

# Supplementary Material for Stochastic cortical neurodynamics underlying the memory and cognitive changes in aging

Edmund T. Rolls, Oxford Centre for Computational Neuroscience, Oxford, UK\*  
and University of Warwick, Department of Computer Science, Coventry CV4 7AL, UK

and

Gustavo Deco, Universitat Pompeu Fabra, Theoretical and Computational Neuroscience  
Roc Boronat 138, 08018 Barcelona, Spain  
and Institutio Catalana de Recerca i Estudis Avancats (ICREA)

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\*Corresponding author. Oxford Centre for Computational Neuroscience, Oxford, UK. Email: Edmund.Rolls@oxcns.org, Url: <http://www.oxcns.org>

# 1 Supplementary Material

## 1.1 Implementation of neural and synaptic dynamics

We use the mathematical formulation of the integrate-and-fire neurons and synaptic currents described by Brunel and Wang (2001). Here we provide a brief summary of this framework.

The dynamics of the sub-threshold membrane potential  $V$  of a neuron are given by the equation:

$$C_m \frac{dV(t)}{dt} = -g_m(V(t) - V_L) - I_{syn}(t), \quad (1)$$

Both excitatory and inhibitory neurons have a resting potential  $V_L = -70mV$ , a firing threshold  $V_{thr} = -50mV$  and a reset potential  $V_{reset} = -55mV$ . The membrane parameters are different for both types of neurons: Excitatory (Inhibitory) neurons are modeled with a membrane capacitance  $C_m = 0.5nF$  ( $0.2nF$ ), a leak conductance  $g_m = 25nS$  ( $20nS$ ), a membrane time constant  $\tau_m = 20ms$  ( $10ms$ ), and a refractory period  $t_{ref} = 2ms$  ( $1ms$ ). Values are extracted from McCormick, Connors, Lighthall and Prince (1985).

When the threshold membrane potential  $V_{thr}$  is reached, the neuron is set to the reset potential  $V_{reset}$  at which it is kept for a refractory period  $\tau_{ref}$  and the action potential is propagated to the other neurons.

The network is fully connected with  $N_E = 800$  excitatory neurons and  $N_I = 200$  inhibitory neurons, which is consistent with the observed proportions of the pyramidal neurons and interneurons in the cerebral cortex (Braitenberg and Schütz 1991, Abeles 1991). The synaptic current impinging on each neuron is given by the sum of recurrent excitatory currents ( $I_{AMPA,rec}$  and  $I_{NMDA,rec}$ ), the external excitatory current ( $I_{AMPA,ext}$ ) the inhibitory current ( $I_{GABA}$ ):

$$I_{syn}(t) = I_{AMPA,ext}(t) + I_{AMPA,rec}(t) + I_{NMDA,rec}(t) + I_{GABA}(t). \quad (2)$$

The recurrent excitation is mediated by the AMPA and NMDA receptors, inhibition by GABA receptors. In addition, the neurons are exposed to external Poisson input spike trains mediated by AMPA receptors at a rate of 2.4 kHz. These can be viewed as originating from  $N_{ext} = 800$  external neurons at an average rate of 3 Hz per neuron, consistent with the spontaneous activity observed in the cerebral cortex (Wilson, O'Scalaidhe and Goldman-Rakic 1994, Rolls and Treves 1998). The currents are defined by:

$$I_{AMPA,ext}(t) = g_{AMPA,ext}(V(t) - V_E) \sum_{j=1}^{N_{ext}} s_j^{AMPA,ext}(t) \quad (3)$$

$$I_{AMPA,rec}(t) = g_{AMPA,rec}(V(t) - V_E) \sum_{j=1}^{N_E} w_{ji}^{AMPA} s_j^{AMPA,rec}(t) \quad (4)$$

$$I_{NMDA,rec}(t) = \frac{g_{NMDA}(V(t) - V_E)}{1 + [Mg^{++}] \exp(-0.062V(t))/3.57} \times \sum_{j=1}^{N_E} w_{ji}^{NMDA} s_j^{NMDA}(t) \quad (5)$$

$$I_{GABA}(t) = g_{GABA}(V(t) - V_I) \sum_{j=1}^{N_I} w_{ji}^{GABA} s_j^{GABA}(t) \quad (6)$$

