

MODELLING AND SIMULATION OF A BIOLOGICAL PROCESS (NEURAL ACTION POTENTIAL) WITH HYBRID TOOLS USED IN COMPUTER SCIENCE

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Abstract

This paper shows an approach to model a complex biological process with hybrid tools used in computer science, in particular in software engineering.

The goal was to capture the behavior of an axon with its neural action potentials by combining state based description techniques and continuous equations. The axon was modelled and the behavior simulated afterwards.

On the basis of tests which are also used in "real" biological experiments it was shown that the model is accurate enough to reproduce biological reality. The results of the model resemble the results of experiments in biology with high accuracy.

The model and its simulation are used in a practical course at the University of Ulm which is aimed to help the students gain a better understanding of complex processes in biology.

1 Introduction

We made efforts to research the possibility of using software engineering tools to model complex biological structures and their behavior. The components of the axon needed to be modelled in detail, and the collaboration of these components during the stimulus conduction were simulated by

a tool. We wanted the parameter settings to be easily manipulable to allow the user experimentation with the model. As mentioned before, the model is used in a practical course for education in which students work with the biological experiments and in parallel with the model on a computer.

The paper consists of two parts. In the first part the modelling of the components of an axon is described; this includes the tools that were used and the setup of the model as a whole. The second part deals with the simulation and the usage in the practical course. The results are illustrated by an example of an experiment.

2 Modelling an axon

First we will give a short introduction of neurons, the axon and the action potential.

For the research done so far only the signal transfer within a singular neuron was examined. The neuron sends a signal called the *action potential* down the axon, away from the cell body. Neurons send signals electrochemically. The chemicals which are electrically charged ions cause an electric signal at the cell membrane by passing the membrane through ionic channels. For more information on these topics please see [Alb02], [Ude94] and [Hi192].

When modelling an axon two components at top level are very important. The first of these com-

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ponents are the nodes of Ranvier. Only at these small nodes electric activity takes place. The second component is the transfer of the voltage (spike propagation) from one node of Ranvier to another; this is called *stimulus conduction*. The electric impulse jumps from one node to the next. This is called *saltatory conduction* [Col].

The first section in this chapter deals with the modelling of the nodes of Ranvier, the second section talks about the spike propagation on the axon.

2.1 Modelling a node of Ranvier

When we examined the procedure of an action potential it became evident that the use of hybrid models would be the best way to model an axon and its behavior. The combination of discrete events in statecharts and the continuous calculation of parameters is well suited for modelling this biological process. The itemized components of the axon are modelled with statecharts, and the calculation of the results is made by a tool using continuous differential equations.

We chose to use Stateflow [Theb] and Simulink [Thea] from *The Mathworks, Inc.* Both tools are integrated into MATLAB and work together very well. Simulink offers a simple way of simulating a model.

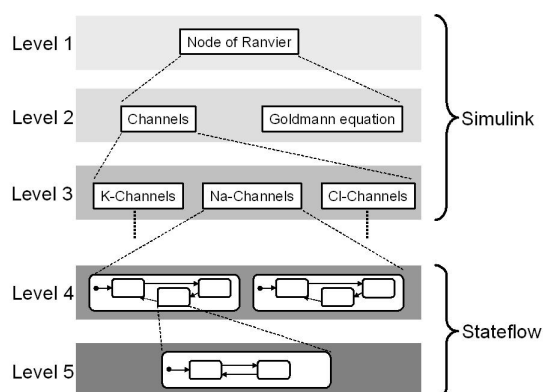


Figure 1: Abstract of the model.

The model of a node of Ranvier in our work is composed of five hierarchical levels, as shown in Figure 1. The three top levels are modelled in Simulink, and the two bottom levels which contain the singular components of an axon are modelled in Stateflow. The five levels are introduced from top to bottom in the following. The topmost level contains a single node of Ran-

vier with an incoming impulse (for example a mechanical stimulus) and an outgoing calculated voltage value (see figure 2).

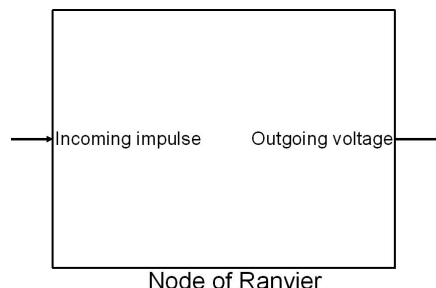


Figure 2: Level 1 – a node of Ranvier

It is simple to connect several nodes of Ranvier by structuring the model in this way. Information about the transfer of the voltage follows in section 2.2.

