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# Detection and suppression of epileptiform seizures via model-free control and derivatives in a noisy environment

Cédric Join<sup>1,6</sup>, D. Blair Jovellar<sup>2,3</sup>, Emmanuel Delaleau<sup>4</sup> and Michel Fliess<sup>5,6</sup>

**Abstract**—Recent advances in control theory yield closed-loop neurostimulations for suppressing epileptiform seizures. These advances are illustrated by computer experiments which are easy to implement and to tune. The feedback synthesis is provided by an intelligent proportional-derivative (iPD) regulator associated to model-free control. This approach has already been successfully exploited in many concrete situations in engineering, since no precise computational modeling is needed. iPDs permit tracking a large variety of signals including high-amplitude epileptic activity. Those unpredictable pathological brain oscillations should be detected in order to avoid continuous stimulation, which might induce detrimental side effects. This is achieved by introducing a data mining method based on the maxima of the recorded signals. The real-time derivative estimation in a particularly noisy epileptiform environment is made possible due to a newly developed algebraic differentiator. The virtual patient is the Wendling model, i.e., a set of ordinary differential equations adapted from the Jansen-Rit neural mass model in order to generate epileptiform activity via appropriate values of excitation- and inhibition-related parameters. Several simulations, which lead to a large variety of possible scenarios, are discussed. They show the robustness of our control synthesis with respect to different virtual patients and external disturbances.

**Index Terms**—Epileptiform seizures, neurostimulation, seizure detection, seizure suppression, model-free control, intelligent proportional-derivative controller, noise removal, algebraic differentiator, data mining.

## I. INTRODUCTION

The complexity of brain explains why the *closed-loop*, or *feedback*, setting, which is a key concept in control theory, is so underdeveloped in computational neuroscience as analyzed in several recent publications (see, e.g., [1], [2], [3], [4], [5]), in spite of some preliminary attempts (see, e.g., [6]). This is confirmed [7] by the secondary role of brain research in *systems biology*, a discipline that focuses on the connections between biology and control systems (see, e.g., [8], [9]).

This communication reports some preliminary computer experiments on *epilepsy*, an important neurological disorder, also known as a *seizure disorder* [10]:

<sup>1</sup>CRAN (CNRS, UMR 7039), Université de Lorraine, BP 239, 54506 Vandœuvre-lès-Nancy, France. @: [cedric.join@univ-lorraine.fr](mailto:cedric.join@univ-lorraine.fr)

<sup>2</sup>Department of Neurology & Stroke, University of Tübingen, Tübingen, Germany. @: [desiree-blair.jovellar@uni-tuebingen.de](mailto:desiree-blair.jovellar@uni-tuebingen.de)

<sup>3</sup>Hertie-Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany.

<sup>4</sup>ENI Brest, IRDL (CNRS, UMR 6027), 29200 Brest, France. @: [delaleau@enib.fr](mailto:delaleau@enib.fr)

<sup>5</sup>LIX (CNRS, UMR 7161), École polytechnique, 91128 Palaiseau, France. @: [Michel.Fliess@polytechnique.edu](mailto:Michel.Fliess@polytechnique.edu), [michel.fliess@swissknife.tech](mailto:michel.fliess@swissknife.tech)

<sup>6</sup>AL.I.E.N., 7 rue Maurice Barrès, 54330 Vézelize, France. @: [{cedric.join,michel.fliess}@alien-sas.com](mailto:{cedric.join,michel.fliess}@alien-sas.com)

1) A closed-loop seizure suppression is proposed. It is based on an *intelligent* regulator derived from *model-free* control (MFC) [11], [12]. This setting has already led to many concrete applications (see, e.g., references in [11], [12]). Let us emphasize here a most recent comparison [13] with other popular types of control synthesis in some specific questions arising in intelligent transportation systems, where the superiority of MFC is asserted. See below some of its main features:

- MFC does not necessitate any mathematical modeling, and therefore neither delicate parameter identification procedures.
- It is much easier to tune than proportional-integral-derivative (PID) controllers which are the most popular industrial feedback loops (see, e.g., [14]).
- It has already been successfully illustrated in biomedicine and bioengineering [15], [16], [17], [18], [19].

