

# Identifiability of a Hodgkin-Huxley type ion channel under voltage step measurement conditions

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**Abstract:** In this paper, we analyze the identifiability properties of a Hodgkin-Huxley (HH) type voltage dependent ion channel model under voltage clamp circumstances. The elimination of the differential variables is performed, and the identifiability of various parameters is analyzed using the differential algebra approach and the algorithm based on the Taylor series expansion of the output. It is shown that the model is structurally non-identifiable using certain commonly applied parametrizations, and hidden dependences between physical parameters are unravelled. Using the results of the identifiability analysis, physically meaningful examples are shown when the model parameters are different but the system outputs are identical.

Keywords: Modeling and Identification; Control Applications in Biological Processes

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## 1. INTRODUCTION

The aim of the paper is to present structural identifiability results for simple ion channel models under voltage clamp measurement conditions. The Hodgkin-Huxley (HH) model form of membrane currents and cell electrophysiology is widely used for modeling excitable cells such as neurons [Hodgkin and Huxley, 1952]. HH models that are essentially nonlinear electric circuit models, are composed of parallel voltage dependent or independent conductances that correspond to different membrane currents. The dynamical descriptions of neuronal behavior, ranging from the fundamental theoretical principles [Izhikevich, 2000, 2003, 2005] to the wide range of applications with special focus [Shorten and Wall, 2000, Komendantov et al., 2007, Roth and Hausser, 2001, Borg-Graham et al., 1998, Fletcher and Lee, 2009], are predominantly based on this model class.

Once the model structure is fixed, the next key step of the modelling process is parameter estimation, the quality of which is crucial in later usability of the obtained model [Ljung, 1987]. The identifiability properties of the system describe whether there is a theoretical possibility for the unique determination of system parameters from appropriate input-output measurements or not. Basic early references for studying identifiability of dynamical systems are the books [Walter, 1982, 1987]. The study and development of differential algebra methods, that are used for identifiability analysis, contributed to the better understanding of important system theoretic problems [Diop and Fliess, 1991, Fliess and Glad, 1993]. The most important definitions and conditions of structural identifiability for general nonlinear systems were presented in [Ljung and Glad, 1994] in a very clear way. Further developments in

the field include the identifiability conditions of rational function state-space models [Margaria et al., 2001] and the possible effect of special initial conditions on identifiability [Saccomani et al., 2003].

For process systems Rodriguez-Fernandez et al. [2007] have clearly shown that prior structural identifiability analysis is an important step in the solution of model calibration problems. Davidescu and Jorgensen [2008] solves the problem of structural parameter identifiability for chemical reaction network models. Following this line, this paper presents the first study of identifiability of HH models.

Although several articles have been published which are focusing on parameter estimation problem in the case of HH based models under various assumptions, see [Tabak et al., 2000, Tabak and Moore, 1998, Willms et al., 1999, Tien and Guckenheimer, 2008, Lee et al., 2006, Huys et al., 2006], there is a lack of literature data which addresses the identifiability properties of such models.

Both the articles [Lee et al., 2006] and [Willms et al., 1999] recognized the problems of the conventional estimation algorithms, and provided improved methods for the estimation of HH models. Lee et al. [2006] proposed a new numerical approach to interpret voltage clamp experiments. As one of the main results of [Lee et al., 2006], it is stated, that all channel parameters can be determined from a single appropriate voltage step, but no rigorous proof has been provided.

## 2. HODGKIN-HUXLEY TYPE MATHEMATICAL MODELING OF ION CHANNELS

The basic modelling assumptions of the HH model, which are based on the kinetic description of the behavior of multiple voltage-dependent subunits [Hille, 2001], are evident and well formulated from the physical perspective. In contrast, if we analyze the model from the point of view of systems theory, as a nonlinear state-space model (a system of nonlinear ordinary differential equations, ODE's), several interesting questions arise, related not only to the bifurcation structure of the model, but also to the identifiability properties of the system class.

