CCN Assignment 1: Inhibitory Stabilised Networks, Paradoxical Inhibition, and the Stabilised Supralinear Network

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Submission Details

The deadline for this assignment is 12th February at 4pm (standard late penalties apply). The assignment should be submitted via the course Learn page in pdf format, using the naming convention lastname-firstname-ccn1.pdf. You should also submit the code you used to produce any figures in the assignment (the code will not be marked, but may be checked where results are wrong and/or for plagiarism detection purposes, do not include any code in your main report). Your submission should be no longer than **8 pages** (excluding any bonus questions and code).

Background

In this assignment you will investigate two network models discussed in the lectures: the *Inhibitory-Stabilised Network* (ISN) associated with "paradoxical inhibition" (Tsodyks et al., 1997) and the *Supralinear Stabilised Network* (SSN), which has been proposed to account for various contextual influences on responses of neurons in visual cortex (Ahmadian et al., 2013; Rubin et al., 2015).

You will be asked to simulate the equations for these networks numerically and interpret your findings in the context of biology and sensory processing. You may find it helpful to read some of the papers cited in this document, and also to do your own reading around the subject. Some of the questions are open ended, in which case you may supplement your answers with additional simulations, mathematical analysis, and/or findings from the literature provided it is properly cited and credited (although this is not required, and should only be included if directly relevant).

You should present your findings in the style of a scientific report. By this we mean that the document should include text, equations, figures (with axes clearly labeled and font size large enough to read, and with figure captions to explain the content - figures that are not referred to within the text will not be considered), and references where relevant. You should consider how to best communicate your findings in a clear and concise way - good presentation style will be considered when marking. There is no need to aim for an 8 page report if you can convey your findings more succinctly (be sure to consider how best to convey your findings as figures, for example by making use of subplots and plotting multiple things on the same graph to save space).

You may discuss this assignment with others, but direct copying of code, text, or mathematical results is not allowed.

Inhibitory Stabilized Networks and Paradoxical Inhibition (50 marks)

Tsodyks et al. (1997) considered the following linear model[1] of an excitatory-inhibitory network:

$$\tau_E \frac{dr_E}{dt} = -r_E + \beta \left(W_{EE} r_E - W_{EI} r_I + u_E \right) \tag{1}$$

$$\tau_I \frac{dr_I}{dt} = -r_I + \beta \left(W_{IE} r_E - W_{II} r_I + u_I \right) \tag{2}$$

where $W_{EE}, W_{EI}, W_{IE}, W_{II}, \beta \geq 0$ are all scalar numbers.

Tsodyks et al. analysed this model mathematically and found that, in certain situations, the network exhibits an unexpected phenomenon they called "paradoxical inhibition". Moreover, they showed that this phenomenon is closely linked to the role of inhibition in stabilising the network, which led them to call such networks "Inhibitory Stabilised Networks". While the model of Tsodyks et al. was purely theoretical, it is now known that the phenomena of inhibitory stabilisation and paradoxical inhibition are a core feature of the operating regime of cortical circuits (Sanzeni et al., 2020; Sadeh and Clopath, 2020) and are important for various aspects of sensory processing (Ozeki et al., 2009), some of which are considered in the bonus section of this assignment.

In this first part of the assignment you will analyse the model of Tsodyks et al. through numerical simulations in order to investigate paradoxical inhibition and its relationship to inhibitory stabilisation. For the following questions you should set $\beta = 1$, $\tau_E = 10$, $\tau_I = 10$, $W_{EI} = 1.8$, $W_{IE} = 1.8$, $W_{II} = 1$. For numerical simulations, you should use the Euler method with time steps of size $\delta t = 1$ and an initial condition of $r_E(0) = 0$, $r_I(0) = 0$ (units of time are arbitrary, but can be interpreted as milliseconds). You will consider two networks, Network 1 with $W_{EE} = 0.5$ and Network 2 with $W_{EE} = 1.5$ (all other parameters being as already stated, except u_E,u_I which are stated for each question below).

1. Comment on the biological relevance of the model given by equations (1,2) - how would you interpret the various terms in the equations? Describe some of the most obvious ways in which the model could be considered biologically unrealistic. Why might one choose to study a model such as this rather than a more biologically realistic one? (7 marks)

2. Consider Network 1, and set $u_E = 1$, $u_I = 1$. Simulate equations (1, 2) for $N_t = 500$ time steps[2] (i.e., 500 ms real time). Plot r_E and r_I as a function of time. (5 marks)

3. Repeat this simulation, this time increasing u_I after 500 time steps and simulating for a further 500 time steps at the new value ($N_t = 1000$ in total, with $u_I = 1$ for the first 500 steps and $u_I = 2$ for the second 500 steps). Plot r_E and r_I as a function of time. Comment on what you observe. (5 marks)

[1] In fact Tsodyks et al. used a model with threshold-linear-threshold activation function, but restricted their analysis to the case in which neuronal activity is within the linear regime. For the purposes of this assignment, you can assume the model is linear everywhere.