Following [12], the use of an *intelligent proportional-derivative* controller, or *iPD*, seems more adapted to regulate, via electric stimulations, a large variety of high-amplitude epileptic activity.

2) Those aberrant burst events recur unpredictability and often are separated by long interictal time lapses. A continuous stimulation like above might therefore induce detrimental side effects [20]. A real-time seizure detection is thus necessary for triggering the above feedback. Frequency-domain techniques are today a crucial ingredient in most publications on this subject (see, e.g., [21], [22], [23], [24], [25], and references therein). We follow here another quite recent route using algebraic manipulations in the time-domain (see [26], [27], [28], for the theoretical background and the presentation of successful applications), and more specifically, here, via a new data mining viewpoint [29] where the maxima of the recorded signal are determined. Let us summarize this approach:

- Maxima in a seizure are large and close to each other.
- Using derivatives for seizure detection, which involves a noisy environment, is a known challenge in engineering.
- Our *algebraic differentiator*, which is borrowed from [30] (see, also, [31]), does not necessitate any probabilistic and/or statistical assumption on the noise corruption.

3) The *virtual* patient, i.e., the epileptiform signal, is

provided by Wendling's neural mass model [32]. This computational model, which is now recognized as an efficient approach to get insights into this disease, is deduced from the well-known Jansen-Rit set of ordinary differential equations [33] (see also [34], [35]). The stimulators location mimics [36], [37]. Modifying the many parameters of Wendling's model makes it easy to verify the inherent robustness of our model-free control.

Our paper is organized as follows. After a short presentation in Sect. II of Wendling's model where some stimulators are added, Sect. III summarizes the derivatives estimation in a noisy environment and proposes a seizure detection algorithm, which is illustrated by computer experiments. After a review of some basic aspects of model-free control, Sect. IV is discussing several scenarios on seizure suppression. See Sect. V for short concluding remarks.

## II. MODEL

The following modification of Wendling's model [32], which is due to [36], [37], is obtained by adding stimulation (see [38] for a slightly different choice):

$$\begin{cases} \ddot{y}_0 = Aa\mathfrak{S}(u + y_1 - y_2 - y_3) - 2a\dot{y}_0 - a^2y_0 \\ \ddot{y}_1 = Aa(p + C_2\mathfrak{S}(u + C_1y_0)) - 2a\dot{y}_1 - a^2y_1 \\ \ddot{y}_2 = BbC_4\mathfrak{S}(u + C_3y_0) - 2b\dot{y}_2 - b^2y_2 \\ \ddot{y}_3 = GgC_7\mathfrak{S}(u + C_5y_0 - y_4) - 2g\dot{y}_3 - g^2y_3 \\ \ddot{y}_4 = BbC_6\mathfrak{S}(u + C_3y_0) - 2b\dot{y}_4 - b^2y_4 \end{cases} \quad (1)$$

where

- $A, a, B, b, G, g, C_1, \dots, C_7$  are positive constants;
- $A, B$  and  $G$  represent the amplitude of average excitatory (EPSP), slow and fast inhibitory (IPSP) postsynaptic potentials, respectively.
- The variables  $y_0, y_1, y_2, y_3, y_4$  represent the post-synaptic potentials of pyramidal cells, excitatory feedback, and both slow and fast inhibitory interneurons, respectively.
- $p(t)$  is an external perturbation corresponding to excitatory inputs from neighboring areas. There are various representations in the existing literature: white Gaussian noise, constant value, sum of them...
- The electrical stimulation  $u(t)$  is the control variable. This follows the assumption that the stimulation generates an electric field with a direct de- or hyperpolarizing linear effect onto the mean membrane potential of the neuronal subsets [39].
- The sigmoid function  $\mathfrak{S}(\square)$  reads

$$\begin{aligned} \mathfrak{S}(\square) &= \frac{v_{\max}}{2} \left( 1 + \tanh \frac{r}{2} (\square - v_0) \right) \\ &= \frac{v_{\max}}{1 + \exp(r(v_0 - \square))} \end{aligned}$$

where  $v_{\max}$  is the maximum firing rate,  $v_0$  is the average membrane potential acting as a firing threshold,  $v_{\max}$  is the maximum firing rate, and  $r > 0$  is a constant.

