Identifiability and Limit Cycles

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Abstract

The report discusses when the non-linear dynamic equations of a non-linear system in a limit-cycle can be determined from measured data. The minimal order needed for this turns out to be the minimal dimension in which the stable orbit of the system does not intersect itself. This is illustrated with a fourth order spiking neuron model, which is identified using a non-linear second order differential equation model.

I. INTRODUCTION

Stable oscillations are very common in biological and chemical systems [14], [15]. A few examples include neuron spiking [1], [6], regulatory processes in genomes [10], [18], movement [5], and oscillatory chemical reaction kinetics [2], [3]. In this report the well known Hodgkin-Huxley squid axon model [4] is used to investigate the fundamentals of the non-linear dynamic system identification [20] problem in systems biology, more precisely how to construct an underlying differential equation model using only measured data. The main contribution of the report proves that it may be impossible to *uniquely* determine the original non-linear ordinary differential equation (ODEs), from data obtained during stable oscillation. This is so since an ODE can always be found that represents the data, as long as the stable orbit of the ODE does not intersect itself in the phase plane that represents the state of the ODE. Whenever the dimension of the phase plane of the so identified ODE is lower than the dimension of the original ODE generating the data, non-uniqueness follow. Fig. 1 gives an illustration of this, elaborated further in the report, where a fourth order Hodgkin-Huxley neuron model is identified with a second order non-linear ODE model. The result is of general validity when the dynamics of biological systems in stable oscillation is identified using measured data, in particular when conclusions are drawn on the model structure of the underlying system. In the report simulations are used exclusively in order not to obscure the key point made, since modeling errors would occur if live data would be used.

The relevance of the report is evident from the much more studied problem concerning the prediction of the existence of oscillations, given a biological ODE model. Also here spiking neuron models appear frequently in the literature, see e.g. [1], [6], [9], [11], [13], [16]. Results with relevance for molecular systems biology are also available from the field of reaction kinetics [3]. Such kinematic equations are typically written down from first principles like conservation of mass, charge and reaction laws like the law of mass action. As a consequence the resulting system of ordinary differential equations often have right hand sides where fractions of polynomials in the states appear. The mathematical results on periodic orbits are typically derived from classical stability theory [8]. The second order case is particularly rich in results due to the Poincaré-Bendixon theorem [8].

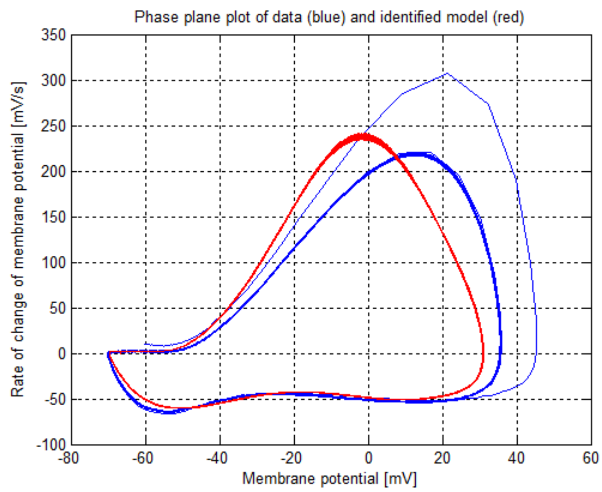

Fig. 1. **The figure illustrates modeling of the fourth order Hodgkin-Huxley neuron model of [17]. Simulation generated the data (blue), which was then identified with a second order model with 16 parameters used to model a polynomial right hand side of the second order ODE (red). The similarity of the orbits is striking. The report predicts an exact match when the number of parameters tends to infinity.**

Previous work related to the present report include the vast literature on dynamic neuron modeling starting with [4]. However, results related to the main contribution of the report does not seem to be available, except for bifurcation analysis of different authors of the Hodgkin-Huxley model, e.g. [11], [27]. In [27] the dimensionality of the oscillation mode is stated to be 2-dimensional, but no general conclusions on the system identification implications are made. Algorithms for identification of non-linear autonomous systems with stable periodic orbits are also scarce. One reason for that is that the system identification problem is difficult, with an identified model that cannot be asymptotically stable [3], [8]. The least squares (LS) technique can of course always be tried, see e.g. [3]. However, since there is no feedback from a simulated model in a least squares algorithm, the identified model often lack periodic orbits. Early recursive algorithms for identification of autonomous systems were developed in [25] and [26]. Recently, convex optimization was applied to solve the non-linear autonomous system identification problem in [13]. That work builds on the work of [21].

