Analysis and control of the bifurcation of Hodgkin–Huxley model

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Abstract

The Hodgkin–Huxley (HH) equations are parameterized by a number of parameters and show a variety of qualitatively different behaviors depending on the various parameters. This paper finds the bifurcation would occur when the leakage conductance \( g_l \) is lower than a special value. The Hopf bifurcation of HH model is controlled by applying a simple and unified state-feedback method and the bifurcation point is moved to an unreachable physiological point at the same time, so in this way an absolute bifurcation control is achieved. The simulation results demonstrate the validity of such theoretic analysis and control method. This new method could be a great help to the design of new closed-loop electrical stimulation systems for patients suffering from different nerve system dysfunctions.

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1. Introduction

The work of Hodgkin and Huxley on nerve conduction has long been recognized as an outstanding scientific achievement. Their papers were published in 1952 [3–6]. They used voltage-clamp methods to obtain extensive quantitative experimental results and proposed a system of four-dimensional autonomous differential equations containing messy nonlinear functions, which is called Hodgkin–Huxley model. The HH model not only contains the voltage-clamped experimental data but also is remarkably successful in simulating action potential responses, which offers a brilliant future for the quantitative research of excitable physiological nerve character. It explains experimental phenomena accurately and quantitatively analyze the change of voltages and currents on the nerve cell membrane.

Hassard, Rinzel and Troy demonstrated that bifurcation would occur at the equilibrium of HH model with a charge in the current \( I_{ext} \) which was injected into the cell membrane [7,8]. Rinzel and Miller analyzed the stable and unstable solutions of HH model with variant input current \( I_{ext} \), and the influence of temperature at the bifurcation point [7]. Guckenheimer and Labouriau [9] analyzed the HH model’s bifurcation when the input current \( I_{ext} \) and steady state potassium ionic battery \( V_k \) vary, respectively. Bedrov and his fellows studied the possible bifurcation with sodium...
conductance $\tilde{g}_{Na}$ and maximal potassium conductance $\tilde{g}_{K}$ \cite{10,11}. Medical researches show that many diseases are related to the aberrance of cell trans-membrane ion channels \cite{12}. In this paper, we employ the physiological data obtained from rat's muscles voltage-clamped experiments carried by Adrian and Marashall \cite{13}, and take the Hodgkin–Huxley model for muscles (HHM) as study object. The dynamic bifurcation analysis about single parameter of leakage conductance is performed on the model with the help of algebra criterion in high dimension equations.

Bifurcation refers to qualitative changes in the solution structure of dynamical systems occurring with slight variation in system parameters. Bifurcation control means to design a controller that can modify the bifurcation properties of a given nonlinear system, so as to obtain some desired dynamical behaviors. Many positive results of the researches in this field have been achieved \cite{35–48}. Typical examples include delaying the onset of an inherent bifurcation, relocating an existing bifurcation point, modifying the shape or type of a bifurcation chain, introducing a new bifurcation at a preferable parameter value, stabilizing a bifurcated periodic trajectory, changing the multiplicity, amplitude, and/or frequency of some limit cycles emerging from bifurcation, optimizing the system performance near a bifurcation point, or a certain combination of some of these. System bifurcation can be controlled by different methods, such as linear delayed state-feedback \cite{15,16,37,45,47}, or nonlinear state-feedback \cite{17,44,46}, using a wash-out filter \cite{18,39}, hybrid control for discrete time model \cite{32,34,36,38,40}, employing harmonic balance approximation \cite{19}, and applying the quadratic invariants in the normal form \cite{20}.

