[Re] Modeling GABA Alterations in Schizophrenia: A Link Between Impaired Inhibition and Gamma and Beta Auditory Entrainment

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A reference implementation of

→ Modeling GABA Alterations in Schizophrenia: A Link Between Impaired Inhibition and Gamma and Beta Auditory Entrainment, D. Vierling-Claassen, P. Siekmeier, S. Stufflebeam and N. Kopell, Journal of Neurophysiology(99):2656-2671, 2008, doi:10.1152/jn.00870.2007

Introduction

We provide an implementation of [5], which models impaired auditory entrainment in the gamma range for schizophrenic patients. Particularly, we only reimplement the simplified network model and do not replicate the biophysically more detailed Genesis model which is also developed in the article.

In the original article the authors conduct an MEG study of auditory entrainment and find changes in gamma and beta range entrainment found in schizophrenic patients. These changes in oscillatory dynamics in patients are important for two reasons: First, gamma range oscillations emerge in a variety of different tasks and are thought to underlie many cognitive processes (see e.g. [2, 3]). Furthermore, impaired gamma range oscillations in schizophrenic patientas have been found in most of these tasks and might offer an explanation for the cognitive deficits found in patients. Therefore, the study of the mechanisms underlying oscillatory entrainment might shed light on the basic principles that are responsible for a wide range of deficits in schizophrenic patients Second, oscillatory entrainment is a promising candidate for a neurophysiological biomarker for schizophrenia [4]. In the original article they develop two models that are able to account for the changes they find in their experimental data. One is a biophysically detailed network model and the other one a simplified network model. In both models a prolonged decay at GABAergic inhibitory synapses causes the reduction in gamma entrainment and the increase in beta entrainment. The simplified network model, despite its many simplifications, offers insight into the mechanisms underlying these entrainment deficits while focusing on a few key parameters. This makes it easy to distill and understand underlying dynamics and mechanisms and, at the same time, makes simulations computationally very inexpensive allowing for an extensive exploration of the parameter space. Additionally, again because of the simplicity, the model can easily be extended to study the effect other parameters (e.g. sparsity of connections, different populations of inhibitory neurons, different types of synaptic receptors,...), without loosing much of its simplicity.

We focus on the main results of the original article: an increase in inhibitory decay time constants leads to a reduction of power in the gamma range and an increase in power in the beta range, replicating experimental findings for schizophrenic patients. Therefore, we reproduce Figures 4,5,6,7,10 and 11 of the original paper. The original model is implemented using Matlab but the source code is not publicly available. The model and analysis scripts are implemented using Python 2.7.9. All simulations were run under Ubuntu 15.04.

Methods

The model was implemented solely from the paper description, since the original code is not publicly available. The model is a simple model consisting of two neural populations (excitatory and inhibitory cells). Individual cells are modeled as theta neurons (for a detailed discussion of this neuron model see [1]). The neuron is described by a single variable θ, which can be regarded as the membrane voltage, subject to the following dynamics

$$\frac{d\theta}{dt} = 1 - \cos\theta + (b + S + N(t)) \cdot (1 + \cos\theta),$$

where b is an externally applied current, S is the total synaptic input to the cell and $N(t)$ is a time-varying noise input. Total synaptic input to a cell in a network is calculated as

$$S_k = \sum_{j=1}^{n} \alpha_j \cdot g_{jk} \cdot s_{jk},$$

where $\alpha_j = \pm 1$ controls excitation and inhibition, g_{jk} is the synaptic strength from cell j to cell k and s_{jk} is the synaptic gating variable from cell j to cell k. Synaptic gating variables are subject to the following dynamics

$$\frac{ds_{jk}}{dt} = -\frac{s_{jk}}{\tau_j} + e^{-\eta\cdot(1+\cos\theta_j)} \cdot \frac{1 - s_{jk}}{\tau_R},$$

where τ_j is the synaptic decay time and τ_R the synaptic rise time. The network receives excitatory drive input at click train frequency from a single pacemaker cell. Additionally, Poissonian noise input is also given to all cells in the network. A noise spike at time t_n elicits the following 'EPSC'

$$N = H(t - t_n) \cdot \frac{A \cdot g_{gmax} \cdot (e^{-(t-t_n)/\tau_{exc}} - e^{-(t-t_n)/\tau_R})}{\tau_{exc} - \tau_R},$$

where $A \cdot g_{gmax}$ is the strength of the noise and again τ_{exc} is the synaptic decay time and τ_R the synaptic rise time.

