Subthreshold cross-correlations between cortical neurons:
A reference model with static synapses

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Abstract

The structure of cross-correlations between subthreshold potentials of neocortical neurons was recently examined. Characteristic features included broad widths and significant peak advances. It was suggested that dynamic synapses shape these cross-correlations. Here a reference model is developed comprising leaky integrators with static synapses. Subthreshold correlations are derived analytically for two different forms of synaptic input: steady drive and population bursts. For the latter case the model captures the widths seen in experiment. However, the model could not account for the peak advance. It is concluded that models with static synapses lack the necessary biological details for describing these cortical dynamics.

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1. Introduction

Exploring correlated activity between neurons is essential for the understanding of how information is processed in cortex. In recurrent microcircuits the activity of each neuron is inter-related, either through direct connection or through higher-order indirect connections. A recent experimental study examined correlations of subthreshold voltage due to the network activity in an active slice [5]. The subthreshold voltage responds to the activity of many thousands of presynaptic cells and contains more information than the spike trains [3, 6, 7], which have been the subject of previous correlation studies (see [8] for an information-theoretic approach). The experiment [5] was performed in an active slice in which the network was in one of two states, either a steady-firing state or intermittent bursts of activity. The experimental paradigm involved the injection of a hyperpolarising current bringing each of the pair of neurons near to the reversal potential for inhibitory synapses. As well as keeping the neurons in the subthreshold regime, this method isolates the excitatory input by suppressing the membrane response to inhibition. Characteristic features of the measured cross-correlations in this paradigm were broad widths (100s of milliseconds for the case of population bursts) and a significant advance to the peak ($50 \sim 100$ms between pyramidal and certain interneuron types).

Here it is examined whether a model comprising a pair of leaky integrators with static synapses is sufficient to capture these basic experimental features. The neuronal model is first introduced and the widths and peak shifts of the cross-correlation then derived as a function of the membrane and synaptic

parameters. The paper closes with an examination of the descriptive scope of models with static synapses and the suggestion of possible extensions that might allow for a better agreement with the experimental results.

2. The model

Two leaky-integrator neurons, with membrane potentials $V_1(t)$ and $V_2(t)$, receive input from a common and separate pool of presynaptic neurons. Only excitatory post-synaptic potentials (EPSPs) are considered, consistent with the experimental procedure described above. Though the inhibitory inputs have an indirect effect through the conductance increase, in the present study this effect is neglected for both the excitatory and inhibitory drive. It will be shown later that our conclusions are not affected by this approximation.

The differential equation describing the dynamics of the subthreshold potential, subject to a synaptic input I_{syn}, is the following:

$$\tau_m \dot{V} = -V + R I_{syn}(t) \quad \text{where} \quad I_{syn}(t) = \frac{q}{\tau_f} \sum_{\{t_k\}} \Theta(t - t_k) \exp\left(-\frac{t - t_k}{\tau_f}\right).$$

The quantities introduced are; τ_m the membrane time constant, R the neuronal input resistance, τ_f the falling time constant, q is the total amount of charge in a synaptic current pulse and $\{t_k\}$ the set of arrival times for all synaptic inputs. These parameters will be later subscripted by the labels $1, 2$ for each of the neurons. The subthreshold potential above is measured from the reversal potential of the inhibitory drive (near -70mV) and can be written as a summation of EPSPs $\mathcal{E}(t)$

$$V(t) = \int_0^\infty \mathrm{d}s \mathcal{E}(s) \sum_{\{t_k\}} \delta(s - (t - t_k)) \quad \text{with} \quad \mathcal{E}(t) = qR \frac{(e^{-\frac{t}{\tau_m}} - e^{-\frac{t}{\tau_f}})}{(\tau_m - \tau_f)} \qquad (1)$$

3. The cross-correlation function

Throughout this paper, the cross-correlation function is defined as follows

$$\mathcal{C}(\Delta) = \langle V_1(t)V_2(t + \Delta)\rangle - \langle V_1\rangle \langle V_2\rangle \tag{2}$$

where it is stressed that $\mathcal{C}(\Delta)$ is *not* normalised. Inserting the form of the voltage given in equation (1) yields:

$$\mathcal{C}(\Delta) = \int_0^\infty\!\!\int_0^\infty \mathrm{d}s_1\mathrm{d}s_2\mathcal{E}_1(s_1)\mathcal{E}_2(s_2)(r_c\delta(s_1-s_2+\Delta) + r_0\rho(s_1-s_2+\Delta) - r_0^2) \tag{3}$$

where r_c is the average common rate and r_0 is the average total rate. The quantity $\rho(t)$ is the cross-conditional probability of finding a pulse at a time t in the input of one neuron given a pulse at $t=0$ in the input of the other.

