Gating Deficits in Model Networks: A Path to Schizophrenia?

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Abstract

Gating deficits and hallucinatory sensations are prominent symptoms of schizophrenia. Comparing these abnormalities with the failure modes of network models is an interesting way to explore how they arise. We present a network model that can both propagate and gate signals. The model exhibits effects reminiscent of clinically observed pathologies when the balance between excitation and inhibition that it requires is not properly maintained.

Gating deficits, which involve difficulty in filtering external stimuli on the basis of their importance, and hallucinatory sensations, involving a failure to distinguish between real and imagined experiences, are debilitating aspects of schizophrenia [15]. Both of these can be categorized as problems of information propagation and management. Signal propagation has been studied extensively in network models [1,2,7,8,12,23,25,26], and these provide a useful platform for considering the mechanisms and underlying pathologies that cause such deficits.

Theoretical arguments [19,22] as well as experimental findings [10,20] suggested that excitation and inhibition are globally balanced in cortical circuits. In a balanced network, each neuron receives approximately equal amounts of excitatory and inhibitory input that tend to cancel each other. Fluctuations in the balance of the total synaptic input produce the asynchronous and irregular patterns of spiking characteristic of cortical activity [3,5,24]. A leading idea among researchers working on schizophrenia is that at least some of its symptoms arise from an imbalance between excitation and inhibition in specific circuits [14,28], so studies of balanced network models seems highly relevant to schizophrenia research.

The model we review here extends the concept of global balance to specific subcircuits [27]. We embed a two-layered feedforward pathway into a network of about 20,000 integrate-and-fire neurons with global and local connectivity. In addition to globally balanced inputs, the neurons in layer 2 of the feedforward pathway receive correlated excitatory inputs from layer 1. In contrast to traditional embedded feedforward networks (**Fig. 1a**), the projections from layer 1 target both excitatory neurons in layer 2 and also locally connected interneurons (**Fig. 1b**). As a result, the excitatory neurons in layer 2 still receive approximately equal amounts of total excitation and inhibition. As a consequence of this local or what we call "detailed balance", activation of layer 1 produces little response in the (excitatory) majority of the target neurons in layer 2. However, the signal can be gated on, producing layer 2 activity that mirrors that of layer 1, by a command signal that suppresses the inhibition and thus disrupts the detailed balance.

This model offers an interesting alternative to the more traditional model of gating in which it is necessary to fully inhibit neurons that are not supposed to receive or transmit the signal [4,17]. In such a system, the default state of the signal chain is to propagate signals, and a cognitive controller needs to decide when to disrupt the signal flow. Our model has this inverted: the inattentive state is actively maintained, presumably in parallel, in many modules responsible for different features of a stimulus. In the default state of the system, all these features are balanced out and thus not processed. If one feature of the stimulus is "interesting", a control mechanism can pull that feature out by unbalancing the respective module and propagate that signal further downstream. It may be easier for a relatively uncon-

