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Membrane Potential and Response Properties of Populations of Cortical Neurons in the High Conductance 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 adiabaticlike 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 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, τ_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, τ_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 τ_m does not become so short, its value *in vivo* is presumably smaller than τ_{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 τ_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

$$C_m \dot{V}(t) = -g_L(V - V_L) - I_{bg}(t) - I_s \qquad (1)$$

$$I_{bg}(t) = g_E(t)(V - V_E) + g_I(t)(V - V_I), \qquad (2)$$

but whenever V reaches a threshold value Θ 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_k's are the reversal potentials and the $g_k(t)$'s the conductances of the excitatory and inhibitory background synapses ($k = E, I$). These conductances are modeled by filter equations with synaptic time constants τ_k [6]

$$\tau_k \dot{g}_k(t) = -g_k(t) + g_{k,0} + \sqrt{2\tau_k}\sigma_k\eta_k(t), \qquad (3)$$

producing fluctuating conductances with mean $g_{k,0}$ and deviation σ_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

$$g_k(z_k) = (g_{k,0} + z_k\sigma_k)^+, \qquad (4)$$

$$\dot{z}_k(t) = -\frac{z_k(t)}{\tau_k} + \sqrt{\frac{2}{\tau_k}}\eta_k(t), \qquad (5)$$

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 $\vec{z} \equiv (z_E, z_I)$ and $|z|^2 = z_E^2 + z_I^2$ this density reads

$$p(\vec{z}) = \frac{e^{-|z|^2/2}}{2\pi}. \qquad (6)$$

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

$$\frac{C_m}{g_{\text{tot}}(\vec{z})}\dot{V} \equiv \tau_m(\vec{z})\dot{V} = -V + V_R(\vec{z}), \qquad (7)$$

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$$g_{\text{tot}}(\vec{z}) \equiv g_L + g_s + \sum_{k=E,I}(g_{k,0} + z_k\sigma_k)^+, \qquad (8)$$

$$V_R(\vec{z}) \equiv \frac{g_L V_L + g_s V_s}{g_{\text{tot}}(\vec{z})} + \sum_{k=E,I} V_k \frac{(g_{k,0} + z_k\sigma_k)^+}{g_{\text{tot}}(\vec{z})}, \qquad (9)$$

where $g_{\text{tot}}(\vec{z})$ is the time dependent total conductance and $V_R(\vec{z})$ is the effective reversal potential. Equation (7) reveals that the voltage evolves with an effective membrane time constant $\tau_m(\vec{z}) = C_m/g_{\text{tot}}(\vec{z})$. Since typically $\sigma_k/g_{k,0} < 1$ (see, e.g., [6]), the mean values of $g_{\text{tot}}(\vec{z})$ and $V_R(\vec{z})$ can be computed as if the rectifying functions in Eqs. (8) and (9) were not present:

$$g_{\text{tot}} = g_L + g_s + g_{E,0} + g_{I,0} \qquad (10)$$

$$V_R = g_{\text{tot}}^{-1}(g_L V_L + g_s V_s + g_{E,0} V_E + g_{I,0} V_I). \qquad (11)$$

Then the mean value of the membrane time constant is $\tau_m \sim C_m/g_{\text{tot}}$. As we said above, τ_m becomes quite small in the presence of intensive synaptic activity.

Our aim is to understand the properties of a large population of independent neurons, each receiving a common stimulus I_s and an independent realization of background activity. We describe a stationary population by the joint probability density $P(V, \vec{z})$ of having a neuron with potential V and a background fluctuation $\vec{z}$. The stationary density $P(V, \vec{z})$ associated with Eqs. (5) and (7) obeys the Fokker-Planck equation (FPE) [7]

$$\left[\frac{\partial}{\partial V}\left(\frac{V - V_R(\vec{z})}{\tau_m(\vec{z})}\right) + \frac{L_{z,E}}{\tau_E} + \frac{L_{z,I}}{\tau_I}\right]P(V, \vec{z}) = -p(\vec{z})\nu(\vec{z})\delta(V - H), \qquad (12)$$

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

$$\nu(\vec{z}) = \left(\frac{V_R(\vec{z}) - \Theta}{\tau_m(\vec{z})}\right)P(\Theta|\vec{z}). \qquad (13)$$