II. Main result

The main result of the report is a consequence of Theorem 2 of [24] that appears as Lemma 1 below. Lemma 1 states conditions under which a periodic signal $\varphi(t)$ can be represented by an ordinary differential equation of order $n+1$. In fact, [24] defines a complete procedure for construction of such an ODE. Example 2 of that paper illustrates the procedure by a construction of the harmonic oscillator, starting with the signal $\varphi(t) = \cos(t)$.

To state the result of this report a number of quantities need to be defined. The definitions follow [24]. First, the state vector is selected as

$$x(t) = (x_1(t) \ \ ... \ \ x_{n+1}(t))^T = (\varphi(t) \ \ ... \ \ \varphi^{(n)}(t))^T, \tag{1}$$

where $^{(n)}$ denotes differentiation n times. The set S^{n+1} can then be defined, where

$$S^{n+1} = \{x \in R^{n+1} \mid x = (\varphi(t) \ \ ... \ \ \varphi^{(n)}(t))^T, \ t \in R\}. \tag{2}$$

The construction of the ODE, outlined in [24], now first selects a *finite* number of points $\{x(t)\}_{k=1}^{K} \in S^{n+1}$, ordered clockwise or counterclockwise around the curve $(\varphi(t) \ \ ... \ \ \varphi^{(n)}(t))^T$ in the state space. The times t_k corresponding to the selected points are then computed. For this purpose the procedure in [24] uses the implicit function theorem [8] to solve *each* state component equation of (1) separately for t_k, resulting in

$$t_k = h_{k,i,j}(x_{k,i,j}), \quad i = 1, ..., n+1, \ j = 1, ..., J(i,k). \tag{3}$$

The reason for the multiple solutions indexed by j is that the curve is closed, hence there may be more than one solution for each state component. The implicit function theorem also secures the existence of a neighborhood around all solutions, where the inverse function is valid. The procedure in [24] then combines the appropriate solutions and neighborhoods of (3) to a complete non-linear function that constitute the right hand side of the sought ODE. The key is to select the *finite* number of points so that the union of the selected neighborhoods cover a complete period T of the orbit.

The validity of Lemma 1 requires that the following conditions are satisfied:

- A1) $\varphi(t+T) = \varphi(t)$, $\forall t \in R$, $0 < T < \infty$.
- A2) The signal is not subject to measurement disturbances.
- A3) $\varphi(t)$ is $n+1$ times continuously differentiable.
- A4) $\forall \ (\varphi \ \ ... \ \ \varphi^{(n)})^T \in S^{n+1} \subset R^{n+1}$: $(\varphi(t_1) \ \ ... \ \ \varphi^{(n)}(t_1))^T = (\varphi(t_2) \ \ ... \ \ \varphi^{(n)}(t_2))^T \Rightarrow t_1 = t_2 + kT, k \in Z$.
- A5) $\exists \delta > 0, 0 < L_1 < L_2 < \infty$ such that $|t_1 - t_2| < \delta \ \Rightarrow L_1|t_1 - t_2| \ \leq \|(\varphi(t_1) \ \ ... \ \ \varphi^{(n)}(t_1))^T - (\varphi(t_2) \ \ ... \ \ \varphi^{(n)}(t_2))^T\| \ \leq L_2|t_1 - t_2|$.
- A6) The number of points defining the neighborhoods obtained with the implicit function theorem is finite.
- A7) The neighborhoods obtained with the implicit function theorem can be combined so that their union covers a complete period of the orbit in R^{n+1}.

Here t denotes continuous time and T the period.

The conditions A1 and A2 formalize the periodicity of the signal. The regularity introduced by A3 is natural considering the fact that the signal $\varphi(t)$ is to be described as a solution to an n:th order ODE in the state space (1). The condition A4 formalizes the assumption that the curve in the state space does not intersect itself. A5 ensures that the speed of the curve, $\sqrt{(\varphi(t) \ \ ... \ \ \varphi^{(n)}(t))^T(\varphi(t) \ \ ... \ \ \varphi^{(n)}(t))}$, is always finite and positive. This rules out the existence of cusps where the curve could otherwise change direction in one point in the state space. Hence A4 and A5 ensure that the curve is well behaved and does not intersect itself. A6 and A7 states that the solutions and neighborhoods obtained by the inverse function theorem can be merged to cover the whole curve in the state space with an open set.

The following result is then obtained as Theorem 2 in [24],

Lemma 1 (High Order Loop Criterion): Consider the periodic signal $\varphi(t)$. Assume that A1 - A7 hold. Then there exist a function $h_{Period}(x_1, ..., x_{n+1})$ and a $n+1$:th order ODE

$$\begin{pmatrix} \dot{x}_1 \\ \vdots \\ \dot{x}_n \\ \dot{x}_{n+1} \end{pmatrix} = \begin{pmatrix} x_2 \\ \vdots \\ x_n \\ \varphi^{(n+1)}(h_{Period}(x_1, ..., x_{n+1})) \end{pmatrix}$$

with solution given by $(x_1 \ \ ... \ \ x_{n+1}) = (\varphi(t) \ \ ... \ \ \varphi^{(n)(t)})$.

