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Numerical Study of the Bistability of a Mathematical Model of Neocortical Pyramidal Neurons

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Abstract

A mathematical model of neocortical pyramidal neurons was reported in a previous study. This model was constructed based on the Hodgkin–Huxley concept and is described by a system of nonlinear ordinary differential equations. Under certain conditions, this model shows bistable behavior, i.e., the coexistence of two stable solutions (one is a steady state solution, and the other is a repetitive spiking solution). Under such bistable conditions, a certain external perturbation such as current pulse stimulation can transform the dynamical state of the model from a steady state to a repetitive spiking state; the transformation can also occur in the opposite direction. The present study focused on the transition from a repetitive spiking to a steady state. This transition is regulated by three parameters: the amplitude, duration, and timing of the current pulse. However, previous studies did not investigate the effect of variations in these three parameters in detail. The present computer simulation analysis of the model varied these parameters to reveal in detail the conditions in which the transition occurred. Because of the complexity of varying these three parameters, the duration was fixed to be a certain short time in the present study, and only the values of amplitude and timing were changed. Simulation analysis revealed that at each timing, the transition from repetitive spiking to the steady state requires a certain threshold amplitude. In addition, early and late timings differed in the sensitivity of their threshold amplitude to variations in the timing. These results contribute to a deeper understanding of the bistability of the neocortical pyramidal neuron model.

Mathematics Subject Classification: 37N25, 92C20

Keywords: Mathematical Model; Computer Simulation; Neocortical Pyramidal Neurons; Bistability

1 Introduction

Mathematical models describing the dynamics of excitable cells such as neurons, endocrine cells, and heart cells have been extensively studied in applied mathematics and theoretical physics [1-4]. These models are based on the Hodgkin–Huxley formulation [5]. An example of the Hodgkin–Huxley type mathematical models that describe the neuron dynamics is the mathematical model of neocortical pyramidal neurons proposed by Delord *et al.* [6]. A system of nonlinear ordinary differential equations (ODEs) describes this model which contains three voltage-dependent ionic conductances: a fast sodium conductance, a fast potassium conductance, and a persistent sodium conductance.

In addition, under certain conditions this model shows bistable behavior; under certain parameter conditions, both a steady state and a repetitive spiking state coexist. In this bistable system, transient external perturbations such as a current pulse stimulation can transform the dynamical state of the model from a steady state to a repetitive spiking state and vice versa [6-8]. In particular the condition of the current pulse stimulation required for the transition from repetitive spiking to a steady state is very complicated. The pulse’s condition is regulated by three parameters: amplitude, duration, and timing. Previous studies of a bistable circadian pacemaker neuron model reported that such a model, like the neocortical pyramidal neuron model, can also show the coexistence of a steady state and a repetitive spiking state [9, 10]. In addition, the amplitude and timing required for the transition of this model from a repetitive spiking to a steady state was revealed [10]. However, the equations for the circadian pacemaker neuron model and the neocortical pyramidal neuron model are slightly different. For example, the former model contains a calcium conductance parameter whereas the latter model does not. Therefore, the possibility exists that in the neocortical pyramidal neuron model, the amplitude and timing required for the transition from a repetitive spiking state to the steady state is different from those in the circadian pacemaker neuron model. In the present study, a computer simulation analysis of the neocortical pyramidal neuron model was performed to reveal the details of the amplitude and timing for the transition. This investigation will contribute to a fuller understanding of the characteristics of neuronal bistability.

2 Materials and Methods

A mathematical model of neocortical pyramidal neurons was developed in a previous study [6] and was studied numerically in the present study. The model is described by a system of five coupled, nonlinear ODEs, in which state variables are the neocortical pyramidal neurons' membrane potential [V (mV)], and four gating variables of ionic currents (m, h, n, and m_{NaP}). Equations (1)–(5) describe the evolution of these state variables with time:

$$C_m \frac{dV}{dt} = I_{inj}(t) - I_{NaP}(V, m_{NaP}) - I_{Na}(V, m, h) - I_K(V, n) - I_L(V) \tag{1}$$

$$\frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V)m \tag{2}$$

$$\frac{dh}{dt} = \alpha_h(V)(1-h) - \beta_h(V)h \tag{3}$$

$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n \tag{4}$$

$$\frac{dm_{NaP}}{dt} = \frac{1}{\tau_{NaP}(V)}\left(m_{NaP,\infty}(V) - m_{NaP}\right) \tag{5),$$

