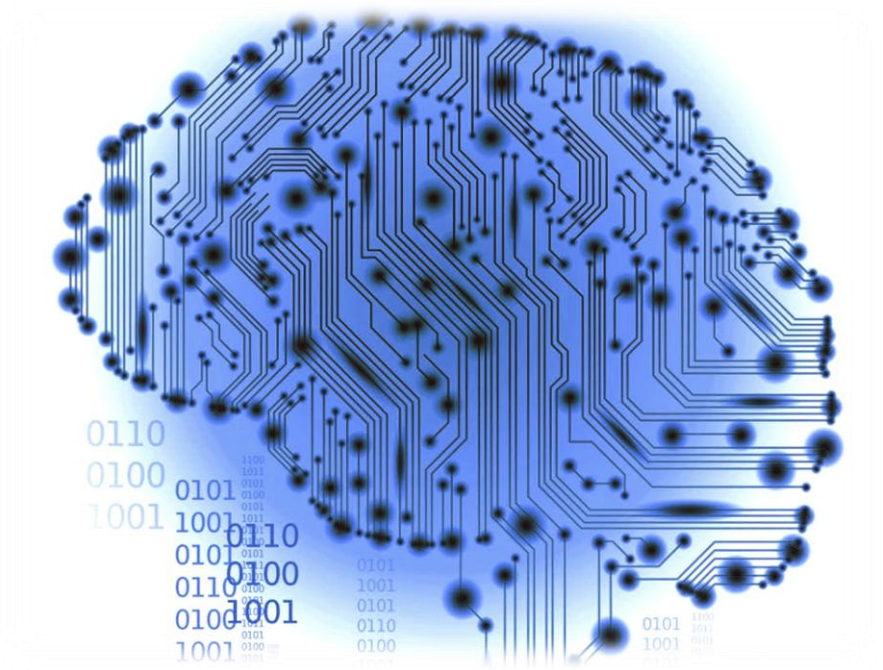
Influence of external input and inhibitory synapses on the balance of a sparsely connected network.

Bachelor thesis psychobiology



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ABSTRACT TO BE DONE

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Introduction

Cortical cells *in vivo* typically show irregular firing in response to sensory stimuli, whereas the same cells show regular firing behavior in response to current injections *in vitro* (Softky & Koch, 1993). How this irregular behavior *in vivo* arises remains a topic for debate. One theory is that if neurons receive a lot of weak input, the average input would be constant and therefore the postsynaptic neuron would fire regularly. To explain the irregular firing behavior, the input should be synchronized or the dendrites should be non linear (Softky & Koch, 1993). A contradictory explanation states that synchronization is not necessary as long as there is a strong balance between excitation and inhibition. As a consequence, the average of the input is subthreshold. Because of the stochasticity of the input, neurons respond to minor deviations from the average, which leads to irregular firing (Shadlen & Newsome, 1998).

The balanced random network (Brunel, 2000; Remme & Wadman, 2012; Yger & Harris, 2013), also called balanced network, is a large-scale network of sparsely connected Leaky Integrate-and-Fire (LIF) neurons. It is called balanced, because the network activity neither attenuates nor increases after initialization. The network activity remains constant over time. A LIF neuron uses a linear approximation of the subthreshold membrane potential, and therefore only uses very few parameters. A spike itself is not modeled. The behavior of a balanced network of the simplest LIF neurons is extensively examined, both analytically and computationally (Brunel, 2000).

Brunel (2000) showed that a balanced network can settle in four different states, which are based on the synchrony of the network and the regularity of single neurons. The network can reach the synchronous regular (SR) state, where single neurons fire regularly with a time constant similar to the refractory period and the network is synchronized. If single neurons fire regularly but the network activity is asynchronous, it is called the asynchronous regular (AR) state. If individual neurons fire irregularly, the network could reach the synchronous irregular (SI) and the asynchronous irregular (AI) states. It which state the network settles depends on several key parameters, including the following: the amount of external input (each neuron receives stochastic background input) and the relative strength of the inhibitory synapses (see Figure 1).

