Membrane Potential and Response Properties of Populations of Cortical Neurons in the High Conduction State

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Because of intense synaptic activity, cortical neurons are in a high conductance state. We show that this state has important consequences on the properties of a population of independent model neurons with conductance-based synapses. Using an adiabatic-like approximation we study both the membrane potential and the firing probability distributions across the population. We find that the latter is bimodal in such a way that at any particular moment some neurons are inactive while others are active. The population rate and the response variability are also characterized.

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Under in vivo conditions cortical action neurons receive a persistent bombardment of presynaptic action potentials coming from a few thousand neurons [1]. This synaptic activity has an important effect on the membrane properties of the postsynaptic neuron. Synaptic ion channels open upon the arrival of these events and the total membrane conductance increases considerably. Even in the absence of sensory stimulation, the neuron is affected by the background activity from other neurons in the population, producing a fivefold increase of its conductance [2]. If the neuron is recorded in vivo under sensory stimulation, its conductance doubles relative to that at rest [3]. Since the cell membrane behaves as an RC circuit, this increase in conductance produces a drastic reduction in its effective membrane time constant, \( \tau_m \) [4]. As an example, if a cortical neuron in vitro has a membrane time constant \( \tau_m \sim 20 \) ms, background activity would reduce it to \( \tau_m \sim 4 \) ms, a value which is further reduced by the stimulus to \( \tau_m \sim 2 \) ms. Therefore, \( \tau_m \) can become shorter than the time constant of both excitatory (\( \tau_{AMPA} \sim 3 \) ms) and inhibitory (\( \tau_{GABA_A} \sim 10 \) ms) synapses. Even when \( \tau_m \) does not become so short, its value in vivo is presumably smaller than \( \tau_{GABA_A} \).

Here we employ a novel technique to study the population properties of model neurons in the high conductance state (HCS). This allows us to derive the membrane voltage and firing probability distributions of model neurons, showing that these exhibit quite different properties from neurons in a low conductance regime. For the sake of simplicity we present both the mathematical solution and the corresponding numerical analysis in the particular situation in which all the synaptic time scales become longer than \( \tau_m \). However, we will see that a similar solution exists if some synaptic channels contribute with fast noise, provided that there is a slow synaptic type.

Neurons are of the integrate-and-fire type [5]: the membrane potential \( V \) follows the equation

\[
C_m \frac{dV}{dt} = -g_L(V - V_L) - I_{bg}(t) - I_s
\]

(1)

\[
I_{bg}(t) = g_E(t)(V - V_E) + g_I(t)(V - V_I)
\]

(2)

but whenever \( V \) reaches a threshold value \( \Theta \) an action potential is fired and \( V \) is reset at a value \( H \). The capacitance \( C_m \), the leak conductance \( g_L \), and the rest reversal potential \( V_L \) describe the passive properties of the membrane. \( I_s \) denotes the total synaptic current produced by the stimulus: \( I_s = g_s(V - V_s) \), where the total sensory conductance \( g_s \) and reversal potential \( V_s \) are assumed to vary in a time scale much slower than the synaptic time constants. \( I_{bg}(t) \) denotes the total synaptic current generated by excitatory \( (E) \) and inhibitory \( (I) \) contributions of the background activity. The \( V_s \)'s are the reversal potentials and the \( g_s(t) \)’s the conductances of the excitatory and inhibitory background synapses \( (k = E, I) \). These conductances are modeled by filter equations with synaptic time constants \( \tau_k \) [6]

\[
\tau_k \frac{dg_k}{dt} = -g_k(t) + g_k(0) + \sqrt{2\tau_k} \sigma_k \eta_k(t),
\]

(3)

producing fluctuating conductances with mean \( g_k(0) \) and deviation \( \sigma_k \) \( (g_k(t) \geq 0) \). The \( \eta_k(t) \) are white noises of zero mean and unit variance.

