CNS Assignment: Inhibitory Stabilisation and Paradoxical Inhibition in Excitatory-Inhibitory Networks

November 2024

Submission Details

The deadline for this assignment is 22nd November at 12pm (standard late penalties apply). The assignment should be submitted via the course Learn page in pdf format, using the naming convention B0123456.pdf (i.e., your exam number). You should include the code you used to produce any figures in the assignment as an appendix (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 references, front matter, and appended code). To ensure fair and consistent marking, any content that extends beyond the 8 page limit will not be awarded any marks.

Plagiarism and Academic Misconduct

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

Any text that is directly copied from other sources should be placed in quotation marks with the source cited at the end of the sentence. Text which is written in your own words but is based on material from other sources also requires a citation.

Please remember the good scholarly practice requirements of the University regarding work for credit. You can find guidance at the School page:

https://web.inf.ed.ac.uk/infweb/admin/policies/academic-misconduct.

This also has links to the relevant University pages.

Background

In this assignment you will investigate a network model discussed in the lectures: the *Inhibitory-Stabilised Network* (ISN) associated with "paradoxical inhibition" (Tsodyks et al., 1997; Sadeh and Clopath, 2020).

You will be asked to simulate this network numerically, perform mathematical analysis of the model, and interpret your findings in the context of biology. You may find it useful to read some of the papers cited in this document, or to do your own reading around the subject. Please remember

that not all questions have a single "right answer" - in that case, you should think critically about what is being asked and attempt to give a reasoned and well-justified answer.

Marks for Style of Presentation (10 marks)

You should present your findings in the style of a scientific report. By this we mean that the document should include text broken into appropriate sections (e.g., by question number and topic), equations (where relevant), figures (with axes clearly labeled, font size similar to the font in the main text, figure captions to explain their content, and numbering/lettering of figures and subpanels in order to refer to them from the main text), and references (if relevant). You should consider how to best communicate your findings in a clear and concise way to the reader. This includes designing figures appropriately, for example by making use of subplots and plotting multiple things on the same graph to save space or for aid of visual comparison, setting the axis limits appropriately, using figure legends and colour schemes to delineate different things plotted on the same graph, etc. To take these factors into account, 10 marks have been allocated for the quality of presentation with regards to the overall layout and style, the quality of figures, and the scientific clarity and precision of written answers.

Models for Excitatory-Inhibitory Network Dynamics (8 marks)

In this assignment you will study the dynamics of excitatory-inhibitory networks of firing rate neurons governed by the equations:

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

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

where $W_{EE}, W_{EI}, W_{IE}, W_{II} \geq 0$ are all positive scalar numbers and:

$$\phi(V) = \beta[V - V_0]_+ = \begin{cases} \beta(V - V_0) & \text{for } V - V_0 > 0 \\ 0 & \text{for } V - V_0 \leq 0 \end{cases} \tag{3}$$

You will use this model to explore the relationship between two properties of cortical networks which have been widely observed in experiments: inhibitory stabilisation and paradoxical inhibition.

1. Comment on the biological relevance of the model given by equations (1-3). In particular, what biological phenomena do these equations describe, and how would you interpret the various terms/variables/parameters 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? (8 marks)

Numerical Analysis (37 marks)

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". Inhibitory stabilisation and paradoxical inhibition have since been confirmed experimentally (Sanzeni et al., 2020; Sadeh and Clopath, 2020) and have been shown to play an important role in some aspects of sensory processing (Ozeki et al., 2009).

In this first part of the assignment you will analyse the model of Tsodyks et al. through numerical simulations in order to investigate the conditions under which paradoxical inhibition emerges and its relationship to inhibitory stabilisation. For the following questions you should set $\beta = 1$, $\tau_E = 20$ ms, $\tau_I = 10$ ms, $V_0 = -55$ mV, $V_{\text{rest}} = -70$ mV, $W_{EI} = 0.65$, $W_{IE} = 1.2$, $W_{II} = 0.5$. For numerical simulations, you should use the Euler method with time steps of size $\delta t = 1$ and an initial condition of $V_E(0) = V_{\text{rest}}$, $V_I(0) = V_{\text{rest}}$. You will consider two networks, Network 1 with $W_{EE} = 0.5$ and Network 2 with $W_{EE} = 1.25$ (all other parameters being as stated above, except u_E,u_I which are stated for each question below).

