Spiking patterns of a hippocampus model in electric fields*

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We develop a model of CA3 neurons embedded in a resistive array to mimic the effects of electric fields from a new perspective. Effects of DC and sinusoidal electric fields on firing patterns in CA3 neurons are investigated in this study. The firing patterns can be switched from no firing pattern to burst or from burst to fast periodic firing pattern with the increase of DC electric field intensity. It is also found that the firing activities are sensitive to the frequency and amplitude of the sinusoidal electric field. Different phase-locking states and chaotic firing regions are observed in the parameter space of frequency and amplitude. These findings are qualitatively in accordance with the results of relevant experimental and numerical studies. It is implied that the external or endogenous electric field can modulate the neural code in the brain. Furthermore, it is helpful to develop control strategies based on electric fields to control neural diseases such as epilepsy.

Keywords: electric field, Pinsky–Rinzel neuron, phase locking, firing pattern

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1. Introduction

The representation of external stimuli in various types of neurons is one of the essential challenges in neuroscience. The hippocampus is the essential brain tissue for associative memory. It is also believed to be crucial in the generation of epileptic seizure.

Electrical fields, which are ubiquitous in the context of neurons, are induced either by external electromagnetic fields or by endogenous electric activities. Many neural diseases that are probably caused by electromagnetic stimuli have been reported.[1,2] Furthermore, endogenous electric field also plays an essential role in modulating neural activities.[3] Thus, it is significant to study the dynamics of neurons exposed to electric fields.

The effects of steady DC electric field on the hippocampus have been investigated through both experiments and numerical simulation.[4,5] Seizure activities in hippocampal slices can be suppressed by a steady DC electric field.[4] Previous experimental studies have revealed that extremely low frequency fields could change the sensitivity of brain tissues.[6,7]

The switches between different firing patterns in a single neuron due to different parameters such as external stimuli have been widely studied.[8−10] With the variation in the amplitude or the frequency of stimulation, an alternating pattern of phase-locked and chaotic responses has been observed in a single excitable neuron.[11−13] Similar behaviours have also been observed in cortical neurons *in vivo*.[14] When interneurons or pyramidal neurons are subjected to sinusoidal stimulation with high frequency, the firing threshold rises sharply.[15]

Studies of single neurons and neuronal networks often adopt single compartment models, such as the integrate-and-fire, FitzHugh–Nagumo, and HH models.[11,16] Firing patterns of a single neuron in electric fields have been studied based on the single compartment model.[13] However, some effects of electric fields such as polarization in pyramidal neurons cannot be reflected by such models.[5] Many researchers have focused on the firing patterns in a compartment model such as the Pinsky–Rinzel (PR) model.[17,18] Therefore, a two-compartment model embedded in a resistive array is more biologically plausible for mod-

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eling the influence induced by electric fields.[5] However, how the firing patterns are modulated in a single neuron has not been investigated in detail. In many studies, the effects of applied electric fields are represented by current injected into soma. Whether it is sufficient to model the effects of electric fields is still an open question.

Oscillatory rhythm is thought to play a significant role in hippocampal cognitive function.[19] Application of a continuous electric field allows the hippocampal to switch between theta, gamma, and mixed theta–gamma regimes.[20] Furthermore, rhythm of endogenous electric field may play an essential role in modulating brain activities.

The rest of the present study is organized as follows. Firstly, a two-compartment PR model embedded in a resistant array under an electric field is developed for a single CA3 neuron in Section 2. Then the corresponding firing patterns of this model in DC electric fields are studied in Section 3. The effects of AC electric field with different frequencies and amplitudes on firing patterns are investigated in Section 4. Finally the conclusions are given in Section 5.

2. Description of the neuronal model in an external electric field

The two-compartment PR model[17] for a CA3 pyramidal cell in hippocampus is chosen in our study. The PR model, as a reduction of a complex 19-compartment cable model,[21] can reproduce similar phenomena to the complex model. A single PR neuron embedded in a resistive array is shown in Fig. 1. An external electric field $V_{\rm ext}$ modulates the activities of neurons through the corresponding resistive array. The parameters in this resistive array are chosen according to Refs. [6] and [7], and the details are shown in Appendix A.

