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Information processes in neurons

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Information processes in neurons

Contents

Abstract **4**

Abstrakt **5**

1 Introduction **6**
1.1 Level of description 6
1.2 Aims of the thesis 8

2 Theory and methods **8**
2.1 Integrate and Fire neuronal model 8
2.1.1 Types of Integrate and fire model 8
2.1.2 The parameters of LIF 10
2.2 Neural code 11
2.2.1 Types of neural code 11
2.2.2 Spatial hearing 13
2.2.3 Neural code for spatial hearing of mammals 14
2.2.4 Low frequency ITD cues and modeling 15

3 Summary of main results **15**

4 Conclusions **18**

References **19**

List of publications **25**

Abstract

Neurons communicate by action potentials. This process can be described by very detailed biochemical models of neuronal membrane and its channels, or by simpler phenomenological models of membrane potential (integrate-and-fire models) or even by very abstract models when only time of spikes are considered.

We took one particular description — stochastic leaky integrate-and-fire model — and compared it with recorded *in-vivo* intracellular activity of the neuron. We estimated parameters of this model, compared how the model simulation corresponds with a real neuron. It can be concluded that the data are generally consistent with the model.

At a more abstract level of description, the spike trains are analyzed without considering exact membrane voltage and one asks how the external stimulus is encoded in the spike train emitted by neurons. There are many neuronal codes described in literature and we focused on the open problem of neural code responsible for spatial hearing in mammals. Several theories explaining the experimental findings have been proposed and we suggest a specific variant of so called slope-encoding model. Neuronal circuit mimicking auditory pathway up to the first binaural neuron was constructed and experimental results were reproduced. Finally, we estimated the minimal number of such parallel circuits needed to reproduce results obtained in psychoacoustic experiments and it is sufficient for estimated number of fibers entering the centers for spatial hearing.

Keywords: binaural hearing in mammals, integrate-and-fire model, neural coding

Abstrakt

Neurony spolu komunikují pomocí posloupností akčních potenciálů. Celý tento proces může být popsán detailními biochemickými modely membrány a iontových kanálů na neuronu nebo jednoduššími fenomenologickými modely (typickým představitelem jsou tzv. “integrate-and-fire” modely) nebo případně ještě více abstraktními modely sledu akčních potenciálů bez přihlédnutí k dynamice membrány neuronu.

Vybrali jsme konkrétní variantu stochastického “leaky integrate-and-fire” modelu a porovnali jí s aktivitou biologického neuronu (nitrobuněčný záznam pořízený *in-vivo*). Provedli jsme statistický odhad parametrů modelu a na základě počítačových simulací úspěšně srovnali modelovaný záznam se záznamem z reálného neuronu.

Při abstraktnější úrovni popisu je sled akčních potenciálů analyzován pouze jako množina bodových událostí v čase a základní otázka zní, jakým způsobem je vnější podnět kódován v zaznamenané posloupnosti akčních potenciálů. Bylo navrženo mnoho odlišných kódů pro řešení rozmanitých úloh v neuronových sítích. My jsme se zaměřili na otevřený problém neuronálního kódu v úloze prostorového slyšení u savců. V současnosti je zvažováno několik teorií vysvětlujících experimentální nálezy. V naší práci navrhujeme specifickou variantu modelu založeného na frekvenčním kódu. Zkonstruovaný neuronový obvod, který simuluje zvukovou dráhu až do úrovně prvního binaurálního neuronu, umožňuje reprodukovat experimentální výsledky. Dále jsme odhadli počet takto paralelně zapojených obvodů potřebných pro reprodukci výsledků známých z psychoakustických experimentů. Získaná hodnota je dostatečná pro odhadovaný počet nervových vláken vstupujících do center prostorového slyšení.

