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Analytical description of coincidence detection synaptic mechanisms in the auditory pathway

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ABSTRACT

Localization of sound source azimuth within horizontal plane uses interaural time differences (ITDs) between sounds arriving through the left and right ear. In mammals, ITDs are processed primarily in the medial superior olive (MSO) neurons. These are the first binaural neurons in the auditory pathway. The MSO neurons are notable because they possess high time precision in the range of tens of microseconds. Several theories and experimental studies explain how neurons are able to achieve such precision. In most theories, neuronal coincidence detection processes the ITDs and encodes azimuth in ascending neurons of the auditory pathway using modalities that are more tractable than the ITD. These modalities have been described as firing rate codes, place codes (labeled line codes) and similarly. In this theoretical model it is described how the ITD is processed by coincidence detection and converted into spikes by summing the postsynaptic potentials. Particular postsynaptic conductance functions are used in order to obtain an analytical solution in a closed form. Specifically, postsynaptic response functions are derived from the exponential decay of postsynaptic conductances and the MSO neuron is modeled as a simplified version of the Spike Response Model (SRM_0) which uses linear summations of the membrane responses to synaptic inputs. For plausible ratios of time constants, an analytical solution used to describe properties of coincidence detection window is obtained. The parameter space is then explored in the vicinity of the analytical solution. The variation of parameters does not change the solution qualitatively.

1. Introduction

Binaural hearing, the ability to localize sound source with two ears, uses high time measurement precision. In most animals, an action potential has a duration in the order of several milliseconds, yet differences in the arrival of the auditory signal to both ears (interaural time difference, ITD) are detected in time units at least two orders of magnitude lower – in the range of tens of microseconds (Klumpp and Eady, 1956). Early explanations of this phenomenon were proposed in 1930 by von Békésy (1930) and by Jeffress (1948). Jeffress's theory was based on asymmetric delays produced by nerve fibers of different lengths, delay lines, and neurons performing time-limited spatial summation of inputs, that is, detecting coincidences. Axonal delay lines were later found in birds (Carr and Konishi, 1988). For mammals, the lack of anatomical evidence of delay lines and the presence of inhibitory inputs prompted new theories of sound localization based on new experiments by McAlpine et al. (2001), Brand et al. (2002), Grothe (2003), Joris et al. (2006), and by other experimentalists. Nevertheless, it is still generally accepted that the first binaural neuron acts as a coincidence detector. This is a computational unit that responds to simultaneous, spatially separated input signals (Colburn et al., 1990; Batra et al., 1997a; Kempter et al., 1998; Marsalek, 2000). A simple example of this is an electronic combinational circuit AND gate, which gives a positive value as a logical output if and only if both inputs are simultaneously set to a logical positive value. A neuron acts as quite a complex logical unit. It has hundreds of input sites and in order to generate an output signal it requires the presence of simultaneous positive input signals on a defined number of inputs. In contrast to an electronic circuit, where the input voltage for the duration of a signal is approximately the same, in the neuronal coincidence detector, due to the complex process of transferring information between neurons, it is somewhat

Abbreviations: AP, action potential; ECD, ICD, excitatory and inhibitory coincidence detection; ITD, T_{ITD}, interaural time difference; PSP, post-synaptic potential; EPSP, IPSP, excitatory and inhibitory PSP; T_{INH}, IPSP delay; T_{MAX}, PSP maximum time; H, Heaviside step function; LSO, lateral superior olive; MSO, medial superior olive; PDF, probability density function; PSG, post-synaptic conductance; SRM_0, Spike Response Model.

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problematic to use the term "simultaneous inputs." The answer to the question of which temporal and spatial separation of signals can be accepted as a coincidence is more complicated not only because of a potentially higher number of required inputs, which are often of a different size and origin, but also due to different delays and spike timing jitter (standard deviation of spike arrival time).

Coincidence detection has been observed in neurons of several brain regions, notably in the cerebral cortex (Kempter et al., 1998). In the auditory pathway, the coincidence detection function is very specific and consequently neurons are highly specialized here. Coincidence detection studied here is performed in the neurons of the medial superior olive (MSO), a nucleus of the mammalian brainstem. The MSO neurons have fast membrane constants and synaptic conductance decay constants (Scott et al., 2005). They are bipolar, having two dendrites, their direction is in a para-sagittal plane, as they process inputs from the left and right ear. From each side, neurons receive both excitatory inputs, which are connected to dendrites, and inhibitory inputs, which are connected to the neuron body. These inputs are strong. Only a few (two to four) excitatory fibers are sufficient to elicit an action potential (AP) (Couchman et al., 2010). Depending on the azimuth of the sound source, inputs from both sides are mutually delayed by a specific time. In order to preserve the interaural time difference (ITD), both excitatory and inhibitory inputs are synchronized with the onset and phase of the auditory signal and have precise timing (Brand et al., 2002). Inhibitory input usually precedes excitatory input from the same side, despite the fact that the inhibitory pathway has an additional synapse – this synapse is, however, fast and reliable (Grothe, 2003; Couchman et al., 2010; Roberts et al., 2013).