See Fig. 1 for a block diagram description of (1), where  $H_a = \frac{Aa}{s^2 + 2as + a^2}$ ,  $H_b = \frac{Bb}{s^2 + 2bs + b^2}$ ,  $H_g = \frac{Gg}{s^2 + 2gs + g^2}$  are transfer

functions. The summation  $y_m = y_1 - y_2 - y_3$  represents the incoming firing rate to the population of pyramidal cells.

## III. SEIZURE DETECTION

### A. Differentiation in a noisy environment

Here we will present a simplified version, borrowed from [26]. Consider the polynomial function  $p_1(t) = a_0 + a_1t$ ,  $t \geq 0$ ,  $a_0, a_1 \in \mathbb{R}$ . Classic *operational calculus* (see, e.g., [40]), or *Laplace transform*, yields  $P_1 = \frac{a_0}{s} + \frac{a_1}{s^2}$ . Multiply both sides by  $s^2$ :

$$s^2P_1 = a_0s + a_1 \quad (2)$$

Deriving both sides with respect to  $s$ , which corresponds in the time domain to the multiplication by  $-t$ , yields  $a_0$ :

$$a_0 = s^2 \frac{dP_1}{ds} + 2sP_1 \quad (3)$$

Then  $a_1$  is given by Eqn. (2)

$$a_1 = -s^3 \frac{dP_1}{ds} - s^2P_1 \quad (4)$$

In order to get rid of the positive powers of  $s$ , which corresponds in the time domain to derivatives w.r.t. time, multiply both sides of Eqn. (3) (resp. (4)) by  $s^{-n}$ , where the integer  $n > 0$  is large enough. It yields in the time domain:

$$\frac{dp_1}{dt} = a_1 = \frac{6}{T^3} \int_0^T (-T + 2\tau) p_1(\tau) d\tau$$

where  $T > 0$  is the window size used for the estimation. The integral, which is mitigating the corrupting noise in the sense of [41], may be in practice replaced by a digital filter. The extension to polynomials of arbitrary degree is obvious and, therefore, also to truncated Taylor expansions. Details and references on the computer implementations may be found in [31], as well as references to many concrete applications.

### B. Seizure detection

A seizure may be characterized by a short time lapse between two large maxima. Those maxima correspond to zero crossings of the derivative.

*An academic illustration:* Take the *chirp*, i.e., a frequency modulated signal, which is familiar in radar engineering (see, e.g., [42]),

$$y(t) = \sin(2\pi t^2) + 5, \quad 0 \leq t \leq 5$$

It is corrupted by an additive white Gaussian noise (mean: 0, standard deviation: 0.1). Fig. 2 exhibits excellent results.

Fig. 3-(a) displays a signal produced by Wendling's model [32], i.e., without stimulation, i.e.,  $u(t) = 0$ , in Eqn. (1). Its right part shows a seizure, which ought to be detected in order to avoid any stimulation when there is no crisis [20]. The derivative of the recorded signal  $y_m(t)$  is reported in Fig. 3-(b). See Fig. 3-(c) for the time lapse between consecutive maxima. The choice of an adequate threshold [29] for this time lapse yields the detection of the seizure.