### 2.1 Ion channel model

We consider a simple hypothetical ion channel with one activation ( $m$ ) and one inactivation variable ( $h$ ). The current, which is the measured variable, is simply described by

$$I = gm^{p_m}h^{p_h}(V - E) \quad (1)$$

where  $V$  is the voltage,  $g$  is the maximal conductance, and  $E$  is the reversal potential of the corresponding ion. The exponents  $p_m$  and  $p_h$  correspond to the number of independent activation and inactivation subunits of the voltage channel protein. We will assume the simplest case in our calculations when  $p_m = p_h = 1$ . Both  $m$  and  $h$  are state variables in the following nonlinear state-space model

$$\frac{dm}{dt} = \frac{m_\infty(V) - m}{\tau_m(V)} \quad (2)$$

$$m_\infty(V) = \left(1 + \exp\left(\frac{V_{1/2m} - V}{k_m}\right)\right)^{-1}, \quad k_m > 0 \quad (3)$$

$$\frac{1}{\tau_m(V)} = \left(c_{bm} + c_{am}\exp\left(-\frac{(V_{Maxm} - V)^2}{\sigma_m^2}\right)\right)^{-1} \quad (4)$$

$$\frac{dh}{dt} = \frac{h_\infty(V) - h}{\tau_h(V)} \quad (5)$$

$$h_\infty(V) = \left(1 + \exp\left(\frac{V_{1/2h} - V}{k_h}\right)\right)^{-1}, \quad k_h < 0 \quad (6)$$

$$\frac{1}{\tau_h(V)} = \left(c_{bh} + c_{ah}\exp\left(-\frac{(V_{Maxh} - V)^2}{\sigma_h^2}\right)\right)^{-1} \quad (7)$$

where  $V_{1/2m}$ ,  $k_m$ ,  $V_{1/2h}$ , and  $k_h$  are the parameters of the Boltzmann functions which describe the steady state activation and inactivation values.  $c_{bm}$ ,  $c_{am}$ ,  $V_{Maxm}$ ,  $\sigma_m$ ,  $c_{bh}$ ,  $c_{ah}$ ,  $V_{Maxh}$  and  $\sigma_h$  denote the parameters of Gauss-functions which describe the voltage dependent time-constants.

We have to note that the approximation of the steady state values with Boltzmann functions is not always valid, as it is described in [Willms et al., 1999]. However in the rest of this paper we assume that this consideration holds. It can be said that in the literature the use of Boltzmann-type sigmoid functions for the description of steady-state values is widespread, but not exclusive (see e.g. Komendantov et al. [2007]).

The description of the voltage dependent time constants in the literature is more diverse. In fact, the variability of time constant curves corresponding to various rate constant functions is described in [Willms et al., 1999]. In this

study we will use standard Gauss functions, parameterized by  $c_{bm}$ ,  $c_{am}$ ,  $V_{Maxm}$ ,  $\sigma_m$ ,  $c_{bh}$ ,  $c_{ah}$ ,  $V_{Maxh}$  and  $\sigma_h$ .

### 2.2 Voltage step protocol

In general, two basic measurement protocols are used for parameter estimation of neuronal models: The voltage clamp protocol, when the voltage is fixed and the transmembrane currents are measured, and the current clamp protocol, in which case an arbitrary value of injected current to the cell is fixed.

In the case of voltage clamp, where the voltage is held constant, the only remaining differential variables are the activation and inactivation variables.

An important subcase of the voltage clamp method is when the voltage, which is in this case the manipulable input ( $u$ ) to the system, is held constant ( $V = V_0 = u$ ,  $\dot{u} \equiv 0$ ) during a known time interval. In this case the constant values of  $m_\infty$ ,  $h_\infty$ ,  $\tau_m$  and  $\tau_h$  can be considered as parameters in addition to  $g$  and  $E$ . This implies that the non-polynomial nonlinearities of Boltzmann and Gauss functions vanish from the equations, and the model will fall into the class of polynomial systems, which makes the application of computer algebra based software tools (e.g. [Bellu et al., 2007]) possible for identifiability testing.

We will denote the voltage independent nature of the above parameters shortly as follows

$$m_\infty(V) = m_\infty(V_0) = m_\infty \quad (8)$$

$$\frac{1}{\tau_m(V)} = \frac{1}{\tau_m(V_0)} = \frac{1}{\tau_m} \quad (9)$$

$$h_\infty(V) = h_\infty(V_0) = h_\infty \quad (10)$$

$$\frac{1}{\tau_h(V)} = \frac{1}{\tau_h(V_0)} = \frac{1}{\tau_h} \quad (11)$$

In this case Eqs. (1-7) simplify to the equations below:

$$I = gmh(V_0 - E) = gmh(u - E) \quad (12)$$

$$y = I, \quad u = V_0$$

$$\frac{dm}{dt} = \frac{m_\infty - m}{\tau_m} \quad (13)$$

$$\frac{dh}{dt} = \frac{h_\infty - h}{\tau_h} \quad (14)$$

where the model parameters are  $E$ ,  $m_\infty$ ,  $\tau_m$ ,  $h_\infty$  and  $\tau_h$ .

