RECONSTRUCTING DYNAMICS OF SPIKING NEURONS FROM INPUT-OUTPUT MEASUREMENTS IN VITRO

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***Abstract*— We provide a method to reconstruct the neural spike-timing behavior from input-output measurements. The proposed method ensures an accurate fit of a class of neuronal models to the relevant data, which are in our case the dynamics of the neuron's membrane potential. Our method enables us to deal with the problem that the neuronal models, in general, not belong to the class of models that can be transformed into the observer canonical form. In particular, we present a technique that guarantees successful model reconstruction of the spiking behavior for an extended Hindmarsh-Rose neuronal model. The technique is validated on the data recorded *in vitro* from neural cells in the hippocampal area of mouse brain.**

I. INTRODUCTION

Mathematical modeling of neural dynamics is essential for understanding the principles behind neural computation. Since the introduction of clamping techniques, which made it possible to measure the membrane potential and currents of single neurons [1], and inspired by the pioneering works of Hodgkin and Huxley [2], a large number of models describing action potential generation of neural cells have been developed (see [3] for a review). These models offer a *qualitative* description of the mechanisms of spike generation in neural cells. To study the specific behavior of neural cells, e.g. the dynamic fluctuations of the membrane potential, a rigid *quantitative* evaluation of these models against empirical data is needed. For the dynamical models this amounts to the identification of the model's states and parameter values from input-output measurements in the presence of noise.

Which of the many available models is the most suitable one for this goal? In general, models of neural dynamics can be classified as biophysically plausible or as purely mathematical. The biophysically realistic conductance based neuronal models describe the generation of the spikes as a function of the individual ionic currents flowing through the neuron's membrane. Although being time consuming, the parameters of these models can, in principle, be partially obtained through measurements. However, complete and accurate estimation of their parameters for a single *living* cell is hardly practicable.

Because of these complications, a number of mathematical models that mimic the spiking behavior of real neurons are introduced throughout the years, e.g. the Hindmarsh-Rose [4] and Fitzhugh-Nagumo [5] neuronal models. These models are simpler in structure and in the number of parameters. Their parameters, however, have no immediate physical interpretation. Hence, they cannot be measured explicitly in experiments. It is showed by Izhikevich [6] that the mathematical models can, depending on their specific parameters, cover a wide range of the dynamics that have been observed in real neurons. Furthermore, they have the advantage of simplicity. This makes model identification an easier task.

Here, we aim at providing a method that allows a successful mapping of mathematical neuronal models to the vast collection of available empirical data. However, fitting these models to given input-output data is a hard technical problem. This is because the internal, non physical, states of the system are not available, and the input-output information that is available is often deficient. Yet, to successfully model the measured data one needs to reconstruct the unknown states and estimate the parameters of the system simultaneously.

The problem of estimating the state and parameter vectors for a given nonlinear system from input-output data is a well established field in system identification [7] and adaptive control [8]. It has a broad domain of relevant applications in physics and engineering, and efficient recipes for solving practical problems are available. In most cases, when state and parameter identification is required, these methods apply to a rich class of systems that can be transformed into the so-called *canonical adaptive observer form* [9]:

$$\begin{aligned} \dot{\mathbf{x}} &= \mathbf{R}\mathbf{x} + \boldsymbol{\varphi}(y(t),t)\boldsymbol{\theta} + \mathbf{g}(t), \\ \mathbf{R} &= \begin{pmatrix} 0 & \mathbf{k}^T \\ 0 & \mathbf{F} \end{pmatrix}, \quad \mathbf{x} = (x_1,\ldots,x_n), \\ y(t) &= x_1(t). \end{aligned} \tag{1}$$

In (1), the functions $\mathbf{g}: \mathbb{R}_{\geq 0} \to \mathbb{R}^n$, $\boldsymbol{\varphi}: \mathbb{R}\times\mathbb{R}_{\geq 0} \to \mathbb{R}^n\times\mathbb{R}^d$ are assumed to be known, $\mathbf{k} = (k_1,\ldots,k_{n-1})$ is a vector of *known* constants, $\mathbf{F}$ is a *known* $(n-1)\times(n-1)$ matrix (usually diagonal) with eigenvalues in the left half-plane of the complex domain, and $\boldsymbol{\theta} \in \mathbb{R}^d$ is a vector containing the *unknown* parameters. Algorithms for the asymptotic recovery of the state variables and the parameter vector $\boldsymbol{\theta}$ can be found in, for instance, [9], [10], [11].

Models of neural dynamics, however, typically do not

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belong to class (1), and cannot be transformed into this specific form. Consider, for instance, the following spiking oscillator models:

$$\begin{cases} \dot{x}_0 = \theta_{0,2}x_0^3 + \theta_{0,1}x_0^2 + x_1 - x_2 + \theta_{0,0} + g(t), \\ \dot{x}_1 = -\lambda_1 x_1 + \theta_{1,1}x_0^2 + \theta_{1,0}, \\ \dot{x}_2 = -\lambda_2 x_2 + \theta_{2,1}x_0 + \theta_{2,0}, \end{cases} \quad (2)$$

$$\begin{cases} \dot{x}_0 = \theta_{0,2}x_0^3 + \theta_{0,1}x_0 - x_1 + \theta_{0,0} + g(t), \\ \dot{x}_1 = -\lambda_1 x_1 + \theta_{1,1}x_0 + \theta_{1,0}. \end{cases} \quad (3)$$

Systems (2), (3) are, respectively, the well-known Hindmarsh-Rose [4] and Fitzhugh-Nugamo [5] models for neuronal activity. The parameters $\theta_{i,j}$, λ_i are unknown. In the notations of (1) this corresponds to the situation that matrix $\mathbf{F}$ is uncertain. So these models are not in the observer canonical form. Hence new methods for estimating the *unknown* $\theta_{i,j}$, λ_i for the relevant classes of systems (2), (3) are required.

