Computational study of action potential initiation and action potential backpropagation in mitral cell of the olfactory bulb

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Abstract. A neuron sends information in the form of electrical activity called an action potential. The action potential propagates along the axon to all parts of the cell body. The opposite phenomena of this mechanism were observed in the neurons from various brain area as action potential backpropagation. We studied computationally the action potential initiation and action potential backpropagation in the model of a mitral cell of the olfactory bulb that consists of soma, primary dendrite, secondary dendrite, tuft dendrite, axon hillock, and initial segment. The neuronal activity was constructed with voltage-dependent sodium channels and potassium channels. In the results, we provide that the action potential initiation occurs in soma with an amplitude of 40 mV and the action potential propagation decrease as the distance gets farther from the soma. By plotting the amplitude as a function of the distance from the soma, we obtain the magnitude of action potential backpropagation amplitude has an average of about 42.7 mV. This result consistent with observations in experiments where the normalization of action potential backpropagation amplitude of the mitral cell as a function of the distance from the soma is constant.

1. Introduction

Action potential (AP) is a way of neurons transmit the information or communicate with one another in the nervous system in the form of an electrical signal. The nerve impulses are generated in the nucleus of nerve cells and travel along an axon that consist of the myelin sheath and the nodes of Ranvier to the axon terminal. The nerve cells are surrounded by a membrane that allows some ions to pass through and block the passage of other ions. The action potential (AP) is the result of ions moving in and out of the cell. The propagation of AP has been widely measured experimentally and studied computationally in various neuronal types. The AP is an all-or-none event with decreasing amplitude as a function of the distance from the soma.

A reverse process of AP has been recorded in some experimental methods as action potential backpropagation that occurs along the axons leading to the dendrite caused by active conduction and triggers a second spike on the dendrite originating from the initiation of the action potential of the axon. Dendritic recording electrophysiology using patch-clamp technique, infra-red differential interference contrast (IR-DIC) optics, and fluorescence imaging technique are an example of an experimental procedure that has been used to measure the AP backpropagation[1, 2]. These measurement techniques provide essential data to understand the mechanism and other properties of backpropagating AP, but they also have a few disadvantages. The study of the computational model is an alternative to overcome the limitation from the experimental methods.
The AP backpropagation has been observed in various mammalian neuronal types such as cerebellar Purkinje cells, hippocampal interneurons, dopamine neurons, and mitral cells. From these varieties, only mitral cells of the olfactory bulb that has been measured in direct recordings from both the thick apical and the thin lateral/basal dendrites[3-9]. The functions of backpropagating APs mainly related to synaptic efficacy that affects synaptic plasticity, neuronal firing, and synchronization of developing a network. One of the functions of AP backpropagation is deal with local synaptic feedback, forming an intricate network of dendro-dendritic synapses as observed in the mitral cells of the olfactory bulb and can be concluded that the AP backpropagation may be responsible towards olfactory function[5].

In studying the AP initiation and AP backpropagation phenomena, we construct a model of the mitral cell of the olfactory bulb that consists of soma, primary dendrite, secondary dendrite, tuft dendrite, axon hillock, and initial segment. The amplitude of AP backpropagation formed at different dendrite location is observed as a function of distance from the soma. The model was simulated with the NEURON program using python. The NEURON simulator provides an environment to simulate a biophysical neural network with realistic biological membranes[10-12].

2. Methodology

In this study, we built the model using the following steps:

2.1. Developing the model

The starting point uses the interface in the NEURON main menu is by clicking Build and then Cell Builder. In the top of cell builder will appear an array of buttons and click the Topology where we can set up the model. In this window, we start to model the mitral cell that consists of soma, dendrite, and axon with make session mode. We label each part of the cell with Basename menu and click on the part of the cell. Another option to develop the model cell is writing script with python with the following steps:

a. Connecting python and NEURON simulators by importing the NEURON module into python.

b. Construct the model of a mitral cell.

