $(-h')$  on the interval

$[\max(\underline{x}_r, \hat{x}_r), \min(\bar{x}_r, \bar{\hat{x}}_r)]$ . Analysis of the proof of Theorem 1 shows that  $H$  can actually be replaced by  $\bar{H}$ , which can appear to be much smaller.

#### IV. NUMERICAL SIMULATIONS

A standard third-order Goodwin's oscillator, i.e.  $x \in \mathbb{R}^3$  is selected for numerical illustration. The plant parameters are  $b_1 = 0.4$ ,  $b_2 = 0.5$ ,  $b_3 = 0.3$ ,  $g_1 = 2.0$ ,  $g_2 = 0.5$ ,  $a = 100$ ,  $K = 0.1$  and  $n = 9$  to obtain sustained oscillations.

For Hill function (4), we have

$$h'(y) = \frac{-aKy^{m-1}}{(1 + Ky^m)^2},$$

and  $h'(0) = 0$ ,  $\lim_{y \rightarrow \infty} h'(y) = 0$ , as well as  $h'(y) < 0$ ,  $y > 0$ . The minimum of  $h'(y)$  is achieved at

$$y_{\min} = \arg \min_y h'(y) = \left( \frac{m-1}{K(m+1)} \right)^{\frac{1}{m}}$$

and, therefore, referring to Assumption 1,

$$H = -\min_y h'(y) = \frac{a(m^2 - 1)}{4my_{\min}}. \quad (15)$$

The dependence of  $H$  on the Hill function parameters  $m$  and  $K$  is shown in Fig. 3. Clearly, the value of  $H$  increases with increasing  $m$  and falling  $K$ .

Observer (7) is implemented for state estimation. The last element in the state vector is assumed to be measurable  $r = 3$ . The initial conditions on the observer are selected as  $\hat{x}(0) = [0.3800 \quad 2.3195 \quad 5.3880]$  while the initial conditions for Goodwin's oscillator are set to result in a stable periodical solution as  $x(0) = [0.2000 \quad 1.2208 \quad 2.8358]$ . The observer gain  $\gamma$  controls the convergence rate of the observer, as seen in Fig. 1. Being initialized at a point in the positive orthant, the observer produces positive state estimates, see Fig. 2. The gain threshold value is

$$\gamma_* = -b_3 + \frac{g_1 g_2 H}{b_1 b_2} \left( \cos \frac{\pi}{4} \right)^4 = 48.4336,$$

illustrating the degree of conservatism in Theorem 1 introduced due to the general form of the considered nonlinearity and lack of localization of the plant states. As Fig. 2 shows, good observer convergence is already achieved for  $\gamma = 3$ .

To illustrate the impact of measurement disturbance, the plant output is corrupted by random noise  $\eta$  uniformly distributed in the interval  $(0, 1.5)$ . The time evolution of the state estimation error for different values of the observer gain  $\gamma$  is depicted in Fig. 4. As pointed out before, the observer performs well with a low gain (e.g.  $\gamma = 3$ ) and the performance actually deteriorates for a high gain. Yet, no peaking phenomena typical to high-gain observers occurs.

#### V. CONCLUSION

In this paper, we propose a Luenberger-type observer for the  $n$ -dimensional Goodwin's oscillator. This state reconstruction algorithm exploits the properties of the nonlinear plant instead of canceling the nonlinearity by means of a high feedback gain. For this reason, our algorithm appears

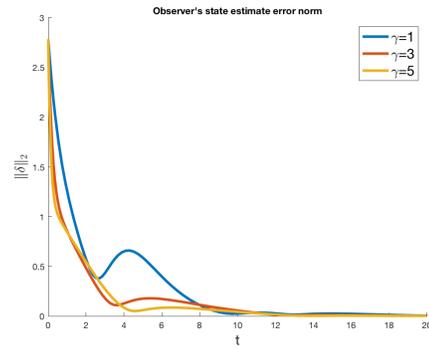


Fig. 1. Euclidean norm of the state estimation error as a function of time for different values of the observer gain  $\gamma$ .

