

Chapter 8

Example: a sensory neuron of *Aplysia*

In this chapter, I illustrate the application of the NeuroSim system with the simulation of a real neural cell: a sensory neuron of the mollusc *Aplysia*. The problem has been formulated in cooperation with neurobiologists expecting that detailed modelling based on the experimental results will help to understand the anatomical structure and mechanism of spike initiation in the sensory neuron of *Aplysia* [6].

8.1 Biological results and problem definition

8.1.1 Neuron functions and structure

The neuron B21 is activated during feeding activity of the mollusc *Aplysia* [62]. It is responsible for stimulation of a muscle tissue, called sub-radula tissue (SRT), that underlies the radula, a structure to move food into the buccal cavity of *Aplysia*. B21 is synaptically connected with a group of neurons that control closure and pulling back of the radula. We have concentrated on the study of the connection of B21 with B8, the radula closer motor neuron; this connection is regulated by an excitatory chemical synapse. The task of our study is to learn about the initiation of postsynaptic potentials (PSPs) in the B8 neuron [11, 62, 16, 15].

The structure of the B21 neuron and its connection with B8 are shown schematically in Fig. 8.1. The soma of B21 is located in the middle of the cell. Two branches of a dendritic tree are located at opposite sides of the soma. The part of the dendritic tree connected to the SRT is called “medial” or “peripheral process”. It innervates the periphery and conducts incoming afferent activity. Another branch of the dendritic tree providing connection with the radula closer motor neuron B8 is called “lateral process”. It can be considered as the output connection of B21.

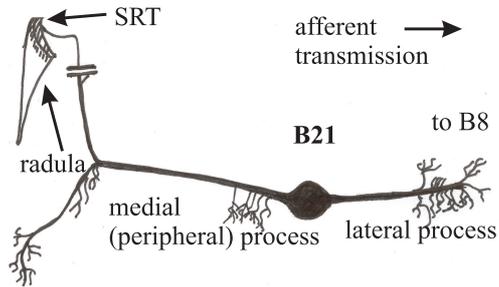


Figure 8.1: Schematic representation of the B21 cell.

It has been shown in the experimental research, that “afferent transmission” underlies the biological process of feeding [16]. The responses to a peripheral stimulus are adjusted by regulation of the spike propagations in neuron B21. The sensory neuron B21 in *Aplysia* was chosen to study the regulation mechanisms of “afferent transmission”, owing to some of its features that facilitate the experiments. First, the size of its structural components is relatively large, which simplifies performing experiments. Second, its soma is located centrally rather than peripherally, which makes it easier to determine the positions of functional parts of the neuron.

Neurobiologists are interested in understanding the mechanisms that gate in afferent activity. Experiments have shown, that when B21 is peripherally activated at its resting membrane potential, postsynaptic potentials (PSPs) are not observed in B8. In contrast, if B21 is centrally depolarized and then peripherally activated, PSPs are observable in B8 [62].

The lateral process of B21 is the primary contact (place of synaptic connection) of B21 with B8. Therefore, understanding of the spike initiation mechanism in the lateral process of B21 can help explain the effect of activation of synaptic channels in the B8 neuron.

8.1.2 Results of biological experiments

Two biological experiments devoted to the investigation of electrical spike propagation and its central regulation in B21 [11] have been used as an experimental basis for our model simulation.

In the first biological experiment, the membrane potential changes through the length of B21 were studied. During this experiment, B21 was only peripherally activated with a current stimulus into peripheral part of the dendritic branch. The voltage was measured at three points on different parts of B21: peripheral process, soma, and lateral process. As we can see from Fig. 8.2(a), the amplitude of the spike measured in the lateral process is attenuated compared to the one measured in the peripheral process. Peripherally triggered spikes

recorded experimentally in the soma had an average value of 35.7 ± 2.6 mV with a half-width of 4.9 ± 0.1 ms. The amplitude of spikes in the lateral process was 10.6 ± 1.1 mV. It has been suggested that attenuated spikes in the lateral process are just passive reflections of spikes generated in the medial part of B21.

