Role of calcium and noise in the persistent activity of an isolated neuron

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The activity of an isolated and auto-connected neuron is studied using Hodgkin–Huxley and Integrate-and-Fire frameworks. Main ingredients of the modeling are the auto-stimulating autaptic current observed in experiments, with a spontaneous synaptic liberation noise and a calcium–dependent negative feedback mechanism. The distributions of inter-spikes intervals and burst durations are analytically calculated, and show a good agreement with experimental data.

Understanding the mechanisms responsible for persistent activity and rhythm settling is of central importance in neuroscience. The persistence of the activity is the neuronal basis of the working memory [1] and brains rhythms ranging from about 0.1 to 200 Hz have been recorded in sleep, waking and pathological states [2]. Such behaviors are usually network properties; for instance oscillations are possibly built on the existence of different e.g. inhibitory and excitatory populations of neurons [3]. From a theoretical point of view, the large number of neurons in networks allows the use of self-consistent (mean-field) methods to determine properties as the average spike emission frequency [4, 5, 6, 7, 8]. It was in particular found that a basis for persistent activity (with firing rate $\sim 10 - 50$ Hz) is the ability of NMDA synaptic channels to integrate afferent inputs with a slow decay time constant ($\sim 0.1$ s) [9].

Interestingly, persistence and rhythm settling have also been experimentally observed in systems made of an isolated and auto-connected excitatory neuron (autapse) [9]. Autapse are produced in vitro by grown excitatory neurons, extracted from rat embryos hippocampal, on coverslips [9, 10, 11]. Neurons normally develop up to 5 weeks and establish connections with themselves when no other neuron is nearby. The number of auto-connections increases with the age, as sketched in Fig. 1. Patch pipettes allow both electrical recording of the neuronal activity and current injection to trigger spikes. After a spike has been triggered, more than 2 week old autapses carry on spiking in a whole burst of activity. Records show that both the time interval between successive spikes (ISI) and the duration of the burst (BD) fluctuate. Surprisingly, while the number of auto-connections increase with the age, the average spike frequency decreases (around 20, 5, 1 Hz for 2, 3, 4 week neurons respectively), see Fig. 1.

The neuron therefore exhibits a negative rate-control feedback mechanism preventing runaway excitations due to the strong, and growing with the age, positive auto-stimulating current. All those experimental results are reported in [9].

This letter presents a theoretical study allowing a quantitative interpretation of the autapse activity. Persistence is due to the interplay of two currents evidenced in experiments [9]: a small and slow postsynaptic component and a random spontaneous synaptic liberation. To model rhythm settling, a calcium dependent negative feedback is introduced. This feedback is at the origin of spike frequency adaptation under an external current, previously modeled [12, 13] and experimentally observed in the autaptic system [11]. ISI and BD distributions are analytically calculated using an Integrate–and–Fire (IF) model, and compared to experimental data and numerical predictions from a detailed Hodgkin-Huxley (HH) model.

Currents in the autaptic system are represented in Fig. 2. Pre-synaptic (spike) currents are introduced in HH through standard Sodium and Potassium gating variables [14, 15], their modeling in IF is discussed below. The experimental characterization of the post-synaptic current [9] has evidenced three auto-stimulating components that follow the spike (Fig. 2):

1. A large amplitude excitatory AMPA component, $I_{AMPA}$, entering just (5 ms) after the spike, and rapidly
decaying. Its amplitude considerably increases with the age of the neuron, due to the growing number of connections (Fig. 1). The AMPA current is modeled, in HH, through an effective exponentially decreasing conductance \( \mathcal{I}_A^{\text{AMP}} \). We stress that the AMPA current arrival falls within the neuron refractory period and thus cannot by itself trigger a new spike; it however leads to a membrane potential depolarization (up to 0 mV), giving a bump in the flank of the spike in voltage records \( \mathcal{V}_s \).