The PR neuron model is governed by the following equations:

$$\begin{aligned} c_m\dot{V}_{\rm s} &= -I_{\rm sLeak} - I_{\rm Na} - I_{\rm KDR} - \frac{I_{\rm DS}}{p} + \frac{I_{\rm s}}{p}, \\ c_m\dot{V}_{\rm d} &= -I_{\rm dLeak} - I_{\rm Ca} - I_{\rm KAHP} - I_{\rm KC} - I_{\rm syn} \\ &\quad -\frac{I_{\rm DS}}{(1-p)} + \frac{I_{\rm d}}{(1-p)}, \\ I_{\rm sLeak} &= g_{\rm L}(V_{\rm s} - V_{\rm L}), \\ I_{\rm dLeak} &= g_{\rm L}(V_{\rm d} - V_{\rm L}), \\ I_{\rm Na} &= g_{\rm Na}m_\infty^2 h(V_{\rm s} - V_{\rm Na}), \\ I_{\rm KDR} &= g_{\rm KDR}n(V_{\rm s} - V_{\rm K}), \\ I_{\rm KC} &= g_{\rm KC}c\chi({\rm Ca})(V_{\rm s} - V_{\rm K}), \\ I_{\rm Ca} &= g_{\rm Ca}s^2(V_{\rm s} - V_{\rm Ca}), \\ I_{\rm KAHP} &= g_{\rm KAHP}q(V_{\rm d} - V_{\rm K}), \end{aligned} \tag{1}$$

where $V_{\rm s}$ and $V_{\rm d}$ are the somatic and the dendritic membrane potentials from a reference potential of -60 mV; $I_{\rm s}$ ($I_{\rm d}$) is the current applied to the soma (dendrite), which is independent of the resistive array; p is the proportion of cell area taken up by the soma.

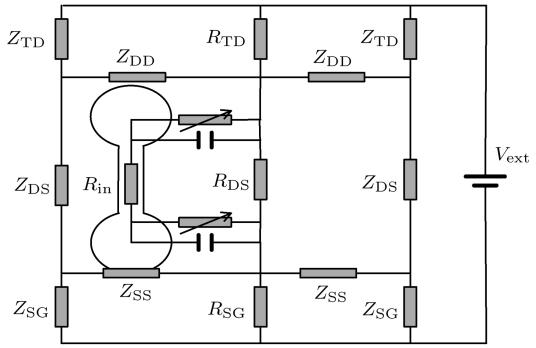


Fig. 1. PR neuron under external electric stimulation. The details of the parameters in the resistance array are given in Appendix A.

The equation for the gating variables h, n, s, c, and q takes the following form:

$$y' = (y_\infty(U) - y)/\tau_y(U), \tag{2}$$

where $U = V_{\rm s}$ for $y = h$, n; $U = V_{\rm d}$ for $y = s$, c; $U = q$ for $y = q$.

$$\begin{aligned} y_\infty &= \alpha_y/(\alpha_y + \beta_y), \\ \tau_y &= 1/(\alpha_y + \beta_y). \end{aligned} \tag{3}$$

The details of α_y and β_y are given in Appendix A. The current flowing from the dendrite to the soma part is governed by the following equation due to the effects of the electric fields:

$$I_{\rm DS}^{\rm in} = g_{\rm c}(V_{\rm d} + V_{\rm DS}^{\rm out} - V_{\rm s}). \tag{4}$$

In this case, the effects of electric fields are reflected mainly by the value of $V_{\rm DS}^{\rm out}$, which is involved in the interaction between the soma and the dendrite.

3. Firing patterns induced by a DC electric field

After the construction of the model, we investigate the firing patterns induced by the DC electric

field. Different firing patterns corresponding to electric fields with different values of intensity $V_{\rm ext}$ and internal conductance $g_{\rm c}$ are shown in Fig. 2. Region I represents no firing, region II represents periodic burst firing, and region III represents periodic firing. When $1 < g_{\rm c} < 3$, the firing patterns move from burst into periodic firing as the intensity of the applied DC electric field increases. For $3 < g_{\rm c} < 5$, the firing patterns first move from slow periodic firing to burst, and then attain fast periodic firing with the increase of $V_{\rm ext}$. The results of numerical stimulation are qualitatively in accordance with the experimental results.[22] It has been reported that negative DC electric field suppresses the firing while a positive field increases the firing rate. It is also found that the threshold of $V_{\rm ext}$ value for a fast periodic firing pattern becomes higher with the increase of $g_{\rm c}$.

