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Functional Roles of the Corticothalamic Feedback Loop

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We build our castles in the air,
And from the air they tumble down
Unless we carry them up there
Until they crack the pate they crown.

Warren S. McCulloch (*The natural fit*, 1959).

To my six eyes

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Resumé

Le thalamus visuel dorsal des vertébrés reçoit des projections de rétroaction du cortex visuel primaire (V1) qui dépassent largement en densité de connection la projection directe, que ce soit au niveau du thalamus ou du cortex. De nombreux travaux expérimentaux et de modélisation ont été consacrés à l'étude en boucle ouverte des projections "feedforward" reliant la rétine, le thalamus et le cortex. Mais la relative paucité des conditions expérimentales et leur absence d'homogénéité et de contrôle paramétrique, le manque de reproductibilité des observations fonctionnelles et les données structurales éparses ont limité jusqu'à présent notre compréhension des fonctions de rétroaction.

Pour synthétiser une image globale cohérente qui lie les observations dans toutes les conditions expérimentales de la littérature, nous avons construit un modèle biologiquement réaliste, à grande échelle de la boucle corticothalamique chez le chat. Le modèle a été contraint par les études anatomiques pour les statistiques de connectivité, les études d'électrophysiologie pour les paramètres cellulaires et les études de population fonctionnelle pour les statistiques des réponses évoquées. En itérant les procédures d'ajustement des réponses enregistrées expérimentalement à six configurations de stimuli, présentées dans des conditions où la boucle corticothalamique était intacte, inactivée de diverses manières, ou complètement supprimée, nous avons convergé sur un ensemble de paramètres uniques permettant de concilier la plus grande partie d'observations expérimentales.

Nous avons étudié l'influence de la rétroaction corticale sur le traitement du thalamus et du cortex lui-même. En se plaçant d'un point de vue centré sur le thalamus, le modèle souligne le rôle de l'inhibition périgéniculée thalamique et l'antagonisme en miroir de l'organisation spatiale réciproque des champs

récepteurs corticaux et thalamiques. En se plaçant d'un point de vue centré sur le cortex, le modèle montre comment la boucle permet la compétition entre les représentations corticales en contrôlant l'équilibre des entrées excitatrices et inhibitrices. En réunissant ces deux points de vue, nous proposons que la boucle de rétroaction permette la fusion et la concurrence entre prédictions fonctionnelles multiplexées temporellement au sein du même réseau cortical.

Abstract

The vertebrate visual dorsal thalamus receives feedback projections from primary visual cortex (V1) that greatly outnumber its feedforward projections to V1. Extensive experimental and modeling work has been devoted to the feedforward pathway linking retina, thalamus, and cortex. But the paucity and diversity of experimental conditions, the lack of reproducibility of functional observations, and the sparseness of structural data have been hindering our understanding of feedback functions. To reach a coherent global picture that binds experimental observations across conditions, we built a large-scale spiking model of the cat thalamo-cortico-thalamic loop. This simplified model of the early visual system was constrained by anatomical studies for connectivity statistics, single cell electrophysiology studies for cell parameters, and functional population studies for the firing statistics of evoked responses. By iterating through the reproduction of experimentally recorded responses to six test stimuli configurations, presented in conditions where the corticothalamic loop was either intact, variously inactivated or totally suppressed, we converged on a single parameter set that enabled us to reconcile a number of experimental observations. We studied the influence of cortical feedback on the processing of both thalamus and cortex itself. Under a *thalamus-centered viewpoint*, the model highlights the role of thalamic perigeniculate inhibition and the mirror antagonism of the reciprocal spatial organization of cortical and thalamic receptive fields. Under a *cortex-centered viewpoint*, the model shows how the loop enables competition among cortical representations by controlling the balance of cell excitatory and inhibitory inputs. Joining these views, we propose that the feedback loop enables the fusion and competition among temporally multiplexed and spatially overlaid cortical predictions.

1 Introduction

1.1 Motivation

The central nervous system of all vertebrates presents a high degree of recurrence at all its levels. In the forebrain, a major recurrence is that between cerebral cortex and thalamus. What is its functional role? To date, we lack a widely accepted answer.

Providing an answer to that question requires first to unravel the recurrent nature of such a complex system, and then to show how the recurrence weaves basic properties into more complex ones.

For the unraveling, two approaches are often adopted. One approach focuses on its nested organization, explaining the complexity in terms of interrelated sub-systems (Simon 1962). The other approach focuses more on its information flow, explaining the complexity in terms of incremental steps between modules (Hubel and Wiesel 1962). Both approaches are well established in the experimental practice.

However, complex systems dominated by recurrent dynamics are notoriously difficult to fully understand by such purely reductionist approaches, and a more synthetic treatment has to follow. But the dominant practice is to present the processing that takes place in the nervous system as a linear and feedforward chain of relays. For example, in the early visual system, linear system theory principles are usually applied to extract a reasonably "good" approximation of the functioning of each relay station, going from retina to thalamus to primary visual cortex (Bonin et al. 2005, Olshausen and Field

2005, Vintch et al. 2015). This over-simplifying approach ignores the large set of embedded recurrent loops, including corticothalamic feedback connections and thus cannot offer insight into the role of these recurrences in cortical processing (Sherman and Koch 1986, Basso et al. 2005).