## 3. BASIC NOTIONS ON STRUCTURAL IDENTIFIABILITY

In general, let us consider the following class of models

$$\dot{x} = f(x, u, \theta), \quad x(0) = x_0 \quad (15)$$

$$y = h(x, u, \theta)$$

where  $x \in \mathbb{R}^n$  is the state vector,  $y \in \mathbb{R}^m$  is the output,  $u \in \mathbb{R}^k$  is the input, and  $\theta \in \mathbb{R}^d$  denotes the parameter vector. We assume that the functions  $f$  and  $h$  are polynomial in the variables  $x, u$  and  $\theta$ . We have to note that the HH model class in general is non-polynomial, but under the circumstances of the voltage step protocol, it can

be casted into this class. Furthermore, it can be shown [Hernández-Bermejo and Fairen, 1997] that majority of nonlinear state-space models with smooth right-hand sides can also be embedded in the above polynomial model form.

Shortly speaking, *global structural identifiability* means that

$$y(t|\theta') \equiv y(t|\theta'') \Rightarrow \theta' = \theta'' \quad (16)$$

where

$$y(t|\theta) = h(x(t, \theta), u(t), \theta) \quad (17)$$

and  $x(t, \theta)$  denotes the solution of (15) with parameter vector  $\theta$ . This means that if the system outputs are identical, then the underlying parameters are the same: this is a model property, e.g. the property of (15).

The following notations, definitions and conditions are mostly taken from [Ljung and Glad, 1994]. Let us denote a differential polynomial  $F(u, \dot{u}, \dots, y, \dot{y}, \dots)$  by  $F(u, y; p)$  where  $p = \frac{d}{dt}$ .

The structure (15) is *globally identifiable* if and only if by differentiating, adding, scaling and multiplying the equations the model can be rearranged to the parameter-by-parameter linear regression form:

$$P_i(u, y; p)\theta_i - Q_i(u, y; p) = 0 \quad i = 1, \dots, d \quad (18)$$

It is visible from (18) that  $\theta_i$  can be expressed as

$$\theta_i = \frac{Q_i(u, y; p)}{P_i(u, y; p)} \quad i = 1, \dots, d \quad (19)$$

if  $P_i$ s are non-degenerate. The non-degenerate condition can be fostered by ensuring that the inputs excite the system dynamics sufficiently so that the parameter vector can be determined in a numerically well-conditioned way.

### 3.1 Structural identifiability analysis using Taylor series expansion of the output

Consider again the nonlinear model structure in (15). Walter and Pronzato [1996] gives the following condition for global structural identifiability, that is based on the Taylor series expansion of the system output. Let

$$c_k(\theta) = \lim_{t \rightarrow 0^+} \frac{d^k}{dt^k} y(t, \theta) \quad (20)$$

Then a sufficient condition of global structural identifiability is

$$c_k(\theta_1) = c_k(\theta_2), \quad k = 0, 1, \dots, k_{max}, \implies \theta_1 = \theta_2 \quad (21)$$

where  $k_{max}$  is a positive integer (small enough for the symbolic computations to remain tractable). It is important to remark that the lack of global solvability of  $c_k$  for the system parameters in the case of a given  $k$  value is generally not enough for proving non-identifiability, since the inclusion of higher derivatives (new  $c_k$ -s) may result in the solvability of the corresponding system of nonlinear equations.

