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RESEARCH ARTICLE

Nonlinear optimal control for the synchronization of biological neurons under time-delays

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Abstract

The article proposes a nonlinear optimal control method for synchronization of neurons that exhibit nonlinear dynamics and are subject to time-delays. The model of the Hindmarsh–Rose (HR) neurons is used as a case study. The dynamic model of the coupled HR neurons undergoes approximate linearization around a temporary operating point which is recomputed at each iteration of the control method. The linearization procedure relies on Taylor series expansion of the model and on computation of the associated Jacobian matrices. For the approximately linearized model of the coupled HR neurons an H-infinity controller is designed. For the selection of the controller's feedback gain an algebraic Riccati equation is repetitively solved at each time-step of the control algorithm. The stability properties of the control loop are proven through Lyapunov analysis. First, it is shown that the H-infinity tracking performance criterion is satisfied. Moreover, it is proven that the control loop is globally asymptotically stable.

Keywords Biological neurons · Nonlinear optimal control · H-infinity control · Approximate linearization · Taylor series expansion · Jacobian matrices · Riccati equation · Lyapunov analysis · Global stability · Time-delays

Introduction

Synchronization of biological neurons is important for many functions of the human body and many medical treatments pursue to achieve artificially such a synchronization through the application of voltage excitation to neurons (Rigatos 2013; Nguyen and Hang 2013; Panchak et al. 2013; Ding and Han 2015). To this end, the article's results can be meaningful for biomedical applications such as the treatment of neuro-degenerative diseases. They can also help to gain an insight about the pacemaking properties of the nervous system, which in turn affect the functioning of several organs (Nakano and Saito 2004; Ruths et al. 2014; Rehan et al. 2011; Li et al. 2010; Che et al. 2009b). From the control theory point of view, the solution of the problem of synchronization of coupled biological neurons is a nontrivial one due to the nonlinearities of the associated state-space model (Li and Song 2014; Jiang et al. 2006). The problem becomes more complicated if time-delays affecting the model's state variables are also taken into account (Lakshmanan et al. 2017; Yang et al. 2010; Chang et al. 2006; Liu 2009). One can note several approaches on nonlinear control and synchronization of coupled biological neurons (Wan et al. 2017; Li et al. 2013; Wang and Shi 2013; Yu et al. 2012). Such results arrive usually at proving global stability properties for the externally excited biological neurons (Nguyen and Hang 2011; Yu and Peng 2006; Chen et al. 2013; Che et al. 2009a, 2010). Additional findings on control of coupled neural oscillators have shown feedback-induced synchronization (Wang et al. 2013; Kim and Lin 2013; Sun et al. 2012; Liu and Cao 2011). Besides, there exist results on synchronization of interacting neurons which consider

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partial knowledge of the state vector and the dynamic model of such systems (Liu et al. 2012, 2016; Wu et al. 2018). In the present article. the model of coupled Hindmarsh–Rose neurons under time-delays is considered and a nonlinear-optimal (H-infinity) control method is proposed for the neurons' synchronization (Rigatos et al. 2016; Rigatos and Tzafestas 2007; Basseville and Nikiforov 1993; Rigatos and Zhang 2009).

The dynamic model of the coupled HR neurons undergoes first approximate linearization around a temporary operating point (equilibrium) which is recomputed at each iteration of the control algorithm. The linearization point comprises the present value of the system's state vector and the last value of the control inputs vector that was applied to the system. The linearization procedure makes use of Taylor series expansion and of the computation of the associated Jacobian matrices (Rigatos et al. 2016; Rigatos and Tzafestas 2007; Basseville and Nikiforov 1993; Rigatos and Zhang 2009). The modelling error which is due to the truncation of higher order terms in the Taylor series is considered to be a perturbation which is compensated by the robustness of the control algorithm. For the approximately linearized model of the coupled HR neurons an optimal (H-infinity) feedback controller is designed (Rigatos 2011, 2015; Rigatos et al. 2017a).

The proposed H-infinity controller stands for a solution to the optimal control problem of the coupled HR neurons under model uncertainty and external perturbations. Actually, it represents the solution to a min-max differential game in which the control inputs try to minimize a quadratic cost function of the tracking error of the system's state vector, whereas the model uncertainty and the external disturbances try to maximize this cost function (Toussaint et al. 2000; Lublin and Athans 1995). For the computation of the H-infinity controller's feedback gain an algebraic Riccati equation is solved at each time-step of the control method. The stability properties of the control scheme are proven through Lyapunov analysis. First, it is demonstrated that the control loop satisfies the H-infinity tracking performance criterion, which signifies elevated robustness against model uncertainty and external perturbations. Moreover, it is proven that under moderate conditions the control loop is globally asymptotically stable. Finally, to implement state estimation-based feedback control for the model of the coupled HR neurons, the H-infinity Kalman Filter is proposed as a robust state estimator (Rigatos et al. 2017a).

The article has a novel and significant contribution to the control of biosystems, among which the coupled neural oscillators stands for a non-trivial case study. So far, the problem of nonlinear optimal control for coupled neural oscillators has not been sufficiently dealt with. Actually other methods attempting to solve this problem are not equally efficient to the method proposed by the submitted article. For instance Model Predictive Control (MPC) is primarily designed for linear dynamical systems and its application to the nonlinear model of the coupled neural oscillators is likely to result in loss of stability for the control loop. Moreover, Nonlinear Model Predictive Control (NMPC) relies its performance on initial parametrization and its iterative search for an optimum is not of assured convergence. Consequently, the stability properties of the NMPC control loop cannot be ensured either. On the other side the nonlinear optimal (H-infinity) control method which is proposed in the present article is of proven global asymptotic stability. The control method is genuine in several aspects: (i) unlike several results on nonlinear control of biosystems which depend on global linearization approaches, the new control method relies on approximate linearization of the state-space description of the system, (ii) it can be applied to any-type of biosystems and its use is not constrained to coupled neuron models which are in the affine-in-the-input state-space form, (iii) A new algebraic Riccati equation has to be solved at each time-step of the control method, so as to compute the control inputs, (iv) the global asymptotic stability properties of the control method are proven through a novel Lyapunov stability analysis, (v) Unlike global linearization-based control schemes, the proposed control method avoids singularity problems in the computation of the control inputs..

The structure of the manuscript is as follows: in "Dynamic model of the coupled Hindmarsh–Rose neurons" section the dynamic model of the coupled Hindmarsh–Rose neurons is introduced. In "Approximate linearization of the coupled HR neurons model" section approximate linearization is performed on the model of the coupled HR neurons after applying Taylor series expansion and through the computation of the associated Jacobian matrices. In "Design of an H-infinity nonlinear feedback controller" section the H-infinity control problem is formulated for the model of the coupled HR neurons. In "Lyapunov stability analysis" section the stability of the H-infinity control scheme is proven through Lyapunov analysis. In "Robust state estimation with the use of the H_∞ Kalman filter" section the H-infinity Kalman filter is used as a robust state estimator that allows for the implementation of state estimation-based control. In "Simulation tests" section the performance of the proposed nonlinear optimal control scheme is tested through simulation experiments. Finally, in "Conclusions" section concluding remarks are stated.

Dynamic model of the coupled Hindmarsh–Rose neurons

The dynamic model of the Hindmarsh–Rose neurons describes the variation of the voltage of the neurons' membrane as a result of various ion currents going through the membrane and also as a result of external currents applied to the membrane, as shown in Fig. 1 (Rigatos 2013). The dynamic model of the Hindmarsh–Rose neurons is given by Nguyen and Hang (2013) and Lakshmanan et al. (2017)

$$\begin{aligned} \dot{x}(t) &= y - \alpha x^3(t) + bx^2(t) - z(t) + I_{ext} \\ \dot{y}(t) &= c - dx^2(t) - y(t) \\ \dot{z}(t) &= r(s(x(t) - \bar{x})) - z(t) \end{aligned} \tag{1}$$

where x stands for the potential of the neuron's membrane, y is the recovery variable associated with the fast current of Na^+ and K^+ ions, and z is the adaptation current which is associated with the slow current that is generated by Ca^+ ions. By considering small time delays in the effect that state variable z has on state variable x, the dynamic model of the Hindmarsh–Rose neurons is given by Nguyen and Hang (2013) and Lakshmanan et al. (2017)

$$\begin{aligned} \dot{x}(t) &= y - \alpha x^3(t) + bx^2(t) - z(t-\tau) + I_{ext} \\ \dot{y}(t) &= c - dx^2(t) - y(t) \\ \dot{z}(t) &= r(s(x(t) - \bar{x})) - z(t) \end{aligned} \tag{2}$$

By considering also that the time delays are reasonably small the term $z(t-\tau)$ can be approximated by its first order Taylor series expansion, that is

$$\begin{aligned} z(t-\tau) &= z(t) - \tau\dot{z}(t) \Rightarrow \\ z(t-\tau) &= z(t) - \tau[r(s(x(t) - \bar{x})) - z(t)] \end{aligned} \tag{3}$$

In case of coupled HR neurons through a gap junction, and considering that an external control input u_i is applied on the first state-space equation, the associated dynamic model for the i-th HR neuron is given by

$$\begin{aligned} \dot{x}_i(t) &= y_i - \alpha x_i^3(t) + bx_i^2(t) - z_i(t-\tau_i) + I_{ext}^i \\ &\quad + \sum_{j=1,\ldots,N, j\neq i}^{N} p_i(x_i - x_j) + q_i u_i \\ \dot{y}_i(t) &= c - dx_i^2(t) - y_i(t) \\ \dot{z}_i(t) &= r(s(x_i(t) - \bar{x}_i)) - z_i(t) \end{aligned} \tag{4}$$

Without loss of generality a model of three coupled HR neurons is considered:

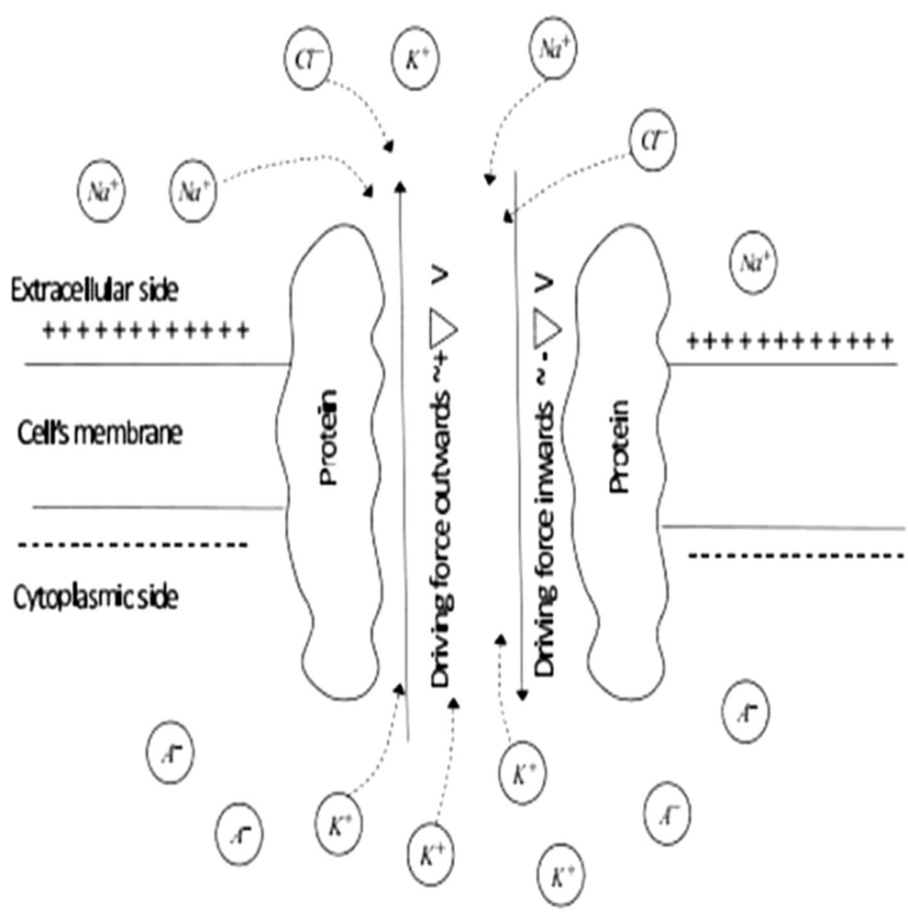

Fig. 1 Ionic currents at the neurons' membrane

$$\begin{aligned}\dot{x}_1 &= y_1 - \alpha_1 x_1^2 + b_1 x_1^2 - z_1 \\ &\quad + \tau_1[r_1 s_1(x_1 - \bar{x}_1) - z_1] \\ &\quad + I_{ext}^1 + p_{11}(x_1 - x_2) + p_{12}(x_1 - x_3) + q_1 u_1 \\ \dot{y}_1 &= c_1 - d_1 x_1^2 - y_1 \\ \dot{z}_1 &= r_1(s_1(x_1 - \bar{x}_1)) - z_1\end{aligned} \tag{5}$$

$$\begin{aligned}\dot{x}_2 &= y_2 - \alpha_2 x_2^2 + b_2 x_2^2 - z_2 + \tau_2[r_2 s_2(x_2 - \bar{x}_2) - z_2] \\ &\quad + I_{ext}^2 + p_{21}(x_2 - x_1) + p_{22}(x_2 - x_3) + q_2 u_2 \\ \dot{y}_2 &= c_2 - d_2 x_2^2 - y_2 \\ \dot{z}_2 &= r_2(s_2(x_2 - \bar{x}_2)) - z_2\end{aligned} \tag{6}$$

$$\begin{aligned}\dot{x}_3 &= y_3 - \alpha_3 x_3^2 + b_3 x_3^2 - z_3 + \tau_3[r_3 s_3(x_3 - \bar{x}_3) - z_3] \\ &\quad + I_{ext}^3 + p_{31}(x_3 - x_1) + p_{32}(x_3 - x_2) + q_3 u_3 \\ \dot{y}_3 &= c_3 - d_3 x_3^2 - y_3 \\ \dot{z}_3 &= r_3(s_3(x_3 - \bar{x}_3)) - z_3\end{aligned} \tag{7}$$

To obtain a unified state-space description for the system its state variables are redefined as follows: $x_1 = x_1$, $x_2 = y_1$, $x_3 = z_1$, $x_4 = x_2$, $x_5 = y_2$, $x_6 = z_2$, $x_7 = x_3$, $x_8 = y_3$, $x_9 = z_3$. The control inputs of the model are defined again as u_1, u_2 and u_3. Thus, the state-space description of the system becomes

$$\begin{pmatrix}\dot{x}_1\\ \dot{x}_2\\ \dot{x}_3\\ \dot{x}_4\\ \dot{x}_5\\ \dot{x}_6\\ \dot{x}_7\\ \dot{x}_8\\ \dot{x}_9\end{pmatrix} = \begin{pmatrix} x_2 - \alpha_1 x_1^3 + b_1 x_1^2 - x_3 + \tau_1[r_1 s_1(x_1 - \bar{x}_1) - x_3] \\ + I_{ext}^1 + p_{11}(x_1 - x_4) + p_{12}(x_1 - x_7) \\ c_1 - d_1 x_1^2 - x_2 \\ r_1(s_1(x_1 - \bar{x}_1)) - x_3 \\ x_5 - \alpha_2 x_4^3 + b_2 x_4^2 - x_6 + \tau_2[r_2 s_2(x_4 - \bar{x}_2) - x_6] \\ + I_{ext}^2 + p_{21}(x_4 - x_1) + p_{22}(x_4 - x_7) \\ c_2 - d_2 x_4^2 - x_5 \\ r_2(s_2(x_4 - \bar{x}_2)) - x_6 \\ x_8 - \alpha_3 x_7^3 + b_3 x_7^2 - x_9 + \tau_3[r_3 s_3(x_7 - \bar{x}_3) - x_9] \\ + I_{ext}^3 + p_{31}(x_7 - x_1) + p_{32}(x_7 - x_4) \\ c_3 - d_3 x_7^2 - x_8 \\ r_3(s_3(x_7 - \bar{x}_3)) - x_9 \end{pmatrix} + \begin{pmatrix} q_1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & q_2 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & q_3 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} u_1 \\ u_2 \\ u_3 \end{pmatrix} \tag{8}$$

In compact vector form, the model of the coupled HR neurons is written as

$$\dot{x} = f(x) + G(x)u \tag{9}$$

where $x \in R^{9\times1}$, $f(x) \in R^{9\times1}$, $G(x) \in R^{9\times3}$ and $u \in R^{3\times1}$, with

$$f(x) = \begin{pmatrix} f_1(x) \\ f_2(x) \\ f_3(x) \\ f_4(x) \\ f_5(x) \\ f_6(x) \\ f_7(x) \\ f_8(x) \\ f_9(x) \end{pmatrix} G(x) = \begin{pmatrix} q_1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & q_2 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & q_3 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \tag{10}$$

The elements of vector $f(x)$ are given by: $f_1(x) = x_2 - \alpha_1 x_1^3 + b_1 x_1^2 - x_3 + \tau_1[r_1 s_1(x_1 - \bar{x}_1) - x_3] + I_{ext}^1 + p_{11}(x_1 - x_4) + p_{12}(x_1 - x_7)$, $f_2(x) = c_1 - d_1 x_1^2 - x_2$, $f_3(x) = r_1(s_1(x_1 - \bar{x}_1)) - x_3$, $f_4(x) = x_5 - \alpha_2 x_4^3 + b_2 x_4^2 - x_6 + \tau_2[r_2 s_2(x_4 - \bar{x}_2) - x_6] + I_{ext}^2 + p_{21}(x_4 - x_1) + p_{22}(x_4 - x_7)$, $f_5(x) = c_2 - d_2 x_4^2 - x_5$, $f_6(x) = r_2(s_2(x_4 - \bar{x}_2)) - x_6$, $f_7(x) = x_8 - \alpha_3 x_7^3 + b_3 x_7^2 - x_9 + \tau_3[r_3 s_3(x_7 - \bar{x}_3) - x_9] + I_{ext}^4 + p_{31}(x_7 - x_1) + p_{32}(x_7 - x_4)$, $f_8(x) = c_3 - d_3 x_7^2 - x_8$ and $f_9(x) = r_3(s_3(x_7 - \bar{x}_3)) - x_9$.

Approximate linearization of the coupled HR neurons model

The dynamic model of the 3 coupled HR neurons that was defined in Eq. (8) undergoes approximate linearization around the temporary operating point (equilibrium), which is defined as (x^*, y^*), where x^* is the present value of the system's state vector and u^* is the last value of the control inputs vector that was applied on it. The linearization procedure makes use of first-order Taylor series expansion and of the computation of the associated Jacobian matrices, and results into the following state-space description

$$\dot{x} = Ax + Bu + \tilde{d} \tag{11}$$

where $\tilde{d}$ is the aggregate vector of disturbances, which are due to modelling errors induced by the approximate linearization procedure and the truncation of higher-order terms in the Taylor series expansion. Moreover, it may comprise external perturbation terms. Matrices A and B are given by

$$\begin{aligned} A &= \nabla_x[f(x) + G(x)u]\big|_{(x^*,u^*)} \Rightarrow A = \nabla_x[f(x)]\big|_{(x^*,u^*)} \\ B &= \nabla_u[f(x) + G(x)u]\big|_{(x^*,u^*)} \Rightarrow B = G(x)\big|_{(x^*,u^*)} \end{aligned} \tag{12}$$

About the Jacobian matrix $\nabla_x f(x)$ of the model of the coupled HR neurons one has:

$$\nabla_x f(x) = \begin{pmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \cdots & \frac{\partial f_1}{\partial x_9} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \cdots & \frac{\partial f_2}{\partial x_9} \\ \cdots & \cdots & \cdots & \cdots \\ \frac{\partial f_9}{\partial x_1} & \frac{\partial f_9}{\partial x_2} & \cdots & \frac{\partial f_9}{\partial x_9} \end{pmatrix} \tag{13}$$

The elements of the Jacobian matrix $\nabla_x f(x)$ are defined as follows:

About the first row of the Jacobian matrix $\nabla_x f(x)$ one has that: $\frac{\partial f_1(x)}{\partial x_1} = -3\alpha_1 x_1^2 + 2b_1 x_1 + \tau_1 r_1 s_1 + p_{11} + p_{12}$, $\frac{\partial f_1(x)}{\partial x_2} = 1$, $\frac{\partial f_1(x)}{\partial x_3} = -1 - \tau_1$, $\frac{\partial f_1(x)}{\partial x_4} = -p_{11}$, $\frac{\partial f_1(x)}{\partial x_5} = 0$, $\frac{\partial f_1(x)}{\partial x_6} = 0$, $\frac{\partial f_1(x)}{\partial x_7} = -p_{12}$, $\frac{\partial f_1(x)}{\partial x_8} = 0$, $\frac{\partial f_1(x)}{\partial x_9} = 0$.