We start by rewriting Eqs. (1)–(3) in a more convenient way. First, we will use normalized conductance fluctuations \( z_k(t) \) instead of the conductances \( g_k(t) \) themselves. We then replace Eq. (3) by

\[
g_k(z_k) = (g_k(0) + z_k \sigma_k)^+,
\]

(4)

\[
\dot{z}_k(t) = -z_k(t) \frac{1}{\tau_k} + \frac{1}{\sqrt{\tau_k}} \eta_k(t),
\]

(5)

where the second equation is an Ornstein-Uhlenbeck process and \( (x)^+ = x \) if \( x > 0 \) and zero otherwise. The steady state probability density of the conductance fluctuations is Gaussian; denoting \( \bar{z} \equiv (z_E, z_I) \) and \( |z|^2 = z_E^2 + z_I^2 \) this density reads

\[
p(\bar{z}) = e^{-|\bar{z}|^2/2} / 2\pi.
\]

(6)

Second, we make explicit the effect of presynaptic activity on \( \tau_m \) by rewriting Eqs. (1) and (2) as

\[
\frac{C_m}{g_{vol}(\bar{z})} \frac{dV}{d\bar{z}} = \tau_m(\bar{z}) \frac{dV}{d\bar{z}} = -V + V_R(\bar{z}),
\]

(7)
when and known, the population firing rate is computed by averaging the driving force at threshold and the probability density (instantaneous rate) of a neuron receiving a background fluctuation $\tilde{z}$. It can be computed in terms of the driving force at threshold and the probability density $P(\Theta | \tilde{z}) = P(\Theta) / p(\tilde{z})$ that the potential is at its threshold value, conditioned to a conductance fluctuation $\tilde{z}$:

$$P(\Theta | \tilde{z}) = \left( \frac{V_R(\tilde{z}) - \Theta}{\tau_m(\tilde{z})} \right) P(\Theta | \tilde{z}).$$

(13)

where $V_R(\tilde{z}) = \frac{\partial}{\partial V} \left( \frac{V - V_R(\tilde{z})}{\tau_m(\tilde{z})} \right) + \frac{L_z E}{\tau E} + \frac{L_z I}{\tau I}$

and $L_z = \frac{\partial}{\partial z} + \frac{\partial^2}{\partial z^2}$. The quantity $\nu(\tilde{z})$ is the firing probability density (instantaneous rate) of a neuron receiving a background fluctuation $\tilde{z}$. It can be computed in terms of the driving force at threshold and the probability density $P(\Theta | \tilde{z}) = P(\Theta) / p(\tilde{z})$ that the potential is at its threshold value, conditioned to a conductance fluctuation $\tilde{z}$:

$$P(\Theta | \tilde{z}) = \left( \frac{V_R(\tilde{z}) - \Theta}{\tau_m(\tilde{z})} \right) P(\Theta | \tilde{z}).$$

(13)

On the right-hand side of Eq. (12) the instantaneous rate is reinserted at $V = \Theta$ to reset the neuron after firing. Equations (12) and (13) have to be solved self-consistently with some additional constraints: (1) $P(\Theta | \tilde{z})$ has to be zero when $V_R(\tilde{z}) < \Theta$; otherwise $\nu(\tilde{z})$ would be negative. (2) $P(V, \tilde{z})$ must adequately vanish at large $\tilde{z}$ and at large negative $V$ to guarantee its normalizability. Once $\nu(\tilde{z})$ is known, the population firing rate is computed by averaging $\nu(\tilde{z})$ over a the region $\Omega$ defined by the condition $V_R(\tilde{z}) > \Theta$,

$$\nu_{\text{pop}} = \int_{\Omega} d\tilde{z} p(\tilde{z}) \nu(\tilde{z}).$$

(14)

Since in a HCS $\tau_m$ can be shorter than the synaptic time constants, we look for an approximation of $P(V, \tilde{z})$ and $\nu(\tilde{z})$ valid in the limit of large $\tau_k$. As $\tau_m$ is quite short, the potential is driven very rapidly to its stationary value. The contribution to the FPE coming from the time evolution of the membrane potential, Eq. (7), should then be treated exactly. Our strategy is to deal with the first term on the left side of Eq. (12) exactly, while the next two terms are treated perturbatively, for large $\tau_k$. Therefore, we expand both the probability density and the instantaneous firing rate as $P(V, \tilde{z}) = P_0(V, \tilde{z}) + O(1/\tau_k)$ and $\nu(\tilde{z}) = \nu_0(\tilde{z}) + O(1/\tau_k)$, obtaining the zeroth order of Eq. (12):

$$\frac{\partial}{\partial V} \left( \frac{V - V_R(\tilde{z})}{\tau_m(\tilde{z})} \right) P_0(V, \tilde{z}) = -p(\tilde{z}) \nu_0(\tilde{z}) \delta(V - H).$$