But even when the role of corticothalamic feedback connections is taken under scrutiny (Wörgötter and Koch 1991, Kirkland and Gerstein 1998, Hillenbrand and van Hemmen 2002), recomposing sparse fragments of the existing functional evidence into a single coherent mosaic proves to be arduous. The thalamus is experimentally difficult to access, consequently it is challenging to test in-vivo hypotheses regarding functional roles of the cortical feedback and its mechanisms.

As a result of the dominance of feedforward approaches and experimental difficulties, previous efforts at synthesizing existing experimental findings into a single theory of thalamocortical computation were limited, often reverting to simple enumeration of functions (Usrey and Alitto 2015, Weyand 2016, Ghodrati et al. 2017). Thus, to advance our understanding of corticothalamic loop, it is imperative to bridge the gaps in our knowledge and consolidate the available experimental findings into a single coherent whole.

In pursuit of this goal, in this Ph.D. thesis, we have built a large-scale, biologically detailed model of the cat thalamo-cortico-thalamic loop in the early visual system, which accounts for an unprecedented range of experimental findings. In order to make sense of the sparse and often puzzling experimental evidence, and to develop our understanding in an integrative manner, we started from the simplest possible feedforward model and incrementally expanded it by adding identified feedback circuits. The resulting comprehensive model provides phenomenological and mechanistic explanations for a set of specific functional features, and offers testable predictions for further explorations.

Our modeling effort outlines how, in the early visual system, the spatial relationships between cortical and thalamic receptive fields, and their reciprocal connectivity, yield as main function of the thalamo-cortical loop the implementation of dynamic context-based confinement, competition, and cooperation between neural representations of the visual scene.

1.2 Summary of the thesis

In the following paragraphs, I provide a brief summary of the individual chapters in this thesis. The chapters present methods and results of our work that have been submitted (in a more condensed form). The appendix collects published works, which are presented in reprinted format.

In **Chapter 2, “Background”**, I present a review of the biological features of the early visual system that are relevant to this thesis, with a focus on the corticothalamic feedback loop. I also introduce some influential theories about perception, together with their proposed functional role for the corticothalamic feedback loop, when available.

In **Chapter 3, “Experimental constraints in modeling strategies”**, I present the experimental and modeling strategies that have been used in the literature to study the corticothalamic feedback in the early visual system. Then I describe the hypotheses and overall strategy guiding my modeling approach: (i) the choice of a Gaussian kernel function for the corticothalamic feedback connectivity, (ii) the building of knowledge through the incremental addition of feedback circuits, and (iii) the expected impact of the corticothalamic feedback on thalamic and cortical processing.

In **Chapter 4, “Methods”**, I present in detail the methods of our study and simulations: the morphological and electrophysiological studies I used as sources to develop, constrain, and validate our model, the several stimulation protocols I derived from the available experimental literature, together with the corresponding analysis workflow.

In **Chapter 5, “Results Overview”**, I summarize the model structure and the various versions of it that we implemented to gradually increase our knowledge and match the experimental studies I took under scrutiny. The modeling results are divided in two complementary points of view, which will be developed in the two following chapters: a *thalamic-centered* point of view (chapter 6), where I look at the functional role of cortical feedback in thalamic processing, and a *cortical-centered* point of view (chapter 7), where I look at the functional role of cortico-thalamo-cortical loop in cortical processing.

In **Chapter 6, “Results — Thalamic-centered viewpoint”**, I present how the responses of cortically-projecting thalamic cells gain in functional capabilities when the model is incrementally enriched by various features of thalamo-cortical circuitry. I first show how the addition of an intrathalamic inhibitory feedback, with its spatial properties, introduces extra-classical surround suppression in the responses of cortically-projecting cells. And then I show how the addition of corticothalamic excitatory feedback enhances the thalamic center-surround response opponency, by selectively amplifying thalamic excitation and inhibition.

In **Chapter 7, “Results — Cortical-centered viewpoint”**, I present how cortical computation is improved by reverberating its activity onto thalamus. I first show how, only in the presence of a closed loop between cortex and thalamus, the cortical orientation preference map is dynamically strengthened. Then I show how the balance of excitation and inhibition of cortical cells changes when the loop between cortex and thalamus is opened or closed. And I also show that, for stimuli varying in size, the cortical surround response is able to dampen the spike-to-field coherence of the cortico-thalamic, only if corticothalamic loop is closed.

In **Chapter 8, “Discussion and Conclusions”**, I weave together the results of the present work and past studies, I outline encountered pitfalls, I provide

future directions of work, and I also speculate over the broader implications of this work for the understanding of the early mechanisms of perception.

In the **Appendix**, I present the reprint of published works.

1.3 Relevant Publication

— Domenico Guarino, Jan Antolík, Andrew P. Davison, Yves Frègnac, (2017), “An integrative model explaining many functions of corticothalamic feedback”, BMC Neuroscience 18(1):59 (doi: 10.1186/s12868-017-0371-2)

— Domenico Guarino, Jan Antolík, Andrew P. Davison, (2014), “Model validation using the Mozaik framework”, Frontiers in Neuroinformatics 37 (doi: 10.3389/conf.fninf.2014.18.00037)

— Samuel Garcia, Domenico Guarino, Florent Jaillet, Todd R Jennings, Robert Pröpper, Philipp L Rautenberg, Chris Rodgers, Andrey Sobolev, Thomas Wachtler, Pierre Yger, Andrew P Davison, (2014), “Neo: an object model for handling electrophysiology data in multiple formats”, Frontiers in Neuroinformatics 20 (doi: 10.3389/fninf.2014.00010)