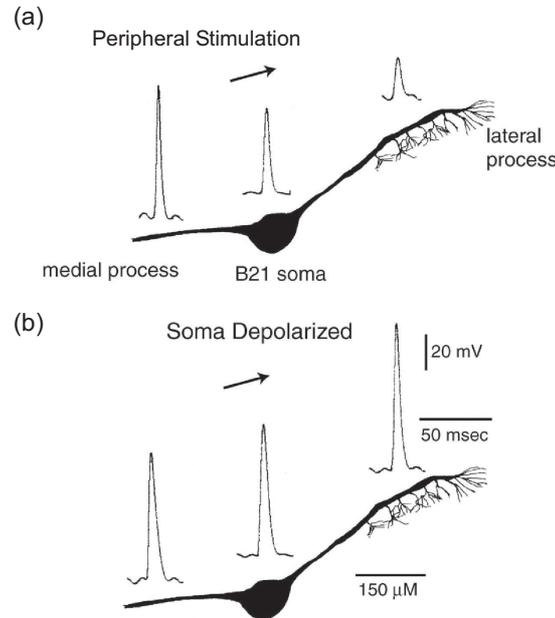


Figure 8.2: Experimental results show spike attenuation in the lateral process of B21. From [11].

The second experiment was performed to study voltage dynamics in B21 [15] when the cell was centrally depolarized (current injected into the soma) and then activated peripherally. Full-size spikes were observed in the lateral process (see Fig. 8.2(b)) with an amplitude of 50.0 ± 2.8 mV. Thus, from the biological experiments, one can suppose that spikes are actively generated in the lateral process when the soma is activated. This suggests that the lateral process is capable of spike generation [11].

In the case of central depolarization, an increase in spike amplitude measured in the soma and its half-width has been observed. By depolarizing the soma just below the threshold of spike generation, spikes were generated with an amplitude of 51.6 ± 3.2 mV with a half-width of 7.4 ± 0.1 ms, compared with the peripherally triggered spikes recorded in the soma with an average value of 35.7 ± 2.6 mV and a half-width of 4.9 ± 0.1 ms.

The aim of our simulation is to develop a mathematical model of the B21 cell and compare its behavior with experimental results. The model based on the real parameters describing the morphology of B21 should help either to refute

the statement about spike generation in the lateral part of B21, or to prove its validity. The simulation can also help us to learn about the mechanism underlying the phenomenon of spike initiation in B21.

8.2 Model definition

The B21 model was constructed using the compartmental modelling approach. The main components of the cell and their connections were included in the model according to the data about the structure of the real cell (see Fig. 8.1). The peripheral process was modelled with ten cylindrical compartments, which are longitudinally connected to the soma. The soma was connected to the lateral process, which was also modelled by ten compartments.

The experiments have strongly suggested that the B21 soma is unexcitable and somatic potentials are always electrotonic.

As model parameters, we have used the parameters based on the data of the cell morphology derived from the experimental studies [6]. In particular, the compartments in the peripheral part were chosen to have a radius of 0.0015 cm and a length of 0.009 cm . The soma was modelled as a cylindrical compartment with a radius of 0.0015 cm and a length of 0.002 cm . The lateral dendritic compartments had a radius of 0.001 cm and a length of 0.007 cm . The specific membrane resistance of the cell was $R_M = 1000 \Omega \cdot \text{cm}^2$, specific axial resistance was $R_A = 100 \Omega \cdot \text{cm}$, and specific membrane capacitance was $C_M = 1 \mu\text{F}/\text{cm}^2$. The resting membrane potential of the cell was $E_{rest} = -65 \text{ mV}$.

From the cable theory (see Section 3.2.2) follows that the space constant λ provides information about the form of the curve representing the potential variation along the cable. The constant λ plays a critical role in spatial integration of an input current in dendritic trees. W. Rall [60] has shown that the potential decays exponentially with the distance λ (Eq. 3.19) in the infinite cable of a passive tree.

The peripheral part of dendritic tree has the length $l = 10 \cdot l_{comp} = 10 \cdot 0.009 = 0.09 \text{ cm}$ in our model. The parameter λ can be calculated as

$$\lambda = \sqrt{\frac{d R_M}{4 R_A}} = \sqrt{\frac{0.003 \cdot 1000}{4 \cdot 100}} = 0.0866, \quad (8.1)$$

which is approximately equal to the length l of the simulated peripheral process.