In this paper we focus in particular on the estimation of the parameters of the Hindmarsh-Rose model. We start with presenting a slight modification of the model (2) and summarize some basic proporties of this model. Second, we consider this modified system and we develop a procedure allowing successful fitting of the model to measured data. Third, we demonstrate how our approach can be used for the reconstruction of the spiking dynamics of single neurons in slices of hippocampal tissue in vitro.

The paper is organized as follows. In Section II we introduce the modified Hindmarsh-Rose model and we present the notations that will be used throughout this paper. Section III contains formal statement of the identification problem. In Section IV we describe our parameter estimation procedure and we give sufficient conditions for convergence of the estimates. Section V describes the details of the application of this procedure to the problem of reconstructing the spikes of hippocampal neurons from mice. In Section VI we discuss these results, and Section VII concludes the paper.

II. Preliminaries

Consider the following slight modification of the Hindmarsh-Rose equations (2):

$$\begin{cases} \dot{x}_0 = \theta_{0,3}x_0^3 + \theta_{0,2}x_0^2 + \theta_{0,1}x_0 + \theta_{0,0} \\ \qquad + x_1 - x_2 + g(t), \\ \dot{x}_1 = -\lambda_1 x_1 + \theta_{1,2}x_0^2 + \theta_{1,1}x_0 + \theta_{1,0}, \\ \dot{x}_2 = -\lambda_2 x_2 + \theta_{2,1}x_0 + \theta_{2,0}, \end{cases} \quad (4)$$

where $\theta_{i,j}$ are unknown constant parameters and λ_1, λ_2 are the unknown time constants of the internal states. The state x_0 represents the membrane potential, x_1 is a fast internal variable, x_2 is a slow variable ($\lambda_2 \ll 1$) and $g(t)$ is an external applied clamping current. The system (4) has, compared to the original equations (2), a full third order polynomial of x_0 in the first equation and a full order second order polynomial of x_0 in the second equation. The modified model can adapt to arbitrary time-scales and has less restrictions on the shape of the spikes.

The specific behavior of the Hindmarsh-Rose model can be analyzed by decomposition into fast and slow subsystems (see for instance [12], [13]), where the fast subsystem is composed by the states x_0 and x_1, and the slow subsystem is given by state x_2. Hence, the following proporties hold for the Hindmarsh-Rose system:

1) the shape of the spikes is mainly determined by the fast subsystem,
2) the firing frequency of the spikes in absence of the slow subsystem ($x_2 = 0$) is dictated by the amplitude of the external current $g(t)$,
3) the third equation, i.e. the slow variable, perturbs the input $g(t)$ and modulates the firing frequency such that, depending on the parameters, the model can produce periodic bursts, aperiodic bursts or spiking behavior; firing frequency is adaptable.

For the sake of convenience, we introduce some notations that will be used throughout the paper. The symbol $\mathbb{R}$ denotes the real numbers, $\mathbb{R}_{>0} = \{x \in \mathbb{R} \mid x > 0\}$. The symbol $\mathbb{Z}$ denotes the set of integers. Consider the vector $\mathbf{x} \in \mathbb{R}^n$ that can be partitioned into two vectors $\mathbf{x}_1 \in \mathbb{R}^p$ and $\mathbf{x}_2 \in \mathbb{R}^q$, $p+q = n$, then $\oplus$ denotes their concatenation, i.e. $\mathbf{x}_1 \oplus \mathbf{x}_2 = \mathbf{x}$. The Euclidian norm of $\mathbf{x} \in \mathbb{R}^n$ is denoted by $\|\mathbf{x}\|$. Finally, let $\epsilon \in \mathbb{R}_{>0}$, then $\|\mathbf{x}\|_\epsilon$ stands for the following:

$$\|\mathbf{x}\|_\epsilon = \begin{cases} \|\mathbf{x}\| - \epsilon, & \|\mathbf{x}\| > \epsilon, \\ 0, & \|\mathbf{x}\| \leq \epsilon. \end{cases}$$

III. Problem Formulation

Consider the following class of nonlinear neuronal models:

$$\begin{aligned} \dot{x}_0 &= \theta_0^T \boldsymbol{\phi}_0(x_0(t), t) + \sum_{i=1}^{n} x_i, \\ \dot{x}_i &= -\lambda_i x_i + \theta_i^T \boldsymbol{\phi}_i(x_0(t), t), \end{aligned} \quad (5)$$

where

$$\boldsymbol{\phi}_i : \mathbb{R} \times \mathbb{R}_{\geq 0} \to \mathbb{R}^{d_i}, \quad d_i \in \mathbb{N}\backslash\{0\}, \ i = \{0, \ldots, n\}$$

are continuous functions. Variable x_0 in system (5) represents the dynamics of the cell's membrane potential, variables x_i, $i \geq 1$ are internal states that can be associated with the ionic currents flowing in the cell and the parameters $\theta_i \in \mathbb{R}^{d_i}$, $\lambda_i \in \mathbb{R}_{>0}$ are constant. Clearly, the models (2)–(4) belong to the particular class of systems (5).

