A MATHEMATICAL MODEL OF THE COLLECTIVE BEHAVIOUR OF EMBRYONIC CORTICAL NEURONS CULTURED IN VITRO

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Abstract: Coupling planar microelectrode arrays to populations of neurons cultured in vitro allows the researcher to record / stimulate for a long period of time signals from several units in a network. This represents a new framework for experiments expressly dealing with the collective behaviour displayed by networks of neurons under various chemical - physical conditions. The availability of multisite electrophysiological signals recorded under well described experimental conditions offers the opportunity to develop detailed biophysical models of specific networks of neurons. The resulting computer simulations can then be used to interpret the experimental data in terms of collective behaviour and elementary neurocomputational rules.

Introduction

A substantial experimental contribution to the investigations of the auto-organisation properties of the nervous system and the cellular basis of the behaviour (i.e. motor patterns generation and simple forms of learning) is expected to be provided by experimental techniques enabling the reproducible culture of dissociated neurons in vitro, where nerve cells grow and reorganise their neurites and synapses, under highly controlled chemical and physical conditions. Under these perspectives, an unconventional new electrophysiological technique, based on the use of substrate transducers, i.e. arrays of planar microtransducers forming the adhesion surface for the reorganising 2D cell network, was recently developed to deal with such experimental conditions. Such a technique, resulting from the advances of microelectronics and nanotechnologies, is characterised by several advantages over standard intracellular and patch-clamp recordings, related to the possibility of long-term non-invasive monitoring/stimulation of the electrochemical activities of several cells in an independent and simultaneous fashion, appropriately for recording the electrical activity of developing networks of embryonic cortical cultured neurons with a high degree of spatial resolution [1, 2].

Under these perspective, the increasing amount of electrophysiological data collected by means of such arrays of planar microelectrodes lead us to define a mathematical model, describing the behaviour of networks of synaptically connected neurons.

Materials and Methods

Most of mathematical models of membrane excitability, at the subcellular and circuit level, retains the general format originally introduced by Hodgkin and Huxley. Specifically, in our model a single embryonic cultured rat cortical neuron was described by a single-compartment conductance-based model, i.e. the same voltage across membrane for the entire cell was assumed, neglecting the complex geometry of dendritic arborisations and spatially distributed properties of the neuronal membrane.

In order to describe observed electrophysiological properties, such as excitability, adaptation to long-lasting external current stimuli and dependency of some membrane conductance on various ionic concentrations, the total membrane current was represented by the following contributions [3]: the fast sodium current $I_{Na}$, the fast potassium current $I_{K}$, the fast calcium current $I_{Ca}$, the voltage-independent calcium-dependent potassium current, known as after-hyperpolarization current $I_{AHP}$, and the transient outward potassium current $I_{K}$.

Numerical values of maximal conductances, reversal potentials and other parameters of the model were estimated on the basis of published experimental data, provided by measurements in vitro [1, 2, 4].

The total synaptic current due to N independent chemical synapses was modelled introducing time-dependent synaptic conductances, evolving according to a Markov model of the interaction between neurotransmitter molecules and the membrane receptors [5, 6, 7]. Such a choice efficiently describes the occurrence of miniature potentials in post-synaptic neurons and leads to an efficient iterative calculation of the network equations related to synaptic transmission [6, 7]. Such a description for the spontaneous subthreshold activity can be considered a realistic representation of the in vitro condition, where hundreds of synaptic contacts reach each neuron from the surrounding regions.

Results

Results of extensive computer simulations show that the impact of the neurotransmitter spontaneous release, occurring at synapses of each neuron, consists of a net change in the potential, due to capacitive properties of
the membrane, and can generate an endogenous electrical activity. Due to the accumulation of intracellular calcium ions, and to the slow regulatory effects mediated by \( I_{AHP} \) current, periodic - non periodic bursting or tonic oscillations can arise spontaneously in a model neuron that is not an intrinsic (bursting) pace-maker. Because of the intrinsic randomness in generating the spontaneous release events at each synaptic site, loci of spontaneous burst randomly vary in space.

**Figure 1:** *(left)* In a high Mg\(^{2+}\) condition, simulated global electrical activity is poorly spatially correlated, while *(right)* in Mg\(^{2+}\)-free medium clusters organise and spread through the network.

The temporal dynamics of intracellular free calcium concentration accounts for the slow accumulation of ions due to repetitive electrical activity and for ionic pump exchange mechanisms. Calcium concentration is characterised by oscillations decreases in the absence of any inward ion current contribution with a time constant considerably slower.

The effect of a single excitatory post-synaptic potential (EPSP) cannot in our model trigger any action potential in the post-synaptic neuron but, as already investigated in simplified model networks, it contributes to synchronise local clusters activity. Specific excitatory local connectivity patterns can produce interesting phenomena of activity spreading through the network eliciting bursting also in units that are not directly connected to the sources (see fig. 1). Such activity clusters are characterised in time and in space by a refractory period subsequent an high income of free calcium ions that produce a strong long-lasting hyperpolarisation via the calcium-dependent potassium current \( I_{AHP} \).

**Discussion**

With the aim of quantitatively characterising the electrophysiological behaviours of *in vitro* cultured dissociated rat cortical neurons, coupled to arrays of planar microelectrodes, in this work a mathematical model that describes networks of synaptically connected neurons was developed and computer simulated, including detailed mathematical descriptions of cellular mechanisms responsible for the non-linear ion permeabilities of the membrane, the generation of bursts of activity, spontaneous sub-threshold activity, chemical synaptic signal transduction, and space/time co-ordinated electrical activity. The predictions of such a model network can be then directly compared with the results of ad hoc designed long-term real experiments where patterns of coherent activity are expected to emerge and evolve in space and time.

**REFERENCES**


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