where C_m (=1 μF/cm^2) is the membrane capacitance; $I_{inj}(t)$ is the externally injected current (a detailed explanation is given in the next paragraph); I_{NaP} (V, m_{NaP}), I_{Na} (V, m, h), I_K (V, n), and $I_L(V)$ are the persistent sodium current, fast sodium current, fast potassium current, and leakage current, respectively, which are defined in Equations (6)–(9) below; $\alpha_x(V)$ (x = m, h, n), $\beta_x(V)$ (x = m, h, n), $\tau_{NaP}(V)$, and $m_{NaP,\infty}(V)$ are the voltage-dependent rates of activation of the gating variables (i.e., m, h, and n), the voltage-dependent rates of inactivation of these variables, the voltage-dependent time constant of m_{NaP}, and the voltage-dependent steady-state function of m_{NaP}, respectively, which are defined in Equations (10)–(17) below.

$$I_{NaP}(V, m_{NaP}) = g_{NaP} m_{NaP} \left(V - V_{NaP}\right) \tag{6}$$

$$I_{Na}(V, m, h) = g_{Na} m^3 h \left(V - V_{Na}\right) \tag{7}$$

$$I_K(V, n) = g_K n^4 \left(V - V_K\right) \tag{8}$$

$$I_L(V) = g_L \left(V - V_L\right) \tag{9}$$

$$\alpha_m\left(V\right)=\frac{0.55(V+45.5)}{1-e^{(-V-45.5)/4}} \tag{10}$$

$$\alpha_h\left(V\right)=0.115e^{(-V-48)/18} \tag{11}$$

$$\alpha_n\left(V\right)=\frac{0.0178(-V-50)}{e^{(-V-50)/5}-1} \tag{12}$$

$$\beta_m\left(V\right)=\frac{0.44(V+18.5)}{e^{(V+18.5)/5}-1} \tag{13}$$

$$\beta_h\left(V\right)=\frac{3.6}{1+e^{(-V-25)/5}} \tag{14}$$

$$\beta_n\left(V\right)=0.28e^{(-V-55)/40} \tag{15}$$

$$\tau_{NaP}\left(V\right)=\frac{1}{\left(\frac{0.0333(V+45.5)}{1-e^{(-V-45.5)/4}}\right)+\left(\frac{0.0271(V+18.5)}{e^{(V+18.5)/5}-1}\right)} \tag{16}$$

$$m_{NaP,\infty}\left(V\right)=\frac{1}{1+e^{(-V-51)/4}} \qquad (17),$$

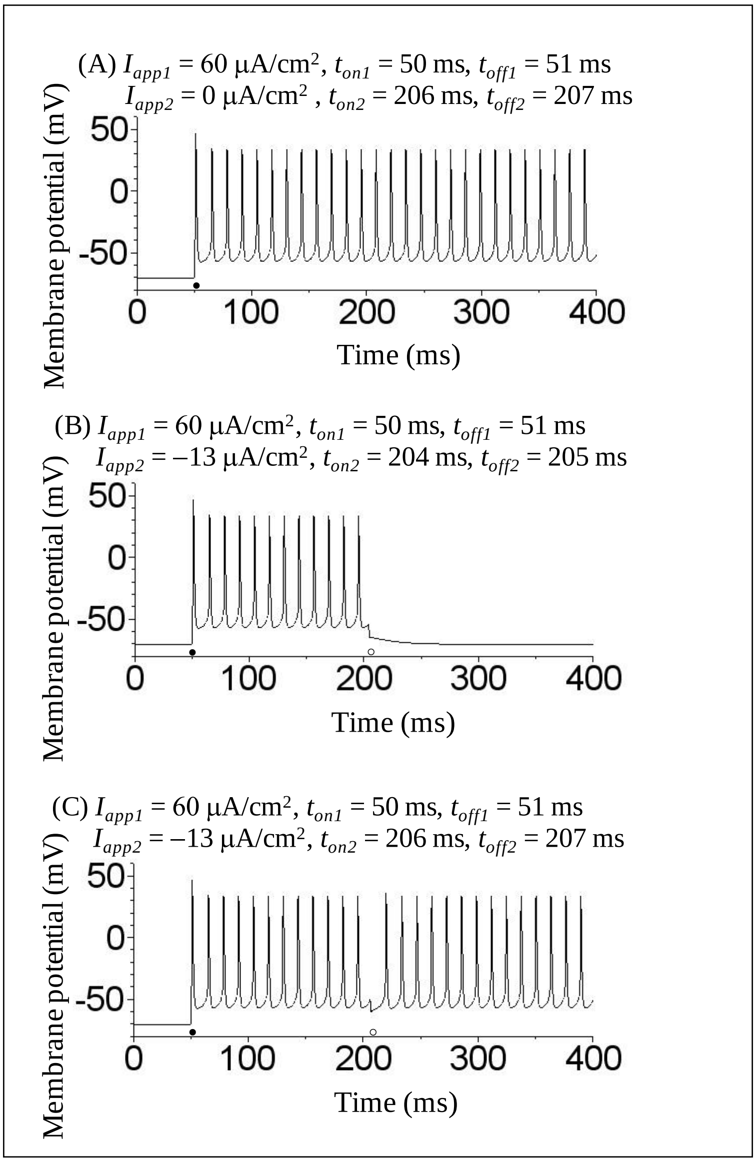
where g_{NaP} (= 0.10 mS/cm^2), g_{Na} (= 20 mS/cm^2), g_K (= 2 mS/cm^2), and g_L (= 0.08 mS/cm^2) are the maximal conductances of I_{NaP} (V, m_{NaP}), I_{Na} (V, m, h) I_K (V, n), and $I_L(V)$, respectively; and V_{NaP} (= 45 mV), V_{Na} (= 45 mV), V_K (= –85 mV), and V_L (= –71.5 mV) are the reversal potentials of I_{NaP} (V, m_{NaP}), I_{Na} (V, m, h), I_K (V, n), and $I_L(V)$, respectively. Refer to [6] for detailed explanations of the Equations (1)–(17).

