Relative contributions of cortical and thalamic feedforward inputs to V2

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Abstract

Feedforward connections from one visual cortical area to another have been used to organize the cortex into a hierarchy. In addition to direct corticocortical projections, primary and secondary visual cortex are connected via an indirect pathway through the pulvinar, a higher order thalamic nucleus. These two feedforward pathways from V1 to V2 have the potential to differentially affect downstream activity through their connection strengths and conduction delays. To investigate the contributions of corticocortical and cortico-thalamocortical pathways to downstream population activity, these areas are modeled with linear rate variables which take into account the network architecture of cortex and thalamus. Synaptic weights are varied to assess the affects of driver and modulator afferent strengths. Pulvinar inactivation is simulated to provide a prediction for future experiments. Finally, the effects of conduction delays are considered on the dynamics of network activity.

1 Introduction

In addition to sending direct projections to secondary cortical areas, primary sensory cortex also communicates to downstream cortical areas via indirect projections through higher order thalamic nuclei. Since hierarchically organized areas are connected through at least two feedforward pathways, then, the classical view of corticocortical information flow [1] is oversimplified. Both pathways to secondary sensory cortex project to multiple layers, including layer IV, which is the input layer of sensory cortex. Inactivating primary visual cortex (V1) shuts down activity in the secondary visual cortex (V2) [2]. From those experiments, it is still unclear whether V2 activity is reduced due to the loss of direct information from V1 or from the pathway through the pulvinar, which is a higher order visual thalamic nucleus driven by V1 that also

projects to V2. Complicating the picture is the fact that excitatory transmission can be either driving or modulating in nature [3]. Driver neurons terminate in large boutons which target proximal sites on postsynaptic cells. Their EPSCs are fast, depressing, and large in amplitude. Conversely, modulator neurons have small axon terminals which target distal dendrites. Their EPSCs are small, slower, facilitating, and partially comprised of metabotropic responses. Therefore, an anatomical pathway from one area to another may have a strong effect, or it may be modulating. While the route through the pulvinar has been shown to drive responses in V2, the corticocortical pathway has a mix of driving and modulating properties [4-5].

One proposed set of experiments to address the relative contributions of these two pathways in visual processing is to selectively inactivate either projection population. An experimental tool to accomplish this inactivation is inhibitory optogenetics. By genetically expressing a variant of Channelrhodopsin which is permeable to chloride (iC++) instead of cations, it is possible to hyperpolarize neurons by shining blue light onto them [6]. When light is applied not to the upstream regions, but to V2, only the axon terminals in V2 should be inactivated, leaving activity of the soma and other projection populations intact. In this way, even when the corticocortical pathway is inhibited, V1 will still be broadcasting sensory information to the pulvinar. Likewise, the effect of pulvinar-V1 feedback will not be disrupted by this method.

The following model aims to simulate the population effects of these inactivation experiments. V1, V2, the pulvinar, and the thalamic reticular nucleus (TRN) (an thalamic nucleus which inhibits the pulvinar and receives cortical and thalamic input) are represented as homogeneous populations of excitatory and/or inhibitory neurons. The activity of these populations is represented as a rate variable, which evolves linearly based on incoming synaptic activity. To address the possibilities of either driving or modulating feedforward corticocortical excitation, synaptic weights are varied as either driving or modulating. Synaptic connections from the pulvinar to V2 are varied to assess the affects of inactivation on network activity. Finally, the effects of conduction delays are analyzed, and I consider the frequency response properties of V2 in each of these network regimes.

2 Methods

2.1 Network architecture

A network model of V1, V2, and the thalamus was created and simulated using the ode45 solver in Matlab 2016b. Six rate variables were defined to represent each population of neurons. The resulting activity has arbitrary units and is representative of the magnitude of multi-unit activity, which is the combined spike rate of many recorded neurons. Because this is a linear network, the activity of the cells can be thought of as representing the “simple cells” in the visual system. This is an oversimplification of the nonlinear processing which occurs in visual cortex; however, both V1 and V2 have simple cell populations.