A recent study showed that a network model with more biological plausible LIF neurons, in which the synapse is described in more detail, can reach the balanced state as well (Yger &

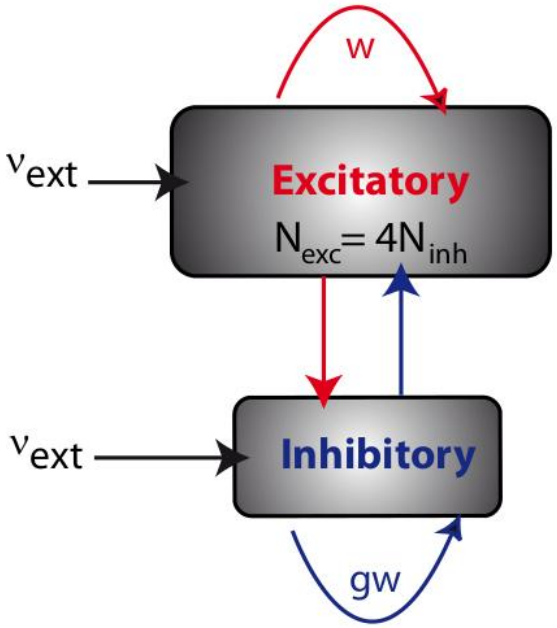

Figure 1. Visualization of a balanced network. A balanced network with populations of excitatory and inhibitory neurons, each connected both with itself and with each other. Each neuron receives 4 times more excitatory than inhibitory connections. Moreover each neuron receives external input. In this network model, w is the synaptic strength of the excitatory connections, g is the relative weight of the inhibitory connections and ν_{ext} is the frequency of the external input . (From Yger, n.d.)

Harris, 2013). However, it is still unknown if these networks can reach the different states of synchrony and regularity, and whether the transitions between these states are similar to those of the network with a simpler synapse model. **Therefore, in this thesis I examined whether a network model with more biological plausible synapses can reach the same states as the original network with respect to synchrony and regularity.** The hypothesis is that a balanced state will be reached, and that it is possible to differentiate between the different states, although the exact ranges of parameter values at which the transitions occur will differ from the simpler model.

To examine this hypothesis, I implemented a balanced network of LIF neurons and systematically quantified the regularity of the individual spike trains and the synchrony of the network. Different combinations of two parameters were used: the external input and relative strength of inhibitory synapses, which were the key parameters in Brunel (2000. It is expected that it is possible to differentiate between the four states based on the quantification. Whether the ranges of the parameter values are similar to the simple model is unknown, as the involved parameter influence many other parameters in the model as well.

Materials and Methods

Simulations

Simulations of the spiking neural networks were performed using the BRIAN 2 simulator (Goodman & Brette, 2009) with a fixed time step $dt = 0.1\,ms$ and a membrane time constant of $\tau_m = 20\,ms$. All simulations were performed on a Packard bell EasyNote TK with 4GB RAM and 2,3 GHz AMD Athlon II P360 processor.

Simple neuron model

For the simple LIF neuron model (adapted from Brunel, 2000*)* the following equation is used:

$$\tau_m \frac{dV_i}{dt} = -V_i + RI_{ext_i}(t),$$

where $RI_{ext_i}(t)$ is the external input each neuron receives. It is assumed that the external input each neuron receives is an excitatory Poisson spike train with frequency ν_{ext}. This external input is described by the following equation:

$$RI_{ext_i}(t) = \mu_{ext} + \sigma_{ext}\sqrt{\tau}\eta_i(t),$$

where μ_{ext} represents the mean of the Poisson spike train and is described by the following equation:

$$\mu_{ext} = \nu_{ext}\theta$$

θ is the spike-threshold of the neuron. The second part of the external input,

$\sigma_{ext}\sqrt{\tau}\eta_i(t)$, represents the fluctuations around the mean where σ_{ext} is described by

$$\sigma_{ext} = J\sqrt{C_E \nu_{ext} \tau}$$

J represents the PSP amplitude, C_E represents the number of connections of excitatory neurons and $\eta_i$represents Gaussian white noise with mean = 0 and SD = 1. Besides external input, each neuron receives input from other neurons in the network. The change of the membrane potential $V_i(t)$ is described by:

$$V_i(t) \rightarrow V_i(t) + \Delta V$$

$$\Delta V = -g_{ij}J$$

where ΔV is the change of the postsynaptic membrane potential (i) as a consequence of presynaptic spike firing (j) and g is the relative strength of a inhibitory synapse ($g = -1$ for excitatory synapses). The other parameter values were kept fixed at the following values: $\theta = 20\,mV$, $J = 0.1\,mV$, the transmission delay $D = 1.5\,ms$, the refractory period $\tau_{rp} = 2\,ms$ and the reset value after a spike $V_r = 10mV$, all extracted from *Brunel, 2000*. Because the study of *Brunel, 2000* showed that the relative strength of the inhibitory synapses g and the external firing rate ν_{ext} separated the four states best, I used these as the parameters which are varied in order to differentiate between the different states.

