Simple model neurons with AMPA and NMDA filters. The role of the synaptic time scales

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Abstract

Many central neurons receive inputs that are filtered by a variety of synaptic types with very different time constants. We study the response properties of a leaky integrate-and-fire (LIF) model neuron in the presence of both fast AMPA and slow NMDA filters and find an analytical formula valid when the membrane time constant τ_m of the neuron is short. When the NMDA/AMPA abundances are similar to those found in cerebral cortex and cerebellum, the neuron mainly responds to particular large fluctuations in its inputs. These results suggest that NMDA receptors play a crucial role in shaping the neuron response in central neurons.

Key words: Integrate-and-fire neuron; AMPA and NMDA receptors; neuron response; slow filters.

1 Introduction

Spikes arriving at many central neurons can generate at the same time fast and slow unitary currents at their membranes. Fast AMPA receptors filter presynaptic inputs with a time constant $\tau_{AMPA} \sim 1 - 10ms$, while NMDA receptors filter them with a longer time scale $\tau_{NMDA} \sim 50 - 150ms$ (1). Because both receptor types normally coexist in central neurons, the information contained in the inputs is present in the membrane potential at these two time scales. Using a simple model neuron with AMPA and NMDA filters we show that, for values of NMDA/AMPA ratio abundances found in cortex (2; 3; 4) and cerebellum (5), these neurons acquire specific detection capabilities which are not present in neurons with only AMPA synapses. This work generalizes the results found in (6; 7), where a neuron with a single type of filter was shown to behave as a detector of well-defined synaptic events. All the results can be

seen from simulations as well as from an analytical expression for the output mean firing rate of the model neuron (eq. (8)), which we derive by means of simple arguments (the same formula could be found using a more rigorous treatment (6; 7)).

2 Model neuron and mean firing rate

The membrane potential V of the model neuron obeys

$$\tau_m \, \dot{V} = -V + \tau_m \, I(t) \tag{1}$$
$$I(t) = \; I_{AMPA}(t) + I_{NMDA}(t) \; , \tag{2}$$

where $I_{AMPA}(t)$ and $I_{NMDA}(t)$ are the pre-synaptic currents filtered by AMPA and NMDA synapses. A spike is produced whenever V reaches a threshold value Θ, after which it is reset to H.

Cortical and cerebellar neurons receive a large number of presynaptic spikes through their AMPA and NMDA receptors. We model their contribution to the total input current by two white noise processes with means μ_{AMPA} and μ_{NMDA}, and variances σ^2_{AMPA} and σ^2_{NMDA} (10; 9), which represents well the current generated by many afferent Poisson spike trains. In this model, the presynaptic signal generates the following AMPA and NMDA currents

$$\begin{aligned} \tau_{AMPA}\dot{I}_{AMPA}(t) &= -I_{AMPA}(t) + \mu_{AMPA} + \sigma_{AMPA} \, \eta(t) \; , \\ \tau_{NMDA}\dot{I}_{NMDA}(t) &= -I_{NMDA}(t) + \mu_{NMDA} + \sigma_{NMDA} \, \eta(t) \; , \end{aligned} \tag{3}$$

where $\eta(t)$ is a Gaussian white noise with zero mean and unit variance. Notice that since both filters receive the same spikes, they integrate the same white noise, what introduces a high degree of correlation between both currents (as it will be checked later; see top panels in Fig. (1)). Writing the current without driving forces is justified because V is very far from the reversal potential of excitatory synapses for typical (under threshold) values.

We start by providing a qualitative derivation of an expression for the firing rate of this model neuron valid for $\tau_{NMDA} >> \tau_m$ and τ_{AMPA} comparable to τ_m (or longer), which is the realistic case (8). Since the synaptic time constants are either longer (τ_{NMDA}) or at most comparable (τ_{AMPA}) to τ_m, we assume that the current is approximately constant during a time period τ_m, that is, $I(t) = I$. A LIF neuron receiving such a constant current fires at the instantaneous

constant rate (10)

$$\nu^{-1}(I) = \tau_m \ln\left(\frac{\tau_m I - H}{\tau_m I - \Theta}\right) . \tag{4}$$

