Biophysical Modelling of the Triadic Synapse in the Lateral Geniculate Nucleus

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Abstract – The lateral geniculate nucleus (LGN) is responsible for transmitting visual information from the optic nerve to the primary visual cortex. Located within the LGN is the triadic synapse, an unusual yet fundamental structure wherein a retinal ganglion cell simultaneously synapses onto a relay cell and an interneuron, with the same interneuron also providing inhibition to the relay cell. Despite the large body of physiological data available for each of these cell types individually, the triadic synapse's behaviour and function in information processing remains poorly understood. In this work, we create a biophysical model of the triadic synapse using Python with Neuron. Our model is based on specifications from literature and consists of retinal ganglion inputs, an interneuron and a relay cell synapsing in appropriate triad formation. Computational simulations through the model find that triadic inhibition alone causes faster neuronal repolarisation following excitation than axonal inhibition alone, granting temporal precision to visual signals. Importantly, we find that our triad model expresses temporal selectivity by boosting coincident retinal spikes to selectively pass significant visual events over network noise. This occurs as synchronous retinal inputs elicit a strong relay cell response, whilst asynchronous inputs produce overlapping excitation and inhibition, thus driving relay cells less effectively. This validates the feasibility of temporal selectivity as a core functional property of the synapse and compounds current computational research in investigating triadic circuitry behaviour.

Keywords: Interneurons, Action Potentials, Triadic Synapses, Lateral Geniculate Nucleus, Visual Processing

1. Introduction

In the mammalian visual system, the lateral geniculate nucleus (LGN) is the thalamic structure responsible for transmission of visual information from the optic nerve to the primary visual cortex (V1) [1]. Its main constituent cells are relay cells (RCs), which project to the visual cortex, and interneurons (INs). Although the LGN was traditionally viewed as a passive relay station, recent literature suggests it may modulate visual signals before they reach V1 and therefore play an important role in processing visual information [2], [3]. As its precise purpose is still not fully understood, computational modelling is essential to develop a mechanistic understanding of circuitry function.

The triadic synapse, formed between RCs, INs and retinal ganglion cells (RGCs) within LGN circuitry, holds key importance in this modulatory process. Within this arrangement, an IN dendritic terminal simultaneously receives excitatory input from a RGC and provides dendrodendritic inhibition to a RC, with the RGC also providing direct excitation to the RC [4], [5]. The same IN provides direct axosomatic inhibition to the RC [6]. In comparison to other neuronal systems, the triadic synapse remains remarkably unexplored, perhaps due to its unusual structural complexity.

Despite the triad's prominent position within the early visual pathway, limited attempts have been made to elucidate its significance. An emerging theory for its function is temporal selectivity, by which triads may increase temporal precision of RC responses [7]. It is postulated that synchronous retinal inputs may have a summative excitatory effect on the RC preceding IN inhibition [8], while asynchronous spikes produce overlapping excitation and inhibition within the synapse and therefore permit only poor transmission of action potentials. As a result, synchronous RGC inputs are much more effective at driving an RC response than asynchronous inputs [7], [9]. Triadic circuits would therefore preferentially boost coincident retinal spikes to selectively pass significant visual events over network noise [10]. However, there is a notable lack of research investigating this hypothesis.

Computational modelling is essential in understanding the function of the triadic synapse within the LGN. Neuronal models that simulate RCs or INs independently are scarce [5], [11], [12]. Moreover, to our knowledge, only a single published study to date integrates both RCs and INs in a single model simulate the triadic synapse [13]. While this work provides the foundations for further investigation into triadic activity, it is highly complex and requires high computing power to run. Consequently, through this work we aimed to create an accessible, simple model.

2. Materials and Methods
2.1 Software
Modelling was carried out using NEURON, a widely used simulation environment for building both single-neuron and complex neural network models de novo. The bulk of the code was written in Python 3, with NEURON essentially functioning as library. LFPy, a Python package that simulates local field potentials and functions as an API to enable increased model complexity, was used to integrate additional membrane mechanisms from [13] into our IN model to simulate an extensive range of ion channels.

2.2 Modelling
An initial model was created by building and connecting single IN and RC cells with excitatory inputs from a single RGC added using the 'NetStim'/'Exp2Syn' stimulus protocol outlined below. The IN model was built based on specifications from [13], with additional complexity from [12]. It consists of a cell body (diameter 17.4μm, length 15.3μm) connected to a single dendrite and a single axon with the same dimensions (proximal diameter 4μm tapering to 0.3μm over length 100μm, then consistent diameter 0.3μm for distal 400μm). The RC was assumed to be electrotonically compact [14], and thus took the form of a single-compartment soma (diameter 47μm, length 50μm) [15]. Biophysical parameters were adjusted such that the model exhibited biologically accurate behaviour in response to basic stimuli. Synaptic weights were chosen based on literature to support fast dendrodendritic time-locked inhibition and lagged axosomatic inhibition [16]. The primary purpose of this model was to evaluate the mechanism chosen for modelling the triadic synapse and test the resulting inhibition properties of the model before extending the model to incorporate multiple inputs.

