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Observability of Minimal Cell Modelse

Research Article

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Abstract

Identifying and modeling of biological systems is very useful to understand cell's dynamic. To know what really happens inside the cell we need to observe the state of a cell. In fact observability is a structural property of a control system defined as the possibility to deduce the state of the system from observing its input-output behavior. Any complex cell model is a combination of some minimal models which are simpler than complex cell model because they have two dimensions. These models can describe the behavior of the cell. The property of observability for nonlinear systems is very useful in analyzing such systems. This paper deals with the observability of minimal cell models. Based on the fact that the minimal cell models are nonlinear, analyzing the property of these models need nonlinear methods. The method has been used for observability is Lie Derivative. The results indicate observability of minimal cell models.

KeyWords: Observability; Lie Derivative; Nonlinear Systems; Hodgkin-Huxley Model; Minimal Cell Models.

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Introduction

Neurons are responsible for transmitting messages throughout the body via long distance electrical signals known as action potentials(AP). These depend on the active transport of sodium and potassium ions across the cell membrane. At the cellular level, the electrical signal excitable cells amplify and propagate is a change in the potential across a cell's membrane, caused by different ion currents flowing through the membrane's channels. In fact for each excitation event, the electrical signal is called an AP. For non-pacemaking excitable cells, an AP is an externally triggered all or nothing response to an external stimulus: if the stimulus is sufficiently strong, the cell fires an excitation AP [1]. The effect of various drugs on the process of neuron firing is a current research interest. The Hodgkin-Huxley equations mathematically model the influx and efflux of these ions across the cell membrane. One of the most important models in computational neuroscience is the Hodgkin-Huxley model of the squid giant axon [2]. The Hodgkin-Huxley model is a combination of minimal models. A mixture of one amplifying and one resonant gating variable results a minimal model. Each minimal model can oscillate at least from some values of its parameters. There are

only few minimal models and understanding their dynamics can shed light on dynamics of more complicated electrophysiological models [3].

To know what really happens inside the cell we need to observe the state of a cell. In fact observability is a structural property of a control system defined as the possibility to deduce the state of the system from observing its input-output behavior [4]. In some cases these states cannot be measured directly. Here we need to observe them by an observer and check the observability of such systems. Observability is a useful property for analyzing minimal models. Minimal models can be represented by nonlinear differential equations. So we must use nonlinear approach to analyze the properties of such systems.

Problem Formulation

a) Hodgkin-Huxley Model

Using pioneering experimental techniques of that time, Hodgkin and Huxley in 1952 [8] determined that squid axon has three major current: voltage gated persistent K^+ current with four activation gates (n^4 term), voltage gated transient Na^+ current with three activation gates and one inactivation gate (m^3h term) and Ohmic leak current, I_L, which is carried mostly by Cl^- ions. The complete set of space clamped Hodgkin-Huxley equations is [3]:

$$C\dot{V} = I - \overbrace{g_K n^4 (V - E_K)}^{I_K} - \overbrace{g_{Na} m^3 h (V - E_{Na})}^{I_{Na}} - \overbrace{g_L (V - E_L)}^{I_L}$$
$$\dot{n} = (n_\infty(V) - n)/\tau_n(V)$$
$$\dot{m} = (m_\infty(V) - m)/\tau_m(V)$$
$$\dot{h} = (h_\infty(V) - h)/\tau_h(V)$$

$$(1)$$

Where
$$n_\infty = \alpha_n/(\alpha_n + \beta_n), \tau_n = 1/(\alpha_n + \beta_n)$$
$$m_\infty = \alpha_m/(\alpha_m + \beta_m), \tau_m = 1/(\alpha_m + \beta_m)$$
$$h_\infty = \alpha_h/(\alpha_h + \beta_h), \tau_h = 1/(\alpha_h + \beta_h)$$

$$(2)$$

By using this formulation, we obtain the minimal cell models.

b) Minimal Cell Models

Let us do the following thought experiment: Consider a conductance-based model capable of exhibiting periodic spiking and remove completely a current or one of its gating variables, and if the reduced model has a limit cycle attractor at least for some values of parameters, we arrive at the model that satisfies the following two properties:

- It has a limit cycle attractor, at least for some values of parameters.
- If one removes any current or gating variable, the model has only equilibrium attractors for any values of parameters.