A great deal of effort has been made to explore the mechanisms of coincidence detection in the MSO neurons. However, many recent studies differ with regard to coincidence detection in the MSO neurons and the specific role of synaptic inhibition (Jercog et al., 2010; van der Heijden et al., 2013; Roberts et al., 2013; Myoga et al., 2014; Franken et al., 2015). Several studies have focused on the relationship between input and output spike trains (Marsalek and Kofranek, 2005; Bures, 2012; Franken et al., 2014).

Model neurons are often reduced to a simple mathematical formulation – spikes are represented by point processes and the neurons detect coincidences if and only if spikes are closer in time than a certain constant coincidence window. Let us call these black box models with a coincidence window. As these models do not deal with the biophysical parameters of neurons, they do not question how these parameters affect the duration and position of a coincidence window.

Let us emphasize differences between (1) models with a deterministic central unit, such as the Hodgkin–Huxley models, formal neuron models with fixed thresholds, or black box models with a coincidence window, where the probability of spiking as a function of ITD is a direct consequence of the stochasticity of the inputs (Colburn et al., 1990; Kempter et al., 1998; Marsalek and Santamaria, 1998; Marsalek, 2000; Brand et al., 2002; Zhou et al., 2005), and (2) models where the probability of spiking correlates with the maximal membrane potential achieved by the summation of PSPs (Batra et al., 1997b,a; Leibold, 2010). While in the former models it is only relevant whether the threshold was crossed or not, in the latter models the probability of firing increases with higher values of membrane potential. This means that in the first group one can essentially replace the neuron model with the mathematical construction mentioned above, black box with a coincidence window.

As the complexity of anatomical and electrophysiological research often does not allow for a straightforward confirmation of models, a detailed description of their properties would be useful. The starting point for the present paper is the black box model with a coincidence window used for the probabilistic description of input delays (Marsalek and Kofranek, 2004; Marsalek and Lansky, 2005). A detailed model of the first binaural neuron, based on the interactions of PSPs, is presented. The model enables to directly relate basic neuron properties such as membrane time constant, conductance decay constants, relative AP threshold, and relative synaptic strengths to the duration and position of the coincidence window. Main results are expressed in analytical form and the model of the course of PSPs was also selected with this purpose in mind.

Let us use the experimental paper by Brand et al. (2002) as an example to show difficulties related to the use of complex neuronal models. To support their arguments in describing the mechanism of the azimuth encoding, the authors utilize numerical simulation of the MSO neuron. They use the Hodgkin–Huxley model in particular. In order to determine the extensive set of parameters and constants used in the model, they refer to a detailed model of bushy cells in the ventral cochlear nucleus by Rothman et al. (1993). These cells are known to have high time precision and to project to the nuclei of superior olive.

With the complex models, specifically those using the Hodgkin–Huxley dynamics, a problem of identifying all their numerous parameter values arises. Although these models are frequently used, they contain many unknown or poorly determined parameters. Moreover, these models are neither that stable in the sense of variation of parameters nor are they stable in their numerical solution. Next, the essential property of the Hodgkin–Huxley equations is that the only available solution is the numerical integration of these equations.

In an attempt to overcome the aforementioned limitations of complex numerical models, we asked the following questions. What is a minimal model that captures the salient features needed for the high time precision of the MSO neuron? Is there a simpler modeling approach than using the Hodgkin–Huxley equations or other complex models? Would it be possible to obtain an analytical solution and thus eliminate the need to use a numerical method? These questions motivated the search for simpler model in this work. Another aim of the work presented here was to validate mostly numerical results in Sanda and Marsalek (2012), where both simplified and detailed descriptions of the auditory periphery were used with comparable and reproducible behaviors. Although this numerical model was capable of incorporating the model of auditory periphery by Meddis et al. (1990), this was just another numerical design. The objective here is to use other then numerical methods. In the following sections, particular solutions to these problems are presented.

2. Methods and models

2.1. Probabilistic description of delays

In the probabilistic delay model (Marsalek and Kofranek, 2004), the central computing unit is a coincidence detector with two inputs labeled as side A and side B. The arrival times of presynaptic potentials from side A, or side B are labeled as D_A, or D_B, respectively. The parameters in this model are the size of the coincidence window Δ and probability density function (PDF) F. There are two types of coincidence detections – excitatory coincidence detection (ECD), where both inputs are excitatory, and inhibitory coincidence detection (ICD), where one input is inhibitory and the other is excitatory (Marsalek and Lansky, 2005).

In both cases, the central computing unit is a black box model with a coincidence window Δ. ECD reports coincidence if $|D_A - D_B| \leq \Delta$ and ICD reports coincidence if $0 \leq D_A - D_B \leq \Delta$. This means that for the ECD it is sufficient for both input potentials to be closer in time than Δ. The ICD also requires the potential from

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