Each population connects to itself and to the other with an all-to-all connectivity. Both populations also have two sources of input, the oscillatory drive input and a background noise input. The drive input periodically sends spikes to both populations with a given frequency, whereas the background noise input sends noise spikes at times drawn from a Poisson distribution. Table 1 summarizes the network model. Tables 2 and 3 list the parameters of the model and the simulations, their definitions and values, respectively.

The model was implemented using Python 2.7.9 using numpy 1.9.3. Visualisation of results was also done in Python using the matplotlib module (matplotlib 1.4.3). Furthermore, since the model is computationally very inexpensive, we did not aim to provide the most efficient implementation but rather an implementation that is clear, and easy to understand and use.

All differential equations are solved using a simple forward Euler scheme. As in the original article a single simulation simulatesa 500ms trial and the time step is chosen such that this results in 2ˆ13 = 8192 data points. However, the main results are unaffected by a smaller time step.

Table 1: Model summary

Populations	One excitatory and one inhibitory population
Topology	None
Connectivity	All-to-all
Neuron model	Theta model
Synapse model	(Quasi-)Instantaneous rise, exponential decay
External input	Poisson noise and periodic drive to both populations
Recordings	Theta variables (both populations); 'MEG' signal (summed EPSCs at exc. neurons)

Table 2: Model parameters

Parameter	Definition	Value
n_E	Exc. population size	20
n_I	Inh.population size	10
τ_R	Synaptic rise time	0.1
τ_{exc}	Excitatory decay time	2.0
τ_{inh}	Inhibitory decay time (control)	8.0
τ_{inh}	Inhibitory decay time (schizophrenia)	28.0
g_{ee}	E-E synaptic strength	0.015
g_{ei}	E-I synaptic strength	0.025
g_{ie}	I-E synaptic strength	0.015
g_{ii}	I-I synaptic strength	0.02
g_{de}	Synaptic strength of drive to E cells	0.3
g_{di}	Synaptic strength of drive to I cells	0.08
b	Applied current (regardless of cell type)	-0.1
Ag_{max}	Scaling factor for noise EPSCs	0.5

Table 3: Simulation parameters

Parameter	Value
Time step (dt)	0.061
Number of data points	8192 ($= 2^{13}$)
Total time	500ms

Results

As explained in the introduction, we only replicated the simple model from [5], and **not** the GENESIS model. We aimed to reproduce Figures 4 (raw, simulated MEG signal) and 5 (power spectra for MEG signals from Figure 4) from [5], which show the main results of the model (summarized in Table 4).

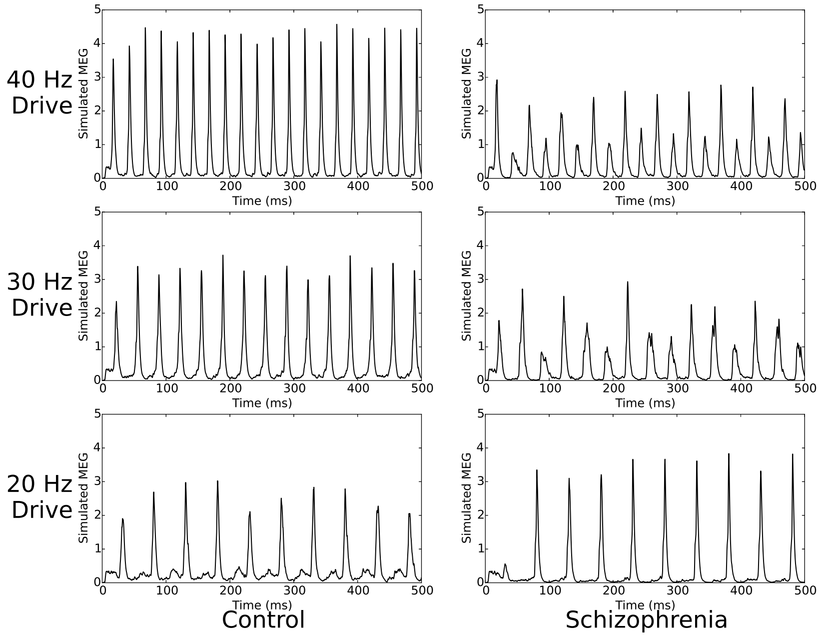

Figure 1: Replication of Figure 4: Raw simulated MEG signals (averaged over 20 trials) for the control and the schizophrenic network at the three different driving frequencies.