We refer to such models as being minimal or irreducible for spiking. Thus, minimal models can exhibit periodic activity, but their reductions cannot. According to this definition, any space-clamped conductance-based model is a combination of some minimal ones. If not, then it can be reduced to a new minimal model. For example, the Hodgkin-Huxley model considered is not minimal for spiking. This model consists of three current: leakage I_L, transient sodium $I_{Na,t}$ (gating variables m and h) and persistent potassium I_k (gating variable n).

For definition of the minimal models we employ here a bottom-up approach, which is based on the following rule: A mixture of one amplifying and one resonant gating variable (plus an ohmic leak current) results in a minimal model. Indeed neither of the variables alone can produce oscillation but both are enough [3].

The amplifying gating variable is the activation variable m for voltage gated inward current or inactivation variable h for voltage gated outward current. These variables amplify voltage changes via a positive feedback loop. Indeed a small depolarization increases m and decreases h which in turn increases inward and decrease outward current and produce more depolarization. Similarly a small hyper polarization decreases m and increases h, resulting in less inward and more outward current and hence in more hyper polarization.

The resonant gating variable is the inactivation variable h for an inward current or activation variable n for an outward current. These variables resist voltage changes via negative feedback loop. A small depolarization decreases h and increases n which in turn

decreases inward and increases outward current and produce a net outward current that resists the depolarization. Similarly a small hyper polarization produces inward current and possibly rebound depolarization.

A typical neuronal model consists of at least on amplifying and at least one resonant gating variable. Two amplifying and two resonant gating variables produce four different combinations depicted in Figure. However, the number of minimal models is not four, but six. The additional models arise due to the fact that a pair of gating variables may describe activation/inactivation properties of the same current or of two different currents [3].

$I_{Na,p} + I_k$-model

One of the most fundamental models in computational neuroscience is the $I_{Na,p} + I_k$-model consisting of a fast Na^+ current and a relatively slower K^+ current

$$C\dot{V} = I - \overbrace{g_L(V - E_L)}^{leak\ I_L} - \overbrace{g_{Na}m(V - E_{Na})}^{I_{Na,P}} - \overbrace{g_K n(V - EK)}^{I_K}$$
$$\dot{m} = (m_\infty(V) - m)/\tau_m(V)$$
$$\dot{n} = (n_\infty(V) - n)/\tau_n(V)$$

$$(3)$$

Here m(t) is much faster than the voltage variable V(t), so that m approaches the asymptotic value $m_\infty(V)$ instantaneously. In this case we can substitute $m = m_\infty(V)$.

$$C\dot{V} = I - \overbrace{g_L(V - E_L)}^{leak\ I_L} - \overbrace{g_{Na}m_\infty(V)(V - E_{Na})}^{I_{Na,P}} - \overbrace{g_K n(V - E_K)}^{I_K}$$
$$\dot{n} = (n_\infty(V) - n)/\tau_n(V)$$

$$(4)$$

$I_{Na,t}$-model

An interesting example of a spiking mechanism is given by the $I_{Na,t}$-model which consisting only of an ohmic leak current and a transient voltage-gated inward Na^+ current.
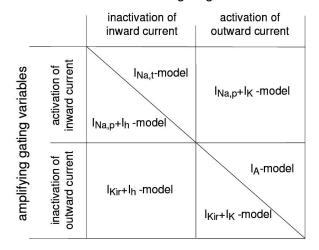
$$C\dot{V} = I - \overbrace{g_L(V - E_L)}^{leak\ I_L} - \overbrace{g_{Na}m^3 h(V - E_{Na})}^{I_{Na,t}}$$
$$\dot{m} = (m_\infty(V) - m)/\tau_m(V)$$
$$\dot{h} = (h_\infty(V) - h)/\tau_h(V)$$

$$(5)$$

Figure 1: Any combination of one amplifying and one resonant gating variables results in a spiking model [3].