— Andrew P. Davison, Yves Frègnac, Thierry Brizzi, Domenico Guarino, Olivier Manette, Cyril Monier, Yves Frègnac, (2013), “Helmholtz: a customizable framework for neurophysiology data management”, Frontiers in Neuroinformatics 25 (doi: 10.3389/conf.fninf.2013.09.00025)

1.4 Additional Works

— Domenico Guarino, (2018), “Krauzlis’ strange inversion of reasoning”, Frontiers in Systems Neuroscience 12(34) (doi: 10.3389/fnsys.2018.00034)

— Assunta Pelosi, Domenico Guarino, (2015), “Striatal cholinergic interneurons modulate action selection and reinforcement learning”, *Frontiers in Neural Circuits* 9(15) (doi: 10.3389/fncir.2015.00015)

2 Background

2.1 What is the thalamus?

Sitting in the center of all vertebrates' brain, there is a midline symmetrical structure called thalamus. The name was given by the greek physician Galen of Pergamon that compared the human brain to the plan of a greek mansion with, at its heart, the bridal chamber (θάλαμος, from θολος: 'vault'), emphasizing the central position and role of thalamus ("De Usu Partium Corporis Humani", 133-200 CE). So central that, only through the misleading confusion with the lateral walls of the ventricles, René Descartes (1639) hypothesized its importance as a relay of images from the eyes to be later merged by the homunculus, and Wilhelmus Stein ("De thalamo et origine nervi optici in homine et animalibus vertebratis", Copenhagen 1834) as well as Jules Bernard Luys (1865) devised the role of thalamus in sensorimotor loops (see figure 2.1), and William Benjamin Carpenter considered it as the seat of consciousness (in "Principles of mental physiology", London 1874). In fact, the mammal thalamus is variously connected to evolutionarily older structures of the midbrain (like lemniscus, tectum, cerebellum, hippocampus, and basal ganglia) and newer structures like the cortex (Jones 1985). In addition, especially for its inner structure and its connections to other structures, the thalamus has changed little across mammal species (Rouiller and Welker 2000).

The thalamus contains several nuclei that are grouped into three major anatomical subdivision made by the internal medullary lamina: anterior,

medial, and lateral parts (Jimenez-Castellanos 1949, Jones 1985). The **anterior** part contains intrinsic nuclei (lateral and anterior parts of the ventral nucleus and the anterior nuclei) that are the sites of termination of paths from other portions of the brain (like cerebellum, basal ganglia and hypothalamus). The **medial** part contains intrinsic nuclei (intralaminar nuclei) that are sites of termination of paths from cortex to brainstem nuclei (like subthalamic nuclei and spinothalamic tracts). A large number of thalamic nuclei are not primarily driven by sensory signals nor do they exclusively target the cortex, but the **lateral** part contains extrinsic nuclei (medial and lateral geniculate bodies and posterior part of the ventral nucleus) that are the sites of termination of afferent paths from peripheral receptors to the cortex through the bundles of fibers known as thalamocortical radiation.

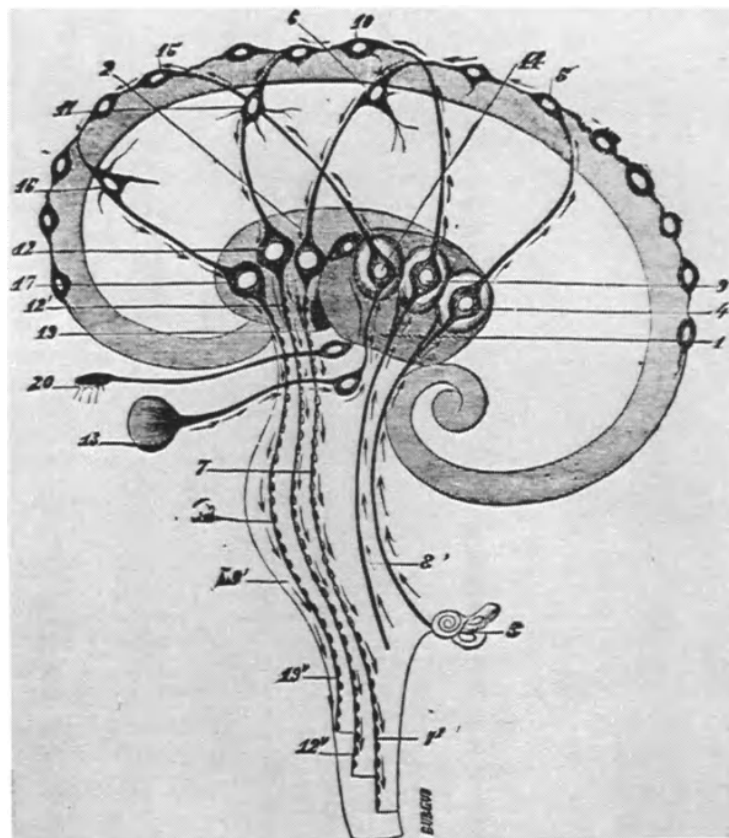


Figure 2.1. Role of thalamus in the sensorimotor loop according to Luys (1865). The thalamus (in the center, with scheme number 1) contains extrinsic nuclei relaying, among others, visual stimuli (14) to the visual (5) and other sensory cortices. Cortical cells then stimulate the basal ganglia (2) and corresponding centers in the brainstem (12) that initiate motor activities (reproduced from archive.org/details/b21968457).

The human thalamus shares basic organizing principles with other higher mammals, notably primates and other carnivores like cats and ferrets (Hasse and Briggs 2017), which is the reason why they were the subjects of anatomical studies (Jones 1985). In the reminder of this work we will focus on cat thalamus.

