Computational Neuroscience: Inhibitory-Stabilised Networks

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1 Introduction

Several brain regions, including the neocortex and hippocampus [1] contain local recurrently connected networks of excitatory and inhibitory neurons. Understanding how those networks function and react to external inputs is important for analysing how the brain operates. This report will introduce the concept of such networks, discuss their biological relevance, present a mathematical model, and provide computer simulations as well as mathematical analysis of the model.

The network is viewed as consisting of 2 pools of neurons: excitatory and inhibitory. Each pool projects to the other, and to itself, forming a recurrent neural network. Excitatory feedback can lead to runaway excitation, which is prevented by the inhibitory feedback. This allows the network to stabilise, earning it the name Inhibitory-Stabilised Network (ISN).

To understand how the system comes together, it is important to get a sense of what the underlying model of each individual nueron is and how the interaction between them integrates.

1.1 Leaky Integrate-and-Fire Neuron

In 1907, Louis Édouard Lapicque [2] introduced the concept of the integrate-and-fire neuron model. Even though the model was developed before scientists had a chance to describe the biophysical mechanics of the neuron, it captured the behaviour of the neuron in a way that was useful for understanding [3].

The neuron is viewed as an electric circuit with a capacitor and a resistor connected in parallel. The membrane has some resistance, which is assumed to be constant and can be described by Ohm's law: $V = IR$, and therefore the resistor current is $I = \frac{V}{R} = gV$, where g is conductance of the cell. The relationship between the current and the voltage across the capacitor is described by the following equation: $C = \frac{Q}{V}$, where C is the capacitance, Q is the charge stored in the capacitor, and V is the voltage across the capacitor. Knowing this, the current in the circuit:

$$I = \frac{dQ}{dt} = \frac{dCV}{dt} = C\frac{dV}{dt}$$

Real neurons, however, receive current from other neurons via dendrites from synapses, and induce own **ionic** current by letting charged particles in and out of the cell. Therefore, the total current is the sum of the ionic current plus any external input: $I = \sum_i g_i V + I_{ext} = g_m V + I_{ext}$. Neurons are generally **negatively charged** relative to the outside, and therefore the flow outside the cell is treated as positive. Since the size of the cell and its channels is comparable to that of ions, effect of electric attraction is comparable with that of diffusion, and there exists a point, where one balances out the other, resulting in the zero net current flow. This point is called the resting potential V_{rest} of the neuron, and therefore any current should be measured relative to this potential.

$$C\frac{dV}{dt} = -g_m(V - V_{\text{rest}}) + I_{\text{ext}}$$

Dividing by conductance, we get the following equation:

$$\tau_m \frac{dV}{dt} = -(V - V_{\text{rest}}) + \frac{I_{\text{ext}}}{g_m}$$

where τ_m is the membrane time constant, describing how quickly it reacts to input.

Now, the external current is the component of interest, by extending this component, we can integrate input from

other neurons. Neurons communicate by sending electrical signals to each other, via the synapse of emitting through the dendrites of the receiving neuron. This interaction can be modelled as a synpatic current, weighted by the strength of connection. Dale's Law[4] states that a neuron can only be either excitatory or inhibitory, and therefore we can simplify the model, and approximate the synaptic current as a function of emitting neuron's voltage: $I_{\text{syn},i} = W\phi(V_i)$, where W is the synaptic weight (+ for excitatory, − for inhibitory), and $\phi(V)$ is the transfer function of the neuron. The actual external current collapses into $I_{ext}/g_m = u_{ext}$.

Combing all component, we obtain a system of equations:

$$\tau_E \frac{dV_E}{dt} = -(V_E - V_{\text{rest}}) + W_{EE}\phi(V_E) - W_{EI}\phi(V_I) + u_E \quad (1)$$

$$\tau_I \frac{dV_I}{dt} = -(V_I - V_{\text{rest}}) + W_{IE}\phi(V_E) - W_{II}\phi(V_I) + u_I \quad (2)$$

where V_{rest} is the resting potential of the neuron, W_k are the synaptic weights, u_k are the external inputs to neurons, and $\phi(V)$ is the transfer function of a neuron, that acts as a communication channel between the neurons and is defined as a scaled ReLU function:

$$\phi(V) = \beta[V - V_0]_+ \quad (3)$$

Now that we have the model and its origins, it's important to outline the benefits and limitations of the model.

