High discharge variability in neurons driven by current noise

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Abstract

Cortical neurons *in vivo* show a highly irregular spontaneous discharge activity, characterized by a gamma statistics and coefficient of variation around unity. Modelling studies showed that this irregularity is a consequence of the high-conductance state caused by the ongoing activity in the cortical network. Here, we investigate to which extend this high discharge variability can be reproduced *in vitro* using current noise injection. In agreement with numerical studies, we found that equalizing the time constant of the noisy input with the membrane time constant may lead to an irregular discharge activity which, however, departs from a gamma statistics.

Key words: cerebral cortex, irregularity, dynamic-clamp, Gamma process

1 Introduction

The spontaneous activity of cortical neurons recorded *in vivo*, as well as the response to a sensory stimulus, is highly irregular [1–3]. This irregularity is quantified by a coefficient of variation (C_V), defined as the ratio between the standard deviation and the mean interspike interval (ISI), close to unity. Another property of spontaneous discharge activity *in vivo* is that the distribution of ISIs follows Gamma statistics, i.e. is both exponentially distributed for large intervals with refractory period for small intervals and independent.

In computational studies of reconstructed cortical neurons it was shown [4] that for spontaneous rates below 50 Hz, a high discharge variability following gamma statistics was always paralleled with a high-conductance state [5]. Moreover, using effective models of synaptic noise, either in form of stochastic conductances or stochastic currents described by random walk processes [6,7], it was found that current noise, in general, leads to a lower C_V compared to conductance noise. However, under specific condition, such as for a large time-constant of the stochastic current, the discharge can be highly irregular (C_V close to 1) but deviates from the gamma distribution.

Here, we investigate to which extend current noise can be used to reproduce the irregular spontaneous discharge of cortical neurons (e.g. [8]). We recorded from regular spiking cortical neurons *in vitro* subject to current and conductance noise, and compared the C_V in both conditions. The discharge variability depended on the noise time constants (see also [9]) and, for current noise, high C_V values were always paralleled by a non-gamma statistics of the ISIs.

2 Methods

Intracellular recordings *in vitro* were performed on slices from ferret occipital cortex. To obtain spontaneous activity, current or conductance noise based on random-walk processes [6,7] was injected into the cell. Injection of conductance noise was performed using the dynamic-clamp technique utilizing a modified version of the NEURON simulation environment ([10]; Le Masson, unpublished). To investigate if the spike trains followed gamma statistics, the ISI histograms (ISIH) were fitted by a gamma distribution $\rho_{ISI}(T) = ar(rT)^q e^{-rT}/q!$, where a, r, and q are parameters and T denotes the lag time. The fitting procedure consisted in finding the parameter set which minimizes the root mean square error. In addition, autocorrelograms of the output spike trains were constructed to evaluate the degree of independence of the ISIs.

Two simplified models of the time-dependent membrane current due to synaptic noise $I_{syn}(t)$ were used: The first was a fluctuating conductance model [6], in which $I_{syn}(t)$ was decomposed into two time-dependent conductances (excitatory $g_e(t)$ and inhibitory $g_i(t)$, with mean g_{e0}, g_{i0}, standard deviation σ_e, σ_i and time constant τ_e, τ_i, respectively), each described by an Ornstein-Uhlenbeck (OU) stochastic process. The second model used was a fluctuating current model, where $I_{syn}(t)$ was directly described by an one-variable OU process with mean I_0, standard deviation σ_I and time constant τ_I.

3 Results

Intracellular recordings were obtained from layer V regular spiking pyramidal cells in the occipital cortical regions. In order to investigate the discharge activity in high-conductance states, we injected conductance noise into the soma using a dynamic-clamp protocol (see Methods). Here, in accordance with

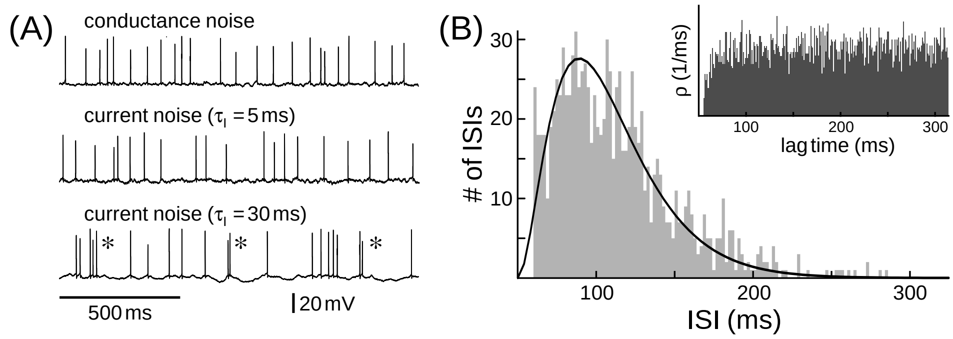

Fig. 1. Discharge activity under current and conductance noise. In the presence of conductance noise, neurons fire highly irregular (A, top; $C_V = 0.7$) in a gamma distributed fashion, characterized by a gamma distributed ISIH (B, black solid; fit: $q = 2$, $a = 1996.5$, $r = 0.051$ ms^{-1}) and flat autocorrelogram (B, inset). In contrast, under current noise the discharge is either more regular (A, middle; $C_V = 0.65$), or irregular due to "burst-like" clustering of spikes (A, bottom; stars; $C_V = 0.78$). Parameters: I_0=0.225 nA, σ_I=0.1 nA, τ_I=2 ms (A, middle), τ_I=30 ms (A, bottom); g_{e0}=g_{i0}=6 nS, σ_e=1 nS, σ_i=2 nS, τ_e=2.72 ms, τ_i=10.49 ms.