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

$$\nu_{\text{pop}} = \int_\Omega d\vec{z}p(\vec{z})\nu(\vec{z}). \qquad (14)$$

Since in a HCS τ_m can be shorter than the synaptic time constants, we look for an approximation of $P(V, \vec{z})$ and $\nu(\vec{z})$ valid in the limit of large τ_k. As τ_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 τ_k. Therefore, we expand both the probability density and the instantaneous firing rate as $P(V, \vec{z}) = P_0(V, \vec{z}) + O(1/\tau_k)$ and $\nu(\vec{z}) = \nu_0(\vec{z}) + O(1/\tau_k)$, obtaining the zeroth order of Eq. (12):

$$\frac{\partial}{\partial V}\left(\frac{V - V_R(\vec{z})}{\tau_m(\vec{z})}\right)P_0(V, \vec{z}) = -p(\vec{z})\nu_0(\vec{z})\delta(V - H). \qquad (15)$$

This expansion corresponds to an *adiabatic approximation* where the voltage state of the neurons is computed exactly at a fixed level $\vec{z}$ 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

$$P_0(V, \vec{z}) = \left[\frac{\tau_m(\vec{z})\nu_0(\vec{z})\mathcal{H}(V - H)}{V_R(\vec{z}) - V} + \delta(V - V_R(\vec{z}))\right]p(\vec{z}), \qquad (16)$$

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

$$\nu_0^{-1}(\vec{z}) = \tau_m(\vec{z})\log\left(\frac{V_R(\vec{z}) - H}{V_R(\vec{z}) - \Theta}\right) \qquad (17)$$

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

The joint distribution $P_0(V, \vec{z})$ [Eq. (16)] has two terms, originated from different subpopulations. Neurons characterized by a conductance fluctuation $\vec{z}$ such that $V_R(\vec{z}) \geq \Theta$ contribute only to the first term. These neurons are *active*, fire with an instantaneous rate $\nu_0(\vec{z})$, 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 $V_R(\vec{z}) < \Theta$ contribute only to the second term. These are *inactive* and their membrane potential is clamped at $V_R(\vec{z})$. The distribution of membrane potentials across the total population, $P_0(V)$, is obtained by integration of $P_0(V, \vec{z})$ over $\vec{z}$.

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 $\vec{z}$ of either the first or the second term in Eq. (16), respectively. The first term in $P_0(V, \vec{z})$ becomes important when the population spends most of the time firing. This corresponds to a population in the suprathreshold regime
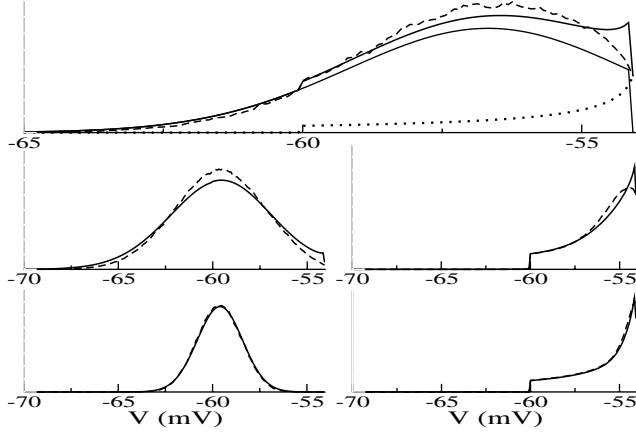
FIG. 1. Membrane potential distribution. The analytical re-
sults, $P_0(V)$, (full thick lines) are compared with the simulated
distributions (dashed lines). Top: relatively short synaptic time
constants, $\tau_{E(I)} = 10$ ms, in a subthreshold condition with $g_s =$
30 nS, $V_s = -60$ mV (giving $V_R = -56.7$ mV) and $\sigma_E =$
3.95 nS, $\sigma_I = 5.59$ nS. The contributions from the active (thin
line) and the inactive (dotted line) subpopulations are also
shown. Middle: as before but in two different conditions: sub-
threshold with $g_s = 25$ nS, $V_s = -72$ mV (left, $V_R =$
-59.6 mV) and suprathreshold with $g_s = 37.5$ nS, $V_s =$
-48 mV (right, $V_R = -52.8$ mV). Bottom: same as the middle
graphs but for longer synaptic time constants, $\tau_{E(I)} = 50$ ms.
Besides $\sigma_E = 1.77$ nS, $\sigma_I = 2.5$ nS. In this case the prediction
is much better and the distributions become narrower. The other
parameters are: $C_m = 0.25$ nF, $g_L = 12.5$ nS, $g_{E,0} = 20$ nS,
$g_{I,0} = 40$ nS, $\Theta = -54$ mV, $H = -60$ mV, $V_L = -65$ mV,
$V_E = 0$ mV, and $V_I = -80$ mV. With these values $\tau_m \sim 3$ ms.

