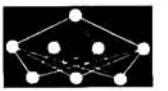

AN INTRINSIC BISTABLE MECHANISM IN NEOCORTICAL PYRAMIDAL NEURONS MIGHT BE INVOLVED IN THE GENERATION OF SUSTAINED DISCHARGE PATTERNS RELATED TO WORKING MEMORY

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1. Introduction

Long lasting neuronal activities have been recorded in several cortical areas during completion of tasks requiring working memory [10, 12]. These activities have been correlated with several processes related to working memory such as: short term memorization of past events, expectation of forthcoming events, preparation of behavioral reaction. In all cases, the existence of sustained patterns of activity appears essential to the "mediation of cross-temporal contingencies" [11]. However, the mechanisms responsible for the generation of these long-lasting activities are still unknown.

Theoretical studies have mostly emphasized the existence of long-lasting activities as a product of neuronal network operations through recurrent excitatory and inhibitory connections [5, 18, 30, 31]. Alternatively, intrinsic properties of a single neuron might endow it with bistable property. It is well known that sustained temporal patterns may appear as a solution of coupled non-linear differential equations [7, 24]. I_{NaP} activates significantly at potentials encountered during inter-spike intervals, and deactivates at hyperpolarized voltages [25]. It could thus both generate sustained discharge and allow a stable silent state to take place. Outward currents are likely to interact with I_{NaP}-mediated repetitive firing. Due to their decay time constant, most of them (I_A, [4]; I_{AHP} and I_C, [22]), should mainly modify frequency of the discharge. On the other hand, slowly inactivating potassium currents (Ks)

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might have a strong effect on the discharge pattern. For example, a delayed discharge in response to a long depolarizing pulse was attributed to a Ks conductance in neocortical ($I_K s$; [13]), hippocampal (I_D; [26]) and thalamic neurons ($I_K 2$; [15, 16]). These conductances might participate to the timing (onset and offset) of sustained discharges.

A compartmental model of a neocortical pyramidal neuron was used to address the possible role of somatic persistent sodium (NaP) and slowly-inactivating potassium (Ks) conductances (in addition to action potential fast sodium and fast potassium conductances) in the generation of sustained discharges. The response to a transient synaptic input was systematically studied as a function of NaP and Ks maximal conductances.

2. Material and Methods

The pyramidal neocortical neuron model incorporated a soma and branched apical and basal dendritic trees. A "Cartoon" representation of the neuron was used [27]. All dendritic and somatic segments were divided into spatially discrete compartments. Voltages and conductances were calculated within each compartment. Membrane passive constants were $R_m = 25000\ \Omega.\mathrm{cm}^2$, $C_m = 1\ \mu\mathrm{F/cm}^2$, and $R_i = 250\ \Omega.\mathrm{cm}$ ($\tau_m = 25$ ms). These values are close to those used in recent compartmental models of neocortical neurons (e.g. [3]). A wide range of values were used for R_m (15 to 150 $\mathrm{k}\Omega.\mathrm{cm}^2$) and R_i (70 to 500 $\Omega.\mathrm{cm}$) in order to confirm the robustness of the results. Membrane resistance r_m^k, membrane capacitance c_m^k, and intracellular resistance r_i^k, were calculated for each compartment with dx usually taken as 10–100 μm.

Using Kirchhoff's current law for the k-th compartment led to a spatially discrete form of the cable equation

$$\begin{aligned} c_m^k \frac{dV^k}{dt} &= \left(\frac{2}{r_i^{k-1}+r_i^k}\right)(V^{k-1}-V^k)+ \\ &+\left(\frac{2}{r_i^k+r_i^{k+1}}\right)(V^{k+1}-V^k) - \frac{V^k}{r_m^k} - i_{synaptic}^k - i_{active}^k \end{aligned} \tag{1}$$