Klíčová slova: prostorové slyšení savců, model “integrate-and-fire”, neuronální kód

1 Introduction

Starting with the work of Santiago Ramón y Cajal, neuronal cells in the brain were recognized as independent units which communicate via the contact of axons to dendrites and the body of nerve cells, and create neuronal circuits through branching of their fibers (Ramon y Cajal, 1899), English translation Ramon y Cajal (1995).

Simultaneously to Cajal's morphological findings, a larger group of scientists discovered the existence of action potentials (impulses, spikes) traveling through nerve fibers. Since these impulses are similar in duration and shape, this naturally lead to the binary all-or-none concept. As part of what would be later called the *neuronal doctrine,* Cajal proposed unidirectional transmission of nerve impulses from dendrites through soma to axon and called it the law of dynamic polarization.

In the same way as Cajal postulated the neuron as a basic anatomical unit, McCulloch and Pitts postulated the neuron as a basic unit of information processing and used the all-or-none concept for modeling nervous activity on the basis of logical calculus. In their seminal work a formal model of the neuron was formulated and it was even indicated that a network of such formal neurons is Turing-complete (McCulloch and Pitts, 1943).

With experimental research developing, such level of formal description of information processing in a neuron was no more adequate. No later than in 1959 it was observed that many electrical events on the membrane are of a continuous nature and that there exists some background spontaneous activity (Bullock, 1959). The following decades added new findings, which were either beyond neuronal doctrine or even contradicting it and the whole picture became more complicated (Bullock et al., 2005). Similarly the question *where* and on *which scale* (or level of description) information processing takes place became problematic. For example glia cells were found to communicate with each other via transmitters and gap junctions (Fields and Stevens-Graham, 2002), chemical synapses between glia cells and neurons were found as well (Bergles et al., 2000). Thus, it is possible that there is parallel information processing going on at slower time scales.

1.1 Level of description

Another ambiguity stems from the choice of the proper level of description. We can distinguish the level of large neural networks, simple circuits, individual neurons, the sub-cellular level, membranes and the underlying biochemistry. Traditionally the community around artificial neuronal networks does not use a detailed description of neurons and is satisfied with abstract models not much different from the original McCulloch-Pitts neuron. This abstraction would be hardly acceptable for the community studying the features of single neurons and their membrane for its drastic simplification since it would be impossible to mimic many of the effects observed in physiological experiments. However, it does not automatically follow that a more detailed description opens up a better understanding of the system as a whole.

One such example is Hopfield's work on the neural network for content-addressable memory (Hopfield, 1982). According to the critics of this paper, the neurons should have continuous input-output relations, moreover real neurons and circuits have integration time delays due to the capacitance of the neuronal membrane. Therefore, the time evolution of the state of such systems should be represented by a continuous time representation. In his response Hopfield showed that the important properties of the original model remain intact when these two simplifications of the model are eliminated (Hopfield, 1984).

On the other hand, a more detailed model can completely change the way how information processing is implemented. For example in order to compute a certain formula from logical calculus, the classical McCulloch-Pitts approach needs to assemble a circuit from neurons in a similar fashion as when logical gates are assembled in modern digital computers. However, when we stop to look at a neuron as a simple one-point integrator of incoming signal and make a detailed model of a branching dendritic tree, we get a very different picture of possible computations within a single neuron only. Decomposing the dendritic tree of the neuron into subunits (Koch et al., 1982) shows that the combination of a specific branching topology, and the precise timing of excitatory and inhibitory inputs implements the approximation of logical gates (AND NOT, OR, AND) and even multiplicative arithmetical operations. Since all logical operations can be defined via AND and AND NOT gates, any logical operation can be synthesized by local circuits consisting of synapses between the dendrites of two or more neurons (Koch et al., 1983).

The discussion about the level of detail and precision in the modeling of information flow inside the nervous system does not necessarily end at the level of membrane biophysics. In a series of papers Hjelmfelt showed that even enzymatic reactions inside cells can be interpreted as information processing and he also showed that it is possible to construct a universal Turing machine based on such reactions (Hjelmfelt et al., 1991; Hjelmfelt and Ross, 1992, 1993).