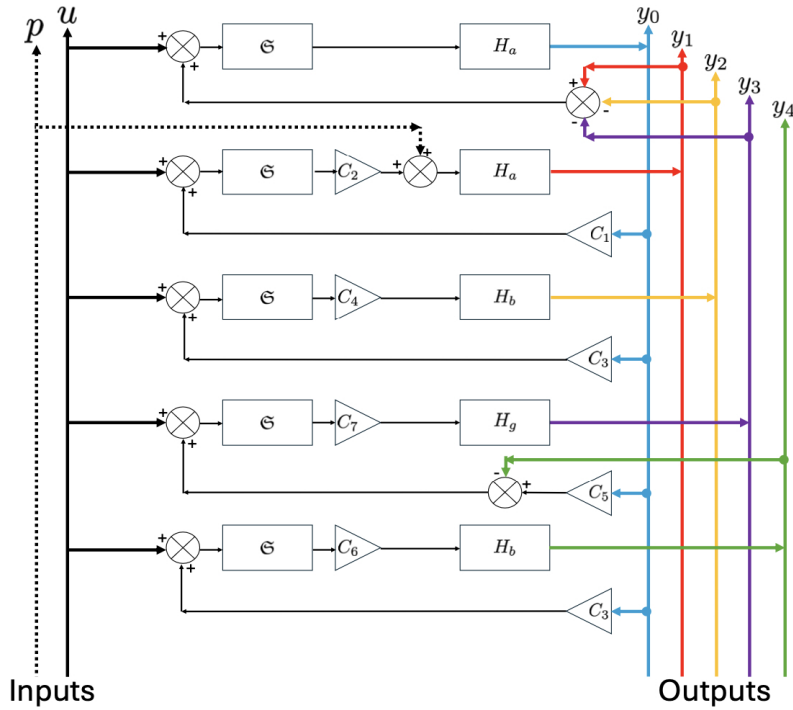
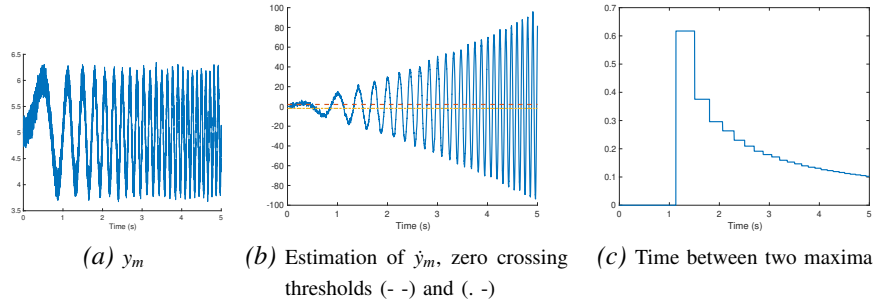


Fig. 1. Model scheme: block diagrams

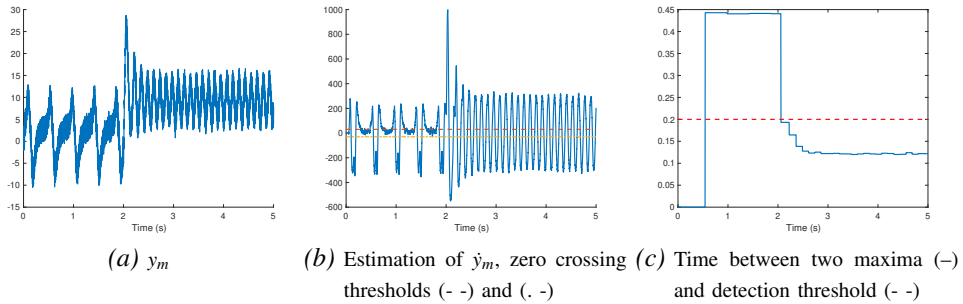


(a)  $y_m$

(b) Estimation of  $\dot{y}_m$ , zero crossing thresholds (- -) and (.-)

(c) Time between two maxima

Fig. 2. Radar signal: Seizure detection



(a)  $y_m$

(b) Estimation of  $\dot{y}_m$ , zero crossing thresholds (- -) and (.-)

(c) Time between two maxima (-) and detection threshold (- -)

Fig. 3. Epilepsy: Seizure detection

#### IV. CLOSED-LOOP CONTROL

##### A. The ultra-local model

Consider, following [12], the *ultra-local model* of order 2

$$\ddot{y}(t) = F(t) + \alpha u(t) \quad (5)$$

- $\alpha \in \mathbb{R}$ ,  $\alpha \neq 0$ , is a constant such that the three terms in

Eqn. (5) are of the same magnitude. Therefore  $\alpha$  does not need to be precisely determined.

- The *data-driven* quantity  $F$ , which subsumes not only the poorly known system structure but also any external perturbation, may be estimated via the measurements of  $u$  and  $y$ .