Similarly, the parameter λ is calculated for the lateral dendritic part as

$$\lambda = \sqrt{\frac{d R_M}{4 R_A}} = \sqrt{\frac{0.002 \cdot 1000}{4 \cdot 100}} = 0.07. \quad (8.2)$$

The length of the lateral process is $l = 10 \cdot l_{comp} = 10 \cdot 0.007 = 0.07 \text{ cm}$, which also corresponds to the space constant λ .

The fact that peripheral and lateral processes have lengths equal to the space constant λ shows that significant attenuation of the spikes should take place in our case. One expects slower attenuation of the spike with distance in our dendrite compared to the case of the infinite cable (see Section 3.2.3).

We have used this fact for explanation of the observed experimental behavior and building of the simulation model as it will be shown below.

8.3 Simulation of regulated transmission

The simulation based on the proposed model has been used to study the effects observed in the experiments: spike initiation in the medial process, its transmission to the lateral process, and the central regulation of the transmission mechanism.

In biological experiments, it has been shown that spikes can be initiated in the peripheral process of B21 just by peripheral stimulation. But in this case, their amplitude is reduced as the distance to the soma increases. One can assume that the peripheral process should start with compartments consisting of voltage-gated channels and then continue with passive compartments. Therefore, attenuated spikes are just a passive reflection of spikes generated in the first peripheral compartment.

The model should also take into account that when the soma is depolarized by a current injection, no attenuation in the amplitude of spikes in the lateral process was observed in experiments. Therefore, we have assumed that some compartments located at the end of the lateral process consist of voltage-gated channels and are capable of full-amplitude spike generation.

Moreover, according to the experimental results, when B21 is centrally depolarized the amplitude of spikes measured in the soma have a maximum value (see Fig. 8.2). But when B21 was only peripherally stimulated, spikes in the soma were attenuated. These two facts point to the idea that the compartment in the lateral process near the soma should be capable of spike generation, i.e. these compartments consist of ionic channels, since the soma itself does not contain ionic channels. Soma depolarization only helps to overcome the activation potential in the first lateral compartment and evokes spike generation when a peripherally stimulated spike arrives. Spikes are not initiated in the case of peripheral activation because their amplitude is below a threshold and we only see a passive reflection of the spike in the first compartments of the peripheral process.

The model was chosen from several tested models because it showed the best agreement with experimental results. The first four compartments in the peripheral part of the dendritic tree consist of Hodgkin-Huxley type ionic channels. The next peripheral compartments are passive (from fifth to tenth). The peripheral part is longitudinally connected with the passive compartment of a soma. The soma is connected with the lateral process. The first lateral compartment that is near the soma and the three last are inhomogeneous with Hodgkin-Huxley ionic channels, all other lateral compartments are passive (from second to seventh).

Fig. 8.3 shows the model structure of B21 defined with NeuroSim, where compartments with Hodgkin-Huxley channels are distinguished and the current stimuli are also distinctly marked.

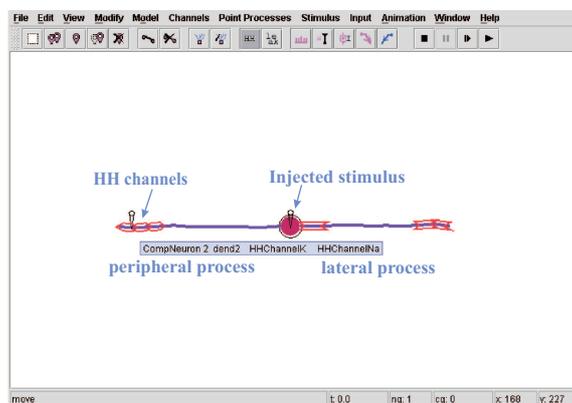


Figure 8.3: The model structure of B21 defined with NeuroSim.