While the advantages of a more detailed description are clear, there is also a price to be paid. Firstly, more details of the model usually require more parameters and it is often hard or even impossible to obtain such parameters from experimental setup. Secondly, a more detailed description might be intractable from a mathematical point of view, and no deeper insight about the dynamics of the system can be obtained. Thirdly, when we are interested in dynamics of large scale networks, the simulation of detailed models can be very demanding on the computational power. To sum up, there is no "proper" level of description unless we take into account the aim and context of the study.

1.2 Aims of the thesis

We will focus on stochastic descriptions of the neuronal activity. First, we will have a look at the class of simplified models of the neuronal membrane. Then we will inquire into possible encoding schemes of the action potential sequences ("*spike-trains*") generated by the neurons (or by their models respectively). Finally we will concentrate on the problem of spatial hearing and the different neuronal coding mechanisms used to explain animal sensitivity of sound localization. The aim is to estimate parameters of the chosen models and understand how they influence the neural coding dynamics of information processed in neurons or small neuronal networks.

2 Theory and methods

2.1 Integrate and Fire neuronal model

2.1.1 Types of Integrate and fire model

Three basic types of models of a single neuron can be distinguished - digital (all-or-none) and continuous, which can be subsequently modeled either as a single point in a space or with more unit compartments simulating morphology of the real neuron and its branching structure (Segev, 1992). We shall focus on the single-point continuous models only.

Generally, the family of continuous models is described by an electrical circuit representing the iso-potential patch of a membrane. The simplified model of a neuron membrane as an electrical circuit consisting of capacitor with leak was first proposed by Lapicque (1907), translation and review Lapicque (2007); Brunel and van Rossum (2007). It was, however, before the mechanisms of the action potential firing were understood and the first formulations of the whole *leaky-integrate-and-fire* (**LIF**) model appeared later (Stein, 1965; Knight, 1972).

The most simple version of the model circuit consists of capacitor C only (representing lipid layers of the membrane) and is called *perfect integrator* (Koch, 2005). Membrane voltage $V(t)$ can be written in this case as

$$C\frac{dV(t)}{dt} = I(t)\,, \tag{1}$$

where $I(t)$ represents the current from synaptic input at time t (or intracellular electrode). The spiking mechanism is missing in this model and it is usually described just as a complete reset after certain voltage threshold S is reached; switch through which the accumulated voltage is discharged would implement such behaviour inside electrical circuit.

If the neuronal membrane consists only of a twofold lipid layer, the voltage would increase no matter how slowly the incoming current arrives since the membrane functions as a perfect insulator. In biological reality the membrane contains also proteins which form specific channels through which various ions can flow and leak the charge. In such case the voltage on the membrane does not integrate as above and additional resistor R implementing this leakage is added in parallel to capacitor in the electric circuit thus forming *leaky-integrate-and-fire* (or *forgetful*) model. The current through the resistor follows Ohm's law and the equation (1) can be rewritten as

$$C\frac{dV(t)}{dt} + \frac{V(t)}{R} = I(t)\,. \tag{2}$$

Again, the voltage is integrated in subthreshold regimen (see section 2.1.2) and once threshold S is reached, voltage is reset to its initial value and integration starts anew.

Specific integrate-and-fire (**IF**) models which employ spike generation as integral and emergent part of the model have been proposed, for example by Fitzhugh (1961) who suggested simplification of the Hodgkin-Huxley model (see below) and Nagumo et al. (1962) who formulated a corresponding electronic circuit. The system is described by two coupled differential equations and its advantage compared to the Hodgkin-Huxley model is that the mathematical properties can be understood quantitatively.