where  $V_E = 0$  mV,  $V_I = -70$  mV,  $w_j$  are the synaptic weights,  $s_j$ 's the fractions of open channels for the different receptors and  $g$ 's the synaptic conductances for the different channels. The NMDA synaptic current depends on the membrane potential and the extracellular concentration of Magnesium ( $[Mg^{++}] = 1$  mM (Jahr and Stevens 1990)). The values for the synaptic conductances for excitatory neurons are  $g_{AMPA,ext} = 2.08$  nS,  $g_{AMPA,rec} = 0.104$  nS,  $g_{NMDA} = 0.327$  nS and  $g_{GABA} = 1, 25$  nS ; and for inhibitory neurons  $g_{AMPA,ext} = 1.62$  nS,  $g_{AMPA,rec} = 0.081$  nS,  $g_{NMDA} = 0.258$  nS and  $g_{GABA} = 0.973$  nS. These values are obtained from the ones used by Brunel and Wang (2001) by correcting for the different numbers of neurons. The conductances were calculated so that in an unstructured network the excitatory neurons have a spontaneous spiking rate of 3 Hz and the inhibitory neurons a spontaneous rate of 9 Hz. The fractions of open channels are described by:

$$\frac{ds_j^{AMPA,ext}(t)}{dt} = -\frac{s_j^{AMPA,ext}(t)}{\tau_{AMPA}} + \sum_k \delta(t - t_j^k) \quad (7)$$

$$\frac{ds_j^{AMPA,rec}(t)}{dt} = -\frac{s_j^{AMPA,rec}(t)}{\tau_{AMPA}} + \sum_k \delta(t - t_j^k) \quad (8)$$

$$\frac{ds_j^{NMDA}(t)}{dt} = -\frac{s_j^{NMDA}(t)}{\tau_{NMDA,decay}} + \alpha x_j(t)(1 - s_j^{NMDA}(t)) \quad (9)$$

$$\frac{dx_j(t)}{dt} = -\frac{x_j(t)}{\tau_{NMDA,rise}} + \sum_k \delta(t - t_j^k) \quad (10)$$

$$\frac{ds_j^{GABA}(t)}{dt} = -\frac{s_j^{GABA}(t)}{\tau_{GABA}} + \sum_k \delta(t - t_j^k), \quad (11)$$

where  $\tau_{NMDA,decay} = 100$  ms is the decay time for NMDA synapses,  $\tau_{AMPA} = 2$  ms for AMPA synapses (Hestrin, Sah and Nicoll 1990, Spruston, Jonas and Sakmann 1995) and  $\tau_{GABA} = 10$  ms for GABA synapses (Salin and Prince 1996, Xiang, Huguenard and Prince 1998);  $\tau_{NMDA,rise} = 2$  ms is the rise time for NMDA synapses (the rise times for AMPA and GABA are neglected because they are typically very short) and  $\alpha = 0.5$  ms<sup>-1</sup>. The sums over  $k$  represent a sum over spikes formulated as  $\delta$ -Peaks  $\delta(t)$  emitted by presynaptic neuron  $j$  at time  $t_j^k$ .

The equations were integrated numerically using a second order Runge-Kutta method with step size 0.02 ms. The Mersenne Twister algorithm was used as random number generator for the external Poisson spike trains and different trials for equal parameter configurations were run with different random seeds (as the only difference).

## Connection Matrices

### Fraction of pool sizes $f_i$

Values are relative to all neurons, not only the excitatory portion.

S1	S2	NS	IH
0.08	0.08	0.64	0.2

**Connection matrix for AMPA and NMDA – [from, to]**

	S1	S2	NS	IH
S1	$w_+$	$w_-$	1	1
S2	$w_-$	$w_+$	1	1
NS	$w_-$	$w_-$	1	1
IH	0	0	0	0

where  $w_- = \frac{0.8-f_{S1}w_+}{0.8-f_{S1}}$ .

