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Non-monotonic Current-to-Rate Response Function in a novel Integrate-and-Fire Model Neuron

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Abstract. A novel integrate-and-fire model neuron is proposed to account for a non-monotonic *f-I* response function, as experimentally observed. As opposed to classical forms of adaptation, the present integrate-and-fire model the spike-emission process incorporates a state - dependent inactivation that makes the probability of emitting a spike decreasing as a function of the mean depolarization level instead of the mean firing rate.

1 Introduction

Recent experimental evidence indicates that, at relatively high firing rates (*e.g.* 50 Hz), the *in vitro* response of neocortical neurons to the injection of a noisy current, emulating the heavy barrage of *in vivo* presynaptic bombardment (see e.g. [1, 2]), shows a non-stationary behavior. In particular, such neurons cannot sustain high rates for a prolonged time (*e.g.* 30 s), ultimately reducing their spiking frequency or stopping firing [1]. Furthermore, in *in vitro* disinhibited cultured networks of dissociated spinal cord neurons a similar phenomenon seems to characterize the intrinsic firing properties of a specific neuronal subclass (see [3]), whose activity decreases or completely shuts down as the excitatory afferent synaptic current from the network becomes large. Interestingly, the last phenomenon has been hypothesized to be involved in determining and shaping the slow spontaneous rhythmic collective activity, characterizing such an *in vitro* neurobiological system at the network level. Moreover, previous theoretical studies also pointed out that similar single-neuron response behaviors might substantially improve performances in attractor neural networks [4].

Although the underlying detailed sub-cellular mechanisms are not yet fully understood, and it is still not clear if these are *in vitro* artifacts or if they play any *in vivo* physiological role at the network level, the described phenomena result in a steady-state non-monotonic *f-I* response function (RF) for individual neurons.

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Such an excitability modulation should not be regarded as a form of classical frequency-dependent adaptation, by which neurons are known to accommodate their responses to transient as well as sustained stimulations. Actually, it is widely accepted that such class of adapting behaviors relies on the accumulation of intracellular ion-species (*e.g.* calcium ions), whose concentration reflects on a first approximation the mean firing rate, and can only account for a saturating RF and not for a non-monotonic relationship [5].
A feasible alternative interpretation may trace such an activity-dependent reduction of excitability back to the biophysical bases of action potentials generation. Specifically, the progressive voltage-dependent reduction of recovery from inactivation in voltage-dependent membrane inward currents (*i.e.* such as the fast-inactivating TTX-sensitive sodium currents) might play a substantial role in decreasing the output spike-rate and ultimately affecting the generation of further action potentials, as the total number of *non-inactive* channels becomes small. Such a working hypothesis can be tested in the framework set by a conductance-based mathematical description of neuronal excitability, incorporating for instance only Hodgkin-Huxley-like fast-inactivating sodium currents and delayed-rectifier potassium currents. Although under noisy current injection such a model qualitatively reproduces a non-monotonic dependence (see Fig 1), an extensive analysis performed at the network level is not possible, given the complexity of the model and the consequent heavy computational loads of large-scale simulations.
In order to investigate at the network level the relevance and the impact of a non-monotonic response function, in the present contribution we propose a novel integrate-and-fire (IF) model neuron, reproducing the described phenomena and well-suited to undergo a full statistical analysis.

2 The model

2.1 *Integrate-and-may-fire* (IMF) model neuron: uncertain spike emission

Below the excitability threshold θ, the behavior of the novel IMF neuron schematically resembles a linear integrator of the afferent current $I(t)$, as for the linear integrate-and-fire model (LIF) [6, 1]. As a consequence, the subthreshold membrane depolarization $V(t)$ evolves in time according to the following differential equation:

$$\frac{dV(t)}{dt} = -\beta + I(t) \tag{1}$$

where β is a constant decay ($\beta > 0$) that, in the absence of afferent currents, drives the depolarization to the resting potential $V_{rest} = 0$. The resting potential is a reflecting barrier, i.e. the depolarization cannot be driven below zero [6]. Compared to conventional IF dynamics described in the literature, when V crosses the threshold θ, the IMF neuron does not always emit a spike. In other words, for the IMF neuron the spike emission process has been assumed