Because of the random nature of incoming synaptic signal, a stochastic version of integrate-and-fire model has been developed. Initial work was done by Gerstein and Mandelbrot (1964) who used random walk to mimic excitatory and inhibitory input pulses. The random walk counterpart of the leaky model has been formulated by Stein (1965, 1967). Subsequently, a continuous model can be obtained as a limit case thus obtaining *Ornstein-Uhlenbeck* model (Uhlenbeck and Ornstein, 1930; Ricciardi and Sacerdote, 1979), which can be written as the equation

$$C\frac{dV(t)}{dt} + \frac{V(t)}{R} - C\sigma\xi(t) = I(t)\,, \tag{3}$$

where ξ represents white noise from the synaptic input and σ its variability.

A plethora of integrate-and-fire model variants can be found in a recent review of Burkitt (2006a,b).

2.1.2 The parameters of LIF

Because IF models have been widely employed in neuronal modeling, there is always question whether these models are sophisticated enough to mimic the behaviour of biological neurons (Feng, 2001). Despite of wide usage of IF models in the theoretical literature there has never been an attempt to check IF models accuracy and assumption against intracellular recordings of the membrane voltage (the traditional attempts were more focused on the interspike intervals (**ISI**) statistics obtained from extracellular recordings). In a couple of papers we compared *in-vivo* intracellular neuronal recordings and stochastic variant of LIF model (3)

$$\frac{dV(t)}{dt} = -\beta(V(t) - x_0) + \mu + \sigma\xi(t),\, V(0) = x_0 \tag{4}$$

with few modifications, namely we assume that input μ is constant in time and the process starts at the resting level x_0. The (constant) parameters C, R form the so-called membrane time constant $\tau = RC$, which we use here inversely as $\beta = \frac{1}{RC}$ to conform with notation used later in our work and let the reader directly delve into it. As in other LIF models spike is not intrinsic part of description and membrane potential is reset to x_0 whenever $V(t)$ reaches the threshold S.

Parameters of such model are traditionally divided into those, which depend on membrane properties (β – inverse of the membrane time constant, S – threshold, x_0 – resting level) and those, which depend on the input signal (μ – mean signal, σ – signal variability).

The asymptotic mean depolarization derived from (4) as $E(V(\infty)) = x_0 + \mu/\beta$ determines three regimes of neuronal firing — the subthreshold regimen ($\mu/\beta \ll S - x_0$), the threshold regimen ($\mu/\beta \approx S - x_0$), and the suprathreshold regimen ($\mu/\beta \gg S - x_0$). The firing regime determines the form of the eventual spike train and thus distribution of ISIs.

The currently dominating opinion is that for neural coding the evolution details of the membrane potential are not important. What matters is just the time when the potential reaches the threshold for firing and the question is whether such simplified models can reliably predict occurrence of spiking times. The ability to predict spiking behaviour has been shown for particular types of neurons in this class of models (Kistler et al., 1997; Keat et al., 2001; Jolivet et al., 2006; Kobayashi et al., 2009).

2.2 Neural code

2.2.1 Types of neural code

Let us now abstract from the underlying spiking mechanisms and focus only on the resulting sequence of spikes. Such spike train is often considered as a code through which information is conveyed across the neural system. Beginning with the pioneering work of Lord Adrian who showed the relation between the frequency of spikes of frog muscle receptors and the stretching the muscle with different weights (Adrian and Zotterman, 1926), the idea of firing *rate code* became the textbook model of neural coding.

This idea suggests that there is continuous function $f(t)$ according to which resulting spike train is produced, more precisely $p = \int_{t_0}^{t_0+\Delta t} f(t)dt$ determines the number of spikes expected to occur in the interval $[t, t + t_0]$. In case Δt is sufficiently small so that $p \leq 1$ we can interpret p as a probability that the spike occurs in $[t, t+t_0]$. Of course such rate function is not directly visible and we experimentally observe only realization of spikes sampled from f. The conventional way of estimating such background rate function is recording multiple trials with identical stimuli and average the rate over all recorded trials into post-stimulus time histogram. Another approach which has the advantage of creating smooth function even for single recorded trial is kernel smoothing (Nawrot et al., 1999). In this method the spike train is convolved with kernel of a particular shape and width. Common problem of both post-stimulus time histogram and kernel based method is ad-hoc choice of the histogram bin-size/kernel width which results in different firing rate estimates. In series of papers Shimazaki and Shinomoto (2007, 2010) suggested method for determining optimal width, based on the assumption that the underlying spike generation process is Poissonian. We employed the kernel optimization method for the analysis of experimental recordings of olfactory neurons and found it computationally demanding. In order to speed up the width determination we analyzed the algorithm and transformed it into the parallel one which allowed online interactive work with the data. The details are covered in Šanda (2010).