Now consider the periodic signal $\varphi(t)$ and the sets

$$S^{m+1} = \{x \in R^{m+1} \mid x = (\varphi(t) \ \ ... \ \ \varphi^{(m)}(t))^T,$$
$$t \in R\}, m = 1, ..., M, \tag{4}$$

where $M+1$ is the order of the ODE that generated $\varphi(t)$ in the first place. By A1, A2 and A3 applied for $m = n$ it follows that the exact curve $(\varphi(t) \ \ ... \ \ \varphi^{(m)(t)})$ can be constructed by differentiation of $\varphi(t)$. This shows that also S^{m+1} can be constructed. The following result is then implied by Lemma 1

Theorem 1: Consider the periodic signal $\varphi(t)$. Assume that A1 and A2 hold and that A3 hold for $n \leq M$. If there is a $m_{\min} = \inf m < M$ such that A4 - A7 hold for $m_{\min}$, then the original ODE of order $M+1$ cannot be uniquely determined only from measured data.

Proof: The result follows from Lemma 1 by observing that since A1-A7 hold for $m_{\min}$ there is an ODE of order $m_{\min} + 1 < M + 1$ that can generate $\varphi(t)$.

Remark 1: The formulations of Lemma 1 and Theorem 1 do not rely on a unique solution of the ODE of Lemma 1. In case that would be preferred such a result follows from results outlined in Corollary 1 and Corollary 2 of [24], by addition of a Lipschitz condition to A1-A7.

Remark 2: The result is tied to the selection of the state space (1). It is easy to see that it is invariant under linear transformations. The implications of non-linear transformations on the result is a topic for future research. A starting point may be found in [22] where transformations based on the implicit function theorem are applied.

III. Algorithms

A. Model

The papers [25] and [26] present algorithms for recursive identification of a periodic signal with a second order ODE. The algorithms of the papers are based on Kalman filtering and least squares techniques, respectively. Here the algorithms of [25] will be used.

The continuous time model structure is given by

$$\begin{pmatrix} \frac{dx_1(t)}{dt} \\ \frac{dx_2(t)}{dt} \end{pmatrix} = \begin{pmatrix} x_2(t) \\ f_2(x_1(t), x_2(t), \theta_2) \end{pmatrix}, \tag{5}$$

where the non-trivial right hand side component $f_2(x_1(t), x_2(t), \theta)$ is parameterized as a polynomial in the states with the coefficients being the parameters of the parameter vector θ, i.e.

$$f_2(x_1(t), x_2(t), \theta_2) = \sum_{l=0}^{L_2} \sum_{m=0}^{M_2} \theta_{2,l,m} x_1^l(t) x_2^m(t). \tag{6}$$

The model structure is then discretized with a numerical integration method. In [25] the Euler forward method is used for simplicity. This allows the following discrete time model to be formulated on regression form

$$\begin{pmatrix} x_1(t+T_s) \\ x_2(t+T_s) \end{pmatrix} = \begin{pmatrix} x_1(t) + T_s x_2(t) \\ x_2(t) + \phi_2^T(x_1(t), x_2(t))\theta_2 \end{pmatrix}, \tag{7}$$

where

$$\phi_2(x_1(t), x_2(t)) = T_s \begin{pmatrix} 1 & \ldots & x_2^{M_2} & \ldots & x_1^{L_2} & \ldots & x_1^{L_2} x_2^{M_2} \end{pmatrix}^T \tag{8}$$

$$\theta_2 = \begin{pmatrix} \theta_{2,0,0} & \ldots & \theta_{2,0,M_2} & \ldots & \theta_{2,L_2,0} & \ldots & \theta_{2,L_2,M_2} \end{pmatrix}^T. \tag{9}$$

B. The Kalman Filter Algorithms

To obtain a Kalman filter based recursive system identification algorithm the state vector is first augmented with the parameter vector to obtain

$$x_\theta = \begin{pmatrix} x_1(t) & x_2(t) & \theta \end{pmatrix}^T, \tag{10}$$

see [7]. The next step would be to write down a set of linear system equations, based on (5)-(7). Unfortunately, the non-linear state dependence of (6) prevents this. Here two approximations are used to solve the problem, leading to one linear parameter varying type Kalman filter, and one extended Kalman filter (EKF).