The above Equations (1)–(17) were solved numerically using the free and open-source software Scilab (http://www.scilab.org/). Initial conditions were set such that V = –71.5 mV, m = 0.1, h, = 0.9, n = 0.1, and m_{NaP} = 0.1. In all the simulations, the total simulation time was 400 ms. The time-dependent function $I_{inj}(t)$ is defined as follows: $I_{inj}(t) = I_{app1}$ (= 60 μA/cm^2 in all the simulations of the present study) during the time interval between t_{on1} and t_{off1}, while $I_{inj}(t) = I_{app2}$ (I_{app2} is a non-positive value) during the time interval between t_{on2} and t_{off2}. Otherwise $I_{inj}(t)$ = 0. In other words, the present study uses two types of current pulse stimulation: I_{app1}, t_{on1}, and t_{off1} define the first current pulse, and I_{app2}, t_{on2}, and t_{off2} define the second. I_{app2}, t_{on2}, and $t_{off2} - t_{on2}$ correspond to the amplitude, timing, and duration, respectively, of the current pulse stimulation that are required to move from repetitive spiking to a steady state.

3 Results

The mathematical model of neocortical pyramidal neurons shows bistable behavior, and stimulation by a transient positive current pulse can transform the dynamical state of the model from the steady state to a repetitive spiking state [6]. This transition was reproduced by the present study: the membrane potential's time course of the model shows that a transient positive current pulse (60 $\mu A/cm^2$ in amplitude and 1 ms in duration) that is applied at 50 ms can change the dynamical state of the model from the steady state to a repetitive spiking state (Figure 1A). The present study aimed to clarify the condition of the transient current pulse stimulation required for the transition to take place in the opposite direction (i.e., from repetitive spiking to the steady state). Figure 1B shows an example in which this transition occurs: A negative current pulse (–13 $\mu A/cm^2$ in amplitude and 1 ms in duration) applied at 204 ms induces the transition from repetitive spiking to the steady state. In contrast, Figure 1C gives an example in which the transition does not occur: A negative current pulse with the same amplitude and duration as in Figure 1B but with a different timing does not induce the same transition (i.e., repetitive spiking behavior is recovered after spiking behavior is transiently suppressed by the negative current pulse).