8.3.1 Parameters of channel dynamics

The parameters of the Hodgkin-Huxley channels (Eq. 3.5, Eq. 3.6, Eq. 3.10) were varied to get the best agreement with experimental data. The values of the parameters of the Hodgkin-Huxley channels in our model differ from the standard ones (see Section 3.2.1). The maximum magnitude of generated spikes is about 50 mV above the resting potential (100 mV in the standard case). Opening of the sodium channel leads to an increase in the compartment voltage towards the sodium equilibrium potential E_{Na} (usually 45 mV), which corresponds to the rising phase of the action potential. To fit the experimental data, I have chosen $E_{Na} = 0.0\text{ mV}$, $E_K = -82.0\text{ mV}$.

The maximum magnitude of the action potential has been set smaller than in the standard case. This value influences the dynamics of the activation and inactivation variables, so that the sodium and potassium channels are closed and opened, correspondingly, at different times. The changing mechanism of closing/opening channels leads to attenuation of spike amplitudes with time. The parameter g_k , the maximum channel conductance, can be used to regulate these processes.

The following values have been set for the channels in peripheral dendritic compartments: g_{Na} is 500 mS per square centimeter of membrane area and g_K is 40 mS/cm^2 .

To simulate the effect of non-activation of the channels in the lateral process for the case of peripheral stimulation, one needs to adjust the value of threshold spike generation (about -50 mV for the standard channels). This effect can be achieved by modifying the parameter V_0 (see Eq. 3.2.1) in α - and β functions of the activation/inactivation variables. For the channels in the lateral compartments, I have set this value 10 mV higher than the value for standard channels. From the simulation tests that I describe in the next section, one can observe non-activation of channels in the lateral process after peripheral depo-

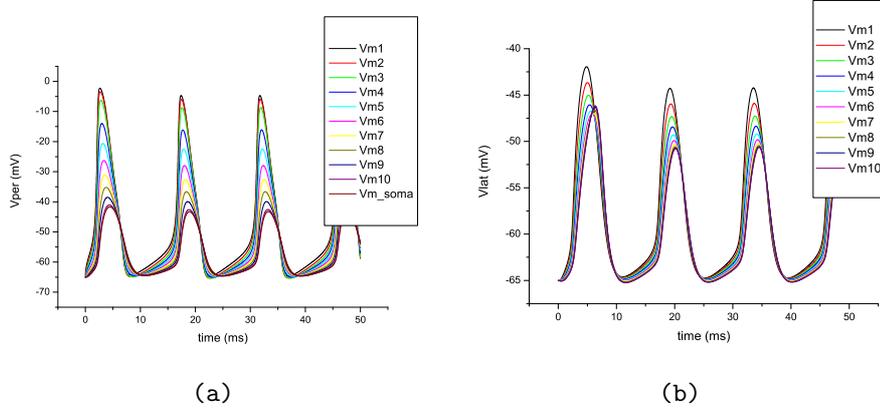


Figure 8.4: Peripheral depolarization of the B21 cell. Graphs of the voltage spread: a) in the peripheral dendritic compartments; b) in the lateral dendritic compartments. V_{mi} is the voltage of i -th compartment, V_{msoma} is the voltage of the soma compartment.

larization. The values of the potential in lateral compartments are less than -42 mV, which is shown in Fig. 8.4, presenting simulation results for the case of a peripheral stimulus. The activation curves for the peripheral activation and additional central stimulation are shown in Fig. 8.6, where the values of m^3h for sodium and n^4 for potassium have been plotted; the other parameters in the channel current do not depend on the voltage (see Eq. 3.11).

The maximum channel conductances have been chosen as $g_K = 40$ mS/cm² and $g_{Na} = 700$ mS/cm², because the increase of the threshold potential value reduces the time between opening and closing of the channels.

For channels in the last three dendritic compartments, the following parameters have been chosen: $E_{Na} = 0.0$ mV, $E_K = -82.0$ mV, $g_K = 40$ mS/cm², and $g_{Na} = 500$ mS/cm².

8.3.2 Simulation results

The model was first tested with a peripherally activated cell. Depolarization with the injected current $I = 10$ nA produces the spike initiation in the first compartments of B21 (see Fig. 8.4(a)). The spike amplitude decrease during propagation through the peripheral process. Spike attenuation is also observed in the lateral dendritic part (see Fig. 8.4(b)), which confirms our hypothesis about non-activation of spikes in the lateral process after peripheral activation. The result of this simulation test are demonstrated in Fig. 8.6 showing the activation curves of the sodium and potassium channels in the first lateral compartment.

