Hippocampal Mossy Fiber Boutons as Dynamical Synapses

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Abstract

In this work the consequences on the activity of CA3 pyramidal neurons of the dynamic properties (facilitation and depression) associated with hippocampal mossy fiber boutons are explored; namely, a study is carried on the dependence of the pyramidal cell activity with the input stimulus frequency to the mossy fiber boutons as well as the influence of the single vesicle post-synaptic response magnitude on this dependence. We calculate tuning curves for the mossy fiber boutons excitatory post-synaptic potentials as a function of pre-synaptic frequency and we show how this property, together with channels that contribute to spike frequency adaptation, makes the activity of CA3 pyramidal neurons strongly dependent on the temporal patterns of mossy fibres pre-synaptic signals.

Key words: Hippocampus, Mossy fiber boutons, Dynamical synapses

1 Introduction

Hippocampal mossy fibers have their origin in dentate granule cells and terminate on the proximal dendrites of CA3 pyramidal cells where their activity produces fast glutamergic excitatory post-synaptic potentials (EPSPs). They have a strong influence on CA3 pyramidal neurons activity not only due to the proximal location but also because of the multiple release sites, up to 37 [1], which generate large EPSPs. Due to this strong efficiency and efficacy, it is natural to assume that the activity dynamics of the boutons will be strongly transfered to the soma.

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Viewing the boutons as dynamical synapses with short-term memory mechanisms like facilitation and depression, with the associated filtering properties, and considering the fact that CA3 pyramidal neurons have spike frequency adaptation ionic currents present in their proximal dendrites and soma, brings interesting consequences in terms of the neuron's activity dependence with the input temporal patterns of mossy fiber boutons.

2 Methods

All simulations were performed with *NEURON* [4] using a realistic model of a CA3 pyramidal neuron [7] which includes Na, t, L high threshold, N, T low threshold, A, K, M, K, Ca and Ca ionic currents. Some of them (M) contribute to spike frequency adaptation or (A and K, Ca) affect interspike time interval. All the parameters used were based in experimental results. The temperature was set to 30 Celsius.

Using *NMODL* (*NEURON* Model Description Language) a model was created for the mossy fiber synapse based on the probabilistic model for dynamic synapses suggested in [3], which accounts for depression processes. According to that, P_r, the probability of release for every release site at time of a spike, t_{sp}, is given by $P_r(t_{sp}) = P_{vr} \cdot P_{va}$ where P_{vr} is the probability of vesicle release for a release site with an available vesicle (affected directly by facilitation) and P_{va} is the probability of a vesicle to be available for release at time t (directly affected by depression). The dynamics are:

$$\frac{dP_{va}}{dt} = \frac{1 - P_{va}}{\tau_{rec}} - P_{va} \cdot P_{vr} \cdot \delta(t - t_{sp}) \tag{1}$$

where δ is the delta function, t_{sp} is the time of arrival of a spike and τ_{rec} the relaxation time constant of depression.

For the facilitation process, P_{vr} was made proportional to the calcium concentration inside the bouton with $P_{vr} = 1$ when $[Ca^{2+}] \geq 0.2\mu M$.

The post-synaptic response is then calculated according to the classical quantal model of release: $PSR = q \cdot n \cdot P_r$, where q is the the post-synaptic response to the release of each vesicle and n is the number of vesicle release sites. p and n are related with pre-synaptic processes/mechanisms whereas q is post-synaptic related. The conductance q is assumed to be affected by learning (i.e. long term potentiation/depression).

The value used for τ_{rec} was 300 ms which is in close agreement with biological measured values [6]. The post-synaptic conductance was modelled as a two

state kinetic scheme synapse described by rise time of 0.5 ms and decay time constant of 5 ms [5].

On this model a small number of mossy fiber synapses (5) with 30 release sites were connected to the CA3 pyramidal neuron with a associated unitary, i.e. per vesicle, conductance ranging from 1 to 20 nS. The synapses were placed in the proximal region (proximal apical dendrites) and all received the same spike train characterised by a specific constant frequency (no variability was added to the interspike time intervals). We here assume that among the approximately 50 contacts that each pyramidal cell receives from granule cells [9], only a small percentage were active in a limited time window and with the same, or very similar, temporal pattern.

The dependence of the activity of the pyramidal neuron with the frequency of mossy fibre inputs and the post-synaptic conductance was measured as the number of spikes generated in a specific time window.

The effect of the dynamic properties of the mossy fiber boutons on the activity of the neuron was also studied when the soma is bombarded by small EPSPs generated by several poissonian point processes randomly distributed in the dendritic tree. The mean frequency of the Poisson spike train for each point process representing an non-dynamic dual exponential synapse, was randomly chosen in the 0 to 60 Hz spectrum. In this more realistic context, the activity of the pyramidal neuron was measured again in terms of its average firing rate as a function of the mossy fiber spike train frequency.

3   Results

The tuning curves for all the analysed unitary conductances (q) were plotted and the optimal input frequency was calculated fitting the data points with a dual exponential expression (with typical $R^2 \geq 0.9$). An example for $q = 4nS$ data points and the fitted tuning curves for other three different conductances is shown in Fig.1.

Changing the post-synaptic response through the variable q, has the effect of moving the peak frequency. The calculated fitting surface, as a function of q and the input frequency is shown in the left side of Fig.2. The dark line represent the optimal input frequency (associated with the highest soma activity) for each unitary conductance. This optimal frequency curve is presented in more detail in the right side of Fig.2.