To construct the Kalman filter algorithm, the state $x_1(t)$ is replaced in (8) by the measured signal $\varphi(t)$ and the state $x_2(t)$ is replaced in (8) with a signal obtained from a filter that differentiate $\varphi(t)$, to obtain $\dot{\varphi}_d(t)$. It is then straightforward to see that (5)-(10) give the following dynamical state space model,

$$\begin{aligned} x_\theta(t+T_s) &= F(T_s, \varphi(t), \dot{\varphi}_d(t)) x_\theta(t) + w(t) \\ &= \begin{pmatrix} 1 & T_s & 0^T \\ 0 & 1 & \phi_2^T(\varphi(t), \dot{\varphi}_d(t)) \\ 0 & 0 & I \end{pmatrix} x_\theta(t) + w(t). \end{aligned} \tag{11}$$

$$y_\theta(t) = H x_\theta(t) + e(t) = \begin{pmatrix} 1 & 0 & 0^T \end{pmatrix} x_\theta(t) + e(t) \tag{12}$$

$y_\theta(t)$ is the model of the measured signal. The Kalman filter algorithm then follows by introduction of assumptions on the systems noise $w(t)$ and the measurement noise $e(t)$. These are given by

$$w(t) = \begin{pmatrix} w_1(t) & w_2(t) & w_\theta(t) \end{pmatrix}, \tag{13}$$

$$E[w(t) w^T(t + kT_s)] = \delta_{k,0} R_1, \tag{14}$$

$$E[e(t) e(t + kT_s)] = \delta_{k,0} R_2. \tag{15}$$

Here $E[\cdot]$ denotes mathematical expectation, while R_1 and R_2 denote the covariance matrices of the systems noise and the measurement noise, respectively. The Kalman filter is now obtained by a replacement of $\tilde{F}(t)$ with $F(T_s, \varphi(t), \dot{\varphi}_d(t))$ in (18).

The EKF algorithm is obtained by using the estimated states directly in the model. The Kalman gain and the corresponding update equations are obtained by linearizing (7)-(9) around the latest state estimate, see [7]. The nonlinear model of the EKF is hence given by

$$\begin{aligned} x_\theta(t+T_s) &= F(T_s, x_1(t), x_2(t))x_\theta(t) + w(t) \\ &= \begin{pmatrix} 1 & T_s & 0^T \\ 0 & 1 & \phi_2^T(x_1(t), x_2(t)) \\ 0 & 0 & I \end{pmatrix} x_\theta(t) + w(t). \end{aligned} \tag{16}$$

$$y_\theta(t) = Hx_\theta(t) + e(t) = \begin{pmatrix} 1 & 0 & 0^T \end{pmatrix} x_\theta(t) + e(t). \tag{17}$$

Following [19], the EKF then becomes

$$\begin{aligned} K(t) &= P(t|t-T_s)H^T \left(HP(t|t-T_s)H^T + R_2\right)^{-1} \\ \hat{x}(t|t) &= \hat{x}(t|t-T_s) + K(t)(y_\theta(t) - H\hat{x}_\theta(t|t-T_s)) \\ P(t|t) &= P(t|t-T_s) - P(t|t-T_s)H^T \\ &\quad \times \left(HP(t|t-T_s)H^T + R_2\right)^{-1} HP(t|t-T_s) \\ \hat{x}_\theta(t+T_s|t) &= F(T_s, \hat{x}_\theta(t|t))\hat{x}_\theta(t|t) \\ \tilde{F}(t) &= \frac{\partial\left(F(T_s,x)x\right)}{\partial x}|_{\hat{x}_\theta(t|t)} \\ P(t+T_s|t) &= \tilde{F}(t)P(t|t)\tilde{F}^T(t) + R_1. \end{aligned} \tag{18}$$

Here $K(t)$ is the Kalman gain, $P(t|t-T_s)$ the covariance matrix of the state prediction $\hat{x}_\theta(t|t-T_s)$ and $P(t|t)$ the covariance matrix of the state estimate $\hat{x}_\theta(t|t)$.

IV. Identification of the Hodgkin-Huxley Neuron Model

The Hodgkin-Huxley neuron model uses a non-linear ODE to describe the action potentials in a neuron. As discussed in the introduction many authors have studied this model since its appearance in 1952. Here, the model will be used to illustrate the main result of the report - on model order selection and identifiability.