About the second row of the Jacobian matrix $\nabla_x f(x)$ one has that: $\frac{\partial f_2(x)}{\partial x_1} = -2d_1 x_1$, $\frac{\partial f_2(x)}{\partial x_2} = -1$, $\frac{\partial f_2(x)}{\partial x_3} = 0$, $\frac{\partial f_2(x)}{\partial x_4} = 0$, $\frac{\partial f_2(x)}{\partial x_5} = 0$, $\frac{\partial f_2(x)}{\partial x_6} = 0$, $\frac{\partial f_2(x)}{\partial x_7} = 0$, $\frac{\partial f_2(x)}{\partial x_8} = 0$, $\frac{\partial f_2(x)}{\partial x_9} = 0$.

About the third row of the Jacobian matrix $\nabla_x f(x)$ one has that: $\frac{\partial f_3(x)}{\partial x_1} = r_1 s_1$, $\frac{\partial f_3(x)}{\partial x_2} = 0$, $\frac{\partial f_3(x)}{\partial x_3} = 1$, $\frac{\partial f_3(x)}{\partial x_4} = 0$, $\frac{\partial f_3(x)}{\partial x_4} = 0$, $\frac{\partial f_3(x)}{\partial x_5} = 0$, $\frac{\partial f_3(x)}{\partial x_6} = 0$, $\frac{\partial f_3(x)}{\partial x_7} = 0$, $\frac{\partial f_3(x)}{\partial x_8} = 0$, $\frac{\partial f_3(x)}{\partial x_9} = 0$.

About the fourth row of the Jacobian matrix $\nabla_x f(x)$ one has that: $\frac{\partial f_4(x)}{\partial x_1} = p_{11}$, $\frac{\partial f_4(x)}{\partial x_2} = 0$, $\frac{\partial f_4(x)}{\partial x_3} = 0$, $\frac{\partial f_4(x)}{\partial x_4} = -3\alpha_2 x_4^3 + 2b_2 x_4 + \tau_2 r_2 s_2 + p_{21} + p_{22}$, $\frac{\partial f_4(x)}{\partial x_5} = 1$, $\frac{\partial f_4(x)}{\partial x_6} = -1 - \tau_2$, $\frac{\partial f_4(x)}{\partial x_7} = -p_{22}$, $\frac{\partial f_4(x)}{\partial x_8} = 0$, $\frac{\partial f_4(x)}{\partial x_9} = p_{11}$.

About the fifth row of the Jacobian matrix $\nabla_x f(x)$ one has that: $\frac{\partial f_5(x)}{\partial x_1} = 0$, $\frac{\partial f_5(x)}{\partial x_2} = 0$, $\frac{\partial f_5(x)}{\partial x_3} = 0$, $\frac{\partial f_5(x)}{\partial x_4} = -2d_2 x_4$, $\frac{\partial f_5(x)}{\partial x_5} = -1$, $\frac{\partial f_5(x)}{\partial x_6} = 0$, $\frac{\partial f_5(x)}{\partial x_7} = 0$, $\frac{\partial f_5(x)}{\partial x_8} = 0$, $\frac{\partial f_5(x)}{\partial x_9} = 0$.

About the sixth row of the Jacobian matrix $\nabla_x f(x)$ one has that: $\frac{\partial f_6(x)}{\partial x_1} = 0$, $\frac{\partial f_6(x)}{\partial x_2} = 0$, $\frac{\partial f_6(x)}{\partial x_3} = 0$, $\frac{\partial f_6(x)}{\partial x_4} = r_2 s_2$, $\frac{\partial f_6(x)}{\partial x_5} = 0$, $\frac{\partial f_6(x)}{\partial x_6} = -1$, $\frac{\partial f_6(x)}{\partial x_7} = 0$, $\frac{\partial f_6(x)}{\partial x_8} = 0$, $\frac{\partial f_6(x)}{\partial x_9} = 0$.

About the seventh row of the Jacobian matrix $\nabla_x f(x)$ one has that: $\frac{\partial f_7(x)}{\partial x_1} = -p_{31}$, $\frac{\partial f_7(x)}{\partial x_2} = 0$, $\frac{\partial f_7(x)}{\partial x_3} = 0$, $\frac{\partial f_7(x)}{\partial x_4} = -p_{22}$, $\frac{\partial f_7(x)}{\partial x_5} = 0$, $\frac{\partial f_7(x)}{\partial x_6} = 0$, $\frac{\partial f_7(x)}{\partial x_7} = -3\alpha_3 x_7^2 + 2b_3 x_7 + \tau_3 r_3 s_3 + p_{31} + p_{32}$, $\frac{\partial f_7(x)}{\partial x_8} = 1$, $\frac{\partial f_7(x)}{\partial x_9} = -1 - \tau_3$.

About the eight row of the Jacobian matrix $\nabla_x f(x)$ one has that: $\frac{\partial f_8(x)}{\partial x_1} = 0$, $\frac{\partial f_8(x)}{\partial x_2} = 0$, $\frac{\partial f_8(x)}{\partial x_3} = 0$, $\frac{\partial f_8(x)}{\partial x_4} = 0$, $\frac{\partial f_8(x)}{\partial x_5} = 0$, $\frac{\partial f_8(x)}{\partial x_6} = 0$, $\frac{\partial f_8(x)}{\partial x_7} = -2d_3 x_7$, $\frac{\partial f_8(x)}{\partial x_8} = -1$, $\frac{\partial f_8(x)}{\partial x_9} = 0$.

About the ninth row of the Jacobian matrix $\nabla_x f(x)$ one has that: $\frac{\partial f_9(x)}{\partial x_1} = 0$, $\frac{\partial f_9(x)}{\partial x_2} = 0$, $\frac{\partial f_9(x)}{\partial x_3} = 0$, $\frac{\partial f_9(x)}{\partial x_4} = 0$, $\frac{\partial f_9(x)}{\partial x_5} = 0$, $\frac{\partial f_9(x)}{\partial x_6} = 0$, $\frac{\partial f_9(x)}{\partial x_7} = r_3 s_3$, $\frac{\partial f_9(x)}{\partial x_8} = 0$, $\frac{\partial f_9(x)}{\partial x_9} = -1$.

Design of an H-infinity nonlinear feedback controller

Equivalent linearized dynamics of the coupled HR neurons model

After linearization around its current operating point, the coupled HR neurons' model is written as

$$\dot{x} = Ax + Bu + d_1 \tag{14}$$

where matrices A and B are given by

$$A = \nabla_x[f(x) + g(x)u] \\ B = \nabla_u[f(x) + g(x)u] \tag{15}$$

Parameter d_1 stands for the linearization error in the coupled HR neurons' model appearing in Eq. (14). The reference setpoints for the coupled HR neurons' model are denoted by $\mathbf{x_d} = [x_1^d, x_2^d, x_3^d, \cdots, x_9^d]$. Tracking of this trajectory is achieved after applying the control input u^*. At every time instant the control input u^* is assumed to differ from the control input u appearing in Eq. (14) by an amount equal to Δu, that is $u^* = u + \Delta u$

$$\dot{x}_d = Ax_d + Bu^* + d_2 \tag{16}$$

The dynamics of the controlled system described in Eq. (14) can be also written as

$$\dot{x} = Ax + Bu + Bu^* - Bu^* + d_1 \tag{17}$$

and by denoting $d_3 = -Bu^* + d_1$ as an aggregate disturbance term one obtains

$$\dot{x} = Ax + Bu + Bu^* + d_3 \tag{18}$$

By subtracting Eq. (16) from Eq. (18) one has

$$\dot{x} - \dot{x}_d = A(x - x_d) + Bu + d_3 - d_2 \tag{19}$$

By denoting the tracking error as $e = x - x_d$ and the aggregate disturbance term as $\tilde{d} = d_3 - d_2$, the tracking error dynamics becomes

$$\dot{e} = Ae + Bu + \tilde{d} \tag{20}$$

The above linearized form of the coupled HR neurons' model can be efficiently controlled after applying an H-infinity feedback control scheme.

The nonlinear H-infinity control

The initial nonlinear description of the coupled HR neurons' model is in the form

$$\dot{x} = f(x, u) \quad x \in R^n, \quad u \in R^m \tag{21}$$

Linearization of the coupled HR neurons' model, is performed at each iteration of the control algorithm round its present operating point $(x^*, u^*) = (x(t), u(t - T_s))$. The linearized equivalent of the system is described by

$$\dot{x} = Ax + Bu + L\tilde{d} \quad x \in R^n, \quad u \in R^m, \quad \tilde{d} \in R^q \tag{22}$$

where matrices A and B are obtained from the computation of the system's Jacobians and vector $\tilde{d}$ denotes disturbance terms due to linearization errors. The problem of disturbance rejection for the linearized model that is described by

$$\begin{aligned} \dot{x} &= Ax + Bu + L\tilde{d} \\ y &= Cx \end{aligned} \tag{23}$$

where $x \in R^n$, $u \in R^m$, $\tilde{d} \in R^q$ and $y \in R^p$, cannot be handled efficiently if the classical LQR control scheme is applied. This is because of the existence of the perturbation term $\tilde{d}$. The disturbance term $\tilde{d}$ apart from modeling (parametric) uncertainty and external perturbation terms can also represent noise terms of any distribution.