Following single-input model parameterisation, experimental confirmation was obtained that the model expressed appropriate triadic behaviour. Further complexity was added by increasing the number of RGCs that synapse onto the RC, from one to three, concurrent with the number of RGCs found to synapse onto a single LGN RC in current literature [17]. To investigate temporal selectivity, alterations to the stimulus protocol were made as outlined below. Temporal selectivity was tested by specifying that each of the simulated RGC inputs be delivered at a different time and observing the efficacy of each input for eliciting an action potential in the RC in response. Inhibition mechanisms were then isolated to investigate their contributions to the observed RC response.

2.3 Stimulus Protocol
In the initial model, NEURON objects 'NetStim', 'NetCon' and 'Exp2Syn' were used to generate spike trains which depolarised the cell membrane to a specified potential. When simulating multiple RGC inputs applied at different times, this approach was no longer sufficient to yield accurate results as it did not produce the desired summative behaviour of action potentials. Therefore, in the multi-input model, the NEURON object 'IClamp' was used to simulate the effect of the input stimuli as excitatory postsynaptic current (EPSC) injections. With this approach, the EPSCs exhibit temporal summative behaviour, therefore simulating the behaviour of excitatory postsynaptic potentials (EPSPs) observed in real biological systems [18]. At this stage, we also improved biological accuracy by incorporating additional membrane mechanisms, including but not limited to L-type and T-type Ca^{2+}-currents, slow Ca^{2+}-dependent K^+-currents and Ca^{2+}-vesicle pools. These were also used in the model by Heiberg *et al.* based on experiments in [19].

3. Results

Triadic behaviour was initially assessed through a single RGC input model. By isolating component inhibition mechanisms, it was found that triadic inhibition alone generates faster RC repolarisation than axonal inhibition alone. Combined, they exhibit a strong summative repolarisation response (Figure 1A).

The multi-input model allowed for subsequent investigation into triadic synapse dynamics. To test for temporal selectivity, the comparison of RC responses to synchronous versus asynchronous stimuli is shown in Figure 1B. It shows that synchronous inputs produce strong RC depolarisation, with efficacy for eliciting a response decreasing as the delay between inputs increases. Similarly, three synchronous RGC stimuli are more effective at inducing RC response than two synchronous RGCs. The latter are in their turn more effective than a single RGC stimulus (Figure 1E). Increasing the number of synchronous inputs into the triad thereby strengthens output RC response.

Finally, by modelling the triad with three synchronous RGC inputs we found that speed and intensity of RC depolarisation is similar regardless of inhibition state, while repolarisation occurs faster when triadic inhibition is present (Figure 1C). When the synapse is modelled with three asynchronous inputs, however, we find that RC response with triadic inhibition is weaker than without inhibition, and repolarisation again occurs faster (Figure 1D). Overall, this shows that, with triadic inhibition, synchronous inputs are more effective at driving RC response, while without triad mechanics RC response remains similar regardless of input synchronicity.
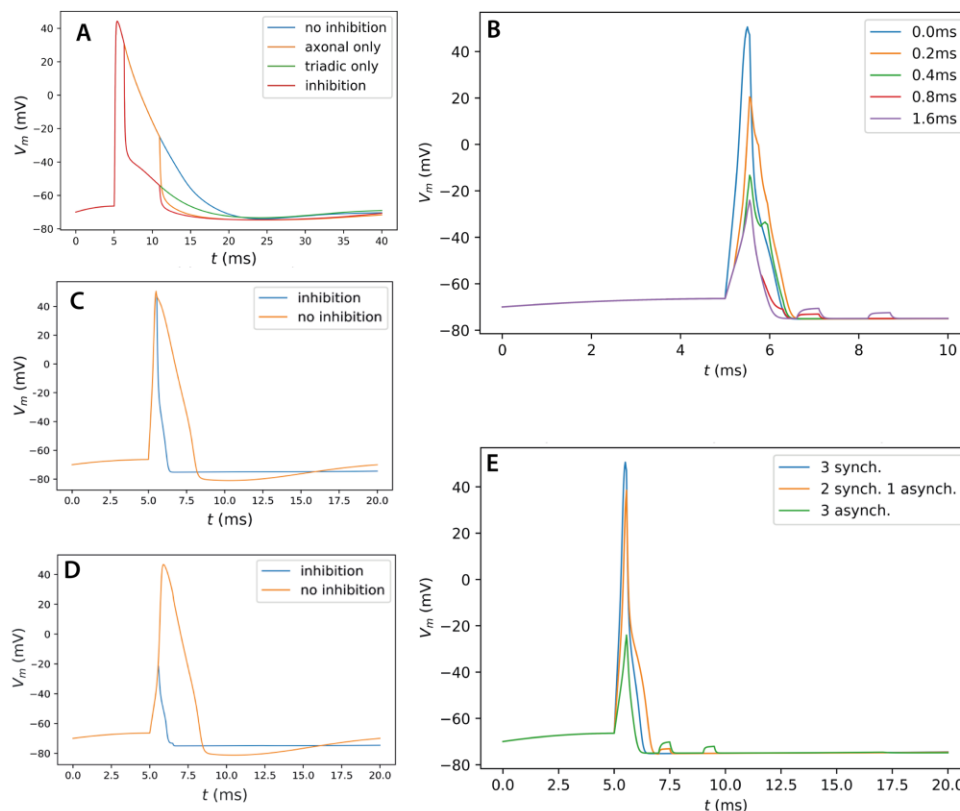