The model described in [17] is used here since it is accompanied with MATLAB code and a detailed parameter description that is useful for simulation purposes. The mathematical model of [17] is given by

$$\frac{dv}{dt} = \frac{1}{C_m}\left(I - g_{na}m^3h(v - E_{na})\right.$$

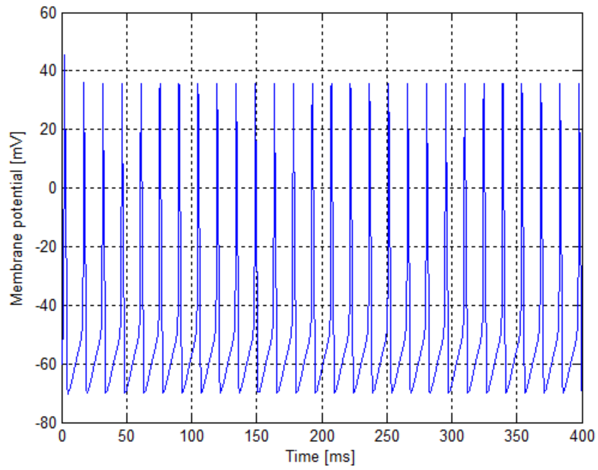

Fig. 2. **The time evolution of the simulated membrane potential v of the Hodgkin-Huxley model.**

$$-g_K n^4(v - E_K) - g_l(v - E_l)\big) \tag{19}$$

$$\frac{dn}{dt} = \alpha_n(v)(1-n) - \beta_n(v)n \tag{20}$$

$$\frac{dm}{dt} = \alpha_m(v)(1-m) - \beta_m(v)m \tag{21}$$

$$\frac{dh}{dt} = \alpha_h(v)(1-h) - \beta_h(v)h. \tag{22}$$

Here v denotes the potential, while n, m and h relate to each type of gate of the model [17] and their probabilities of being open. I denotes the applied current. The six rate constants are non-linear functions of the potential. The discussion in [17] shows that they can be well described by

$$\alpha_n(v) = \frac{0.01(v+50)}{1-e^{-(v+50)/10}} \tag{23}$$

$$\beta_n(v) = 0.125e^{-(v+60)/80} \tag{24}$$

$$\alpha_m(v) = \frac{0.1(v+35)}{1-e^{-(v+35)/10}} \tag{25}$$

$$\beta_m(v) = 4.0e^{-0.0556(v+60)} \tag{26}$$

$$\alpha_h(v) = 0.07e^{-0.05(v+60)} \tag{27}$$

$$\beta_h(v) = \frac{1}{1+e^{-0.1(v+30)}}. \tag{28}$$

The constants appearing in the ODEs have numerical values given by $C_m = 0.01\ \mu F/cm^2$, $g_{Na} = 1.2\ mS/cm^2$, $E_{Na} = 55.17\ mV$, $g_K = 0.36\ mS/cm^2$, $E_K = -72.14\ mV$, $g_l = 0.003\ mS/cm^2$, and $E_l = -49.42\ mV$. See [17] for further details.

The software of [23] was then used to simulate the model (19)-(28), resulting in the data depicted in Fig. 2 and Fig. 3. The sampling period was $0.04\ ms$ and the built in MATLAB integrator ODE45 was used. The depicted

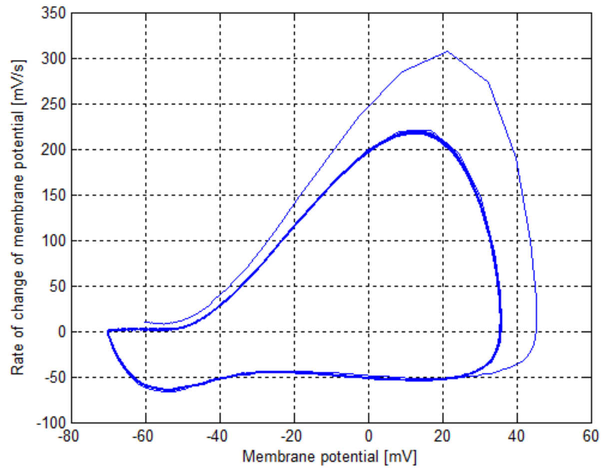

Fig. 3. **The selected 2-dimensional phase plane of the simulated spiking neuron model.**

data was scaled down with a factor 0.02 in order to give signals with numerical values of the order of 1. Such scaling is common practice when non-linear polynomial models are used in system identification. The resulting simulated model signals were then scaled up with a corresponding factor 50, to facilitate the comparison with the simulated data. The number of samples in all simulations was 10000. No measurement error was added, in order to be consistent with the Theorem 1. This is admittedly a limitation. However, a quite extensive evaluation of the effects of noise on the algorithms of this report appears in [26].