$(V_R > \Theta)$, in which the distribution of V is close to the
threshold potential (right curves). In contrast, when the
population is in the subthreshold regime $(V_R < \Theta)$, the
voltage fluctuates around the effective reversal potential
for long periods before any neuron fires. Now the second
term in Eq. (16) gives the largest contribution (left curves).
Predictions are good except very close to the threshold,
where the adiabatic approach predicts a sharp edge which
is absent in the simulations. However, the predicted value
at $V = \Theta$ is accurate.

The population rate is obtained from Eqs. (6), (14), and
(17),

$$\nu_{\text{pop}} = \int_\Omega \frac{d\vec{z}}{2\pi} e^{-|z|^2/2} \nu_0(\vec{z}). \qquad (18)$$

This expression can be understood qualitatively: since in
the HCS the synapses have a slower dynamics than the
membrane, for any given $\vec{z}$ the firing probability takes the
value $\nu_0(\vec{z})$ 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 τ_m are
present, provided that there is at least one slow synaptic
type. Now, while the slow synapses produce the required
slow fluctuation $\vec{z}$, the membrane dynamics reaches its
stationary state *in the presence of the fast noise* of variance

σ_f, producing spikes with firing probability density
$\nu_0(\vec{z}, \sigma_f)$ (e.g., the one given in [5]). We analytically
checked that Eq. (18) is still valid by just replacing the
instantaneous rate $\nu_0(\vec{z})$ given in Eq. (17) by this $\nu_0(\vec{z}, \sigma_f)$.
Because of the fast noise, the integration domain Ω is
simpler: all values of $\vec{z}$ may give some contribution. If
the fast noise is weak, $\nu_0(\vec{z}, \sigma_f) \sim \nu_0(\vec{z})$, 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* $V_R(\vec{z}) \geq \Theta$, it be-
haves as a detector of fluctuations $\vec{z}$ satisfying this condi-
tion. This property is also present in neurons with synapses
described as simple slow filters [8]. Although Eq. (18) can
be used to compute ν_{pop}, we will now derive a simpler
equation. Let us define u and v as linear combinations of z_E
and z_I,

$$u = -\gamma^{-1}[\sigma_E(\Theta - V_E)z_E + \sigma_I(\Theta - V_I)z_I]$$
$$v = \gamma^{-1}[\sigma_I(\Theta - V_I)z_E - \sigma_E(\Theta - V_E)z_I] \qquad (19)$$
$$\gamma^2 = \sum_{k=E,I} \sigma_k^2(\Theta - V_k)^2.$$

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

$$\nu_{\text{pop}} = \int_{u_{\min}}^\infty \frac{du}{\sqrt{2\pi}} e^{-u^2/2} \nu_0(u), \qquad (20)$$