The intrinsic connections of V1 and V2 are identical and include reciprocally connected excitatory (E) and inhibitory (I) populations which each have recurrent connections onto themselves. Only E populations have feedforward connections to other brain areas. The V1 E population connects to both E and I in V2, and V2 E sends feedback projections to both E and I populations in V1. V1 E also projects to the pulvinar, which is represented by an E population (the mouse LP nucleus has no inhibitory interneurons). The pulvinar, in turn, sends feedback to both E and I populations in V1, and it sends feedforward

connections to both E and I populations in V2. The pulvinar receives feedback projections from the V2 E population, and it is reciprocally connected with the TRN, which is an inhibitory population. The TRN also receives a feedback projection from the V2 E population. In total, this network architecture produces six nodes with 18 synaptic weight parameters. Input to this system is modeled as a sinusoidal wave, which represents the response of the LGN to a drifting sinusoidal grating visual stimulus. Only V1 E and I populations receive external input.

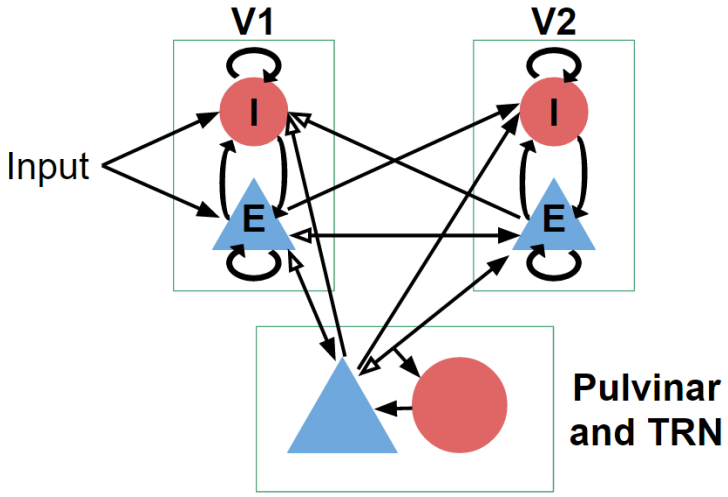

Figure 1 Network Diagram

The following simplified rate equations, which are modeled after those in Dayan and Abbott [7], govern the dynamics of the activity variables:

$$\tau_e \frac{dA}{dt} = -A + \left[W_{AA}A + W_{BA}B + W_{CA}C + W_{PA}P + I_{ext}(t)\right]_+$$

$$\tau_i \frac{dB}{dt} = -B + \left[W_{BB}B + W_{AB}A + W_{CB}C + W_{PB}P + I_{ext}(t)\right]_+$$

$$\tau_e \frac{dC}{dt} = -C + \left[W_{CC}C + W_{DC}D + W_{AC}A + W_{PC}P\right]_+$$

$$\tau_i \frac{dD}{dt} = -D + \left[W_{DD}D + W_{CD}C + W_{AD}A + W_{PD}P\right]_+$$

$$\tau_e \frac{dP}{dt} = -P + \left[W_{AP}A + W_{CP}C + W_{RP}R\right]_+$$

$$\tau_i \frac{dR}{dt} = -R + \left[W_{RR}R + W_{CR}C + W_{PR}P\right]_+$$

Each variable evolves with one of two time constants, τ_e or τ_i, depending on whether it is an E or I population. W_{ij} are the synaptic weights associated with the activity of presynaptic populations. A is the V1 E population, B is the V1 I population, C is the V2 E population,

and D is the V2 I population. P is the pulvinar, and R is the thalamic reticular population. Local E and I populations within a cortical area are connected with equal synaptic weights, which are opposite in magnitude. Feedforward connections between areas are modeled with synaptic weights either equal to 0.25 for modulators or 1 for drivers. Feedback connections are modulatory. The full set of synaptic weights can be found in the attached Matlab scripts. To simulate optogenetic inactivation of the pulvinar – V2 pathway, the synaptic weights for those connections was changed from 1 to 0.

LGN input was defined by the following function:

$$I_{ext} = 50\sin(2\pi ft) + 30$$

2.2 Modeling network activity with conduction delays

Realistically, a neuron is influenced not by the instantaneous activity of its presynaptic partners, but by the activity at a previous time. Depending on the distance between neurons and the conduction velocity of an axon, signals can be delayed by a range of 2-20 ms. Because the corticocortical pathway is monosynaptic and the transthalamic route is disynaptic, one important difference between these two pathways may be their offset phases. To add conduction delays to the network model, I implemented a numerical solver with time step of 0.5 ms. In each of the rate equations, the activity variables from other populations were evaluated at some time t – delay. Delays were 4 ms for local connections, 10 ms for intercortical connections, and 16 ms for thalamocortical connections.

