Supplementary Material: A Neurodynamical Model of Schizophrenia

For:
Computational models of schizophrenia and dopamine modulation in the prefrontal cortex
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For simulations of large attractor networks with noise, we used a mathematical formulation of the integrate-and-fire neurons and synaptic currents described in Brunel & Wang (2001). A detailed study of this system is published in Loh, Rolls & Deco (2007).

Simulation summary

We (Loh, Rolls & Deco 2007) assessed the stability of an integrate-and-fire simulation of a single attractor network with two possible short-term memory states stored in the increased excitatory synaptic strengths between two sets of neurons in the network. Both the ability of a short-term memory state to persist reliably, and the ability of the spontaneous firing state to remain stable and not enter one of the two attractors, were investigated. The spiking noise in the network was simulated, as the neurons in this model were spiking neurons.

When the attractor network was triggered into a high firing rate attractor state by stimulus S1 that was normally maintained until the end of a short term memory period, it was found that a reduction in the NMDA conductance reduced the stability of the high firing rate persistent attractor state, and frequently the state had been lost with only low, spontaneous, firing rates present at the end of a trial. In addition, the network was more distractible in that if a second stimulus S2 followed S1, the network was more likely to be distracted out of the S1 state. We hypothesized that such effects, if expressed in the dorsolateral prefrontal cortex, might be related to the cognitive symptoms, as they indicate reduced stability of the working memory. The reduction in NMDA conductances was shown to reduce the firing rates of the excitatory neurons, and this effect, when occurring in the orbitofrontal and anterior cingulate cortex, was related to the negative symptoms.

In the same simulations, a reduction in synaptic currents activated by GABA receptors produced a slight reduction in the stability of the spontaneous state (in that the network was more likely to jump to a high firing rate attractor state even if no stimulus had been presented), and an increased stability of the high firing rate persistent attractor state. When both NMDA and GABA are reduced one might think that these two counterbalancing effects (excitatory and inhibitory) would cancel each other out. However, this is not the case. The stability of both the spontaneous and the persistent states is reduced. Indeed, under these conditions, the network wandered freely between the two short-term memory states S1 and S2 in the network and the spontaneous state. We relate this pattern to the positive symptoms of schizophrenia, in which both the spontaneous and attractor states are shallow, and the system jumps, helped by the statistical fluctuations, between the different attractor states and the spontaneous state.
Neural and synaptic dynamics

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

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

(1)

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

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

The network is fully connected with $N_E = 400$ excitatory neurons and $N_I = 100$ inhibitory neurons, which is consistent with the observed proportions of the pyramidal neurons and interneurons in the cerebral cortex (Braitenberg & Schütz 1991, Abeles 1991). Full connectivity is a technical simplification, since cortical networks in the brain are usually sparsely connected. It enables faster simulations and, more importantly, the implementation of the mean-field approach. Nevertheless, the properties of attractor networks are still found with sparse connectivity (Treves & Rolls 1991). The synaptic current impinging on each neuron is given by the sum of recurrent excitatory currents ($I_{\text{AMPA,rec}}$ and $I_{\text{NMDA,rec}}$), the external excitatory current ($I_{\text{AMPA,ext}}$), and the inhibitory current ($I_{\text{GABA}}$):

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

(2)

The recurrent excitation is mediated by the AMPA and NMDA receptors, and 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 $N_{\text{ext}} = 800$ external neurons at average rate of 3 Hz per neuron, consistent with the spontaneous activity observed in the cerebral cortex (Wilson et al. 1994, Rolls & Treves 1998). The currents are defined by:

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

(3)

$$
I_{\text{AMPA,rec}}(t) = g_{\text{AMPA,rec}}(V(t) - V_E) \sum_{j=1}^{N_E} w_{ij} \text{AMPA}_j \text{AMPA,rec}_j(t)
$$

(4)

$$
I_{\text{NMDA,rec}}(t) = \frac{g_{\text{NMDA}}(V(t) - V_E)}{1 + [\text{Mg}^{2+}]^\frac{1}{3.57}} \sum_{j=1}^{N_E} w_{ij} \text{NMDA}_j \text{NMDA,rec}_j(t)
$$

(5)

$$
I_{\text{GABA}}(t) = g_{\text{GABA}}(V(t) - V_I) \sum_{j=1}^{N_I} w_{ij} \text{GABA}_j \text{GABA}(t)
$$