Next, we investigated in detail the dependence of the transition from repetitive spiking to the steady state on the current pulse conditions: amplitude [I_{app2}], duration [$t_{off2} – t_{on2}$], and timing [t_{on2}]. In particular, the present study fixed $t_{off2} – t_{on2}$ to be 1 ms, and changed I_{app2} and t_{on2}. I_{app2} was varied between –1 and –15 $\mu A/cm^2$ at intervals of 1 $\mu A/cm^2$, and t_{on2} was varied between 198 and 206 ms at intervals of 2 ms (Figure 2A shows one cycle of repetitive spiking and the timings within this cycle). How the transition from repetitive spiking to the steady state depends on the amplitude and timing is shown in Figure 2B. At each timing, when I_{app2} is decreased (i.e., making the value of I_{app2} more negative) below a certain threshold, the current pulse induces the transition from repetitive spiking to the steady state. In addition, early and late timings differ quantitatively in the effect of variation in them on the threshold: in early timings, increasing t_{on2}, e.g. 198 → 200 → 202 s, slightly changes the threshold (i.e., –5 → –5 → –7 $\mu A/cm^2$), whereas in late timings, an increase in t_{on2} such as 202 →204 →206 s drastically changes the threshold (i.e., –7 μ → –9 μ → –15 $\mu A/cm^2$).

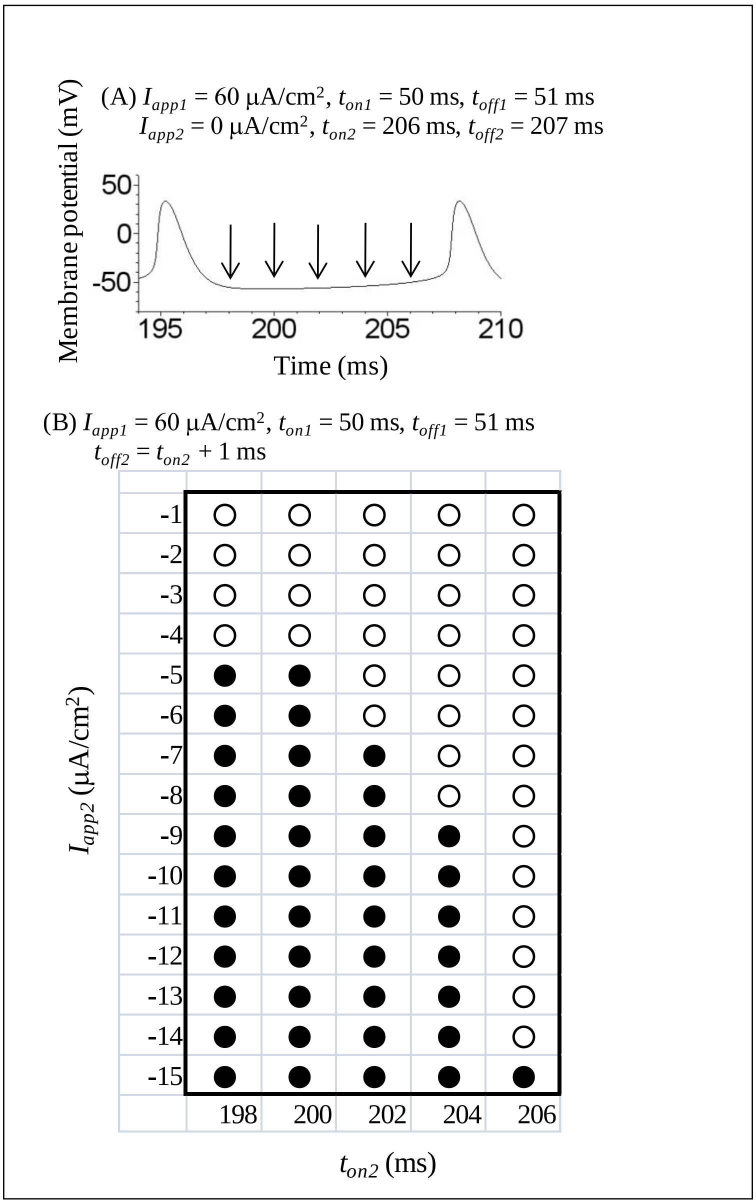


(A) $I_{app1} = 60\ \mu\text{A/cm}^2$, $t_{on1} = 50$ ms, $t_{off1} = 51$ ms
$I_{app2} = 0\ \mu\text{A/cm}^2$, $t_{on2} = 206$ ms, $t_{off2} = 207$ ms

(B) $I_{app1} = 60\ \mu\text{A/cm}^2$, $t_{on1} = 50$ ms, $t_{off1} = 51$ ms
$I_{app2} = -13\ \mu\text{A/cm}^2$, $t_{on2} = 204$ ms, $t_{off2} = 205$ ms