In the H_∞ control approach, a feedback control scheme is designed for setpoint tracking by the system's state vector and simultaneous disturbance rejection, considering that the disturbance affects the system in the worst possible manner. The disturbances' effects are incorporated in the following quadratic cost function:

$$\begin{aligned} J(t) = \frac{1}{2}\int_0^T &[y^T(t)y(t) + ru^T(t)u(t) \\ &- \rho^2\tilde{d}^T(t)\tilde{d}(t)]dt, \quad r, \rho > 0 \end{aligned} \tag{24}$$

The significance of the negative sign in the cost function's term that is associated with the perturbation variable $\tilde{d}(t)$ is that the disturbance tries to maximize the cost function $J(t)$ while the control signal $u(t)$ tries to minimize it. The physical meaning of the relation given above is that the control signal and the disturbances compete to each other within a min-max differential game. This problem of min-max optimization can be written as $min_u max_{\tilde{d}} J(u, \tilde{d})$.

Computation of the feedback control gains

For the linearized system given by Eq. (23) the cost function of Eq. (24) is defined, where the coefficient r determines the penalization of the control input and the weight coefficient ρ determines the reward of the disturbances' effects. It is assumed that (i) The energy that is transferred from the disturbances signal $\tilde{d}(t)$ is bounded, that is $\int_0^\infty \tilde{d}^T(t)\tilde{d}(t)dt < \infty$, (ii) matrices [$A$, B] and [A, L] are stabilizable, (iii) matrix [A, C] is detectable. Then, the optimal feedback control law is given by

$$u(t) = -Kx(t) \tag{25}$$

with $K = \frac{1}{r}B^T P$, where P is a positive semi-definite symmetric matrix which is obtained from the solution of the Riccati equation

$$A^T P + PA + Q - P\left(\frac{1}{r}BB^T - \frac{1}{2\rho^2}LL^T\right)P = 0 \tag{26}$$

where Q is also a positive definite symmetric matrix. The worst case disturbance is given by $\tilde{d}(t) = \frac{1}{\rho^2}L^T Px(t)$. The diagram of the considered control loop is depicted in Fig. 2.

The parameter ρ in Eq. (24), is an indication of the closed-loop system robustness. If the values of $\rho > 0$ are excessively decreased with respect to r, then the solution of the Riccati equation is no longer a positive definite matrix. Consequently there is a lower bound ρ_{min} of ρ for which the H_∞ control problem has a solution. The acceptable values of ρ lie in the interval $[\rho_{min}, \infty)$. If ρ_{min} is found and used in the design of the H_∞ controller, then the closed-loop system will have increased robustness. Unlike this, if a value $\rho > \rho_{min}$ is used, then an admissible stabilizing H_∞ controller will be derived but it will be a suboptimal one (Rigatos 2011).

Lyapunov stability analysis

Through Lyapunov stability analysis it will be shown that the proposed nonlinear control scheme assures H_∞ tracking performance for the coupled HR neurons' model, and that asymptotic convergence to the reference setpoints is achieved.

The tracking error dynamics for the coupled HR neurons' model is written in the form

$$\dot{e} = Ae + Bu + L\tilde{d} \tag{27}$$

where in the coupled HR neurons' case $L = I \in R^9$ with I being the identity matrix. Variable $\tilde{d}$ denotes model uncertainties and external disturbances of the coupled HR neurons' model. The following Lyapunov equation is considered

$$V = \frac{1}{2}e^T Pe \tag{28}$$

where $e = x - x_d$ is the tracking error. By differentiating with respect to time one obtains

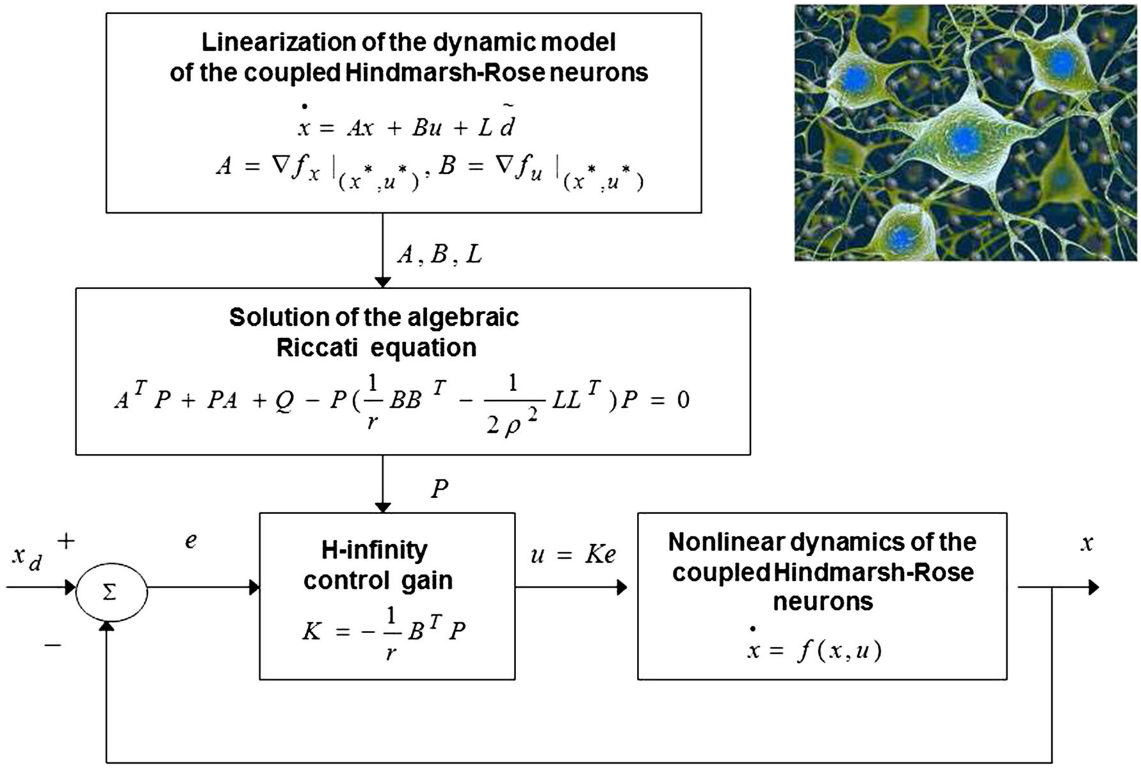

Fig. 2 Diagram of the control scheme for the coupled Hindmarsh–Rose neurons model

$$\dot{V} = \frac{1}{2}\dot{e}^T Pe + \frac{1}{2}eP\dot{e} \Rightarrow$$
$$\dot{V} = \frac{1}{2}[Ae + Bu + L\tilde{d}]^T Pe + \frac{1}{2}e^T P[Ae + Bu + L\tilde{d}] \Rightarrow \tag{29}$$

$$\begin{aligned}\dot{V} = &\frac{1}{2}[e^T A^T + u^T B^T + \tilde{d}^T L^T]Pe \\ &+ \frac{1}{2}e^T P[Ae + Bu + L\tilde{d}] \Rightarrow\end{aligned} \tag{30}$$

$$\begin{aligned}\dot{V} = &\frac{1}{2}e^T A^T Pe + \frac{1}{2}u^T B^T Pe + \frac{1}{2}\tilde{d}^T L^T Pe \\ &+ \frac{1}{2}e^T PAe + \frac{1}{2}e^T PBu + \frac{1}{2}e^T PL\tilde{d}\end{aligned} \tag{31}$$

The previous equation is rewritten as

$$\begin{aligned}\dot{V} = &\frac{1}{2}e^T(A^T P + PA)e + (\frac{1}{2}u^T B^T Pe + \frac{1}{2}e^T PBu) \\ &+ \left(\frac{1}{2}\tilde{d}^T L^T Pe + \frac{1}{2}e^T PL\tilde{d}\right)\end{aligned} \tag{32}$$

Assumption For given positive definite matrix Q and coefficients r and ρ there exists a positive definite matrix P, which is the solution of the following matrix equation

$$A^T P + PA = -Q + P(\frac{2}{r}BB^T - \frac{1}{\rho^2}LL^T)P \tag{33}$$

Moreover, the following feedback control law is applied to the system

$$u = -\frac{1}{r}B^T Pe \tag{34}$$

By substituting Eqs. (33) and (34) one obtains

$$\begin{aligned}\dot{V} = &\frac{1}{2}e^T\left[-Q + P\left(\frac{2}{r}BB^T - \frac{1}{\rho^2}LL^T\right)P\right]e \\ &+ e^T PB\left(-\frac{1}{r}B^T Pe\right) + e^T PL\tilde{d} \Rightarrow\end{aligned} \tag{35}$$

$$\begin{aligned}\dot{V} = &-\frac{1}{2}e^T Qe + \frac{1}{r}PBB^T Pe - \frac{1}{2\rho^2}e^T PLL^T Pe \\ &-\frac{1}{r}e^T PBB^T Pe) + e^T PL\tilde{d}\end{aligned} \tag{36}$$

which after intermediate operations gives

$$\dot{V} = -\frac{1}{2}e^T Qe - \frac{1}{2\rho^2}e^T PLL^T Pe + e^T PL\tilde{d} \tag{37}$$

or, equivalently

$$\begin{aligned}\dot{V} = &-\frac{1}{2}e^T Qe - \frac{1}{2\rho^2}e^T PLL^T Pe \\ &+\frac{1}{2}e^T PL\tilde{d} + \frac{1}{2}\tilde{d}^T L^T Pe\end{aligned} \tag{38}$$

Lemma 1 *The following inequality holds*

$$\frac{1}{2}e^T PL\tilde{d} + \frac{1}{2}\tilde{d}L^T Pe - \frac{1}{2\rho^2}e^T PLL^T Pe \leq \frac{1}{2}\rho^2\tilde{d}^T\tilde{d} \quad (39)$$