Bibliography
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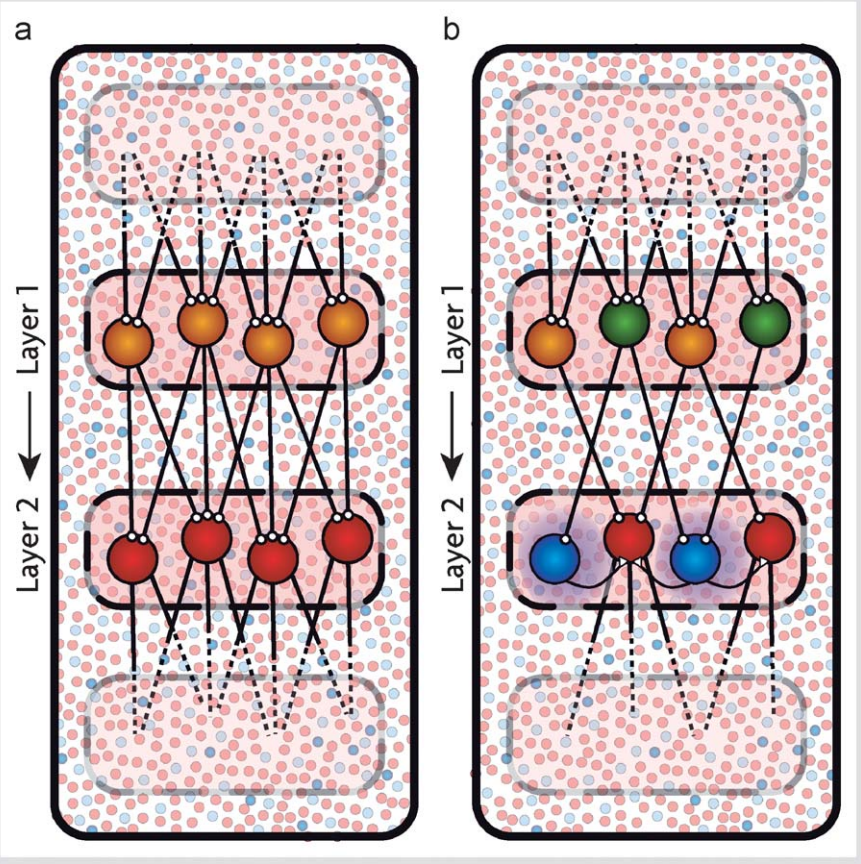

Fig. 1 Embedded Feedforward Networks: **a**) Traditional all-to-all feedforward wiring scheme between groups of excitatory neurons. **b**) Balanced feedforward wiring: Some of the feedforward connections are made to inhibitory cells that, in turn, synapse onto their excitatory neighbors.