The number of excitatory (N_E) versus inhibitory (N_I) neurons are, resembling the ratio of anatomical estimates for neocortex, respectively 1600 and 400. The sparseness of the network (ε), which is described by

$$\varepsilon = \frac{\text{total number of synapses}}{\text{total number of all possible synapses}}$$

was 0.1 with a total number of neurons $N_{tot} = 12500$ (Brunel, 2000). However, to keep simulations feasible, the number of neurons was scaled down to $N_{new} = 2000$. As a consequence, the sparseness had to be scaled as well in order to preserve the same balance (Golomb & Hansel, 2000). This new sparseness (ε_{nieuw}) value is described by:

$$\frac{1}{\varepsilon_{new}} - \frac{1}{N_{new}} = \frac{1}{\varepsilon_{old}} - \frac{1}{N_{old}}$$

where $N_{new} = 2000$, $\varepsilon_{old} = 0.1$ and $N_{old} = 12500$. After application of this scaling, the sparseness of the network ε_{new} = 0.4098. This means that every neuron has a probability of 0.4098 it receives a connection from any other neuron.

More complex neuron model

In the biologically more realistic network, a similar neuron model was used as in Brunel (2000), but the synapses were modeled differently. After a presynaptic spike, not the postsynaptic membrane potential was updated, but the postsynaptic conductance, following a linear differential equation (Yger & Harris, 2013). This conductance change indirectly leads to a change in membrane potential.

In this network model model, the membrane potential of each neuron is given by:

$$\begin{aligned} C_m \frac{dV}{dt} = {} & g_{leak}(V_{leak} - V) \\ & + g_{exc}(t)(E_{exc} - V) \\ & + g_{inh}(t)(E_{inh} - V) \end{aligned}$$

where C_m is the membrane conductance, here defined as $\tau_m g_{leak}$. Remaining parameter values were extracted from Yger & Harris (2013) and kept fixed. These values are as follows: the leak conductance $g_{leak} = 10\,nS$, the resting membrane potential $V_{leak} = -75\,mV$, the threshold $V_{thresh} = -50\,mV$, the reset potential $V_{reset} = -55\,mV$ and the refractory period $\tau_{refrac} = 5\,ms$.

The synapses are modeled as instant changes in conductance when a spike is triggered,

followed by an exponential decay, described by:

$$\tau_{exc}\frac{dg_{exc}}{dt} = -g_{exc}$$

$$\tau_{inh}\frac{dg_{inh}}{dt} = -g_{inh}$$

where the excitatory and inhibitory synaptic time constant are $\tau_{exc} = 5\,ms$ and $\tau_{inh} = 10\,ms$ respectively and reversal potentials are $E_{exc} = 0\,mV$ and $E_{inh} = -80\,mV$.

To keep the simulations feasible, 800 excitatory and 200 inhibitory neurons are used. The sparseness ε = .1915, scaled from .05 with 4500 neurons, as described previously, in order to maintain the level of balance. Synaptic delays are randomly chosen from a uniform distribution between 0.1 and 5 ms. Initial synaptic conductances were randomly chosen from Gaussian distributions with means g_{exc} and g_{inh}, and standard deviations equal to a third of their means. The value of g_{exc} is kept fixed, $g_{exc} = 1\,nS$, whereas the value of g_{inh} is varied in order to examine its influence. Finally, each neuron receives input from an independent Poisson spike train at 300 Hz, through an excitatory synapse with conductance of g_{ext}. Because Brunel (2000) showed that variations of external input and the relative strength of the inhibitory synapses caused different balanced states, I use these parameters in this network model as well. Therefore, the inhibitory conductance, g_{inh}, and the conductance of the external input, g_{ext}, are varied in the simulations.

Quantification of regularity and synchrony of the more complex model

For the parameters g_{inh} and g_{ext} exploratory simulations, based on previous studies (Brunel, 2000; Yger & Harris, 2013), were performed in order to determine the range of values for the simulations. Based on these exploratory simulations, the range was set for g_{inh} between 1 and 10 nS and for g_{ext} between 2 and 11 nS, as values for $g_{ext} < 2\,nS$ result in a network with too little activity. Parameter values greater than the chosen range did not show different behavior than the highest values within the chosen range, and therefore were left out.

For these combinations of parameter values the single neuron activity is quantified for regularity and the network activity for synchrony. The regularity of a network is quantified as the average regularity over its neurons, given by the coefficient of variation (CV), of the inter-spike interval distribution of each spike train:

$$CV_{net} = \frac{1}{N}\sum_{i=1}^{N}\frac{SD_{ISI_i}}{mean_{ISI_i}}$$

where CV_{net} is the average CV value of a network, N the number of neurons in the network and ISI the distribution of the inter-spike-intervals for each neuron.