resonant gating variables

		inactivation of inward current	activation of outward current
amplifying gating variables	activation of inward current	I_Na,t-model / I_Na,p+I_h -model	I_Na,p+I_K -model
	inactivation of outward current	I_Kir+I_h -model	I_A-model / I_Kir+I_K -model

The upstroke of an action potential is generated because of the regenerative process involving the activation gate m. This mechanism is similar to the one in the Hodgkin-Huxley model or in the $I_{Na,p}$+ I_k-model: Increase of m results in increase of the inward current, hence more depolarization and more increase of m until the excited state is achieved. At the excited state there is a balance of the Na^+ inward current and the leak outward current.

Assuming that activation dynamics is instantaneous, we use $m = m_\infty(V)$ in the voltage equation and obtain:

$$C\dot{V} = I - \overbrace{g_L(V - E_L)}^{leak\,I_L} - \overbrace{g_{Na}m_\infty^3(V)h(V - E_{Na})}^{I_{Na,t}\,with\,inst.active}$$
$$\dot{h} = (h_\infty(V) - h)/\tau_h(V) \tag{6}$$

$I_{Na,p}$+I_h-model

The system describes the essence of the mechanism of slow sub threshold voltage oscillations in some cortical, thalamic, and hippocampal neurons.

$$C\dot{V} = I - \overbrace{g_L(V - E_L)}^{leak\,I_L} - \overbrace{g_{Na}m(V - E_{Na})}^{I_{Na,P}} - \overbrace{g_h h(V - E_h)}^{I_h}$$
$$\dot{m} = (m_\infty(V) - m)/\tau_m(V)$$
$$\dot{h} = (h_\infty(V) - h)/\tau_h(V) \tag{7}$$

We assume that the activation kinetics of the Na^+ current is instantaneous, and use $m = m_\infty(V)$ in the voltage equation to obtain a two-dimensional system:

$$C\dot{V} = I - \overbrace{g_L(V - E_L)}^{leak\,I_L} - \overbrace{g_{Na}m_\infty(V)(V - E_{Na})}^{I_{Na,P}} - \overbrace{g_h h(V - E_h)}^{I_h}$$
$$\dot{h} = (h_\infty(V) - h)/\tau_h(V) \tag{8}$$

I_h+ I_{kir}-model

The persistent Na^+ current, which amplifies damped oscillations in the $I_{Na,p}$+I_h-model, can be substituted by the K^+ inwardly rectifying current I_{kir} to achieve the same amplifying effect.

$$C\dot{V} = I - \overbrace{g_L(V - E_L)}^{leak\,I_L} - \overbrace{g_{Kir}h_{Kir}(V - E_K)}^{I_{Kir}} - \overbrace{g_h h(V - E_h)}^{I_h}$$
$$\dot{h}_{Kir} = (h_{Kir,\infty}(V) - h_{Kir})/\tau_{Kir}(V)$$
$$\dot{h} = (h_\infty(V) - h)/\tau_h(V) \tag{9}$$

Since kinetics of I_{kir} is practically instantaneous, we can use $h_{Kir}=h_{Kir,\infty}(V)$, in the voltage equation above and consider the two-dimensional system

$$C\dot{V} = I - \overbrace{g_L(V - E_L)}^{leak\,I_L} - \overbrace{g_{Kir}h_{Kir,\infty}(V - E_K)}^{I_{Kir}} - \overbrace{g_h h(V - E_h)}^{I_h}$$
$$\dot{h} = (h_\infty(V) - h)/\tau_h(V) \tag{10}$$

I_k+I_{kir}-model

In the I_k+I_{kir}-model

$$C\dot{V} = I - \overbrace{g_{Kir}h(V - E_K)}^{I_{Kir}} - \overbrace{g_K n(V - E_K)}^{I_K}$$
$$\dot{n} = (n_\infty(V) - n)/\tau_n(V)$$
$$\dot{h} = (h_\infty(V) - h)/\tau_h(V) \tag{11}$$

The amplifying current is I_{kir} with inactivation gating variable h, and the resonant current is I_k with activation variable n.