2.3 Frequency response analysis

One useful way to characterize a linear system is to analyze the gain and phase angle of the system's output in relation to input signals of varying frequencies. To evaluate the activity of V2 in response to varying input frequencies, the amplitude and phase angle of the steady state response (200-500 ms) were empirically quantified for a range of 50 frequency values from 10^0.7 – 10^2 using a custom Matlab script. This analysis was repeated for the model with and without conduction delays to assess the affects of delays on filtering properties.

3 Results

The full network was successfully simulated with conditions of different V1 projection strengths, pulvinar inactivation, and conduction delays. The full set of parameters which produced a stable, convergent solution are contained in the attached Matlab scripts.

3.1 Effects of synaptic weights on network activity

3.1.1 Network activity when V1-V2 projection is driving

To evaluate the network activity when the V1 to V2 projections are driving, I set the synaptic weights for that connection to 1. The behavior of V1, V2, and thalamic E and I populations are shown below for two different inputs at ~5 and ~22 Hz.

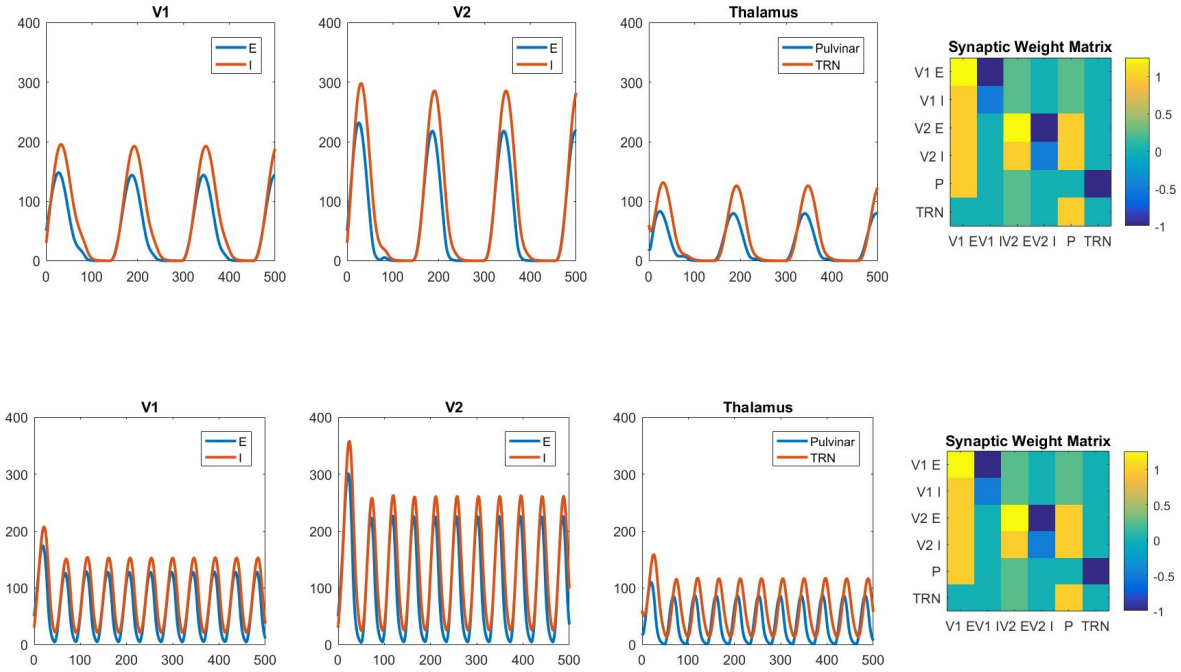

Figure 2 Network Activity at ~5 Hz (top) and ~22 Hz (bottom) when V1 – V2 Projections are Driving.

As shown in Fig 2, all three brain areas exhibit the same frequency as the input, as expected for a linear system. In all cases, inhibitory activity has a slightly higher DC gain than excitatory activity. V2 activity is higher than both V1 and thalamic activity. To characterize the gain of V2 relative to the input frequency, a magnitude response is shown below.