The synchrony of the network is quantified by the following synchrony measure (SM). The average of the three highest peaks of the global network activity is defined as the synchrony peak average (SPA). In order to correct for the total activity of the network, a randomly distributed Poisson spike train, with the same amount of spikes as the network model, is simulated. For this global activity the SPA is calculated as well. Then, the SM is described as follows:

$$SM_{net} = \frac{SPA_{net}}{SPA_{pst}}$$

where SM_{net} is the measure for synchrony of the network, SPA_{net} is the synchrony peak average of the network model and SPA_{pst} the synchrony peak average of the Poisson spike train, containing the exact same amount of spikes, but randomly distributed.

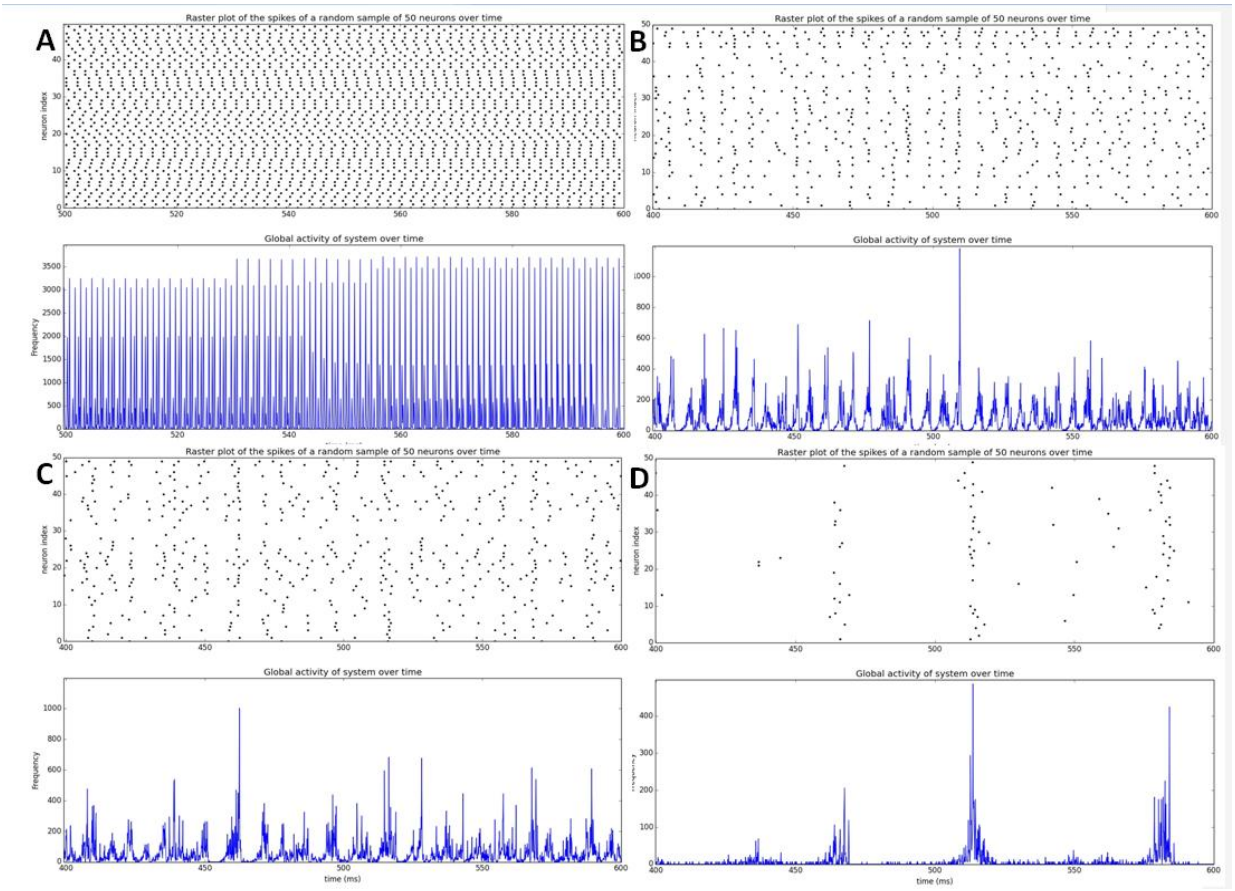

Figure 2. Classification of different states of a balanced network of the simple neuron model. Simulation of a network of 1600 excitatory and 400 inhibitory neurons with a sparseness of 0.4098. For all four situations the spiking behavior of 50 randomly chosen neurons of the population is shown in the upper plot, and the global activity of the network in the lower plot. **A.** The Synchronous Regular (SR) state, where neurons are synchronized and neurons spike regularly (only the during refractory period the neurons are silent; $g = 3$ & $\nu_{ext} = 2$). **B.** The Synchronous Irregular (SI) state, where there is synchrony in the global activity, but single neurons fire irregularly ($g = 6$ & $\nu_{ext} = 4$). **C.** The Asynchronous Regular (AR) state, where the network activity is asynchronous, but single neurons do tend to fire regularly ($g = 5$ & $\nu_{ext} = 2$). **D.** The Asynchronous Irregular (AI) state, where the network activity is asynchronous, and single neurons spike irregularly ($g = 4.5$ & $\nu_{ext} = 0.9$).