Introduce the *intelligent proportional-derivative* controller, or *iPD*,

$$u(t) = -\frac{F_{\text{est}}(t) - \dot{y}^*(t) + K_P e(t) + K_D \dot{e}(t)}{\alpha} \quad (6)$$

where

- $F_{\text{est}}(t)$  is an estimate of  $F$  (see Eqn. (7));
- $y^*(t)$  is a *reference* trajectory, and  $e(t) = y(t) - y^*(t)$  is the *tracking* error;
- $K_P, K_D \in \mathbb{R}$  are *tuning* gains.

Eqn. (5) and (6) yield  $\ddot{y}(t) + K_D \dot{e}(t) + K_P e(t) = F(t) - F_{\text{est}}(t)$ . Select  $K_P, K_D$  such that the real parts of the roots of the polynomial  $s^2 + K_D s + K_P$  are strictly negative. It ensures that  $\lim_{t \rightarrow +\infty} e(t) \approx 0$  if the estimate  $F_{\text{est}}$  is “good” i.e.,  $F(t) - F_{\text{est}}(t) \approx 0$ . Thus local stability around the reference trajectory is trivially ensured via this feedback loop. The following estimate of  $F$  in Eqn. (5) is borrowed from [12]:

$$F_{\text{est}}(t) = \frac{60}{\tau^5} \int_0^\tau (\tau^2 + 6\sigma^2 - 6\tau\sigma)y(t - \tau + \sigma)d\sigma - \frac{30\alpha}{\tau^5} \int_0^\tau (\tau - \sigma)^2 \sigma^2 u(t - \tau + \sigma)d\sigma \quad (7)$$

- It is a real-time estimate:  $\tau > 0$  is “small.”
- It is indeed data-driven: the numerical value of  $F_{\text{est}}$  results from the knowledge of the control and output variables  $u$  and  $y$ .
- It is a “low pass filter” thanks to the integrals in Formula (7): noise in the sense of [41] are removed.

1) *Riachy’s trick*: It permits [12] to avoid the calculation of the derivative  $\dot{e}$  in Eqn. (6). Rewrite (5) as  $\ddot{y}(t) + K_D \dot{y}(t) = F(t) + K_D \dot{y}(t) + \alpha u(t)$ . Set

$$Y(t) = y(t) + K_D \int_c^t y(\sigma)d\sigma, \quad 0 \leq c < t$$

It yields  $\ddot{Y}(t) = \ddot{y}(t) + K_D \dot{y}(t)$ . Set  $\mathcal{F}(t) = F(t) + K_D \dot{y}(t)$ . Eqn. (5) becomes  $\ddot{Y}(t) = \mathcal{F}(t) + \alpha u(t)$ . Eqn. (6) reads now

$$u(t) = -\frac{\mathcal{F}_{\text{est}}(t) - \dot{y}^*(t) + K_P e(t) + K_D \dot{y}^*(t)}{\alpha} \quad (8)$$

where the derivative of  $y$  and, therefore,  $e$  disappears. The estimate  $\mathcal{F}_{\text{est}}$  in Eqn. (8) may be computed via Formula (7) by replacing  $y$  by  $Y$ .

## B. Computer simulations

1) *Presentation*: The numerical values of the parameters in Eqn. (1) are taken from [36], [37]:  $C_1 = 135$ ,  $C_2 = 0.8C_1$ ,  $C_3 = 0.25C_1$ ,  $C_4 = 0.25C_1$ ,  $C_7 = C_2$ ,  $C_5 = 0.3C_1$ ,  $C_6 = 0.1C_1$ ,  $A = 3.25$ ,  $B = 22$ ,  $G = 20$ ,  $a = 100$ ,  $b = 30$ ,  $g = 350$ . Following again [36], [37], set

- $p = 200$ ,  $0 \leq t \leq 2s$ , for a regular behavior;
- $p = 800$ ,  $t > 2s$ , for an abnormal behavior.

Moreover,  $p$  is corrupted by an additive white Gaussian noise (mean: 0, standard deviation: 10).

The stimulation begins when the anomaly is detected. Several scenarios are now presented.