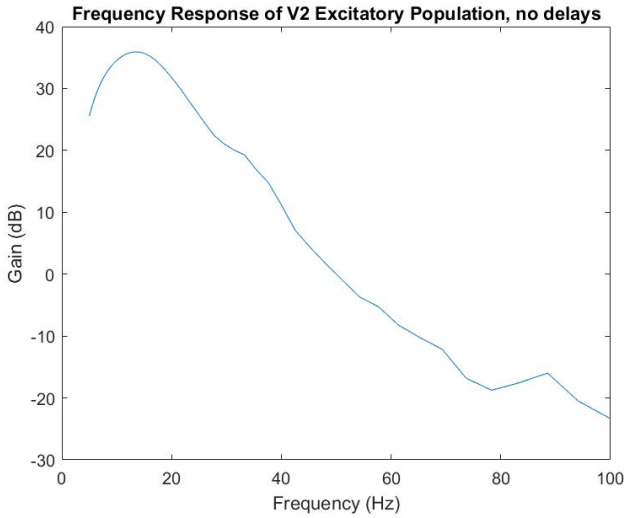

Figure 3 Magnitude of the V2 transfer function.

V2 acts as a low-order low pass filter that amplifies input frequencies below 40 Hz and attenuates frequencies above 40 Hz (Fig 3). Peak amplification of about 36 dB occurs near 13 Hz.

3.1.2 Network activity when V1-V2 projection is modulatory

When the V1 to V2 projection is modulating instead of driving, the gain of V2 is lower, and it is closer to the activity of V1. Shown below is the network activity at the two input frequencies from above, ~5 and ~22 Hz.

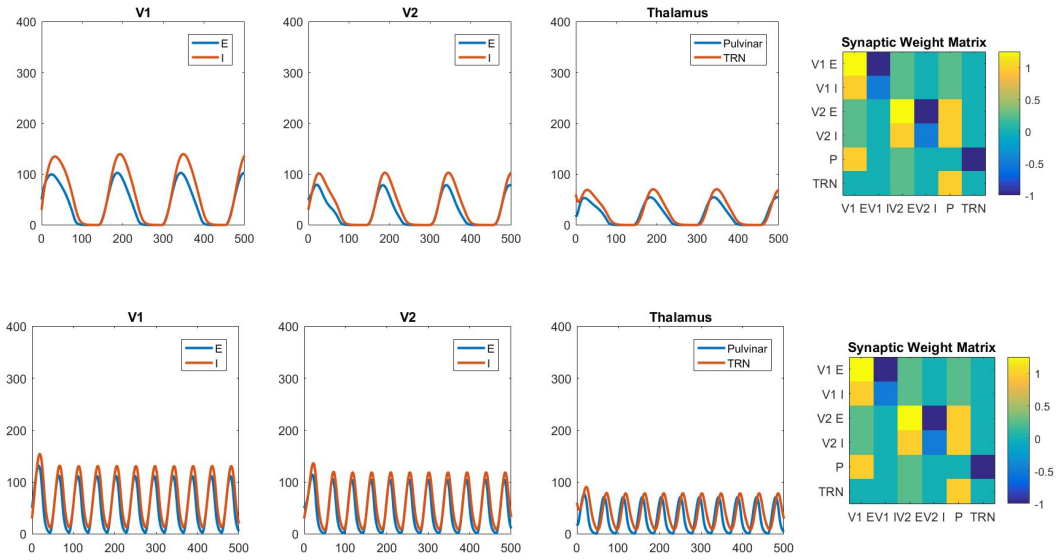

Figure 4 Network Activity at ~5 Hz (top) and ~22 Hz (bottom) when V1-V2 connections are modulatory

In addition to reducing V2 activity, V2 modulating projections also result in the depression of activity in all regions of the network. This broad reduction demonstrates the important role of feedback in facilitating sensory responses. The reduction in V2 activity was consistent across a range of input frequencies, as demonstrated by the DC gain shift of the frequency response in Fig 5.

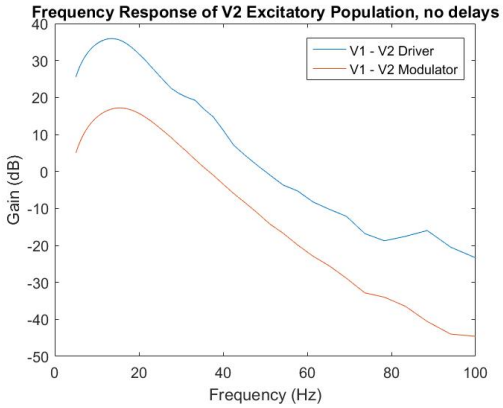

Figure 5 V2 frequency response magnitude for driver (blue) and modulator (orange) input from V1

3.2 Inactivating the pulvinar – V2 projection

To simulate the effects of optogenetically inactivating the pulvinar afferents projecting to V2, I repeated the previous network analysis with the synaptic weights from pulvinar to V2 set to zero. Figures below show V2 activity simulated with an input frequency of ~13 Hz.

