Time Precision of Hippocampal CA3 Neurons

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Received September 16, 2005, Accepted November 4, 2005

Key words: Temporal coding – Computer simulation – Synaptic background noise – Synaptic unreliability – Channel noise

This work was supported by the grants GA UK 203212 32/05 and GA ČR 201173 305/05/P198

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Abstract: Time precision of generation of action potentials (AP) is limited by the electrical properties of neuronal membrane, by the probabilistic nature of synaptic transmission and by the membrane noise. In the software environment GENESIS 2.2, we constructed a multicompartmental model of a rat hippocampal neuron, made up of soma, dendritic tree and axonal initial segment (IS). In the model were implemented channel and thermal noise, corrupting the propagation of postsynaptic signal at the soma-dendritic (SD) membrane and the AP initiation at the IS. Various levels of synaptic redundancy, connecting the presynaptic neurons with the SD membrane by various numbers *N* of unreliable synapses of varying probability *P* of vesicle release, were modelled. During simulations, random spatio-temporal patterns of synaptic activity were presented to the neuron repeatedly, eliciting sequences of APs, which were further statistically processed. The influence of *P*, *N*, channel and thermal noise on the time precision of AP generation was tested by repeated stimulation of identical input. The precision was mostly influenced by the synaptic unreliability and substantially dependent upon values *N* and *P*. The channel noise was about an order less corruptive than the synaptic unreliability, causing the time precision of neuronal responses to vary from submilliseconds to tens of microseconds, depending on the values *P* and *N*.

Introduction

The time precision with which neurons fire action potentials (APs), together with the reliability of this process limit the possible spectrum of neuronal codes used by the nervous system (NS). In the NS such codes probably evolved under the selective evolutionary pressure, which optimally bypass "weaker" and exploit "stronger" features of the NS to preserve during processing as much information as possible. Different conceptions about neuronal coding have been proposed, some of them suppose information is encoded by precise occurrences of APs (*temporal codes*) [1], the others state that only average frequency, measured during relevant time window, represents information (*rate codes*) [2]. For *temporal codes* be plausible, neurons should be endowed with mechanisms enabling them to generate APs with sufficient reliability and time precision. To what extent are neurons able to employ *temporal coding* depends partly on the temporal richness of their inputs, on the arrangement of neuronal "hardware" and also on the neuronal noise interfering with the signal. The last feature causes the process of spike encoding is noisy, which results in variable timing of individual action potentials in response to identical inputs [3, 4, 5].

One important source of noise resides in the probabilistic nature of synaptic transmission. Many central synapses, e.g. these in hippocampal CA3 area, possess at average only one release zone, with the probability *P* of release of one synaptic vesicle ranging from 0.1 to 0.9 [6, 7, 8]. This probabilistic nature is potentiated by the variation of vesicle quantal size, by the number of available postsynaptic

receptors and by the unpredictable diffusion of the neurotransmitter. It makes the postsynaptic response to the presynaptic event to vary from one trial to the next [9, 10]. This means that the presynaptic events are smeared due to synaptic transmission, and only the postsynaptic content of the presynaptic signal can be processed by the postsynaptic neuron.

The other source of noise, the membrane noise is composed mainly of the thermal and channel noise, the first originating in the thermal agitation of ions in an electrical conductor (neuronal membrane), the second in the random fluctuations of states of ionic channels [11, 12, 13]. At the dendritic tree and soma, the channel and thermal noise interact with the signal transmission [14], altering the signal read at the axonal initial segment (axonal hillock). Along with this action, the mechanism of generation of APs at the axonal initial segment is influenced by the channel noise [15, 5, 16] of the adjacent, densely accumulated voltage gated ionic channels [17]. It causes the voltage threshold for AP initiation at the axonal initial segment to fluctuate, imposing neuronal responses to vary with the repeated stimulus.