2) *Scenarios 1 and 2*: Assume that  $y_1(t)$  is available. Set  $y(t) = y_1(t)$  in Eqn. (5), where  $\alpha = 10^4$ .<sup>1</sup> Set  $K_P = 100$ ,  $K_D = 20$  in Eqn. (6).

In Scenario 1 (Fig. 4) a constant reference is perfectly tracked (Fig. 4-(b)) with very reasonable values of the stimulation:  $0 \leq u(t) \leq 15$  (Fig. 4-(c)). It is quite obvious to check that the very nature of the sigmoid function in Eqn. (1) prevents to track references of arbitrary magnitude. In Scenario 2 (Fig. 5) the reference trajectory is reproducing a crisis-free recording (Fig. 5-(b)). The tracking is again excellent.

3) *Scenario 3 – Several virtual patients*: Set in Scenario 3 (Figs. 6, 7, 8)  $y(t) = y_m(t)$ ,  $\alpha = -10^5$  in Eqn. (5), and  $K_P = 400$ ,  $K_D = 40$  in Eqn. (6). The following numerical variations on  $C_i$ ,  $i = 1, \dots, 7$  correspond to different virtual patients. Take  $0.9 \times C_i$  (resp.  $1.1 \times C_i$ ),  $i = 1, \dots, 7$ . Results are reported in Fig. 6 (resp. Fig. 7). See Fig. 8 for the results with the nominal values of  $C_i$ . Tracking is excellent in all three cases.

4) *Scenario 4 – Measurement noise*: Again  $y(t) = y_m(t)$ ,  $\alpha = -10^5$  in Eqn. (5), and  $K_P = 400$ ,  $K_D = 40$  in Eqn. (8). In Scenario 4 (Fig. 9) an additive white Gaussian noise has been added as a measurement noise (mean: 0, standard deviation: 0.5). Performances deteriorate only slightly with a chattering control variable.

## V. CONCLUSION

Our communication suggests that some recent control techniques, which were already most useful in industry, might also be helpful for implementing closed-loop neurostimulations for curing epileptiform seizures. Even if our results seem, to the best of our knowledge, to surpass the existing literature, there is still a lot of work to be done to go beyond virtual patients. Future publications will soon examine other topics in neuroscience, like Parkinson’s disease and brain plasticity.

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<sup>1</sup>This numerical value might seem huge to readers which are used to this model-free approach. It is easily explained here by looking at the second line of Eqn. (1) and computing the product  $AaC_2$  in front of the sigmoid function.