In Figure 8.5, the voltage changes in the peripheral process, soma, and lateral process are shown together. The spike amplitude in the first peripheral

compartment is about 60 mV above the membrane resting potential, 25 mV above the resting potential in the soma, and 15 mV above the resting potential in the lateral process, which is in good agreement with the experimental data (see Fig. 8.2(a)).

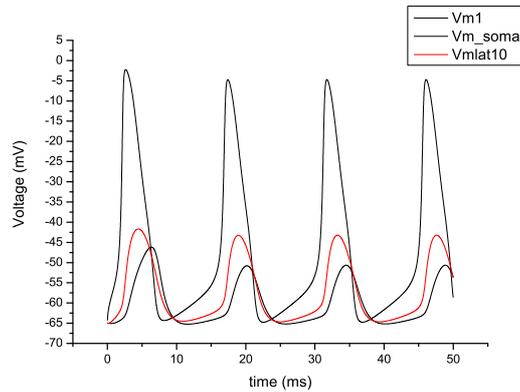


Figure 8.5: Peripheral depolarization of the B21 cell. The graphs show voltage spread in the first peripheral compartment ($Vm1$), in the soma (Vm_{soma}), and in the last lateral compartment ($Vmlat10$).

Next, the model of B21 with the above-mentioned structure was tested in the case of central depolarization. In addition to peripheral stimulation, a current $I = 13\text{ nA}$ was injected. It stimulates the opening Hodgkin-Huxley channels in the first lateral compartment, leading to an increase in spike amplitude in the soma. Figure 8.6 shows how the channel activation is increased in the case of the additional central activation compared with the case when the cell was only peripherally activated.

The spike actively generated in the first lateral compartment propagates through the lateral process and evokes an increase in voltage in the compartments composed of Hodgkin-Huxley channels, which is followed by their opening. Opening the channels causes the initiation of full-amplitude spikes in compartments at the end of the lateral process.

Figure 8.8 illustrates the voltage curves for the first peripheral compartment, the soma, and the last lateral compartment in the case of central depolarization of the B21 cell.

Simulation results have shown an increase in the half-width of the action potential measured in the soma, which is in agreement with the experimental data. The experiments show that these values change from 4.9 to 7.4 ms , in the cases of peripheral stimulation and central depolarization. Simulation results show an increase from 3.2 to 5.2 ms for the same cases. The effect of the increase of the action potential can be explained by the influence of spikes generated both

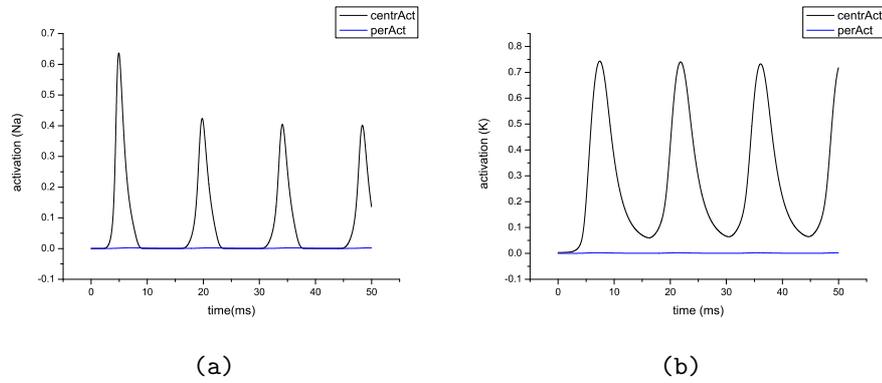


Figure 8.6: Channel activation curves of the first lateral compartment in the cases of peripheral and additional central activation: a) values of m^3h for sodium channels; b) values of n^4 for potassium channels.