(6)

where $V_E = 0 \text{ mV}$, $V_I = -70 \text{ mV}$, $w_{ij}$ is the synaptic weight from neuron $j$ to neuron $i$, $s_j$ refers to the fractions of open channels for the different receptors, and $g$ refers to the
synaptic conductances for the different channels. The NMDA synaptic current depends on the membrane potential and the extracellular concentration of Magnesium ([Mg$^{2+}$] = 1 mM, Jahr & Stevens (1990)). The values for the synaptic conductances for excitatory neurons are $g_{AMPA,ext} = 2.08$ nS, $g_{AMPA,rec} = 0.208$ nS, $g_{NMDA} = 0.654$ nS and $g_{GABA} = 2.50$ nS; and for inhibitory neurons $g_{AMPA,ext} = 1.62$ nS, $g_{AMPA,rec} = 0.162$ nS, $g_{NMDA} = 0.516$ nS and $g_{GABA} = 1.946$ nS. These values are obtained from the ones used by Brunel & 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:

$$\frac{ds_{j,ext}(t)}{dt} = -\frac{s_{j,ext}(t)}{\tau_{AMPA}} + \sum_k \delta(t - t_{jk}^k)$$

$$\frac{ds_{j,rec}(t)}{dt} = -\frac{s_{j,rec}(t)}{\tau_{AMPA}} + \sum_k \delta(t - t_{jk}^k)$$

$$\frac{ds_{j,NMDA}(t)}{dt} = -\frac{s_{j,NMDA}(t)}{\tau_{NMDA,decay}} + \alpha x_j(t)(1 - s_{j,NMDA}(t))$$

$$\frac{dx_j(t)}{dt} = -\frac{x_j(t)}{\tau_{NMDA,\text{rise}}} + \sum_k \delta(t - t_{jk}^k)$$

$$\frac{ds_{j,GABA}(t)}{dt} = -\frac{s_{j,GABA}(t)}{\tau_{GABA}} + \sum_k \delta(t - t_{jk}^k),$$

where $\tau_{NMDA,\text{decay}} = 100$ ms is the decay time for NMDA synapses, $\tau_{AMPA} = 2$ ms for AMPA synapses (Hestrin et al. 1990, Spruston et al. 1995) and $\tau_{GABA} = 10$ ms for GABA synapses (Salin & Prince 1996, Xiang et al. 1998); $\tau_{NMDA,\text{rise}} = 2$ 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$^{-1}$. The sums over $k$ represent a sum over spikes formulated as $\delta$-Peaks $\delta(t)$ emitted by presynaptic neuron $j$ at time $t_{jk}^k$.

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

For the simulations, we (Loh, Rolls & Deco 2007) used a simple system consisting of two selective pools (S1, S2), one non-selective pool (NS) and one inhibitory pool (IH). This is the minimal architecture to study stability and distractibility. The network structure between excitatory neurons was set up by Hebbian principles: Neurons within the same populations are more strongly connected than neurons in different populations. Neurons within each of the specific excitatory populations S1 and S2 are mutually coupled with a strong weight $w_+$. Since the populations S1 and S2 encoding different items have uncorrelated activity, these have a weaker connection strength $w_-$ between them. Neurons in the inhibitory population are mutually connected with an intermediate weight $w = 1$. They are also connected with
all excitatory neurons with the weight $w = 1$. Neurons in a specific excitatory population are connected to neurons in the nonselective population in the same layer with a feedforward synaptic weight $w = 1$ and a feedback synaptic connection of weight $w_−$.

**Fraction of pool sizes $f_i$**

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

<table>
<thead>
<tr>
<th></th>
<th>$S_1$</th>
<th>$S_2$</th>
<th>NS</th>
<th>IH</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.08</td>
<td>0.08</td>
<td>0.64</td>
<td>0.2</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>$S_1$</th>
<th>$S_2$</th>
<th>NS</th>
<th>IH</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_1$</td>
<td>$w_+$</td>
<td>$w_-$</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>$S_2$</td>
<td>$w_-$</td>
<td>$w_+$</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>NS</td>
<td>$w_-$</td>
<td>$w_-$</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>IH</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th></th>
<th>$S_1$</th>
<th>$S_2$</th>
<th>NS</th>
<th>IH</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_1$</td>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$S_2$</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NS</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IH</td>
<td>1</td>
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**References**