Proof The binomial $(\rho\alpha - \frac{1}{\rho}b)^2$ is considered. Expanding the left part of the above inequality one gets

$$\rho^2 a^2 + \frac{1}{\rho^2}b^2 - 2ab \geq 0 \Rightarrow \frac{1}{2}\rho^2 a^2 + \frac{1}{2\rho^2}b^2 - ab \geq 0 \Rightarrow$$
$$ab - \frac{1}{2\rho^2}b^2 \leq \frac{1}{2}\rho^2 a^2 \Rightarrow \frac{1}{2}ab + \frac{1}{2}ab - \frac{1}{2\rho^2}b^2 \leq \frac{1}{2}\rho^2 a^2 \quad (40)$$

The following substitutions are carried out: $a = \tilde{d}$ and $b = e^T PL$ and the previous relation becomes

$$\frac{1}{2}\tilde{d}^T L^T Pe + \frac{1}{2}e^T PL\tilde{d} - \frac{1}{2\rho^2}e^T PLL^T Pe \leq \frac{1}{2}\rho^2\tilde{d}^T\tilde{d} \quad (41)$$

Equation (41) is substituted in Eq. (38) and the inequality is enforced, thus giving

$$\dot{V} \leq -\frac{1}{2}e^T Qe + \frac{1}{2}\rho^2\tilde{d}^T\tilde{d} \quad (42)$$

Equation (42) shows that the H_∞ tracking performance criterion is satisfied. The integration of $\dot{V}$ from 0 to T gives

$$\int_0^T \dot{V}(t)dt \leq -\frac{1}{2}\int_0^T ||e||_Q^2 dt + \frac{1}{2}\rho^2\int_0^T ||\tilde{d}||^2 dt \Rightarrow$$
$$2V(T) + \int_0^T ||e||_Q^2 dt \leq 2V(0) + \rho^2\int_0^T ||\tilde{d}||^2 dt \quad (43)$$

Moreover, if there exists a positive constant $M_d > 0$ such that

$$\int_0^\infty ||\tilde{d}||^2 dt \leq M_d \quad (44)$$

then one gets

$$\int_0^\infty ||e||_Q^2 dt \leq 2V(0) + \rho^2 M_d \quad (45)$$

Thus, the integral $\int_0^\infty ||e||_Q^2 dt$ is bounded. Moreover, *V*(*T*) is bounded and from the definition of the Lyapunov function *V* in Eq. (28) it becomes clear that *e*(*t*) will be also bounded since $e(t) \in \Omega_e = \{e|e^T Pe \leq 2V(0) + \rho^2 M_d\}$. According to the above and with the use of Barbalat's Lemma one obtains $lim_{t\to\infty} e(t) = 0$.

Elaborating on the above, it can be noted that the proof of global asymptotic stability for the control loop of the coupled HR neurons' model is based on Eq. (42) and on the application of Barbalat's Lemma. It uses the condition of Eq. (44) about the boundedness of the square of the aggregate disturbance and modelling error term $\tilde{d}$ that affects the model. However, as explained above, the proof of global asymptotic stability is not restricted by this condition. By selecting the attenuation coefficient ρ to be sufficiently small and in particular to satisfy $\rho^2 < ||e||_Q^2/||\tilde{d}||^2$ one has that the first derivative of the Lyapunov function is upper bounded by 0. Therefore for the i-th time interval it is proven that the Lyapunov function defined in Eq (28) is a decreasing one. This also assures the Lyapunov function of the system defined in Eq. (28) will always have a negative first-order derivative.

Robust state estimation with the use of the H_∞ Kalman filter

The control loop has to be implemented with the use of information provided by processing only a small number of state variables, such as x_1, x_4 and x_7 describing the voltage of the individual neurons' membrane. To reconstruct the missing information about the state vector of the coupled HR neurons' model, it is proposed to use a filtering scheme and based on it to apply state estimation-based control (Rigatos et al. 2017a). The recursion of the H_∞ Kalman Filter, for the cells signaling pathway model, can be formulated in terms of a *measurement update* and a *time update* part

Measurement update

$$D(k) = [I - \theta W(k)P^-(k) + C^T(k)R(k)^{-1}C(k)P^-(k)]^{-1}$$
$$K(k) = P^-(k)D(k)C^T(k)R(k)^{-1}$$
$$\hat{x}(k) = \hat{x}^-(k) + K(k)[y(k) - C\hat{x}^-(k)] \quad (46)$$

Time update

$$\hat{x}^-(k+1) = A(k)x(k) + B(k)u(k)$$
$$P^-(k+1) = A(k)P^-(k)D(k)A^T(k) + Q(k) \quad (47)$$

where it is assumed that parameter θ is sufficiently small to assure that the covariance matrix $P^-(k)^{-1} - \theta W(k) + C^T(k)R(k)^{-1}C(k)$ will be positive definite. When $\theta = 0$ the H_∞ Kalman Filter becomes equivalent to the standard Kalman Filter. As noted above, measurements can be obtained only about the voltage of the individual neurons' membrane in the coupled HR neurons' model, while the rest of the state variables can be estimated through filtering.

Simulation tests

The performance of the proposed nonlinear optimal (H-infinity) control scheme is tested through simulation experiments. It is shown that under the proposed control

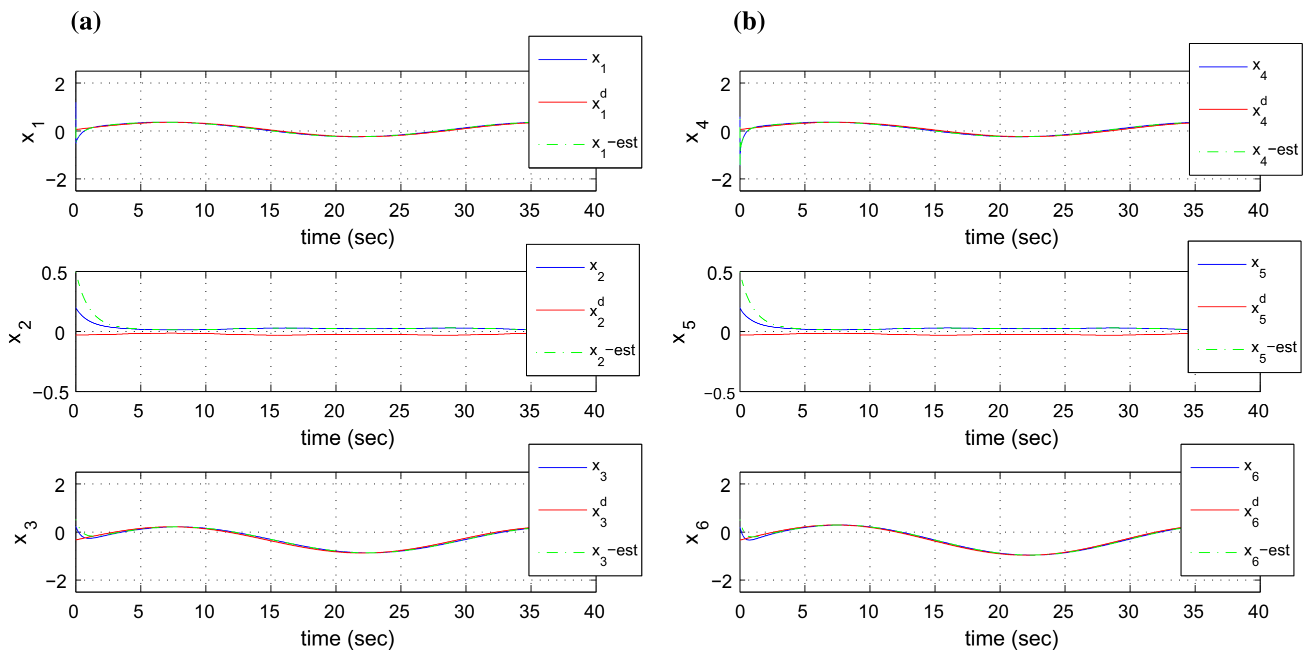

Fig. 3 Test 1 for the synchronization of the coupled Hindmarsh–Rose neurons: **a** convergence of state variables x_1 to x_3 (1st neuron) to the reference setpoints: **b** convergence of state variables x_4 to x_6 (2nd neuron) to the reference setpoints

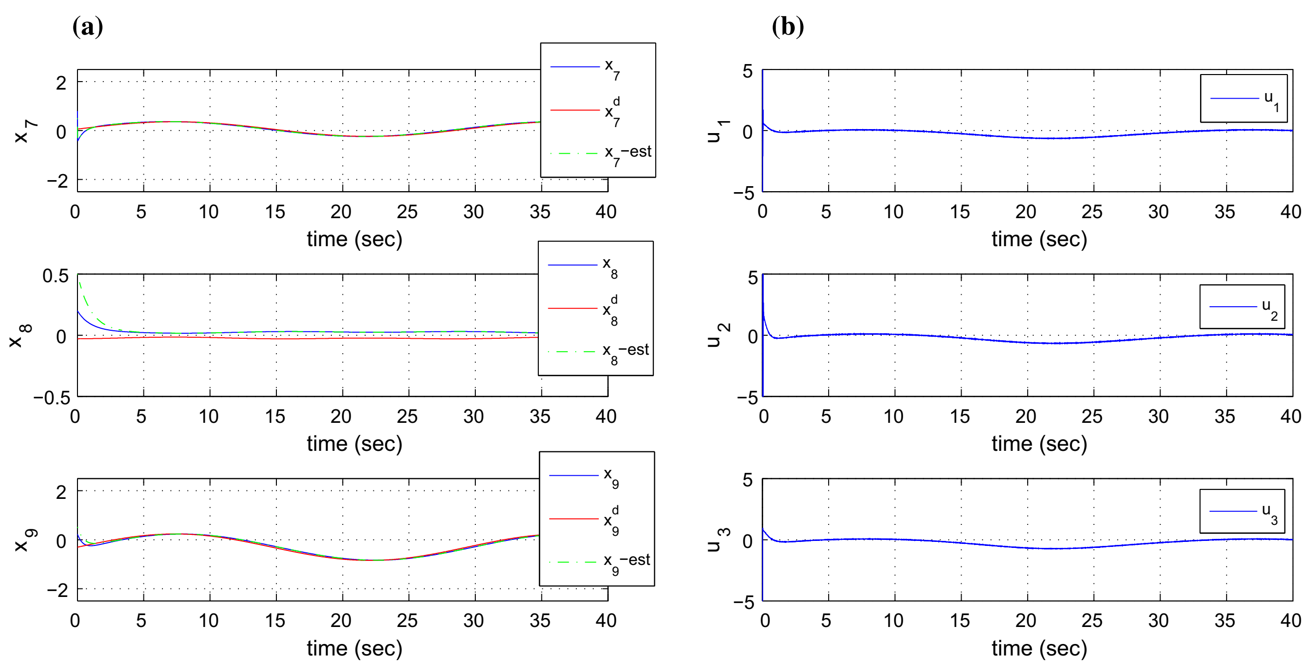

Fig. 4 Test 1 for the synchronization of the coupled Hindmarsh–Rose neurons: **a** convergence of state variables x_7 to x_9 (3rd neuron) to the reference setpoints: **b** variation of control inputs u_1 to u_3