The model of the mitral cell is constructed based on the experimental morphological results with details of topology, segments, and geometry. The morphology specifications of the mitral cell are presented in Table 1.

| Table 1. The morphology of mitral cell[13] |
|-------------------------------------------|
| Soma          | Pri | Tuft | Sec | Axon hillock | Initial Segmen | Node of Ranvier | Myelin sheath |
| Diameter (μm) |  20 |  3.5 | 0.51|  3.4         |  20:1.5         |  1              |  1.5          |
| Length (μm)   |  25 | 370  | 180 |  500         |  5              |  20             | 1000          |

c. Connecting each part of the cell

All part of the cell is being connected to form a morphology of mitral cell. The dendrites begin with two dendritic tuft branches and then connected with two long primary dendrites, and the last connected to soma are two secondary dendritic branches. The axon starts with the axon hillock that connects the soma with the initial segment axon. There are two initial axon segments which are connected to five nodes of Ranvier and myelin sheaths that form a long axon.
2.2. The kinetic models

In modeling the AP initiation, we have to set the parameter value of each section. The parameters used in the model are initial resistance ($R_i$) and membrane capacitance ($C_m$) with the value equal to 100 $\Omega\text{cm}^2$ and 1 $\mu\text{f/cm}^2$ respectively. These parameters were set to have the same value in every part of the mitral cell. We have to add the parameter of resistance formed after the action potential ($R_m$) for the process of AP backpropagation and give the value equal to 2800 $\Omega\text{cm}$. There are two kinetic models used in the program, active kinetic model and passive kinetic model. An active kinetic model that is used in modeling the AP initiation is Hodgkin-Huxley neuron model to modeling the dynamics of the action potential initiation membrane in soma, axon hillock, and axon initial segment. This model include sodium conductance ($g_{Na}$), potassium conductance ($g_K$), leak conductance ($g_L$) and leak reversal potential ($E_L$) with the value are 0.12 S/cm$^2$, 0.036 S/cm$^2$, 0.0003 S/cm$^2$, and -54.3 mV respectively. In the AP backpropagation, the chemical mechanism was scripted in NMODL language. NMODL files will be extracted into files with the extension of .c and .o so that they can be recognized. NMODL is used to model a chemical mechanism that occurs in mitral cell that involves potassium ions and sodium ions. In this model, there are two potassium ion channels and three sodium ion channels written in NMODL syntax. The solution of the potential equation for the ion channels use the exponential Euler method. The NMODL files are inserted in each part of the mitral cell with different ion gate compositions according to the specifications of the mitral cell. There are two sodium ion channels in soma and one potassium ion channel, while in dendrites there is one sodium ion channel and three potassium ion channels. A passive kinetic model is used in the tuft dendrite, primary dendrite, and secondary dendrite. The passive kinetic model includes passive conductance ($g$) and leak reversal potential ($E$) with the value 0.001 S/cm$^2$ and -65 mV, respectively. The stimulus is inserted onto the soma to induce the membrane dynamics. In this model, we use IClamp stimulus model with an amplitude of 25 mV, a delay of 20 ms and a duration of 1 ms for AP initiation, while the amplitude of 0.8 mV, a delay of 1 ms and a duration of 1 ms were set for AP backpropagation.

2.3. Plotting the graphs

In this model, we use the matplotlib packages feature in python to plot the graph. The graph visualizes the AP initiation in the soma, the AP propagation along an axon, and the AP backpropagation on the soma, secondary dendrite, primary dendrite, and tuft dendrite.

3. Results and Discussion

The model of mitral cell is described in figure 1. The mitral cell consists of two dendritic tuft branches, two secondary dendritic branches, primary dendrite, soma and axon with five myelin and five nodes of Ranvier. The mitral cell that is constructed with nrngui is shown differently from the plotting graph with the python script.