The values of the variable $x_0(t)$ are assumed to be available at any instance of time and the functions $\boldsymbol{\phi}_i(x_0(t), t)$ are supposed to be known. The variables x_i, $i = \{1, \ldots, n\}$, however, are not available. The actual values of the parameters $\theta_0, \ldots, \theta_n$, $\lambda_1, \ldots, \lambda_n$, are unknown *a-priori*. We assume that domains of admissible values of θ_i, λ_i are known or can at least be estimated. In particular, we consider the case where $\theta_i \in [\theta_{i,\min}, \theta_{i,\max}]$, $\lambda_i \in [\lambda_{i,\min}, \lambda_{i,\max}]$, and the values of $\theta_{i,\min}$, $\theta_{i,\max}$, $\lambda_{i,\min}$, $\lambda_{i,\max}$ are available.

For notational convenience we denote

$$\boldsymbol{\theta} = \theta_0 \oplus \theta_1 \oplus \cdots \oplus \theta_n, \ \boldsymbol{\lambda} = \lambda_1 \oplus \cdots \oplus \lambda_n,$$

the vectors $\hat{\boldsymbol{\theta}}$ and $\hat{\boldsymbol{\lambda}}$ denote the estimations of $\boldsymbol{\theta}$ and $\boldsymbol{\lambda}$, and the domains of $\boldsymbol{\theta}$, $\boldsymbol{\lambda}$ are given by the symbols Ω_θ and Ω_λ, respectively.

The problem is how to derive an algorithm which is capable of reconstructing the states and estimate the unknown parameters of the system (5) solely depending on the signal $x_0(t)$. In the present work we consider this problem within the framework of designing an observer for the dynamics and parameters of (5) that is driven by the measured signal $x_0(t)$ and has dynamics of the form:

$$\begin{aligned}\dot{\hat{\mathbf{x}}} &= \mathbf{f}(\hat{\mathbf{x}}, \mathbf{z}, x_0(t)),\\ \mathbf{z} &= \mathbf{h}(\hat{\mathbf{x}}),\end{aligned} \tag{6}$$

where $\hat{\mathbf{x}} \in \mathbb{R}^n$ is the approximation of states of the system (5) and $\mathbf{z} = \hat{\boldsymbol{\theta}} \oplus \hat{\boldsymbol{\lambda}}$ contains estimates of the parameters of the system. Hence, the goal is to find conditions such that for some given small numbers $\delta_x, \delta_z \in \mathbb{R}_{>0}$ and all $t_0 \in \mathbb{R}_{\geq 0}$ the following properties hold:

$$\exists\ t' \geq t_0 \quad \text{s.t.} \quad \forall\ t \geq t' \quad : \begin{cases} \|\hat{\mathbf{x}}(t) - \mathbf{x}(t)\| \leq \delta_x, \\ \|\mathbf{z}(t) - \boldsymbol{\vartheta}\| \leq \delta_z. \end{cases} \tag{7}$$

where $\mathbf{x} = [x_0, \ldots, x_n]^T$ and $\boldsymbol{\vartheta} = \boldsymbol{\theta} \oplus \boldsymbol{\lambda}$.

IV. Main Results

Let us first, for notational convenience, introduce the following function

$$\begin{aligned}&\boldsymbol{\phi}(x_0(t), \boldsymbol{\lambda}, t) = \\ &\quad \boldsymbol{\phi}_0(x_0(t), t) \bigoplus_{i=1}^{n} \int_0^t e^{-\lambda_i (t-\tau)} \boldsymbol{\phi}_i(x_0(\tau), \tau) d\tau.\end{aligned} \tag{8}$$

This function $\boldsymbol{\phi}(x_0(t), \boldsymbol{\lambda}, t)$ is a concatenation of $\boldsymbol{\phi}_0(\cdot)$ and the integrals

$$\int_0^t e^{-\lambda_i (t-\tau)} \boldsymbol{\phi}_i(x_0(\tau), \tau) d\tau, \quad i = \{1, \ldots, n\}. \tag{9}$$

Then, using (8), the system (5) can be written in the more compact form:

$$\dot{x}_0 = \boldsymbol{\theta}^T \boldsymbol{\phi}(x_0(t), \boldsymbol{\lambda}, t). \tag{10}$$

Given that functions $\boldsymbol{\phi}_i(\cdot)$ are known and that the values of $x_0(\tau)$, $\tau \in [0, t]$ are available, the integrals (9) can be calculated explicitly as functions of λ_i and t. Taking into account that the time variable t can be arbitrarily large, explicit calculation of integrals (9) is expensive in the computational sense and, in principle, requires infinitely large memory. For this reason approximation of the function $\boldsymbol{\phi}(x_0(t), \boldsymbol{\lambda}, t)$ is used.

In the case that the signal $x_0(t)$ is periodic, bounded, and the functions $\boldsymbol{\phi}_i(x_0(t), t)$ are locally Lipschitz in x_0 and periodic in t with the same period, the functions $\boldsymbol{\phi}_i(x_0(t), t)$ can be expressed in a Fourier series expansion:

$$\begin{aligned}&\boldsymbol{\phi}_i(x_0(t), t) = \\ &\quad \frac{a_{i,0}}{2} + \sum_{j=1}^{\infty} \left(a_{i,j} \cos(\omega_j t) + b_{i,j} \sin(\omega_j t)\right).\end{aligned} \tag{11}$$

Taking a finite number N of members from the series expansion (11), the following approximation of (9) holds:

$$\begin{aligned}&\int_0^t e^{-\lambda_i (t-\tau)} \boldsymbol{\phi}_i(x_0(\tau), \tau) d\tau \simeq \\ &\frac{a_{0,i}}{2\lambda_i} + \sum_{j=1}^{N} \frac{a_{i,j}}{\lambda_i^2 + \omega_j^2} \left(\sin(\omega_j t)\omega_j + \lambda_i \cos(\omega_j t)\right) \\ &+ \sum_{j=1}^{N} \frac{b_{i,j}}{\lambda_i^2 + \omega_j^2} \left(-\cos(\omega_j t)\omega_j + \lambda_i \sin(\omega_j t)\right) + \epsilon(t),\end{aligned} \tag{12}$$

where $\epsilon(t) : \mathbb{R}_{\geq 0} \to \mathbb{R}$ is an exponentially decaying term.