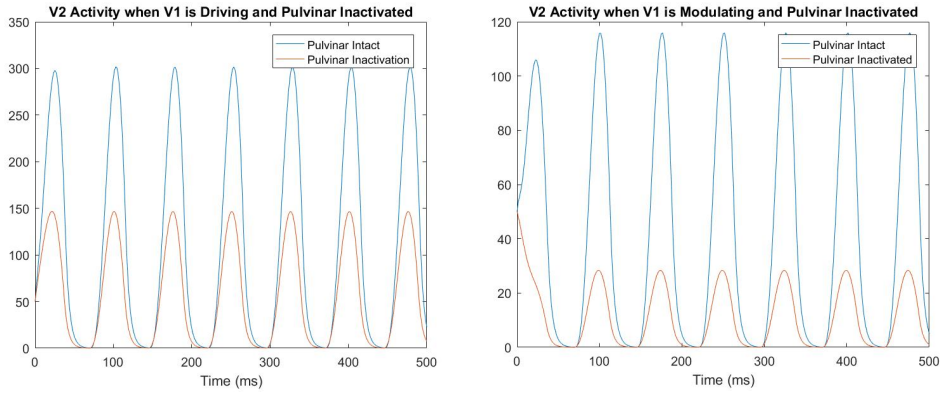

Figure 6 V2 activity when pulvinar afferents are inactivated and V1 is driving (left) and modulating (right)

For both cases when V1 is driving and modulating, inactivating the pulvinar projection to V2 has the simple effect of reducing the gain. This reduction is more pronounced when V1 has a modulating projection to V1.

The frequency responses for the pulvinar inactivation are shown in Figure 7 below. In both cases, the gain reduction is a DC offset.

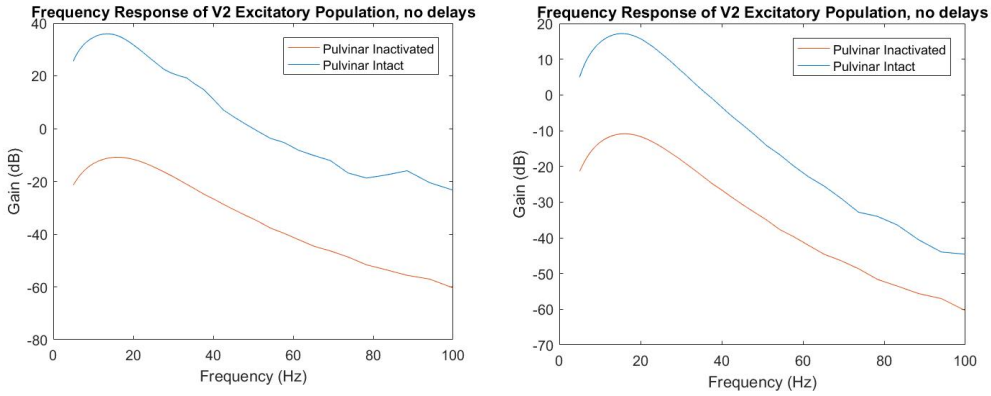

Figure 7 V2 frequency response magnitude with pulvinar inactivation and V1 driving (left) and modulating (right) V2 activity

3.3 Modeling network activity with conduction delays

In the above model, inputs from the pulvinar and V1 arrive at V2 simultaneously. However, input from the pulvinar would realistically reach V2 later than input from V1 in relation to the input stimulus because the pathway is disynaptic rather than monosynaptic. To model this feature of the thalamocortical network, I added conduction delays to each connection.