The Kalman filter and the EKF algorithms of [23] and [25], outlined above, were then applied to the data, using all combinations of polynomial degrees $L_2 = 1, ..., 4$ and $M_2 = 1, ..., 4$. The estimated parameters were then used to simulate the model (5). Not all combinations of polynomial degrees generated models with simulated stable periodic orbits. The reason for this included divergence of the EKF and an estimated model from the Kalman filter that did not generate a stable orbit. It is well known that the extended Kalman filter may diverge, the reason being that it is a non-linear recursive estimator. The reason why the Kalman filter may not generate a stable orbit is that it processes measurement data directly, without building on feedback from a simulated model as the EKF does. The successful runs are depicted in Fig. 4 - Fig. 9.

A visual inspection indicates that the polynomial degrees $L_2 = 4$ and $M_2 = 2$ generated the best result, see Fig. 8. A comparison with the data for this case appears in Fig. 1. Furthermore, the simulated membrane potential and parameter convergence corresponding to Fig. 8 appear in Fig. 10 - Fig. 12.

It can be noted that all successful runs resulted in models that resemble the phase plane of the data, despite the fact that this phase plane has a quite complicated and irregular shape, with one quite sharp corner. The accuracy seems to be best when the polynomial degree L_2 is larger than the polynomial degree M_2. The best results are obtained with the EKF. This is expected since that algorithm is based on feedback from the simulated model (7). The Kalman filter has no such feedback mechanism, it is rather based on differentiation of the measured signal.

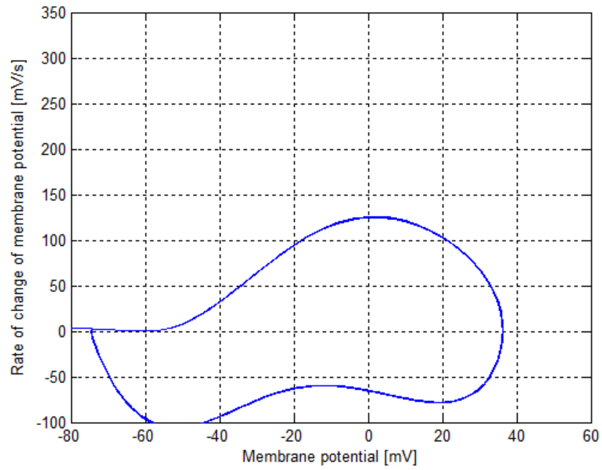

Fig. 4. **The phase plane of the simulated model obtained by the Kalman filter for the polynomial degrees $L_2 = 3$ and $M_2 = 1$.**

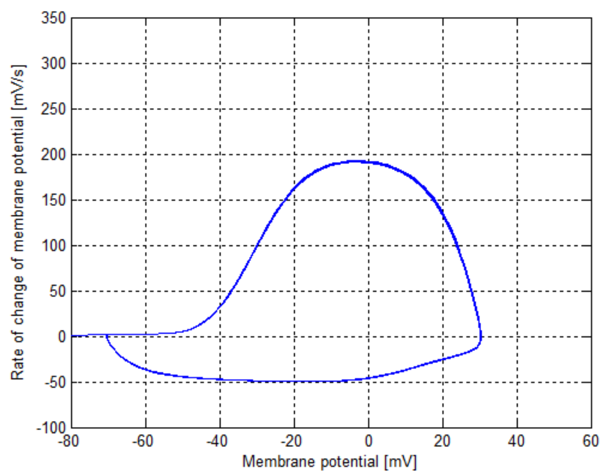

Fig. 5. **The phase plane of the simulated model obtained by the Kalman filter for the polynomial degrees $L_2 = 2$ and $M_2 = 3$.**

The benefit of using simulated model feedback is well known in so called output error identification in system identification, see e.g. [12]. Admittedly, the model is not perfect. One reason for this may be the degree of the polynomial model. A related problem that needs to be overcome in future work is to obtain algorithms with better numerical properties that are capable of using higher degrees. An alternative could be to use other basis functions than polynomials.

When the best result is compared to the data, as in Fig. 1, it can be concluded that the applied algorithms are capable of generating a second order ODE that can explain the data quite well in the phase plane. The simulated

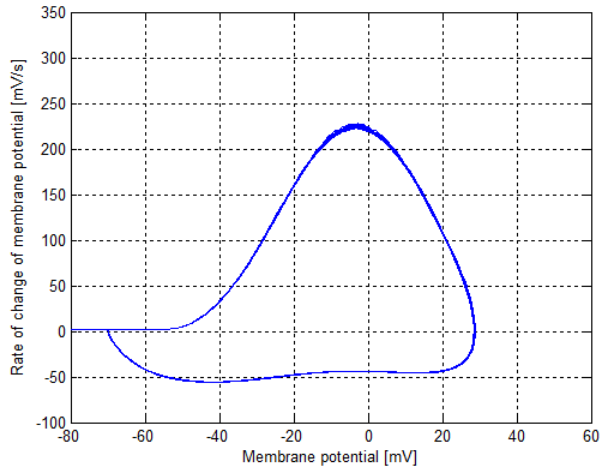

Fig. 6. **The phase plane of the simulated model obtained by the EKF for the polynomial degrees $L_2 = 3$ and $M_2 = 2$.**