Many papers deal with the membrane noise, but only few of them investigate the influence of the above mentioned noise on the coding accuracy by examining the precision of neuronal responses [5, 18, 19, 20, 21]. The role of synaptic unreliability has been also studied and discussed many times, but its direct influence on the neuronal response reproducibility is very little examined so far [22]. Therefore, in the present work we tried to focus on these problems by the use of computer simulations, which enabled, among others, to adjust experimental conditions (like the full control over presynaptic inputs) that can be hardly realized in today's in vivo experiments.

Methods

We adopted the multicompartmental model of a rat hippocampal CA3 pyramidal neuron [23, 42] and modified it in the GENESIS simulator (GEneral NEural SImulation Software; [24]). The voltage dependent events were modelled by delayed K rectifier ($g_{K(DR)}$) and fast Na (g_{Na}) conductances of different kinetics at the SD membrane and at the membrane of axonal initial segment (IS):

IS membrane

$g_{Na\ activation}$ (m):

$a_m = 0.8 \times (17.2 - V_{rest}) / (\exp((17.2 - V_{rest})/4) - 1)$

$b_m = 0.7 \times (V_{rest} - 42.2) / (\exp((V_{rest} - 42.2)/5) - 1)$

$g_{Na\ inactivation}$ (h):

$a_h = 0.32 \times \exp((42.0 - V_{rest})/18)$

$b_h = 10/(1 + \exp((42.0 - V_{rest})/5))$

$g_{K(DR)\ activation}(n)$:
$a_n = 0.03 \times (17.2 - V_{rest})/(\exp((17.2 - V_{rest})/5) - 1)$
$b_n = 0.45 \times \exp((12 - V_{rest})/40)$

SD membrane
$g_{Na\ activation}(m)$:
$a_m = 0.32 \times (13.1 - V_{rest})/(\exp((13.1 - V_{rest})/4) - 1)$
$b_m = 0.28 \times (V_{rest} - 40.1)/(\exp((V_{rest} - 40.1)/5) - 1)$

$g_{Na\ inactivation}(h)$:
$a_h = 0.128 \times \exp((17.0 - V_{rest})/18)$
$b_h = 4/(1 + \exp((40.0 - V_{rest})/5))$

$g_{K(DR)\ activation}(n)$:
$a_n = 0.016 \times (35.1 - V_{rest})/(\exp((35.1 - V_{rest})/5) - 1)$
$b_n = 0.25 \times \exp((20 - V_{rest})/40)$
[units in ms^{-1}]

The V_{rest} is the membrane resting potential set to –70 mV. The SD Na^+ and K^+ channel densities gradually changed from that at the soma (10 Na^+/mm^2; 30 K^+/mm^2) to those at the tip of the apical dendrites (0 Na^+/mm^2; 1 K^+/mm^2). The channel densities at the axonal initial segment were 300/mm^2 for both Na^+ and K^+ channels. Everywhere at the SD and IS membrane, the single channel conductances were 14 pS and 20 pS for the Na^+ and K^+ channels. The morphology of the real neuron that was used for compartmental transformation is depicted in Figure 1, together with the scheme of the structure of its compartmental model. The passive parameters of the SD membrane were Rm=2.5 Wm^2, Ra=2 Wm, Cm=0.0075 F/m^2, and of the IS membrane Rm=0.1 Wm^2, Ra=1 Wm, Cm=0.0075 F/m^2. The voltage attenuation along the dendritic tree was 3-fold for the DC input and 15-fold for the synaptic input, both applied to the apical dendrites and measured at the soma. The corresponding filtering-induced delay was approximately 15 ms.