method, synchronization is achieved between the individual HR neurons. The parameters of the neurons' dynamic model and the associated time delay terms were taken to be different for each neuron. The obtained results are depicted in Figs. 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12. For the computation of the controller's feedback gain the algebraic Riccati equation appearing in Eq. (33) had to be repetitively solved at each time-step of the control method. It can be observed that fast and accurate tracking of the reference setpoints is achieved, while the system's control inputs exhibit smooth and moderate variations.

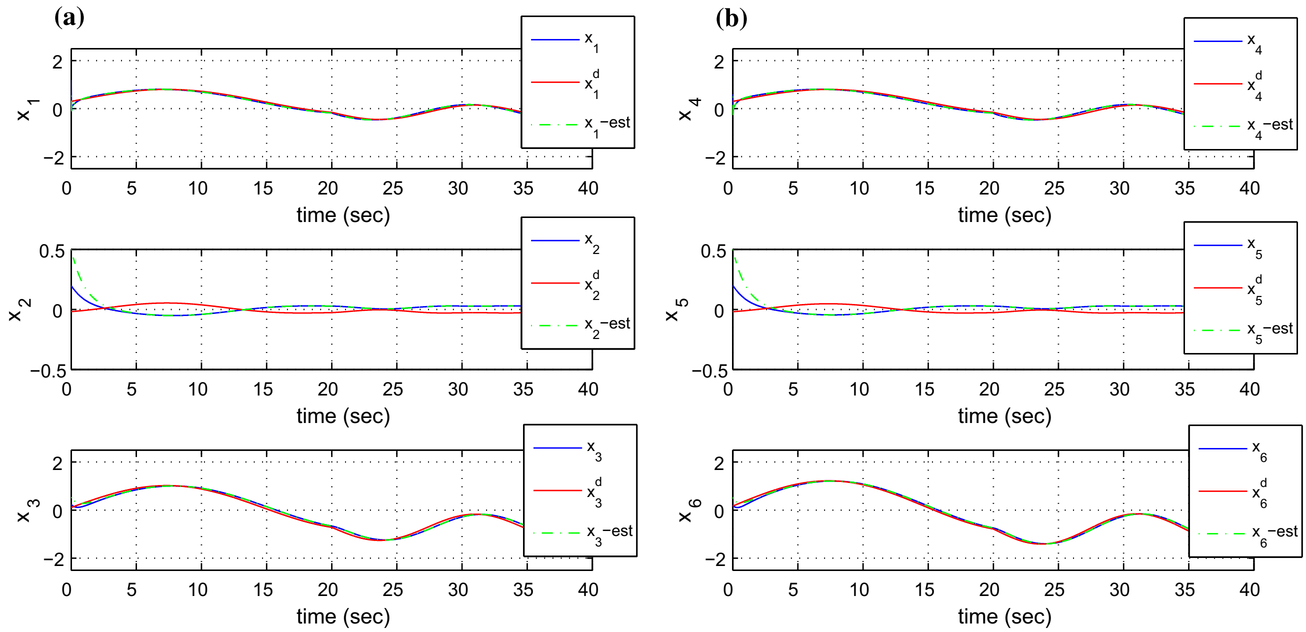

Fig. 5 Test 2 for the synchronization of the coupled Hindmarsh–Rose neurons: **a** convergence of state variables x_1 to x_3 (1st neuron) to the reference setpoints: **b** convergence of state variables x_4 to x_6 (2nd neuron) to the reference setpoints

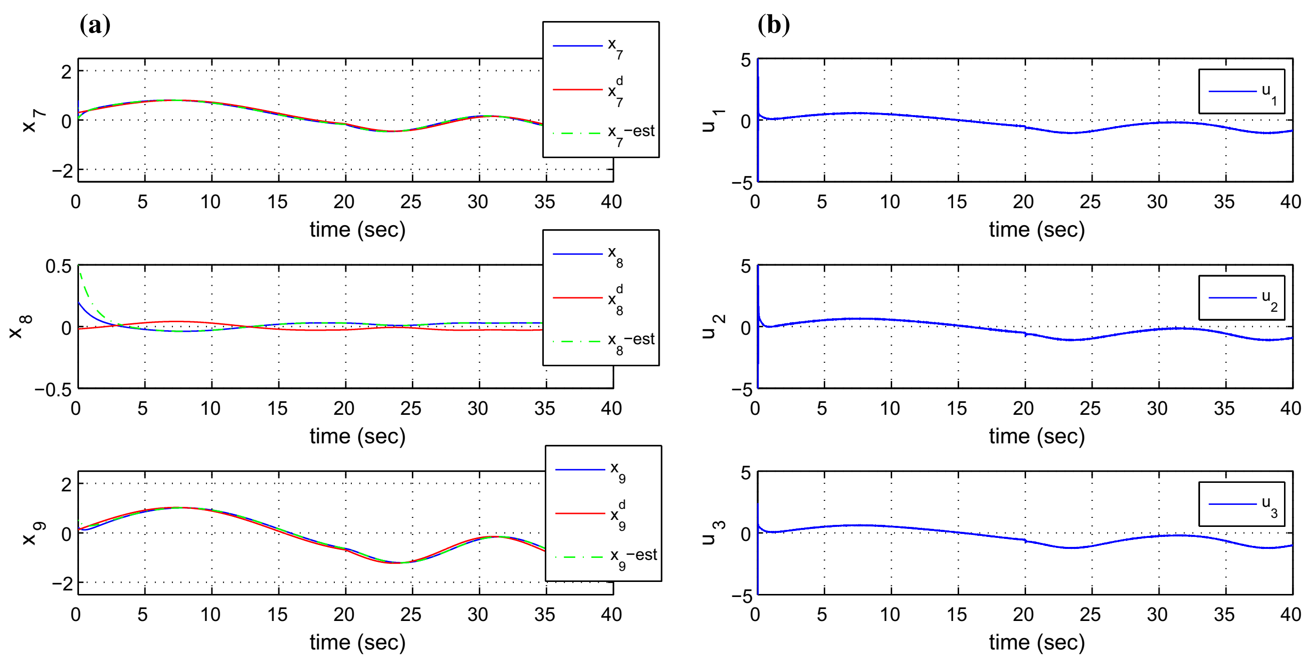

Fig. 6 Test 2 for the synchronization of the coupled Hindmarsh–Rose neurons: **a** convergence of state variables x_7 to x_9 (3rd neuron) to the reference setpoints: **b** variation of control inputs u_1 to u_3

For the implementation of state estimation-based control for the model of the coupled HR neurons, the H-infinity Kalman Filter has been used as a robust state estimator. The measured outputs where taken to be voltages of the neurons' membranes, as denoted by state variables x_1, x_4 and x_7. In the obtained results the real values of the state variables are printed in blue, the estimated variables are printed in green, whereas the reference setpoints are printed in red. Taking into account that in this specific biosystem it is impossible to measure its entire state vector, the significance of the use of the H-infinity Kalman Filter becomes clear.

Despite its computational simplicity, the proposed nonlinear optimal (H-infinity) control method performs

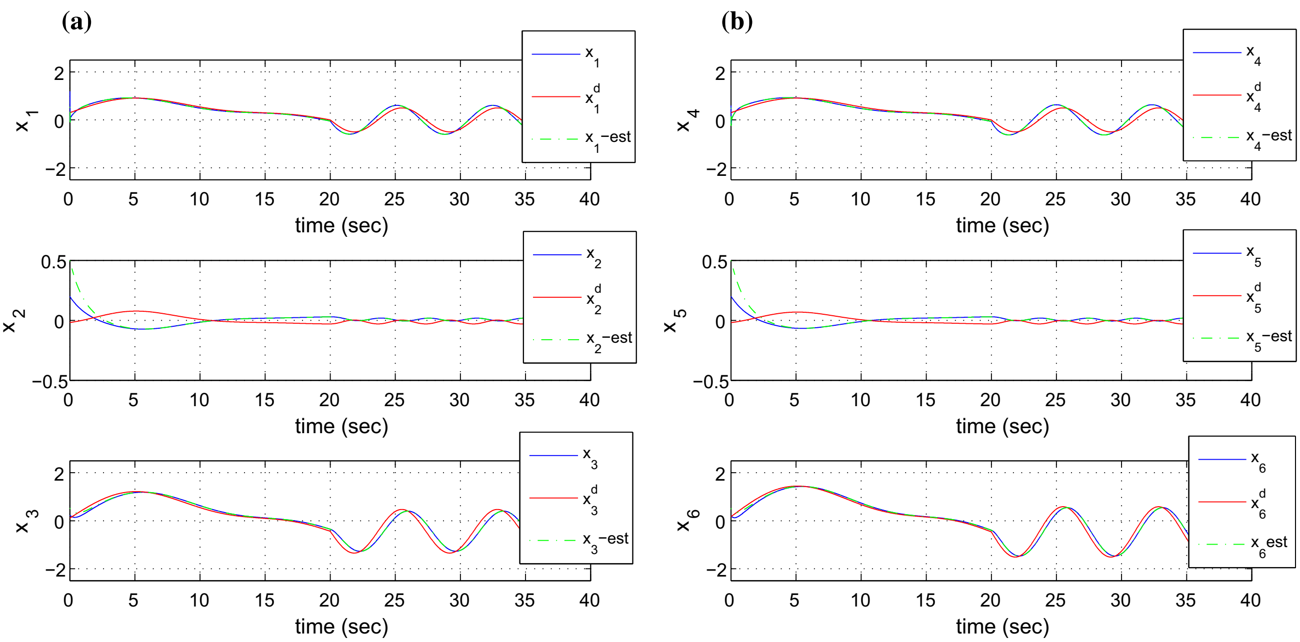

Fig. 7 Test 3 for the synchronization of the coupled Hindmarsh–Rose neurons: **a** convergence of state variables x_1 to x_3 (1st neuron) to the reference setpoints: **b** convergence of state variables x_4 to x_6 (2nd neuron) to the reference setpoints

