On Duration and Dopamine Modulation of Sustained Activity in Prefrontal Cortex Using Conductance-Based Network Models

Marcelo Camperi[1] and María Virginia Manías[2]

[1]*Physics Department, University of San Francisco (USA)*

[2]*Present address: Theoretical Physics Group, LBNL (USA); permanent address: Physics Department, UNLP and IFLP, CONICET (Argentina).*

Abstract

We investigate the cellular mechanisms underlying the generation, duration, and dopaminergic modulation of working-memory sustained activity in prefrontal cortex by means of computational modeling. We use a conductance-based network model endowed with all relevant PFC conductances found in the experimental literature, considering two-population-networks with AMPA-, NMDA-, and GABA-like synaptic connections. We study dopamine modulation by means of a mechanism in which delay-period activity is modulated locally by dopaminergic levels. These levels in turn are modulated by local neuronal activity and afferent and external inputs.

Keywords: working memory, delay-period activity, dopamine modulation.

1. Introduction

Sustained, memory-related activity is observed in many brain areas, such as parietal cortex, hippocampus, inferotemporal cortex and motor areas [7,13]. However, there is overwhelming evidence locating it predominantly in the dorsolateral prefrontal cortex (PFC), associated with short-term memory processes, where it has been shown to be more robust and to persist even in the presence of interfering stimuli [13]. Moreover, some PFC neurons fire maximally in tune with, for example, particular spatial memory cue locations (“memory fields” [4,7,8])

Working memory processes — short-term memory processes involved in organizing behavior, language, and thinking — are sensitive to dopaminergic modulation [4,5,6,10,13]. Neuronal activity is controlled by the neurotransmitter and experiments have revealed that iontophoresis of D_1 dopamine receptor agonists in PFC produces an increase in persistent activity, while D_1 antagonists decrease it [11]. In addition, dopamine (DA) may also stabilize neural functions in PFC, increasing the robustness of sustained delay activity with respect to distracting input and noise [5]. There appears to be an optimal level of dopamine modulation and, under differential D_1 activation of synaptic transmission on pyramidal cell and interneurons, working memory displays a characteristic inverted-U curve [9].

2. The Model

We present a conductance-based network model exhibiting delayed-period sustained activity in the form of network bistability brought forth by graded recurrent excitation and inhibition. The network consists of N_E pyramidal neurons and N_I interneurons, in a setup akin to that in the tasks in [7,8]. Spatially localized transient inputs bring the network to an excited state, whereby synaptic recurrent excitation sustains the network activity after the input has been turned off.

The model equations (see Appendix) incorporates all relevant PFC conductances. In modeling DA modulation, we concentrate on D_1 receptors, since they are much more abundant in PFC and, more importantly, both working memory performance and delay-period activity recorded in vivo are susceptible mainly or exclusively to D_1 receptor agonists and antagonists [1,9,11]. We simulate natural and forced changes in local DA levels via the introduction of both local and global dynamically modulated changes in maximal conductances, thresholds, and synaptic strengths.

All dopaminergic effects are contained in a dynamical equation that depends on external sources and internal afferent factors, as well as on local cortical activity:

$$\tau_{dopa}^{E,I}\frac{dD_i^{E,I}}{dt} = D_{dopa}^{E,I}(1 - D_i^{E,I})D_i^{E,I} - f_{step}\left(V_i^{E,I}\right)D_i^{E,I}$$

where the ρ_i represent the local dopamine concentration (per neuron), *f(V)* is a "step" spiking threshold function, and D_i is a function representing local and global dopamine and dopamine receptor effect, external and afferent. The variables ρ are then dynamically linked to the various equations needed to reproduce the effects reported for PFC neurons, which include enhancing the persistent Na current (shifting its activation threshold toward more hyperpolarized potentials), reducing the slowly inactivating K+ current in pyramidal cells, reducing the high-voltage-activated (HVA) Ca-current, and enhancing NMDA-like synaptic currents while reducing AMPA-like ones (the overall effect of combined DA-induced changes in AMPA and NMDA currents reduces the EPSP amplitude but prolongs the duration). DA also enhances GABA-like synaptic currents, increasing the spontaneous activity of interneurons and increasing IPSP amplitude. DA-affected maximal conductances, synaptic strengths, and thresholds are thus modulated via equations of the form