In the case that the signal $x_0(t)$ is not periodic in t or the functions $\boldsymbol{\phi}_i(x_0(t), t)$ are not periodic in t, the integrals (9) can be approximated as:

$$\begin{aligned}&\int_0^t e^{-\lambda_i (t-\tau)} \boldsymbol{\phi}_i(x_0(\tau), \tau) d\tau \simeq \\ &\int_{t-T}^t e^{-\lambda_i (t-\tau)} \boldsymbol{\phi}_i(x_0(\tau), \tau) + \epsilon(t),\end{aligned}$$

where $T \in \mathbb{R} > 0$ is sufficiently large.

Let the function $\bar{\boldsymbol{\phi}}(x_0(t), \hat{\boldsymbol{\lambda}}, t)$ be the computationally realizable approximation of (8) such that $\bar{\boldsymbol{\phi}}(x_0(t), \hat{\boldsymbol{\lambda}}, t)$ satisfies:

$$\|\bar{\boldsymbol{\phi}}(x_0(t), \hat{\boldsymbol{\lambda}}, t) - \boldsymbol{\phi}(x_0(t), \hat{\boldsymbol{\lambda}}, t)\| \leq \Delta,$$

for all $t \in \mathbb{R}_{>0}$ and some small $\Delta \in \mathbb{R}_{>0}$.

Consider the following observer that estimates the states and the parameters $\boldsymbol{\theta}$ of the systems (10):

$$\begin{cases} \dot{\hat{x}}_0 = -\alpha(\hat{x}_0 - x_0) + \hat{\boldsymbol{\theta}}^T \bar{\boldsymbol{\phi}}(x_0, \hat{\boldsymbol{\lambda}}, t), \\ \dot{\hat{\boldsymbol{\theta}}} = -\gamma_\theta(\hat{x}_0 - x_0) \bar{\boldsymbol{\phi}}(x_0, \hat{\boldsymbol{\lambda}}, t), \quad \gamma_\theta, \alpha \in \mathbb{R}_{>0}. \end{cases} \tag{13}$$

Defining

$$\mathbf{q} = (\hat{x}_0 - x_0) \oplus (\hat{\boldsymbol{\theta}} - \boldsymbol{\theta}),$$

the closed loop system (10), (13) can be written as

$$\dot{\mathbf{q}} = \mathbf{A}(x_0(t), \hat{\boldsymbol{\lambda}}(t), t)\mathbf{q} + \mathbf{b}\ u(x_0(t), \boldsymbol{\lambda}, \hat{\boldsymbol{\lambda}}, t), \tag{14}$$

where

$$\begin{aligned}&\mathbf{A}(x_0(t), \hat{\boldsymbol{\lambda}}(t), t) = \\ &\quad \begin{pmatrix} -\alpha & \bar{\boldsymbol{\phi}}(x_0(t), \hat{\boldsymbol{\lambda}}(t), t)^T \\ -\gamma_\theta \bar{\boldsymbol{\phi}}(x_0(t), \hat{\boldsymbol{\lambda}}(t), t) & 0 \end{pmatrix}, \\ &\mathbf{b} = (1, 0, \ldots, 0)^T,\end{aligned}$$

and

$$\begin{aligned}u(x_0(t), \hat{\boldsymbol{\lambda}}, \boldsymbol{\lambda}, t) &= \boldsymbol{\theta}^T (\bar{\boldsymbol{\phi}}(x_0(t), \hat{\boldsymbol{\lambda}}, t) - \bar{\boldsymbol{\phi}}(x_0(t), \boldsymbol{\lambda}, t)) \\ &\quad + \boldsymbol{\theta}^T (\bar{\boldsymbol{\phi}}(x_0(t), \boldsymbol{\lambda}, t) - \boldsymbol{\phi}(x_0(t), \boldsymbol{\lambda}, t)).\end{aligned}$$

The closed loop system (14) consists of the time-varying linear system $\dot{\mathbf{q}} = \mathbf{A}(\cdot, \cdot, \cdot)\mathbf{q}$ which is perturbed by the function $u(x_0(t), \hat{\boldsymbol{\lambda}}, \boldsymbol{\lambda}, t)$. Note, in addition, that

$$\limsup_{\hat{\boldsymbol{\lambda}} \to \boldsymbol{\lambda}} \|u(x_0(t), \hat{\boldsymbol{\lambda}}, \boldsymbol{\lambda}, t)\| \leq \|\boldsymbol{\theta}\| \Delta.$$

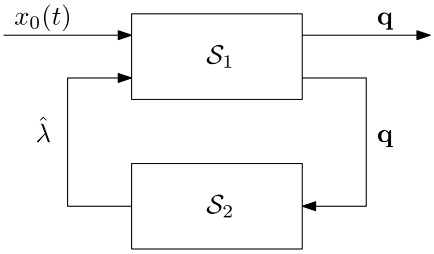

Fig. 1. The interconnected systems $\mathcal{S}_1$ and $\mathcal{S}_2$.