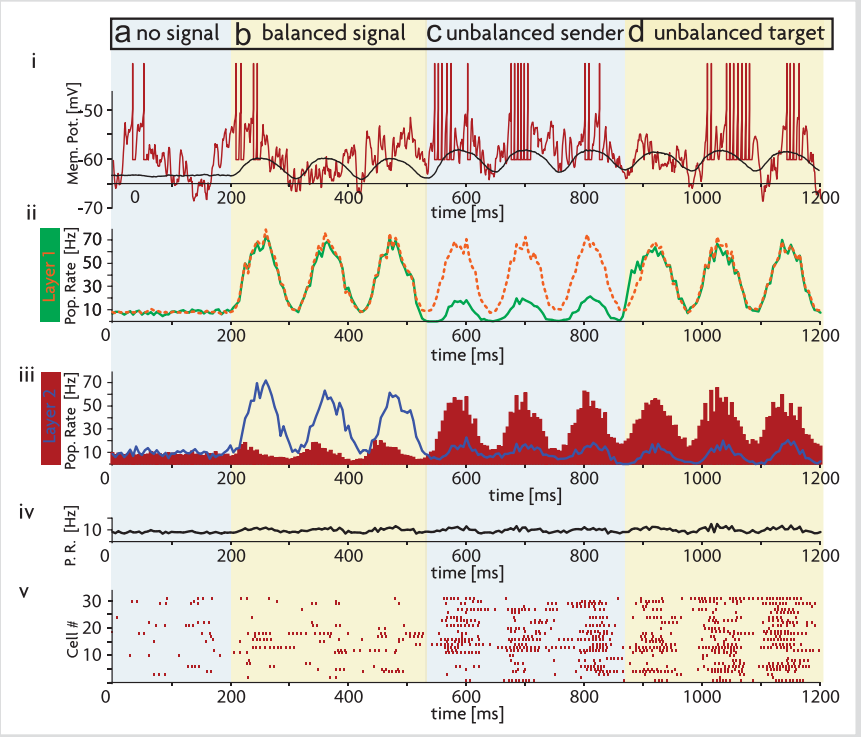

Fig. 2 Detailed Balance in a network: i) Voltage trace of a randomly chosen excitatory layer 2 neuron. The red trace shows a single run, and the average membrane potential excluding refractory periods is in black. **ii**) Average firing rates over 5 trials, calculated in 5 ms bins, for excitatory-excitatory (orange) and excitatory-inhibitory (green) layer 1 neurons responding to a sinusoidally varying input. **iii**) Average firing rates for the inhibitory (dark blue trace) and excitatory (histogram in red) neurons in layer 2 responding to their respective inputs. **iv**) Population firing rate of the entire network. **v**) Spike raster plot of 30 randomly selected excitatory layer 2 neurons. **a**) **No signal**. All involved neurons fire at background rates. **b**) **Balanced signal**. All layer 1 neurons fire in a correlated manner in response to the input signal and project the input pattern to their respective target neurons. The inhibitory layer 2 neurons reproduce the input pattern, preventing their excitatory neighbors from doing the same. **Unbalanced signal**. By decreasing the responsiveness of either the excitatory layer 1 neurons projecting to inhibitory layer 2 neurons (**c**) or the inhibitory layer 2 neurons themselves (**d**), the signal balance in the excitatory layer 2 neurons shifts in favor of excitation, and the signal pattern is reproduced.

scious system to keep track of what is interesting in a broad band signal stream, than to keep track of all the uninteresting things to suppress.

Detailed Balance in a Network Model

Our model network consists of about 20,000 excitatory and inhibitory leaky integrate-and-fire neurons. The excitatory neurons have a global random connectivity with a 2% connection probability between any two neurons. The same holds for 65% of

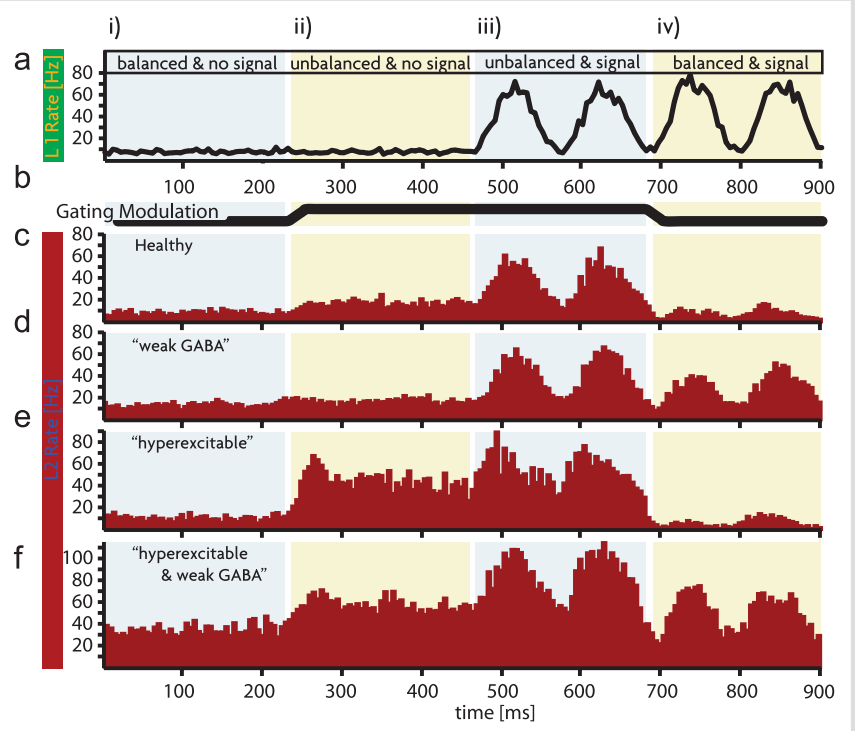

Fig. 3 **a) Network Pathologies:** Network response to various tuning defects for a given input (**a**) and modulatory scheme (**b**). Conditions are as follows: **i**) No signal and no modulation; **ii**) no signal but "gated on"; **iii**) signal on, "gated on" and **iii**) the signal in the absence of modulation. **c**) Correctly tuned. **d**) Weakened local inhibition leads to gating deficits. **e**) A hyperactive target region causes high firing rates even in the absence of a signal. The network deficits of (**f**) and (**g**) can be combined (**h**), leading to a "schizophrenic" network state. Note that modulation affects solely the inhibitory cells of layer 2.

the inhibitory neurons, but the remaining 35% have only local connectivity, synapsing randomly onto approximately 200 of the 500 neurons in their immediate neighborhood.