1.2 Considerations (Q1)

1. The model abstracts away certain biological complexity, such as stochasticity and variability of individual ion channels (both in somas and synapses), described in great detail by the Hodgkin-Huxley model [5], which is a more biologically plausible model of the neuron, but is also signficantly more complex.

2. Synaptic weights are assumed to be constant, whereas in reality they are subject to plasticity, and can change over time. The weights themeselves are a heuristic approximation, by making which we sacrifice details of spiking patterns assuming them to be a linear function of the voltage. * assumes constant voltage - not realistic

3. The membrane time constant that comes from conductance is assumed to be constant, and relies on Ohm's law, which is a simplification of the actual behaviour of the neuron. However, it is a good approximation for the passive dynamics of a neuron.

4. The LIF model is a lot more computationally affordable, requires 4 ODEs per neuron in the HH model, instead of 1 in the LIF model, which allows us to run large scale simulations and analyse the network behaviour faster. The model is also more amenable to theoretic analysis, which helps to explain certain activity patterns in the network.

5.

In essence, we trade off biological accuracy for computational efficiency and analytic tractability.

2 Computer Simulations

In this section, simulations of the network are presented, where the network is stimulated with various external inputs for both excitatory and inhibitory pools, and the response of the network is approximated numerically using the Euler method.

In our simulations, we study 2 networks with the following base parameters:

$$V_{\text{rest}} = -70\text{mV},\ V_0 = -55\text{mV},\ \beta = 1$$

$$\tau = \begin{pmatrix}\tau_E \\ \tau_I\end{pmatrix} = \begin{pmatrix}20 \\ 10\end{pmatrix} \text{ms}$$

$$u = \begin{pmatrix}u_E \\ u_I\end{pmatrix} = \begin{pmatrix}20 \\ 20\end{pmatrix}$$

$$W = \begin{pmatrix}W_{EE} & W_{EI} \\ W_{IE} & W_{II}\end{pmatrix} = \begin{pmatrix}W^n_{EE} & 0.65 \\ 1.2 & 0.5\end{pmatrix}$$

Where W^n_{EE} is the weight of the excitatory feedback for a given network. The 2 networks differ in the weight of the excitatory feedback, where one is weaker is $W^1_{EE} = 0.5$ and the other is stronger $W^2_{EE} = 1.25$.

2.1 Stable External Input (Q2)

We first study both networks subjected to a stable external input of 20mV to both neurons. Both neurons start from the resting potential. The simulation is ran for 500ms with 1ms time steps. The results are shown in Figure **??**.

Looking at the results for network 1 (solid lines), we can see that both neurons gradually begin responding to the