numerical studies [4], the neuronal discharge at rates typical for spontaneous activity in the cortex (Fig. 1A, top) had a high C_V ($C_V > 0.7$) and followed a gamma statistics. The discharge was characterized by a gamma-distributed ISIH and flat autocorrelogram (Fig. 1B). To ensure that this result was not a consequence of the experimental procedure but rather a consequence of the high-conductance state created intracellularly by the injected synaptic noise, we analyzed the irregularity of discharge during natural up-states occurring in the cortical slices *in vitro* and lasting a few hundred milliseconds [11]. Also here we found a high irregular discharge activity ($C_V \sim 0.72$) with rates around 20 Hz and gamma statistics (data not shown).

We next addressed the question to which extend the irregular discharge statistics in high-conductance states can be reproduced by injecting current noise into the cell [8]. In particular, we studied the statistics of spontaneous responses for current noise with variable time constant τ_I. In accordance with numerical studies [4], for small τ_I (< 20 ms), the C_V was low around 0.6 (Fig. 2A), and the ISIH was well described by a gamma distribution (Fig. 2B, top). Increasing τ led to an increase in the ISI variability, and for large noise time constants (> 30 ms), the C_V was around 0.8. However, the distribution of ISI and autocorrelograms showed a clear deviation from what is expected from a gamma process (Fig. 2B, middle and bottom). The strong peak at low ISIs indicates the preference to produce "bursts" in response to the driving current, a behaviour which can also be seen in the autocorrelograms. Here, a peak for small lag times suggests that the spikes are statistically not independent.

In modelling studies we reproduced these findings. For membrane time constants typical of low-conductance states ($\sim$ 20 ms), current noise injection led to a rather regular ($C_V < 0.5$) spontaneous discharge at rates between

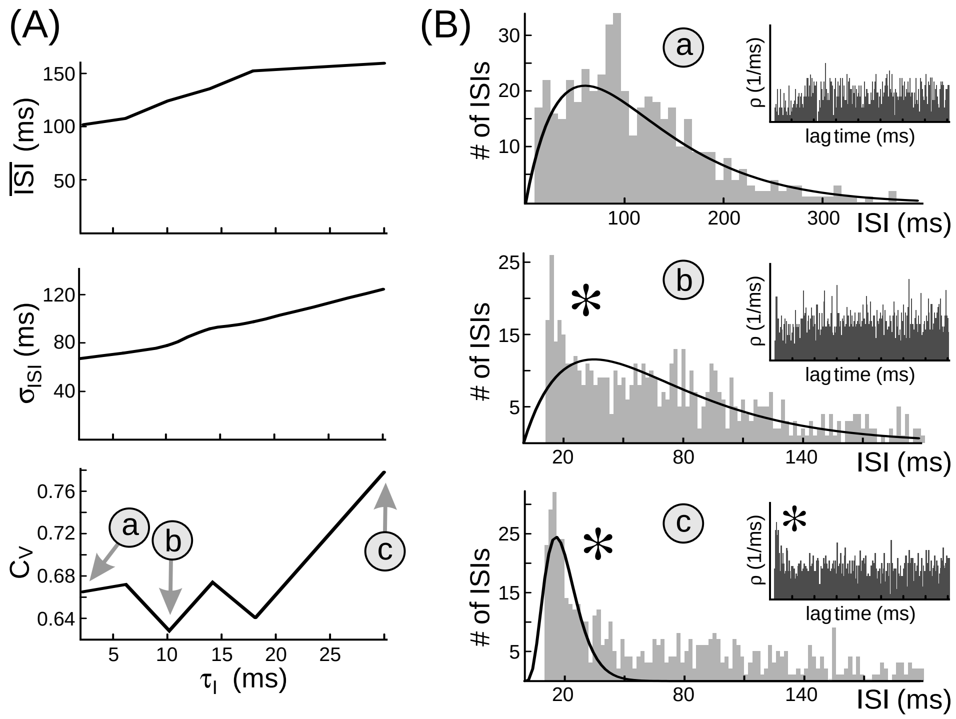

Fig. 2. Discharge statistics for neurons *in vitro* subject to current noise of variable time constant τ_I. A: Mean ISI, ISI standard deviation and C_V as function of τ_I. An increase in τ_I leads to an increase in the C_V (A), but the spike distribution does no longer follow gamma statistics. B: ISI histograms and autocorrelograms (insets) for different τ_I (a: 2 ms; b: 10 ms; c: 30 ms). The ISIHs follow gamma distributions (black solid) only for small τ_I values (low C_V; top), but deviate for larger τ_I values from gamma statistics (middle and bottom). Fits: q=1, a=3786.7, r=0.018 ms^{-1} (A); q=1, a=1108.9, r=0.028ms^{-1} (B); q=3, a=538.3, r=0.188 ms^{-1} (C).