2. Consider Network 1, and set $u_E = 20$, $u_I = 20$. Simulate equations (1-3) for $N_t = 500$ time steps (i.e., 500 ms real time). Plot V_E and V_I and $\phi(V_E)$, $\phi(V_I)$ as a function of time. Comment on what you observe - how do the V terms differ from their $\phi(V)$ counterparts and how does this relate to their biological interpretation? (6 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 $u_I = 20$ for the first 500 steps and $u_I = 26$ for the second 500 steps). Plot V_E, V_I and $\phi(V_E)$, $\phi(V_I)$ as a function of time. How do the E and I populations respond to the increase in u_I - are these results in line with intuition (justify your answer)? (6 marks)

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 V_I and $\phi(V_I)$ following increased u_I in Network 2 considered "paradoxical"? (5 marks)

5. Repeat the simulation of questions 3 and 4, but this time increase u_E rather than u_I. Plot V_E and V_I and $\phi(V_E)$, $\phi(V_I)$ as a function of time for Networks 1 and 2. What happens if you clamp V_I to remain constant when you increase u_E. How the two networks differ? How do you interpret these results? (6 marks)

6. A network is called "inhibitory-stabilised" if the excitatory subnetwork is unstable in isolation, but the full excitatory-inhibitory network is stable. Based on the above simulations, can you speculate on a relationship between inhibitory-stabilisation and paradoxical inhibition? Explain your reasoning. (4 marks)

7. Why are the above simulations not sufficient to demonstrate a general relationship between paradoxical inhibition and inhibitory-stabilisation? How would you go about trying to find out if this relationship holds more generally? (5 marks)

8. Assuming that this general relationship does hold within the model defined by equations (1)-(3), suggest an experiment to test whether networks in the brain are in the inhibitory-stabilised regime. Are there any caveats in this modelling approach that might limit your confidence in making experimental predictions in this way? (5 marks)

Mathematical Analysis (25 marks)

In this section of the assignment, you will investigate the model analytically in order to explore the relationship between inhibitory stabilisation and paradoxical inhibition. To make the analysis simpler, you may assume that both populations are above threshold, so that equations (1-3) become:

$$\tau_E \frac{dV_E}{dt} = -(V_E - V_{\text{rest}}) + W_{EE}\beta\,(V_E - V_0) - W_{EI}\beta\,(V_I - V_0) + u_E \tag{4}$$

$$\tau_I \frac{dV_I}{dt} = -(V_I - V_{\text{rest}}) + W_{IE}\beta\,(V_E - V_0) - W_{II}\beta\,(V_I - V_0) + u_I \tag{5}$$

9. The above equations can be written in the form $\frac{d\mathbf{V}}{dt} = A\mathbf{V} + \mathbf{x}$, where $\mathbf{V} = \begin{pmatrix} V_E \\ V_I \end{pmatrix}$. Write down expressions for the matrix A and vector $\mathbf{x}$ (5 marks).

10. The steady state network response V_E^*, V_I^* is defined by $\frac{dV_E^*}{dt} = 0, \frac{dV_I^*}{dt} = 0$. Write down an expression for V_I^* in terms of the model parameters[1]. (5 marks)

11. Derive an expression for $\frac{dV_I^*}{du_I}$. Under what condition is $\frac{dV_I^*}{du_I} < 0$? (5 marks)

12. How do your analytical findings relate to your numerical simulations? In particular, what do your analytical findings say about the relationship between paradoxical inhibition and inhibitory stabilisation[2]? (5 marks)

13. Using this method, can you say whether it is possible for this network model to exhibit paradoxical excitation (defined analogously to paradoxical inhibition)? (5 marks)

References

Ozeki, H., Finn, I. M., Schaffer, E. S., Miller, K. D., and Ferster, D. (2009). Inhibitory Stabilization of the Cortical Network Underlies Visual Surround Suppression. *Neuron*.

Sadeh, S. and Clopath, C. (2020). Inhibitory stabilization and cortical computation. *Nature Reviews Neuroscience*.

Sanzeni, A., Akitake, B., Goldbach, H. C., Leedy, C. E., Brunel, N., and Histed, M. H. (2020). Inhibition stabilization is a widespread property of cortical networks. *eLife*.

Tsodyks, M. V., Skaggs, W. E., Sejnowski, T. J., and McNaughton, B. L. (1997). Paradoxical effects of external modulation of inhibitory interneurons. *J Neurosci*, 17(11):4382–4388.

[1] Hint: Use the formula for the 2×2 matrix inverse $A^{-1} = \frac{1}{\det(A)} \begin{pmatrix} a_{22} & -a_{12} \\ -a_{21} & a_{11} \end{pmatrix}$, where $\det(A) = a_{11}a_{22} - a_{12}a_{21}$.

[2] Hint: You may use the fact that a 1D system $\frac{dy}{dt} = ay + b$ is unstable if $a > 0$, and that a 2D system $\frac{d\mathbf{y}}{dt} = A\mathbf{y} + \mathbf{b}$ is unstable if $\det(A) < 0$.