**Connection matrix for GABA – [from, to]**

	S1	S2	NS	IH
S1	0	0	0	0
S2	0	0	0	0
NS	0	0	0	0
IH	1	1	1	1

## 1.2 Calcium-dependent spike frequency adaptation mechanism

A specific implementation of the spike-frequency adaptation mechanism using  $\text{Ca}^{++}$ -activated  $\text{K}^+$  hyper-polarizing currents (Liu and Wang 2001) is described next, and was used by Deco and Rolls (2005). We assume that the intrinsic gating of  $\text{K}^+$  After-Hyper-Polarizing current ( $I_{\text{AHP}}$ ) is fast, and therefore its slow activation is due to the kinetics of the cytoplasmic  $\text{Ca}^{2+}$  concentration. This can be introduced in the model by adding an extra current term in the integrate-and-fire model, i.e. by adding  $I_{\text{AHP}}$  on the right hand of equation 12, which describes the evolution of the subthreshold membrane potential  $V(t)$  of each neuron:

$$C_m \frac{dV(t)}{dt} = -g_m(V(t) - V_L) - I_{\text{syn}}(t) \quad (12)$$

where  $I_{\text{syn}}(t)$  is the total synaptic current flow into the cell,  $V_L$  is the resting potential,  $C_m$  is the membrane capacitance, and  $g_m$  is the membrane conductance. The extra current term that is introduced into this equation is as follows:

$$I_{\text{AHP}} = -g_{\text{AHP}}[\text{Ca}^{2+}](V(t) - V_K) \quad (13)$$

where  $V_K$  is the reversal potential of the potassium channel. Further, each action potential generates a small amount ( $\alpha$ ) of calcium influx, so that  $I_{\text{AHP}}$  is incremented accordingly. Between spikes the  $[\text{Ca}^{2+}]$  dynamics is modelled as a leaky integrator with a decay constant  $\tau_{\text{Ca}}$ . Hence, the calcium dynamics can be described by following system of equations:

$$\frac{d[\text{Ca}^{2+}]}{dt} = -\frac{[\text{Ca}^{2+}]}{\tau_{\text{Ca}}} \quad (14)$$

If  $V(t) = \theta$ , then  $[\text{Ca}^{2+}] = [\text{Ca}^{2+}] + \alpha$  and  $V = V_{\text{reset}}$ , and these are coupled to the equations of the neural dynamics provided here and elsewhere (Rolls and Deco 2010). The  $[\text{Ca}^{2+}]$  is initially set to be 0  $\mu\text{M}$ ,  $\tau_{\text{Ca}} = 300$  ms,  $\alpha = 0.002$ ,  $V_K = -80$  mV and  $g_{\text{AHP}} = 0-40$  nS.  $g_{\text{AHP}} = 40$  nS simulates the effect of high levels of acetylcholine produced alertness and attention, and  $g_{\text{AHP}} = 0$  nS simulates the effect of low levels of acetylcholine in normal aging.

### 1.3 The model parameters used in the simulations of memory

The fixed parameters of the model are shown in Table 1, and not only provide information about the values of the parameters used in the simulations, but also enable them to be compared to experimentally measured values.

Table 1: Parameters used in the integrate-and-fire simulations

$N_E$	800
$N_I$	200
$r$	0.1
$w_+$	2.1
$w_I$	1.0
$N_{\text{ext}}$	800
$\nu_{\text{ext}}$	2.4 kHz
$C_m$ (excitatory)	0.5 nF
$C_m$ (inhibitory)	0.2 nF
$g_m$ (excitatory)	25 nS
$g_m$ (inhibitory)	20 nS
$V_L$	-70 mV
$V_{\text{thr}}$	-50 mV
$V_{\text{reset}}$	-55 mV
$V_E$	0 mV
$V_I$	-70 mV
$g_{\text{AMPA,ext}}$ (excitatory)	2.08 nS
$g_{\text{AMPA,rec}}$ (excitatory)	0.104 nS
$g_{\text{NMDA}}$ (excitatory)	0.327 nS
$g_{\text{GABA}}$ (excitatory)	1.25 nS
$g_{\text{AMPA,ext}}$ (inhibitory)	1.62 nS
$g_{\text{AMPA,rec}}$ (inhibitory)	0.081 nS
$g_{\text{NMDA}}$ (inhibitory)	0.258 nS
$g_{\text{GABA}}$ (inhibitory)	0.973 nS
$\tau_{\text{NMDA,decay}}$	100 ms
$\tau_{\text{NMDA,rise}}$	2 ms
$\tau_{\text{AMPA}}$	2 ms
$\tau_{\text{GABA}}$	10 ms
$\alpha$	0.5 ms <sup>-1</sup>

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