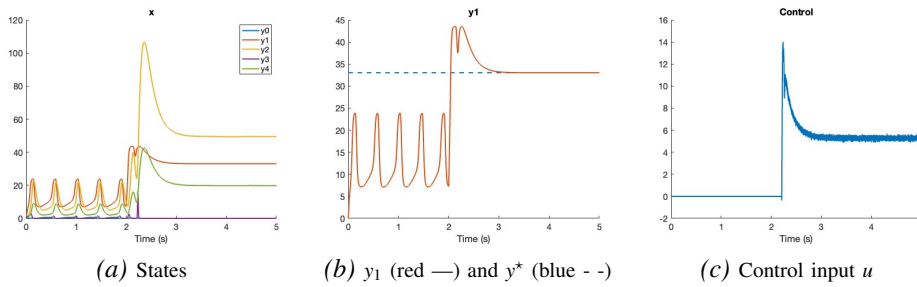


Fig. 4. Closed loop result: Scenario 1

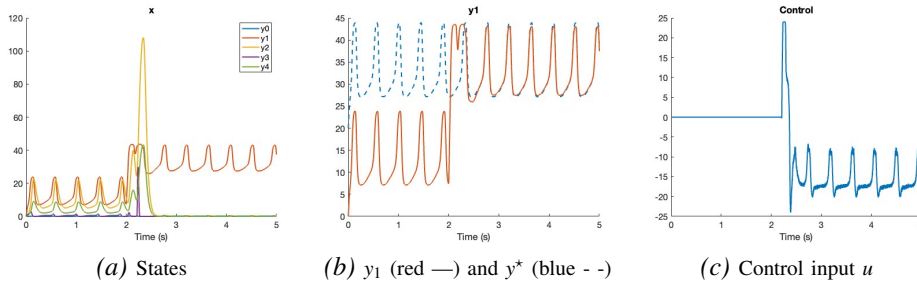


Fig. 5. Closed loop result: Scenario 2

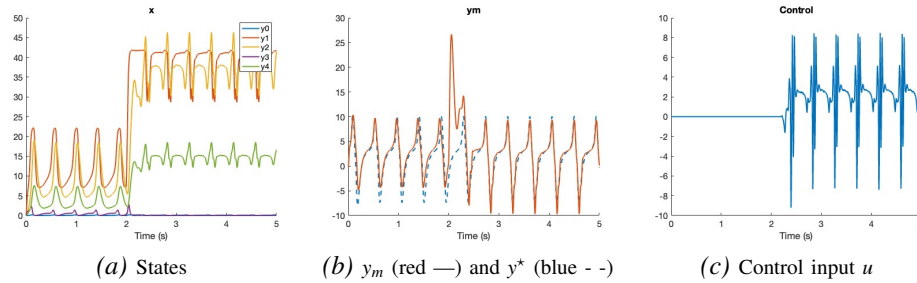


Fig. 6. Closed loop result: Scenario 3a

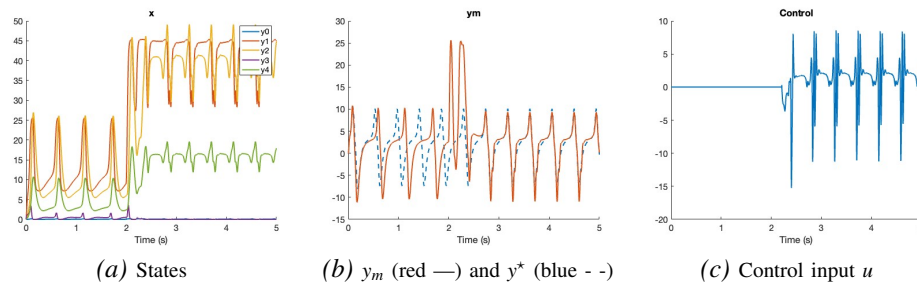


Fig. 7. Closed loop result: Scenario 3b

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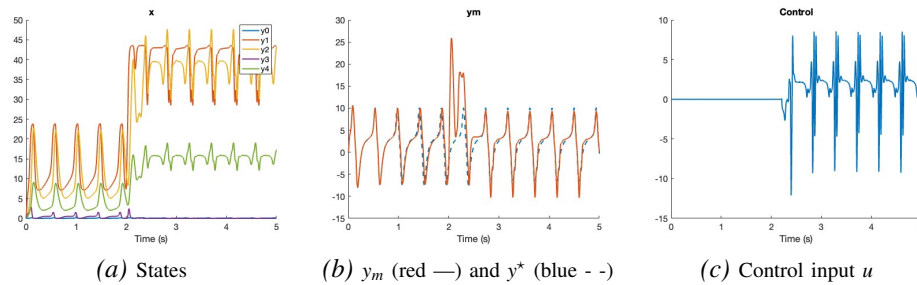


Fig. 8. Closed loop result: Scenario 3c

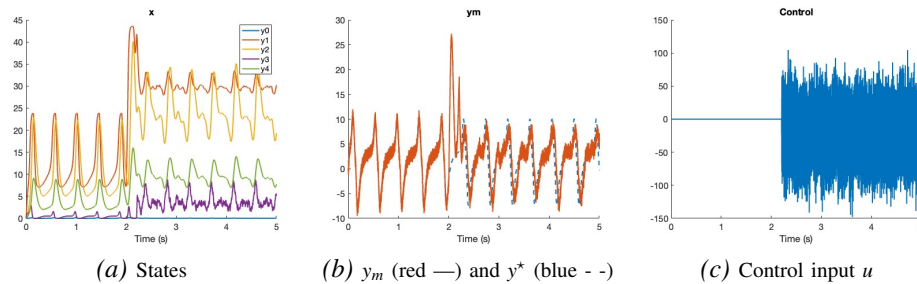


Fig. 9. Closed loop result: Scenario 4

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