The AMPA depolarization has two consequences. It first slows down Na and K gating variable resets, increasing the refractory period. Secondly, it allows more calcium to enter the cell via voltage-gated channels, as soon as membrane potential exceeds -20 mV. In IF, AMPA, Na and K currents are altogether accounted for by the calcium \( \mathcal{I}_{Ca}^{\text{AMP}} \) entering at each spike, and the refractory period \( t_r \). These two parameters (which depend on the age of the autapse) and the threshold \( \theta \) for spike firing are determined from the numerical analysis of HH \( \mathcal{I}_A, \) see Fig. 2 and [13].

2. A small amplitude and slow decaying component, \( \mathcal{I}_D \), due to NMDA and ICAN conductances \( \mathcal{I}_D \). \( \mathcal{I}_D \) depolarizes the membrane potential \( \mathcal{V} \) during a burst to \( \sim -55 \) mV; after the burst halts, \( \mathcal{V} \) decays to the rest value \( \mathcal{V}_l = -60 \) mV with a time constant \( t_D \) ranging from 300 ms in young cells (2 weeks) to 1 s in mature cells (3 and 4 weeks). In both HH and IF, \( \mathcal{I}_D \) is modeled as an exponentially decaying current, \( \mathcal{I}_D(t) = \mathcal{I}_D^0 e^{-(t-t_0)/t_D} \), released with a delay \( \delta t = 5 \) ms after the spike occurring at time \( t_i \); the amplitude is set to \( \mathcal{I}_D^0 = 2 \) mA/cm\(^2\), and corresponds to a depolarization of the membrane potential of 5 mV.

3. A spontaneous and random synaptic release, called miniatures, \( \mathcal{I}_S = g_s \mathcal{V} s(t) \). Both amplitude and frequency of the miniatures \( s(t) \) are stochastic \( \mathcal{I}_S \). The time interval between miniatures during a burst has been fixed to its average value \( \delta s = 20 \) and 10 ms for 2-3 and 4 week neurons respectively. \( \delta s \) increases to its (much larger) rest value \( \sim 0.1 \) s in about 5 s after the end of the burst. Release times are hence discrete and multiple of \( \delta s \), which makes the IF model mathematically tractable (taking into account the stochasticity in times between miniatures does not significantly affect the outcome \( \mathcal{I}_A \)). The distribution \( P \) of the released amplitude \( \sigma \) is Poissonian; the mean \( m \) and the conductance \( g_s \) are fitted from experiments \( \mathcal{P}_s \), and given in caption of Fig. 3. After release at time \( i \times \delta s \), the miniature exponentially decays, \( s(t) = (s^- + \sigma(i)) e^{-(t-i \delta s)/t_s} \) with \( t_s = 5 \) ms (\( < \delta s \)) from experiments. Parameter \( s^- = m/(e^{\delta s/t_s} - 1) \) is the average residual amplitude before the release.

In addition, an inhibitory feedback due to the presence of a Calcium–dependent After Hyperpolarizing current, \( \mathcal{I}_{AHP} = g_{AHP} \frac{Ca}{k_{AHP}} (\mathcal{V} - \mathcal{V}_K) \), is introduced. Such a component is modeled as in \( \mathcal{I}_{AHP} \) for HH and \( \mathcal{I}_{AHP} \) for IF. Parameters values are \( g_{AHP} = 5 \) mS/cm\(^2\), \( \mathcal{V}_K = -80 \) mV,