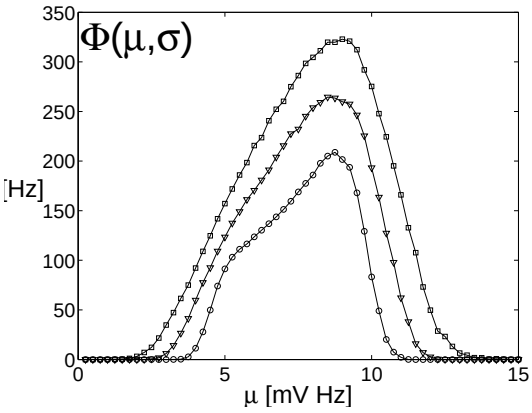

Fig. 1. Conductance-based model neuron: the mean firing rates, assessed across 60 s of simulation time after discarding a transient of 1 s, have been plotted versus the mean injected current μ, for increasing values of the amplitude of its fluctuations σ (circles, triangles and squares) in a Hodgkin-Huxley-like model. Spikes were detected by a positive threshold-crossing criterium either in the amplitude vs time or in the slope vs time domains: for large input currents, such a criterium let us discriminate between large fluctuations of the membrane potential and spikes.

to be not fully determined by the dynamics of the membrane depolarization alone but to depend on additional intrinsic biophysical mechanisms, not explicitly modeled. More precisely, if $V(t_0) = \theta$ the emission of a spike at t_0 is an event occurring with an activity-dependent probability $q \leq 1$. After the spike emission, V is clamped to the value H_1 ($0 < H_1 < \theta$), for an absolute refractory time τ_{arp}, after which the current integration starts again. However, each time the excitability threshold θ is crossed and no spike has been generated (*i.e.* an event with probability $1 - q$), V is reset to H_2 ($0 < H_1 < H_2 < \theta$) and no refractoriness entered.

In order for the IMF neuron to have a non-monotonic RF, we made the additional assumption that q is a decreasing function of a slow voltage-dependent variable w, reminiscent of the sigmoidal voltage-dependence of the fast inactivation state variables that characterize conductance-based model neurons:

$$q = \left(1 + e^{\frac{(w - w_o)}{\sigma_w}}\right)^{-1} \tag{2}$$

where w evolves by eq. (3) below, corresponding on a first approximation to the average transmembrane electric field experienced by individual ion channels and affecting their population-level activation and inactivation.

$$\tau_w \frac{dw(t)}{dt} = \frac{V(t)}{\theta} - w \tag{3}$$

We note that $0 < w < 1$ and that, in the limit $\tau_w \to +\infty$, it approximates the expected normalized depolarization $\langle V \rangle / \theta$, providing a negative-feedback on

the spike-emission mechanisms that depends on the statistics of the membrane voltage.

2.2 The afferent current

We assume that at any time t, the overall afferent current $I(t)$ can be approximated by a Gauss distributed variable [7] with mean $\mu_I(t)$ and variance $\sigma_I^2(t)$ in unit time, so that, from eq. (1), the depolarization is a stochastic process obeying:

$$dV = \mu(t)dt + \sigma_I(t)z(t)\sqrt{dt} \tag{4}$$

where $\mu(t) \equiv -\beta + \mu_I(t)$, and $z(t)$ represents a random Gauss distributed process with $E[z] = 0$ and $E[z(t)z(t')] = \delta(t - t')$. For the sake of simplicity, we neglect that realistic synaptic dynamics introduce time correlations in the resulting afferent current $I(t)$.

3 Results

3.1 IMF steady-state response function

Taking advantage of the simplified mathematical expression of Eq. 1, we analytically characterized the statistical properties of the IMF model neuron under a noisy current injection, first assuming q to be a constant. For comparison with the numerical simulations, we included the dependence of q on w, by solving self-consistent equations at the steady-state, accounting for the behavior of the full model. We note that an equation of motion can be derived for the probability density that at time t the neuron has a depolarization $V = v$, under the diffusion approximation (see e.g. [8]):

$$\frac{\partial p}{\partial t} = -\frac{\partial}{\partial v}\left(\mu p - \frac{1}{2}\sigma^2 \frac{\partial p}{\partial v}\right) \tag{5}$$

This is the Fokker-Planck equation for $V(t)$ and it must be complemented by appropriate boundary conditions at $v = 0$, $v = \theta$, $v = H_1$ and $v = H_2$ in the case of the IMF neuron (see [6, 8]). At the steady-state, eq. 5 turns into a second-order ordinary linear differential equation and it gives rise to closed-form expressions for the stationary RF $\Phi_{\mu,\sigma,q}$ and the steady-state expected value of the membrane voltage $\langle V \rangle_{\mu,\sigma,q}$.

$$\Phi_q(\mu, \sigma) = q\ \nu \tag{6}$$

$$\langle V \rangle_{\mu,\sigma,q} = \frac{1}{2\mu}\left[\nu\left(\theta^2 - \overline{H^2}\right) + \sigma^2\left(q\ \nu\ \tau_{arp} - 1\right)\right] + q\ \nu\tau_{arp}\ H_1 \tag{7}$$

with ν given by:

$$\nu = \left[q\tau_{arp} + \frac{1}{\mu\lambda}\left(e^{-\lambda\theta} - \overline{e^{-\lambda H}}\right) + \frac{\left(\theta - \overline{H}\right)}{\mu}\right]^{-1} \tag{8}$$

and $\lambda = \frac{2\mu}{\sigma^2}$, $\overline{e^{-\lambda H}} = qe^{-\lambda H_1} + (1-q)e^{-\lambda H_2}$, $\overline{H} = qH_1 + (1-q)H_2$ and $\overline{H^2} = qH_1^2 + (1-q)H_2^2$.