where $\nu_0^{-1}(u) = \tau_{\text{eff}}(u) \log[(u - u_H)/(u - u_{\min})]$, $u_H =$
$g_{\text{tot}}(H - V_R)/\gamma_H$, $\tau_{\text{eff}}^{-1}(u) = g_{\text{tot}}/C_m - u\sum_{k=E,I}\sigma_k^2(\Theta -$
$V_k)/C_m\gamma$, and $\gamma_H = \gamma^{-1}\sum_{k=E,I}\sigma_k^2(\Theta - V_k)(H - V_k)$.
In Fig. 2 the population firing rate and the coefficient of
variation (CV) of the inter-spikes-intervals (ISI's) are plot-
ted 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 τ_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
$O(\tau_k)$ [this is also true for u, see Eqs. (5) and (19)], neurons
make transitions between the active and inactive subpopu-
lations. However, in the stationary regime, the fraction of
neurons firing at a given instantaneous rate ν remains con-
stant. We then proceed to evaluate the probability density
$f(\nu)$ of having a neuron with firing probability density ν.
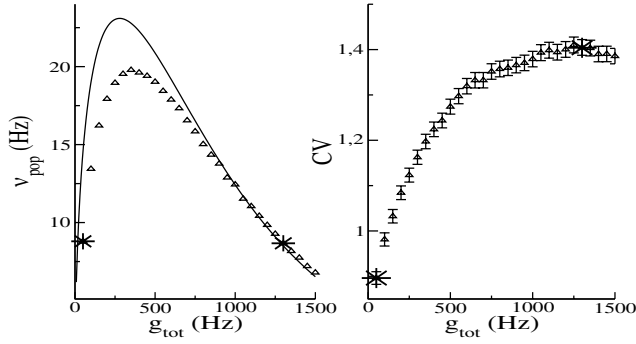Since $f(\nu)d\nu = p(u)du$, with u normally distributed,

FIG. 2. Population firing rate and *CV* as a function of g_{tot}. Input noises are changed as $\sigma_E^2 = 6.25 \times 10^{-4} C_m g_{tot}/\tau_E$, $\sigma_I^2 = 125 \times 10^{-4} C_m g_{tot}/\tau_I$, and $V_R = -55.7$ mV remains fixed. Besides $\tau_E = 3$ ms, $\tau_I = 10.5$ ms, $V_I = -70$ mV, and the other parameters are as in Fig. 1. Triangles are the results from simulations and full curves the prediction of Eq. (18). Asterisks in the left graph correspond to a population with low conductance (left) and another with high conductance (right) firing with approximately the same rate. Asterisks in the right graph indicate their *CV*'s.

$$f(\nu) = \left| \frac{du(\nu)}{d\nu} \right| \frac{e^{-u(\nu)^2/2}}{\sqrt{2\pi}} + \delta(\nu) \int_{-\infty}^{u_{min}} \frac{ds}{\sqrt{2\pi}} e^{-s^2/2},$$

where $u(\nu)$ is the inverse of $\nu_0(u)$. Figure 3 shows that this distribution is *bimodal*. Here the population is in the sub-threshold regime ($V_R < \Theta$) and then a large fraction of neurons is inactive. This is because in the subthreshold regime u_{min} is positive and in the HCS it is large (then $u_{min} > 1$), so that for most neurons $u < u_{min}$ and they stay silent. This subpopulation is represented with a vertical bar at $\nu = 0$. However, there is a small fraction of neurons having high probability of firing (those with $u > u_{min}$, i.e., $V_R(\vec{z}) > \Theta$). As g_{tot} increases, keeping the input variances fixed, the right peak becomes lower and shifts to higher instantaneous rates (data not shown).
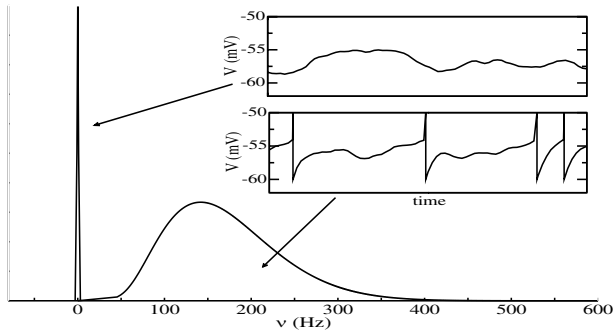

FIG. 3. Distribution of firing probability densities across a population of neurons in the HCS. The example shown is in the subthreshold regime. Although most neurons are silent (vertical bar) a small subpopulation fires (smooth curve). The probability of a neuron being in the latter is 0.05. The membrane potentials of an inactive (top inset) and of an active (bottom inset) neuron are plotted for 60 ms (simulations). Parameters are as in the top panel of Fig. 1 except $\sigma_E = 2.5$ nS, $\sigma_I = 3.95$ nS.

We computed an estimator ν_{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, $f'(\nu_{est})$, 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, $f'(\nu_{est})$ 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 τ_m lies between the fast *AMPA* (excitatory) and the slower *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 *GABA_A*. The same is true if the noise is mainly produced by *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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