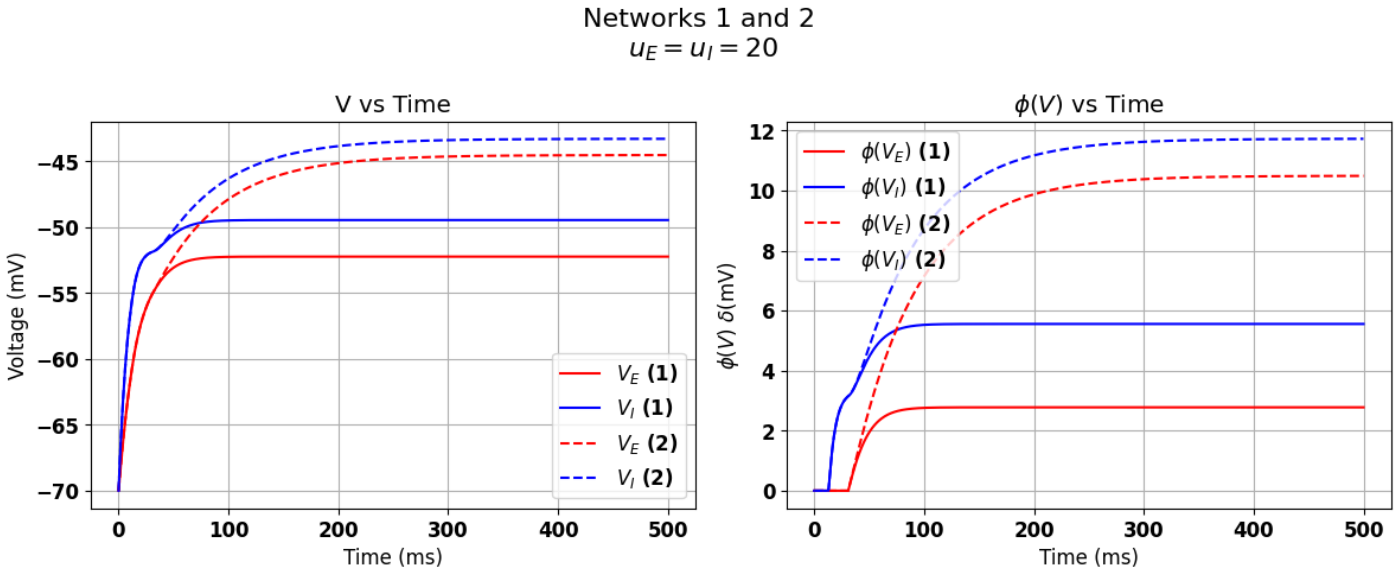

Figure 1: **Stable** external input to both neurons.
Excitatory potentials are red, inhibitory potentials are blue.
Network 1 is solid, Network 2 is dashed.

external input. Since $\tau_I < \tau_E$, one might expect the inhibitory neuron (blue) to respond faster, which is exactly what is observed. The transfer function $\phi(V)$ is not immediately responding to the increase in voltage as a neuron has to reach the threshold potential, which matches with the timeline of both neurons reaching $V_0 = -55mV$ and begin firing to provide input to the other. After about 5τ, as expected with a capacitor behaviour, the system reaches a stable state and both neurons' activity plateaus. At this point, V_I, however, is about 3mV above V_E, which could be due to a stronger W_{IE} connection relative to W_{EI}, given that the feedback strength to both neurons is equal, excitation of I is stronger than inhibition of E, and therefore less V_E is needed to balance out V_I.

2.2 Inhibitory Input Increase (Q3-4)

The network is further simulated for another 500ms with the increase of u_I from 20 to 26mV. The results for this simulation are shown in Figure **??**.

both neurons

2.3 Excitatory Input Increase Q5

Stable excitatory input - both networks increase activity and stabilise at a higher level. The gap between the

2.4 Stabilisation and Paradoxical Inhibition Q6

ISN if if the excitatory subnet is unstable in isolation but the full EI net is stable.

Speculate on relationship between inhibitory stabilisation and paradoxical inhibition.

2.5 Discussion Q7-8

Why the simulations are not sufficient to explain the relationship between the inhibitory stabilisation and paradoxical inhibition. How to do it more generally

Assuming the relationship holds, suggest an experiment to test whether brain networks are in the ISN regime. Any caveats to the experiment?