The current defined in eqs. (2,3) is a random variable which we describe with a density distribution $\rho(I)$. Then, the mean firing rate can be computed by averaging the rate at constant current, eq. (4), with the density $\rho(I)$:

$$\nu_{out} = \int_{I_{min}}^{\infty} dI \rho(I)\, \nu(I) , \tag{5}$$

where the integral extends from $I_{min} = \Theta/\tau_m$. This *threshold current* is the minimal current required for the neuron to fire (see eq. (1)). To evaluate the firing rate we still need the distribution $\rho(I)$ for the stochastic process defined in eqs. (2,3). Since $\rho(I)$ is Gaussian (11), it is fully determined by its mean μ and variance σ_I^2. The mean is simply the sum of the AMPA and NMDA mean currents, $\mu = \mu_{AMPA} + \mu_{NMDA}$. To obtain the variance we first solve eqs. (3) with the initial condition $I_k(0) = 0$ ($k = {}_{AMPA,NMDA}$) to obtain

$$I_k(t) = \mu_k(1 - e^{-t/\tau_k}) + \frac{\sigma_k}{\tau_k} e^{-t/\tau_k} \int_0^t ds\; e^{s/\tau_k}\; \eta(s) . \tag{6}$$

The variance σ_I^2 is computed as

$$\begin{aligned} \sigma_I^2 &= lim_{t\to\infty} < (I_{AMPA}(t) + I_{NMDA}(t) - \mu)(I_{AMPA}(t) + I_{NMDA}(t) - \mu) > \\ &= \frac{1}{2}\left(\frac{\sigma_{AMPA}^2}{\tau_{AMPA}} + \frac{\sigma_{NMDA}^2}{\tau_{NMDA}} + 4\frac{\sigma_{AMPA}\sigma_{NMDA}}{\tau_{AMPA} + \tau_{NMDA}}\right) . \end{aligned} \tag{7}$$

The first two terms are the current variances generated by the AMPA and NMDA input fluctuations, while the third positive term arises from the correlations between AMPA and NMDA input fluctuations. Notice that if AMPA and NMDA filters were driven by two independent white noises, the third term would not be present. Notice also that the effect of combined AMPA and NMDA events is to increase the synaptic noise relative to that provided by independently driven synapses, with the same variances. After determining $\rho(I)$ with μ and σ_I^2 in the way just described and using eq. (4), the firing rate eq.(5) can be finally written as

$$\nu_{out} = \int_{I_{min}}^{\infty} \frac{dI}{\sqrt{2\pi}\sigma_I \tau_m} e^{-\frac{(I-\mu)^2}{2\sigma_I^2}} \ln^{-1}\left(\frac{\tau_m I - H}{\tau_m I - \Theta}\right) . \tag{8}$$

This expression generalizes the result recently found in (6) for a current filtered through a single slow synaptic filter. The firing rate for this particular case is readily obtained from eq. (8) by setting to zero the mean and variance of one of the two receptors.

3 Results

To illustrate how the behavior of the neuron depends on the nature of their synapses, we have plotted in Fig. (1) the voltage traces when the neuron receives 1) a sum of AMPA and NMDA synaptic currents, 2) only AMPA current, and 3) only NMDA input. The comparison is done at a fixed mean current, and it is set at a subthreshold value, where firing is produced by synaptic fluctuations. The AMPA and NMDA currents have been generated using eqs. (1-3) (top two traces). Notice that when the neuron integrates both AMPA and NMDA currents, there is a big chance of evoking action potentials when the total current $I(t)$ is above the threshold level $I_{min} = \Theta/\tau_m$. Remind that if, otherwise, $I(t) < I_{min}$, spikes cannot be evoked. We want to determine whether this "threshold effect" is due to either the AMPA or the NMDA filters, or whether it arises as a cooperative effect derived from the coexistence of both filters. To this end we have plotted the voltage responses when an AMPA current is injected with no additional NMDA current, and when an NMDA current is injected in the absence of AMPA current. With only AMPA, the threshold effect is not present: although $I(t)$ exceeds I_{min} several times, action potentials are sparse. However, with only NMDA current, the neuron fires with large probability when $I(t) = I_{NMDA}(t)$ is above I_{min}.

We can also quantify this effect by calculating for each case the probability that at least an action potential is evoked when the synaptic drive $I(t)$ is above I_{min}. For that, we have counted the number of times that $I(t)$ crosses I_{min} upwards and we have called it C. If at least an action potential was elicited by $I(t)$ during the time it stays above I_{min}, then we add one to a counter E. The probability of detection of the event $I(t) > I_{min}$ was then calculated as the fraction E/C [1] and the values we have found for the cases with NMDA only, AMPA only and both with AMPA and NMDA currents have been presented in Fig. 2. These results show that the detection behavior is only present when strong noise fluctuations are produced by NMDA synapses. The reason for this behavior is that NMDA synapses are slow filters, and whenever a large fluctuation exists, it survives for a time long enough to likely produce action potentials (6). From here it is clear that what determines the threshold detection effect is a large ratio $\sigma^2_{NMDA}/\sigma^2_{AMPA}$, and not the ratio between the means, μ_{NMDA}/μ_{AMPA}. A weak synergistic phenomena is found when the noise of both AMPA and NMDA receptors is the same (see eq.(3)), as it can be observed by comparing its detection probability with the case in with noise in

[1] Although this probability diverges for the process defined in eqs. (2,3), taking a smoother version of $I(t)$ gives finite values in the fraction E/C. For simplicity we have used $I(t)$ discretized in $1ms$ bins. For shorter bins, lower probabilities are found, as the number of crossing increases, although the relation between probabilities in the different cases is approximately maintained.