## 4. STRUCTURAL IDENTIFIABILITY OF ION CHANNEL MODELS

### 4.1 Identifiability analysis using differential algebra

The identifiability analysis requires to eliminate the differential (state) variables  $m$  and  $h$  from the model Eqs. (12)-(14) and then to find the parameter groups that can be

determined from the resulting equations. For convenience, let us introduce the following parametrization:

$$\begin{aligned} x_1 &= m, \quad x_2 = h \\ p_1 &= \frac{1}{\tau_m}, \quad p_2 = m_\infty, \quad p_3 = \frac{1}{\tau_h} \\ p_4 &= h_\infty, \quad p_5 = g, \quad k_1 = u - E \end{aligned} \quad (22)$$

It can be seen that the physical system parameters are trivially computable, if  $p_1, \dots, p_5$  are given. In general, we assume that  $k_1$  is known, and we are searching for the largest subset in  $\{p_1, \dots, p_5\}$  that is globally identifiable. Using eq (22), the state and output equations of the simple model can be written as

$$\dot{x}_1 = p_1(p_2 - x_1), \quad \dot{x}_2 = p_3(p_4 - x_2) \quad (23)$$

$$y = k_1 p_5 x_1 x_2 \quad (24)$$

To get a pure input-output relation, we have to eliminate the state variables from eqs. (23)-(24). For this, the time-derivative of  $y$  is taken that gives

$$\dot{y} = (-p_1 - p_3)y + k_1 p_5 p_3 p_4 x_1 + k_1 p_5 p_1 p_2 x_2. \quad (25)$$

By taking the second derivative of  $y$  with respect to time, the following equation is obtained

$$\begin{aligned} \ddot{y} &= (-p_1 - p_3)\dot{y} - k_1 p_5 p_1 p_3 p_4 x_1 - k_1 p_1 p_1 p_2 p_3 x_2 \\ &\quad + 2k_1 p_1 p_2 p_3 p_4 p_5 \end{aligned} \quad (26)$$

It can be observed that both eqs. (25) and (26) depend linearly on  $x_1$  and  $x_2$ , therefore the state variables can be expressed from them and substituted to the original output equation (24) in a straightforward way. This shows that the system is *algebraically observable* [Diop and Fliess, 1991, Bellu et al., 2007] in this case. The expression and substitution results in the following lengthy input-output relation

$$\begin{aligned} 0 &= (-a_0 - a_1 a_5 - a_1 a_3)y - (a_1 a_4 - a_1 a_2)\dot{y} \\ &\quad - 2a_1 \ddot{y} + (a_2 a_5 + a_3 a_4)y\dot{y} + (a_2 + a_4)\dot{y}\ddot{y} + (a_3 + a_5)y\ddot{y} \\ &\quad + a_3 a_5 y^2 + a_2 a_4 \dot{y}^2 + \dot{y}^2 + a_1^2 \end{aligned} \quad (27)$$

where  $a_0, \dots, a_5$  are defined as

$$a_0 = (p_3^2 - p_1 p_3)(k_1 p_1^2 p_2 - k_1 p_1 p_2 p_3)^2 p_4 p_5,$$

$$a_1 = 2k_1 p_1 p_2 p_3 p_4 p_5, \quad a_2 = 2p_1 + p_3$$

$$a_3 = p_1^2 + p_1 p_3, \quad a_4 = p_1 + 2p_3, \quad a_5 = p_1 p_3 + p_3^2 \quad (28)$$

The coefficients in eq. (27) define the following set of equations

$$-a_0 - a_1 a_5 - a_1 a_3 = c_1 \quad (29)$$

$$-a_1 a_4 - a_1 a_2 = c_2 \quad (30)$$

$$-2a_1 = c_3 \quad (31)$$

$$a_2 a_5 + a_3 a_4 = c_4 \quad (32)$$

$$a_2 + a_4 = c_5 \quad (33)$$

$$a_3 + a_5 = c_6 \quad (34)$$

$$a_3 a_5 = c_7 \quad (35)$$

$$a_2 a_4 = c_8 \quad (36)$$

$$a_1^2 = c_9 \quad (37)$$

The solvability of eqs. (29)-(37) with respect to the parameters  $p_1, \dots, p_5$  can be checked by e.g. Buchberger's algorithm (see, e.g. Saccomani et al. [2003]). Using this method, the following parameter-pairs can be shown to be globally identifiable:  $(p_1, p_2)$ ,  $(p_1, p_4)$ ,  $(p_1, p_5)$ ,  $(p_2, p_3)$ ,  $(p_3, p_4)$ ,  $(p_3, p_5)$ . The following parameter combinations

turned out to be locally identifiable (with 2 possible solutions for each):  $(p_1, p_3)$ ,  $(p_1, p_2, p_3)$ ,  $(p_1, p_3, p_4)$ ,  $(p_1, p_3, p_5)$ .