We attached to the SD membrane evenly distributed excitatory AMPA and inhibitory $GABA_A$ synapses modelled by an α-function with $t_{peak} = 0.5$ ms, $g_{peak} = 1.5$ nS for AMPA and $t_{peak} = 10$ ms, $g_{peak} = 1$ nS for $GABA_A$ [25, 43]. The synapses worked with a probabilistic transmission mechanism, so that they delivered a postsynaptic current (PSC) with the probability *P*, as response to the presynaptic AP. Altogether 6000 (3000 excitatory and 3000 inhibitory) synapses were attached to the CA3 neuron, approaching the number of synapses commonly found in real neurons [26]. This enabled to connect to our neuron 6000 independently acting presynaptic neurons. However, in order to simulate multiple synapses coming from individual presynaptic neurons (functional contacts per axon

with one releasing site; the number of contacts denoted *N*), the number of presynaptic neurons varied from 60 to 6000. Hence, the number of randomly distributed single synapses (containing one releasing zone) belonging to one presynaptic neuron varied from 1 to 100. This variation enabled to examine the role of synaptic redundancy on the time precision of neuronal responses. Because the postsynaptic effect of presynaptic neuron connected through multiple synapses resembles the effect of synchronously firing presynaptic neurons, the variation of *N* also provided a substrate for examining the influence of neuronal synchronization on the precision of neuronal responses.

The firing of each presynaptic neuron was modelled by the Poisson pointprocess of 0 or 1 states, representing the silence or firing of AP. The firing of presynaptic neurons was mutually independent, with the average discharge frequency of 70 Hz, what is close to the firing frequency of the task related hippocampal state. To evaluate the influence of neural noise on the precision of AP generation, the presynaptic neurons discharged many times repeatedly with the same spike pattern and delivered the same input throughout each simulation run. Time sequences of APs elicited by multiple repetition of the input were processed by Matlab to get the peri-stimulus time histogram (PSTH). The PSTH represents the probability of firing APs throughout stimulation with the peaks that represent clusters of APs with smaller time jitters. To produce sufficient number of APs needed for statistical processing, the input was presented to the neuron 100 (100 ms long simulation) or 1000 (10 ms long simulation) times repeatedly. The

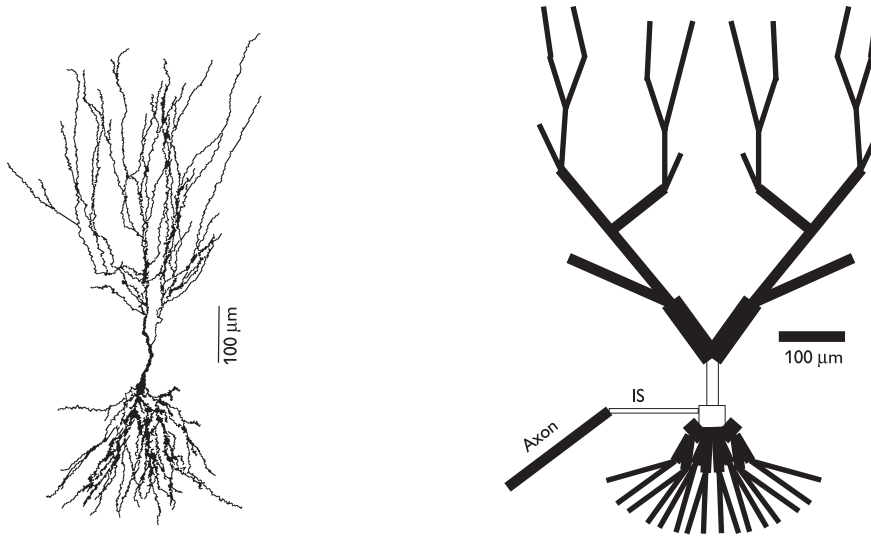

Figure 1 – To the left the morphology of the biocytin stained and afterwards scanned CA3 hippocampal pyramidal neuron is shown. To the right is shown the scheme of the compartmental model, with the apical and basal dendrites connected to the soma from which the axonal initial segment (IS) separates.

PSTHs were statistically processed to get the standard deviations σ [s] of AP clusters.