The study of electrical stimulation of nerve cell activity has a long history \cite{30,31,33,41,42}, many existing nerve stimulation protocols are basically simple feedforward schemes where the exact dynamics of the biophysical states of the targeted neurons is disregarded \cite{22,23,25}. To design controllers allowing dynamic time-course control of biophysical state variables, advanced control algorithms are required, since inherent nonlinearities and biological constraints limit the application of linear feedback control strategies \cite{20,21}. The nonlinearities of HH nerve cell dynamics require nonlinear control strategies to achieve efficient and precise control \cite{26–29}. Furthermore, such a controller will eventually interact with biological tissue, which is sensitive to disturbances \cite{1,2,24,43}. Feedback control schemes based on biophysical states in nerve cells might lead to the development of new electrical stimulation systems as neural prostheses for patients suffering from loss of function or aberrant electrical signal generation in the nervous system caused by accident or disease. For example, single cell stimulation is of major interest for suppression of undesired neural oscillation as it occurs in patients with Parkinson’s disease or epilepsy \cite{14}.

This paper firstly analyzes the Hopf bifurcation of Hodgkin–Huxley model, then applies a developed linear or nonlinear state feedback method to such a model and successfully achieves the control of nonlinear nerve cell Hopf bifurcation. The simulation results verify the validity of such theoretic analysis and control method.

2. HHM model and bifurcation

2.1. HH model description

The HH equations \cite{3–6} are comprised of four coupled, nonlinear differential equations describing the temporal evolution of the membrane voltage $V$ in dependence of an externally injected current $I_{ext}$ in a spatially localized axonal compartment. Eq. (1) and Fig. 1 below shows it in details.

![Fig. 1. Circuit description of the HH model.](image-url)
Here, potassium ions is determined by a maximal potassium conductance $\tilde{g}_K$, as ionic battery $V_e$ expressing steady-state potassium ion separation, and activation $n$ describing the dynamics of the potassium channel opening. Similarly, sodium ion current is modeled with a maximal sodium conductance $\tilde{g}_Na$, an ionic battery $V_{Na}$, and activation and inactivation variables $m$ and $h$. The former describes the dynamics of opening of the sodium channels, whereas the latter models the dynamics of their closing. The remaining ion currents are collectively modeled by a leakage current (conductance $\tilde{g}_l$, ionic battery $V_l$). Furthermore, since the cell membrane stores charge, capacitive current needs to be taken into account as well (capacitance $C_M$). Potassium activation $n$, sodium activation $m$ and sodium inactivation $h$ are dimensionless state variables which take on continuous values between zero and one. Their dynamics are modeled with first-order differential equations listed in Eq. (2). The parameters $\alpha_m, \beta_m, \alpha_n, \beta_n$ and $\beta_h$ depend on membrane voltage $V$ in a nonlinear manner [3–6].

$$\frac{dx}{dt} = \frac{g_K m h}{1 - \exp(-V - V_m)} n,$$

$$\frac{dx}{dt} = \frac{\alpha_m(V)}{\beta_m(V)(1 - n)} - \alpha_n(V)(1 - m),$$

$$\frac{dx}{dt} = \frac{\alpha_n(V)}{\beta_n(V)(1 - n)} - \beta_n(V)n.$$

### 2.2. Equilibriums of HH model and their physiological meaning

**HHM model as a complex nonlinear system**

We assume that HHM model, as an autonomy system, has equilibrium point $X_e = (V_e, m_e, h_e, n_e)$, which makes the right side of Eq. (1) equal zero, and therefore Eq. (1) becomes

$$\tilde{g}_Na m^2 h (V_e - V_{Na}) + \tilde{g}_K n^2 (V_e - V_K) = -\tilde{g}_l (V_e - V_1),$$

$$m = \frac{\alpha_m(V)}{\alpha_n(V) + \beta_m(V)}$$

$$h = \frac{\alpha_h(V)}{\beta_n(V) + \alpha_h(V)}$$

Taking the data in Table 1, three isolated equilibrium points are obtained as listed in Table 2:

<table>
<thead>
<tr>
<th>$C_M$</th>
<th>1.9 μF/cm²</th>
<th>$K_{fin}$</th>
<th>18.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tilde{g}_Na$</td>
<td>50.0 mS/cm²</td>
<td>$\alpha_n$</td>
<td>0.006 mS⁻¹</td>
</tr>
<tr>
<td>$\tilde{g}_K$</td>
<td>22.0 mS/cm²</td>
<td>$\beta_n$</td>
<td>1.3 mS⁻¹</td>
</tr>
<tr>
<td>$g_l$</td>
<td>0.4 mS/cm²</td>
<td>$V_h$</td>
<td>-41.0 mV</td>
</tr>
<tr>
<td>$V_{Na}$</td>
<td>50.0 mV</td>
<td>$K_{ah}$</td>
<td>14.7</td>
</tr>
<tr>
<td>$V_K$</td>
<td>-70.0 mV</td>
<td>$K_{ah}$</td>
<td>7.6</td>
</tr>
<tr>
<td>$V_1$</td>
<td>-81 mV</td>
<td>$\beta_h$</td>
<td>0.0088 mS⁻¹</td>
</tr>
<tr>
<td>$\alpha_m$</td>
<td>0.08 mS⁻¹</td>
<td>$\beta_h$</td>
<td>0.037 mS⁻¹</td>
</tr>
<tr>
<td>$\beta_m$</td>
<td>0.8 mS⁻¹</td>
<td>$V_n$</td>
<td>-40.0 mV</td>
</tr>
<tr>
<td>$V_m$</td>
<td>-56.0 mV</td>
<td>$K_{an}$</td>
<td>7.0</td>
</tr>
<tr>
<td>$K_{nn}$</td>
<td>6.8</td>
<td>$K_{fin}$</td>
<td>40.0</td>
</tr>
</tbody>
</table>
In the vicinity of each point $X_\epsilon$ there is only one $(X_\epsilon)$ equilibrium. Fig. 2 shows their relations. The solid beeline means leakage conductance, and the two dashed curves represent potassium and sodium ionic current, respectively. The solid curve is the sum of potassium and sodium ionic current. The intersection of solid line and solid curve represents equilibrium points of HH model. Point A refers to cell resting state (here the resting potential is $-81 \text{ mV}$), point C determines the maximum value of action potential during the process of depolarization, and point B is some transient state between the resting state and the max-depolarization state.

After the stability analysis of equilibrium [35,48], equilibrium point A will remain steady when the parameters in HHM varied, and at point B its curve will drift, but the state at point C is not approximately stabilization, it is an unstable spiral point or focus which will result in the change of topology structure.

2.3. Bifurcation of the HH model

With respect to the model described in Eq. (1), assign all parameters value from Table 1 except for $g_l$, a single parameter system is obtained where the bifurcation parameter is $g_l$:

$$\dot{X} = f(X, g_l), \quad X = [V, m, h, n] \in \mathbb{R}^4, \quad g_l \in \mathbb{R}^1$$

\begin{table}[h]
\centering
\caption{Dynamic steady point of HHM}
\begin{tabular}{|c|c|c|c|c|}
\hline
Equilibrium points & $V_e$ (mV) & $m_e$ & $h_e$ & $n_e$ \\
\hline
A & -81.0000 & 0.01351471113 & 0.9315694776 & 0.009933359801 \\
B & -65.1530 & 0.1433815730 & 0.376828476 & 0.08276135123 \\
C & -47.8901 & 0.6193937147 & 0.02499417132 & 0.4247083348 \\
\hline
\end{tabular}
\end{table}

Fig. 2. Equilibrium point of HHM.