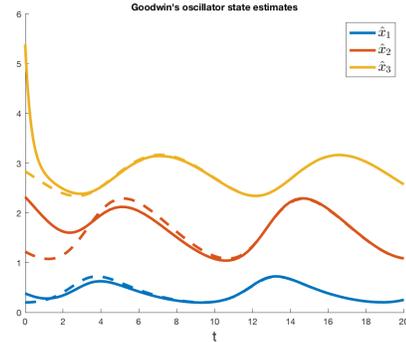


Fig. 2. The observer state estimates function of time (solid lines) compared to the actual states of Goodwin's oscillator (dashed lines). The observer gain  $\gamma = 3$ . Notice the positivity of the observer estimates.

to be free of many flaws inherent to standard high-gain and LMI-based observers (e.g. exaggerated peaks in the state estimation error). The results are illustrated by numerical simulation for a classical third-order model.

#### REFERENCES

- [1] G. Besançon, Ed., *Nonlinear Observers and Applications*. Springer, 2007.
- [2] H. Khalil, *High-Gain Observers in Nonlinear Feedback Control*. Philadelphia, PA: Society for Industrial and Applied Mathematics, 2017.
- [3] J. M. Ali, N. H. Hoang, M. Hussain, and D. Dochain, "Review and classification of recent observers applied in chemical process systems," *Computers & Chemical Engineering*, vol. 76, pp. 27–41, 2015.
- [4] L. Glass, "Synchronization and rhythmic processes in physiology," *Nature*, vol. 410, pp. 277–284, March 2001.
- [5] G. Leonov and N. Kuznetsov, "Hidden attractors in dynamical systems. from hidden oscillations in Hilbert-Kolmogorov, Aizerman, and Kalman problems to hidden chaotic attractor in Chua circuits," *International Journal of Bifurcation and Chaos*, vol. 23, no. 1, 2013.
- [6] B. Goodwin, "Oscillatory behaviour in enzymatic control processes," *Advances in Enzyme Regulation*, vol. 3, pp. 425–438, 1965.
- [7] D. Gonze, "Modeling circadian clocks: From equations to oscillations," *Cent. Eur. J. Biol.*, vol. 6, no. 5, pp. 699–711, 2011.
- [8] D. Gonze and W. Abou-Jaoude, "The Goodwin model: Behind the Hill function," *PLoS One*, vol. 8, no. 8, p. e69573, 2013.
- [9] S. Doubabi, "Study of oscillations in a particular case of Yates-Pardee-Goodwin metabolic pathway with coupling," *Acta Biotheoretica*, vol. 46, pp. 311–319, 1999.
- [10] H. Taghvafard, A. Proskurnikov, and M. Cao, "Stability properties of the Goodwin-Smith oscillator model with additional feedback," *IFAC-PapersOnLine*, vol. 49, no. 14, pp. 131–136, 2016.

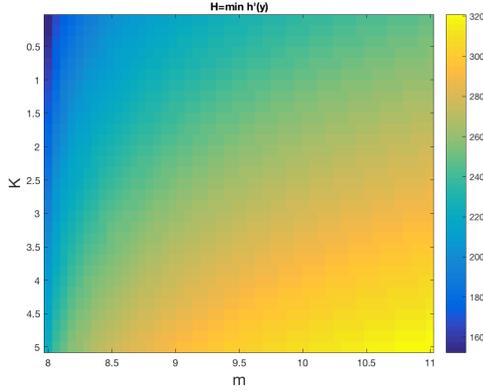


Fig. 3. Minimal value of  $h'(y)$  as a function of  $m$  and  $K$  (heat map).

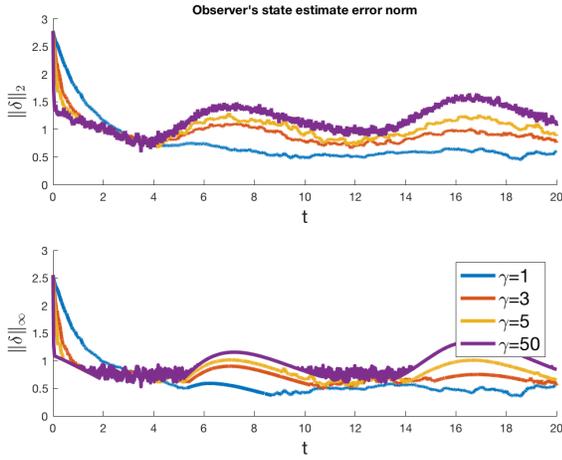


Fig. 4. The estimation error's norms  $\|\delta\|_2$  (upper plot) and  $\|\delta\|_\infty$  (lower plot) under measurement disturbance for different values of the observer gain  $\gamma$ : the trade-off between convergence rate and steady-state error.