The relationship between the mean firing rate and the conveyed information has been found in various systems. For some time it was assumed that such code captures all relevant information because the firing-rate coding scheme was robust against unreliability and noise observed in neuronal activity. Later decades brought experimental findings which showed that what was often considered as erratic behaviour was rather misunderstanding of the code transmitted and neurons can be thought as a reliable unit of transmission (Barlow, 1972).

In an influential workshop report by Perkel and Bullock (1968) it was concluded that one should not expect universal coding principle independent of the context and an extensive list of possible neuronal codes was given. Experimental evidence of codes which depend on precise timing of individual spikes started to appear at that time (Segundo et al., 1963; Chung et al., 1970). Moreover, it was shown that spiking mechanism can be very reliable (Bryant and Segundo, 1976; Mainen and Sejnowski, 1995). Subsequently the term *temporal coding* was coined for the situation when precise timing of spikes matters, however, a precise definition is missing and the term may be used to refer to different concepts.

One important concept is that of synchronous firing across neurons at the same time leading to the coherent firing of spatially distributed neurons (Bialek et al., 1991). Although a vast body of work focuses on the visual system, this type of coding has been found both in auditory (deCharms and Merzenich, 1996) and in olfactory systems (Wehr and Laurent, 1996; Laurent et al., 1996). Compared to rate coding where fundamental operation would be the temporal integration, basic operation for this type of code would be coincidence detection for spikes coming from different inputs. Such summation based on the activity of synchronized inputs would be more effective than code based on the firing rate (Singer and Gray, 1995).

Another type of coding given by topographic position of a neuron is not characterized by the type of neural firing activity but by the spatial position of the active neuron in the brain tissue alone. An example of such "code" is the mapping human anatomy in motor cortex (Penfield and Boldrey, 1937) or representation of sound source spatial azimuth in nucleus laminaris in birds (Carr and Konishi, 1988).

From the point of view of the whole network more codes can be used simultaneously and even single spike train can encode multiple features, for example Keat et al. (2001) shows how three different features – *what*, *when*, *how much*, are assembled into waveform shape, precise latency and firing rate of action potentials. Another example is our proposal of a neural circuit computing sound azimuth in mammals (Sanda and Marsalek, 2012) which uses a combination of topographic code (auditory nerve fibers are sensitive to narrow range of frequencies), time coding (coincidence detection of appropriate spikes from ipsi- and contra-later fibers) and rate code (capturing the final azimuth), details are depicted in section 2.2.4.

After introducing basic types of neural code we will focus on a particular topic of binaural hearing, where most types of the aforementioned codes occur in parallel.

2.2.2 Spatial hearing

In order to determine the direction of a sound source the neural circuit needs to compute azimuth and elevation of the sound source given then input signal. The important auditory cues are interaural time differences (**ITD**[1]), interaural intensity differences (**IID**) and spectral content of the signal. We will focus on the computational processing of auditory cues occurring in initial parts of auditory pathway.