2.2 The lateral geniculate nucleus as a model sensory thalamic nucleus

The lateral part of thalamus contains the dorso-lateral **geniculate nucleus** (LGN), also called lateral geniculate body or complex, which is the main extrinsic thalamic nucleus in the visual pathway linking the eyes to the visual cortices. The LGN is usually taken as a model thalamic nucleus because its basic circuit features are also found in other thalamic nuclei (Sherman and Guillery 2001).

2.2.1 From the eye to the LGN

As light enters the eye, photosensitive cells of the **retina** transduce changes in amount of photon energy into changes of ionic currents passing through their membrane. Following phototransduction, visual signals are further processed by bipolar cells and **retinal ganglion cells** (RGCs), whose axons exit from the posterior of the eye, conducting membrane potential spikes towards the brain.

All along the sensory pathways, a stimulus is what makes the firing frequency of a neuron (Sherrington 1906, Hartline 1940) or its membrane potential (Frégnac et al. 1996) change only for a restricted portion of sensory space, referred to as **receptive field** (RF). Proceeding through the sensory system hierarchy, the trigger features of the RF become progressively more complex. For vision, at retinal level, RGCs have RFs roughly shaped as two concentric circular opponent subfields, a center with a surrounding ring of opposite polarity (Barlow 1953, Hubel and Wiesel 1962, Hammond 1974). A

cell is labeled as **On-center** RGC when its firing rate is increased by a positive contrast change in the center of its RF. Conversely, an **Off-center** RGC has opposite characteristics: its firing rate is decreased by a positive contrast increase at the RF center and increased by light within the surround (Koffler 1952). This antagonism between center and surround renders the RGCs local contrast detectors since they differentiate the luminance profile in the immediate neighborhood of their receptive field center, responding strongly to spots of light (or darkness) enclosing only their RF centers. Together with the spatial properties of RFs, cell responses may also be filtered in time, resulting in **spatio-temporal** RF properties. The spatial properties are usually studied using stimuli varying in their **spatial frequency**, which for a sinusoidal grating stimulus, is defined as the number of cycles in one degree of visual angle, measured in cycles per degree (c/deg). The temporal properties are measured as the **temporal frequency**, defined as the number of cycles shifting under the RF, expressed as cycles per second or Hertz (Hz). In the cat, RGCs are classically classified as X-, Y-, or W-cells (there are more than three RGC types, but this classification covers the majority), differing in their morphology and the linearity of their RF response properties (Enroth-Cugell and Robson 1966, Shapley and Victor 1979, Troy and Shou 2002). **X-cells** are characterized by having small cellular bodies, slow conducting axons (Humphrey et al. 1985), and a linear spatio-temporal RF that, when quantitatively analyzed, can be well approximated by two linearly separable components: one **spatial component** – usually modeled as a difference of two Gaussian functions for the concentrically opposing center and surround (Rodieck 1965) – and one **temporal component** – usually modeled as a sum of two Gamma functions for the response change over time (Rodieck 1965, Cai et al. 1997). **Y-cells** are characterized by having large cellular bodies, fast conducting axons and a complex spatio-temporal RF that cannot be linearly separated (Humphrey et al. 1985). **W-cells** have even smaller cellular bodies, with slower conduction velocities, complex spatio-temporal RF, and project subcortically, mainly to the superior colliculus (Berson 1988).

2.2.2 Geniculate cells and their properties

Through the **optic nerve**, RGCs send their axons to the ipsilateral and contralateral LGN. The cat LGN is organised into three layers (called 'laminae') with alternating exclusive ocular dominance, called **A** (receiving from the contralateral retina) and **A1** (receiving from the ipsilateral retina), where retinal X- and Y-cells terminations are intermingled, and **C**, where only W-cells project. Each lamina is set apart from the other by interlaminae, containing white matter (neuron axons) and also cell bodies (figure 2.2).

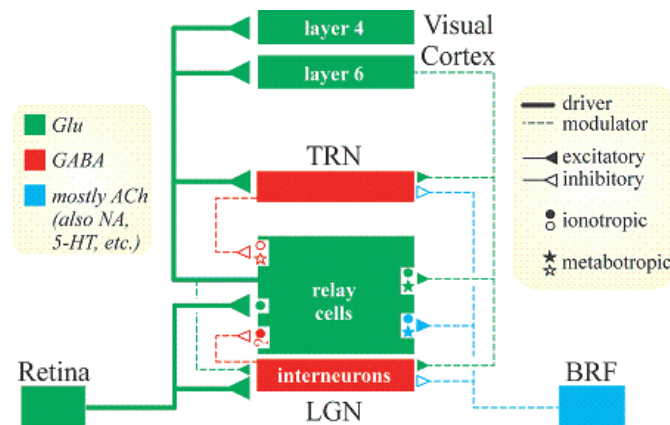


Figure 2.2. Circuitry of the lateral geniculate nucleus. The inputs to each type of thalamic cell population (boxes) are mapped together with the neurotransmitters they use (colors), and the type of connection they form (line weights and arrow shapes) and postsynaptic receptors involved. Abbreviations: LGN, lateral geniculate nucleus; BRF, brainstem reticular formation; TRN, thalamic reticular nucleus (Adapted from Sherman 2004).

Geniculate principal cells, also known as **relay cells** since they project to visual primary cortex, totaling approximately 4.5×10^5 in the cat (Sanderson 1971, Sherman and Koch 1986), have two notable properties, whose functional implications have been studied in depth.