[2] Note that the two equations are coupled, so both r_E and r_I need to be updated at each simulation time step (they should be updated simultaneously based on their values at the previous time step). Alternatively, the two equations can be written as a single vector/matrix equation.

4. Now perform the simulation of question 3 for Network 2 and plot the results as before. How do the results differ from Network 1? Why is the change in r_I following increased u_I in Network 2 considered "paradoxical"? (5 marks)

5. Using the results from the simulations you performed in questions 3 and 4, plot the excitatory, inhibitory, and external input to I cells ($W_{IE}r_E$, $-W_{II}r_I$, and u_I respectively) as a function of time for Network 1 and Network 2. Based on these plots, provide an explanation in terms of the various inputs to I cells as to why a paradoxical response of r_I occurs in Network 2 but not Network 1. (5 marks)

6. For each of the two networks, now set $u_I = 1$ throughout the simulation and instead increase increase u_E for the second 500 time steps ($u_E = 1$ for the first 500 and $u_E = 2$ for the second 500 time steps). Plot r_E and r_I against time. How do r_E and r_I in each network respond to the increase in u_E? (5 marks)

7. Repeat the simulation of question 6 for each network, but this time freeze r_I on the 500th timestep, holding it at that value for the remainder of the simulation but continuing to update r_E. Plot r_E and r_I against time for each network. Comment on what happens to r_E in each network after u_E is increased. (5 marks)

8. Based on the simulations in this section, comment on the role of inhibition in dynamically stabilising network responses and the relationship of this to paradoxical inhibition. (4 marks)

9. Tsodyks et al. derived all of the results of this section analytically, without requiring any simulations. What advantages might there be to taking an analytical approach as opposed to the simulation-based approach you took here? (4 marks)

10. Based on your findings in this section, what would you suggest your experimental colleagues do in order to determine whether networks in the brain are inhibitory-stabilised or not[3]? Can you think of any caveats to the modelling approach[4] of this section that might make it difficult to confidently make experimental predictions? (5 marks)

Supralinear Stabilized Network: Reduced Two-Dimensional E-I Model (50 marks)

While the linear network of Tsodyks et al. is convenient to work with analytically, the assumption of linear dynamics limits the kinds of behaviour it can produce, and is inconsistent with various non-linear phenomena observed in real neuronal networks. One model for the nonlinear response properties of neurons in visual cortex is the Stabilized Supralinear Network (SSN), defined by the following equations:

$$\tau_E \frac{dr_E}{dt} = -r_E + \phi(W_{EE}r_E - W_{EI}r_I + u_E) \tag{3}$$

$$\tau_I \frac{dr_I}{dt} = -r_I + \phi(W_{IE}r_E - W_{II}r_I + u_I) \tag{4}$$

[3]By inhibitory-stabilised we mean stable in the intact network but unstable when inhibition is frozen. You should assume that it is not experimentally possible to simply freeze inhibition as in your simulations.

[4]Note that this question is referring the choice of model itself, not the distinction between analytical or simulation-based approaches as in the previous question.

where:

$$\phi(x) = \begin{cases} \beta x^\gamma & \text{for } x > 0 \\ 0 & \text{for } x \leq 0 \end{cases} \tag{5}$$

As before, $W_{XY} \geq 0$ for all $X, Y = E, I$ and $\beta, \gamma > 0$ are scalar constants.

The choice of a threshold-power law transfer function for ϕ is motivated by two key observations: first, it has been shown to emerge from threshold-linear transfer functions in the presence of noise, and second, has been shown to be the unique transfer function which generates contrast-invariant tuning curves in simple single-neuron feedforward models (Miller and Troyer, 2002; Hansell and Van Vreeswijk, 2002). Rubin et al., (2015) show that the SSN network model can account for a wide range of contextual influences on orientation tuning in visual cortex, including surround suppression and cross-orientation suppression. The orientation tuning properties of the SSN are the focus of the bonus section of this assignment. In this section, we restrict our analysis to a reduced two-dimensional E-I population model as in the previous section (as studied in depth by Ahmadian et al. (2013)).