Table 4: Model parameters

Drive	Control subjects	Schizophrenic patients
40 Hz	Strong entrainment to the drive, no power in frequency bands apart from 40 Hz	Weaker entrainment to the drive, emergence of a subharmonic component (at 20 Hz)
30 Hz	Strong entrainment to the drive, no power in frequency bands apart from 30 Hz	Strong entrainment to the drive, no power in frequency bands apart from 30 Hz
20 Hz	Entrainment to the drive, however, more power in the harmonic 40 Hz band	Stronger entrainment to the drive, less power in the harmonic band

Figures 1 and 2 show the output of the replicated model for the same simulations as for Figures 4 and 5 from the original article. The main charactersitics described above can be clearly seen. However, in our model these main features are a little bit less pronounced than in the original model. Since the network model receives Poissonian noise (which is quite strong), this difference may simply stem from a difference in noise. Furthermore, we have to mention the differences in amplitude for the simulated MEG signals (and accordingly the power spectra thereof) between the original model and our replication, which we believe stems from a scaling in the original model. However, since the original source code is not available, we cannot verify that.

After having looked at the model output averaged over 20 trials with different noise, we also show single trial data which exemplify the main model features , as was done in the original article. Figures 3 and fig:Vierling7 show the model output in response to 40 Hz drive input for the control and the schizophrenia network, respectively. The strong entrainment in the control case, the reduction of entrainment and the emergence

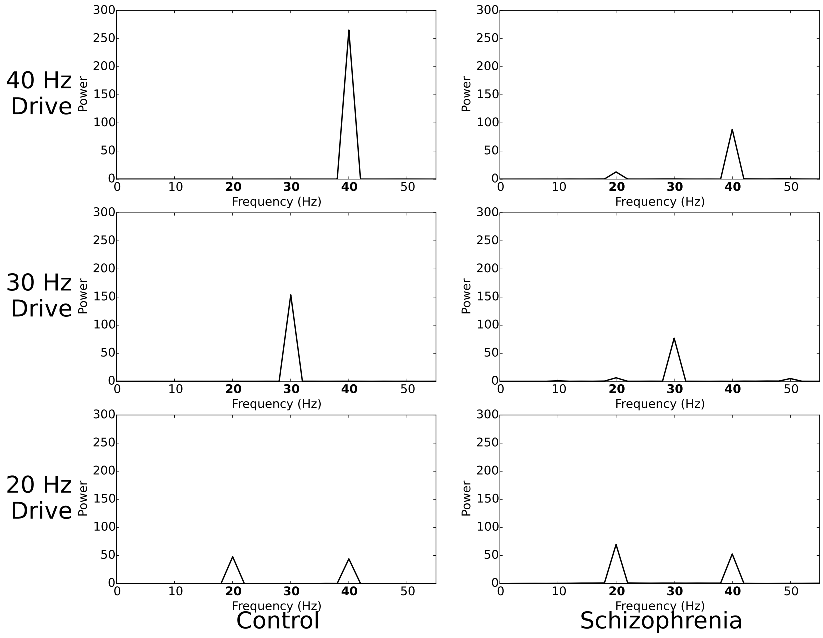

Figure 2: Replication of Figure 5: Power spectra of the averaged MEG signals from 1

of a subharmonic 20 Hz component are again clearly visible. However, as before, in our model implementation the emergent 20 Hz component is less pronounced than in the original implementation (best seen in the excitatory population activitydisplayed in the raster plot of 4).

Figures 5 and 6 show the model output in response to 20 Hz drive for the control and the schizophrenia network, respectively. Again, main features of the original model are faithfully reproduced.

Conclusion

Overall, we believe we have faithfully reproduced the main fetaures of the simple model from [5]. However, we note that overall features a re a little bit less pronounced in our reimplementation compared to the original model. This may simply stem from a difference in noise between the two sets of simulations.

References

[1] Christoph Börgers and Nancy Kopell. "Synchronization in networks of excitatory and inhibitory neurons with sparse, random connectivity". In: *Neural computation* 15.3 (2003), pp. 509–538.

[2] Pascal Fries. "A mechanism for cognitive dynamics: neuronal communication through neuronal coherence". In: *Trends in cognitive sciences* 9.10 (2005), pp. 474–480.

[3] Pascal Fries. "Rhythms for cognition: communication through coherence". In: *Neuron* 88.1 (2015), pp. 220–235.

[4] Peter J Siekmeier. "Computational modeling of psychiatric illnesses via well-defined neurophysiological and neurocognitive biomarkers". In: *Neuroscience & Biobehavioral Reviews* 57 (2015), pp. 365–380.