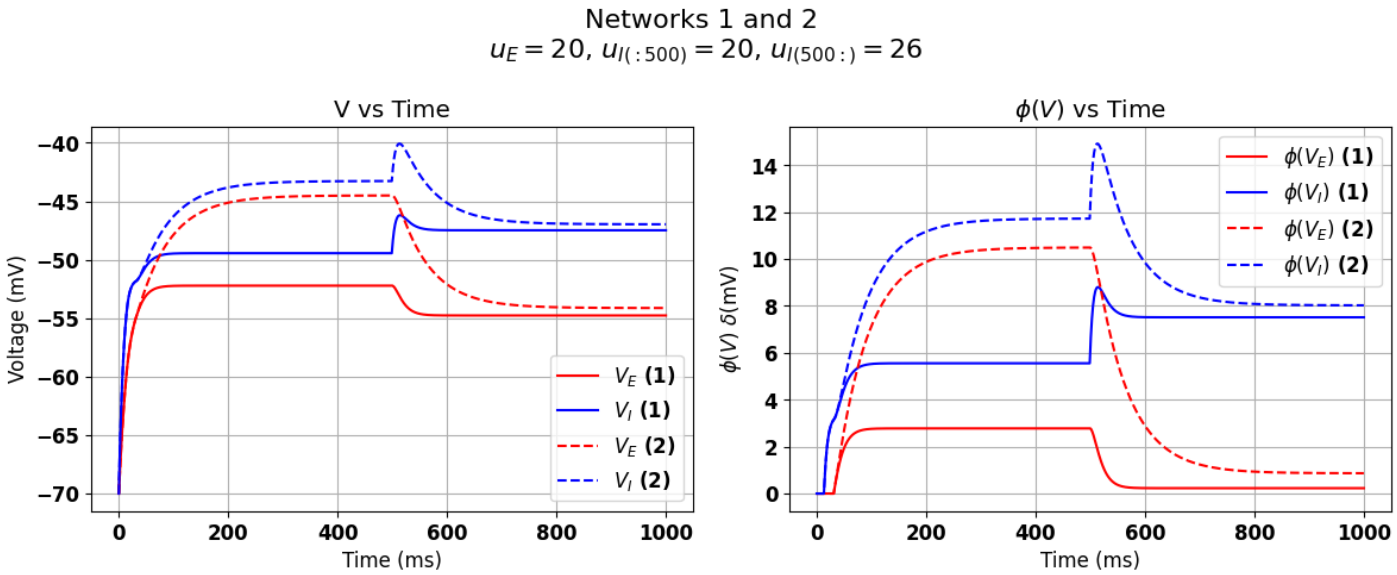

Figure 2: External **inhibitory** input increase after 500ms.
Excitatory potentials are red, inhibitory potentials are blue.
Network 1 is solid, Network 2 is dashed.