where V^k is the voltage in the k-th compartment, $i_{synaptic}^k$ is the sum of the synaptic currents and i_{active}^k is the sum of the voltage-dependent active currents. We used *Backward-Euler* time-discretisation, where the voltage time-derivative is defined backwards in time. We derived a numerically solvable form of the cable equation. Details of algorithmic procedures and numerical resolutions have been described previously [6, 19, 20, 21]. Voltage-gated conductances were defined only at the soma in our model. We thus considered the dendritic compartments to be purely passive. This assumption is an oversimplification of dendrite properties, but seems to be reasonable for our purpose, since the work focuses on somatic interactions. Active currents were related to their corresponding ionic conductances by equation (2), where *rev* is the reversal potential of the current:

$$I_t = g_t(V_t - V_{rev}) \tag{2}$$

Fast sodium conductance (g_{Na}) parameters were similar to those used by Huguenard and McCormick [16], and derived from Huguenard et al. [14]. The gating

Channel/State variable	Forward ()	Backward ()
m_{Na}	$\alpha_{m,Na} = \frac{0.091(V_t-32)}{\left[1-\exp\left(\frac{-V_t+32}{5}\right)\right]}$	$\beta_{m,Na} = \frac{0.062(V_t-32)}{\left[1-\exp\left(\frac{-V_t+32}{5}\right)\right]}$
h_{Na}	$\alpha_{h,Na} = 0.016\exp\left(\frac{-V_t+15}{15}\right)$	$\beta_{h,Na} = \frac{2.07}{\left[1+\exp\left(\frac{-V_t+87}{21}\right)\right]}$
n_K	$\alpha_{n,K} = \frac{0.01(-V_t+25)}{\left[\exp\left(\frac{-V_t+25}{5}\right)-1\right]}$	$\beta_{n,K} = 0.17\exp\left(\frac{-V_t+20}{40}\right)$
m_{NaP}	$\alpha_{m,NaP} = \frac{0.091(V_t-12)}{\left[1-\exp\left(\frac{-V_t+12}{5}\right)\right]}$	$\beta_{m,NaP} = \frac{-0.062(V_t-12)}{\left[1-\exp\left(\frac{V_t-12}{5}\right)\right]}$

Tab. 1. *Forward and backward rate functions of the activation and inactivation state variables of fast sodium, fast potassium and persistent sodium conductances. The modeled fast sodium conductance possessed an activation (m_{Na}) and an inactivation (h_{Na}). The modeled fast potassium and persistent sodium conductances possessed only an activation state variable, respectively n_K and m_{NaP}. Note that 0 mV in our model corresponds to −70 mV in actual recordings. See* **Materials and Methods** *for more details.*

model for sodium conductance was of the $m^3 \times h$ type. Rate functions for activation (m) and inactivation (h) state variables are summarized in Tab. 1. The maximal conductance, $g_{Na}max$, was taken as 5 mS/cm^2, which value was high enough for the somatic compartment to produce an action potential. The reversal potential of the sodium current was $V_{Na} = 120$ mV.

The action potential potassium conductance (g_K) was also taken from Huguenard and McCormick [16]. The gating model excluded the inactivation gate. The activation gate (n) was elevated to the fourth power. Rate functions are given in Tab. 1. Maximal conductance $g_K max$ was taken as 5 mS/cm^2. The reversal potential of the potassium current was $V_K = -15$ mV.

Persistent sodium conductance (g_{NaP}) have elementary electrical properties very similar to that of the fast sodium conductance [1]. Its conductance-voltage activation curve is shifted toward lower voltages than that of the fast sodium conductance. Persistent sodium activation was thus modeled as a similar but shifted (−20 mV) version of the fast sodium conductance-voltage activation (see Tab. 1.). We assumed that I_{NaP} was carried by a non-inactivating conductance [8, 29]. The gating model was thus of the m^3 type. Rate functions are summarized in Tab. 1. The persistent sodium maximal conductance ($g_{NaP}max$) was used as a variable in our simulations over a range corresponding to several thousandths of the action potential sodium maximal conductance, according to experimental estimations made by Alzheimer et al. [1]. Reversal potential was $V_{NaP} = 120$ mV.

