Simulation of neuronal activity

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Abstract
Our aim is to design a model which demonstrates inhibitory and excitatory effects as observed in a neuronal network cultivated on a multielectrode array (MEA) neurochip.

1 Background

1.1 Experimental background
A mouse has four millions of cortical neurons [1]. In an in-vitro experiment approximately 10,000 neurons of the frontal cortex of embryonic mice [2] are cultivated on a MEA neurochip (figure 1). A matrix of 64 microelectrodes is fixed on a glass plate. Each electrode can be subdivided in maximum four units each of which represents a neuron. The electrodes are isolated from each other and connected to an amplifier where the signals from the neurons are digitised [3,4]. Spike trains (figure 6) which are sequences of action potentials are recorded.

Biochemical substances are added to the neuronal network on the MEA neurochip [5]. The neurons can react with e.g. a decrease or increase of their activity. Based on the recorded data, various features [6] are calculated adapted from spikes, single action potentials, and bursts, a cascade of spikes. The features are separately displayed in concentration-response curves (figure 2) [7] which show on the x-axis the logarithm of the substance concentration and on the y-axis the chosen feature. Currently, over 200 features can be calculated.

Multielectrode arrays are used to examine toxicity and risks of biochemical substances. These substances have to be tested on response and side effects with animal experiments for a long time period. Costs and the number of animals can be reduced when using MEA neurochips.

1.2 Modelling aims
Neuronal models exhibit a simplified image of the reality in different detailedness. We have developed a phenomenological model where the neurons are described as black boxes. The aim was to vary the parameters of the model in such a way that we obtain a sigmoid (S-shaped function) concentration-response curve to simulate...
excitatory and inhibitory effects in neuronal networks.

2 Methods

2.1 Real native spike trains
For the aimed model an exponential distribution of the inter-spike intervals (distance between two spikes) of real native (without added substance) spike trains is required. Inter-spike interval histograms are plotted for 36 units with a bin size of 10 msec and a maximal value of mean(isi)+2*std(isi). A $\chi^2$-test is used to test whether the inter-spike intervals are exponentially distributed.

2.2 INEX (inhibitory-excitatory) model
The developed model is a cellular automaton whose cells are neurons with two possible states: ON or OFF. Each neuron obtains several inputs and produces exactly one output (0 or 1). Neurons are connected by either inhibitory or excitatory synapses with varying strength. The network is fully connected and has no direct feedbacks (figure 3).

Figure 3: Left: Weighting matrix. Right: Example of a modelled neuronal network.

The probability $P$ if a spike occurs in time slice $\Delta t$ or not is calculated by [8]:

$$P[n \text{ spikes within } \Delta t] = e^{-\lambda \Delta t} \left( \frac{\lambda \Delta t}{n!} \right)^n,$$

where $\lambda$ donates the firing rate (frequency of spikes). We can assume $n=1$ because $\Delta t$ is sufficiently small. In order to model spontaneous activity without external input which is observed in MEA experiments the probability is calculated using a Poisson process. For each time slice the algorithm tests if $x \leq P$ where $x$ are uniformly distributed random values. We also added a spike time history so that $x$ decreases when a spike in the last time slice occurred.

A network with ten neurons ran over 10 seconds with varying weights and $\Delta t = 1 \text{ msec}$. Nine inhibitory synapses with weights between -0.2 and 0 and one excitatory synapse with a weight between 0 and 0.7 are used. The bursts are defined as follows: maximal distance of two spikes between 40 and 200 ms, minimum 1 msec duration and minimal two spikes in a burst.

2.3 Validation: Comparison to real native spike trains
The examined real native spike trains are results of experiments with MEA neurochips where tissue of the frontal cortex extracted from embryonic mice. The burst definition is the same as described above. The analysis of 201 units (= neurons) in eleven experiments exhibits a mean spike rate of 104.86 spikes/min and a mean burst rate of 14.06 bursts/min. These values are compared to the two features obtained by the model.

3 Results and Discussion

3.1 Real native spike trains
Using a 5%- $\chi^2$-test all 36 examined native spike trains exhibit exponentially distributed inter-spike intervals (figure 4).

Figure 4: Example of an exponentially distributed inter-spike interval histogram.
3.2 INEX model
We detected spikes and bursts (figure 5 and table 1) as known from experiments with MEA neurochips (figure 6). Our hypothesis is that without inhibitory synapses characteristic burst patterns do not occur.

Figure 5: Modelled spike trains of 10 neurons.

Table 1: Spike rate and burst rate of the first three neurons.

<table>
<thead>
<tr>
<th>Neuron</th>
<th>Spikes per minute</th>
<th>Bursts per minute</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.137</td>
<td>0.275</td>
</tr>
<tr>
<td>2</td>
<td>0.0193</td>
<td>0.0228</td>
</tr>
<tr>
<td>3</td>
<td>0.0193</td>
<td>0.264</td>
</tr>
</tbody>
</table>

3.3 Validation: Comparison to real native spike trains
For visual validation spike trains of native neurons are displayed (figure 6). Note that the time scale of figures 5 and 6 are different. Both spike rate and burst rate have to be reduced.

Figure 6: Real native spike trains derived from the frontal cortex.

4 Conclusions and Further Research
The INEX model shows potential to simulate inhibitory and excitatory effects which are also observed in experiments with MEA neurochips. The next steps will be adapting the parameters to achieve spike rates and burst rates of real native spike trains. In this context a network with 1000 or more neurons will be a challenge. We will work on parallelisation of processes to decrease the run time of the algorithm. We will reduce the excitatory weights to obtain a decreasing sigmoid concentration-response curve (cf. figure 2) [9]. Furthermore we will examine global bursts [10], mutual bursting of several neurons, in more detailedness.

5 References


About the Author

Kerstin Lenk is currently working on her doctoral dissertation in computational neuroscience. She graduated from Hochschule Lausitz (FH) as Diplom-Informatikerin in 2009 with focus on medical informatics.