(15)

This expansion corresponds to an adiabatic approximation where the voltage state of the neurons is computed exactly at a fixed level $\tilde{z}$ of background activity. This technique

was first introduced in [8] to study the effect of synaptic filtering by a model neuron without reversal potentials. Solving Eq. (15) for $V \leq \Theta$ leads to

$$P_0(V, \tilde{z}) = \left[ \frac{\tau_m(\tilde{z}) \nu_0(\tilde{z}) \mathcal{H}(V - H) + \delta(V - V_R(\tilde{z}))}{V_R(\tilde{z}) - V} \right] p(\tilde{z}),$$

(16)

where $\mathcal{H}(x) = 1$ for $x > 0$ and zero otherwise. Besides

$$\nu_0^{-1}(\tilde{z}) = \frac{V_R(\tilde{z}) - H}{V_R(\tilde{z}) - \Theta}.$$

(17)

if $V_R(\tilde{z}) > \Theta$ and $\nu_0(\tilde{z}) = 0$ otherwise. This is the firing probability density of an integrate-and-fire neuron, as in Eq. (7), with effective membrane time constant $\tau_m(\tilde{z})$ and reversal potential $V_R(\tilde{z})$, in a constant background $\tilde{z}$.

The joint distribution $P_0(V, \tilde{z})$ [Eq. (16)] has two terms, originated from different subpopulations. Neurons characterized by a conductance fluctuation $\tilde{z}$ such that $V_R(\tilde{z}) > \Theta$ contribute only to the first term. These neurons are active, fire with an instantaneous rate $\nu_0(\tilde{z})$, and their membrane potential is distributed spanning the range between the reset and the threshold potentials. The intuitive interpretation of this result is simple: after the neuron fires and the potential is reset at $H$, the potential undergoes a continuous depolarization until it reaches again its threshold value. In contrast, those neurons where $V_R(\tilde{z}) < \Theta$ contribute only to the second term. These are inactive and their membrane potential is clamped at $V_R(\tilde{z})$. The distribution of membrane potentials across the total population, $P_0(V)$, is obtained by integration of $P_0(V, \tilde{z})$ over $\tilde{z}$.

We have simulated a population of neurons [9] using Eqs. (5) and (7) and compared the simulated distribution with the analytical result in Fig. 1. The top picture also shows the contributions to $P_0(V)$ from the active and inactive subpopulations, which come from integration over $\tilde{z}$ of either the first or the second term in Eq. (16), respectively. The first term in $P_0(V, \tilde{z})$ becomes important when the population spends most of the time firing. This corresponds to a population in the suprathreshold regime
This expression can be understood qualitatively: since in the HCS the synapses have a slower dynamics than the membrane, for any given $\tilde{z}$ the firing probability takes the value $\nu_0(\tilde{z})$ corresponding to a neuron receiving a constant fluctuation. Equation (16) can be explained in similar terms. Notice that this argument can be used to justify an equation similar to (18) when synapses faster than $\tau_m$ are present, provided that there is at least one slow synaptic type. Now, while the slow synapses produce the required slow fluctuation $\tilde{z}$, the membrane dynamics reaches its stationary state in the presence of the fast noise of variance $\sigma_f$, producing spikes with firing probability density $\nu_0(\tilde{z}, \sigma_f)$ (e.g., the one given in [5]). We analytically checked that Eq. (18) is still valid by just replacing the instantaneous rate $\nu_0(\tilde{z})$ given in Eq. (17) by this $\nu_0(\tilde{z}, \sigma_f)$.

Because of the fast noise, the integration domain $\Omega$ is simpler: all values of $\tilde{z}$ may give some contribution. If the fast noise is weak, $\nu_0(\tilde{z}, \sigma_f) \sim \nu_0(\tilde{z})$, it will not affect much the properties of the population. Here we will only analyze the case without fast noise.