For comparison, the identifiability analysis technique based on the Taylor series expansion of the output has been applied, too, that is described in the following subsection.

#### 4.2 Structural identifiability analysis using the Taylor series method

To keep the original physical parameters (or their simple transformations), let us use the previously defined parametrization (22) of the ion-channel-model

The solution of the state equation (23) is easy to give with zero initial condition:

$$x_1(t) = -p_2 e^{-p_1 t} + p_2 \quad (38)$$

$$x_2(t) = -p_4 e^{-p_3 t} + p_4 \quad (39)$$

From this, the output and its successive derivatives are given by

$$\begin{aligned} y(t) &= k_1 p_2 p_4 p_5 (1 + e^{-(p_1+p_3)t} - e^{-p_1 t} - e^{-p_3 t}) \\ \dot{y}(t) &= k_1 p_2 p_4 p_5 (-(p_1 + p_3)e^{-(p_1+p_3)t} + p_1 e^{-p_1 t} + p_3 e^{-p_3 t}) \\ &\dots \\ y^{(k)}(t) &= k_1 p_2 p_4 p_5 ((-1)^k (p_1 + p_3)^k e^{-(p_1+p_3)t} + \\ &\quad + (-1)^{k+1} (p_1^k e^{-p_1 t} + p_3^k e^{-p_3 t})), \quad k \geq 1. \end{aligned} \quad (40)$$

From Eq. (40), the coefficients  $c_k(\theta)$  can be computed as

$$\begin{aligned} c_0(\theta) &= 0 \\ &\dots \\ c_k(\theta) &= k_1 p_2 p_4 p_5 ((-1)^k (p_1 + p_3)^k + \\ &\quad + (-1)^{k+1} (p_1^k + p_3^k)), \quad k \geq 1. \end{aligned} \quad (41)$$

By the symbolic solution of (41), the following parameter pairs were found to be globally identifiable:  $(p_1, p_5)$ ,  $(p_1, p_2)$ ,  $(p_3, p_2)$ ,  $(p_3, p_5)$ ,  $(p_1, p_4)$ ,  $(p_3, p_4)$ . The pair  $(p_1, p_3)$  was found to be locally identifiable with 2 possible solutions as well as the triplets  $(p_1, p_3, p_5)$ ,  $(p_1, p_3, p_4)$ ,  $(p_1, p_3, p_2)$

*Brief comparison of the results obtained by the two methods*  
The necessary symbolic computations for both methods were performed using the freely available Sage software environment (see. e.g. Stein and Joyner [2005], Beezer [2009]). The two methods gave exactly the same globally and locally identifiable parameter combinations. An advantageous property of the differential algebra approach is that eq. (27) defines a possible convex parametrization of the model which can be very useful in practical parameter estimation. However, the smaller set of nonlinear equations in the case of the Taylor series method was much more easily tractable with symbolical software. Furthermore, it can be conjectured from the closed form of eqs. (41) that neither  $(p_2, p_4, p_5)$ , nor any pair from these three parameters can be globally identifiable.

## 5. EXAMPLES ILLUSTRATING THE LACK OF GLOBAL IDENTIFIABILITY

In this section, we show physically meaningful examples that illustrate the non-global identifiability of the ion channel model with respect to the three parameters (namely,

$g$ ,  $m_\infty$ , and  $h_\infty$ ) that often have to be estimated. Other model parameters are assumed to be known in the examples

### 5.1 Identifiability of $g$ , $m_\infty$ and $h_\infty$ at constant input voltage

To check and support our former hand calculations in section 4.1, we used the differential algebra software DAISY [Bellu et al., 2007]. Firstly, the output of DAISY showed that the model is algebraically observable, which is in good agreement with our results regarding the elimination of differential variables. Secondly, according to the identifiability results of the analysis, the parameters  $m_\infty$ ,  $h_\infty$  and  $g$  (i.e.  $p_2, p_4, p_5$ ) are not globally identifiable. Moreover, no pair from these three parameters are identifiable. This fact also matches the results of sections 4.2 and 4.3 where we couldn't show that these three parameters (or any two of them) are identifiable under voltage clamp measurement conditions. These results are trivial in the case of steady state, when  $m = m_\infty$  and  $h = h_\infty$ , because in this case only the product of the three parameters appears as output in  $y = I = gmh(V - E)$ . However, the dependence also holds during the transient period.