First, principal cells are selectively innervated by only one type of RGC cell (X- or Y-cell, On- or Off-center) and therefore inherit almost completely the retinal RF properties of the respective type (Sherman and Koch 1986). And the inheritance is not reduced to single cell properties. The RGC axons terminating in each layer of the LGN preserve their spatial layout forming a

retinotopic map such that neighboring regions of the retina are represented by neighboring regions of the LGN (Sanderson 1971). This retinotopic mapping is preserved across the visual hierarchy, and is particularly precise in the early visual system, but becomes fuzzier when progressing from primary and secondary visual cortices to ventral, lateral, and dorsal occipital cortices (Gilbert and Kelly 1975, Tretter et al. 1975), to frontal motor areas triggering saccade movements (Schlag and Lindsley 1970).

Second, at the intrinsic excitability level, the membrane of principal cells expresses a dense distribution of T channels in its soma and dendrites, whose activation gives rise to depolarizing **T current** (Jahnsen and Llinas 1984, Sherman and Guillery 2001), leading eventually to the intracellular generation of a Ca^{2+} spike. The importance of such Ca^{2+} spike is it triggers dendritic reverberating events resulting in a burst formed of transient, high frequency burst of conventional action potentials. It has otherwise slow inactivating properties which will damp the shape of the regenerative potentials. Therefore thalamic principal cells are capable of working in two modes of firing: tonic and bursting. The **tonic mode** of firing happens when the principal cell is depolarized for while (≥ 100 msec), causing T channels to be inactivated. In this case, an incoming depolarizing current pulse causes unitary action potentials for the duration of the stimulus. The **bursting mode** of firing happens when the principal cells is hyperpolarized for a while (≥ 100 msec), causing T channels to be ready to open (de-inactivated). In this case, the incoming depolarizing current pulse open the T channels and the Ca^{2+} spike trigger a burst of several (2-10) action potentials (Guido et al. 1992, Sherman 2001). The functional role of these two modes of firing has been investigated yielding an important conclusion: the same input can be differently relayed to further processing stages. The tonic mode of firing linearly follows the stimulus: the larger the stimulus depolarization, the greater the firing rate. This offers the functional advantage of faithful encoding and transmission of stimulus features. By contrast, the bursting mode of firing is non-linear: small or large stimulus depolarizations do not

matter, they lead to a burst. The advantage of this latter firing mode is that small stimulus changes drive large response changes that are thus easier to detect for visual cortex due to the fast adaptation of thalamocortical synapses (Sherman 2001, Swadlow and Gusev 2001). Therefore, the bursting mode could serve as a "wake-up call" to cortex, signaling when something has changed in the environment (Sherman 2001).

In the LGN, there are also local GABAergic **interneurons** dispersed among the principal cells, which they inhibit. The ratio of principal cells to interneurons is between three and four to one, as for other parts of the brain (Sanderson 1971), and the RF of interneurons was reported to be similar to that of principal cells (Dubin and Cleland 1977), also preserving retinotopy (Mastrorade 1992). More recently, it has been shown that LGN interneurons tend to have a RF organization opponent to the principal cell they innervate (Wang et al. 2011). However, several morphological studies found no axon on LGN interneurons (Sherman and Guillery 2001), which makes it difficult to attribute direct functional roles to the interneurons (von Krosigk et al. 1990, Crandall and Cox 2012, 2013). The most peculiar anatomical feature of LGN interneurons is that they participate to **triadic synaptic complexes**, globular structures (also called 'glomeruli') where retinal axons, principal cell dendrites, and interneuron dendrites are entwined. In the triad, interneuron terminals can release GABA when the retinal firing increases, even without any membrane change in the parent interneuron. Given these properties, Sherman (2004) proposed that the main functional role of the interneurons is to provide a gain control of the retinal input (see also Hanes et al. 2011). It is unclear whether thalamic interneurons possess tonic and bursting firing modes, although these cells possess T currents (Pape and McCormick 1995).

Surrounding the dorsal part of the thalamus and sending its projections to it, there is the **thalamic reticular nucleus** (also called reticular thalamic nucleus). The portion surrounding the LGN takes the name of **peri-geniculate nucleus** (PGN). Neurons of the PGN are also GABAergic and inhibit their geniculate targets (both principal cells and interneurons). The PGN cells

receive collaterals from LGN principal cell axons, without cell-type specificity (Sherman and Guillery 2001). Their RFs have been shown to retain the retinotopic organization of their LGN afferents, although they cover larger portion of the visual space, due to the convergence of multiple LGN afferents onto each PGN cell. Their functional response properties are opponent to those of their afferents (Funke and Eysel 1998). The cells of the PGN also show T channel activity with tonic and bursting firing modes, although the details of T channel voltage and time dependencies vary slightly from those of principal cells (Huguenard and Prince, 1992, Higashikubo and Moore 2017). In this case, the functional role of spiking modes is less clear (Mistry et al. 2008).