The channel noise was modelled using the algorithm exploiting Bernoulli's probability distribution of channel states [11], which is described in detail in our previous paper [27]. The membrane without channel noise was modelled by Hodkin-Huxley deterministic equations [28]. The thermal noise was modelled by connecting mutually independent random number generators to all employed membrane compartments, injecting into them the current with amplitudes of Gaussian distribution. All simulations were realized on the supercomputer IMB SP2, at the Centre for High Performance Computing CVUT Prague. The output data were processed using Matlab 5.3. In order to simulate correctly the frequency domain of the channel noise, the simulation step was set to 1 μs. The total simulation time, comprising all simulation adjustments running simultaneously at the 10 CPUs was 300 hours.

Results

First, we examined the influence of the synaptic unreliability on the time precision of neuronal responses. The thermal and channel noise was off. For each simulation adjustment, the random synaptic input lasting 100 ms was linked to the neuron repeatedly 100 times. The PSTHs in Figure 2 encompass the AP time jitters for three different probabilities *P* with the *N* set to 3 (number of synapses coming from presynaptic neuron). After few milliseconds the AP jitters differentiate, depending on the structure of synaptic activity preceding AP initiation. Governed mainly by the spatio-temporal balance between excitatory and inhibitory events, some APs were elicited by flatter and some by steeper course of depolarization at the IS, influencing the effect of synaptic failures (deviating the otherwise deterministic voltage course at the IS) on the AP time precision. The most precise responses caused by the steepest depolarization are apparent by the narrowest and highest peaks (the PSTHs with $P=0.5$ and $P=0.9$) whereas due to the distorting effect of low *P* on the synaptic transmission, the PSTHs with $P=0.1$ are appreciably smeared. By increasing the value of *P*, the individual peaks narrow, similarly as they do by increasing the value of *N* (representing the increasing neuronal synchronicity and redundancy of synaptic connections, see Methods). This is clearly demonstrated by the standard deviations σ in panels C and D representing the measure of the AP time precision in dependence on *P* and *N*. Because in the panel C and D all AP clusters were processed to get the average AP time precision, we tried to pick up the most precise responses (narrowest AP clusters caused by the steepest depolarization at the IS) and their σ are shown in panel B. Setting the number *N* of synapses coming from a presynaptic neuron to the value commonly considered in real CNS neurons [30], together with the appropriate value of *P* ($P=0.3 - 0.9$, [8]), the PSTHs in Figure 2 illustrate the reproducibility of neuronal responses evoked by the synaptic activity of 2000 desynchronised presynaptic neurons. Depending on the actual spatio-temporal pattern of synaptic events, the model was able to generate APs with the precision varying from few

milliseconds to 0.5 ms in average. Exposing our neuron with synapses having value $P=0.5$ to the input made up of predominantly synchronous presynaptic events ($N=100$), we can see that even highly reproducible responses of submillisecond precision could be produced.

Next, we investigated the influence of the channel and thermal noise on the AP time precision. All synapses were 100% reliable and firstly the channel noise was implemented only in the SD membrane. In Figure 3A to the left, the four traces represent the PSTHs of 100 ms lasting stimulations. We could see that also here the synaptic redundancy and synaptic synchronicity significantly influenced the AP