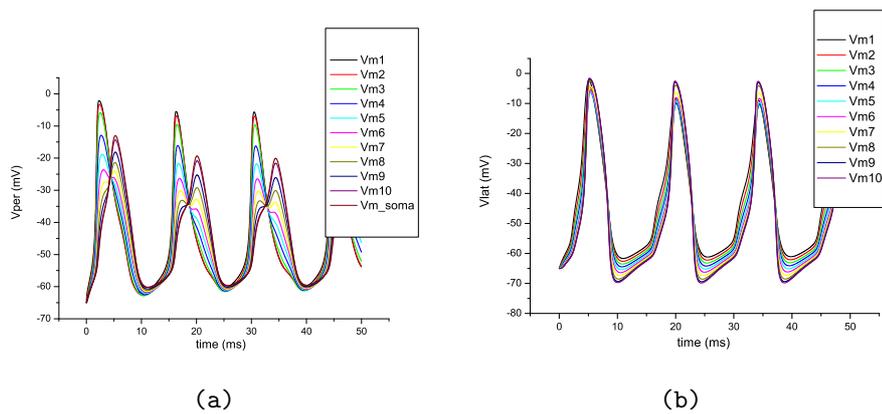


Figure 8.7: Central depolarization of B21. Graphs of the voltage spread: a) peripheral dendritic compartments; b) lateral dendritic compartments. V_{mi} is the voltage of i -th peripheral compartment, V_{mlati} is the voltage of i -th lateral compartment.

in the peripheral and lateral processes.

8.4 Conclusions and outlook

The functioning of the sensory neuron B21 of the mollusc *Aplysia* was studied. With that we have illustrated the application of NeuroSim for simulation of a real neurobiological system. A model of the B21 cell based on the behavior observed in neurobiological experiments was suggested. The simulated behavior

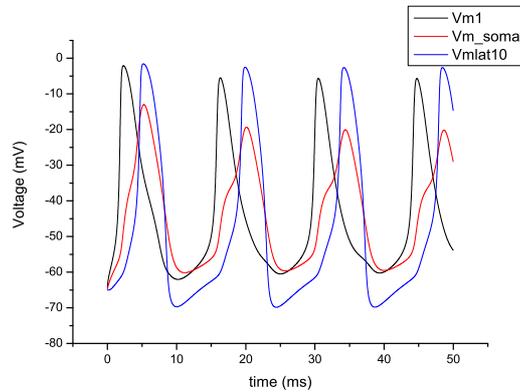


Figure 8.8: Central depolarization of B21: graphs of the voltage spread in the first peripheral compartment (V_{m1}), in the soma (V_{msoma}), and in the last lateral compartment (V_{mlat10}).

has shown good agreement with experimental data.

Recent independent experimental work performed by E. C. Cropper and C. G. Evans [15] confirms the B21 structure suggested in simulation. They found that a branch in the medial process of the B21 cell, referred to as a T-junction, is capable of spike initiation, and in this region, full-size action potentials can be recorded even when active propagation to the lateral process fails (see Fig. 8.9). We can relate the T-junction region to the region of the four medial compartments composed of active channels in our model. Also, the experimental tests have shown that the peripheral dendritic compartments next to the soma is passive and spike propagation in this part is electrotonic. Moreover, the lateral dendritic compartments near to the contact of B21 with B8 has been shown to be capable of active spike generation. Thus, our suggested cell model structure has found confirmation in experimental neurobiological tests.

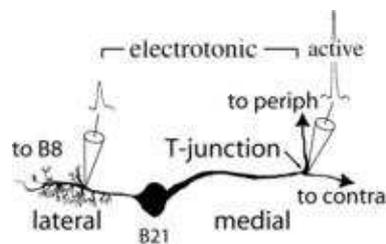


Figure 8.9: The structure of B21 from biological studies. From [15].

The simulation results propose further detailed study of the B21 structure. Judging from our simulation tests, it would be interesting to conduct further experiments to learn more about properties of the lateral cell segment near the soma. From simulation curves in the case of central depolarization (see Fig. 8.7(a)), it follows that it would also be interesting to record the peripherally triggered spikes in the peripheral segments close to the soma. The simulation shows the paired spikes that have been combined from the channel activations in the peripheral and lateral processes.

The simulation results can be used for further understanding of the mechanism of “afferent transmission” regulation. They allow study of the influences of cell morphology and channel dynamics on the regulation mechanisms of spike initiation and propagation along the lateral process of B21.