The kinetics of the amplifying current I_{kir} is relatively fast so that h = $h_\infty(V)$ can be used in the voltage equation to reduce the three-dimensional system above to a two dimensional system.

$$C\dot{V} = I - \overbrace{g_{Kir}h_\infty(V)(V - E_K)}^{I_{Kir}} - \overbrace{g_K n(V - E_K)}^{I_K}$$
$$\dot{n} = (n_\infty(V) - n)/\tau_n(V) \tag{12}$$

I_A -model

The last minimal voltage-gated model has only one transient K^+ current, often referred to as being A-current I_A, yet it can also generate sustained oscillations. In some sense, the model is similar to the $I_{Na,t}$ -model. Indeed, each consists of only one transient current and an Ohmic leak current. The only difference is that A-current is outward, and as a result, the action potentials are fired downward. The A-current has activation and inactivation variables m, and h, respectively, and the model has the form:

$$C\dot{V} = I - \overbrace{g_L(V - E_K)}^{I_L} - \overbrace{g_A m h(V - E_K)}^{I_A}$$
$$\dot{m} = (m_\infty(V) - m)/\tau_m(V)$$
$$\dot{h} = (h_\infty(V) - h)/\tau_h(V) \tag{13}$$

We are tempted to substitute $m = m_\infty(V)$ into the voltage equation above and reduce the I_A -model to a two-dimensional system, which hope-fully would have the right kind of nullclines and a limit cycle attractor.

$$C\dot{V} = I - \overbrace{g_{Kir}h_\infty(V)(V - E_K)}^{I_{Kir}} - \overbrace{g_K n(V - E_K)}^{I_K}$$
$$\dot{n} = (n_\infty(V) - n)/\tau_n(V) \tag{14}$$

Then we define the observability property of systems.

Method

Observability

Consider the nonlinear system [5]:

$$\dot{x} = f(x,u)$$
$$z = h(x) \tag{15}$$

Two states x_0 and x_1 are distinguishable if there exists an input

function μ such that:

$$z(x_0) \neq z(x_1)$$

The system is locally observable at x_0 if exists a neighborhood of x_0 such that every x in that neighborhood other than x_0 is distinguishable from x_0. A test for local observability is that [6]:

$$O(x_0, u) = \frac{\partial l(x_0, u)}{\partial x}\bigg|_{x=x_0} \quad (16)$$

Must have rank n, where n is the rank of x and:

$$l(x_0, u) = \left[L_f^0(h_1), \cdots, L_f^{n-1}(h_1)\right]^T \quad (17)$$

Where the output of nonlinear system is:

$$z = [h_1, \cdots, h_P]^T \quad (18)$$

Generally h_1 to h_P are nonlinear functions of x, and:

$$O(x_0, u) = \begin{bmatrix} d\,L_f^0(h_1) \cdots d\,L_f^0(h_P) \\ \vdots & \ddots & \vdots \\ d\,L_f^{n-1}(h_1) \cdots d\,L_f^{n-1}(h_P) \end{bmatrix} \quad (19)$$

Here $L_f(h)$ is the Lie derivative of h with respect to f which is defined below [6]:

$$L_f(h_i) = \nabla h_i \cdot f = \left[\frac{\partial h_i}{\partial x_1}, \cdots, \frac{\partial h_i}{\partial x_n}\right]\begin{bmatrix} f_1(x) \\ \cdots \\ f_n(x) \end{bmatrix} \quad (20)$$

By definition, $L_f^0(h) = h$.
We can also define higher-order Lie Derivatives [7]:

$$L_f^2(h) = \frac{\partial}{\partial x}\left[L_f^1(h)\right]f \; etc \cdots \quad (21)$$

By this test method, we check the observability of each minimal cell model.