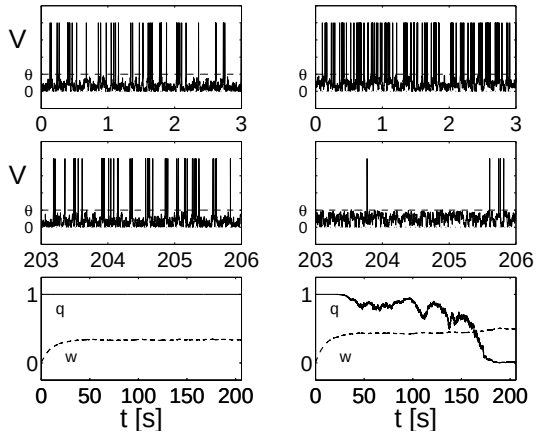

Fig. 2. Transient temporal evolution of the depolarization V of the IMF neuron: although at low firing rates (left panels, $\mu = -10\theta mVHz$, $\sigma^2 = 15\theta^2 mV^2 Hz$) a stationary behavior is maintained indefinitely, higher rates are only transiently sustained (right panels, $\mu = 10\theta mVHz$, $\sigma^2 = 15\theta^2 mV^2 Hz$) as the IMF ultimately relaxes to a much lower firing regime; bottom panels show the temporal evolution of q (continuous line) and w (dashed line) in the two situations. The characteristic time scales depend on the choice of τ_w (i.e. $10s$ in the reported simulations).

3.2 Numerical results vs simulations

We have simulated the IMF model neuron (Eqs. 1, 2 and 3) to evaluate its RF for different values of μ and σ. Firing rates above a certain value (set by w_o) cannot be sustained for periods larger than a few τ_w, after which the rate decreases or the firing completely shuts down (see Fig. 2). Fig. 3 shows the agreement between theory (self-consistent solutions of Eqs. 2, 6, 7 and 8, replacing w with $\langle V \rangle / \theta$) and simulations. The decrease in the agreement for large μ is due to the decrease in accuracy while approximating w (*i.e.* the temporal average over a time window $\sim \tau_w$ of V/θ) with the expected value $\langle V \rangle / \theta$. Furthermore, for large σ and large firing rates, the agreement between theory and simulations slightly decreases, resulting in an underestimation of the simulated firing rates. Such a loss of accuracy is mainly due to the finite numerical integration time step employed in eq. 4, corresponding to a worse numerical approximation of a delta-correlated Gaussian stochastic process.

4 Conclusions

In the present contribution, we have introduced a novel IF model characterized by a non-monotonic *f-I* response function. The spike-emission process is not regarded as relying on the instantaneous temporal evolution of the membrane depolarization alone, but it shows a state-dependent *inactivation*, accounting for the recent evidence that *in vitro* cortical and spinal cord neurons cannot sustain high-frequency regimes for a long time [1, 3]. The statistical steady-state behavior

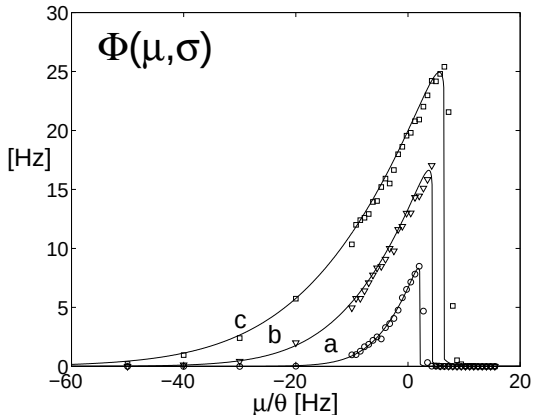

Fig. 3. Current-to-rate response function as predicted by the theory (continuous lines) and numerically simulated, assessing mean-rates across 50 s, after discarding a transient of $7\tau_w$: simulations refers to three increasing values of σ^2 (a: $5\theta^2$ - circles, b: $10\theta^2$ - triangles and c: $15\theta^2$ - squares).

of the depolarization was computed analytically and the agreement between the theory and the simulation of the IMF neuron is excellent, under white noise afferent current injection. Together with its simpler analytical tractability, this makes the IMF neuron an ideal candidate as a realistic reduced point-neuron model to investigate the impact of a non-monotonic transfer function and more complex collective phenomena at the network level.

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