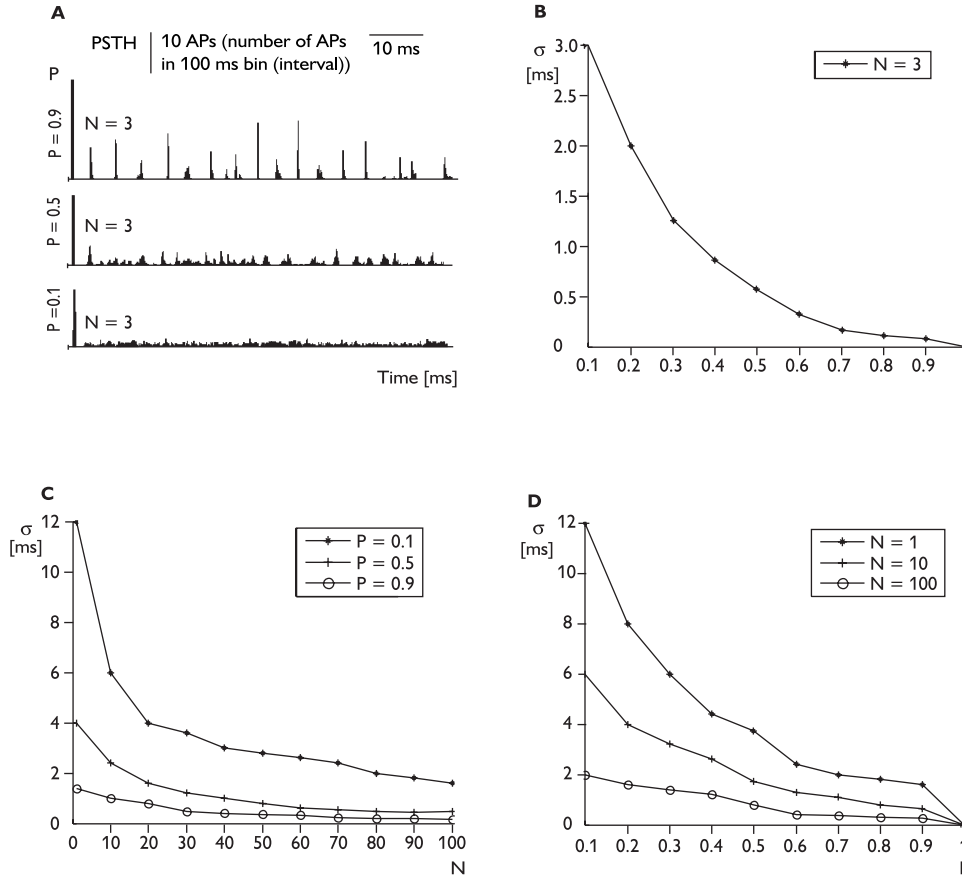

Figure 2 – The three traces in the panel A show the peri-stimulus time histograms (PSTHs), encompassing time jitter of elicited APs. Each trace represents the 100 ms time interval, during which the random pattern of synaptic activity lasting 100 ms was presented to the neuron repeatedly 100 times for each value of P (probability of synaptic transmission). N represents the number of functional synaptic contacts coming from one presynaptic neuron. In the panel C and D, the average AP precision is expressed as the dependence between the σ (standard deviations of AP clusters in PSTHs) and parameters P and N. The panel B shows the σ only of the most precise neuronal responses (narrowest AP clusters) during the stimulation.

time precision, enhancing it from submillisecond (N=1, 3, 10) to microsecond level (N=100) which is evident on the graph to the right demonstrating this dependency by standard deviations σ. Comparing the influence of the synaptic unreliability with that of the channel noise, it is apparent that the corrupting effect of the channel noise on the AP time precision is by an order smaller than that of the synaptic unreliability.

Because the abovementioned results demonstrate the corrupting effect of channel noise on the integrative processes of SD membrane, we also tried to examine its effect on the mechanism of AP generation at the axonal hillock. The SD membrane was therefore without channel noise and only the IS membrane generated channel noise. It is apparent from the four traces in Figure 3B to the left, that also here the instantaneous synaptic activity influences the AP time precision, forming the voltage course at the IS and causing those APs generated by steep depolarization are fired