Historically two mechanisms of localization in the horizontal plane were proposed by Békésy (von Békésy, 1930; van Bergeijk, 1962) and Jeffress (1948). Von Békésy model assumes neurons in unspecified brain nucleus on which fibers from left and right ear converge. The first arriving signal from

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[1] Sound arrives at different times on the left and right ear. This difference defines ITD and is dependent on the sound source position and the head size.

left/right (L/R) defines tuning of the neuron (*channel)* to be L or R respectively. L/R signals traveling through the nucleus tune the whole population of the neurons and higher centers integrate the number of L/R-tuned neurons. In parallel more intensive stimuli from one side is able to excite larger population of neurons tuned to that side. The final azimuth is determined by the ratio of L/R tuned neurons.

Later and more widespread concept of delay lines (Jeffress, 1948) assumes array of neurons each acting as a coincidence detector for the signal from left and right side. The axonal fibers have systematically different lengths so that additional time needed for the action potential to traverse fiber from one side exactly compensates ITD. Thus each neuron is tuned to narrow sector of the azimuthal space and the array of such neurons create a whole topographical map of the azimuthal space.

The research on barn owls (Carr and Konishi, 1990) convincingly showed that Jeffress delay lines are employed in birds and although it is known that binaural hearing evolved independently in different species (birds, reptiles and mammals in particular) the Jeffress model became textbook model for binaural hearing. Last decade, however, brought controversy over the mechanism of binaural hearing in mammals.

2.2.3 Neural code for spatial hearing of mammals

Experimenting and theorizing about the mechanism of (human) spatial hearing dates back to the psychoacoustic works of Thompson (1882) and Rayleigh (1907) who formalized the duplex theory. In this theory low frequency sounds are localized by ITD while high frequency sounds by IID. In general contours this distinction holds even nowadays, anatomical and physiological findings confirmed this distinction on physiological and anatomical level (Yin, 2002; Tollin, 2003). Additionally, research showed that spectral cue is actively used for sound source elevation (Davis et al., 2003). There seems to be agreement on the general mechanism of IID processing (roughly speaking subtraction of excitatory signal from ipsilateral side and inhibitory signal from contralateral side (Covey et al., 1991)). The mechanisms of ITD processing particularly in low frequencies is a matter of discussions and poses open problem.

2.2.4 Low frequency ITD cues and modeling

While the anatomical evidence for delay lines in birds is solid, there is a weak anatomical evidence for delay lines in mammals. Moreover there are contradictions in physiological recordings on small mammals, which show rather broadly tuned neurons (channels) and bring back the attention to the Békésy concept (McAlpine et al., 2001; McAlpine and Grothe, 2003).

In series of experiments the key role of synaptic inhibition on the first binaural neuron in MSO was elucidated (Brand et al., 2002; Grothe, 2003; Pecka et al., 2008). The key finding is that synaptic inhibition on the critical neuron shifts maximum of the broad ITD curve out of physiological range relevant for the animal. It was suggested that azimuth is in this case encoded in the slope part within physiological range of the ITD curve by the firing rate of binaural neuron. Marsalek and Lansky (2005) took this concept and proposed stochastic model for the spike interaction in this first binaural neuron. We expanded this model by employing small circuit representing auditory pathway up this neuron, results can be found in the next section.

3 Summary of main results

In the first part of our work we concentrated on the description of neuronal membrane potential by the LIF model (3). Initially, in Lansky et al. (2006), we obtained parameters and compared different estimation methods for the spontaneous part of the experimental recordings and checked basic assumptions of the model. We found, that in general the data are consistent with the model. The spontaneous part is in subthreshold noise-driven regimen and ISIs are exponentially distributed, which suggests they are generated in accordance with Poisson process. There were, however, also inconsistencies with the model. The model assumes that spectra of the input signal should be flat, while we found characteristic hump around the frequency of 2200 Hz in data, which was subsequently eliminated by filtering. Next, the subthreshold regime requires the asymptotic depolarization far below the threshold. In our case the asymptotic threshold is below the threshold, but it is less than two-standard-deviations envelope. The model also assumes a fixed value of the reset depolarization x_0, which did not hold, the effect of this discrepancy for the model performance is negligible, however.