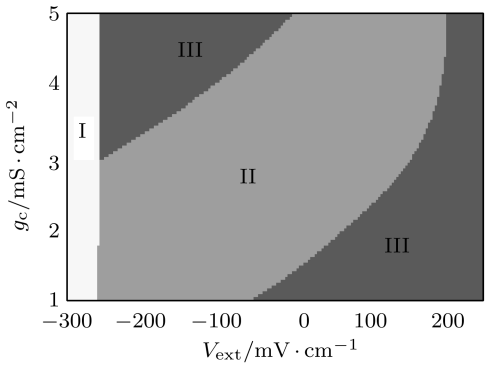


Fig. 2. Different firing patterns in the parameter space of $V_{\rm ext}$ and $g_{\rm c}$.

The threshold between periodic and burst firing patterns is very important for feature detection.[23,24] Lisman[25] has suggested that bursts rather than action potentials could be the fundamental unit of information, as burst firing may be far more reliable than a single action potential. So DC electric field can modulate the neural code in the hippocampus by changing the firing patterns.

In some reports, the effect of applied electric field is represented by the current applied to soma without considering the existence of the dendrites. In this assumption, the applied electric field is considered as a current source. However, in the framework based on a resistant array, the applied electric field is considered as a voltage source cascaded with a resistor for an individual neuron.

The bifurcation diagram of inter-spike intervals (ISIs) induced by DC electric fields is shown in Fig. 3. The firing patterns change from burst to periodic firing with the increase of electric field $V_{\rm ext}$ and the firing frequency also becomes larger. The details of the burst and periodic firing patterns with different DC electric fields are shown in Fig. 4.

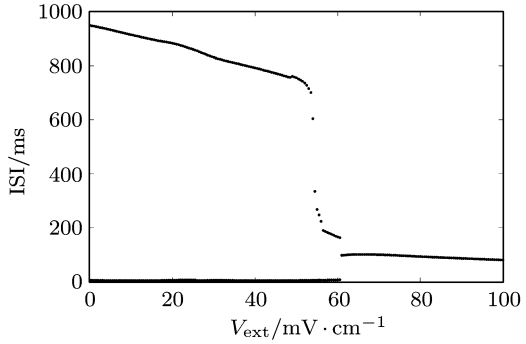


Fig. 3. ISI bifurcation diagram of different electric field amplitudes. All ISIs within a 5-s window after transients states are used.

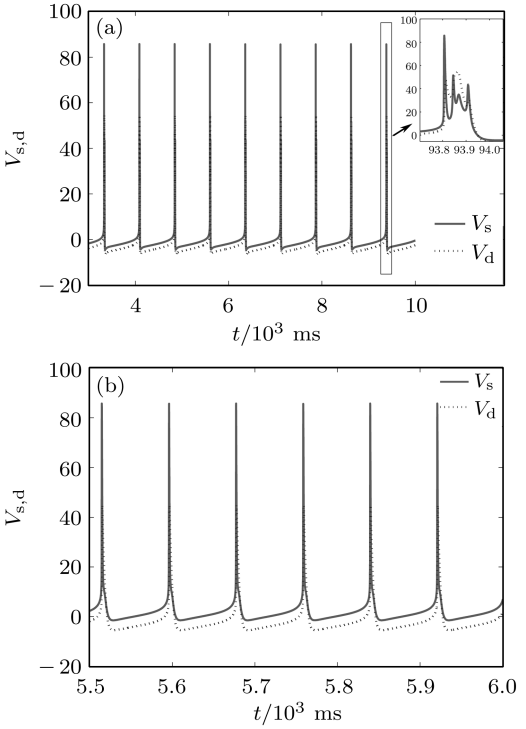


Fig. 4. Firing patterns of a PR neuron with DC electric field of different intensities. (a) Burst firing pattern when $V_{\rm ext} = 50$ mV, and the subplot embedded in the figure indicates the waveform of a single burst; (b) fast periodic firing when $V_{\rm ext} = 100$ mV.

Unlike the firing patterns induced by the injected current,[17] irregular firing patterns do not exist in this parameter space, because the electric interaction between soma and dendrite involves significant coupling current that flows back and forth. The irregular firing arises due to the complex interaction between soma and dendrite induced by the injected current. Electric fields result in the presence of biases between the

values of $V_{\rm s}$ and $V_{\rm d}$, which makes the interaction between soma and dendrite less complex. Therefore, the chaotic firing pattern cannot be observed in this parameter space.