The embedded pathway consists of two layers of neurons. Layer 1 receives correlated input from a source external to the network and mimics the temporal firing pattern of the external signal [26]. Layer 1 excitatory neurons are divided into two groups, one that sends long-range projections to about 500 excitatory neurons in layer 2, and the other that projects to about 70 locally connecting interneurons within layer 2 which in turn contact their excitatory neighbors. Detailed balance is imposed by adjusting the strengths of the projections of these two groups of excitatory layer 1 neurons so that the effect of monosynaptic excitation within the excitatory layer 2 neurons is balanced by the disynaptic inhibition produced by the same signal through the local inhibitory neurons of layer 2.

Balance as a Default State

With appropriately adjusted parameters, this network displays irregular, "bursty" firing at low rates, with broad distributions of interspike intervals (ISIs) and coefficients of variation of ISIs slightly larger than 1, indicative of a globally balanced network state.

Because of the detailed balance condition we have imposed, input delivered from layer 1 is balanced within the excitatory neurons of layer 2. Therefore, the default state of the signal-carrying pathway is "gated off" (**Fig. 2b**). Patterns in the firing rates of the sender neurons in layer 1 (green and orange traces in **Fig. 2b(ii)**) are reproduced in the activity of the inhibitory neurons of layer 2 (dark blue trace in **Fig. 2b(iii)**), but the excitatory layer 2 neurons show only modest firing rate fluctuations (red histogram in **Fig. 2b(iii)**) and little evidence of the signal in their firing rasters (**Fig. 2b(iv)**).

Gating Propagation On

Signals are "gated on" within this network by unbalancing the excitatory and inhibitory components of the signal to layer 2. This can be done, for example, by weakening the inhibitory component of the signal transmitted to the excitatory neurons of layer 2, which can be accomplished either by either decreasing the responsiveness of the sender neurons projecting to the inhibitory neurons in layer 2 (**Fig. 2c**), or by decreasing the responsiveness of the local inhibitory interneurons themselves (**Fig. 2d**). Both of these forms of modulation produce robust firing in the excitatory neurons of layer 2 that is locked to the temporal pattern of the input signal (**Fig. 2c, d(i, iii, iv)**). In the first case, the effect of decreasing the gain of the neurons in layer 1 that project to inhibitory target neurons can be seen in the reduced amplitude of the firing rate variation of these neurons (green trace in **Fig. 2c(ii)**). When, instead, the gain of the local inhibitory neurons in layer 2 is decreased, there is no effect on the firing in layer 1 (green trace in **Fig. 2c(iii)**), but the temporal variations in the firing rate of the inhibitory neurons in layer 2 are reduced in amplitude (dark blue trace in **Fig. 2d(iii)**) just as they are when the sender neurons in layer 1 are modulated (**Fig. 2d(iii)**).