The control problem is now, in terms of (7), to find values $\hat{\boldsymbol{\lambda}}$ close to $\boldsymbol{\lambda}$, and conditions such that $\lim_{t\to\infty}\|\mathbf{q}(t)\| \leq \delta_q$, with small $\delta_q \in \mathbb{R}_{>0}$.

Let, therefore, the components of vector $\hat{\boldsymbol{\lambda}}$ evolve according to the following equations:

$$\begin{cases} \dot{\xi}_{1,i} = \gamma_i \sigma(\|x_0 - \hat{x}_0\|_\varepsilon) \cdot \\ \qquad \left(\xi_{1,i} - \xi_{2,i} - \xi_{1,i}\left(\xi_{1,i}^2 + \xi_{2,i}^2\right)\right), \\ \dot{\xi}_{2,i} = \gamma_i \sigma(\|x_0 - \hat{x}_0\|_\varepsilon) \cdot \\ \qquad \left(\xi_{1,i} + \xi_{2,i} - \xi_{2,i}\left(\xi_{1,i}^2 + \xi_{2,i}^2\right)\right), \\ \hat{\lambda}_i(\xi_{1,i}) = \lambda_{i,\min} + \dfrac{\lambda_{i,\max} - \lambda_{i,\min}}{2}(\xi_{1,i} + 1), \end{cases} \tag{15}$$

$$\hat{\xi}_{1,i}^2(t_0) + \hat{\xi}_{2,i}^2(t_0) = 1, \tag{16}$$

where $i = \{1, \ldots, n\}$, $\sigma(\cdot) : \mathbb{R} \to \mathbb{R}_{\geq 0}$ is a bounded function, i.e. $\sigma(s) \leq S \in \mathbb{R}_{>0}$, and $|\sigma(s)| \leq |s|$ for all $s \in \mathbb{R}$. The constants $\gamma_i \in \mathbb{R}_{>0}$ and let γ_i be *rationally-independent*, i.e.:

$$\sum \gamma_i k_i \neq 0, \ \forall \ k_i \in \mathbb{Z}.$$

The systems (15) with initial conditions (16) are forward-invariant on the manifold $\xi_{1,i}^2(t) + \xi_{2,i}^2(t) = 1$. Taking into account that the constants γ_i are rationally-independent, we can conclude that trajectories $\xi_{1,i}(t)$ densely fill an invariant n-dimensional torus [14]. In other words, the system (15) with initial conditions (16) is Poisson-stable in $\Omega_x = \{\xi_{1,i}, \xi_{2,i} \in \mathbb{R}^{2n} | \xi_{1,i} \in [-1, 1]\}$. Furthermore, notice that trajectories $\xi_{1,i}(t)$, $\xi_{2,i}(t)$ are globally bounded and that the right-hand side of (15) is locally Lipschitz in $\xi_{1,i}$, $\xi_{2,i}$. Hence the following estimate holds:

$$\|\dot{\hat{\boldsymbol{\lambda}}}(t)\| \leq \gamma^* M, \quad M \in \mathbb{R}_{>0}, \ \gamma^* = \max_i\{\gamma_i\}.$$

We may consider (14) and (15) as two interconnected systems $\mathcal{S}_1$ and $\mathcal{S}_2$, respectively. The system $\mathcal{S}_2$ takes values $\hat{\boldsymbol{\lambda}}$ from the compact domain Ω_λ as function of the output of the system $\mathcal{S}_1$. These values $\hat{\boldsymbol{\lambda}}$ are, in turn, injected into the system $\mathcal{S}_1$. The system $\mathcal{S}_1$ is driven by the measured data and the estimates $\hat{\boldsymbol{\lambda}}$ and will provide estimates of the state $x_0(t)$ and the parameters $\boldsymbol{\theta}$. A schematic representation of the structure of these interconnected systems is provided in Fig. 1.

We will now pose conditions such that the solutions of the system $\mathcal{S}_1$ converge to an invariant attracting set in the neighborhood of the origin. In particular, we will show that the systems (13), (15) serve as the desired observer (6) for the class of systems specified by equations (5), i.e. the proporties of (7) are satisfied. Our result is based on the concept of non-uniform convergence [15], [16], non-uniform small-gain theorems [17], and the notion of λ-uniform persistency of excitation:

Definition 1 (λ-uniform persistency of excitation [18]): Let function $\boldsymbol{\varphi} : \mathcal{D}_0 \times \mathcal{D}_1 \times \mathbb{R}_{\geq 0} \to \mathbb{R}^{n\times m}$ be continuous and bounded. We say that $\boldsymbol{\varphi}(\sigma(t), \boldsymbol{\lambda}, t)$ is λ-uniformly persistently exciting (λ-uPE) if there exist $\mu, L \in \mathbb{R}_{>0}$ such that for each $\sigma(t) \in \mathcal{D}_0$, $\boldsymbol{\lambda} \in \mathcal{D}_1$

$$\int_t^{t+L} \boldsymbol{\varphi}(\sigma(t), \boldsymbol{\lambda}, t)\boldsymbol{\varphi}(\sigma(t), \boldsymbol{\lambda}, t)^T d\tau \geq \mu I, \quad \forall t \geq 0.$$

The latter notion, in contrast to the conventional definitions of persistency of excitation, allows us to deal with the parameterized regressors $\boldsymbol{\varphi}(\sigma(t), \boldsymbol{\lambda}, t)$. This is essential for deriving the asymptotic properties of the interconnected $\mathcal{S}_1$, $\mathcal{S}_2$ systems. These properties are formulated in the theorem below:

Theorem 1: Let the systems (10), (13), (15) be given. Assume that function $\bar{\boldsymbol{\phi}}(x_0(t), \boldsymbol{\lambda}, t)$ is λ-uPE, bounded, i.e. $\|\bar{\boldsymbol{\phi}}(x_0(t), \boldsymbol{\lambda}, t)\| \leq B$ for all $t \geq 0$ and $\boldsymbol{\lambda} \in \Omega_\lambda$, and Lipschitz in $\boldsymbol{\lambda}$:

$$\|\bar{\boldsymbol{\phi}}(x_0(t), \boldsymbol{\lambda}, t) - \bar{\boldsymbol{\phi}}(x_0(t), \boldsymbol{\lambda}', t)\| \leq D\|\boldsymbol{\lambda} - \boldsymbol{\lambda}'\|.$$

Then there exist a number γ^* satisfying

$$\gamma^* = \frac{\mu}{4BDLM},$$

and a constant $\varepsilon > 0$ such that for all $\gamma_i \in (0, \gamma^*]$:

1) the trajectories of the closed loop system (13), (15) are bounded;
2) there exists a vector $\boldsymbol{\lambda}^* \in \Omega_\lambda$: $\lim_{t\to\infty}\hat{\boldsymbol{\lambda}}(t) = \boldsymbol{\lambda}^*$;
3) there exist positive constants $\kappa = \kappa(\alpha, \gamma_0)$ and δ such that the following estimates hold:

$$\limsup_{t\to\infty} \|\hat{\boldsymbol{\theta}}(t) - \boldsymbol{\theta}\| < \kappa(D\delta + 3\Delta),$$
$$\lim_{t\to\infty} |\hat{\lambda}_i(t) - \lambda_i| < \delta,$$
$$\lim_{t\to\infty} \|\hat{x}_0(t) - x_0(t)\|_\varepsilon = 0.$$

The proof of Theorem 1 is based on Theorem 1 and Corollary 4 in [17]. Its details are made available in [19].

Theorem 1 assures that the estimates $\hat{\boldsymbol{\theta}}(t)$, $\hat{\boldsymbol{\lambda}}(t)$ converge to a neighborhood of the actual values $\boldsymbol{\theta}$, $\boldsymbol{\lambda}$ asymptotically. Given that $\|\hat{x}_0(t) - x_0(t)\|_\varepsilon \to 0$ as $t \to \infty$, the size of this neighborhood can be specified as a function of the parameter ε. The value of ε in turn depends on the amount of noise in the driving signal, and the values of Δ and γ_i (the smaller the Δ, γ_i the smaller the ε) such that the former, taking the presence of noise into account, can in principle be made sufficiently small.

V. Experimental validation

Let us demonstrate how these results can be applied to the problem of estimating the parameters of a neuronal model from *in vitro* measurements of single neurons. In particular, we construct an algorithm that allows fitting the modified Hindmarsh-Rose model (4) to a spike train recorded from real neural cells in slices of hippocampal tissue of mouse. Since the measured signal contains solely spiking dynamics we can neglect the third equation of the Hindmarsh-Rose model, i.e. the slow variable. Hence, the problem reduces to finding the parameters $\theta_{0,0}$, $\theta_{0,1}$, $\theta_{0,2}$, $\theta_{0,3}$, $\theta_{1,0}$, $\theta_{1,1}$, $\theta_{1,2}$, λ_1 of the reduced version of (4):

$$\begin{cases} \dot{x}_0 = \theta_{0,3}x_0^3 + \theta_{0,2}x_0^2 + \theta_{0,1}x_0 + \theta_{0,0} + x_1 + g(t), \\ \dot{x}_1 = -\lambda_1 x_1 + \theta_{1,2}x_0^2 + \theta_{1,1}x_0 + \theta_{1,0}. \end{cases} \tag{17}$$

In our experimental data the input function $g(t)$ was a constant current such that $g(t)$, in this case, can be contained in the parameter $\theta_{0,0}$. Notice also that the value of $\theta_{1,0}$ can be aggregated into the parameter $\theta_{0,0}$. Thus instead of (17) we obtain the following equations:

$$\begin{cases} \dot{x}_0 = \theta_{0,3}x_0^3 + \theta_{0,2}x_0^2 + \theta_{0,1}x_0 + \theta_{0,0}^* + x_1, \\ \dot{x}_1 = -\lambda_1 x_1 + \theta_{1,2}x_0^2 + \theta_{1,1}x_0. \end{cases} \tag{18}$$

From (13), (15) and Theorem 1 the following system is capable of estimating the unknown parameters of (18):

$$\begin{aligned} \dot{\hat{x}}_0 &= -\alpha(\hat{x}_0 - x_0(t)) + \hat{\boldsymbol{\theta}}^T \bar{\boldsymbol{\phi}}_0(x_0(t), \hat{\lambda}_1(t), t), \\ \dot{\hat{\boldsymbol{\theta}}} &= -\gamma_\theta(\hat{x}_0 - x_0(t))\bar{\boldsymbol{\phi}}_0(x_0(t), \hat{\lambda}_1(t), t), \\ \hat{\lambda}_1(t) &= \lambda_{1,\min} + \frac{\lambda_{1,\max} - \lambda_{2,\min}}{2}(\xi_{1,1}(t) + 1), \\ \dot{\xi}_{1,1} &= \gamma_1 \sigma(\|\hat{x}_0 - x_0(t)\|_\varepsilon) \cdot \\ &\quad \left(\xi_{1,1} - \xi_{2,1} - \xi_{1,i}\left(\xi_{1,1}^2 + \xi_{2,1}^2\right)\right), \\ \dot{\xi}_{2,1} &= \gamma_1 \sigma(\|\hat{x}_0 - x_0(t)\|_\varepsilon) \cdot \\ &\quad \left(\xi_{1,1} + \xi_{2,1} - \xi_{2,1}\left(\xi_{1,1}^2 + \xi_{2,1}^2\right)\right), \\ \sigma(\cdot) &= \arctan(\cdot). \end{aligned} \tag{19}$$