4. Firing patterns induced by a sinusoidal electric field

Rhythmic activity is the most basic property in the brain. All neurons in the brain are influenced by the endogenous electric field, which is the result of collective electric activity induced by large neuronal populations. Therefore, effects of sinusoid electric fields with different frequencies on the firing patterns of neurons are important. We introduce a sinusoidal electric field

$$V_{\rm ext} = A\sin(2\pi ft) + A_b.$$

Here A and f denotes the amplitude and the frequency of the sinusoidal electric field and A_b denotes the DC component of the electric field.

The electric field modulates neuronal activities through a resistive array. To investigate its effects on the PR neuron, ISI bifurcation diagrams of electric field frequency are shown in Fig. 5. Phase-locking states (1:1, 2:1, and 3:1) can be observed in certain parameter ranges. Irregular firing patterns including burst firing can be found in a parameter range for phase locking. By comparing Fig. 5(a) with Fig. 5(b), it is found that the parameter ranges for phase locking shift toward the right due to the effect of the DC component in the electric field. As the transition between irregular burst firing and periodic firing is very important, the frequency of the electric field can be used to control the neural activities. This implies the potential role of the endogenous electric field. A hypothesis can be proposed that the generation of rhythm of the hippocampus may be attributed to the positive feedback between the neurons and the endogenous field. Details on phase locking and chaotic firing are shown in Fig. 6. Figures 6(a)–6(c) are corresponding to phase locking states (1:1, 2:1, and 3:1) in Fig. 5(a), and a chaotic firing pattern is observed when $f = 42$ Hz in Fig. 6(d).

To investigate the effect of the electric field on firing pattern more systematically, firing patterns induced by sinusoidal electric fields with different frequencies and amplitudes based on firing rates and regularities are shown in Fig. 7. Interspike intervals (ISIs) are often used to characterize the features of neural signals. The variability of the ISI is quantified by the coefficient of variation of the ISI distribution C_V. In addition to firing rate, spiking regularity can reflect some features of temporal coding to some extent. C_V^j is calculated as follows:

$$C_V^j = \sqrt{\mathrm{Var}(T_k^j)}/\langle T_k^j\rangle_t,$$

where T_k^j is the ISI time series of the neuron j, $\langle\bullet\rangle_t$ denotes the average value over time, and $\mathrm{Var}(T_k^j)$ denotes the variation of the ISI time series of neuron j. C_V is obtained by averaging C_V^j for each neuron. When C_V value is near zero, the neuron is in a phase-locking state. Several phase-locking regions can be observed in the two-parameter space of frequency and amplitude. There also exist irregular firing regions between these phase-locking regions as shown in Fig. 7(b). By comparing Fig. 7(a) with Fig. 7(b), it is found that a low firing rate state is related to irregular firing patterns in general.

It is indicated that sinusoidalal electric field can switch firing patterns from chaotic to periodic, or *vice versa*. The firing pattern is sensitive to the frequency and the amplitude of the applied electric field.

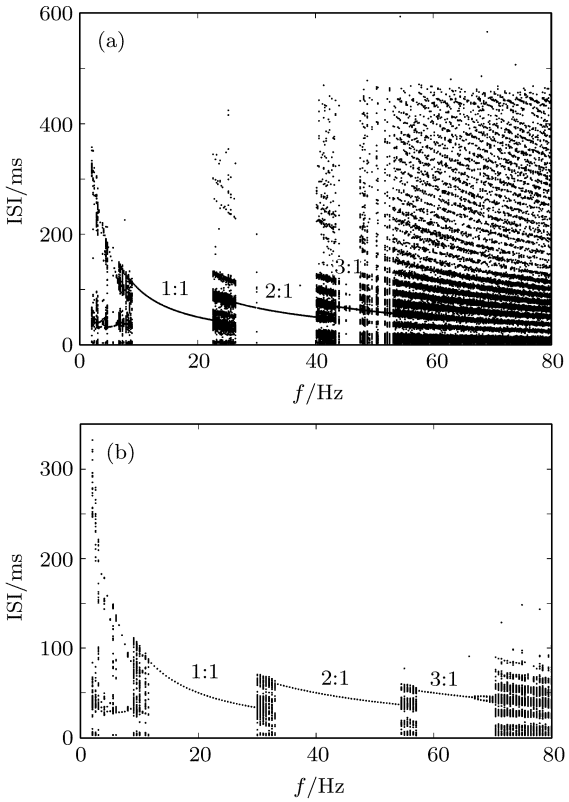


Fig. 5. ISI bifurcation diagrams of electric fields with different frequencies: (a) $A = 300$ mV and $A_b = 0$ mV; (b) $A = 300$ mV and $A_b = 100$ mV.