In the example of **Fig. 2**, we modified the responsiveness of particular neurons through gain modulation. Such modulation can be realized in two equivalent ways: either by reducing the strength of all the synapses onto the modulated neuron or by scaling its input-output transfer function so that the same synaptic current generates a smaller response. No matter whether it was generated by reducing the responsiveness of excitatory sender or inhibitory target neurons, the modulation in this example was such that the response gain of local inhibitory neurons in layer 2 was reduced to 15% of its control value. To control gating from layer 1, two distinct subgroups that target different types of neurons in layer 2 must exist (see **Fig. 1**). Evidence for anatomical specificity in the wiring to interneurons has been

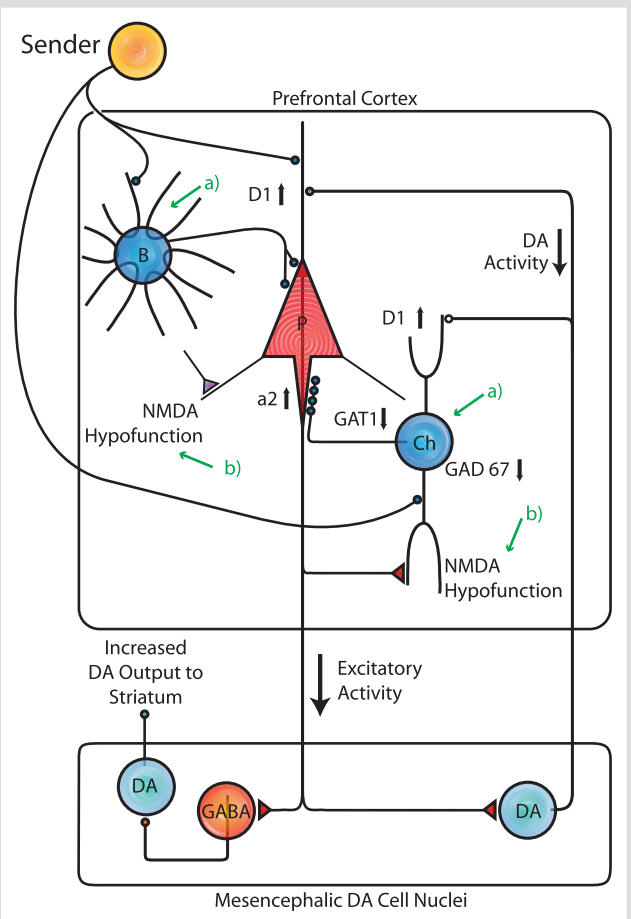

Fig. 4 Potential cellular and synaptic pathologies in schizophrenia (denoted by green arrows) that may be related to network detunings described in the text. **a**) GAD 67 down regulation is thought to decrease the functionality of PV+ interneurons, similar to the case described in **Fig. 3d**. NMDA hypofunction is thought to have possible effects on the excitability of the same cell type as well as pyramids, and could lead to deficiencies related to those shown in **Fig. 3e**. Figure adapted from [13].

uncovered recently [9]. For the sake of simplicity, we control gating from now on solely through gain modulation of the inhibitory neuron population in layer 2.

Network Pathologies

Even though fairly robust, signal gating and detailed balance require a well adjusted network. Neither the command modulation that is used to unbalance pathways and turn on signal propagation nor the signal itself can have an excessively destabilizing effect on the global excitatoryinhibitory balance of the network. Such tuning presents a challenge, and it may be nontrivial to maintain in real networks. Therefore, we might expect to see certain pathologies arising from failure to maintain proper tuning.

To test the network in various states of detuning, we impose the input shown in **Fig. 3a** with the modulatory scheme indicated in **Fig. 3b**. Panel i is the control condition with no signal or modulation imposed, panel ii has no signal but the signal-carrying pathway is gain modulated, and panels iii and iv show the signal in the presence (iii) and absence (iv) of modulation. When correctly tuned, the excitatory neurons of the target subnetwork responds as in **Fig. 3c**, with a slight elevation in firing rate due to the activation of the gain modulation (panel ii), a strong response to the input signal in the presence of modulation (panel iii) and a weak response when the signal is present but modulation is not (panel iv).