2.2.3 From the LGN to cortex ...

The thalamic principal cells send their axons to primary sensory cortices, exciting their targets in a topographically ordered fashion (Jones 1985, Sherman and Guillery 2001). The **mammalian primary visual cortex** (V1) is organized into 6 distinct layers, differing in cellular morphology, density, and connections. The layers are labeled from I to VI, with layer I at the surface and layer VI at the bottom of the cortical gray matter. Majority of thalamic afferents end in layer IV, while also branching to establish further connections of modulatory character in the lower (V-VI) layers (Constantinople and Bruno 2013; Sherman 2012) and upper (I-II/III) layers. Two main types of V1 excitatory cells are the spiny stellate cells and pyramidal cells. **Spiny stellate cells** are restricted to layer IV, where their dendrites and axons form dense local connections. They are considered as the main population of thalamo-recipient cells since they receive predominantly LGN axons (Ferster and LeVay 1978). **Pyramidal cells** are the most numerous types in the cortex with axons and dendrites projecting throughout all cortical layers. In addition to a remarkably invariant intracolumnar circuit (Bolz and Gilbert 1986, Gilbert and Li 2012), linking supragranular and infragranular layers with a feedback to layer 4, pyramidal neurons are also the output cells of V1 establishing (lateral) connections with

other cortical areas from supragranular layers (Gilbert and Kelly 1975, Gilbert and Wiesel 1989, see Figure 2.3) and with subcortical structures such as the LGN and Pulvinar from infragranular layers (Jones 1985).

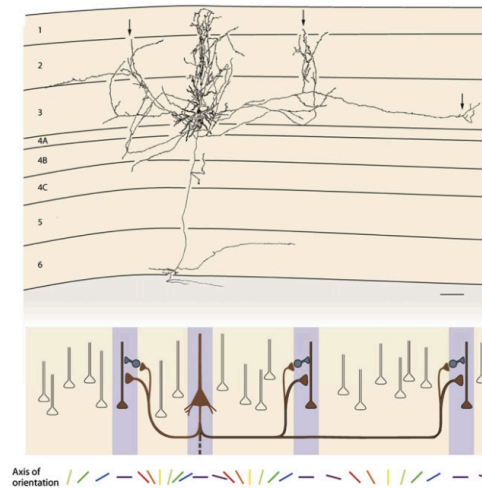


Figure 2.3. V1 selective horizontal circuitry. A deep layer 2/3 cortical pyramidal cell forms long-range horizontal connections that extend for several millimeters (scale = 100 μm). Such connections enable cortical cells to integrate at the subthreshold level information over an area of visual field much larger than their classical discharge field. The combination of labeling and intrinsic optical imaging techniques established the relationship between horizontal axon collaterals and the columnar functional architecture (bottom schema), where supragranular long-range connections tend to link preferentially columns of similar orientation preference (reproduced from Gilbert 2012).

In their pioneering study in 1962, David Hubel and Torsten Wiesel first reported V1 neurons having elongated RFs: they responded strongly to bars presented with a specific (called ‘preferred’) orientation, while not responding to or being suppressed by an orthogonal orientation. Following Hubel and Wiesel, RF properties can be classified in two alternative classes: **simple** and **complex** cells. Hubel and Wiesel also proposed (in 1965) a hierarchical model for simple and complex RFs, where the cortical RF organization was given by the summation of topological specifically arranged individual RFs of its presynaptic afferents. Initially, Hubel and Wiesel thought that the opponent sidebands of the simple cell were formed by the opponent surround part of the thalamic RFs of a given type, but this assumption was proven to be

wrong. In fact, the ON-center subfield (conversely OFF-) is formed by a row of ON-center (conversely OFF-) LGN cells (Alonso et al. 2006). Multiple LGN cells would converge to a single cortical simple cell, forming in each simple cell an elongated RF that is responsive to elongated bars or edges. In the hierarchical model of Hubel and Wiesel, the **complex cells** have a RF that is the topological union of its afferent RFs, i.e. the summation and integration of numerous simple cells RFs. As the simple cells, complex cells are tuned to stimuli of specific orientations, although there is a broad overlap of ON- and OFF-responses within their RF. Simple and complex cells are distributed unevenly among V1 layers. Simple cells can be found predominantly in layer IV and VI, while complex cells are predominantly found in deeper layer V and superficial layers II and III (Payne and Peters 2002).

V1 simple and complex cells respond preferentially to different ranges of temporal and spatial frequencies (Movshon 1975, Berardi et al. 1982, Movshon and Newsome 1996). The majority of V1 neurons in cat area 17 are tuned to low (2-4 Hz) temporal frequencies, and complex cells tend to prefer faster temporal frequencies than simple cells (Movshon et al. 1978). They are also tuned to a range of spatial frequencies from 0.3 to 3 cpd, and complex cells are rather less selective for spatial frequency than simple cells (Movshon et al. 1978). In addition, some complex cells optimally respond only to motion in a preferred **direction** (Hubel and Wiesel 1962, Bishop et al. 1973).

2.2.4 ... and back to LGN

From pyramidal cells in layers V and VI of primary visual cortex arise **corticothalamic feedback** axons, estimated in the cat to be about 3.2×10^6 (Sherman and Koch 1986). Those arising in layer V form projections leading mainly to the pulvinar nucleus of the dorsal thalamus (Sherman and Guillery 2001). Those arising in layer VI form the projection to the LGN and, en route, also give collaterals in the PGN (Gilbert and Kelly 1975, Lund et al. 1975). But these axons also branch profusely, ascending to cortical layers IV and III (Gilbert and Wiesel 1989, Jones 1985, daCosta and Martin 2009). In fact, both

in layer VI and IV, these corticothalamic pyramidal cells form synapses with thalamic axons (White and Hersch 1982) such that, in the cat, some are activated by stimulation of the optic tract with latencies compatible with monosynaptic activation from thalamocortical fibers (Bullier and Henry 1979, Constantinople and Bruno 2013). However, layer VI pyramidal cells have large receptive fields and lack the simple concentric RF typical of cells receiving their major afferent from the LGN (Gilbert 1977, Harvey 1978, Tsumoto and Suda 1980).