The slowly-inactivating potassium conductances found in the thalamus [15, 16], hippocampus [26], and frontal cortex [13] all have very similar voltage-dependences and kinetics of activation and inactivation. Huguenard and McCormick [15, 16] have described and modeled the voltage- and time-dependence of a thalamic (g_{K2}) slowly-inactivating conductance. We therefore used parameters of the K2 conductance [15, 16] as a model of the cortical slowly-inactivating conductance ($g_K s$). The gating model incorporated an activation (m) and a double exponential inactivation

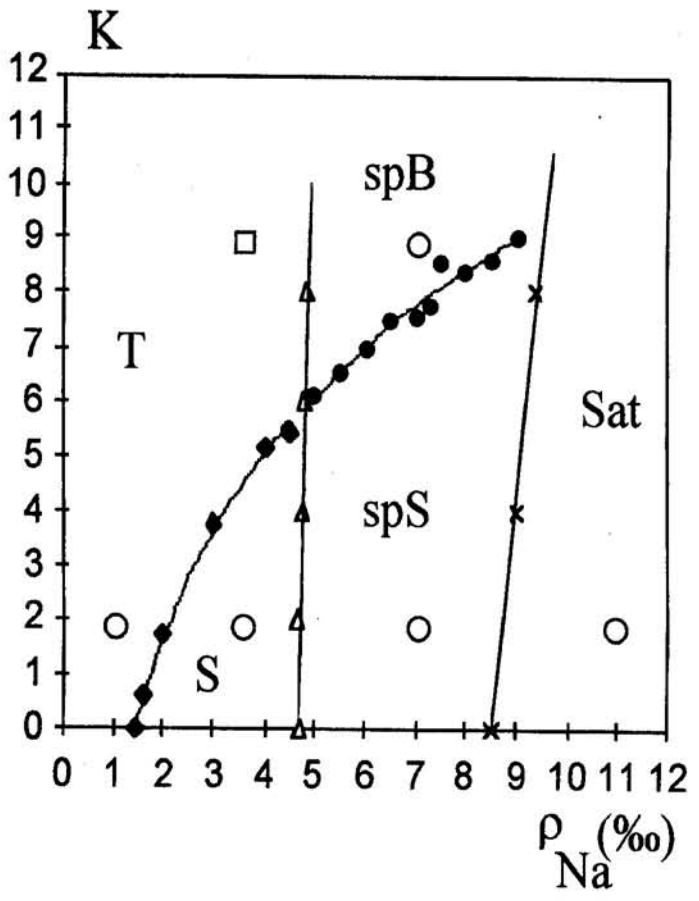

Fig. 1.

(h) and was thus of the $m(\rho h_1 + (1-\rho)h_2)$ type, with $\rho = 0.4$. Gates were determined by steady-state and time-constant functions, and are summarized in Tab. 2. We assumed that slowly-inactivating conductances, like non-inactivating conductances, can have a great influence on somatic discharge, with a relatively small maximal conductance, compared to the fast action potential conductances. We thus set slowly-inactivating potassium maximal conductances ($g_K$smax) within a range equivalent to several thousandths of $g_K$max, in a way similar to the ratio adopted between g_{NaP}max and g_{Na}max. The reversal potential was $V_{Ks} = -15$ mV.

Therefore, the sum of the active currents through the membrane was written as:

$$\begin{aligned} i_{active}^{soma} &= \bar{g}_{Na} m_{Na}^3 h_{Na} (V^{soma} - V_{Na} \\ &+ \bar{g}_{NaP} m_{NaP}^3 (V^{soma} - V_{NaP}) \\ &+ \bar{g}_K n_K^4 (V^{soma} - V_K) \\ &+ \bar{g}_{Ks} m_{Ks} (\rho h_1 + (1-\rho) h_2)(V^{soma} - V_{Ks}) \end{aligned} \tag{3}$$