Clustering

After the quantification of both regularity and synchrony is completed, a k-means analysis was performed in order to objectively cluster the different parameter sets into different states (Arthur & Vassilvitskii, 2007). For the determination of the clusters the Elbow method is used (Ketchen Jr. & Shook, 1996). With this method the number of clusters is plotted against the total distance of the points of a cluster to the centre of that cluster. This distance usually decreases as the number of clusters increases. Initially the decrease is high and there usually is a flipping point after which the decrease is much lower. This is called the elbow point, and the value of the number of clusters of that point is used for the k means analysis. For the k-means analysis the regularity and synchrony data are scaled so both variables have the same weight in the determination of clusters. For the scaling each data point is divided by the total of the variable, so a fraction is used for the analysis.

Results

In order to examine whether the biologically more plausible neuron model can reach different states, based on synchrony and regularity as well, firstly it was examined whether the smaller simple neuron model could reach the same balanced states as in Brunel (2000). This was the case: the Synchronous Regular (SR) state was reached with $g = 3$ & $\nu_{ext} = 2$. The Synchronous Irregular (SI) state was reached with

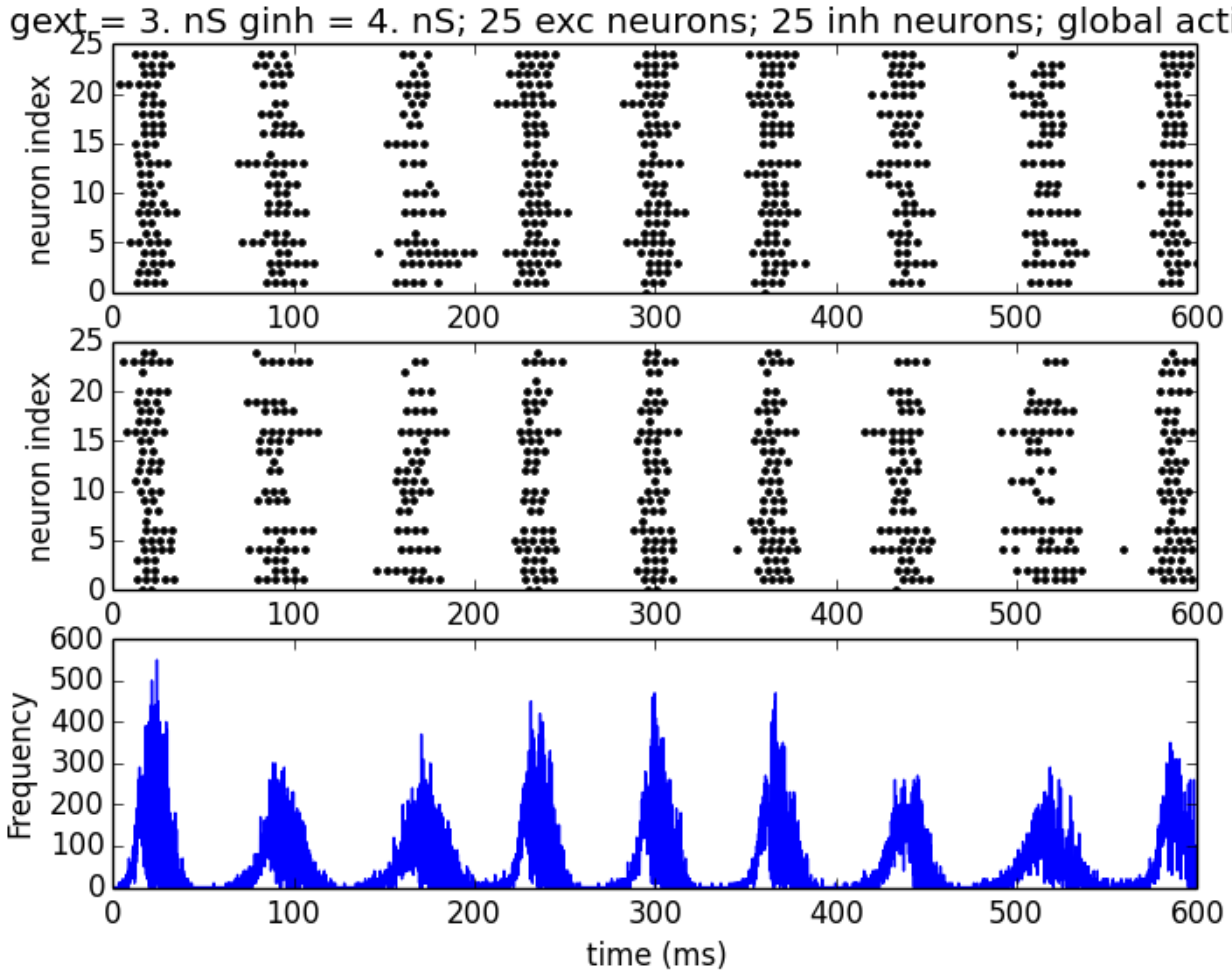

Figure 3. Network activity of a network in the Bursting State (BS). Simulation of a more complex neuron network of 800 excitatory and 200 inhibitory neurons with a sparseness ε =0 .1915. The spiking behavior of 50 randomly chosen neurons of the population is shown in the upper plot, and the global activity of the network in the lower plot. Parameters used are $g_{inh} = 4\ nS, g_{ext} = 3\ nS$ and the network shows bursting behavior.