[11] A. A. Salinas-Varela, G.-B. Stan, and J. Goncalves, "Global asymptotic stability of the limit cycle in piecewise linear versions of the Goodwin oscillator," in *Proceedings of the 17th World Congress The International Federation of Automatic Control*, Seoul, Korea, 2008.

[12] H. Taghvafard, A. Proskurnikov, and M. Cao, "Local and global analysis of endocrine regulation as a non-cyclic feedback system," *Automatica*, vol. 91, pp. 190–196, 2018.

[13] Y. Hori, T.-H. Kim, and S. Hara, "Existence criteria of periodic oscillations in cyclic gene regulatory networks," *Automatica*, vol. 47, no. 6, pp. 1203–1209, 2011, special issue on Systems Biology.

[14] T.-H. Kim, Y. Hori, and S. Hara, "Robust stability analysis of gene-protein regulatory networks with cyclic activation repression interconnections," *Syst. Control Lett.*, vol. 60, no. 6, pp. 373–382, 2011.

[15] M. Arcak and E. Sontag, "Diagonal stability of a class of cyclic systems and its connection with the secant criterion," *Automatica*, vol. 42, pp. 1531–1537, 2006.

[16] A. Chirilov, A. Medvedev, and A. Shepeljavyi, "State observer for continuous oscillating systems under intrinsic pulse-modulated feedback," *Automatica*, vol. 48, no. 6, pp. 1117–1122, 2012.

[17] G.-B. Stan and R. Sepulchre, "Analysis of interconnected oscillators by dissipativity theory," *IEEE Trans. Autom. Control*, vol. 52, pp. 256–270, 2007.

[18] A. Hamadeh, G.-B. Stan, R. Sepulchre, and J. Goncalves, "Global state synchronization in networks of cyclic feedback systems," *IEEE Transactions on Automatic Control*, vol. 57, pp. 478–483, 2012.

[19] A. Proskurnikov and M. Cao, "Synchronization of Goodwin's oscillators under boundedness and nonnegativeness constraints for solutions,"

*IEEE Trans. Autom. Control*, vol. 62, no. 1, pp. 372–378, 2017.

[20] L. Danziger and G. Elmergreen, "Mathematical models of endocrine systems," *Bull. Math. Biophys.*, vol. 19, pp. 9–18, 1957.

[21] W. Smith, "Hypothalamic regulation of pituitary secretion of luteinizing hormone – ii. feedback control of gonadotropin secretion," *Bull. of Math. Biol.*, vol. 42, pp. 57–78, 1980.

[22] —, "Qualitative mathematical models of endocrine systems," *Amer. J. Physiology*, vol. 245, no. 4, pp. R473–7, 1983.

[23] M. Morales and D. McKay, "Biochemical oscillations in "constrolled" systems," *Biophys. J.*, vol. 7, pp. 621–625, 1967.

[24] A. Hunding, "Limit-cycles in enzyme-systems with nonlinear negative feedback," *Biohys. Struct. Mechanism*, vol. 1, no. 1, pp. 47–54, 1974.

[25] D. Gonze, S. Bernard, C. Waltermann, A. Kramer, and H. Herzl, "Spontaneous synchronization of coupled circadian oscillators," *Biohys. J.*, vol. 89, pp. 120–129, 2005.

[26] J. Cronin, "The Danziger-Elmergreen theory of periodic catatonic schizophrenia," *Bull. Math. Biol.*, vol. 35, pp. 689–707, 1973.

[27] S. Hastings, "On the uniqueness and global asymptotic stability of periodic solutions for a third order system," *Rocky Mountain J. Math.*, vol. 7, no. 3, pp. 513–538, 1977.

[28] C. Thron, "The secant condition for instability in biochemical feedback control - parts i and ii," *Bulletin of Mathematical Biology*, vol. 53, pp. 383–424, 1991.

[29] H. K. Khalil and L. Praly, "High-gain observers in nonlinear feedback control," *Int. J. Robust. Nonlinear Control*, vol. 24, no. 6, pp. 993–1015, 2014.