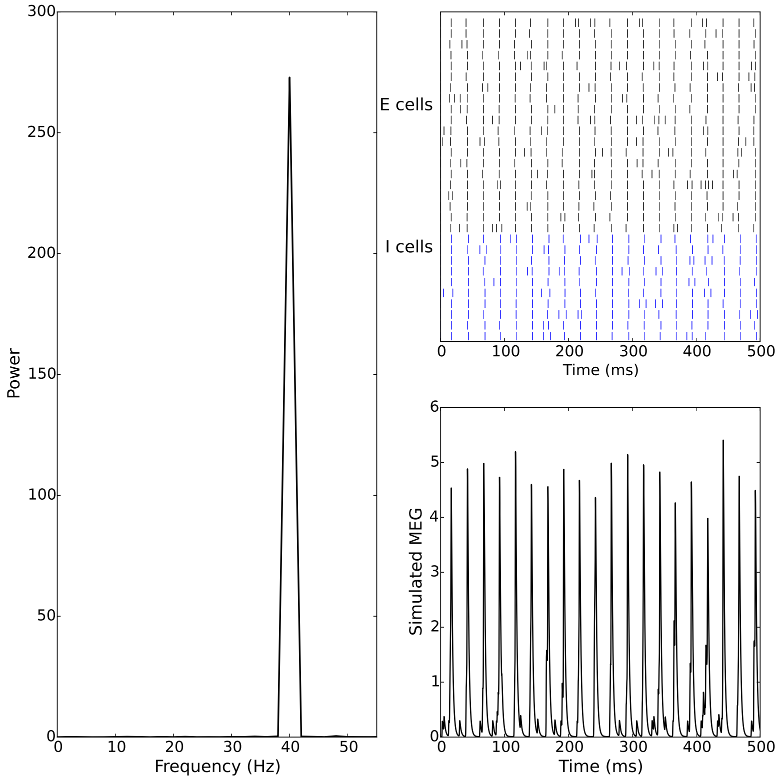

Figure 3: Replication of Figure 6: Single trial from the control network. 40 Hz drive. Network entrains to 40 Hz, as can be seen in the frequency diagram, raster plot and MEG trace.

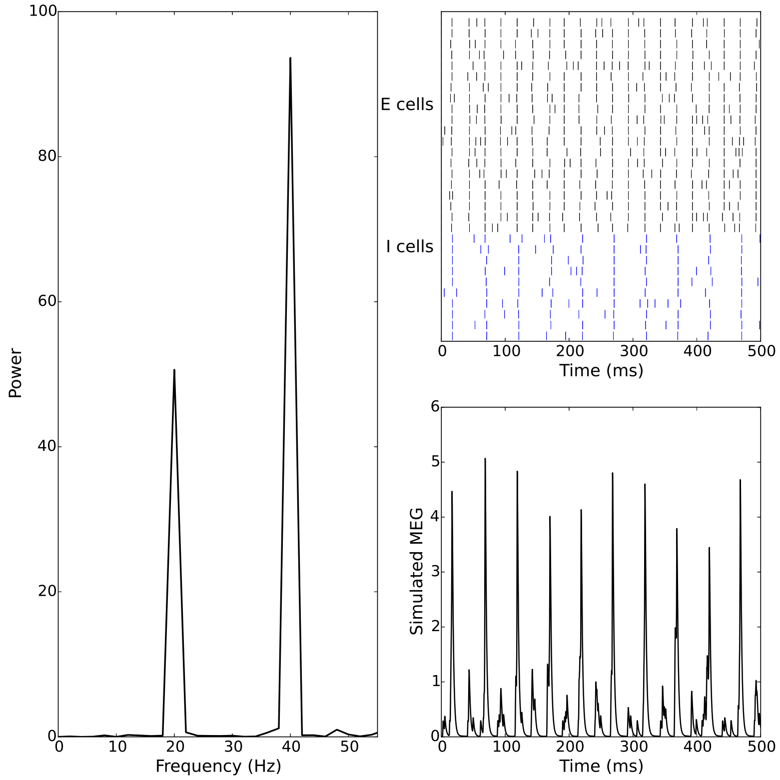

Figure 4: Replication of Figure 7: Single trial from the schizophrenia network. 40 Hz drive. Network entrains to 40 Hz but also shows a strong 20 Hz component, as can be seen in the frequency diagram, raster plot and MEG trace. Especially the inhibitory neurons only entrain to a 20 Hz rhythm (see raster plot).