$g = 6$ & $\nu_{ext} = 4$. The Asynchronous Regular (AR) state was reached with $g = 5$ & $\nu_{ext} = 2$. The Asynchronous Irregular (AI) state, was reached with $g = 4.5$ & $\nu_{ext} = 0.9$ (see figure 2). Since the smaller network could indeed reproduce the results of Brunel (2000), we proceeded with extending the model with the more complex synapse and examined whether that model could reach these four states as well.

To examine the behavior of the activity of the (small) network with the extended synapse model, exploratory simulations were conducted in order to determine the range in which the network activity shows different types of behavior. The initial parameter values of Yger & Harris (2013) were $g_{inh} = 8\ nS$ & $g_{ext} = 1\ nS$. Because all simulations with $g_{ext} = 1\ nS$ showed to little network activity, the ranges used for simulations were for g_{inh} between 1 and $9\ nS$ and for g_{ext} between 2 and $10\ nS$.

When the external input was increased and the inhibitory synaptic strength was kept low, the network reaches the SR state (SEE FIGURE TBD). When the synaptic strength of the inhibitory synapses was increased, roughly between 3 and $5\ nS$, the network reaches a state that was not described in the original network by Brunel (2000): a Bursting Synchronous state (BS; see Figure 3). When inhibition is increased more, the network

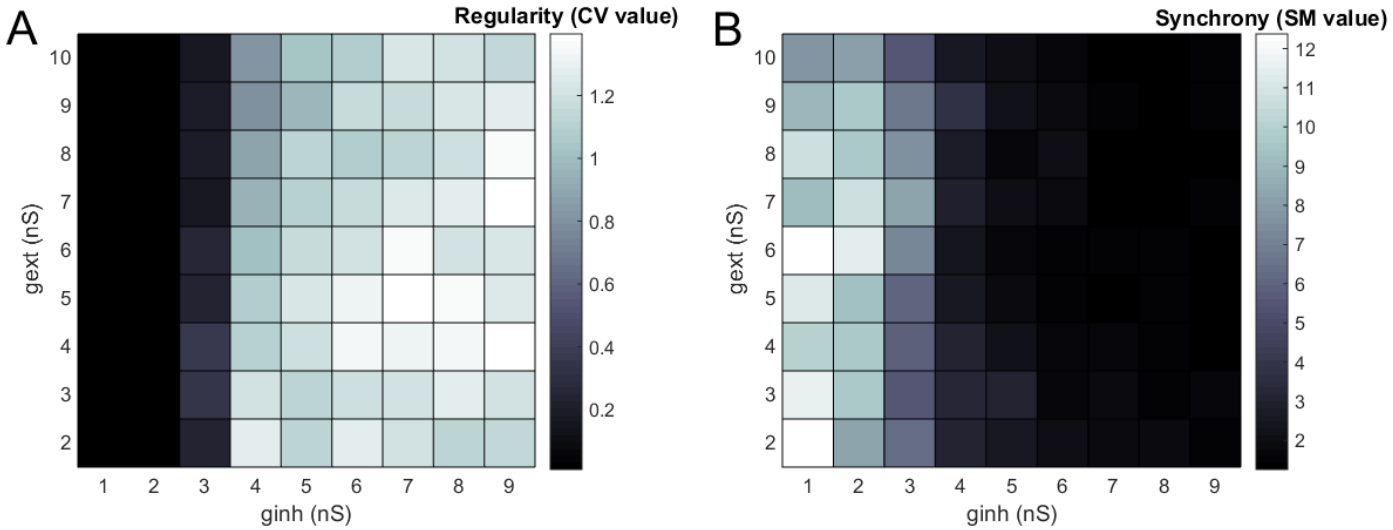

Figure 4. Plots of the degree of regularity (A) and synchrony (B) of balanced networks with more complex neurons with different parameter sets. A. the regularity of the network is plotted for the parameters $g_{inh} = 1 - 10\ nS\ and\ g_{ext} = 2 - 11\ nS$. **B.** the same ranges are used, but now the degree of synchrony is plotted.

activity shows a state similar to the AI state. However, without quantification it is hard to determine whether there are SI and AR states in these ranges of g_{inh} and g_{ext}. Therefore calculations to quantify regularity and synchrony were performed.