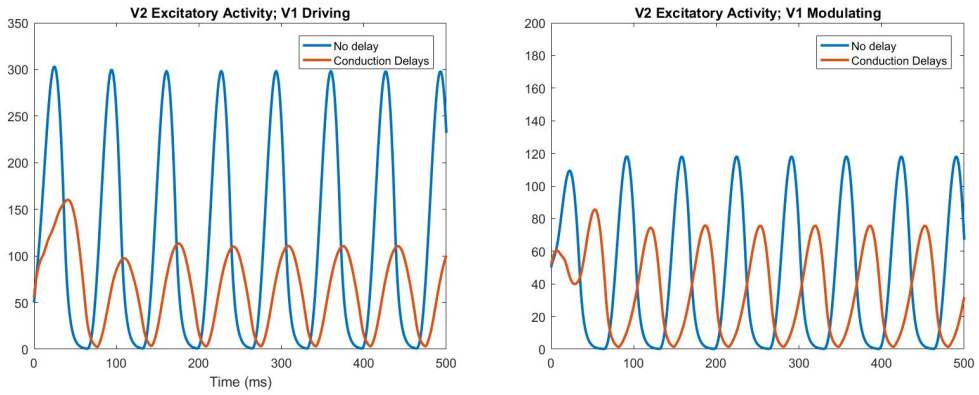

Figure 8 V2 Excitatory activity with (orange) and without (blue) conduction delays for driving (left) and modulating (right) V1-V2 projections

The responses above are to an input frequency of ~13 Hz, which is where the gain was maximum for the system with no delays. As demonstrated in Fig 8, adding conduction delays to the network reduced the V2 gain for the cases when V1 – V2 is a driving and modulating pathway. One interesting difference between these two cases is increase in phase lag of the V2 E activity when V1-V2 is modulating. Here, since the pulvinar is the main driver of V2 activity, the increased delays associated with thalamocortical transmission shifts the response of V2 in time.

To quantify the response attenuation and phase shift associated with adding conduction delays, I calculated the frequency response of V2 (Fig 9) and compared its magnitude to that of the model of V2 with no delays.

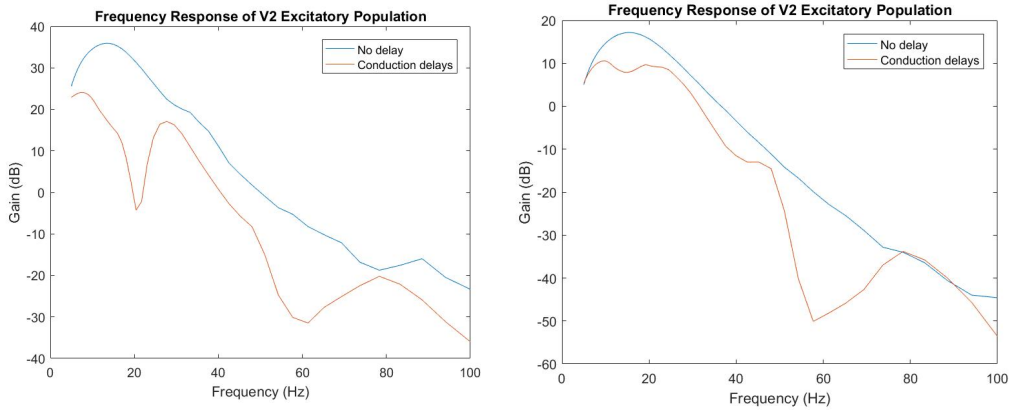

Figure 9 Magnitude of V2 frequency response with (blue) and without (orange) conduction delays when V1 drives (left) and modulates (right) V2 activity.

One notable feature of the magnitude of the V2 frequency response is a strong attenuation of frequencies around 60 Hz, regardless of the strength of V1 projections. Remarkably, the network model with conduction delays results in a notch filter around 20 Hz when V1 to V2 projections are driving, but not when they are modulating. While I have not evaluated the sensitivity of this feature to other network parameters, it would presumably be detrimental to sensory processing if inputs of different frequencies were attenuated in the normal input range. This could be an artifact of model parameters like the delays and time constants, or it could indicate that the network architecture where V1 and pulvinar equally drive V2 is not an optimal configuration.