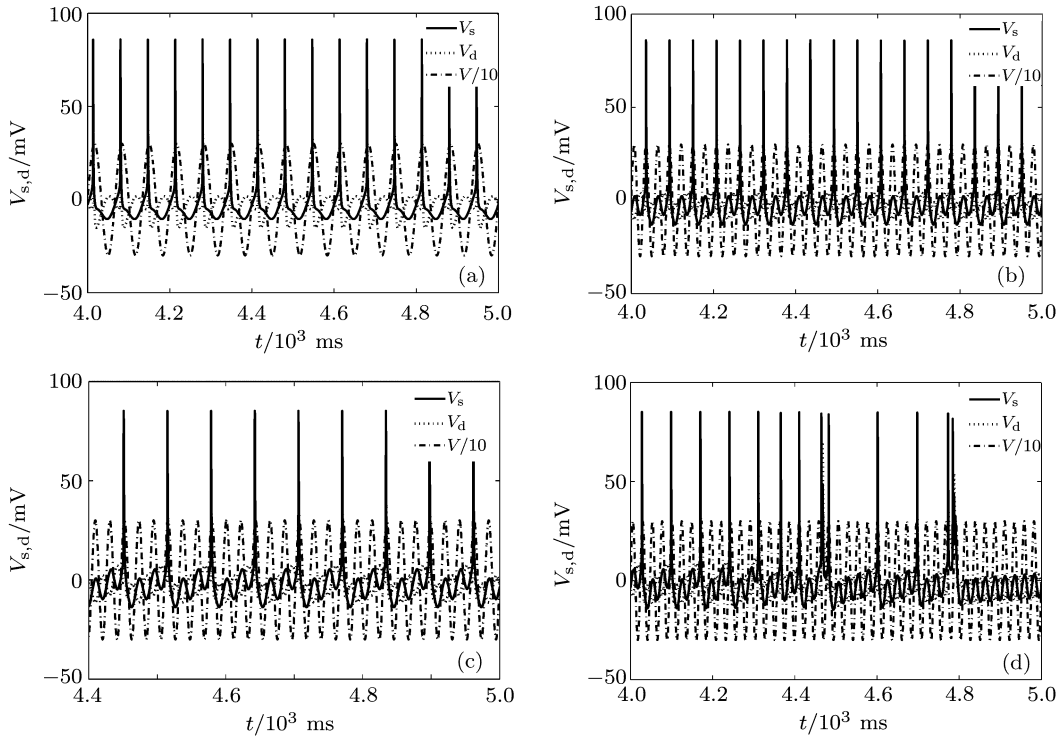


Fig. 6. Examples of firing patterns in a PR neuron with sinusoidal electric fields with different frequencies: (a) 1:1 phase locking with $f = 15$ Hz; (b) 2:1 phase locking with $f = 30$ Hz; (c) 3:1 phase locking with $f = 40$ Hz; (d) chaotic firing with $f = 42$ Hz.

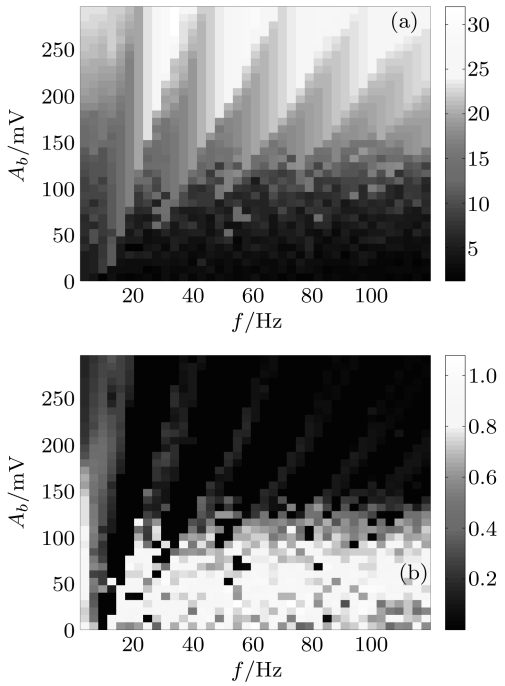


Fig. 7. Firing rates and regularities induced by sinusoidal electric fields with different frequencies and amplitudes. The firing rates (a) and C_V value (b) are denoted based on the colour depth.