Fig. 3. Normal muscle cell action potential.
The system’s Jacobian matrix at point C just contains variable $g_l$.

\[
J(g_l) = \begin{bmatrix}
\frac{\partial F}{\partial V} & \frac{\partial F}{\partial m} & \frac{\partial F}{\partial n} & \frac{\partial F}{\partial h} & \frac{\partial F}{\partial g_l} \\
0 & 0 & 0 & 0 & \frac{\partial F}{\partial g_l} \\
0 & 0 & 0 & 0 & \frac{\partial F}{\partial g_l} \\
0 & 0 & 0 & 0 & \frac{\partial F}{\partial g_l}
\end{bmatrix}
= \begin{bmatrix}
-0.533030502 - 0.526315789g_l & 74.10521313 & 612.1467637 & -78.44914264 \\
0.03888978155 & -1.416022399 & 0 & 0 \\
-0.001512049448 & 0 & -0.3835946452 & 0 \\
0.002097273245 & 0 & 0 & -0.07833923285
\end{bmatrix}
\]

Fig. 4. Action potential waveforms when leakage conductance $g_l$ equals a bifurcation value: (a) bifurcation of trans-membrane voltage $V$, (b) $m$, (c) $n$, (d) $h$, (e) trace of $m$, $h$ and $n$, (f) trace of $V$, $m$ and $n$. 

According to algebra criterion in high dimension equations the system will have a sub-critical Hopf bifurcation when \( g_1 = 0.299406 \) mS/cm\(^2\) which means that limit cycle emerges and bifurcation happens. Generally, the cell will yield a single action potential after stimulation and then eventually come to a resting state; the simulation result is given in Fig. 3. When \( g_1 \) is lower than 0.299406 mS/cm\(^2\) the system’s trace will have limit cycle and not return to resting state. Under this condition periodic solution is generated which means the nerve cell will have continuous action potentials after the cell membrane being stimulated and the system will bifurcate and results show in Fig. 4.

3. Control of Hopf bifurcation in the HHM model

Consider a parameterized two-dimensional continuous-time autonomy system [16,21]:

\[
\begin{aligned}
\dot{x} &= f(x,y;\mu), \\
\dot{y} &= g(x,y;\mu)
\end{aligned}
\]  

Design a simple controller as

\[ u(t;\mu) = u(x,y;\mu) \]  

If the controller (5) is designed to satisfy

\[ (x^*,y^*,\mu) = 0 \]

then it will not change the original equilibrium point, \((x^*,y^*)\), of the given system (4). The controlled system is as follow

\[
\begin{aligned}
\dot{x} &= f(x,y;\mu), \\
\dot{y} &= g(x,y;\mu) + u(x,y;\mu)
\end{aligned}
\]

It has the Jacobian at point \((x^0,y^0)\)

\[ J(\mu) = \begin{bmatrix} f_x & f_y \\ g_x + u_x & g_y + u_y \end{bmatrix}_{x=x^0,y=y^0} \]

where \( f_x = \partial f/\partial x \) and \( g_y = \partial g/\partial y \), with eigenvalues:

\[ \lambda_{1,2}^*(\mu) = \frac{1}{2}(f_x + g_x + u_x) \pm \frac{1}{2} \sqrt{(f_x + g_x + u_x)^2 - 4(f_x(g_x + u_x) - f_y(g_y + u_y))} \]

To simplify, here we consider \( f_x := \tilde{f}_x|_{x=x^0,y=y^0}, g_y := \tilde{g}_y|_{x=x^0,y=y^0} \), in order to achieve control of Hopf bifurcation at point \((x^0,y^0,\mu^0)\), from the classical Hopf bifurcation theory we have following conditions:

1. \((x^0,y^0)\) is an equilibrium point of the controlled system (7) to all \( \mu \in R \)

\[
\begin{aligned}
f(x^0,y^0;\mu) &= 0, \\
g(x^0,y^0;\mu) + u(x^0,y^0;\mu) &= 0
\end{aligned}
\]

2. At point \((x^0,y^0,\mu^0)\) the controlled system (7) have pure imaginary eigenvalues \( \lambda_{1,2}^*(\mu) \)

\[
\begin{aligned}
(f_x + g_x + u_x)|_{\mu=\mu^0} &= 0, \\
f_x(g_x + u_x) - f_y(g_y + u_y)|_{\mu=\mu^0} &= 0, \\
(f_x + g_x + u_x)^2 - 4(f_x(g_x + u_x) - f_y(g_y + u_y))|_{\mu=\mu^0} &= 0
\end{aligned}
\]