In the following, we present an interesting example illustrating non-identifiability when the parameters of the system are different, but the outputs of the two systems are identical. The key issue for this counterexample is the appropriate modification of the initial values of the state variables. The free choice of initial values is not too realistic in the case of voltage clamp measurements, but this calculation will help us to provide a more realistic counterexample in the following subsection.

The inactivation steady-state values, the time parameters and the reversal potential were the same in the two cases:

$$\begin{aligned} h_\infty &= p_4 = 0.75, \quad V_{Maxm} = -78mV, \quad \sigma_m = 34, \\ c_{am} &= 8.7ms, \quad c_{bm} = 0.8ms, \quad E = -93mV, \\ V_{Maxh} &= -23mV, \quad \sigma_h = 24, \quad c_{ah} = 6.9ms, \quad c_{bh} = 9ms \end{aligned} \quad (42)$$

*Parameter set 1* In the first case, in addition to the parameters in (42),  $p_2$  was defined as 0.2 and  $p_5$  was chosen to be 67 nS. The initial values of the state variables were  $x_1(0) = 0.35$ ,  $x_2(0) = 0.25$ . The current  $I = y$  is measured in pA units. The trajectory of the state-space variables can be expressed as:

$$\begin{aligned} x_1 &= p_2 + (x_1(0) - p_2)e^{-p_1 t} \\ x_2 &= p_4 + (x_2(0) - p_4)e^{-p_3 t} \end{aligned} \quad (43)$$

The current can be computed as

$$y(t) = p_5 k_1 (p_2 + (x_1(0) - p_2)e^{-p_1 t} (p_4 + (x_2(0) - p_4)e^{-p_3 t})) \quad (44)$$

*Parameter set 2* In the second case, the parameters which are considered unknown were changed as follows (the superscript \* refers to case 2). Let us introduce a scaling parameter  $\lambda > 0$ .  $p_2^* = \lambda \cdot p_2 = 0.3$  and  $p_5^* = p_5/\lambda$ . The initial values of the state variables were  $x_1^*(0) = \lambda \cdot x_1(0)$ ,  $x_2^*(0) = x_2(0) = 0.25$ . The current can now be written as

$$\begin{aligned} y^*(t) &= p_5^* k_1 x_1^* x_2^* \\ &= k_1 p_5^* (p_2^* + (x_1^*(0) - p_2^*)e^{-p_1 t}) (p_4 + (x_2^*(0) - p_4)e^{-p_3 t}) \\ &= k_1 \frac{p_5}{\lambda} (\lambda p_2 + (\lambda x_1(0) - \lambda p_2)e^{-p_1 t}) (p_4 + (x_2(0) - p_4)e^{-p_3 t}) \\ &= y(t) \end{aligned} \quad (45)$$

It is clearly visible from Eq. (45) that the measured membrane current can be the same when the time functions of the state variables are different.

This analysis shows that under the measurement conditions of constant voltage, known time constants and reversal potential, together with unknown initial values of state variables, it may be theoretically impossible to uniquely determine the parameters  $m_\infty$ ,  $h_\infty$  and  $g$  from a single measurement record.

The above case is not likely in the case of a standard voltage clamp protocol, where the voltage is held at an other constant value (the holding potential  $V_{hold}$ ) before the voltage step. The holding potential determines the initial values of the differential variables:  $m(0) = m_\infty(V_{hold})$  and  $h(0) = h_\infty(V_{hold})$ . However, the scenario is not impossible, as we will show in the following example.

### 5.2 Identifiability of $g$ , $m_\infty$ and $h_\infty$ in the case of a single voltage step

Based on the previous results, we will show in the case of two fictitious neurons that the measurable current responses of a voltage step during voltage clamp measurement can be identical in the case of different parameters. In this case, we relax the former assumption that the input voltage is constant during the experiment. This means that we will use the original nonlinear ion channel model given by Eqs. (1)-(7). According to our aim, we shall tune the activation and inactivation characteristics of the neurons in a way that they should reproduce the preliminary defined values at certain voltage values.