The corticothalamic axons terminate in the same thalamic nucleus from which the cortical area (V1, in this case) receives thalamocortical fibers and no other. This peculiar organization is called **principle of reciprocity** (Diamond et al. 1969, Deschenes et al. 1998). This principle is literally valid and the retinotopy of corticothalamic connectivity is as precise as that of thalamocortical connectivity, in a column-like array that includes both LGN (Guillery 1969) and PGN (Ahlsen and Lindstrom 1982). The cortical axons end on secondary and tertiary dendrites of principal LGN cells and on presynaptic dendrites of interneurons (Jones and Powell 1969, McCart and Henry 1994) forming axodendritic synapses (Ohara and Lieberman 1981) releasing glutamate (Guillery 1969).

2.2.5 Driving and modulating the LGN

Considering the sources of synaptic inputs estimated using anatomical and morphological electron microscope studies (Sherman and Guillery 2001), LGN principal cells are minimally innervated by RGC axons (approximately 5%-10% of the synapses), while non-retinal inputs account for the majority of relay cells synaptic inputs (~90%—95%). Of these non-retinal inputs, few (5%) come from local GABAergic interneurons. Another (20%) non-retinal source to the LGN principal cell comes from the PGN. But otherwise, the two major sources of non-retinal input to the LGN are the feedback projections from layer 6 of visual cortex (40%), and the ascending projections from the brainstem reticular formation (35%). These cortical and brainstem inputs also innervate

PGN cells and local interneurons (Erisir et al. 1997, Sillito and Jones 2002, other sources in Jones 1985, Sherman and Guillery 2001).

All these synaptic inputs are operated by chemical synapses, releasing neurotransmitters that activate specific postsynaptic receptors. There are two broad types of such receptors - ionotropic and metabotropic - differing importantly in their time course: **ionotropic receptors** (e.g. AMPA, GABA_A, Nicotinic) produce postsynaptic potentials lasting tens of milliseconds, while **metabotropic receptors** (e.g. GABA_B, Muscarinic) produce postsynaptic potentials lasting hundreds of milliseconds.

Considering the circuitry of the LGN, RGC thick axons form very large terminals and ('giant') synapses, containing only ionotropic receptors, close to principal cells' soma (Sherman and Guillery 2001). In contrast, non-retinal axons form thin terminals, activate both ionotropic and metabotropic receptors, and terminate on the distal dendrites of LGN principal cells. Considering the information content of the signal transmitted, the RF of principal cells is imposed by retinal inputs, with the same center-surround opposition, more than by the unclear context of non-retinal sources. All these considerations led Sherman and Guillery (1998) to formulate the hypothesis that the inputs to thalamus can be functionally divided into drivers and modulators. The **drivers**, such as RGC inputs, are the main information to be relayed, while the **modulators**, such as corticogeniculate feedback inputs, modify how thalamocortical principal cells relay the information to further processing stages (Figure 2.4).

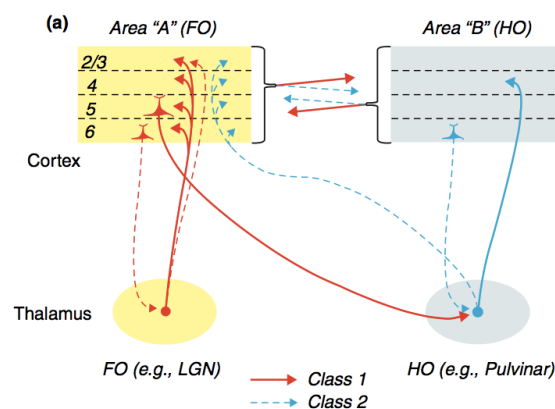


Figure 2.4. Drivers and modulators in the thalamo-cortico-thalamic pathways. Driving or class 1 (solid lines) and modulating or class 2 (dashed lines) projections, to and from a first order thalamic and cortical areas (FO, in red), or between higher order thalamic and cortical areas (HO, in blue), or cortico-cortical projections (in the middle). A thalamo-cortical driver (or class 1) pathway can be followed in the geniculostriate projection of monkeys and cats, where the thalamic driver cell types (X and Y for cats, and M and P for monkeys) from first order thalamic nuclei to first order cortical areas innervate principally layers 4–6, with additional modulatory (W for cats, and K for monkeys) inputs to layers 2/3. Cortico-cortical pathways can be identified between supragranular and infragranular cortical areas, but connections seem quite similar in both directions, providing no clear hierarchical order. On the contrary, a transthalamic pathway can be followed as a feedforward hierarchical route, since the first order thalamic relay provides driver input to the first order cortical area, which provides driver input to a higher order thalamic area innervating a higher order cortical area. In this case the feedback pathway is only modulatory (reproduced from Sherman 2012).

Given the aforementioned properties, Sherman (2006) proposed (among others, see Sherman and Guillery 2001) that the major role of LGN would be to gate and modulate the flow of information to V1. He observed that it would be more efficient to modify the information flow for attention and behavior purposes before it reaches cortex, at the level of thalamus, given its position in the visual stream and the quantity of synapses and cells involved. Sherman attributed all the heavy duty of “modifying the flow” to the modulators, chiefly the corticothalamic feedback. The question that shapes my thesis is: “How, exactly?”