To be able to differentiate between the different states objectively, the Coefficient of Variation (CV) and the Synchrony Measure (SM; for both see Methods) were calculated for regularity and synchrony respectively. A low CV value means that the neurons on average spike regularly, CV values around 1 mean that on average the neural spike trains are similar to a Poisson process, and therefore highly irregular. The different values of the CV are plotted in Figure 4A. The figure shows that values of $g_{inh} < 3$, independent of the value of g_{ext}, all cause very regular spiking behavior. $g_{inh} = 3$ is a transition value, and all values of $g_{inh} > 3$ cause very irregular behavior.

For synchrony a similar approach was used; a high SM value signifies synchronous behavior. The SM values are plotted in figure 4B. Values of $g_{inh} < 3$ show very synchronous behavior. Moreover, for low values of g_{ext} the network shows more synchronous behavior than higher values of g_{ext}. When the measures for regularity and synchrony are combined, the SR state clearly stands out: for $g_{inh} < 3$ the CV values are relatively low and the SM values relatively high. However, classification of other states is harder, because the differences between the CV and SM values are smaller. Therefore, objective clustering is needed.

For objective clustering, the k-means analysis method is used. This is an algorithm which efficiently distributes the data in k clusters, and iterates until the total distance of all data point to the centre of their cluster is minimized (Arthur & Vassilvitskii, 2007). In order to determine the number of clusters, the elbow method is used (see Methods). As shown in Figure 5A, the flipping point is at 5 clusters, so k-means was performed with 5 clusters. The analysis revealed 5 quite clearly separated clusters (figure 5B): cluster 1 and 2 are the SR states. The difference between 1 and 2 is merely based on synchrony: the SM values of cluster 1 are between 10.7 and 12.4, whereas the SM values of cluster 2 are between 7.7 and 10.0. Because both states all states have a very low CV value and a high SM value, they are both classified with the SR state. The third cluster is a transition state, where some neurons are still in the SR state whereas others are more silent. The fourth cluster best represents the bursting state: the