10 and 15 Hz, characterized by gamma statistics (Fig. 3A). An increase in τ_I resulted in an increase in the discharge irregularity, approaching high C_V values when τ_I exceeded the membrane time constant. However, the high discharge irregularity was always paralleled by a strong deviation from a gamma firing statistics: the ISIHs did no longer follow a gamma distribution, and the autocorrelograms showed a pronounced peak at lag times comparable to the membrane time constant (Fig. 3A, right, stars).

When a model cell with leak conductance comparable to the average conductance in high-conductance states was driven with current noise, higher C_V values were obtained (Fig. 3B). Here, a τ_I of the order of the membrane time constant led to C_V values around 1 and a spike pattern with gamma statistics (Fig. 3B, middle). However, for $C_V > 1$ the ISIHs deviated from a gamma distribution, and the autocorrelogram displayed a peak for small lag times, indicating the preference for spike clustering ("burst-like" firing; Fig. 3B, right).

The exploration of this dependence can be done experimentally by combining dynamic-clamp, used here for injecting a constant conductance for altering

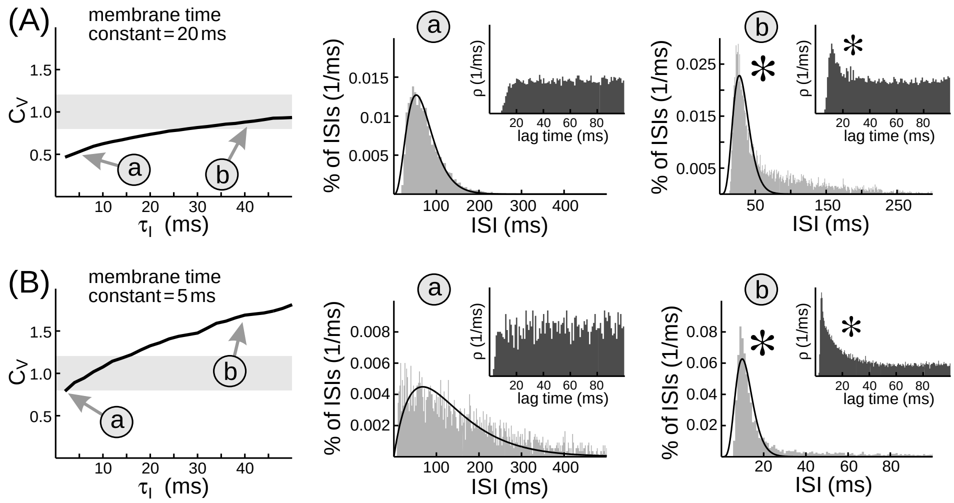

Fig. 3. Dependence of the C_V on the noise time constant τ_I for one-compartment models with large (A) and small (B) membrane time constant driven by current noise (A: I_0=0.75 nA, σ_I=0.2 nA; B: I_0=1 nA, σ_I=1 nA; discharge rate around 15 Hz). The right panels show typical ISIHs (black solid: fitted gamma distribution) and autocorrelograms (insets) at different τ_I values (arrows in left panels).

the membrane time constant, and injection of current noise. Moreover, exploiting the dynamic-clamp protocol for recreating specific high-conductance states *in vitro* [12], the discharge activity in states whose subthreshold intracellular activity resembles that obtained during injection of current noise can be investigated. This will allow to compare the discharge statistics for different synaptic noise models but comparable intracellular states.

4 Conclusions

In contrast to high-conductance states, injecting current noise *in vitro* does not alter the membrane time constant, which typically takes values around 10-30 ms. Such large time constants lead to a severe filtering of higher frequencies in the input signal, accompanied by a decrease in the discharge variability. As we showed, this filtering effect can be reduced by increasing the time constant of the injected current noise. When the noise time constant approaches values comparable to that of the membrane, the cell will effectively respond to the driving current, hence discharge with a higher variability. However, under this condition, the current noise varies slowly, and during depolarizations the cell has time enough to respond with multiple spikes within short time intervals ("burst-like" firing). The resulting ISIH and autocorrelogram indicate that the discharge, although showing a high irregularity, is no longer gamma-distributed. In contrast, the discharge statistics due to conductance noise injected via dynamic-clamp *in vitro* resembles, in a broad parameter range that during natural up-states *in vitro* or spontaneous activity *in vivo*.

In conclusion, high C_V values can be obtained by injection of current noise with a larger time constant, but in this case the gamma statistics of the discharge is lost. It appears that the high-conductance state, caused by the barrage of synaptic inputs stemming from the ongoing activity in the cortical network, is a more natural determinant for the highly variable discharges of cortical neurons. Research supported by CNRS, HFSP and the European Commission (IST-2001-34712).

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