The network is called supralinear because we take $\gamma > 1$. It is called the Stabilised Supralinear Network because it can be stabilised by inhibition (as in the above ISN), despite the fact that the transfer function becomes steeper with stronger inputs (which could cause highly unstable dynamics in the absence of inhibition). In this section of the assignment you will study inhibitory stabilisation and paradoxical inhibition in the SSN.

Unlike the linear network in the previous section, the dynamical properties of nonlinear networks such as the SSN can vary qualitatively when their external input is changed. In simulations of equations (3,4), you will now explore the behaviour of the network as you vary the constant excitatory and inhibitory input u_E and u_I while keeping all other parameters fixed. For this section you should set the parameters to $\gamma = 2$, $\tau_E = 10$, $\tau_I = 10$, $\beta = 1$, $W_{EE} = 1.5$, $W_{EI} = 1.8$, $W_{IE} = 1.8$, $W_{II} = 1$ and simulate the network using the Euler method from an initial condition $r_E(0) = r_I(0) = 0$ with a discretisation timestep of $\delta t = 0.1$. Make sure to simulate for enough time steps that any transient behaviour of the network has settled down.

1. Plot $\phi(x)$ against x with $\beta = 1$ and $\gamma = 2$. Is there anything that could be biologically implausible about this choice of transfer function? (5 marks)

2. Set $u_E = u_I = 1$. Simulate the model for $N_t = 1000$ time steps and plot r_E and r_I against time. (5 marks)

3. Now consider $u_E = u_I = c$, with c a parameter you wish to vary. Vary c systematically[5] from $c = 0$ to $c = 3$ and plot the excitatory and inhibitory steady state responses as a function of c. Comment on what you observe. (10 marks)

4. This model, with $u_E = u_I = c$, has been proposed as a possible explanation for the contrast-dependence of network responses in visual cortex (c stands for stimulus contrast). What aspects of the dependence of r_E on c are consistent with this interpretation[6]? What aspects of the same appear to be inconsistent with this interpretation? (5 marks)

For the following questions you will simulate the same network but with two different choices of input. For Input 1, set $u_E = u_I = 0.1$, for Input 2, set $u_E = 10$, $u_I = 3$.

[5]Hint: You can create a for loop to vary the value of c in small increments and repeat the network simulation for each value

[6]Hint: recall the normalisation model mentioned in Lecture 6, and in Carandini and Heeger (2012)

5. Simulate with Input 1 until steady state has been reached, then increase the inhibitory input to $u_I = 0.2$ and continue the simulation until steady state is again reached for this new value. Plot r_E and r_I against time for the full simulation. Do the same with Input 2, this time increasing the inhibitory input to $u_I = 6$ after the first steady state is reached. Comment on the presence of paradoxical inhibition for the simulation with Input 1 vs Input 2. (7 marks)

6. Simulate with Input 1 until steady state is reached, then freeze r_I at this steady state value and increase the excitatory input to $u_E = 0.11$, continuing the simulation until steady state is reached again for this new value. Do the same for Input 2, this time increasing excitatory input to $u_E = 11$ after the first steady state is reached. Plot r_E and r_I against time for each simulation. Compare the results with and without freezing of r_I. (10 marks)

7. Based on the simulations of this section, comment on inhibitory-stabilisation and paradoxical inhibition in the SSN and how it depends on the external input the network receives. Do you think the same effects would be possible in the linear model of the previous section? Why/why not? Compared to the previous section, how would your findings in this section change your experimental predictions when searching for evidence for inhibitory-stabilisation in the brain? (8 marks)

Bonus Questions: Supralinear Stabilized Network: Orientation Tuning and Cross-Orientation Suppression (20 bonus marks)

Note: The questions in this section are optional. Total marks for this assignment will be capped at 100, but marks lost in the previous sections could be made up by correctly answering these bonus questions. The main assignment must be no more than 8 pages, but for the bonus questions you may exceed that limit.

The reduced two-dimensional E-I model studied above can be extended to account for orientation tuning in the visual cortex. The SSN ring model of Rubin et al., 2015 represents a circuit of V1 neurons, each tuned to a different stimulus orientation, but all tuned to single retinotopic location (i.e., a small patch of the visual field). This model explains various contextual influences on V1 orientation tuning, including cross-orientation suppression and other normalisation-type effects associated with adding multiple stimuli or varying stimulus size or contrast (see Lecture 6, see also Carandini and Heeger (2012)). This bonus section asks you to implement the SSN ring model and reproduce the cross-orientation suppression effect.