For the more realistic situation where the soma is being bombarded by small EPSPs, the properties of the dependence of the pyramidal neuron average
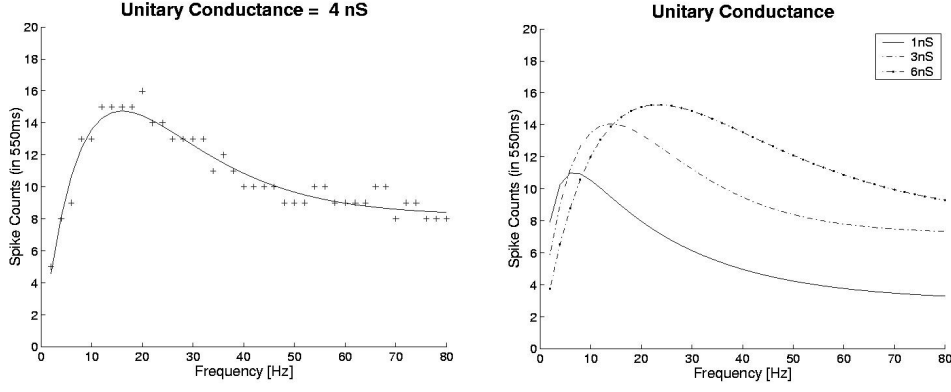
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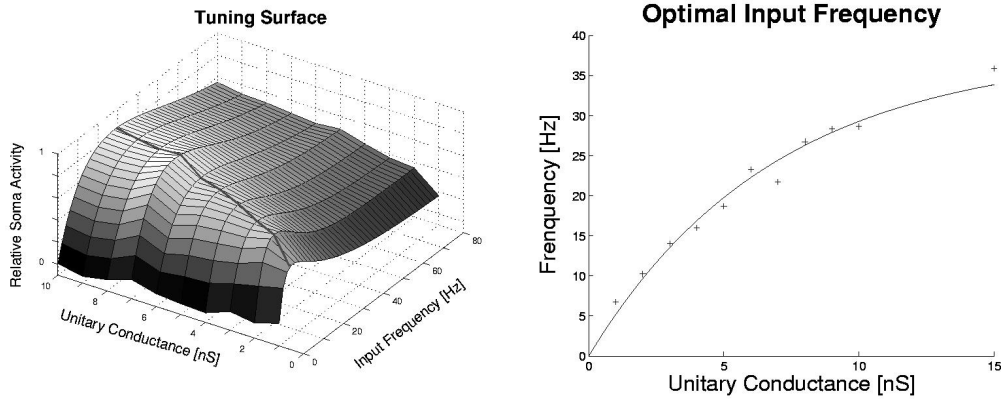Fig. 1. Tuning curves for neuron's activity

Fig. 2. Tuning surface and optimal average rate for the mossy fiber input spike train firing rate with the mossy fiber input frequency, and unitary conductance, were not affected:

For $q = 4$nS, the calculated corresponding optimal input frequency is $f_{opt} \approx$ 62Hz. With the mossy fibers receiving spike trains with this frequency together with the fixed distribution of poissonian point processes with fixed random average rate and small fixed random conductances, the obtained average firing rate of the pyramidal neuron was 24 Hz. This maximal value was significantly higher (50%) than the neuron's firing rate values obtained for input spike train frequencies equal to half the optimal frequency and twice the optimal frequency (14 and 16 Hz respectively). The rate activity of the neuron with silent mossy fibers was 4 Hz.

4 Conclusions

The bandpass filter behaviour of the mossy fiber boutons and the existence of an optimal frequency are mainly consequences of the short-term memory dynamics (facilitation and depression). If instead of efficiency we also analyse

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the efficacy of the boutons, i.e. their contribution for firing the neuron, we observe that the associated conductances also have interesting effects in the non-static, temporal domain, behaviour due to the existence of ionic currents that affect interspike time interval or contribute to spike frequency adaptation.

The fact that in the time domain and in terms of efficacy, the filtering properties of the dynamical synapses change with their strength introduces a new complexity in the understanding of learning mechanisms and it is a very important result if we accept that information may be present in the spike trains time domain.

Furthermore, we can also speculate that the existence of facilitation and depression dynamics in the mossy fiber boutons may create a *transfer switch* in the sense that for the same spatio/temporal input pattern presented to the CA3 neuron through all its synapses, the activity of the neuron will be considerably different when the inputs to the mossy fiber boutons are close to the their respective optimal input frequencies. Through temporal patterns, dentate gyrus neurons would be able to select which populations of CA3 neurons to activate.

Acknowledgements

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Paulo Aguiar (born 1977) studied Physics at the Technical University of Lisbon. After graduating in 2000, he joined the Biophysics and Biomedical Engineering Institute in Lisbon as a postgraduate student. In 2001 started his PhD with David Willshaw's group in the Institute for Adaptive and Neural Computation, University of Edinburgh. He is working in learning and memory mechanisms in the rat hippocampus.

David Willshaw is a member of the UK Medical Research Council External Scientific Staff and concurrently Professor and Head of the Institute for Adaptive and Neural Computation within the School of Informatics, University of Edinburgh, Scotland. He has over 30 years experience in developing and using computational models within neuroscience. He has developed models of memory storage within hippocampus and cerebellum and he has developed models for the formation of connections within the visual system and the neuromuscular system. His current main interests are in molecular mechanisms for the development of connections in the retinotectal system of non-mammalian vertebrates and in information processing in the basal ganglia. Since 1998 he has been Editor-in-Chief of the computational neuroscience journal "NETWORK: Computation in Neural Systems".