$$g^i = g\left\{1 \pm \alpha f_{sat}^{E,I}(\rho_i^{E,I})\right\}$$

Where α is a maximally observed DA effect and *f* is a saturating function. Here, the g^i_X represent the different "constants" that are affected by DA, which becoming local parameters for each neuron.
These complex interdependences and the flexibility we have in choosing the function $D^{E,I}$ provide a dynamical loop that models enhancement and duration effects during delay-period activity, also providing a foundation for a plausible mechanism that explains the observed "inverted-U" behavior (see below).

3. Simulation Results

For testing, we consider a small network of 40 excitatory and 20 inhibitory neurons.

PLACE FIGURE 1 AROUND HERE

Figure 1 shows excitatory and inhibitory neuronal behaviors in the fully connected network model. In the presence of an additional stimulation, a state of high and sustained activity appears. This activity has a frequency of approximately 40Hz and lasts for a few seconds after the input is removed. Recurrent synapses are mediated primarily by NMDA channels [2,12]. However, we find that stability requires also small

amounts of AMPA. Moreover, we find that if the model is to reproduce observations from physiological studies, overall inhibition should dominate [2,12] (see Figure 2).

PLACE FIGURE 2 AROUND HERE

We also study the DA modulation in our model.

PLACE FIGURE 3 AROUND HERE

The three panels in Figure 3 demonstrate timing effects and the existence of the inverted-U effect: On the top panel, the overall DA level is not enough to kick-start the delay-period effect. On the bottom panel, there is too much global DA to start with and thus too much inhibition. The delay-period activity is more erratic and stops relatively quickly. On the middle panel, the overall DA level is just right, and the delay-period activity starts and is sustained. No "off signal" of any kind was used to stop delay-period activity. Its duration is determined by the interplay between the different DA-related dynamical effects present (see below).

4. Conclusions

The network model is dominated by inhibition, in the sense that, for the working parameter regime, overall recurrent excitatory-inhibitory synaptic interactions are balanced toward inhibition. DA increases the firing of interneurons innervating both interneurons and pyramidal cells and therefore enhances action potential-dependent GABAergic inhibitory synaptic transmission. Both AMPA and NMDA excitatory synapses are necessary, although the model produces more stable results when NMDA is dominant. AMPA still needs to be present, albeit in small amounts. We demonstrate the existence of an "inverted-U" optimal dopamine level (or DA-receptor activation) for working memory processes. D_1 receptor modulation must affect differentially pyramidal cells and interneurons. It enhances excitatory inputs to both, but this enhancement is more effective on pyramidal cells than in interneurons. In this way, increasing levels of dopamine stimulation of D_1 receptors will result in enhanced of working memory performance. However, at higher activation levels, modulation of NMDA conductances on pyramidal cells saturates, and further increases in modulatory dopamine levels will result in an enhancement of interneuron activity, since the glutamatergic inputs are

enhanced for both pyramidal cells and interneurons, leading to a reduction in pyramidal cell activity by feed-forward inhibition. The complex dynamical interplay between afferent DA modulation and local spike-dependent effects may be responsible in setting the timing of delay-period activity in PFC.

Appendix: Model Equations

Model equations are of the Hudgkin-Huxley type, where for each neuron *j* we have:

$$\frac{dV_j^X}{dt} = -I_{ionic,j}^X - I_{syn,j}^X + I_{random,j}^X$$

where $X = E$ or I. For *E*-neurons, we consider fast, spike-generating sodium, delayed-rectifier potassium, persistent sodium, high-voltage-activated calcium, slowly inactivating potassium, and fast Ca^{2+}-and voltage-dependent potassium currents. For *I*-neurons, we include just the spiking fast sodium and a delayed-rectifier currents. The "random" currents are independent poisson processes that simulate general neuronal inputs. Finally, the synaptic currents include AMPA, NMDA, and GABA components:

$$I_{syn,i}^E = \sum_{j=1}^{N_E} W_{ij}^{EE} \left[g_{AMPA,ij}^{EE} \, s_{AMPA,j} + \frac{g_{NMDA,ij}^{EE} \, s_{NMDA,j}}{1 + [Mg]\exp(-\beta V_i^E)} \right] \frac{(V_i^E - V^{EE})}{N_E} + \sum_{j=1}^{N_I} g_{GABA,ij}^{IE} \, s_{GABA,j} \, \frac{(V_i^E - V^{IE})}{N_I}$$

$$I_{syn,i}^I = \sum_{j=1}^{N_I} g_{GABA,ij}^{II} \, s_{GABA,j} \, \frac{(V_i^I - V^{II})}{N_I} + \sum_{j=1}^{N_E} \left[g_{AMPA,ij}^{EI} \, s_{AMPA,j} + \frac{g_{NMDA,ij}^{EI} \, s_{NMDA,j}}{1 + [Mg]\exp(-\beta V_i^I)} \right] \frac{(V_i^I - V^{EI})}{N_E}$$

The variables *s* are standard dynamical synaptic variables [2,5,6,12]. The grading function W_{ij}^{EE} in the synaptic equations recreates the experimental conditions found in classic oculomotor tasks: E-cells have effective memory fields on a circle [3]. This is just a simplifying assumption that is not fundamental to our arguments.

REFERENCES

[1] Arnsten A.F., Cai J.X., Murphy B.L., Goldman-Rakic P.S., (1994), Dopamine D_1 receptors mechanisms in the cognitive performance of young and aged monkeys; Psychopharmacology 116, 143-151.

[2] Brunel, N. & Wang, X.J., (2001) Effects of Neuromodulation in a Cortical Network Model of Object Working Memory Dominated by Recurrent Inhibition; Jour.Comput.Neurosc. 11, 63-85.

[3] Camperi, M. & Wang, X.J., (1998) A Model of Visuospatial Working Memory in Prefrontal Cortex: Recurrent Network and Cellular Bistability; Jour.Comput.Neurosc. 5, 383-405.

[4] Desimone, R., (1995); Nature, 376:549-550.

[5] Durstewitz, D., Kelc, M., Gunturkun, O., (1999) A Neurocomputational Theory of the Dopaminergic Modulation of Working Memory Functions; Jour. Neurosc. 19, 2807-2822.

[6] Durstewitz, D., Seamans, J.K. & Sejnowski, T.J., (2000) Dopamine-mediated stabilization of delay-period activity in a network model of prefrontal cortex; J. Neurophysiol., 83, 1733-1750; (2000) Neurocomputational models of working memory; Nature Neurosci, 3, 1184

[7] Funahashi, S., Bruce, C.J. & Goldman-Rakic, P.S. (1989) Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex; J. Neurophysiol., 61, 331-349.

[8] Goldman-Rakic, P.S. (1990) Cellular and circuit basis of working memory in prefrontal cortex of nonhuman primates; Prog. Brain Res., 85, 325-326; (1995) Cellular basis of working memory; Neuron, 14, 477-485.

[9] Goldman-Rakic, P.S., Muly, E.C., Williams, G.V. (2000), D_1 receptors in prefrontal cells and circuits; Brain Research Reviews 31.

[10] Sawaguchi, T and Goldman-Rakic, P; Science, 251:947-950.

[11] Sawaguchi,T (2001) The effects of dopamine and its antagonists on directional delay-period activity of prefrontal neurons in monkeys during an oculomotor delayed-response task; Neuroscience Research 41, 115-128.

[12] Wang, X.J. (1999) Synaptic basis of cortical persistent activity: the importance of NMDA receptors to working memory; J. Neurosci., 19, 9587-9603; (2001) Synaptic reverberation underlying mnemonic persistent activity; Trends Neurosci., 24, 455-463.

[13] Williams, G. and Goldman-Rakic, P.; Nature, 376:572-575.