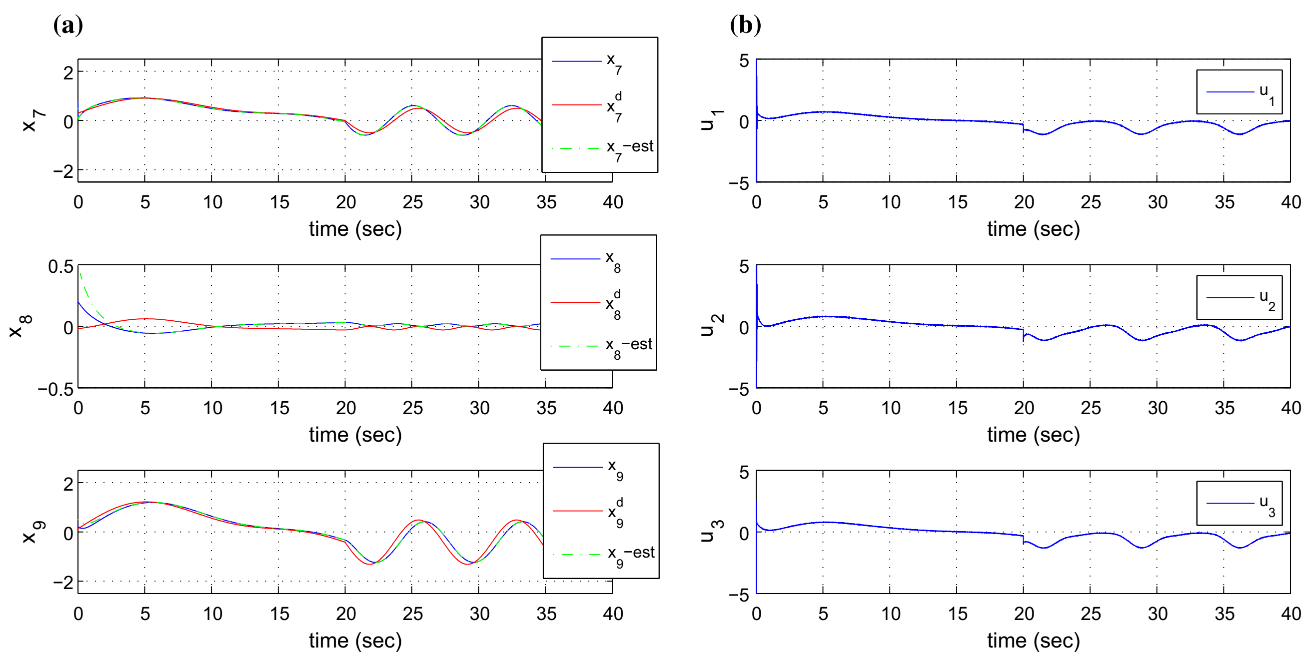

Fig. 8 Test 3 for the synchronization of the coupled Hindmarsh–Rose neurons: **a** convergence of state variables x_7 to x_9 (3rd neuron) to the reference setpoints: **b** variation of control inputs u_1 to u_3

equally well to global linearization-based control schemes. The advantages of the considered control method are outlined as follows: (1) it does not require the elaborated state variables transformations (diffeomorphisms) which are necessary in global linearization-based control approaches, (2) it is applied directly on the initial nonlinear dynamic model of the coupled HR neurons and not on its linearized equivalent representation. Thus, unlike global linearization-based control approaches the nonlinear H-infinity control method avoids inverse transformations and the associated singularity problems, (3) the proposed control method retains the merits of linear optimal control, that is fast and accurate tracking of the reference setpoints under moderate variations of the control inputs.

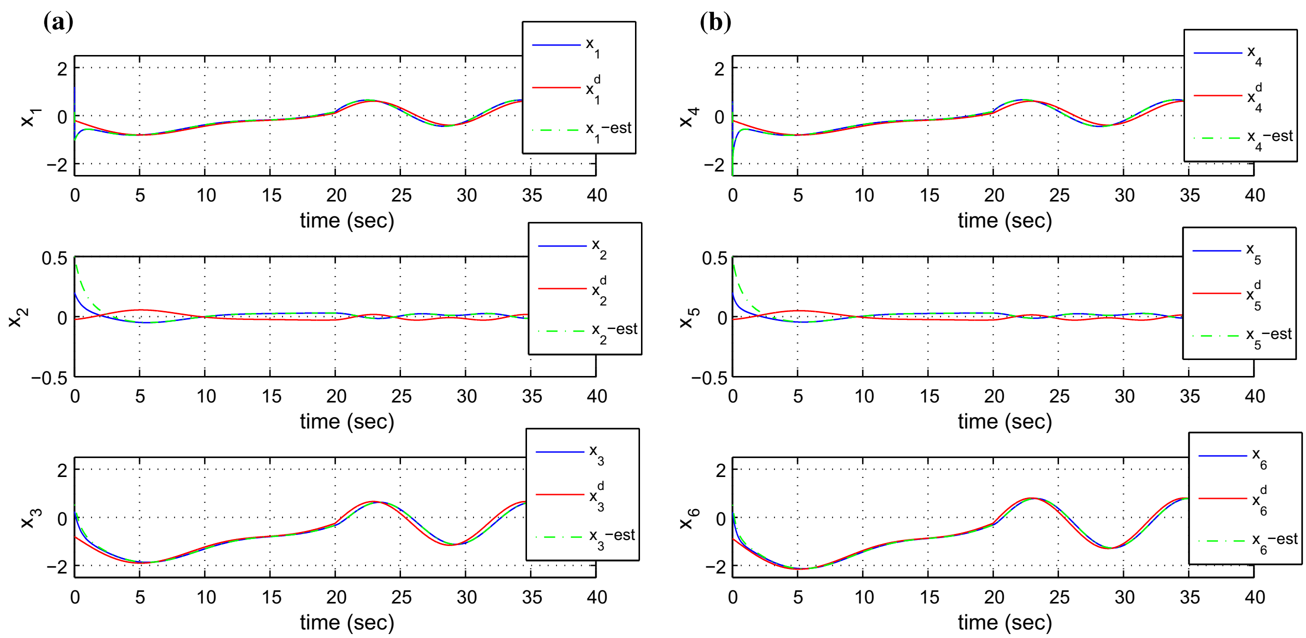

Fig. 9 Test 4 for the synchronization of the coupled Hindmarsh–Rose neurons: **a** convergence of state variables x_1 to x_3 (1st neuron) to the reference setpoints: **b** convergence of state variables x_4 to x_6 (2nd neuron) to the reference setpoints

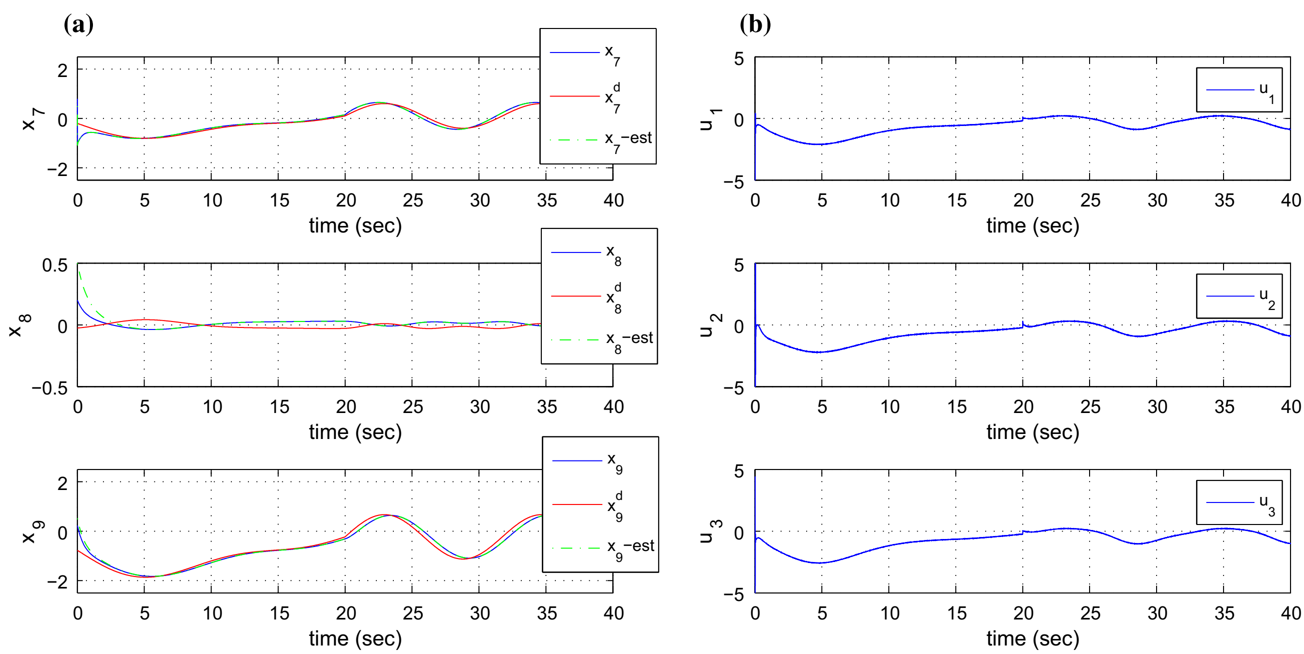

Fig. 10 Test 4 for the synchronization of the coupled Hindmarsh–Rose neurons: **a** convergence of state variables x_7 to x_9 (3rd neuron) to the reference setpoints: **b** variation of control inputs u_1 to u_3