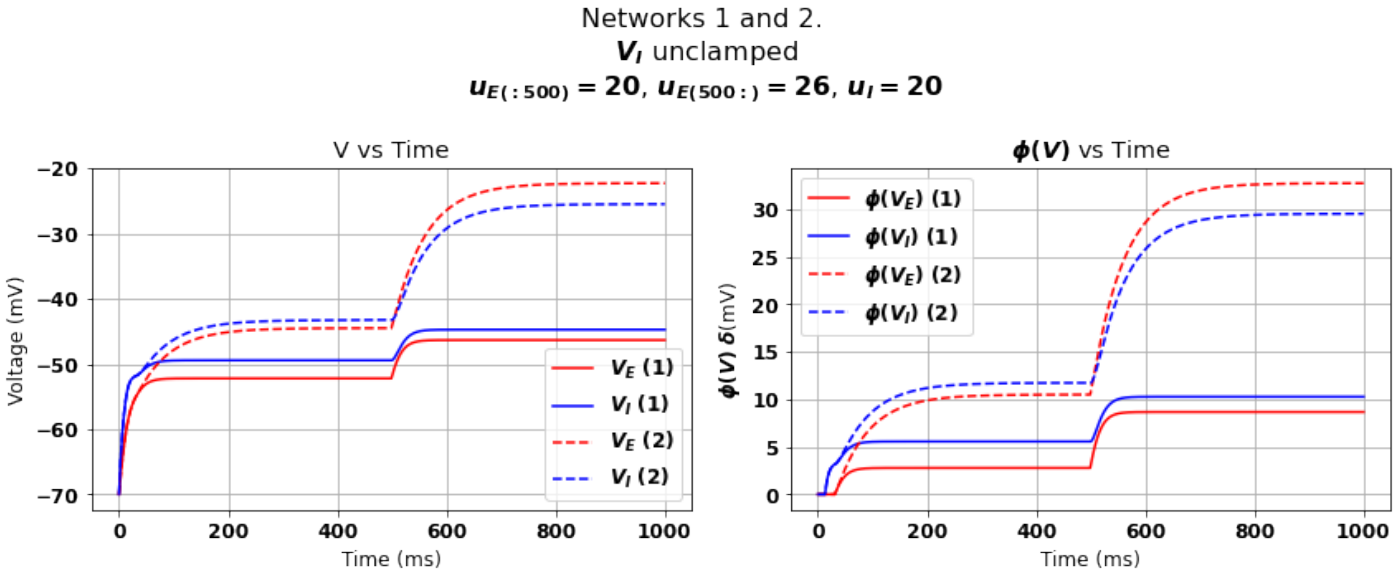

Figure 3: External **excitatory** input increase after 500ms. V_I unclapmed
Excitatory potentials are red, inhibitory potentials are blue.
Network 1 is solid, Network 2 is dashed.

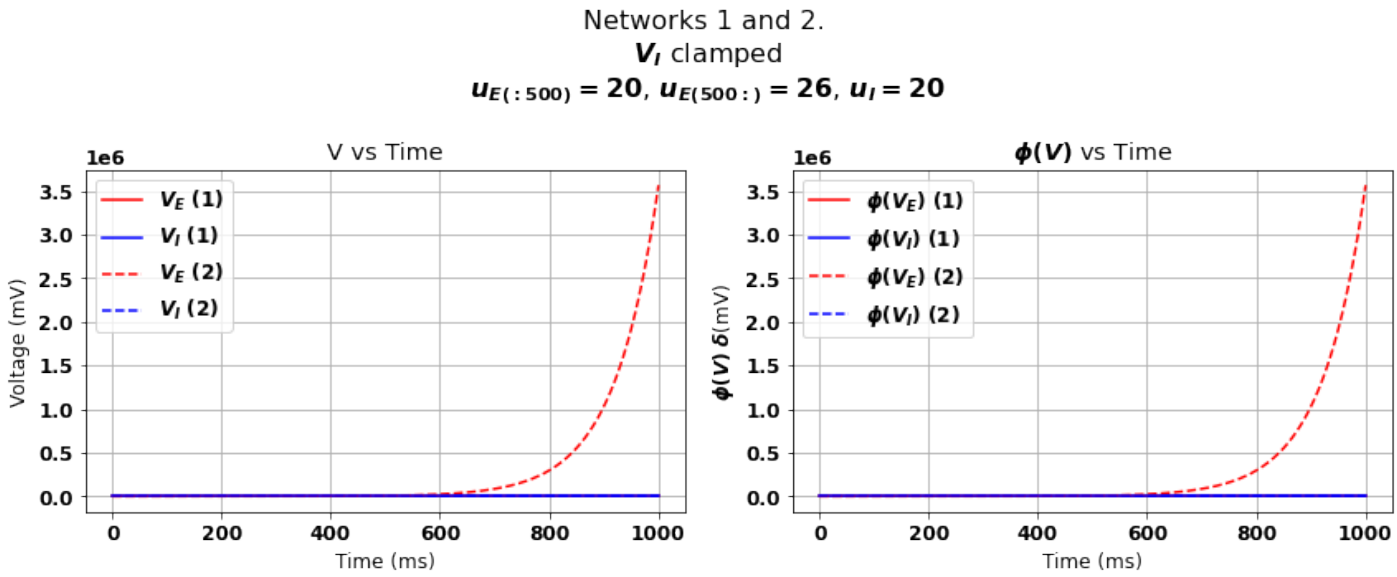

Figure 4: External **excitatory** input increase after 500ms. V_I clapmed
Excitatory potentials are red, inhibitory potentials are blue.
Network 1 is solid, Network 2 is dashed.

3 Mathematical Analysis

In this section, we will provide a mathematical analysis of the network model and explore the relationship between the inhibitory stabilisation and paradoxical inhibition.