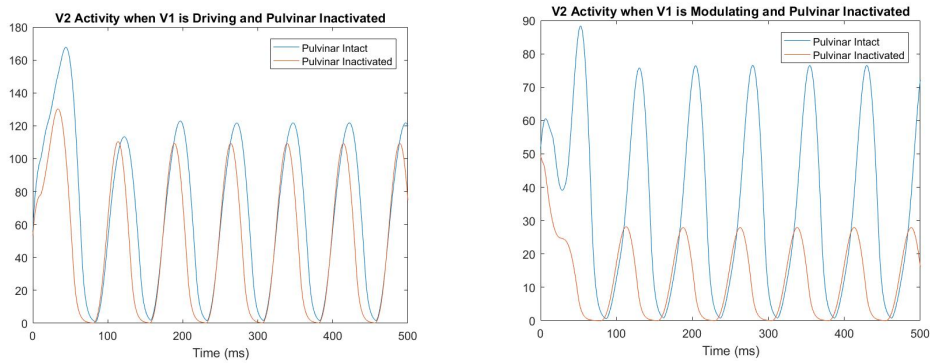

Figure 10 V2 excitatory activity with conduction delays, pulvinar inactivation, and V1 driving (left) and modulating (right) V2

As shown in Fig 10, the effects of pulvinar inactivation change dramatically when conduction delays are included in the model. When V1 projections are drivers, inactivating pulvinar causes only a slight attenuation of V2 activity, and the phase of V2 shifts leftward slightly. When V2 is a modulating projection, however, inactivating the pulvinar reduces V2 gain in much the same manner as the model without conduction delays.

4 Discussion

The phenomenological network presented in the present study represents the simulated activity of primary and secondary visual cortex and the thalamus with anatomically derived feedforward, feedback, and local connectivity. The goal of this model is to establish a baseline expectation of population activity against which to compare future experimental data.

The model with no conduction delays showed the summation of V1 and pulvinar activity in V2, resulting in a very high gain. It is unlikely that the average firing rates in V1 and V2 would be a factor of 2 different. Additionally, the inactivation of the pulvinar in this network led to a dc gain offset with no difference in the phase of V2 activity. While this model is useful in determining the appropriate parameters for the network to be stable, it is not as biologically plausible as the network with conduction delays. For this reason, the major findings are discussed below in the context of the network with conduction delays.

4.1 Network behavior when V1 projections are drivers and modulators

When the V1 projections to V2 are driving, overall network activity is increased compared to when they are modulatory. However, V2 activity is closer in magnitude to V1 than it is without conduction delays. Based just on the network activity, either the driver or modulator network is a plausible one without experimental data to validate it. The frequency response of the driver network, however, has a problematic attenuation of low frequencies, which would be expected to pass through the cortical hierarchy. The modulator network, however, does not have that problem. The frequency response curves indicate that the modulator network may be more biologically plausible – however, the notch filter might also be solved with a more thorough parameter screen. Both networks show the general trend of being a low pass filter, which fits with physiology.

4.2 Effect of pulvinar inactivation on V2 activity

Simulated pulvinar inactivation provides additional information on the expected behavior of driver or modulator networks. One interesting feature of the driver network was that even when V1 and the pulvinar have equivalent synaptic strengths in V2, pulvinar inactivation does not remarkably reduce the gain of the V2. This architecture then would suggest that when V1 projections are drivers, the pulvinar is sufficient but not necessary for driving V2 activity. Instead, it may have a

bigger role in regulating the phase of V2. Theories about the role of the pulvinar in synchronizing distant cortical areas would support this hypothesis.

When V2 projections are modulatory, inactivating the pulvinar has a large effect on the magnitude of V2 responses. Additionally, the phase shifting caused by pulvinar inactivation is stronger in the absence of V1 driving activity.

4.3 Model limitations and future directions

One major limitation of this model is the assumption of homogeneous populations. Anatomical evidence suggests that within V1, different populations of excitatory cells give rise to corticocortical and corticothalamic projections. These distinct populations are likely to carry unique information about the stimulus or the state of the animal, so this model is only appropriate with the assumption that the two streams of activity are somewhat similar.
Another future direction of this model would be to add different time constants for driving vs modulatory transmission. Modulatory glutamatergic transmission is slower than driving, so a longer time constant could endow the network with additional features.
Additionally, the pulvinar receives input from sources other than V1, so this model does not account for the baseline and stimulus-specific pulvinar activity which is independent of V1. One major source of this stimulus-specific information is from the superior colliculus, which relays slightly different visual features than does the cortex.
Finally, the parameters in this network were selected primarily to generate stable responses. Calibration of these parameters to match empirical values of the network activity would make the results of simulated pulvinar inactivation more meaningful.

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