Equation (18) can also be interpreted as the firing rate of a single neuron bombarded by intense presynaptic activity. Since this neuron responds whenever $V_K(\tilde{z}) \geq \Theta$, it behaves as a detector of fluctuations $\tilde{z}$ satisfying this condition. This property is also present in neurons with synapses described as simple slow filters [8]. Although Eq. (18) can be used to compute $\nu_{pop}$, we will now derive a simpler equation. Let us define $u$ and $v$ as linear combinations of $z_E$ and $z_I$,

$$u = -\gamma^{-1}[\sigma_E(\Theta - V_E)z_E + \sigma_I(\Theta - V_I)z_I]$$

$$v = \gamma^{-1}[\sigma_I(\Theta - V_I)z_E - \sigma_E(\Theta - V_E)z_I]$$

$$\gamma^2 = \sum_{k=E,I} \sigma_k^2(\Theta - V_k)^2.$$

Under natural conditions ($V_I < H, \Theta < V_E$ and $V_I < V_L < V_K$), the region $\Omega$ is transformed into $u \geq u_{min} = g_{tot}(\Theta - V_K)/\gamma$ and, for large $g_{tot}$, $v$ can be taken in the interval $(-\infty, 0)$. Thus, Eq. (18) becomes

$$\nu_{pop} = \int_{u_{min}}^{\infty} \frac{du}{\sqrt{2\pi}} e^{-u^2/2} \nu_0(u),$$

where $\nu_0^{-1}(u) = \tau_{eff}(u) \log[(u - u_{min})/(u - u_{min})]$. $\tau_{eff}(u) = g_{tot}(H - V_K)/\gamma_H$, $g_{tot}(H - V_K)/\gamma_H$. $\tau_{eff}(u) = g_{tot}/C_m - u \sum_{k=E,I} \sigma_k^2(\Theta - V_k)/C_m \gamma_H$. $\gamma_H = \gamma^{-1} \sum_{k=E,I} \sigma_k^2(\Theta - V_k)/(H - V_k)$.

In Fig. 2 the population firing rate and the coefficient of variation (CV) of the inter-spike-intervals (ISI’s) are plotted as a function of $g_{tot}$. The variances of the background synaptic conductances have been taken to vary linearly with $g_{tot}$. The prediction is quite good for intermediate $g_{tot}$ and improves for larger values. The population rate reaches a maximum for intermediate values of $g_{tot}$, after which it decreases because a shorter $\tau_m$ reduces the voltage fluctuations. Asterisks indicate two populations, one in a low conductance state and another in a HCS. Both fire with the same rate, but the CV is higher for the second. This shows that high CV’s, as observed in cortical neurons [10], are a natural characteristic of populations in the HCS [11].

We can wonder how the instantaneous rate is distributed across the population. Since fluctuations last for a time $O(\tau_s)$ [this is also true for $u$, see Eqs. (5) and (19)], neurons make transitions between the active and inactive subpopulations. However, in the stationary regime, the fraction of neurons firing at a given instantaneous rate $\nu$ remains constant. We then proceed to evaluate the probability density $f(\nu)$ of having a neuron with firing probability density $\nu$.

Since $f(\nu)d\nu = p(u)du$, with $u$ normally distributed,
We computed an estimator \( \nu_{\text{est}} \) of the instantaneous firing rate of neurons in a simulated population as the inverse of the ISI's. Although the distribution of this estimator, \( f(\nu_{\text{est}}) \), does not provide a good fit of the true instantaneous rate distribution, it does have a bimodal shape when the population is in the HCS. In contrast, \( f(\nu_{\text{est}}) \) loses the bimodality in the low conductance regime, suggesting that it is characteristic of the HCS.

While we have considered the case in which synapses are slower than the neuron dynamics, the situation actually occurring in nature might be more complex. For not too strong presynaptic activity, the total conductance of the neuron could be such that \( \tau_m \) lies between the fast \( \text{AMPA} \) (excitatory) and the slower \( \text{GABA}_A \) (inhibitory) receptors. As we have already discussed, this can be described by an equation similar to Eq. (18) and therefore even in this case the neuron response is as described here, if the noise comes mainly from \( \text{GABA}_A \). The same is true if the noise is mainly produced by \( \text{NMDA} \) (slow excitatory) receptors. Overall, a neural system in which slow noise dominates over fast noise will exhibit the properties discussed in this work.

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[9] Assuming \( g_{E,0} = N_E \nu_E \tau_E \), and taking \( g_{E,0} = 20 \) nS and \( N_E = 2000 \) excitatory synapses, one obtains \( \nu_E = 1 \) Hz, a plausible value of the background activity.