Steady synaptic drive. For Poissonian input the cross-conditional density is constant $\rho_S(t) = r_0$ giving the cross-correlation function for $\Delta > 0$ as

$$\mathcal{C}_S(\Delta) = r_c\int_0^\infty \mathrm{d}s\ \mathcal{E}_1(s)\mathcal{E}_2(s + \Delta) = r_c q_1 q_2 R_1 R_2\left(M_{12}e^{-\Delta/m_2} - F_{12}e^{-\Delta/f_2}\right) \tag{4}$$

$$M_{12} = \frac{1}{(m_2 - f_2)}\frac{m_2^2}{(m_1 + m_2)(m_2 + f_1)}, \quad F_{12} = \frac{1}{(m_2 - f_2)}\frac{f_2^2}{(f_1 + f_2)(m_1 + f_2)}.$$

The notation has been lightened by writing m_1 for τ_{m_1} etc. The cross-correlation function for $\Delta < 0$ takes a similar form, but with the indices and sign of Δ reversed, i.e. $X_{12}(\Delta)$ is replaced by $X_{21}(-\Delta)$.

The peak and mean advance. The time difference Δ_S^* at which the cross-correlation function peaks has the same sign as $m_2 f_2 - m_1 f_1$. When $\Delta_S^* > 0$

$$\Delta_S^* = -\frac{m_2 f_2}{(m_2 - f_2)}\log\left(\frac{m_2}{f_2}\frac{(f_1 + f_2)(m_1 + f_2)}{(m_1 + m_2)(m_2 + f_1)}\right) \qquad V_1 \text{ leads } V_2$$

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The advance can also be measured in terms of the moments of $\mathcal{C}_S(\Delta)$. The mean advance is $\overline{\Delta_S} = (f_2 + m_2) - (f_1 + m_1)$ and of the order of the membrane and synaptic time constants ($\sim 10\text{ms}$).

The width. This is obtained from the moments of the cross-correlation:

$$\overline{(\Delta - \overline{\Delta})_S^2} = m_1^2 + f_1^2 + m_2^2 + f_2^2 \tag{5}$$

Hence the width, measured as the square root of this quantity, is less than twice the longest membrane or synaptic time-scale ($\sim 10\text{s of ms}$).

Population bursts. The populations bursts are modelled here as a Poissonian distributed box-car function, with the burst frequency $r_B = r_{Bc} + r_{Bs}$ where r_{Bc} and r_{Bs} are the common and separate rates within the burst. The burst length is T_B and the average inter-burst interval is T_{IBI}. The required cross-conditional density $\rho(t)$ for this type of presynaptic input is

$$\rho_B(t) = \begin{cases} r_B \left(1 - \left|\frac{t}{T_B}\right|\right) + r_0 & 0 < |t| < T_B \\ r_0 & T_B < |t|. \end{cases} \tag{6}$$

The average rate r_0 is a function of the inter-burst interval $r_0 = r_B T_B / T_{IBI}$ as is the common rate $r_c = r_{Bc} T_B / T_{IBI}$. The correlation function can be written in terms of a convolution with $\mathcal{U}_S = \mathcal{C}_S / r_c$:

$$\mathcal{C}_B(\Delta) = \mathcal{C}_S(\Delta) + r_B r_0 \int_{-T}^{T} d\Delta' \, \mathcal{U}_S(\Delta + \Delta') \left(1 - \frac{|\Delta'|}{T}\right). \tag{7}$$

Performing the integration gives the cross correlation for $\Delta > 0$ as:

$$\begin{aligned}
\frac{\mathcal{C}_B(\Delta)}{r_0 q_1 q_2 R_1 R_2} = {} & \frac{r_c}{r_0} \left(M_{12} e^{-\Delta/m_2} - F_{12} e^{-\Delta/f_2}\right) \\
& + \frac{2r_B}{T} \left(M_{12} m_2^2 e^{-\Delta/m_2} (\cosh(T/m_2) - 1)\right) \\
& - \frac{2r_B}{T} \left(F_{12} f_2^2 e^{-\Delta/f_2} (\cosh(T/f_2) - 1)\right)
\end{aligned}$$

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$$+\frac{r_B}{T}\Theta(T-\Delta)\left(T-\Delta+(m_2+f_2)-(m_1+f_1)\right)$$
$$+\frac{r_B}{T}\Theta(T-\Delta)\left(M_{21}m_1^2 e^{-(T-\Delta)/m_1}-F_{21}f_1^2 e^{-(T-\Delta)/f_1}\right)$$
$$-\frac{r_B}{T}\Theta(T-\Delta)\left(M_{12}m_2^2 e^{(T-\Delta)/m_2}-F_{12}f_2^2 e^{(T-\Delta)/f_2}\right) \quad (8)$$

The cross-correlation for $\Delta < 0$ is obtained by reversing all indices $\{1,2\} \to \{2,1\}$ and the sign of Δ.