5. Conclusion

The properties of a CA3 single neuron in electric fields are studied based on the models we developed in this study. The introduction of a resistive array makes the construction of the model more biologically plausible for CA3 neurons. A positive DC electric field increases the neuronal excitability while a negative field decreases the excitability in single neuron. These findings are qualitatively in accordance with experimental results.[4] It is found that firing activity is sensitive to the frequency and amplitude of the AC electric field. Furthermore, different phase-locking states and chaotic firing regions are observed in the parameter space of frequency and amplitude. Some findings based on experiment and numerical simulation are further confirmed by our study.[4,12–14] It is implied that brain activity could be modulated simply by changing the rhythm of the endogenous electric field. This study may also be potentially helpful in the design of control strategies for the treatment of neural diseases such as epileptic seizure.

Appendix A

Details of the PR neuronal model and the resistive array are given as follows.

The values of the parameters in the resistive network array given bellow are cited from Ref. [5]: $R_{\rm DS} = 0.1R_{\rm in}$, $R_{\rm TD} = 12R_{\rm DS}$, $R_{\rm DD} = 0.1R_{\rm DS}$, $R_{\rm SS} = 0.1R_{\rm DS}$, $R_{\rm SG} = 12R_{\rm DS}$, $Z_{\rm DS} = aR_{\rm DS}$, $Z_{\rm TD} = aR_{\rm TD}$,

$Z_{\rm DD} = bR_{\rm DD}$, $Z_{\rm SS} = bR_{\rm SS}$, and $Z_{\rm SG} = aR_{\rm SG}$. Here $a = 0.0757$, and $b = 2.38$. α_y and β_y are governed by the following equations:

$$\begin{aligned}
\alpha_m &= \frac{0.32(13.1 - V_{\rm s})}{\exp((13.1 - V_{\rm s})/4) - 1},\\
\beta_m &= \frac{0.28(V_{\rm s} - 40.1)}{\exp((13.1 - V_{\rm s})/5) - 1},\\
\alpha_n &= \frac{0.016(35.1 - V_{\rm s})}{\exp((35.1 - V_{\rm s})/5) - 1},\\
\beta_n &= 0.25\exp(0.5 - V_{\rm s}/40),\\
\alpha_h &= 0.128\exp((17 - V_{\rm s})/18),\\
\beta_h &= \frac{4}{1 + \exp((40 - V_{\rm s})/5)},\\
\alpha_{\rm s} &= \frac{1.6}{1 + \exp(-0.072(V_{\rm d} - 65))},\\
\beta_{\rm s} &= \frac{0.02(V_{\rm d} - 51.1)}{\exp((V_{\rm d} - 51.1)/5) - 1},\\
\alpha_c &= \frac{\exp((V_{\rm d} - 10)/11) - \exp((V_{\rm d} - 6.5)/27)}{18.975},\\
\beta_c &= 2\exp((6.5 - V_{\rm d})/27) - \alpha_c.
\end{aligned}$$

If $V_{\rm d} \leq 50$,

$$\begin{aligned}
\alpha_c &= 2\exp((6.5 - V_{\rm d})/27),\\
\beta_c &= 0;
\end{aligned}$$

if $V_{\rm d} \geq 50$,

$$\begin{aligned}
\alpha_q &= \min(0.00002{\rm Ca}, 0.01),\\
\beta_q &= 0.001.
\end{aligned}$$

The standard values of the parameters in PR models are given below.[17] $V_{\rm syn} = 60$, $V_{\rm K} = -15$, $V_{\rm Ca} = 140$, $V_{\rm Na} = 120$, $V_{\rm K} = -15$, $V_{\rm L} = 0$, $p = 0.5$, $c_m = 3$, $g_{\rm L} = 0.1$, $g_{\rm Na} = 30$, $g_{\rm KDR} = 15$, $g_{\rm KC} = 15$, and $g_{\rm KAHP} = 0.8$.

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