We consider two different examples of detuning. In one case, we reduce the synaptic strength of all the locally connected interneurons by 60%. This has a number of effects (**Fig. 3d**). Baseline rates in the control condition are somewhat elevated, even in the balanced state, by the reduced inhibitory activity (**Fig. 3d(i)**). Little change is seen in the response to the gain modulation (**Fig. 3d(ii)**), but **Fig. 3d(iii, iv)** show that the gating mechanism no longer works properly. Due to the weakened inhibition, excitatory inputs to the excitatory neurons of layer 2 cannot be fully balanced by local inhibition, and the signal cannot be gated off entirely (**Fig. 3d(iv)**). If we associated the local inhibitory neurons in our model network with parvalbumin postive (PV+) inhibitory neurons in cortex, the failure of gating in this model with reduced inhibition could provide a functional basis for the hypothesis that reduced GABA production in PV+ interneurons may contribute to gating problems in schizophrenia [13].

Another way to detune the detailed balance in our network model is to increase the strengths of excitatory synapses within the target area, which we do by 60%. Excitatory synapses onto excitatory and inhibitory neurons are both modulated in the same way, so a rough balance is still maintained within layer 2. Like reduced inhibition, this slightly elevates firing rates in the control condition (**Fig. 3e(i)**). In response to gain modulation, reduction of inhibitory activity combined with the enhanced excitation in layer 2 causes high firing rates even in the absence of a signal (**Fig. 3e(ii)**). We hypothesize that upstream areas would have difficulty distinguishing the sharp rise in activity in response to the anticipatory modulatory gating signal from the actual response to the input signal itself (**Fig. 3e(iii)**), which is hardly bigger in this case. Thus, in this state, the network might falsely transmit internally generated activity (the gating signal) as if it were an external signal. The inability to discriminate between external and internal activity could be related to the hallucinatory and delusional effects that have been hypothesized to be due to pathological neuromodulation through defective dopaminergic regulation [15, 18] or NMDA hypofunction [11, 13, 21, 29] in schizophrenia. In the case of excess excitation, gating of the input signal still functions properly (**Fig. 3e(iv)**), but the effects of insufficient local inhibition and excessive excitation can be combined so that gating problems and false signal reporting occur in the same network (**Fig. 3f**).

Schizophrenia is a complicated, multifaceted disorder, and simple models like the one described here unavoidably fail to encompass it. Nevertheless, some parallels are intriguing. **Fig. 4** shows a summary diagram of some of the hypothesized causes of schizophrenia at the cellular and synaptic levels (adapted from [13], see also [6]). Both of the pathologies seen in the wiring scheme in **Fig. 4** — deficits in PV+ interneurons and hyperexcitability due to NMDA/dopamine malfunction — can be related to detuning scenarios we have proposed. The balancing problems we discussed could be found at either the dendritic level, manifesting themselves in dendritic computation and most likely controlled by basket cells, or within the integrating stages at the soma, where detailed balance could be coordinated by chandelier cells. Most likely, imbalance results from a mix-

ture of both of these, and perhaps they are independently controlled by different downstream regions.