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\begin{align*}
\frac{dV}{dt} &= -I_l - \mathcal{I}_{AHP}(Ca) + \mathcal{I}_D - \mathcal{I}_S \quad (1) \\
\frac{dCa}{dt} &= Ca^{\text{sp}} \sum_{n} \delta(t-t_n) - \frac{Ca}{t_{Ca}} \quad (2)
\end{align*}
\]

where \( I_l = g_l (\mathcal{V} - \mathcal{V}_l) \) is the leak current, \( C = 1 \) mF/cm\(^2\).
FIG. 4: From top to down, 2, 3 & 4 week neurons. Left: Calcium levels vs. time during a burst for random –HH, numerical, full– and fixed amplitude –IF; theory, circles– distributions of calcium. Jumps coincide with spikes. Right: IF –theory, full line– and fixed amplitude –IF, theory, circles–. Calcium levels vs. time during a burst for random –HH, numerical, full– and fixed amplitude –IF; theory, circles– distributions of calcium.
nalize $T$ with the result shown in Fig. 3. The ISI distribution can be obtained from the matrix product of $T(i)(Ca)$ and $Q$, and is shown in Fig. 5. It is very peaked around 0.05 (EX) - 0.06 (IF) s for 2 week cells, and spread out for 3 and 4 week neurons, with median 0.2, 0.75 s, respectively, in good agreement with experiments. To calculate the BD distribution, we define the generating function for the probability of an interval $i$ between spikes, $G(x) = \sum Q(i)x^i$. The coefficient of $x^k$ in $G(x)^n$, denoted by $[x^k]G(x)^n$ is the probability that a burst has duration $k\delta_s$. Summing over $n$, we get the probability that a burst has duration $k\delta_s$, $[x^k]G(x)/(1 - G(x))$. The resulting BD distribution is shown in Fig 4; it decays as $e^{-k/k_0}$ where $k_0$ is the root of $G(e^{x/k_0}) = 1$. The agreement with experiments is good, even if comparison suffers from limited data (9, 13, 11 bursts for 2, 3, 4 weeks); it is excellent with HH simulation, which makes the analytical study of IF quite attractive despite the approximations done (discretization of time).

In conclusion, this letter proposes a possible mechanism that accounts for the persistence of activity in an isolated autapse. The slow current $I_D$ sets the neuron in a depolarized 'up' state, also observed in various oscillatory networks [3] where it results from e.g. afferent inputs from other neurons. For 2 week neurons this up state can, by itself, sustain activity while, for 3 and 4 week, activity requires noisy synaptic liberation. Noise is at the same time responsible for persistent dynamics, robust with respect to changes of parameters [14], and the finite duration of bursts. The noise-driven mechanism for burst halting presented here differs from mechanisms based on a slow activity dependent depression [3] (either due to a modulation of cellular excitability, or to synaptic depletion [20]), and is supported by the observed large variability in burst durations. In addition, calcium–dependent spike frequency adaptation can explain the observed pattern of activity as the increase of ISI with the age. Finally, it would be interesting to extend the present study to the case of a network composed of a small number of similar neurons for which experimental data are available.

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[15] Na and K dynamics parameters are borrowed from [12], with temperature constant $\Phi_m = 1, \Phi_p = 0.3$ and conductances $\gamma_{NA} = 3 m S/cm^2, \gamma_K = 1 m S/cm^2$. The amplitude and time constant for the AMPA component are fixed for 2, 3, 4 weeks to 0.1, 3, 20 in mS/cm$^2$ and 10, 20, 30ms respectively [17]. The refractory period in the IF model is $t_r = 10, 16, 85$ ms for 2, 3, 4 weeks.
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[17] Mean value and standard deviation of miniatures conductance in active neurons are $g = 0.45$ nS, $\sigma = 0.2$ nS respectively [11]. Fitting data with a Poissonian distribution [17] and writing $g = g_0 m$, we obtain $m = g^2/\sigma^2 = 5$, $g_0 = \sigma^2/g = .008$ nS, hence a conductance $g_s = g_0/A = 0.002 mS/cm^2$ for a cell surface $A = 4 \times 10^{-6} cm^2$.
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[19] Even if a stationary solution exists, it may be not possible to reach for dynamical reasons e.g. for young neurons with special choices of parameters [17].
[20] Synaptic depletion has been neglected here. Note that experimentally observed autaptic currents are not affected by repeatedly triggered spikes, except at very high stim-
ulation frequency ≃ 10 – 20Hz.