In the second level the voltage is calculated with the Goldmann equation. The potentials of nerves are mainly made up from interactions of three ions: Na^+ , K^+ and Cl^- . The Goldmann equation uses the intracellular and extracellular concentration and the permeability of the ions. For further information see [FB].

The permeability of an ion is composed of the sum of the permeability of every single channel. It describes how many ions pass the membrane through the channels per time unit.

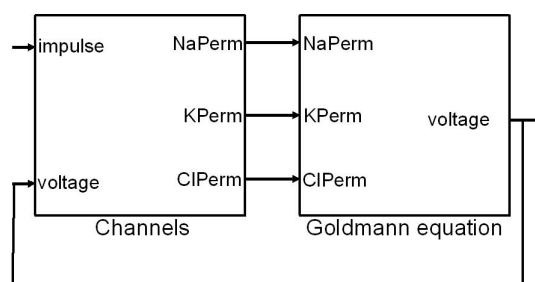


Figure 3: Level 2 – model of node of Ranvier

Figure 3 shows the Simulink model at level two. On the left there is a block called "Channels", on the right is the "Goldmann equation" block. In this block the calculation of the voltage takes place. The "Channels" block contains the channels of the axon, namely the sodium-, potassium- and the chlorine-channels. The stimulus from level one and the calculated voltage are directed to the block, as can be seen in the bottom part of the figure. The channels in an axon are controlled by the voltage, and therefore the voltage

has to be redirected to the channels to control them. This leads to a problem: the channels depend on the very voltage which in turn depends on them. Simulink provides an elegant solution for this problem with the block called "unit delay". The calculated value is directed to the next block with a delay of one simulation step. The channels charge their permeability, the Goldman equation uses these permeabilities to calculate the voltage, and one step later in the simulation this value is directed to the channels. In the very first step the voltage is presumed to be known. The third level in Simulink contains the block for the different ionic channels (see figure 1). In this level the linking of Stateflow and Simulink is arranged; the Stateflow blocks are inserted in the Simulink model.

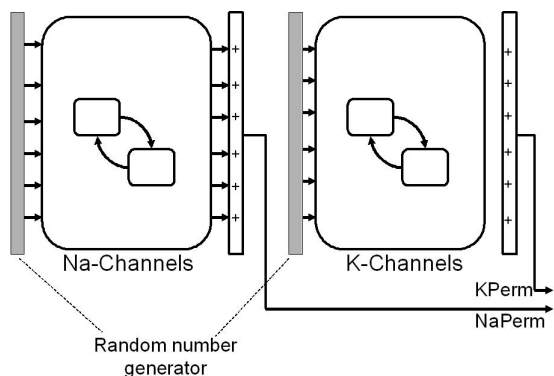


Figure 4: Level 3 – model of the block "Channels"

Figure 4 shows the model at level three. There are two kinds of exemplary channels in the model, the Na^+ - and K^+ -channels. The permeability of the channels modelled in the blocks is an outgoing parameter and is summed up for the permeability of the ion. The grey blocks are random number generators. They deliver a random number for every single channel to make it possible to model the random behavior of the channel. This means that the behavior of a channel is controlled by chance, just like in the biological reality. The channels show a flickering behavior [Alb02].

On the basis of the sodium channels the levels four and five are now exemplified. The other ionic channels have been modelled analogically, adapted to their specific behavior.

Figure 5 shows some modelled sodium channels in a Stateflow model. The channels are framed with a dotted line, which means that they execute in parallel. In a single channel the states are framed with a solid line. These states are mutually exclusive, i.e. the channel is exactly in one

state at a certain time. A channel can either be "open", "closed" or "inacitve" (further information in [Bec01]). The transitions are conditioned by the behavior of the channel; for example, if the channel in the model is in the state "closed" and the voltage reaches a certain value, it switches to the state "open". The transition in this case is conditioned by the incoming voltage.