[30] H. K. Khalil, "High-gain observers in feedback control: Application to permanent magnet synchronous motors," *IEEE Control Systems*, vol. 37, no. 3, pp. 25–41, 2017.

[31] —, "Cascade high-gain observers in output feedback control," *Automatica*, vol. 80, pp. 110 – 118, 2017.

[32] D. Astolfi and L. Marconi, "A high-gain nonlinear observer with limited gain power," *IEEE Transactions on Automatic Control*, vol. 60, no. 11, pp. 3059–3064, 2015.

[33] D. Astolfi, L. Marconi, L. Praly, and A. R. Teel, "Low-power peaking-free high-gain observers," *Automatica*, vol. 98, pp. 169 – 179, 2018.

[34] A. Zemouche, F. Zhang, F. Mazenc, and R. Rajamani, "High-gain nonlinear observer with lower tuning parameter (published online)," *IEEE Transactions on Automatic Control*, 2019.

[35] A. Zemouche and M. Boutayeb, "On lmi conditions to design observers for Lipschitz nonlinear systems," *Automatica*, vol. 49, no. 2, pp. 585 – 591, 2013.

[36] B. Brian, J. Wang, and Z. Qu, "Nonlinear positive observer design for positive dynamical systems," in *Proceedings of American Control Conference*, 2010, pp. 6231–6237.

[37] C. R. Fox, L. S. Farhy, W. S. Evans, and M. L. Johnson, "Measuring the coupling of hormone concentration time series using polynomial transfer functions," *Methods in enzymology*, vol. 384, pp. 82–94, 2004.

[38] D. J. Allwright, "A global stability criterion for simple control loops," *Journal of Mathematical Biology*, vol. 4, pp. 363–373, 1977.

[39] G. Enciso, H. Smith, and E. Sontag, "Nonmonotone systems decomposable into monotone systems with negative feedback," *J. Differential Equations*, vol. 224, pp. 205–227, 2006.

## APPENDIX

To prove the main results, we use the seminal "secant criterion" [15] ensuring stability of circular matrices of certain structure. Suppose that the constants  $\alpha_1, \dots, \alpha_n > 0, \beta_1, \dots, \beta_n > 0$  are given and let

$$M(\theta) \triangleq \begin{bmatrix} -\alpha_1 & 0 & \dots & \dots & -\beta_n \theta \\ \beta_1 & -\alpha_2 & & & \vdots \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & & & \beta_{n-1} & -\alpha_n \end{bmatrix}, \quad \theta > 0. \quad (16)$$

**Lemma 2:** [15], [28] The matrix  $M(\theta)$  is Hurwitz whenever  $\theta > 0$  is sufficiently small, namely

$$\frac{\beta_1 \dots \beta_n \theta}{\alpha_1 \dots \alpha_n} < \left( \sec \frac{\pi}{n} \right)^n. \quad (17)$$

Furthermore, (17) guarantees *diagonal* stability: there exists a diagonal matrix  $D_\theta > 0$  such that  $D_\theta M(\theta) + M^\top(\theta) D_\theta > 0$ .

Obviously, for  $\theta = 0$  the matrix  $M(\theta)$  is also Hurwitz, although formally this situation is uncovered by the secant criterion. More important, the secant criterion remains instrumental at proving stability for systems with a *time-varying* parameter  $\theta(t)$ , with the only difference that (17) should be replaced by a stronger inequality.

*Corollary 1:* For each Lebesgue measurable function  $\theta : [0, \infty) \rightarrow [0, \bar{\theta}]$ , where the constant  $\bar{\theta}$  satisfies the inequality

$$\frac{\beta_1 \dots \beta_n \bar{\theta}}{\alpha_1 \dots \alpha_n} < \left( \sec \frac{\pi}{n+1} \right)^{n+1}, \quad (18)$$

the time-varying system as follows is exponentially stable

$$\dot{x}(t) = M(\theta(t))x(t). \quad (19)$$

Furthermore, (19) is ‘‘uniformly diagonally’’ stable, that is, it admits a quadratic Lyapunov function  $V(x) = x^\top D x$ , where the diagonal matrix  $D > 0$  depends only on  $\alpha_i, \beta_i, \bar{\theta}$  (but not on a specific function  $\theta(\cdot)$ , which can be uncertain).