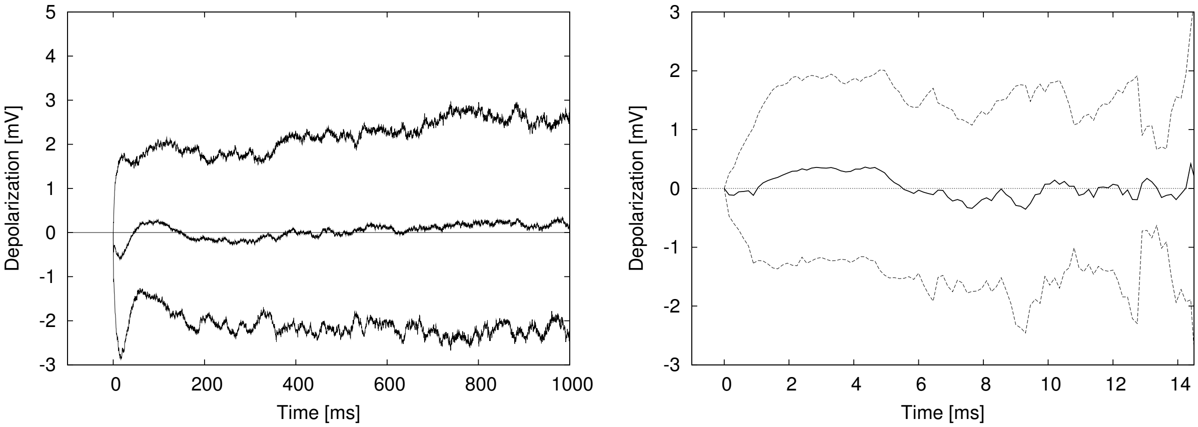

Figure 1: The accuracy of the model simulation compared with the recorded data. The simulation of the model (4) used parameters estimated from the data. The middle line shows the mean difference of the membrane potential between simulations and experimental recordings, while the surrounding lines are 2 standard-deviations envelope. In ideal case we would obtain flat line at 0. Left panel is comparison of the spontaneous part of the record, right panel shows comparison of (acoustically) stimulated part of the record. Different time axis is due to the fact that stimulation brings the neuron to the suprathreshold regime where interspike intervals are much shorter.

In the second analysis (Lansky et al., 2010), we compared activity and estimated parameters for spontaneous and stimulated part of the recordings and discussed their firing regimes. The simulation based on the estimated parameters fits well with the course of the membrane depolarization (see Fig. 1). The parameters dependent on the input signal μ and σ were larger than in spontaneous part and the overall firing regimen is suprathreshold as expected. Despite the assumptions that x_0 is not dependent on input signal our data shows that its value is actually influenced by the stimulation.

To summarize, external stimulation affects input parameters and thus time evolution of membrane voltage in model (4) and it has direct consequence on the ISI statistics, since the stimulated intervals will be generally much shorter.

In the second part of our work we picked-up the stochastic description from of the first binaural neuron in the auditory pathway (Marsalek and Lansky, 2005), which participates on the ITD detection in the task of spatial hearing. First, in Sanda and Marsalek (2012), we built circuit representing the whole auditory pathway up to the first binaural neuron, endowed it with small number of parameters and then explored the parameter space in order to understand the circuit dynamics. Second, we compared the performance of such neuron with known results in psychophysics by employing the concept of ideal observer located at the final stages of the circuit — such observer measures time consumed by the circuit until reliable azimuth estimate is reached.

There are currently two areas of spatial hearing research which usually do not coincide much. Either electro-physiological recording of critical (MSO) neurons on small rodents which provides knowledge about the shape of ITD tuning curves and let us theorize about the neural code used. Or psychophysical experiments on human subjects, which provide us information about spatial accuracy and measurements about minimal time needed for solid azimuth estimate. Providing electro-physiological recording from human subjects or psychological estimates of sound location from small rodents is difficult task from obvious reasons. Our model connects these two separated fields of research.