Results

Observability of Minimal Cell Models

For each minimal model first we construct l matrix then O matrix

and then calculate the rank of O matrix. For some conditions the O matrix is not full rank. So we determine the condition that the O matrix is full rank and then the system is observable.

For example in the following we calculate the O matrix for $I_{Na,p} + I_k$-model and write the details for checking the observability condition.

Equation (3) describes the $I_{Na,p} + I_k$-mode. By using these equations, f_1 and f_2 can be written as below:

$$f_1 = 1/C\,(-g_L\,(V-E_L) - g_{Na}\,m_\infty(V)\,(V-E_{Na}) - g_K\,n\,(V-E_K))$$
$$f_2 = (n_\infty(V) - n)/\tau_n(V)$$
$$h = V \quad (22)$$

Here $I = 0$.

After calculation the Lie derivatives we can construct the l matrix as below:

$$l = [V \; f_1]^T \quad (23)$$

And

$$O = \begin{bmatrix} 1 & 0 \\ w & -g_K(V-E_K) \end{bmatrix}$$
$$w = -g_L - g_{Na}m_\infty(V) - g_{Na}\frac{\partial m_\infty(V)}{\partial V}(V-E_{Na}) - g_K n \quad (24)$$

For observability O must be full rank. So:

$$\det O = -g_K(V-E_K) \neq 0 \stackrel{g_K \neq 0}{\Rightarrow} V \neq E_K \quad (25)$$

With this condition the system is observable. We can run above procedure for other minimal cell model. The results are given in TABLE.

Conclusion

Using the results table, all minimal cell models are observable except on one line in state plane. By this condition we can consider these minimal models observable. Here we analyzed the observability property of minimal cell models. As a result we can use observers like Kalman Filter [8], in this case Extended Kalman Filter to observe the states of this nonlinear systems and via using a state feedback we can control the nonlinear behavior of a cell. In next research we'll focus on controllability property [5,7,9] of minimal cell models.

Table 1: Result of checking the observability of minimal cell models.

Item	Model Name	Observability Condition
A	$I_{Na,p} + I_k$	$V \neq E_k$
B	$I_{Na,t}$	$V \neq E_{Na}$
C	$I_{Na,p} + I_h$	$V \neq E_h$
D	$I_h + I_{kir}$	$V \neq E_h$
E	$I_k + I_{kir}$	$V \neq E_k$
F	I_A	$V \neq E_k$

Reference

[1]. Pei Ye, Emilia Entcheva, Scott A. Smolka, Radu Grosu(2008)"Symbolic Analysis of the Neuron Action Potential", State University of New York at Stony Brook Stony Brook, Department of BioMedical Engineering.

[2]. A. L. Hodgkin, A. F. Huxley,(1952)"A quantitative description of membrane current and its application to conduction and excitation in nerve", J. physiol, 500-544.

[3]. Eugene. M. Izhikevich,(2004)"Dynamical Systems in Neuroscience: The Geometry of Excitability and Bursting", Springer Verlog.

[4]. Milena Anguelova,(2004)"Nonlinear Observability and Identifiability: General Theory and a Case Study of a Kinetic Model", Chalmers University of technology and G¨oteborg University.

[5]. R. Hermann, A. J. Krener,(1977) "Nonlinear Controllability and Observability", IEEE Transaction on Automatic Control, vol. AC-22, No. 5, pp. 728-740.

[6]. J. K. Hedrik, A. Girard, "A Control of Nonlinear Dynamic Systems: Theory and Application" ,2005.

[7]. M. R. James,(1987)"Controllablity and Observability of Nonlinear Systems", Institude for Systems Research, T.R. 87-195.

[8]. MOHINDER S. GREWAL, ANGUS P. ANDREWS,(2008)"KALMAN FILTERING, Theory and Practice Using MATLAB", Third Edition, California State University at Fullerton.

[9]. K. Röbenack,(2003)"Computation of Controllability and Observability Matrices – Duality and Automatic Differentiation", proceeding in Applied Mathematics and Mechanics.