*Proof:* Consider a cyclic  $(n+1) \times (n+1)$  matrix

$$\bar{M} \triangleq \begin{bmatrix} -\alpha_1 & 0 & \dots & \dots & -\beta_n \\ \beta_1 & -\alpha_2 & & & \vdots \\ \vdots & \vdots & \ddots & & \vdots \\ 0 & & & \beta_{n-1} & -\alpha_n \\ 0 & & & \bar{\theta} & -1 \end{bmatrix}. \quad (20)$$

Thanks to Lemma 2, a diagonal matrix  $\bar{D} > 0$  and a constant  $\varepsilon > 0$  exist such that  $\bar{D}\bar{M} + \bar{M}^\top \bar{D} \leq -\varepsilon I_{n+1}$ . Let  $D > 0$  be  $n \times n$  upper left submatrix of  $\bar{D}$  (also diagonal) and  $V(x) = x^\top D x$ . With the column vector  $\bar{x}(t) = (x^\top, \theta(t)x_n(t)^\top)^\top$ , the following inequalities hold

$$\begin{aligned} -\varepsilon|x|^2 &\geq -\varepsilon|\bar{x}|^2 \geq 2\bar{x}^\top \bar{D}\bar{M}\bar{x} = 2x^\top D M(\theta)x + \\ &+ 2d_{n+1}(\bar{\theta}x_n x_{n+1} - x_{n+1}^2) \geq 2x^\top D M(\theta)x \geq \\ &\geq \frac{d}{dt} V(x(t)). \end{aligned}$$

We used the fact that  $\bar{\theta} \geq \theta$  and  $\bar{\theta}x_n x_{n+1} = \bar{\theta}\theta x_n^2 \geq \theta^2 x_n^2 = x_{n+1}^2$ . Hence  $|x(t)|$  vanishes exponentially as  $t \rightarrow \infty$ . ■

#### A. Proof of Lemma 1

Statement (a) is immediate from (8), since  $\gamma > 0$ ,  $h(y) > 0$ ,  $\forall y \geq 0$  and the matrix  $A_\gamma \triangleq A - \gamma e_r e_r^\top$  is Metzler.

To prove (b), notice first that  $e^{tA} - e^{tA_\gamma}$  is a non-negative matrix for any  $\gamma \geq 0$  (and both exponentials are positive matrices). Indeed, consider a nonnegative vector  $\mu_0 \in \mathbb{R}_+^n$ . Then  $\mu(t) = e^{tA_\gamma} \mu_0 \in \mathbb{R}_+^n$  obeys the differential equation

$$\dot{\mu}(t) = A_\gamma \mu(t) \leq A \mu(t), \quad \mu(0) = \mu_0,$$

and therefore<sup>2</sup>  $\mu(t) \leq e^{tA} \mu_0$ . Since  $\mu_0$  is arbitrary, the matrix  $e^{tA} - e^{tA_\gamma}$  is nonnegative. In particular,  $\|e^{tA_\gamma}\|_\infty \leq \|e^{tA}\|_\infty \leq c_1 e^{-\alpha t}$ , where  $c_1, \alpha > 0$  depend only on  $A$ ,

<sup>2</sup>Although the comparison lemma does not hold, in general, for vector differential inequalities, it can be used for the positive LTI system at hand. Since  $\dot{\mu}(t) = A\mu(t) - \rho(t)$ , where  $\rho(t) \geq 0$ , the Cauchy formula entails that  $\mu(t) = e^{tA} \mu_0 - \int_0^t e^{(t-s)A} \rho(s) ds \leq e^{tA} \mu_0$ .

but not on  $\gamma$ . Furthermore,  $A_\gamma^{-1}$  is a negative matrix. A straightforward computation allows to compute the vectors:

$$\zeta(\gamma) \triangleq -\gamma A_\gamma^{-1} e_r, \quad \gamma \geq 0,$$

which are given by  $\zeta_i(\gamma) = 0$  for  $i < r$ ,  $\zeta_r(\gamma) = \gamma/(b_r + \gamma) < 1$ ,  $\zeta_i(\gamma) = \zeta_{i-1}(\gamma)g_{i-1}/b_i$  for  $i > r$  and thus are uniformly bounded in  $\gamma > 0$ . Similarly, it can be checked that  $-A_\gamma^{-1} e_1$  is a bounded function of  $\gamma \geq 0$ .