The synaptic input modeled in our simulations was a non-NMDA, AMPA

State variable	Steady-state function	Time-constant function
m	$m_{Ks}^{\infty} = \frac{1}{\left[1+\exp\left(\frac{-V_t+27}{17}\right)\right]^4}$	$\tau_{m,Ks} = 9.9 + \frac{1}{\left[\exp\left(\frac{-V_t-62.6}{17.95}\right)+\exp\left(\frac{V_t-151}{25.6}\right)\right]}$
h1	$h_{h1,Ks}^{\infty} = \frac{1}{\left[1+\exp\left(\frac{V_t-12}{10.6}\right)\right]}$	$\tau_{h1,Ks} = 120 + \frac{1}{\left[\exp\left(\frac{V_t-1399}{200}\right)+\exp\left(\frac{-V_t-59.7}{7.14}\right)\right]}$
h2	$h_{h2,Ks}^{\infty} = h_{h1,Ks}^{\infty}$	$\tau_{h2,Ks} = \tau_{h1,Ks}$ if $V_t \leq 0$ $\tau_{h2,Ks} = 8930$ if $V_t > 0$

Tab. 2. *Steady-state and time-constant functions of activation and inactivation gates of the modeled slowly-inactivating potassium conductance. The modeled slowly-inactivating potassium conductance possessed one activation (m) and two inactivations (h1 and h2). The gating model is given in* **Materials and Methods.**
Note that 0 mV in our model corresponds to −70 mV in actual recordings.

receptor-mediated current the entering apical dendrite 100 μm from the soma. This input was chosen for two reasons. First, non-NMDA receptors play a major role in local and long cortico-cortical excitatory pathways [17]. Second, most of the local and long cortico-cortical projections (long projections toward layer V excepted) target proximal parts of apical trees and/or basal dendrites [2]. The absence of voltage-dependence and rapid kinetics of AMPA current minimizes its interactions with the somatic discharge, and so limited its action to that of a trigger. The synaptic current was calculated according to:

$$i_{synaptic}^{k}(t) = \bar{g}_{AMPA}\Phi_{AMPA}(t)(V_t^k - V_{AMPA}) \tag{4}$$

with

$$\Phi_{AMPA}(t) = \frac{\exp\left(\frac{-t}{\tau_1}\right) - \exp\left(\frac{-t}{\tau_2}\right)}{\tau_1 - \tau_2} \tag{5}$$

Time constants τ and τ_2 were taken as 3 ms and 0.3 ms respectively. The reversal potential for AMPA current was syn = 70 mV and $\bar{g}_syn$ was taken as 0.1 nS [23].

3. Results

Our results indicate that the response of the neuron to a single transient synaptic input, as well as its spontaneous firing behavior both depend on the respective maximal conductances of NaP and Ks. Indeed, several "discharge domains" were identified. The different domains of discharge are represented on the Fig. 1. in the (ρNa, ρK) plane. An example of each type of discharge is given in the Fig. 2. The locations of the examples in Fig. 1. are given by the open square and the open circles.

A border (open triangles) separated the cases where the neuron possessed a stable resting potential (lower values of ρNa) from cases where the discharge was spontaneous (higher values of ρNa). For low values of ρNa, the response to a transient synaptic input could be transient (T domain) or self-sustained (S domain).

