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Multisynaptic activity in a pyramidal neuron model and neural code

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Abstract

The highly irregular firing of mammalian cortical pyramidal neurons is one of the most striking observation of the brain activity. This result affects greatly the discussion on the neural code, i.e. how the brain codes information transmitted along the different cortical stages. In fact it seems to be in favor of one of the two main hypotheses about this issue, named the *rate code*. But the supporters of the contrasting hypothesis, the *temporal code*, consider this evidence inconclusive. We discuss here a leaky integrate-and-fire model of a hippocampal pyramidal neuron intended to be biologically sound to investigate the genesis of the irregular pyramidal firing and to give useful information about the coding problem. To this aim, the complete set of excitatory and inhibitory synapses impinging on such a neuron has been taken into account. The firing activity of the neuron model has been studied by computer simulation both in basic conditions and allowing brief periods of over-stimulation in specific regions of its synaptic constellation. Our results show neuronal firing conditions similar to those observed in experimental investigations on pyramidal cortical neurons. In particular, the variation coefficient (CV) computed from the inter-spike intervals (ISIs) in our simulations for basic conditions is close to the unity as that computed from experimental data. Our simulation shows also different behaviors in firing sequences for different frequencies of stimulation.

Keywords: Pyramidal neuron; Irregular firing; Neural code; Computer simulation; Synaptic constellation

1. Introduction

The information arriving to brain from external and internal environment must bear the minimum ambiguity possible to be meaningful. By looking at the single neuron, it seems clear that the information is encoded in the spiking activity, but not in single spikes. In fact, spikes present in general the same time-course in a single neuron, while differences in firing sequences can be found for different stimuli. Moreover, different neurons can produce different patterns of firing when stimulated by inputs in the appropriate modality. Hence, it holds that the most probable way neurons code information has to be attributed to spike sequences. In peripheral neurons, and mainly in receptors, the relation between spike sequences and stimuli is more evident being the frequency of spikes related to the stimulus intensity by mathematical laws. These neurons, however, show a rather simple behavior since usually they respond to preferred stimuli and have very few inputs. Different is the case of cortical pyramidal neurons, the main population of excitatory neurons of the neocortex, which receive a large number of synaptic inputs, both excitatory and inhibitory, some of them coming from different regions of the neocortex as well as from deep nuclei and have a very complex activity. In this case, how the output is related to the input is hard to clarify, being also the input very difficult to

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observe and describe due to its complexity. One of the most striking result about the activity of cortical pyramidal neurons derives from electrophysiological studies of visual areas in awake brain of macaque monkey. The time sequences of spikes observed in these neurons are so highly irregular to support the idea of a predominant influence of randomness on their genesis (Softky and Koch, 1993; Shadlen and Newsome, 1994, 1995). In fact, a Poisson process (a typical example of stochastic processes) can adequately describe the spike sequences observed in cortical pyramidal neurons. The randomness of the inter-spike intervals (ISIs) seems to imply that information cannot be coded in the temporal pattern of spikes. Hence, it seems that the firing frequency (averaged on appropriate time intervals) can be considered as a good candidate for coding information (Shadlen and Newsome, 1998). This it the base of the *rate* (or *frequency*) *code* view. In such a framework, the neurons are considered as integrate-and-fire devices which integrate all the inputs (excitatory and inhibitory) arriving from dendritic and somatic synapses. The balancing of the effects of all the inputs at the hillock determines the firing of the neuron as well as the ISIs sequence. Vice versa, a more recent hypothesis assumes that the precise spike times in spike trains, or the inter-spike interval patterns, or the times of the first spike (after an event) are the possible bases of the neural code. It is labeled as the *temporal code* hypothesis and is linked to the view of a neuron as a *coincidence detector* (Konig et al., 1996). The main motivation for this view is the assumption that the transmission of information is related to the synchronous activity of local populations of neurons and, consequently, the detection of coincidences among the inputs is the most prominent aspect of the neuronal function (Abeles, 1982, 1991; DeWeese et al., 2003; Softky, 1995). Some authors considered also the possibility that brain uses not a single coding scheme but a continuum of coding procedures ranging from rate to temporal (Tsodyks and Markram, 1997).

The non-synchronous activity of tens of thousand synapses, placed at different distance from the hillock and producing Post Synaptic Potentials (PSPs) with peak amplitude stochastically distributed, has been considered as an appropriate support on which the neuronal machinery can produce sequences of spikes with stochastically distributed ISIs. A rich investigation field, built on stochastic models of neuronal activity, arose from the early findings (Gerstein and Mandelbrot, 1964; Lansky, 1984; Ricciardi, 1994; Ricciardi and Ventriglia, 1970; Tuckwell, 1975, 1989). Moreover, several attempts by experimental, modeling–computational and mixed experimental–modeling–computational methods, have been carried on to identify the causes of the high irregularity of the firing patterns in pyramidal neurons of cerebral cortex. In some experiments on brain slices, synthetic electrical currents, constructed in a way to simulate the true synaptic activity, have been applied to soma of pyramidal neurons in order to obtain ISIs as irregular as those produced by naturally stimulated neurons (Stevens and Zador, 1998). On the other side, several computational models, with different level of complexity, have been proposed for the same purpose (Softky and Koch, 1993; Shadlen and Newsome, 1994, 1995; Salinas and Sejnowski, 2000; Kuhn et al., 2004; Ventriglia and Di Maio, 2005; Zador, 1998). In some models, the variability of synaptic input has been singled out as the cause of the output variability. In others, the main focus has been given to the dynamic properties of the neuron receiving the stimuli. However, both experimental and computational results still give contradictory interpretations.

The main criticism to the theoretical–computational investigation of the features of the neuronal firing is that the models used to describe pyramidal neuron activity are too simple with respect to the biological *process* they want to simulate and fail to capture relevant information. Stochastic models of integrate-and-fire neuron, for example, reduce to a white noise the effects on membrane potential at the hillock of inputs arriving from synapses of distal dendrites (Di Maio et al., 2004 among many others). In the present paper, we made an attempt to formulate a biophysically realistic model of integrate-and-fire neuron where the contributions of all the synapses to the evolution of membrane potential at the hillock are better considered. To this aim, we have build a geometrical structure of a pyramidal neuron by taking into account the position of all excitatory and inhibitory synapses impinging on such a neuron by using data from literature on hippocampal neurons. In addition, we have used parameters for the description of Excitatory and Inhibitory Post Synaptic Currents (EPSCs and IPSCs) at each synapse, which have been derived from electrophysiological (Forti et al., 1997; Liu et al., 1999; McAllister and Stevens, 2000) and computational data (Ventriglia, 2004; Ventriglia and Di Maio, 2003). The results of several computational experiments, carried out to get information on the causes of the high irregularity of the pyramidal neuron firing and to obtain insights into the nature of the neural code, are discussed here.

2. Model

To study the properties of firing sequences of pyramidal neurons, we constructed a model of neuron by using anatomical information from pyramidal neurons in CA3