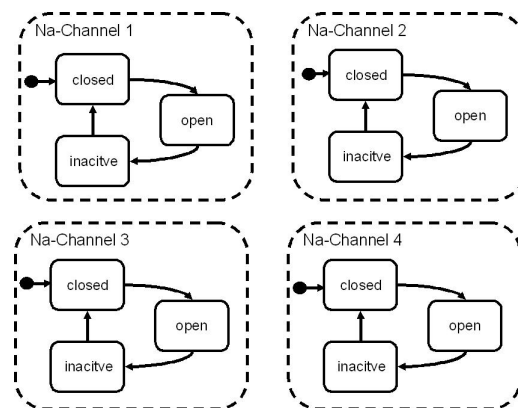


Figure 5: Level 4 – The sodium channels

The permeability of the channel depends on the state in which the model is at that moment (if the channel is "open", then the permeability is high, otherwise low). The states in level four of the model actually do not calculate the permeability of the channel, because the random behavior of the channel has not been considered. Therefore, these states are conceptual, they do not calculate anything.

The calculation of the permeability of the channel takes place in level five and depends on the conceptual state. Here, the random behavior is modelled. Figure 6 shows the "closed"-state of a sodium channel at level five.

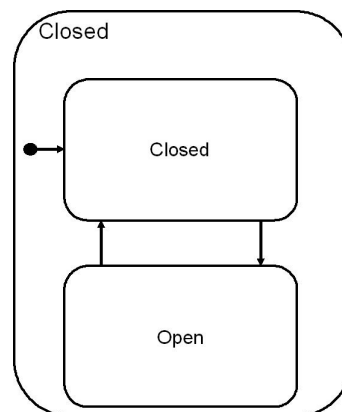


Figure 6: Level 5 – The "closed"-state of a sodium channel

In the states "open" and "close" the calculation of the permeability for the channel takes place. It is made up of the conductance of the channel and an additional factor. This factor is given by the states of the channels. The transitions are conditioned by the probabilities of the channels. In spite of the state "closed", the channel can open for a moment, just like in reality (the flickering behavior).

2.2 The spike propagation

After we have now shown the modelling of a node of Ranvier, we will now look at the transfer of the voltage from one node to another. The following formula (1) calculates the incoming voltage at a node of Ranvier.

$$E_m = E_0 * \exp -\frac{S}{\lambda} \quad (1)$$

E_m is the incoming voltage at the next node. It is calculated from the outgoing voltage of the preceding node (E_0), the distance of the nodes (S) and the membrane length constant λ . For additional information about this formula see [Alb02] and [Pfl].

When using the membrane length constant, the diameter and the myelin sheath of the axon are included in the formula. Thus, all fundamental parameters for the spike propagation are covered: the distance of the nodes, the thickness of the axon and the thickness of the myelin sheath around the axon. These factors determine the transfer of the voltage and they are adjustable in the model.

The formula is modelled as a Simulink block and can easily be included in the model: between two nodes of Ranvier the block "transfer" is inserted. It is possible to simulate an axon with several nodes in this way.

3 The simulation and the usage in a practical course

It was necessary to compare the simulated behavior of the model with the behavior observed in experiments to see how good the model works. Therefore, it should be able to copy biological experiments with the simulation and to compare the results from the simulation with realistic results obtained in experiments.

In order to make it useable in the practical course, we tried to make the simulation of the experimental environment as close to the reality as possible. In [Hit02] several experiments with neurons are characterized.

The voltage applied to the axon (in other words, the stimulus) can be modified in steps of 0.1 mV during the simulation. The level of the stimulus is therefore adjustable. The stimulus is not permanently conducted to the axon, but only for short moments in certain intervals. The duration of the stimulus and the intervals are tunable as well.

With Simulink the simulation is quite easy. Simulink creates the simulation on its own, and the values of the parameters can be observed with so-called monitors placed in proper locations. Particularly interesting for the model are the voltage and the permeability of the ions.

In the practical course at the University of Ulm the students basically make experiments with the distance of the nodes, the thickness of the axon and the thickness of the surrounding myelin sheath. They test how these parameters affect the behavior of the axon. Therefore, these parameters can be adjusted conveniently and individually.

Typically, at the beginning of a session the students in the practical course do some experiments with real dissected axons. Afterwards, they work with the simulation at the computer. Through this combination of biological experiments and the usage of the model the students are able to watch real action potentials on one hand, and on the other hand they have the possibility to adjust those parameters in the simulation that can not be changed in the experiments, for example the axon diameter or the thickness of the myelin sheath.

In the following, we will describe an example of an experiment with the simulation. It is tested how the distance between the nodes of Ranvier affects the spike propagation along the axon. In the model are two nodes; the distance between them is variable. For this experiment the diameter of the axon is $10 \mu\text{m}$ and the thickness of the myelin sheath is $1 \mu\text{m}$.