The model is represented by $N = 180$ excitatory and $N = 180$ inhibitory neurons with connectivity and inputs organised on a ring. Neuron i in population X is assigned an angle $\theta_i^X = i$ degrees (the ring is considered to be 180 degrees in circumference, reflecting the fact that a stimulus can only have orientation between 0 and 180 degrees). The connection weight from neuron j in population Y to neuron i in population X (where X and Y can each be either E or I) is:

$$W_{ij}^{XY} = A^{XY} \exp(-d(\theta_i^X, \theta_j^Y)^2/(2\sigma_W^2)) \tag{6}$$

where $d(\theta_i^X, \theta_j^Y) = \min(|\theta_i^X - \theta_j^Y|, 180 - |\theta_i^X - \theta_j^Y|)$ is the shortest distance between the two neurons on the ring, A^{XY} determines the overall strength of weights from population Y to X and σ_W

determines the spread of weights around the ring. The feedforward inputs for a single oriented grating stimulus are:

$$u_i^X = c \exp(-d(\theta_i^X, \theta_s)^2/(2\sigma_u^2)) \tag{7}$$

σ_u defines the spread of inputs and θ_s defines the stimulus orientation. The parameter c is considered to be the contrast the stimulus. When two grating stimuli with different orientations and contrasts are presented simultaneously, the feedforward inputs are:

$$u_i^X = c_1 \exp(-d(\theta_i^X, \theta_s^{(1)})^2/(2\sigma_u^2)) + c_2 \exp(-d(\theta_i^X, \theta_s^{(2)})^2/(2\sigma_u^2)) \tag{8}$$

The neurons are governed by the following dynamics:

$$\tau_E \frac{dr_i^E}{dt} = -r_i^E + \phi(\sum_{j=1}^{N} W_{ij}^{EE} r_j^E - \sum_{j=1}^{N} W_{ij}^{EI} r_j^I + u_i^E) \tag{9}$$

$$\tau_I \frac{dr_i^I}{dt} = -r_i^I + \phi(\sum_{j=1}^{N} W_{ij}^{IE} r_j^E - \sum_{j=1}^{N} W_{ij}^{II} r_j^I + u_i^I) \tag{10}$$

where ϕ is the same transfer function defined in equation (5).

For the following questions you should set the parameters as: $\tau_E = 20$, $\tau_I = 10$, $\gamma = 2$, $\beta = 0.04$, $A^{EE} = 0.044$, $A^{EI} = 0.023$, $A^{IE} = 0.042$, $A^{II} = 0.018$, $\sigma_W = 32$, $\sigma_u = 30$.

1. Consider two stimuli with $\theta_s^{(1)} = 45$, $\theta_s^{(2)} = 135$ and $c_1 = c_2 = 50$. Simulate[7] and plot the steady state response of the E population to each stimulus presented separately and to both stimuli presented simultaneously. Comment on how the network response differs to separately presented vs simultaneous stimuli. Based on your simulations of increasing c for the reduced two-dimensional SSN model, can you put forward an explanation for why this might be the case? (10 marks).

2. Now consider what happens when the contrasts of the two stimuli differ. Compare the network response when 1) $c_1 = c_2 = 40$ 2) $c_1 = 50, c_2 = 30$ 3) $c_1 = 60, c_2 = 20$ 4) $c_1 = 70, c_2 = 10$. In each case, plot the response of the population of E cells to each stimulus presented individually vs both stimuli presented simultaneously. Based on these network responses, how would the response of a single neuron to a stimulus at its preferred orientation be modulated by the simultaneous presentation of a stimulus with orthogonal orientation? Why is this considered a model for the cross-orientation suppression phenomenon reported experimentally? (10 marks).

References

Ahmadian, Y., Rubin, D. B., and Miller, K. D. (2013). Analysis of the stabilized supralinear network. *Neural Computation*.

Carandini, M. and Heeger, D. J. (2012). Normalization as a canonical neural computation. *Nature Reviews Neuroscience*.

[7] Hint: it is much easier to simulate this model by expressing the equations in terms of vectors and matrices than simulating each neuron individually

Hansell, D. and Van Vreeswijk, C. (2002). How Noise Contributes to Contrast Invariance of Orientation Tuning in Cat Visual Cortex. *Journal of Neuroscience*.

Miller, K. D. and Troyer, T. W. (2002). Neural noise can explain expansive, power-law nonlinearities in neural response functions. *Journal of Neurophysiology*.

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Rubin, D. B., VanHooser, S. D., and Miller, K. D. (2015). The stabilized supralinear network: A unifying circuit motif underlying multi-input integration in sensory cortex. *Neuron*.

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