First we will consider a case when the activation and inactivation characteristics will determine the same initial values. Let us suppose that both neurons to be compared here inhibit only one ion channel, and the activation and inactivation characteristics of the first neuron are described by

$$\begin{aligned} m_\infty(V) &= \left(1 + \exp\left(\frac{V_{1/2m} - V}{k_m}\right)\right)^{-1} \\ h_\infty(V) &= \left(1 + \exp\left(\frac{V_{1/2h} - V}{k_h}\right)\right)^{-1} \end{aligned} \quad (46)$$

The second neuron is characterized by the functions  $m_\infty^*$  and  $h_\infty^*$  with parameters  $V_{1/2m}^*$ ,  $k_m^*$ ,  $V_{1/2h}^*$ ,  $k_h^*$ . The parameter values for the two neurons can be found in Table 1. The parameters of the voltage dependent time constants in both cases are the same as in *Parameter set 1* in subsection 5.1.

Table 1. Parameters of the two neurons

No	$V_{1/2m}$	$k_m$	$V_{1/2h}$	$k_h$	$g$
1	-31.932 mV	13.033	-44.354 mV	-5.139	67 nS
2	-41.056 mV	10.555	-44.354 mV	-5.139	44.67 nS

The voltage dependent characteristics are shown in Fig. 1

As seen in in Fig. 1, the value of  $m_\infty$  is 0.35 at -40mV and it is 0.20 at -50mV. At the same time, the value of  $m_\infty^*$  is 0.525 at -40mV and 0.30 at -50mV. The inactivation curve is the same in both cases. We apply a holding potential of -40 mV and a voltage step to -50 mV at  $t=100$ ms.

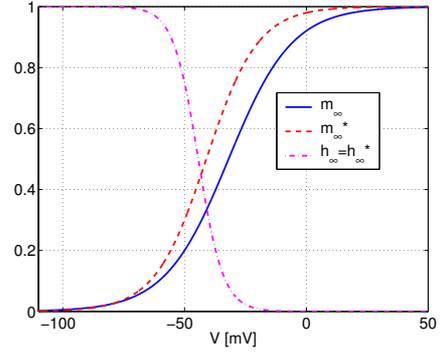


Fig. 1. Voltage dependences of  $m_\infty$ ,  $m_\infty^*$  and  $h_\infty^* = h_\infty^*$

The comparison of trajectories of activation and inactivation variables and the output (the measured current) are depicted in Fig. 2. The figure shows that the outputs are identical in the two cases, although the parameters of the two models are different.

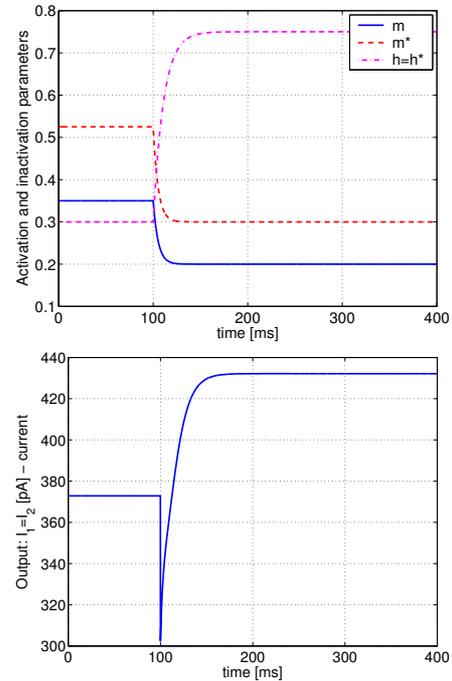


Fig. 2. The activation and inactivation variables, and the output during the voltage step in the case of neuron 1 and 2. The upper index \* refers to the activation and inactivation variables of neuron 2. The measured output current traces are identical in both cases.

## 6. CONCLUSIONS

The identifiability of a simple ion channel model used in Hodgkin-Huxley type neuron models was studied in this paper. Under constant input voltage conditions, the originally nonlinear state equations became essentially linear (with a constant drift term that can contain unknown parameters), and the only nonlinearity remained in the output equation.

Using this simple model structure, two approaches, namely the differential algebraic method and the algorithm based on the Taylor series expansion of the output were applied

to investigate structural identifiability. Both methods require the symbolic solution of nonlinear equations to get identifiability results. It was shown that the two methods usefully complement each other in the identifiability analysis. Based on the analysis results, two illustrative cases were shown (with different assumptions) when the system parameters are different and physically meaningful, while the outputs are identical.

Further work will be focused on the treatment of the situation when the output contains higher powers of the state variables, and on the identifiability analysis of systems containing more than one ion channel.

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