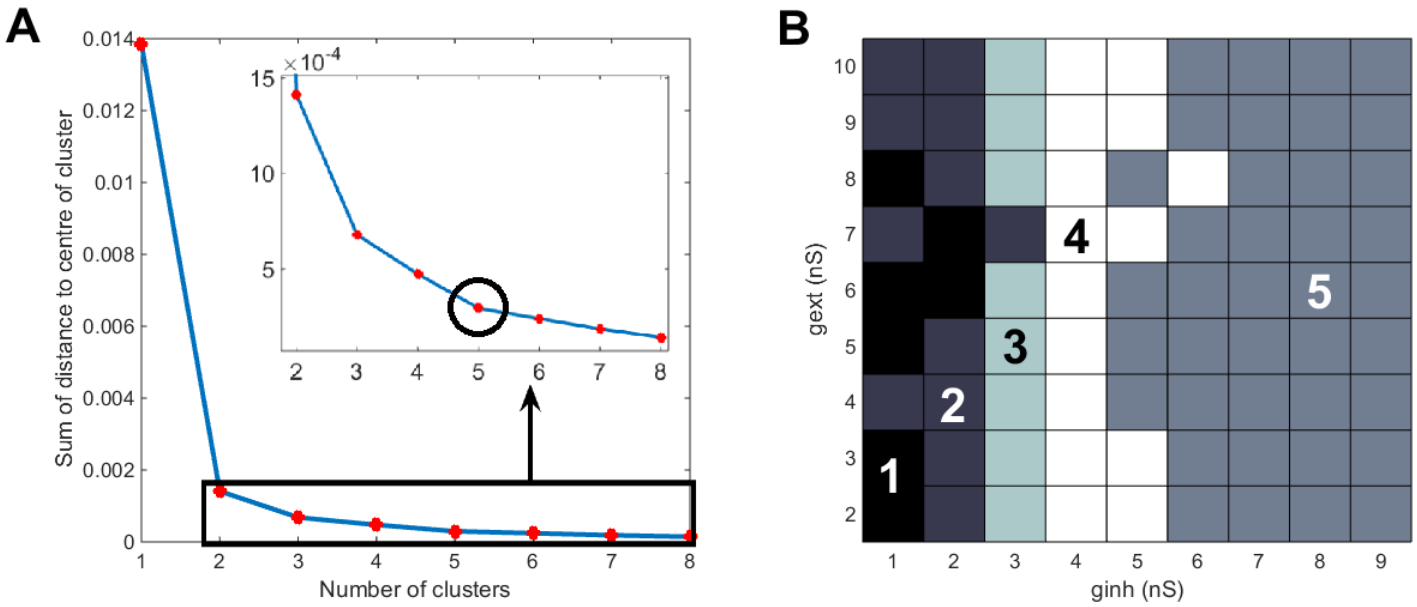

Figure 5. K means analysis of the more complex neuron model to cluster based on regularity and synchrony. A. The elbow method is shown. The flipping point is at 3 cluster, which means that 3 clusters are used for the k means analysis. **B. T**he output of the k means analysis is shown. Five clusters are grouped based on regularity and synchrony. Cluster 1 and 2 are the SR state, cluster 3 is a transition state, cluster 4 the bursting state and the fifth cluster the AI state.

synchrony is pretty high, but there is little regularity as there are within and between bursts phases. Cluster five is the AI state, where irregular neurons fire asynchronously.

Discussion

After four different balanced states of the simple small network model were found, I examined whether a more complex synapse model could settle in the same four different states, based on regularity and synchrony. Cluster analysis revealed five clusters, which could be separated in four different states. There synchronous regular state, a transition state, a bursting state and an asynchronous irregular state. The bursting state could also be called a synchronous irregular state. Compared to the simpler network model, this the more complex network model lacks the asynchronous regular state, and the synchronous irregular state shows strong bursting behavior. So the more complex model could reach balanced states, but the behavior differs from the simple neuron model, as the more complex model shows strong bursting behavior.

This difference in behavior could have several causes. Firstly, the adjusted synapse model, which makes the network more complex, could explain the difference. This conductance model, in which the conductance decays exponentially, causes a long-lasting postsynaptic membrane depolarization after a spike, keeping it close to the threshold when a following spike arrives. This positive feedback causes a high frequency firing, hence the initiation of a burst. Sin

decay of the conductance which was raised after a spike, causes that when a spike is fired, the postsynaptic neuron remains more sensitive for another spike. Therefore a neuron fires regularly in a burst. However, the time constant of the inhibitory synapse is higher, which means the inhibitory neurons remain longer sensitive so eventually the burst is inhibited and there is some time no spiking. After some time the external input is strong enough to get the neuron in a burst again.

Besides this explanation, which could be a plausible one, there is one other difference between the networks which could have a major influence. The more complex neuron

models has initial conductance weights drawn from a Gaussian distribution, whereas the simple model has fixed values. In the network behavior this is represented in the transition states, which is more present in the more complex model. This could be due this neuron characteristic, as there are neurons with low conductance and neurons with high conductance. This means that when g_{inh} increases some neurons with a high initial conductance still receive enough external input to fire regularly, whereas the neurons with a lower conductance receive too little external input en start firing less. This causes less regularity and synchrony, but enough to prevent the bursting state.

Moreover there is a whole range of other parameter set used for the more complex neuron model compared to the simple model. Two different models are used so it is impossible to explain the influence of every parameter. It is probable that the two parameters previously discussed have the biggest share in the different behavior, especially because this could be theoretically explained. However, it should be kept in mind that these two parameters are not the only candidates.

The simple neuron model, thoroughly examined by *Brunel, 2000,* was used to examine irregular behavior of a network in order to say something about was causes the irregular behavior in the human brain. In this study, an adaptation of the model of *Yger & Harris, 2013* is quantified for regularity and synchrony as well, and appears to behave as an asynchronous irregular network as well. As this is a more biological plausible network, it could be used to examine the influence of different parameters on the activity, and predictions for human cortical activity can be made.

Future studies can show what the influence of other parameters is on the activity of a balanced network, especially the irregular asynchronous state. Furthermore, more realistic components of neurons or synapses can be added and their influence examined. With the continuing growth of the computational power, more detailed models of neurons can be connected in a large scale network and simulations can still be run in a reasonable time. This could give more insight in how these networks behave and how they are influenced, and hopefully this will lead to a better understanding of the computations made in the human brain.

Examined is whether a more complex neuron model can reach balanced states similar to a simpler neuron model which can do. It is shown that this more complex neuron model is able to do that, but that the behavior is different, due to extra biological plausible characteristics. This model and extensions of it can be used to examine influence of different parameters of a neuron on the network activity. This network activity resembles the cortical activity in the human brain. Future research can help to understand the underlying mechanisms of this activity and therefore get more insight in the computations of the human cortical brain.

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