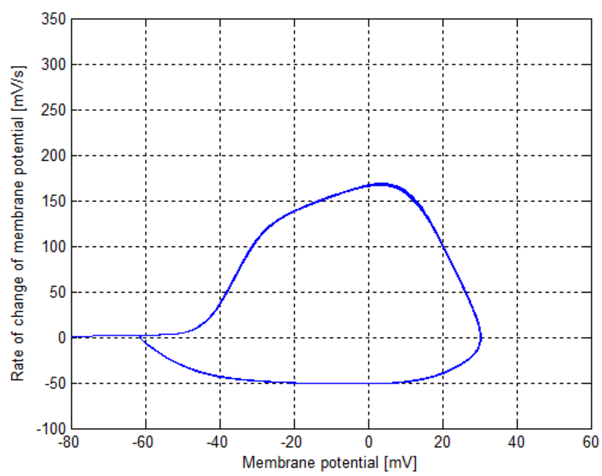

Fig. 7. **The phase plane of the simulated model obtained by the Kalman filter for the polynomial degrees $L_2 = 2$ and $M_2 = 4$.**

membrane potential of the original Hodgkin-Huxley model of Fig. 2 and the simulated membrane potential of the estimated second order ODE of Fig. 10 supports this conclusion. The results hence supports the model order guidance provided by Theorem 1.

So what does this mean? It needs to be stressed that the result of the report *does not* mean that previous work and papers on modeling using the model structure of a complete Hodgkin-Huxley ODE are questionable, see e.g. [1], [9], [16]. The present report only states that there is *also* a possibility to use a model with lower order to achieve the goal of modeling the spiking mode of the system, and in that respect identifiability of the higher order model may be lost. The result of the report is hence in line with the work of [6], [11] and [27].

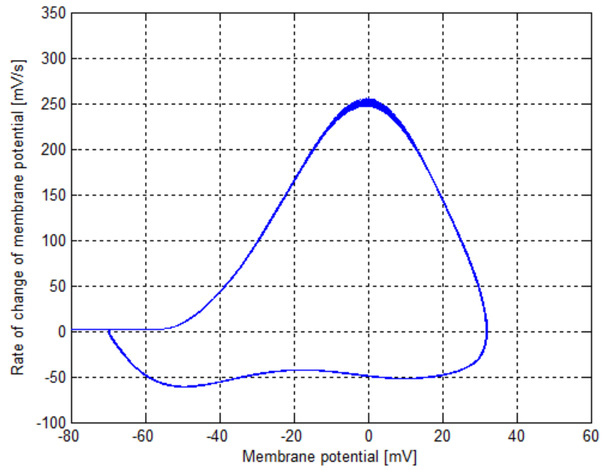

Fig. 8. **The phase plane of the simulated model obtained by the EKF for the polynomial degrees $L_2 = 4$ and $M_2 = 2$.**

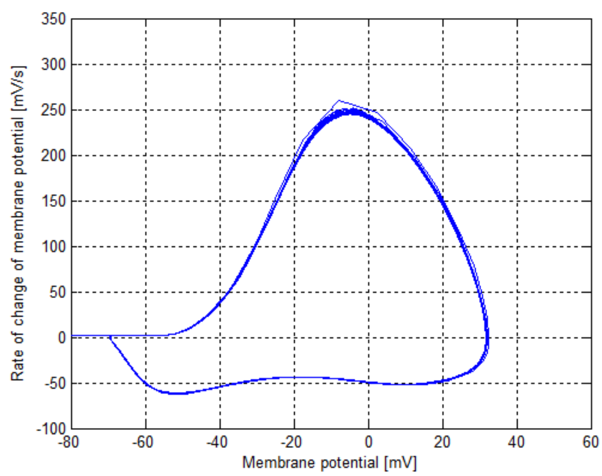

Fig. 9. **The phase plane of the simulated model obtained by the EKF for the polynomial degrees $L_2 = 4$ and $M_2 = 3$.**

V. CONCLUSIONS AND FUTURE RESEARCH

The report presented a result on model order and identifiability, applicable for example when non-linear biological dynamic models are identified from data obtained from a biological system in stable oscillation. It was proved and illustrated with simulation that in such cases care needs to be exercised when the model order is selected or the result may not be unique. More precisely, if the orbit of the data in a state space of a specific dimension does not intersect itself, and the orbits in lower dimensional state spaces do, then the specific dimension defines the model order to use.