The peak and mean advance. In the convolution equation (7), the width of the burst is much greater than the steady-firing cross correlation function. Hence

$$\Delta_B^* \simeq \Delta_S^* + \text{ small corrections} \quad (9)$$

where the corrections come from any skew in $\mathcal{C}_S$. The distance to the peak is close to that predicted for the case of steady drive (~ 10s of ms). Hence the model cannot explain the large peak advances seen in experiment. The mean advance $\overline{\Delta}_B$ is also equivalent to the steady-input result $\overline{\Delta}_S$ given above.

The width. The width is obtained approximately by using equation (7):

$$\overline{(\Delta-\overline{\Delta})_B^2} \simeq (m_1^2+f_1^2+m_2^2+f_2^2)+\frac{T^2}{6} \quad (10)$$

noting that the common input (first term in Eq. 7) is small compared to the within-burst correlations. The model therefore predicts that the width of the cross-correlation is dominated by the burst, in agreement with experiment.

4. Discussion

In this study an analytical approach was developed to examine the neuronal and synaptic mechanisms that underlie features of the cross-correlation seen between cortical neurons [5]. The model comprised a pair of leaky integrator

neurons with static synapses parameterised by membrane and synaptic time constants and subject to two types of drive: steady input and population bursts. We demonstrated that the duration of the population bursts largely determines the width of the cross-correlation. It was seen in experiment that the peak of the cross-correlation showed a significant shift from zero (for the cases of correlations between pyramidal and certain interneuron types). These peaks however could not be explained by our model. The membrane and synaptic time constants do not provide a sufficiently long time-scale to capture the observed peak shifts of $50 \sim 100$ms. We therefore conclude that the model with static synapses and passive membranes is not sufficiently detailed to explain these dynamics of cortical microcircuits.

The model ignored the large synaptic conductance changes seen in neurons embedded in active networks [1]. However, these effects can be well approximated by using a shorter effective membrane time-constant, which would only reinforce our conclusions. Another mechanism that was ignored in this model is the dynamic nature of synapses [2, 4]. That this mechanism is likely to produce the peak shift is supported by the fact that the largest peak delays were seen between neurons pairs in which one had facilitating and the other depressing synapses. The passive neuron models used here also neglected trans-membrane currents. In particular, the I_h current is strongly active at hyperpolarised membrane potentials and has the long time-scale necessary for a mechanism that might underlie the peak advance.

Cross-correlations between subthreshold potentials in anaesthetised cat visual cortex were also characterised in terms of width and peak position

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[3, 6]. A better quantitative understanding of subthreshold correlations therefore promises insight into the coordination of dynamic activity in both the active cortical microcircuit *in vivo* as well as in the isolated brain slice.

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FIGURE 1.
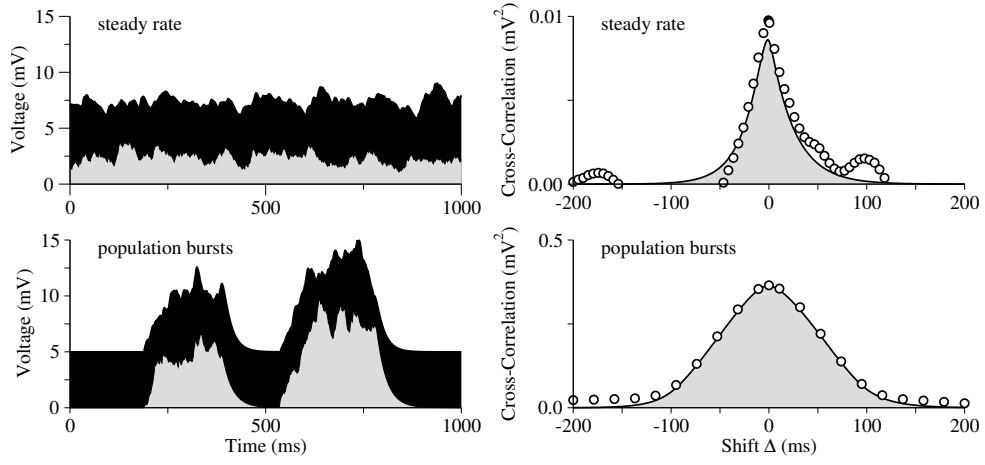
CAPTION FOR FIGURE 1.

(LEFT) Voltage time courses for the neuronal pair for the cases of steady and burst synaptic drive. One of the traces has been offset by 5mV in both cases. (RIGHT) The corresponding cross-correlations. The lines are theoretical results and the symbols Monte-Carlo simulations of duration 30secs to give an idea of the relative level of noise expected in biological data. The case of steady drive is noisier because the correlations come only from the low common input rate. The parameters used are $\{\tau_{m1}=20, \tau_{f1}=5, \tau_{m2}=25, \tau_{f2}=2\}$ms and $q_1 R_1 = q_2 R_2 = 3$, for both cases. For the steady input the common and total rates were 50Hz and 200Hz respectively. For the population burst $r_{cB}=100$Hz $r_{sB}=400$Hz $T_B=100$ms and $T_{IBI}=500$ms.