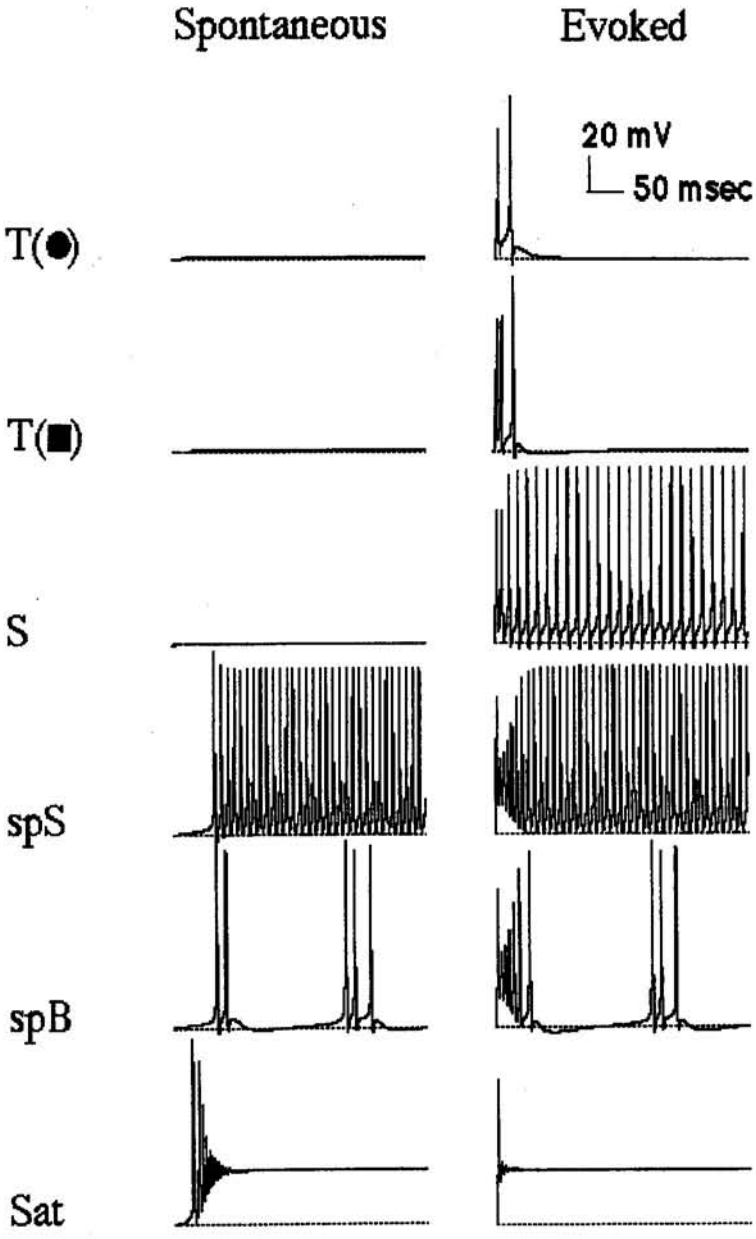

Fig. 2.

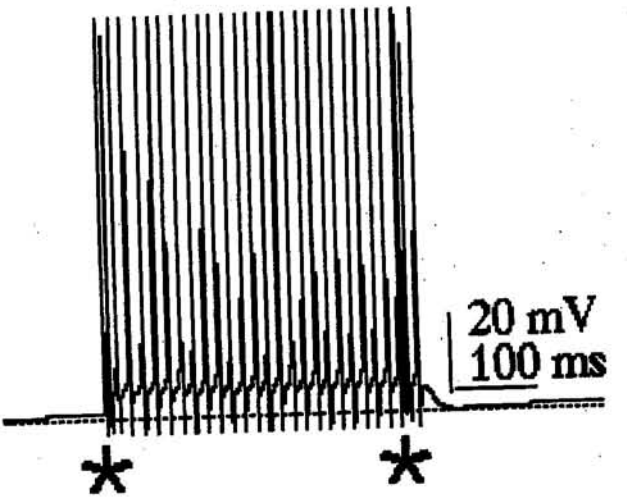

Fig. 3.

In the S domain, the activation of NaP conductance during inter-spike interval permitted the following depolarization and the generation of the next spike. In the T domain, the maximal conductance of NaP was not high enough to drive this regenerative depolarization. The border (filled diamonds) separating T and S domains depended both on ρNa and ρK.

For higher values of ρNa, the spontaneous discharge was self-sustained (spS domain) or bursting (spB domain). The border (filled circles) separating these two domains depended both on ρNa and ρK. A border (crosses) separated spontaneous from saturated (Sat domain) discharge. It mainly depended on ρNa.