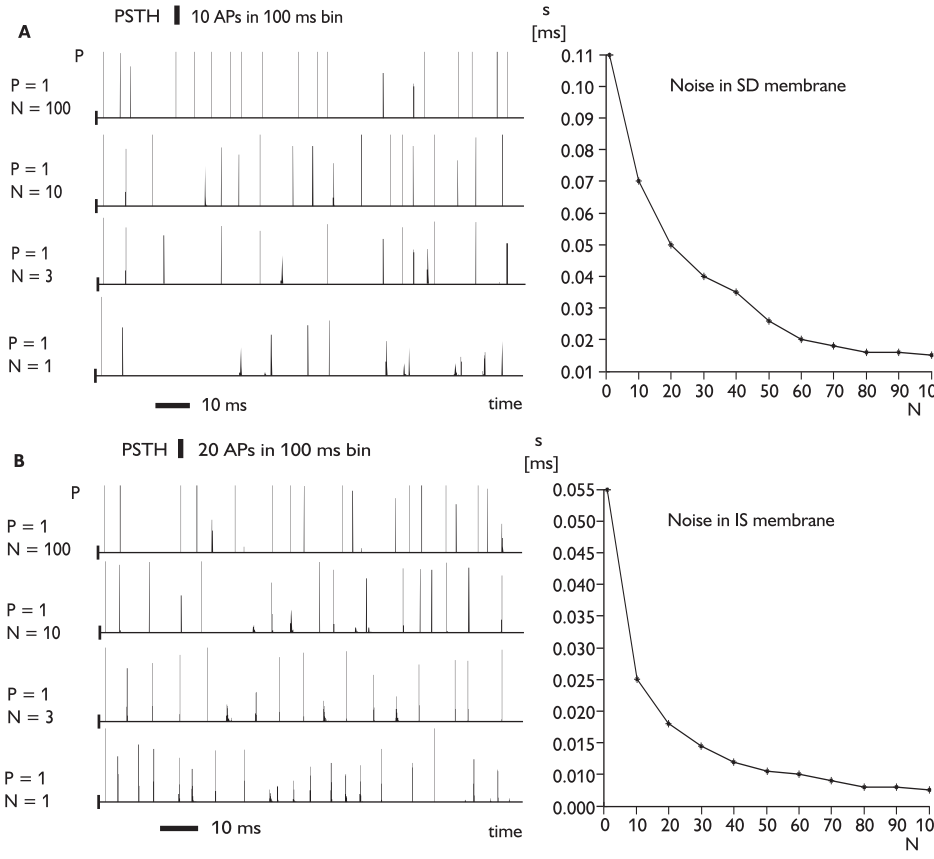

Figure 3 – The PSTHs in the panel A and B illustrate the variability of neuronal responses inluenced only by the channel noise of the SD (soma-dendritic; panel A) and of the IS (initial segment; panel B) membrane. To the right the dependence between the standard deviation δ and N is shown for these two situations.

even with the precision of few microseconds. Comparing the effect of channel noise of the SD membrane with that of the IS membrane, we can conclude that the channel noise of SD membrane influenced the AP time precision approximately to the same extent as the channel noise of IS membrane.

Finally, we investigated the influence of the thermal noise on the AP time precision. Based on our results we can conclude that the impairment of AP time precision caused by the thermal noise is very small, with the average AP jitter reaching approximately 1 μs.

Discussion

It is well known that neurons are able to generate APs with millisecond or submillisecond precision. This has been demonstrated by electrophysiological experiments dealing with the variability of neuronal responses produced by various stimuli [31, 32, 15, 33]. Despite that, the discharge patterns of cortical neurons are also highly irregular in both spontaneous and stimulus-evoked conditions, in most cases not reproducible from trial to trial with the interspike intervals close to a Poisson distribution [34]. It is unclear whether this variability in spike timing represents faithful encoding of temporally varying synaptic inputs or noise inherent in the spike encoding mechanism. Dealing in this work with the precision of neuronal responses, we can conclude from our results that the synaptic unreliability was the major source of imprecision in the timing of APs. Setting the values of N (number of synapses from presynaptic neuron) and P (probability of synaptic transmission) to those found in real CNS neurons, the neuronal responses were reproducible to the millisecond, and by increasing the value of P even to the submillisecond precision. This is interesting, because it is supposed [35, 36] that at the central synapses the facilitation and augmentation, among others, takes place by increasing the value of P (commonly reaching the value of $P=0.9$), with the possible side-effect residing in the increasing of the AP time precision. The precision attained by our model with $P=0.5$ and $N=3$ is notable, because the 70 Hz bombardment of synaptic events coming from of the order of two-thousand independent presynaptic neurons may resemble task-related-hippocampal state. Linking this presynaptic activity to our neuron repeatedly, a relatively reliable AP pattern was produced, what indicates the possibility of extractable temporal information encoded in desynchronised input.