Fig.1: Computational experiments demonstrate that temporal selectivity emerges from triadic inhibition. (A) RC response with isolated inhibition mechanisms. (B) RC response for 3 RGC inputs fired with different delay times. The legend shows inter-stimulus delay. (C, D) RC response to a range of time-delayed spikes with and without inhibition. (C) 3 simultaneous RGC inputs. (D) 3 RGC inputs mutually delayed by 0.5ms. (E) RC response for synchronous and asynchronous RGC inputs. The inserted delay for asynchronous inputs is 2ms.

4. Discussion

Our computational analysis of LGN triadic circuitry has established three salient properties of triadic synapse behaviour. Firstly, we found that triadic inhibition alone activates faster neuronal repolarisation than axonal inhibition. Secondly, we found that synchronous stimuli are more effective at driving RC response with triadic synapses present. Finally, we found that when triadic inhibition is removed, synchronous inputs and asynchronous inputs are equally effective in driving RC response.

The model's isolated triadic inhibition response (Figure 1A), which allows for faster repolarisation to occur than under standard axonal inhibition, concurs with current literature findings that suggest that the triad could proffer increased temporal precision to visual signals by maintaining a narrow neuronal response [7], [16]. When considering a RC network, this increased temporal precision [20] as a result of synaptic triads may facilitate tightly correlated neuronal spiking within the LGN [21], thereby reinforcing thalamic transmission to the cortex and increasing LGN efficiency in driving cortical targets [22].

The increase in RC response that is observed under synchronous RGC input conditions, compared to a significantly lower response under asynchronous inputs (Figures 1B, 1E), demonstrates that the range of response magnitudes is continuous, resulting from the summation property of excitatory post-synaptic potentials and importantly promoting the likely function of temporal selective filtering within triadic circuitry. This allows significant visual inputs to selectively pass significant visual events over network noise [10].

Finally, by showing that complete removal of triadic inhibition from the model results in similar output products with both synchronous and asynchronous stimuli (Figures 1C, 1D), our model confirms the causative relationship between triadic synapses and temporal selectivity that has been previously only hypothesised in literature.

Our model effectively isolates triadic circuitry and enables an accurate analysis within circuitry function alone. However, by virtue of being a standalone structure, it neglects known complex inputs and outputs into the system. There is potential for future studies to embed the triad within more detailed LGN biophysics to approximate physiological conditions of the entire system and fitting the model with experimental data to finalise accurate parametrisation for specific mammals. Overall, in exclusively studying triadic functionality, our research successfully established a functional and adaptable triadic synapse model that confirms the validity of temporal selectivity as a functional property of the triadic synapse.

Conclusion

In this study we created a biophysically accurate model of the triadic synapse within the LGN and subsequently confirmed the validity of temporal selectivity as a possible function. Our computational analysis established three salient properties for the behaviour of triadic synapses, namely: triadic inhibition facilitates faster repolarisation than axonal inhibition; synchronous stimuli are more effective at driving relay cells than asynchronous stimuli with triadic synapses present; when triadic synapses are removed, synchronous and asynchronous are equally effective at driving relay cells, thereby confirming the causative relationship between the triad and temporal selectivity.

Code

The code written for modelling and simulation can be found at: https://github.com/jmckmartin/triadicLGN2020

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