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References

1 *Abeles M*. Corticonics: neural circuits of the cerebral cortex. Cambridge University Press: Cambridge 1991; 28
2 *Aertsen A*, *Diesmann M*, *Gewaltig MO*. Propagation of synchronous spiking activity in feedfor-ward neural networks. J Physiol Paris 1996; 90: 243–247
3 *Amit DJ*, *Brunel N*. Model of global spontaneous activity and local structured activity during delay periods in the cerebral cortex. Cereb Cortex 1997; 7: 237–252
4 *Anderson CW*, *Essen DC Van*. Shifter circuits: a computational strategy for dynamic aspects of visual processing. Proc Natl Acad Sci USA 1987; 84: 6297–6301
5 *Brunel N*. Dynamics of networks of randomly connected excitatory and inhibitory spiking neurons. J Physiol Paris 2000; 94: 445–463
6 *Carlsson A*. The neurochemical circuitry of schizophrenia. Pharmacopsychiatry 2006; 39: S10–S4
7 *Destexhe A*, *Contreras D*. Neuronal computations with stochastic network states. Science 2006; 314: 85–90
8 *Diesmann M*, *Gewaltig MO*, *Aertsen A*. Stable propagation of synchronous spiking in cortical neural networks. Nature 1999; 402: 529–533
9 *Germuska M*, *Saha S*, *Fiala J*, *Barbas H*. Synaptic distinction of laminar-specific prefrontal-temporal pathways in primates. Cereb Cortex 2006; 16: 865–875
10 *Haider B*, *Duque A*, *Hasenstaub AR*, *MacCormick DA*. Neocortical network activity in vivo is generated through a dynamic balance of excitation and inhibition. J Neurosci 2006; 26: 4535–4545
11 *Jackson ME*, *Homayoun H*, *Moghaddam B*. NMDA receptor hypofunction produces concomitant firing rate potentiation and burst activity reduction in the prefrontal cortex. Proc Natl Acad Sci USA 2004; 101: 8467–8472
12 *Kumar A*, *Schrader S*, *Aertsen A*, *Rotter S*. The High-Conductance State of Cortical Networks. Neural Computat 2007, (in press)
13 *Lewis DA*, *Gonzalez-Burgos G*. Patho-physiologically based treatment interventions in schizophrenia. Nat Med 2006; 12: 1016–1022
14 *Lewis DA*, *Hashimoto T*, *Volk DW*. Cortical inhibitory neurons and schizophrenia. Nat Rev Neurosci 2006; 6: 312–324
15 *Moore H*, *West AR*, *Grace AA*. The regulation of forebrain dopamine transmission: relevance to the pathophysiology and psychopathology of schizophrenia. Biol Psychiatry 1999; 46: 40–55
16 *Morrison P*, *Murray R*. M. Primer: Schizophrenia. Curr Biol 2005; 15 (24): 980–984
17 *Olshausen BA*, *Anderson CH*, *Essen DC Van*. A neurobiological model of visual attention and invariant pattern recognition based on dynamical routing of information. J Neurosci 1993; 13: 4700–4719
18 *Seeman P*. Dopamine receptors and the dopamine hypothesis of schizophrenia. Synapse 1987; 1: 133–152
19 *Shadlen MN*, *Newsome WT*. Noise, neural codes and cortical organization. Curr Opin Neu-robiol 1994; 4: 569–579
20 *Shu Y*, *Hasenstaub A*, *MacCormick DA*. Turning on and off recurrent balanced cortical activity. Nature 2003; 423: 288–293
21 *Tamminga C*. Schizophrenia and glutamatergic transmission. Crit Rev Neurobiol 1998; 12: 21–36
22 *Troyer TW*, *Miller KD*. Physiological gain leads to high ISI variability in a simple model of a cortical regular spiking cell. Neural Comput 1997; 9: 971–983
23 *Rossum MC Van*, *Turrigiano GG*, *Nelson SB*. Fast propagation of firing rates through layered networks of noisy neurons. J Neurosci 2002; 22: 1956–1966
24 *Vreeswijk C van*, *Sompolinsky H*. Chaos in neuronal networks with balanced excitatory and inhibitory activity. Science 1996; 274: 1724–1726
25 *Vogels TP*, *Rajan K*, *Abbott LF*. Neural Networks Dynamics. Ann Rev Neurosci 2005; 28: 357–376
26 *Vogels TP*, *Abbott LF*. Signal propagation and logic gating in networks of Integrate-and-Fire Neurons. J Neurosci 2005; 25: 10786–10795
27 *Vogels TP*, *Abbott LF*. Signal gating and detailed balance in neuronal networks submitted 2007
28 *Wang XJ*. Toward a prefrontal microcircuit model for cognitive deficits in schizophrenia. Pharmacopsychiatry 2006; 39: S80–S87
29 *Winterer G*. Cortical microcircuits in schizophrenia–the dopamine hypothesis revisited. Pharmacopsychiatry 2006; 39: S68–S71