3. And these eigenvalues satisfy

\[ \frac{\partial \Re\{\lambda^*(\mu)\}}{\partial \mu}_{\mu=\mu^0} = \frac{\partial (f_x + g_x + u_x)}{\partial \mu}_{\mu=\mu^0} > 0 \]
In order to achieve stability at bifurcation point \((x^*, y^*)\) of the system described in Eq. (1), with the help of theory above we get the controller after calculation:

\[
\begin{align*}
    u &= \left[ \begin{array}{c}
        x' \\
        (V - \frac{\beta_m}{C_3} \frac{V}{C_0} + \frac{\beta_n}{C_2} \frac{V}{C_2}) \\
        h \\
        n \\
        \end{array} \right] \\
    &= \left[ \begin{array}{c}
        \beta' (m - \frac{x_m(V^*)}{(x_m(V^*) + \beta_m(V^*))}) \\
        \lambda' (h - \frac{x_h(V^*)}{(x_h(V^*) + \beta_h(V^*))}) \\
        \delta' (n - \frac{x_n(V^*)}{(x_n(V^*) + \beta_n(V^*))}) \\
    \end{array} \right] \\
\end{align*}
\]  

(13)

Fig. 5. Trans-membrane voltage \(V\) in different \(g_i\): (a) \(g_i = 0.60\) ms/cm\(^2\) and (b) \(g_i = 0.10\) ms/cm\(^2\).

Fig. 6. The responses of \(V, m, n, h\) when \(g_i = 0.299406\) mS/cm\(^2\): (a) \(V\), (b) \(m\), (c) \(n\) and (d) \(h\).
Based on bifurcation theory we can conclude that when $g_l$ is in the range of 0.299406–0.298908 mS/cm$^2$ the system will have oscillation periodic solution, but those outside the range will have no such solution and their waveforms are showed in Fig. 5.

In order to control the system’s bifurcation, we choose the following controller:

$$u = \begin{bmatrix} 0.141v + 6.7363 \\ -0.1(m - 0.62) \\ 0.044(h - 0.025) \\ -1.64(n - 0.425) \end{bmatrix}$$

(14)

At the former bifurcation point $g_l = 0.299406$ mS/cm$^2$, their new dynamical responses to the system with controller are showed in Fig. 6.

From the waveforms, we can conclude that the trans-membrane voltage converges to $-47$ mv, and parameters $m$, $h$ and $n$ all converge to a fixed value. All those values are physiologically meaningful. Their behaviors verify the validity of above mentioned controller.

Under this condition, the bifurcation point is delayed and moved to $g_l = 3.379388$ mS/cm$^2$, and their waveforms are showed in Fig. 7.

The range of $g_l$, as we all know, is very small. So $g_l = 3.379388$ mS/cm$^2$ will not happen, in this kind of situation we can see that the system will never bifurcate again after we apply the controller.

4. Discussion

The Hodgkin–Huxley model will have periodic solution when the leakage conductance $g_l$ decreases to a bifurcation value, which means the nerve cell will have continuous action potential after stimulation. This phenomenon looks like responses of pathological cell’s action potentials caused by muscle tonus. In other words, the bifurcation caused by decrease of leakage conductance maybe is just the cause of tonus. Instead of injecting charge to affect the membrane voltage directly we use closed-loop method to control the bifurcation and this ensures the HHM model will never bifurcate again, it offers a good method to cure such disease. In this way this new method could be a great help to the design of new closed-loop electrical stimulation systems for patients suffering from different nerve system dysfunctions.

The original HH model given by Eq. (1) describes the temporal dynamics of a space-clamped axon where no spatial dynamics occur. In a more realistic model, the spatial spread of an action potential along the axon has to be considered, but the method to analyze it is of the same.
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References