(C) $I_{app1} = 60\ \mu\text{A/cm}^2$, $t_{on1} = 50$ ms, $t_{off1} = 51$ ms
$I_{app2} = -13\ \mu\text{A/cm}^2$, $t_{on2} = 206$ ms, $t_{off2} = 207$ ms

Figure 1. Time courses of the membrane potential of the neocortical pyramidal neuron model. The condition of the first current pulse is $I_{app1} = 60\ \mu\text{A/cm}^2$, $t_{on1} = 50$ ms, $t_{off1} = 51$ ms in (A)–(C). The condition of the second current pulse is (A) $I_{app2} = 0\ \mu\text{A/cm}^2$, $t_{on2} = 206$ ms, $t_{off2} = 207$ ms, (B) $I_{app2} = -13\ \mu\text{A/cm}^2$, $t_{on2} = 204$ ms, $t_{off2} = 205$ ms, and (C) $I_{app2} = -13\ \mu\text{A/cm}^2$, $t_{on2} = 206$ ms, $t_{off2} = 207$ ms. Black circles indicate the timing of the first current pulse, whereas white circles indicate the timing of the second current pulse.



	198	200	202	204	206
-1	○	○	○	○	○
-2	○	○	○	○	○
-3	○	○	○	○	○
-4	○	○	○	○	○
-5	●	●	○	○	○
-6	●	●	○	○	○
-7	●	●	●	○	○
-8	●	●	●	○	○
-9	●	●	●	●	○
-10	●	●	●	●	○
-11	●	●	●	●	○
-12	●	●	●	●	○
-13	●	●	●	●	○
-14	●	●	●	●	○
-15	●	●	●	●	●

Figure 2. The transition from repetitive spiking to the steady state depends on the amplitude and timing of the second current pulse. (A) Timing of the second current pulse (↓) within one spiking cycle that is generated by the first current pulse (I_{app1} = 60 μA/cm^2, t_{on1} = 50 ms, t_{off1} = 51 ms). (B) Combinations of the amplitude and timing of the second current pulse required for the transition from a repetitive spiking state generated by the first current pulse (I_{app1} = 60 μA/cm^2, t_{on1} = 50 ms, t_{off1} = 51 ms) to the steady state. ○ indicates a condition in which the transition does not occur; ● indicates a condition in which the transition occurs. The duration of the second current pulse is fixed to 1 ms.

4 Discussion

In a previous study, a negative current pulse (amplitude -10 μA/cm^2 and duration 3 ms) was shown to be able to transform the dynamical state of the neocortical pyramidal neuron model from repetitive spiking to the steady state [7]. However, whether other amplitudes can induce the same transition was not clarified. In addition, this study did not mention the timing of the current pulse either. An important contribution of the present study is that it clarifies in detail the various combinations of amplitude and timing of the current pulse required to shift the dynamical state from repetitive spiking to the steady state.

The present study is one example of bistable neuron models that can be transferred between different dynamical states by various combinations of amplitude and timing of the current pulse. Previous studies presented other examples: in a study of a leech neuron model the combinations of amplitude and timing of the current pulse required for the transition from a bursting to a steady state were elucidated [11], and studying a snail neuron model revealed that certain combinations of amplitude and timing of the current pulse caused the transition from a bursting to a chaotic spiking state [12]. However, these two studies and the present one are also different; the former studies focused on current pulse timing within a bursting cycle, whereas the latter study investigated the current pulse timing within a spiking cycle. A previous study of a circadian pacemaker neuron model also focused on the timing of the current pulse within a spiking cycle [10]. However, the neocortical pyramidal neuron model and circadian pacemaker neuron model differ in the sensitivity to variation in the timing of their threshold amplitude for the transition from repetitive spiking to the steady state: the sensitivity of the threshold to variation in the timing is smaller in early timing than in late timing in the former model, whereas in the latter model the sensitivity is larger in early timing than in late timing. This difference is considered to be related to the difference in steady states between the former and latter models: the former model displays a hyperpolarized steady state, whereas the latter model has a depolarized steady state.

5 Conclusion

In the present study we did a computer simulation analysis of the neocortical pyramidal neuron model and studied the bistability of the model in more detail than in previous studies. The results of the present study contribute to the deeper understanding of the current pulse conditions required for the transition from repetitive spiking to the steady state to occur in the neocortical pyramidal neuron model.

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