Our results clearly demonstrate the increase of AP time precision as the synaptic redundancy increases implemented by connecting N synapses coming from a presynaptic neuron. This dependence is closely related with the effect of synchronicity of presynaptic neurons on the AP time precision, where the increase of N simulates the increasing synchronicity of presynaptic neurons (see Methods). It is probable that the presynaptic synchronicity and multiple (redundant) connections coupling neurons overcome the noise induced by synaptic failures and quantal fluctuations and increase hereby the time precision of neuronal responses.

Moreover, synchronous arrivals of synaptic events are more likely to cause rapid voltage changes at the axonal hillock, reducing herewith the scope of neuronal noise (mainly of the channel noise) to interfere with the AP initiation at the axonal hillock. This has been already demonstrated by comparing the time precisions of neuronal responses to slow and rapid varying stimuli in behaving animals [37], in neuronal slices [15] or on a patch of noisy neuronal membrane [5].

There is no doubt that the channel noise interferes with the signal transmission and processing at the dendritic tree and soma. Our results show, it is significantly lower than the influence of synaptic unreliability, and comparable with the influence of channel noise on the time precision of AP generation at the axonal hillock. The AP time jitter due to the channel noise in axonal hillock was approximately the same as measured in cortical slices [5], supporting assumptions that in real neurons the mechanism of AP generation at the axonal initial segment is altered mainly by the channel noise. Exposing our neuron with 100% reliable synapses to the highly synchronized synaptic input ($N=100$), the AP generation mechanism at the axonal hillock enabled generation of APs of microsecond precision, reaching herewith the limits possible only when bypassing synaptic unreliability in our neuron. It is known that in the NS there are some neurons, e.g. in the avian nucleus magnocellularis (which corresponds to human anteroventral nucleus of auditory system), that by the use of special synaptic [38] and dendritic arrangement [39] maximally wipe out synaptic unreliability. These neurons relay timing information of sound to the neurons in brain stem, which are able to detect even 20 μs shift of the interaural time difference [40]. Although, our model was not endowed with such special "apparatus", it included relatively extensive dendritic tree with implemented voltage gated ionic channels, underlying not only channel noise but operating as dynamical elements interacting with the signal transmission and processing. The electrotonic structure of our model enabled non-linear spatio-temporal interactions among synaptic events, potentiated by the non-linear operations of voltage-gated ionic channels. Contrary to that, as far as we know, the models used for studying the influence of the synaptic unreliability [22] and membrane noise [18], were predominantly clones of integrate-and-fire neurons, exerting no electrotonic structure and limiting integrative processes at the dendritic tree to be modelled and studied. We might speculate, whether the millisecond or submillisecond AP precision (depending on the synaptic input) of our model may indicate that the temporal relations between synaptic events are not only relevant to the neurons with a special morphofunctional arrangement, exploiting eventual synaptic coincidence, but also to the majority of neurons lacking such arrangement, as it was in our case. Possibly, in this connection, there is interesting the fidelity of myelinated axons [41] and their models [27] – (morphofunctionally corresponding to many axons found in the CNS), transmitting APs over distances of centimetres with submillisecond and even microsecond precision, which could sufficiently serve the submillisecond timing of neuronal APs.

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