In (19) the vector $\hat{\boldsymbol{\theta}}$ is the estimate of $\boldsymbol{\theta} = (\theta_{0,0}^*, \theta_{0,1}, \theta_{0,2}, \theta_{0,3}, \theta_{1,1}, \theta_{1,2})^T$, and $\hat{\lambda}_1$ is the estimate of λ_1. The function $\bar{\boldsymbol{\phi}}_0(x_0(t), \hat{\lambda}_1, t)$ in (19) is the computationally realizable approximation of

$$\boldsymbol{\phi}(x_0(t), \hat{\lambda}_1, t) = \begin{pmatrix} 1 \\ x_0(t) \\ x_0^2(t) \\ x_0^3(t) \\ \int_0^t e^{-\hat{\lambda}_1(t-\tau)} x_0(\tau) d\tau \\ \int_0^t e^{-\hat{\lambda}_1(t-\tau)} x_0^2(\tau) d\tau \end{pmatrix}. \tag{20}$$

Given that $x_0(t)$ is periodic, the Fourier-series expansion (12) is used to approximate (20). The domain Ω_λ is defined as $\Omega_\lambda = [0.5, 2.5]$ with $\lambda_{\min} = 0.5$ and $\lambda_{\max} = 2.5$, respectively. The Fourier-approximation (12) of (20) is persistently exciting for all $\hat{\lambda}_1 \in \Omega_\lambda$. In simulations we used the following set of parameters $\gamma_\theta = 3$, $\gamma_1 = 0.02/\pi$, $\alpha = 20$, and $\varepsilon = 0.12$. The trajectories of the estimates

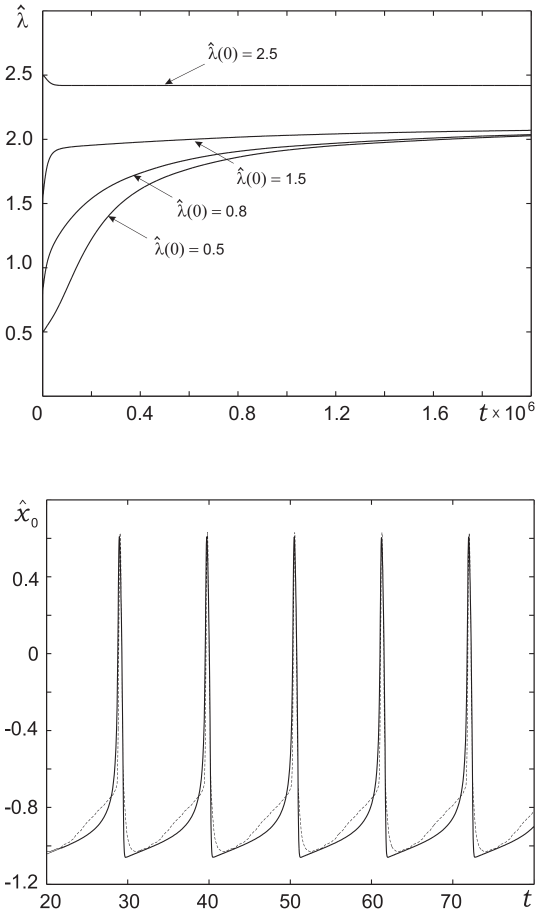

Fig. 2. Top panel – trajectories $\hat{\lambda}(t)$ as functions of time for different values of initial conditions. Bottom panel – trajectory $\hat{x}_0(t)$ of system (18) with parameters (22) (solid line) plotted against the actual data (dashed line).

$\hat{\lambda}_1(t)$ for various initial conditions are shown in the top panel of Fig. 2. We observe that trajectories $\hat{\lambda}_1(t)$ converge to a bounded domain in the interval $[2, 2.4]$. For each value of $\hat{\lambda}_1$ the estimates $\hat{\boldsymbol{\theta}}$ converge to a bounded domain as well. For example, for the trajectory starting at $\hat{\lambda}_1(0) = 0.5$ we have

$$\begin{aligned} &\hat{\theta}_{0,3} \in [-10.4, -10.25],\ \hat{\theta}_{0,2} \in [-4.45, -4.3], \\ &\hat{\theta}_{0,1} \in [6.6, 6.75],\ \hat{\theta}_{0,0}^* \in [0.75, 0.95], \\ &\hat{\theta}_{1,2} \in [-32.5, -32.4],\ \hat{\theta}_{1,1} \in [-32.2, -32.1]. \end{aligned} \tag{21}$$

The range of the estimates (21) corresponds to the amount of uncertainty of in the system (18). We found that the following choice of parameters $\hat{\boldsymbol{\theta}}$, $\hat{\lambda}_1$:

$$\begin{aligned} &\hat{\theta}_{0,3} = -10.4,\ \hat{\theta}_{0,2} = -4.35,\ \hat{\theta}_{0,1} = 6.65, \\ &\hat{\theta}_{0,0}^* = 0.9125,\ \hat{\theta}_{1,2} = -32.45,\ \hat{\theta}_{1,1} = -32.15, \\ &\hat{\lambda}_1 = 2.027, \end{aligned} \tag{22}$$

results in rather accurate fitting. The reconstructed trajectory $\hat{x}_0(t)$ with the parameters (22) is shown in the bottom panel of Fig. 2. Notice that despite the presence of small mismatches along the trajectories, the amplitude and the shape of the spikes do closely follow the measured response of the hippocampal neuron.