Remark 1 The proposed optimal (H-infinity) control method for the model of the coupled neural oscillators performs real-time optimization in two directions: (1) minimization of the tracking error of the state variables of the model of the coupled Hindmarsh–Rose neurons with respect to the related reference setpoints, (2) minimization of the variation of the control inputs, thus ensuring that convergence to the reference setpoints is achieved under minimal energy dissipation. As noted, the proposed H-infinity control method for the dynamic model of the coupled Hindmarsh–Rose neurons stands for the solution of the related optimal control problem under model uncertainty and external perturbations. Actually, it represents a min-max differential game that takes place between (1) the

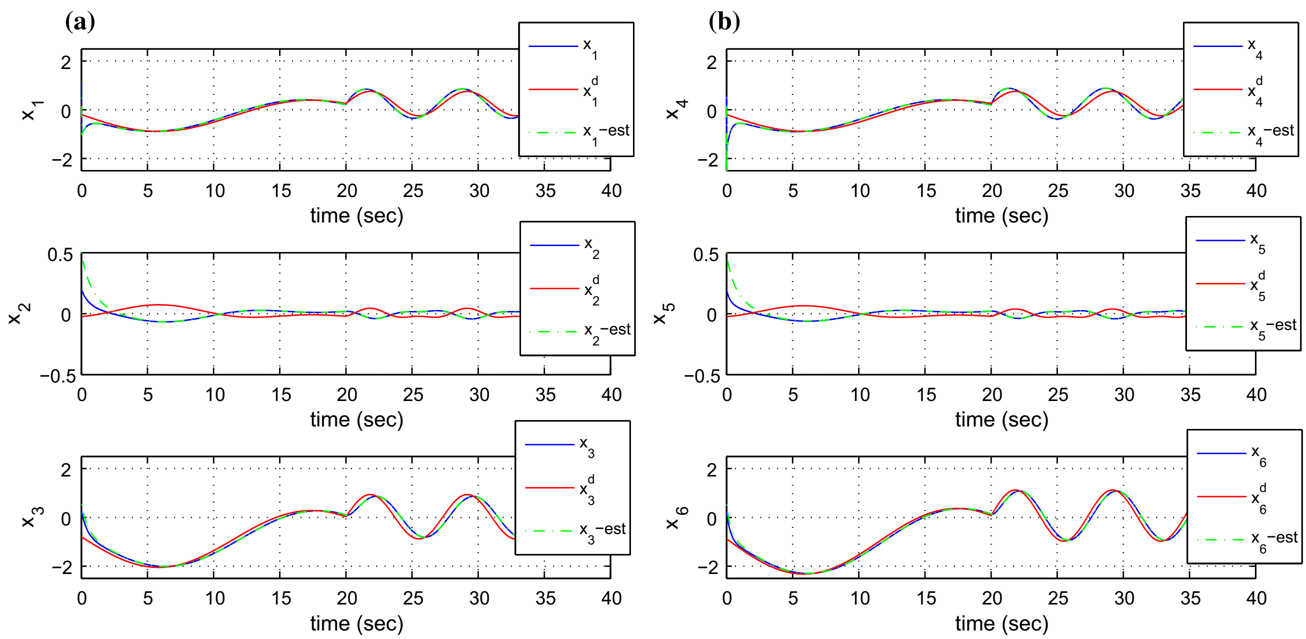

Fig. 11 Test 5 for the synchronization of the coupled Hindmarsh–Rose neurons: **a** convergence of state variables x_1 to x_3 (1st neuron) to the reference setpoints: **b** convergence of state variables x_4 to x_6 (2nd neuron) to the reference setpoints

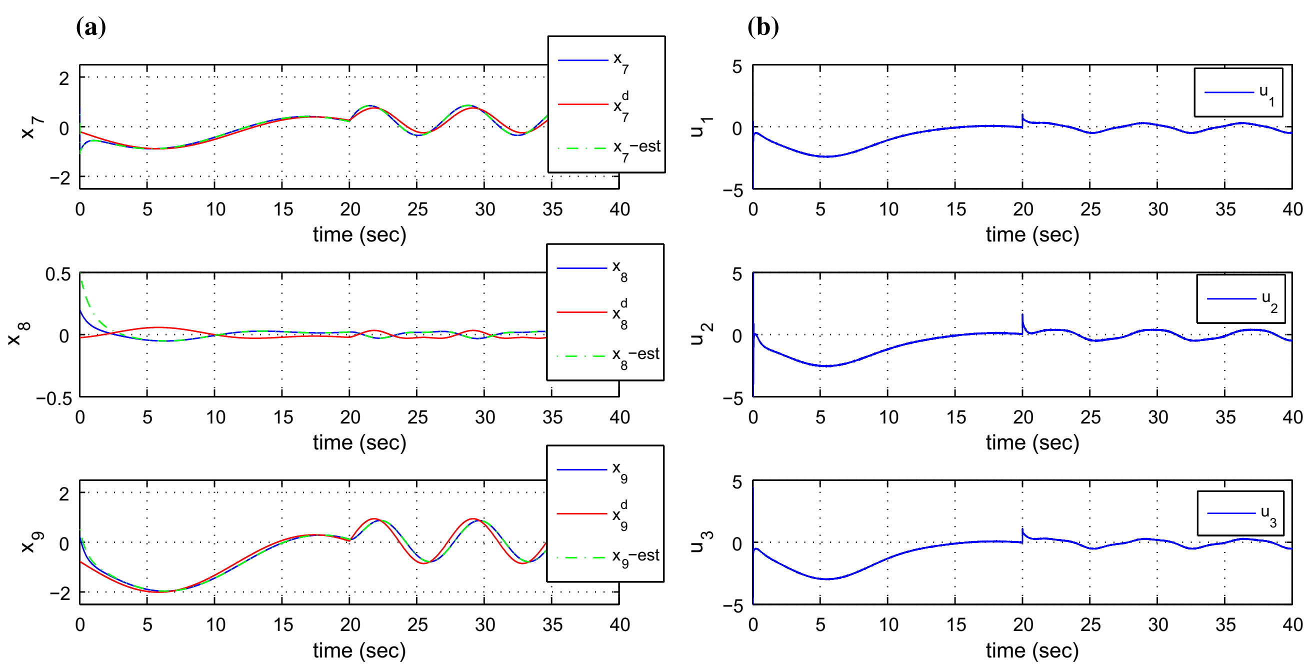

Fig. 12 Test 5 for the synchronization of the coupled Hindmarsh–Rose neurons: **a** convergence of state variables x_7 to x_9 (3rd neuron) to the reference setpoints: **b** variation of control inputs u_1 to u_3

control inputs (which try to minimize a quadratic cost function of the state vector's tracking error) and (2) the model uncertainty and external perturbation terms which try to maximize this cost function. It has been also pointed out that the solution of the optimal control problem for the nonlinear model of the coupled neural oscillators cannot be achieved after using other control approaches, such as the MPC and the NMPC, for instance MPC (Model Predictive Control) and its nonlinear variant NMPC (Nonlinear Model Predictive Control). MPC is primarily designed for linear dynamical systems and its use in the nonlinear model of the coupled Hindmarsh–Rose neurons would signify the loss of stability for the control loop. On the other side the iterative search for an optimum performed by NMPC depends on initial parametrization while not being of assured convergence.

Remark 2 The proposed nonlinear optimal control method for the model of the coupled Hindmarsh–Rose neurons is a generic one and is not hindered by the number of state variables that exhibit time-delays. Actually, time-delays may also appear in state variables x and y or in the control input (external excitation) that is represented by current I_{ext}. The proposed nonlinear optimal control method is of proven global stability and of sufficient robustness. This allows to compensate for time-delays effects.

Remark 3 A research objective remains to move from model-based control approaches to model-free control methods such as those having the form of adaptive control schemes. Actually, a precise model of the dynamics of biological neurons is not always available. Besides, such a model may be time-varying or its parameters have to be estimated separately for each case-study, which is obviously a demanding task. To avoid the dependance of the solution of the control and synchronization problem of the coupled neural oscillators on the precise knowledge of a detailed dynamic model, it becomes apparent that it is necessary to pursue the development of adaptive control approaches. For instance, one can consider the adaptive neurofuzzy H-infinity control methods for nonlinear dynamical systems (Rigatos et al. 2017b).

Conclusions

The article has proposed a nonlinear optimal (H-infinity) control method for synchronization in the model of the coupled Hindmarsh–Rose (HR) neurons. The dynamic model of the coupled HR neurons undergoes first approximate linearization around a temporary operating point which is recomputed at each time step of the control method. The linearization procedure makes use of first-order Taylor series expansion and of the computation of the associated Jacobian matrices. The modelling error which is due to the truncation of higher-order terms in the Taylor series is considered as a disturbance which is compensated by the robustness of the control algorithm. For the approximately linearized model of the coupled HR neurons an H-infinity feedback controller is designed.

This controller represents the solution to a min-max differential game in which the control inputs try to minimize a quadratic cost function of the tracking error of the system's state vector, whereas the model uncertainty and perturbation inputs try to maximize this cost function. For the computation of the controller's feedback gain an algebraic Riccati equation is solved at each iteration of the control method. The global asymptotic stability properties of the control scheme are proven through Lyapunov analysis. Finally, to implement state estimation-based control the H-infinity Kalman Filter has been used as a robust state estimator. The article's results can be meaningful for biomedical applications such as the treatment of neurodegenerative diseases. They can also help to gain an insight about the pacemaking properties of the nervous system, which in turn affect the functioning of several organs.

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