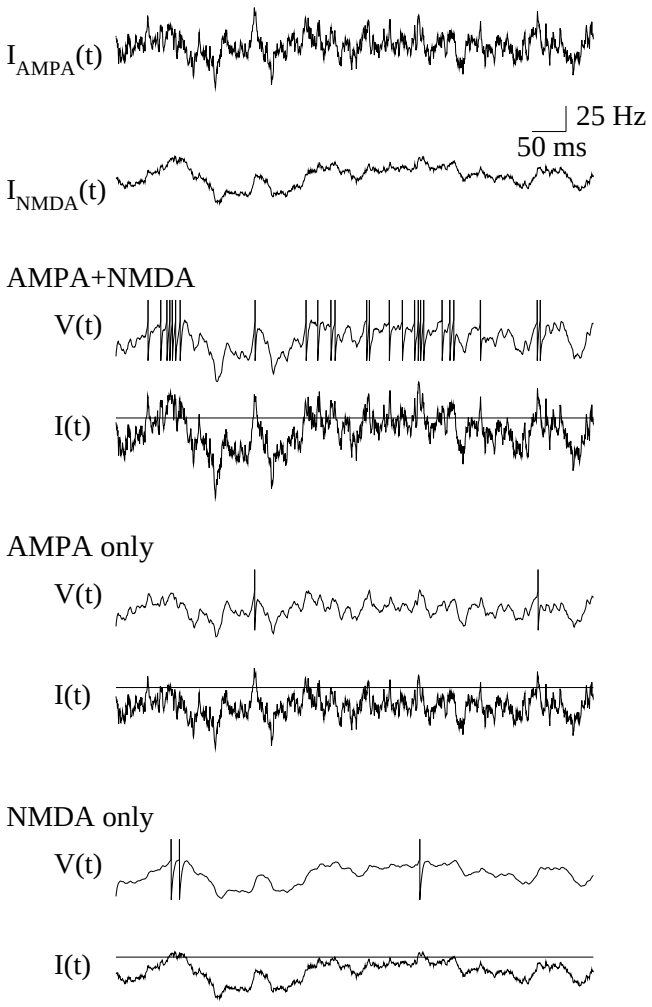

Fig. 1. Simulated membrane potential and $AMPA$ and $NMDA$ synaptic currents traces (eqs. (1-3)). All traces last for one second. The top two traces are the $AMPA$ and $NMDA$ synaptic currents obtained by filtering the same signal (white noise) with the corresponding synaptic time constants: $\tau_{AMPA} = 5ms$ and $\tau_{NMDA} = 100ms$. Pairs of membrane potentials and total synaptic currents are then showed for three different cases: 1) $AMPA$+$NMDA$: both $AMPA$ and $NMDA$ currents are present; 2) $AMPA$ only: the $AMPA$ current is present alone; and 3) $NMDA$ only: $NMDA$ current alone passes through the synapse. The straight lines in the current traces are the threshold current I_{min}. For the three cases, the mean current is $\mu = 180Hz$. In case 1) $\sigma^2_{AMPA} = 1Hz$ and $\sigma^2_{NMDA} = 20Hz$, while in 2) the second variance is zero and in 3) the first one is zero. Neuronal parameters are $\tau_m = 5ms$, $H = 0.8$ and $\Theta = 1$ (without units). With this choice the neuron is in the subthreshold regime ($\mu\tau_m < \Theta$).

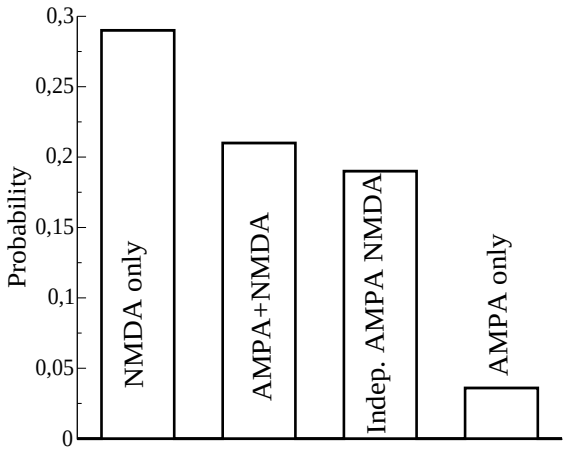

Fig. 2. Probability of evoking at least an action potential when the event "$I(t)$ is above I_{min}" occurs for the same parameter values of Fig.1. Notice that this probability is the biggest when the neuron is driven only by NMDA receptors and the smallest when driven by AMPA receptors. The coexistence of both receptors produce an intermediate detection performance of the events defined by $I(t) > I_{min}$. If AMPA and NMDA receptors would receive two independent white noise inputs, the detection performance is slightly deteriorated.

those receptors is independent in Fig. 2.