Figure 7 shows the results of two tests. The voltage curve at both nodes of Ranvier is displayed on the monitor. In test A (figure 7 A) the distance between the nodes is 1 mm, in test B (figure 7 B) 3 mm. The pink curve shows the course of the voltage for the first node, and the yellow curve for the second node during an action potential (see [Hel98] for an action potential on an oscil-

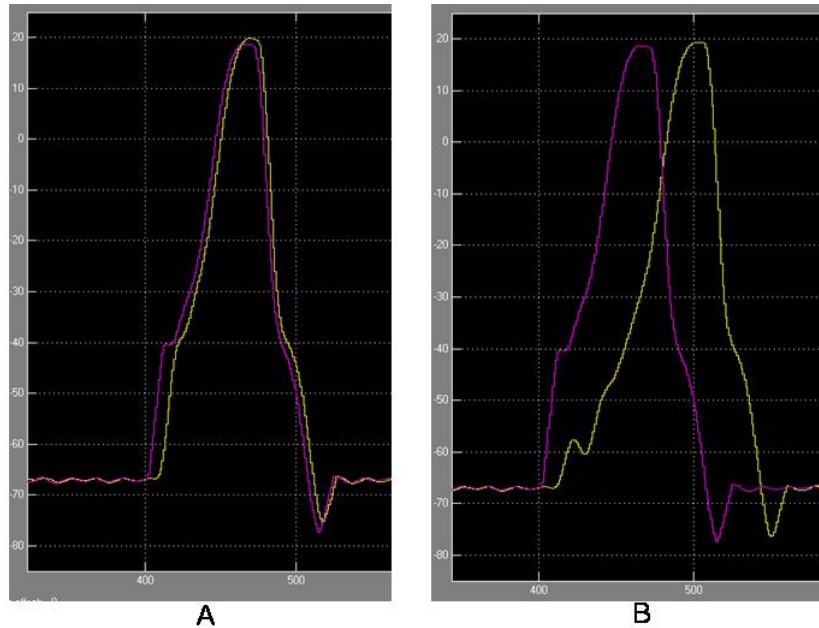


Figure 7: Comparison of the voltage depending on the distance of the nodes of Ranvier

loscope). The curves in A are closely together, whereas in B there is more time (in other words simulation steps) between the curves. The explanation is simple: in test B the incoming voltage is much less than in test A, because the distance is bigger. The more distance there is between the nodes, the less voltage will reach the second node. Therefore, the second node reacts more slowly in test B as in test A, and the elapsed time between the action potentials of the nodes is longer.

By modifying the distance of the nodes the students gather information about how this parameter affects the behavior of the axon. As a result of the multifaceted options of settings in the model a lot of experiments can be duplicated:

- diversification of the axon diameter
- diversification of the thickness of the myelin sheath
- the effect of poison on the axon (for example, blocking the sodium channels)
- determination of the relative and absolute refractory period
- the influence of the probabilities of the channels on the behavior of the axon

We carried out these experiments with the model during the simulation and compared the results

with known biological results. It turned out that the model matched reality in all aspects in a sufficient way [Koh03]. The students have a simple and fast tool to examine the influence of different parameters on the behavior of the axon. It is not possible to change these parameters in biological experiments, so that the use of this model provides further opportunities to analyze the behavior.

There are some difficulties when modelling a biological process: at first, all the basics of the process have to be known. The process of a neural action potential is well known so that data about it is readily available. However, the number of modelled channels presents a problem. Not as many channels as there are in real axons could be modelled due to restricted computing power. The more channels are modelled, the slower the simulation runs. The number of channels that we used in our model however, was still sufficient to achieve good results. We modelled 460 channels per node of Ranvier: 400 Na^+ -, 40 K^+ - and 20 Cl^- channels, which corresponds to the actual ratio of channels in a real node of Ranvier.

The use of hybrid tools with graphic programming has some benefits for the users, too. Non-computer-scientists seem to understand this modelling technique quite easily and fast. The understanding of statecharts is facilitated.

In Stateflow the statecharts can be monitored

during the simulation. The fact that the user can monitor how single components act during an action potential and that the chronological coherence of the components can be seen highly benefits the understanding of the whole process. For the learning and understanding of a complex biological process the traceable results of the simulation are a great advantage.

4 Conclusion

Hybrid tools such as the combination of Simulink and Stateflow are well suited to model and simulate biological processes like a neural action potential. In spite of little difficulties, good results in modelling of biological components and their interaction are attainable.

The use of this modelling technique in education and science offers great advantages for students and research personnel.

The model and its simulation are used successfully in a practical course at the University of Ulm.

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