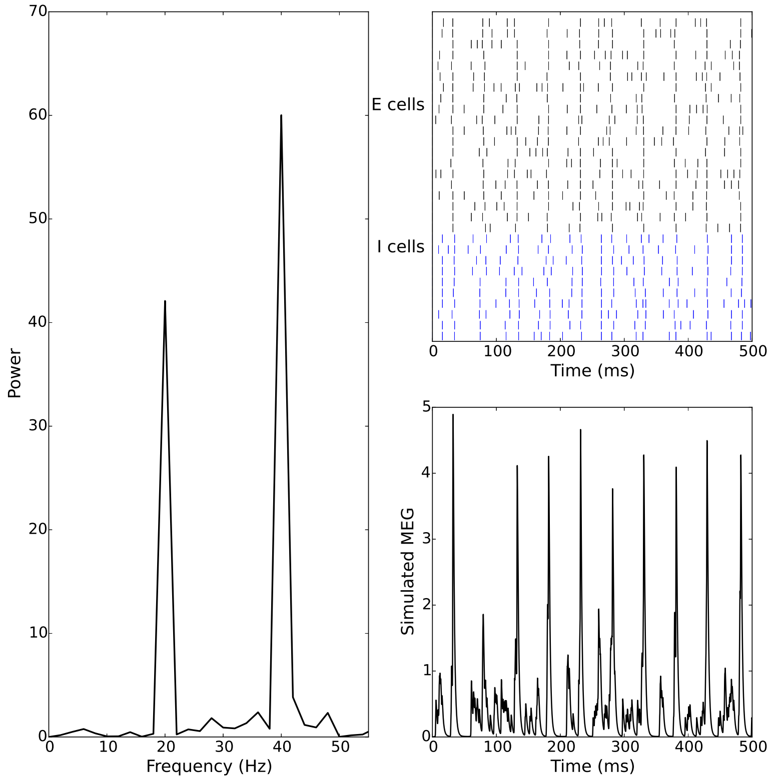

Figure 5: Replication of Figure 10: Single trial from the control network. 20 Hz drive. Network entrains to 20 Hz but also shows a 40 Hz component, as can be seen in the frequency diagram, raster plot and MEG trace.

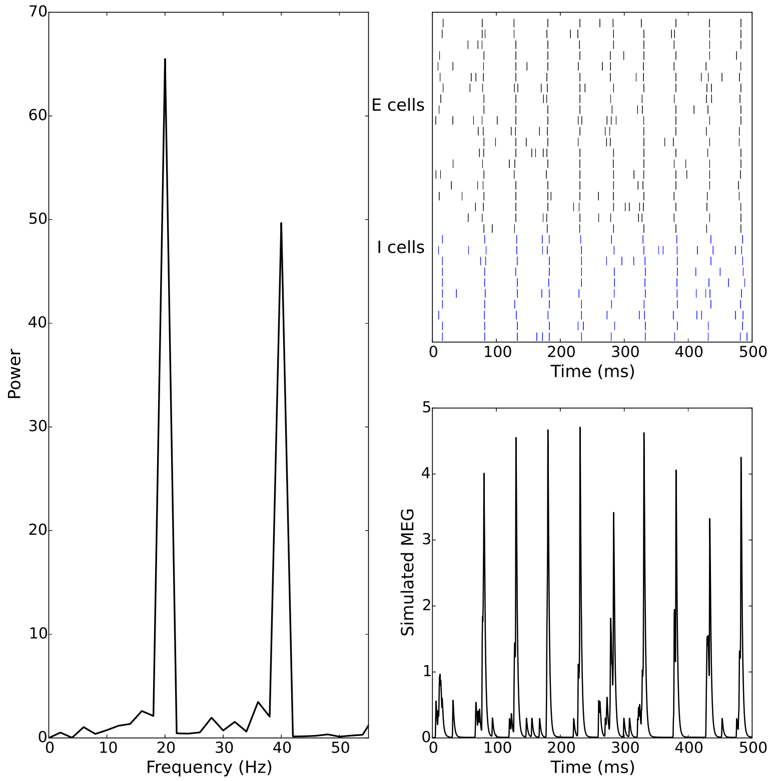

Figure 6: Replication of Figure 11: Single trial from the schizophrenia network. 20 Hz drive. Network entrains to 20 Hz without 40 Hz component, as can be seen in the frequency diagram, raster plot and MEG trace. note that the 40 Hz power in the power spectrum is a harmonic.

[5] Dorea Vierling-Claassen et al. "Modeling GABA alterations in schizophrenia: a link between impaired inhibition and altered gamma and beta range auditory entrainment". In: *Journal of Neurophysiology* 99.5 (2008), pp. 2656–2671.