While the values we have of $\sigma^2_{NMDA}/\sigma^2_{AMPA}$ used in Fig. 2 could correspond to the case encountered in deep cerebellar nuclei (5) and in some cortical areas of some animals (4), where a big NMDA/AMPA peak current contribution is found under subthreshold voltages, realistic NMDA/AMPA peak current values in many other cortical areas (2; 3) give lower ratios such that $\sigma^2_{NMDA}/\sigma^2_{AMPA} \sim 4$. We have also made simulations with these NMDA/AMPA ratios, and using $\mu = 160Hz$, $\sigma^2_{AMPA} = 10$ and $\sigma^2_{NMDA} = 40Hz$ we have found that the coincidence behavior due to NMDA receptors is still present. We have found that for these parameters, the probability of evoking spikes when $I(t) > I_{min}$ is 0.23 with both AMPA and NMDA receptors, 0.28 with NMDA only, and it decreases to 0.04 when only AMPA receptors are present. Notice that although the ratio of the current noise provided by NMDA and AMPA receptors is small (it is expressed as $\sigma^2_{NMDA}\tau_{AMPA}/\sigma^2_{AMPA}\tau_{NMDA} = 0.2$, see eq. 7), the presence of such a weak fluctuating $NMDA$ current is still very important to improve detection of large currents produced by the combination of both AMPA and NMDA currents.

To conclude, we compare in Fig.(3) the firing rates of a neuron receiving both AMPA and NMDA currents obtained by simulations and those predicted by our eq. (8) as a function of τ_{AMPA}. Notice that the prediction is excellent for $\tau_{AMPA} > \tau_m = 5ms$, but it is also in good qualitative agreement with the simulated data for $\tau_{AMPA} < \tau_m$.

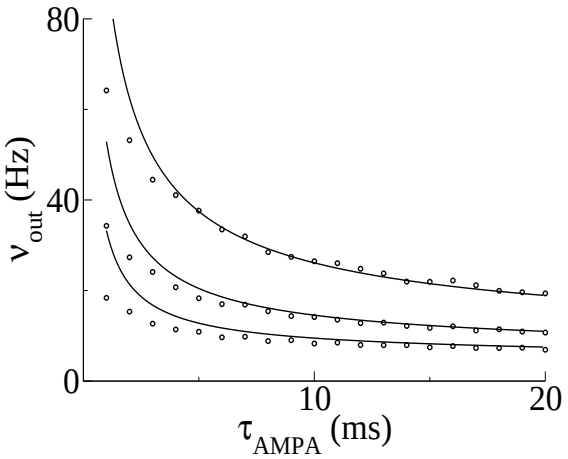

Fig. 3. Simulated (circles) and predicted (full curves) mean firing rates as a function of τ_{AMPA} for $\sigma^2_{AMPA} = 2, 1$ and $0.5Hz$ (from top to bottom). The parameters of the NMDA channel are kept fixed at $\tau_{NMDA} = 100ms$ and $\sigma^2_{NMDA} = 20Hz$. The other parameters are as in Fig. (1).

4 Conclusions

We have shown that a neuron with the NMDA/AMPA abundances found in cortex (2; 3; 4) and cerebellum (5) fires much more likely when particular fluctuations in its input current occur. These events can be easily defined as the periods in which the synaptic current is above a threshold value, and then they describe to what aspects of the input the neuron responds best. As our results show, this behavior is absent when the neuron has only AMPA synapses or when the abundance of NMDA is much lower. Including the active conductances that generate the action potential could give different quantitative results, but our qualitative description of the effect of slow NMDA filtering will be still present in this more sophisticated model neuron, because what we need is that the synaptic current $I(t)$ has a strong slow component. Even when the spiking voltage threshold would be stochastic, our results could be generated to this case.

Overall, we suggest that NMDA filters are crucial in shaping the response of cortical and cerebellar neurons and provide them with particular signal detection capabilities. Interesting interactions between this "detection" mechanism and long-term plasticity can occur, because NMDA receptors participate in this kind of plasticity. One possibility is that the detection mechanism we have proposed produces potentiation of synapses when large synaptic currents (above I_{min}) occurs, what, as we have shown, produce also reliable neuron firing.

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