Whithin the S domain, the neuron was bistable: it was either silent or discharging. Onset and offset of the self-sustained discharge could be triggered by synaptic inputs. An example is given in Fig. 3.: the discharge was triggered and ended by two successive excitatory synaptic inputs (stars). There existed specific thresholds under which synaptic inputs could not trigger onset and offset transitions of the self-sustained activity. The first input depolarized the membrane from resting potential and helped to the generation of a few spikes (during the first 50 ms). NaP conductance then drove the subsequent sustained generation of spikes. The occurrence of the second excitatory synaptic input increased the spike frequency. This led to an overwhelming cumulative recruitment of Ks conductance. The Ks conductance slow deactivation (and slower inactivation) dampened the voltage back to the resting potential, in a way similar to what was observed for transient responses (T domain) to synaptic input (see the two examples given in Fig. 2.).

4. Discussion

Persistent sodium and slowly-inactivating potassium conductances have been already proposed to participate in neuron's excitability [25], temporal integration of inputs [13, 26] and generation of subthreshold oscillations [29]. The present results suggest a new possible functional role of these conductances in the temporal shaping of neuronal discharge. The discharges of the S domain strongly resemble already observed firing patterns by Sylva et al. [28], where intracellular transient depolarizing stimulations induce long lasting sustained discharges in neocortical pyramidal neurons, even when excitatory synaptic transmission is abolished (kynurenic acid, 5mM). The S domain indicates that NaP and Ks conductances may provide neocortical pyramidal neurons with an *intrinsic bistability* property. This property could participate in the onset, maintenance and offset of long-lasting neuronal activities observed in cerebral cortex during short-term memory behavior [9]. Such an intrinsic mechanism lessen the constraints over connectivity and advantage local and modular aspects of the cross-temporal computations performed within the neocortex by populations of pyramidal neurons. It also allows for precise timing and input selectivity of sustained discharges. Furthermore, changes in the ratio of NaP and Ks maximal conductances provide a direct selection of the discharge frequency and pattern. The modulation of Ks and NaP conductances or of factors influencing their interplay would thus constitute a powerful learning mechanism allowing the proper achievement of cross-temporal cortical computations linked to working memory.

References

[1] Alzheimer C., Schwindt P.C., Crill W.E.: Modal gating of Na^+ channels as a mechanisms of persistent Na^+ current in pyramidal neurons from rat and cat sensorimotor cortex. J. Neurosci. **13**, 1993, 660-673.

[2] Arionadou V.A., Keller A.: The patterns and synaptic properties of horizontal intracortical connections in the rat motor cortex. J. Neurophysiol. **70**, 1993, 1553-1569.

[3] Bush P.C., Sejnowski T.J.: Effects of inhibition and dendritic saturation in simulated neocortical pyramidal cells. J. Neurophysiol. **71**, 1994, 2183-2193.

[4] Connor JA, Stevens CF: Prediction of repetitive firing behavior from voltage clamp data on an isolated neuron soma. J Physiol (Lond), **213**, 1971, 31-53.

[5] Dehaene S, Changeux JP: The Wisconsin Card Sorting Test: theoretical analysis and modelling in a neuronal network. Cereb Cortex, **1**, 1991, 62-79.

[6] Delord B., Klaassen A.J., Guigon E., Burnod Y.: Complex plasticity and temporal behavior in prefrontal neurons: a realistic biological simulation using active membrane properties. In: Computer systems and applied mathematics, edited by S. Voitenko. St Petersburg: Springer-Verlag, 1993.

[7] Edelstein-Keshet L.: Mathematical Models in Biology. New York: Random House, 1988.

[8] French CR, Sah P, Buckett KJ, Gage PW: A voltage-dependent persistent sodium current in mammalian hippocampal neurons. J Gen Physiol **95**, 1990, 1139-1157.

[9] Fuster JM, Alexander GE: Neuron activity related to short-term memory. Science **173**, 1971, 652-654.

[10] Fuster JM: Unit activity in prefrontal cortex during delayed-response performance: neuronal correlates of transient memory. J Neurophysiol **36**, 1973, 61-78.

[11] Fuster JM: The Prefrontal Cortex (2nd ed). New York: Raven, 1988.