Assuming, $V > V_0$,

3.1 Reformulation Q9

To simplify the analysis, we can reformulate the system of equations describing the network and express it in the matrix-vector form:

$$\frac{d\mathbf{V}}{dt} = A\mathbf{V} + \mathbf{x} = \begin{pmatrix} A_{EE} & A_{EI} \\ A_{IE} & A_{II} \end{pmatrix} \cdot \begin{pmatrix} \mathbf{V}_E \\ \mathbf{V}_I \end{pmatrix} + \begin{pmatrix} \mathbf{x}_E \\ \mathbf{x}_I \end{pmatrix}$$

where A is the matrix of synaptic weights, and $\mathbf{x}$ is the external input. To find the values of each term, Vs are factored out, and constant terms are grouped together based on equations (1) and (2).

$$\frac{d\mathbf{V}_E}{dt} = \mathbf{V}_E \boxed{\frac{-1 + W_{EE}\beta}{\tau_E}} + \mathbf{V}_I \boxed{\frac{-W_{EI}\beta}{\tau_E}} + \\ + \boxed{\frac{V_{rest} + V_0\beta(W_{EI} - W_{EE}) + u_E}{\tau_E}}$$

$$\frac{d\mathbf{V}_I}{dt} = \mathbf{V}_E \boxed{\frac{W_{IE}\beta}{\tau_I}} + \mathbf{V}_I \boxed{\frac{-1 - W_{II}\beta}{\tau_I}} + \\ + \boxed{\frac{V_{rest} + V_0\beta(W_{II} - W_{IE}) + u_I}{\tau_I}}$$

Now the system can be rewritten in the matrix form:

$$\frac{d\mathbf{V}}{dt} = \begin{pmatrix} \frac{-1+w_{EE}\beta}{\tau_E} & \frac{-w_{EI}\beta}{\tau_E} \\ \frac{w_{IE}\beta}{\tau_I} & \frac{-1-w_{II}\beta}{\tau_I} \end{pmatrix} \begin{pmatrix} \mathbf{V}_E \\ \mathbf{V}_I \end{pmatrix} + \\ + \begin{pmatrix} \frac{V_{rest}+V_0\beta(W_{EI}-W_{EE})+u_E}{\tau_E} \\ \frac{V_{rest}+V_0\beta(W_{II}-W_{IE})+u_I}{\tau_I} \end{pmatrix}$$

3.2 Steady State Q10

The steady state of the system $\mathbf{V}_E^*, \mathbf{V}_I^*$ is defined by both derivatives being zero. Since τ are non-zero constant terms, we can drop them from the equation, and solve for the steady state:

$$\begin{pmatrix} 0 \\ 0 \end{pmatrix} = \begin{pmatrix} A_{EE} & A_{EI} \\ A_{IE} & A_{II} \end{pmatrix} \begin{pmatrix} \mathbf{V}_E^* \\ \mathbf{V}_I^* \end{pmatrix} + \begin{pmatrix} \mathbf{x}_E \\ \mathbf{x}_I \end{pmatrix}$$

Rearranging the terms, the solution for steady state voltages:

$$\begin{pmatrix} \mathbf{V}_E^* \\ \mathbf{V}_I^* \end{pmatrix} = - \begin{pmatrix} A_{EE} & A_{EI} \\ A_{IE} & A_{II} \end{pmatrix}^{-1} \begin{pmatrix} \mathbf{x}_E \\ \mathbf{x}_I \end{pmatrix} = \frac{-1}{det(A)} \begin{pmatrix} A_{II} & -A_{EI} \\ -A_{IE} & A_{EE} \end{pmatrix} \begin{pmatrix} \mathbf{x}_E \\ \mathbf{x}_I \end{pmatrix}$$

From the solution, we can derive the expression for inhibitory voltage V_I^* in terms of network parameters:

$$V_I^* = \frac{-(-A_{IE}\mathbf{x}_E + A_{EE}\mathbf{x}_I)}{det(A)} = \frac{A_{IE}\mathbf{x}_E - A_{EE}\mathbf{x}_I}{det(A)} = \frac{W_{IE}\beta\mathbf{x}_E - W_{EE}\beta\mathbf{x}_I}{det(A)}$$

4 Conclusion

References

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