The report then discussed identification of a non-linear Hodgkin-Huxley neuron model of order four. The model

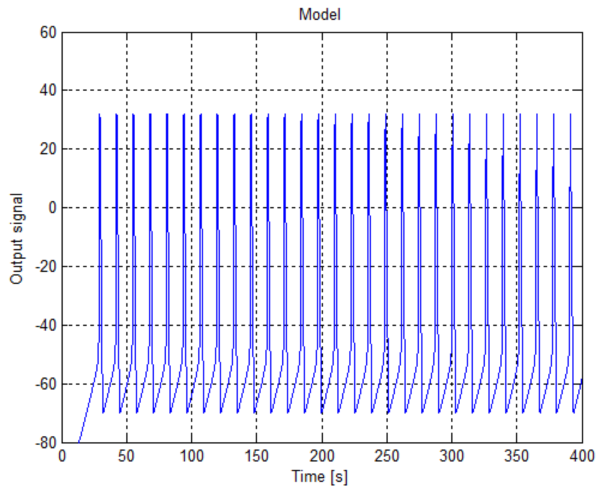

Fig. 10. **The simulated membrane potential using (5) for the polynomial degrees $L_2 = 4$ and $M_2 = 2$.**

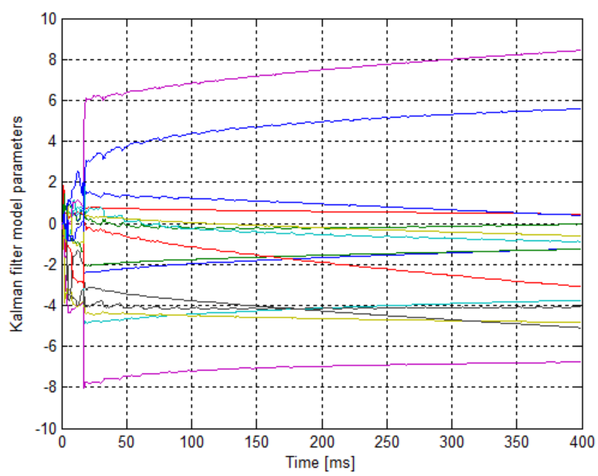

Fig. 11. **The parameter evolution for the Kalman filter for the polynomial degrees $L_2 = 4$ and $M_2 = 2$. The reason why the evolution for the Kalman filter is shown is that the parameters at the end of the run are used as initial values for the EKF algorithm. The latter algorithm only performs fine tuning, as seen in Fig. 12**

was simulated in spiking mode, generating a stable limit cycle. Two simple recursive algorithms based on Kalman filtering techniques then identified a second order non-linear ODE that accurately described the stable oscillation. This was possible using a polynomial model of the right hand side of the ODE, where the total polynomial degree was 6. This provides further motivation for the relevance of Theorem 1 of this report, for oscillatory biological systems.

The result of the identification was accurate but not perfect which implies that there is a need to develop better identification algorithms. In particular Bayesian methods that go beyond the point estimation techniques of the

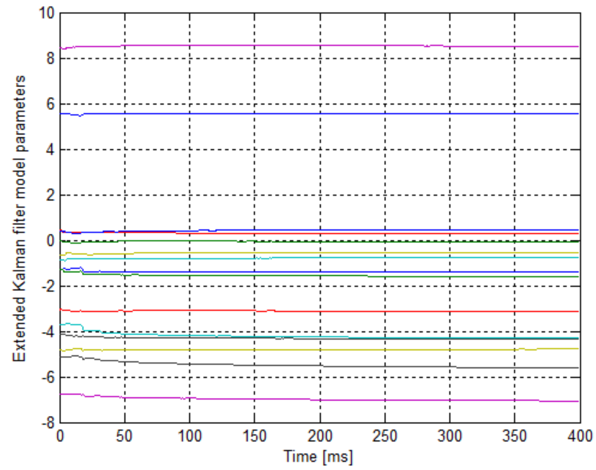

Fig. 12. **The parameter evolution for the EKF for the polynomial degrees $L_2 = 4$ and $M_2 = 2$.**

Kalman filter and EKF may prove useful. It is also essential to consider the tracking problem, since in practice a perfectly periodic signal is seldom available. The recursiveness of the algorithms applied in the report is then an advantage. It would be particularly interesting to proceed with live data test and experiments on other oscillatory systems in systems biology. Theoretically, further results on state space selection would be interesting. A detailed study that ties the result of the report to what is known of the oscillation of the Hodgkin-Huxley model in spaces with a lower dimension than four [27], would also be interesting.

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