![Figure 1. Plotting graph of mitral cell in the program with python (left) and another way to construct a mitral cell using NEURON environment (right)](image_url)
The results of AP initiation in the soma and AP propagation along an axon are shown in figure 2 and figure 3, respectively. The IClamp stimulus model was applied to provide the initial potential and result of the action potential that propagates along an axon. The AP initiation occurs in soma where the stimulus was applied with the amplitude of 40 mV. The AP initiation is the result of the migration of sodium and potassium ion across the nerve cell membrane, thus triggering the occurrence of depolarization. The action potential then propagates with diminishing amplitude along an axon. The amplitude of AP decrease as the function of distance from the center of the electrode stimulus. The AP amplitude decreases from the first myelin sheath to the fifth node of Ranvier before it reaches the nerve terminal.

![Figure 2. The AP initiation in the soma](image1)

![Figure 3. The AP propagation along an axon](image2)

The AP backpropagation in the soma, primary dendrite, secondary dendrite, and tuft dendrite of mitral cell is shown in figure 4 with its enlarged peak. The magnitude of the AP backpropagation amplitude in different parts of the mitral cell as a function of distance from the soma is almost the same, as shown in figure 5. The details data of AP backpropagation amplitude and the distance of each part from the soma is described in Table 2.

![Figure 4. The AP backpropagation of mitral cell along the dendrites (left) and enlarged figure the peak of AP backpropagation (right)](image3)

The magnitude of the amplitude of AP backpropagation is influenced by several things such as the density and character of the ion channel, the neuronal morphology and neuronal activity[14]. Moreover, the AP backpropagation is also influenced by the initial resistance ($R_0$), the resistance formed after the action potential ($R_m$), the distance from the soma ($x$) and diameter ($d$) from the dendrite[15] as described in the following equation

$$V_x = V_0 e^{-\frac{x}{\lambda}}$$

(1)

with $\lambda$ equal to

$$\lambda = \left(\frac{R_m d}{R_0 4}\right)^{\frac{1}{2}}$$

(2)
The kinetic model parameter of AP backpropagation of this mitral cell is $R_a$ and $R_m$ with the same value in each part. The initial amplitude ($V_0$) is determined by the amplitude of the stimulus given at 0.8 mV with the different chemical mechanism of sodium ion channels and potassium ion channels in each part. The AP backpropagation amplitude in this model is determined by the initial amplitude ($V_0$), distance ($x$), and diameter ($d$) of the parameters. The distance and diameter are in the order of the micrometer so that the difference of amplitude in each part of the dendrites. These results are consistent with the equation and experimental research conducted by Waters et al., 2005[5], as illustrated in figure 6. The figure shows the summary of AP backpropagation in different cell types. In the mitral cell, the normalized amplitude of AP backpropagation as a function of the distance from the soma is constant. In our simulation, the difference amplitude of the AP backpropagation in various part of the dendrites is very small, almost constant with an average of about 42.7 mV. The soma section which is the closest part to the axon shows the lowest backpropagation amplitude, due to the special attenuation of the sodium ion channel in soma, while the attenuation in the dendrites is only influenced by distance from the source of stimulus injection[15].

The phenomena of AP backpropagation in different cell types leads to the question on the mechanism of the occurrence of AP backpropagation. The active dendritic conductance and the neuronal morphology of the dendritic tree are considered as the main factor that affects the backpropagation[5]. The synaptic input can modulate the AP backpropagation, and this interaction leads to the enhancement of the backpropagation. In figure 7, we show the modulation AP backpropagation on
each part of the dendrites. The modulation was carried out by varying the stimulus with a magnitude of 0.2 mV, 0.4 mV, 0.6 mV, and 0.8 mV. From the variation of these values, the magnitude of the amplitude is obtained equal to the initial modeling stimulus of 0.8 mV.

![Figure 7. The modulation of AP backpropagation on each part of the dendrites](image)

4. Conclusion
Modeling of the AP initiation and AP backpropagation in the mitral cell of the olfactory bulb has been done using a combination of NEURON and Python simulators. The AP initiation occurs in soma with a magnitude of 40 mV. The AP propagates along an axon with decreasing amplitude as a function of distance from the soma. The AP backpropagation occurs in soma and dendrites with almost the same amplitude in each part of the dendrites about 42.7 mV. The variation of the stimulus was used to modulate the AP backpropagation and result in the amplitude that equal to the initial stimulus about 0.8 mV.

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