[12] Goldman-Rakic PS: Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In: The nervous system, higher functions of the brain. Handbook of Physiology, **5**, 9 (Plum F, ed), 1987, 373-417. Bethesda: American Physiological Society.

[13] Hammond C, Crépel F: Evidence for a slowly inactivating K^+ current in prefrontal cortical cells. Eur J Neurosci, **4**, 1992, 1087-1092.

[14] Huguenard J.R., Hamill O.P., Prince D.A.: Developmental changes in Na^+ conductances in rat neocortical neurons: appearance of a slowly inactivating component. J. Neurophysiol., **59**, 1988, 778-795.

[15] Huguenard J.R., McCormick D.A.: Simulation of the current involved in rhythmic oscillations in thalamic relay neurons. J Neurophysiol, **68**, 1992, 1373-1383.

[16] Huguenard J.R., McCormick D.A.: Vclamp neural simulation instruction manual, 1992.

[17] Huntley G.W., Vickers J.C., Morrison J.H.: Cellular and synaptic localization of NMDA and non-NMDA receptor subunits in neocortex: organizational features related to cortical circuitry, function and disease. Trends Neurosci., **17**, 1994, 536-543.

[18] Kirillov A.B., Myre C.D., Woodward D.J.: Bistability, switches and working memory in a two-neuron inhibitory-feedback model. Biol Cybern, **68**, 1993, 441-449.

[19] Klaassen A.J.: Computing with cables. PhD Thesis, Delft University Press, 1992.

[20] Klaassen A.J., Wiers R.: A method for designing systolic architectures for modelling spatio-temporal properties of neurons using domain decomposition. In: Artificial Neural Networks, edited by T. Kohonen, K. Makisara, O. Simula, and J. Kangas. Amsterdam: Elsevier, 1991, 1549-1552.

[21] Klaassen A.J., Delord B., Burnod Y., Guigon E.: Parallel neuron modelling using domain decomposition: application toward learning sensori-motor sequences in prefrontal cortex. In: Supercomputing in brain research: from tomography to neural networks, edited by H. J. Herrman, D. E. Wolf, and E. Poppel. Singapore: World Scientific, 1994, 361-370.

[22] Numann R.E., Wadman W.J., Wong R.K.S.: Outward currents of single hippocampal cells obtained from the adult guinea-pig. J Physiol (Lond), **393**, 1987, 331-353.

[23] Pongracz F., Poolos P.N., Kocsis D., Shepherd G.M.: A model of NMDA receptor-mediated activity in dendrites of hippocampal CA1 pyramidal neurons. J. Neurophysiol. **68**, 1990, 2248-2259.

[24] Rinzel J., Ermentrout G.B.: Analysis of neural excitability and oscillations. In: Methods in neural modelling (Koch C, Segev I, eds), Cambridge, Mass: The MIT Press, 1989, 135-169.

[25] Stafstrom C.E., Schwindt P.C., Crill W.E.: Negative slope conductance due to a persistent subthreshold sodium current in cat neocortical neurons in vitro. Brain Res **236**, 1982, 221-226.

[26] Storm J.F.: Temporal integration by a slowly inactivating K+ current in hippocampal neurons. Nature, **336**, 1988, 379-381.

[27] Stratford K., Mason A., Larkman A., Major G., Jack J.: The modelling of pyramidal neurons in the visual cortex. In: The Computing Neuron, edited by R. Durbin, C. Miall, and G. Mitchison. Wokingham: Addison Wesley, 1989, 296-321.

[28] Sylva L.R., Amitai Y., Connors B.W.: Intrinsic oscillations of neocortex generated by layer 5 pyramidal neurons. Science, **255**, 1991, 432-435.

[29] Wang X.J.: Ionic basis for intrinsic 40 Hz neuronal oscillations. NeuroReport **5**, 1993, 221-224.

[30] Zipser D. Recurrent network model of the neural mechanism of short-term active memory. Neural Comput **3**, 1991, 179-193.

[31] Zipser D., Kehoe B., Littlewort G., Fuster J.: A spiking network model of short-term active memory. J Neurosci, **13**, 1993, 3406-3420.