Let  $\xi(t) = \xi(t|\xi_0, M_1, M_2)$  stand for the solution to

$$\dot{\xi}(t) = A_\gamma \xi(t) + \gamma M_1 e_r + M_2 e_1, \quad \xi(0) = \xi_0. \quad (21)$$

where  $M_1, M_2 > 0$  are constants and  $\xi_0 \in \mathbb{R}^n$ . Using the Cauchy formula, one arrives at

$$\begin{aligned} e^{tA_\gamma} \xi_0 &\leq \xi(t|\xi_0, M_1, M_2) = e^{tA_\gamma} \xi_0 + \\ &+ \int_0^t e^{sA_\gamma} (\gamma M_1 e_r + M_2 e_1) ds = \\ &= e^{tA_\gamma} \xi_0 - \gamma M_1 A_\gamma^{-1} e_r - M_2 A_\gamma^{-1} e_1 + \\ &+ \underbrace{A_\gamma^{-1} e^{tA_\gamma} (\gamma M_1 e_r + M_2 e_1)}_{\leq 0} \implies \end{aligned} \quad (22)$$

$$|\xi(t|\xi_0, M_1, M_2)|_\infty \leq c_1 e^{-\alpha t} |\xi_0|_\infty + c_2 M_1 + c_3 M_2,$$

where  $c_i, \alpha > 0$  are independent of  $\gamma > 0$ ,  $M_1$  and  $M_2$ . Recalling that  $\eta(t) \leq M_\eta$  and  $0 \leq h(y) \leq h(0)$  for any  $y \geq 0$ , (10) follows from (14). Indeed, let  $M_1 = M_\eta$  and  $M_2 = h(0)$ . Since  $\dot{\delta}(t) \leq A_\gamma \delta + \gamma M_1 e_r + M_2 e_1$ , one obtains that  $\delta(t) \leq \xi(t|\delta(0), M_1, M_2)$ . For the same reason,  $-\delta(t) \leq \xi(t|-\delta(0), -M_1, -M_2)$  due to (14). By noting that  $|\delta|_\infty = \max\{\delta_i, -\delta_i, i \in \overline{1, n}\}$  and using (22), (10) is immediate.

#### B. Proof of Theorem 1

To show the first statement, consider Eq. (14) with  $\eta \equiv 0$  and notice that due to Assumption 1  $h(x_n(t)) - h(\hat{x}_n(t)) = -\theta(t)\delta_n(t)$ , where  $\theta(t) \in [0, H]$  depends on  $x_n(t)$  and  $\hat{x}_n(t)$ . Hence  $\delta(t)$  is a solution to (19), where  $M(\theta)$  is defined in (16),  $\bar{\theta} = H$ ,  $\alpha_i = b_i$  for  $i \neq r$ ,  $\alpha_r = b_r + \gamma$ ,  $\beta_i = g_i$  for  $i < n$  and  $\beta_n = 1$ . In view of (11),  $\gamma > \gamma_*$  is equivalent to (18). The first statement of Theorem 1 now follows from Corollary 1. In presence of disturbance  $\eta(t) \neq 0$ , (14) implies that

$$\dot{\delta}(t) = M(\bar{\theta}(t))\delta(t) + \gamma e_r \eta(t),$$

where  $\bar{\theta}(t) \in [0, H]$  is another function, depending on  $x(t)$  and  $\hat{x}_n(t)$ . Since the quadratic Lyapunov function  $V(x) = x^\top D x$  from Corollary 1 is independent of the specific function  $\theta(\cdot)$  and  $DM(\theta) + M(\theta)^\top D \leq -\varepsilon I_n$  for some constants  $\varepsilon, \varepsilon_0 > 0$  (independent of  $\theta(\cdot)$ ), one has

$$\begin{aligned} \frac{d}{dt} V(\delta) &\leq -\varepsilon|\delta|^2 + \gamma \delta_r \eta \leq -\frac{\varepsilon}{2}|\delta|^2 + \frac{\gamma^2 M_\eta^2}{2} \leq \\ &\leq -V(\delta) + \frac{\gamma^2 M_\eta^2}{2}. \end{aligned}$$

Hence, for a properly chosen constant  $c_4 > 0$ , one has  $\lim_{t \rightarrow \infty} |\delta(t)| \leq c_4 \gamma M_\eta$ . Combining this with (10), inequality (12) follows straightforwardly.