VI. Discussion

We showed that the spiking dynamics measured from a single neuron from the hippocampal area of mouse can be reconstructed with the modified Hindmarsh-Rose model (4). Moreover, the estimated parameters of the model converge to small bounded domains. The size of these domains can, in principle, be decreased by assigning a smaller value to the parameter ε. However, it might be possible that the model is not accurate enough to describe the spikes with such precision. The fact that the modified model's parameters $\theta_{0,1}, \theta_{1,1} \neq 0$ indicates that the equations of the original Hindmarsh-Rose model are too restricted for proper parameter fitting and our choice to use the modified model is justified.

We considered a simplified case where the clamping current applied to the neuron was constant and the neuron produced simple spiking behavior. In general, the output function of neurons is more complicated. Bursting sequences, for instance, are noticed in neurons of the pond snail *Lymnaea* [4] and firing frequency adaptation often occurs when the neuron is stimulated with block shaped currents. In order to mimic this more complicated behavior, the full set of equations of the modified Hindmarsh-Rose model should be taken into account.

VII. Conclusion

We presented a method to estimate the parameters of systems that can not be transformed into the observer canonical form. The proposed method can be applied to systems that are of the class (5), such as (mathematical) models that mimic neuronal behavior. We demonstrated a direct application of the method by means of a successful reconstruction of the states and estimations of the parameters of a modified Hindmarsh-Rose model driven by spikes recorded from a single neuron in vitro.

Acknowledgements

The authors gratefully thank Dr. Alexey Semyanov and Dr. Inseon Song of the Semyanov Research Unit, Riken BSI, for performing the single neuron recordings.

References

[1] C. Koch, *Biophysics of Computation. Information Processing in Signle Neurons*. Oxford University Press, 2002.

[2] A. Hodgkin and A. Huxley, "A quantitative description of membrane current and its application to conduction and excitation in nerve," *J. Physiol.*, vol. 117, pp. 500–544, 1952.

[3] E. M. Izhikevich, "Neural excitability, spiking, and bursting," *International Journal of Bifurcation and Chaos*, vol. 10, pp. 1171–1266, 2000.

[4] J. Hindmarsh and R. Rose, "A model of neuronal bursting using three coupled first order differential equations," *Proc. R. Soc. Lond.*, vol. B 221, no. 1222, pp. 87–102, 1984.

[5] R. FitzHugh, "Impulses and physiological states in theoretical models of nerve membrane," *Biophysical Journal*, vol. 1, pp. 445–466, 1961.

[6] E. M. Izhikevich, "Which model to use for cortical spiking neurons?" *IEEE Transactions on Neural Networks*, vol. 15, pp. 1063–1070, 2004.

[7] L. Ljung, *System Identification: Theory for the User*. Prentice-Hall, 1999.

[8] S. Sastry, *Nonlinear Systems: Analysis, Stability and Control*. Springer, 1999.

[9] G. Bastin and M. Gevers, "Stable adaptive observers for nonlinear time-varying systems," *IEEE Trans. on Automatic Control*, vol. 33, no. 7, pp. 650–658, 1988.

[10] R. Marino and P. Tomei, "Global adaptive output-feedback control of nonlinear systems, part I: Linear parameterization," *IEEE Trans. Automatic Control*, vol. 38, no. 1, pp. 17–32, 1993.

[11] ——, "Adaptive observers with arbitrary exponential rate of convergence for nonlinear systems," *IEEE Trans. Automatic Control*, vol. 40, no. 7, pp. 1300–1304, 1995.

[12] V. Belykh, I. Belykh, M. Colding-Jørgensen, and E. Mosekilde, "Homoclinic bifurcations leading to the emergence of bursting oscillations in cell models," *Euro. Phys. J. E*, vol. **3**, pp. 205–219, 2000.

[13] D. Terman, "Chaotic Spikes Arising from a Model of Bursting in Excitable Membranes," *SIAM J. Appl. Math.*, vol. **51**, pp. 1418–1450, 1991.

[14] V. Arnold, *Mathematical Methods in Classical Mechanics*. Springer-Verlag, 1978.

[15] J. Milnor, "On the concept of attractor," *Commun. Math. Phys.*, vol. 99, pp. 177–195, 1985.

[16] A. Gorban, "Singularities of transition processes in dynamical systems: Qualitative theory of critical delays," *Electronic Journal of Differential Equations*, vol. Monograph 05, 2004.

[17] I. Tyukin, E. Steur, H. Nijmeijer, and C. van Leeuwen, "Non-uniform small-gain theorems for systems with unstable invariant sets," *SIAM Journal on Control and Optimization*, (accepted, preprint available at http://arxiv.org/abs/math.DS/0612381).

[18] A. Loria and E. Panteley, "Uniform exponential stability of linear time-varying systems: revisited," *Systems and Control Letters*, vol. 47, no. 1, pp. 13–24, 2003.

[19] I. Tyukin, E. Steur, H. Nijmeijer, and C. van Leeuwen, "Identification and Modelling of Neural Dynamics," Manuscript in preparation, preprints are available upon request.