The first part of the model we proposed can be seen as formalization of available anatomical and physiological data, while the second "observer" part directly connects its result with psychophysics.

As a short summary the model is able to reproduce the shape and position of ITD tuning curves known from experiments as well as inhibition related results causing tuning curve shift. We identified the main parameter responsible for this shift as coincidence window width. Next, we found that certain amount of jitter actually improves efficiency of the circuit and explored more thoroughly impact of jitter on time efficiency of the circuit in Šanda (2011). Thanks to the observer module and data from psychophysics we estimated value of minimal number of parallel circuits needed to reproduce psychoacoustic experiments.

The actual number of parallel fibers and their convergence on critical neurons is not exactly known and technical difficulties of physiological recordings in MSO neurons do not provide sufficient experimental data to decide the underlying mechanism even after decades of research. Mathematical modeling can thus elucidate restrictions of suggested mechanisms which can be checked by additional experiments.

4 Conclusions

It is widely believed that information processing in and between neurons is mediated by action potentials (spikes) traveling along the neuronal membrane. This process can be described at different levels — starting from detailed biochemical models of membrane, continuing to its phenomenological models (integrate-and-fire models being the typical example) and ending with very abstract models, in which only spike times are considered.

One particular description was chosen — stochastic LIF model — and compared with *in-vivo* intracellular activity of neuron (such analysis has not been done before, only either extracellular or *in-vitro* data are usually available). We estimated parameters of the LIF model and tested in numerical simulations (based on the estimated parameters) how model predictions correspond to the real neuron. Additionally we characterized the difference between spontaneous and acoustically stimulated behavior of the neuron. To conclude, it was found that the data are consistent with the model.

As expected, we found that stimulation brings neuron into suprathreshold regimen which causes the average interspike interval to be shorter than it is in the spontaneous neuronal firing. This observation brings us directly to the more abstract level of description, where we analyze spike trains without considering exact membrane voltage between the spikes. In other words, we ask how the external stimulus is *encoded* in the spike train emitted by neurons.

There are many such neuronal codes described in the literature and we focused on the open problem of neural mechanisms responsible for spatial hearing in mammals. Several theories explaining the experimental findings were proposed and we modeled a specific variant of so called slope-encoding model. Stochastic neuronal circuit mimicking auditory pathway up to the first binaural neuron was constructed. Considering this circuit we were able to reproduce results found in experiments and identify parameters responsible for various observed effects. We also estimate minimal number of parallel circuits needed to reproduce results obtained psychoacoustic experiments on binaural hearing.

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List of publications

Reviewed journals with impact factor

1. Lansky, P. and Sanda, P. and He, J., The parameters of the stochastic leaky integrate-and-fire neuronal model, Journal of Computational Neuroscience, 21:211–223, 2006. (Journal IF: 2.325)
2. Lansky P. and Sanda, P. and He J., Effect of stimulation on the input parameters of stochastic leaky integrate-and-fire neuronal model, Journal of Physiology - Paris, 104:160–166, 2010. (Journal IF: 3.030)
3. Sanda P. and Marsalek P., Stochastic interpolation model of the medial superior olive neural circuit, Brain Research, 1434:257–265, 2012. (Journal IF: 2.623)

Reviewed journals without impact factor

4. Šanda P., Speeding up the Algorithm for Finding Optimal Kernel Bandwidth in Spike Train Analysis, European Journal for Biomedical Informatics, 6:73–75, 2010.
5. Šanda P., Jitter Effect on the Performance of the Sound Localization Model of Medial Superior Olive Neural Circuit, European Journal for Biomedical Informatics, 7:51–54, 2011.

Publications out of the thesis scope

6. Lansky, P. and Sanda, P. and Weiss, M., Modeling the influence of nonadherence on antibiotic efficacy: application to ciprofloxacin, The International Journal of Clinical Pharmacology and Therapeutics, 45:438–447, 2007. (Journal IF: 1.189)