Marcelo Camperi is associate professor of physics at the University of San Francisco. He received his Ph.D. in Physics from Boston University for work in mathematical physics. His current interests include simulating very large networks on parallel computers, dynamical mechanisms for working memory in the prefrontal cortex, and uses of information theory in spike train analysis.

María V. Manías obtained her M.Sc. and Ph.D. degrees from de University of La Plata, Argentina. She worked on Quantum Field Theories, until she moved to Berkeley on September 2000, where she focused her interests in Theoretical Neuroscience. Currently, she is interested in modeling dynamical mechanisms for working memory in prefrontal cortex.

LIST OF FIGURES

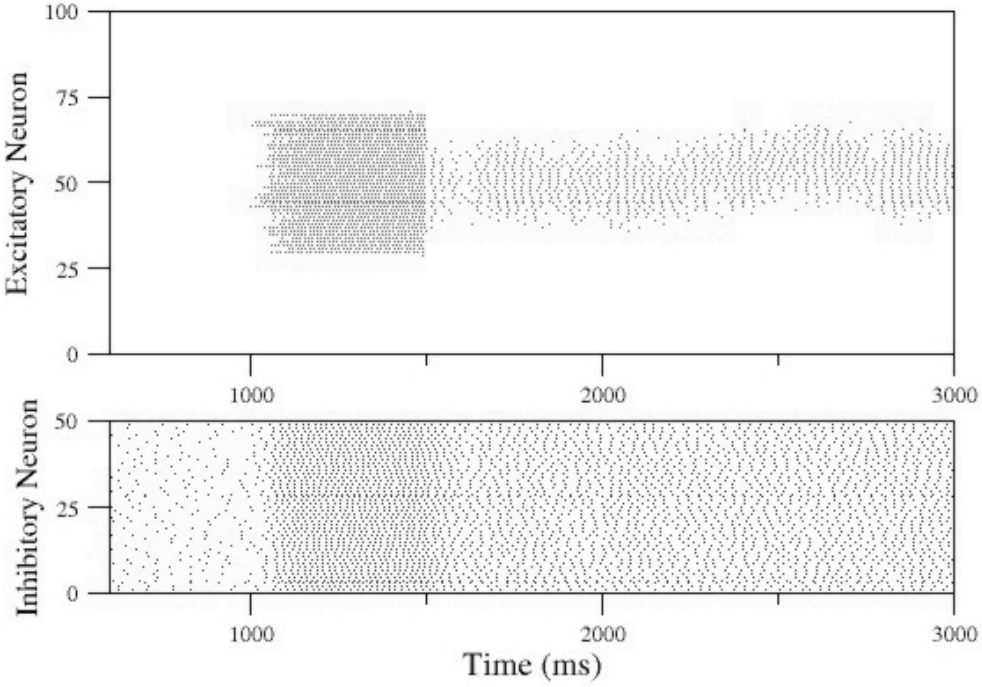

FIGURE 1

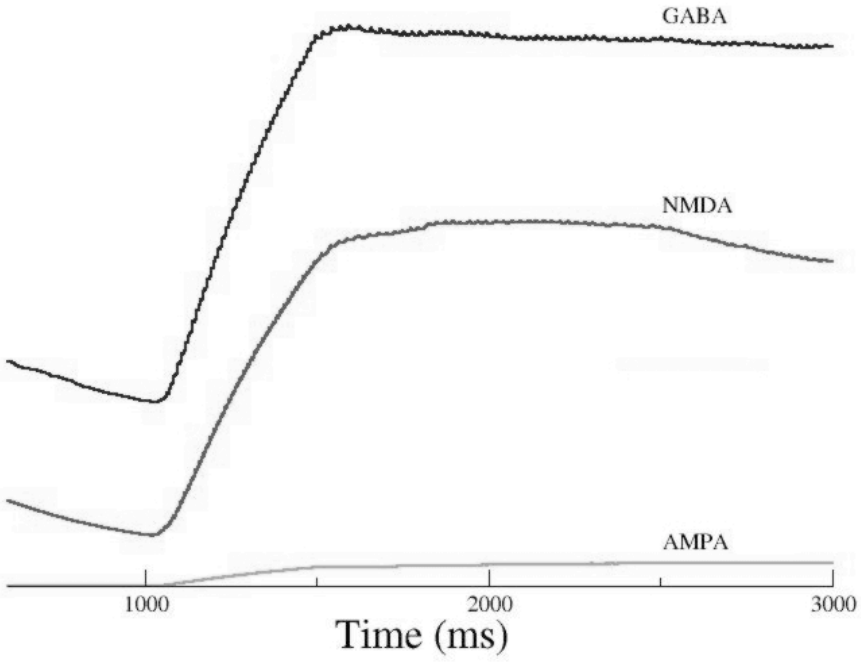

FIGURE 2

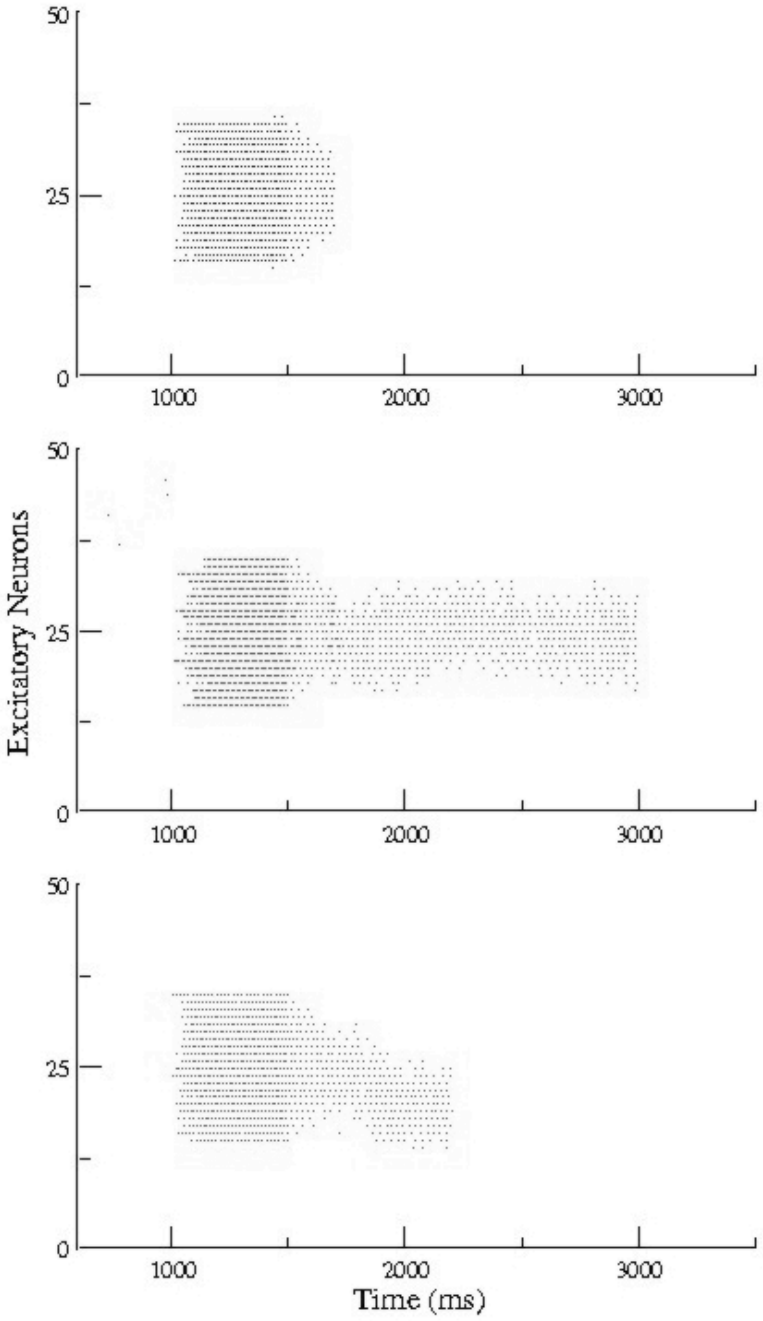

FIGURE 3