2.3 What is the function of corticothalamic loop?

Most models of the early visual system describe it as an open loop hierarchically organized system. However this feedforward description does not agree with the impressive anatomical dominance of distributed feedback from cortex to thalamus. More than 30 years ago, Jones (1985) wrote about the lack of understanding of functional roles for the corticothalamic feedback:

“At least in regard to the three principal sensory relay nuclei we can probably feel that we have a fairly good idea of the nature and quality of much of the information that they transmit to the cerebral cortex. When we come to consider the inverse relationship, i.e., the nature of the information relayed from the cortex back to the thalamus, we have to confess to almost total ignorance. Though the principle of corticothalamic reciprocity is well established anatomically and there is plenty of morphological evidence that the number of corticothalamic synapses made in a thalamic nucleus is quite considerable, so little effect seems to be exerted by these under experimental conditions that they can be virtually ignored, even when the cortex is stimulated to drive thalamo-cortical neurons antidromically. Can it be that such a highly organized and numerically dense projection has virtually no functional significance? One doubts it. The very anatomical precision speaks against it.” (Jones 1985, page 818)

At the present day, our understanding of the corticothalamic feedback has improved, but we are far from asserting any specific function. There are at least two reasons for this condition. First and foremost, most **experimental protocols**, so successful in unraveling cortical functional features, have proven themselves unsuccessful in revealing the functional role of corticothalamic projections, even leading to contrasting results. The last section of this chapter details the main types of preparations and protocols used in the literature. Second, a now classical **computational approach** to vision posits that a good approximation of the early visual system can be obtained by a feedforward cascade of linear filters coupled with static nonlinear output functions (Bonin et al. 2005, Olshausen and Field 2005; but see added complexity in Olshausen, 2013; Fournier et al 2014). This approach avoids altogether the feedback loop by taking the LGN only as a relay station for RGC signals on their way to V1, rendering the large set of corticothalamic feedback connections irrelevant for visual information processing (Sherman and Koch 1986, Basso et al. 2005).

The fact that reasonable approximation of the early visual processing can be obtained by actually ignoring corticothalamic feedback could have consigned the feedback loop to oblivion. But, according to the PubMed keyword trend

analyzer, the number of publications having as topic “corticothalamic function” has grown at +0.25% (± 1.39) per year, from 3 publications in 1975 to 47 publications in 2017, following the growing number of scientific publications. And, over time, the scientific community has speculated upon possible functional roles for the corticothalamic feedback, usually as components of broader theories. In order to evaluate some of these theories, especially from the point of view of corticothalamic feedback, we can assess their accomplishments using the tripartite schema given by Marr 1982. In his seminal book "Vision" (Marr, 1982), he identified three organization levels that need to be understood to study information processing systems. And since the brain is a control device for the body, its functioning can be analyzed in terms of information processing (Dennett 2009). At the top of his hierarchy, the most global level defines the **function**, by answering the questions: “What is the goal of the computation, why is it appropriate, and what is the logic of the strategy by which it can be carried out?”. The second level is **algorithmic**: “According to which (generic) mathematical principle can this theory operate? In particular, what is the computational algorithm?”. The third is the **physical substrate** level: “How can the function and algorithm be implemented physically?” (Marr 1982, page 25; see also discussion in Frégnac 2017).

I organized the proposed theories in terms of their completeness according to Marr’s scheme. In the following sections, I will consider two of them.

2.3.1 Theory 1: the feedback is propagating predictions resulting from cortical inferences

One of the longer lasting functional approaches to the brain is that it accomplishes its work behind the scenes that we experience as reality. Hermann Ludwig Ferdinand von Helmholtz (1821-1894) was a champion of this approach, ushering it from philosophy to science. In philosophy, Helmholtz was influenced by Francis Bacon, the creator of empiricism, through its “Novum Organum” (1620). In opposition to his contemporary

Rene Descartes, who built his method out of **deduction** from pure mind principles, Bacon doubted the mind was able to deduce any truth by itself. On the contrary, he thought that only through a process of collection of evidence and subsequent abstraction - **induction** - the mind achieved its success in steering human actions. Following the inductive approach, Helmholtz pioneered the experimental study of how physical energies (like light and air pressure) transition through our senses to our (visual and auditory) appreciation of them. He used psychophysics as an instrument (his 'organum', exposed in a three-parted book "Handbuch der Physiologischen Optik", 1866) to empirically study the relationship between measured physical stimuli and their effect on human perception (psyche). And, in his third book, he described the **unconscious inference** process (from the German "unbewusste Schluss", unconscious conclusion; §26, pages 25-26). Several properties can be listed for such process. First, it is triggered by automatic "pop-out" low-level reaction (in the integrative sense) to the world rather than by volition: *"[its products] are urged on our consciousness, so to speak, as if an external power had constrained us, over which our will has no control"*. Second, its functioning is opaque to conscious awareness: *"[it] never once can be elevated to the plane of conscious judgments"*, and its products *"strikes our consciousness as a foreign and overpowering force of nature"*. Third, it is mechanical: *"lack the purifying and scrutinizing work of conscious thinking"*. And four, it is relatively immune to conscious control: its products are *"irresistible"* and *"impossible to get rid of"*, and *"the effect of them cannot be overcome"*.

During Helmholtz times, the Cartesian deductive approach to mind (through the Port Royal legacy) prevailed, causing inferential approaches to be dismissed for almost a century. In 1942, Edwin Boring still wrote about Helmholtz: *"Since an inference is ostensibly a conscious process and can therefore be neither unconscious nor immediate, this view was rejected as self-contradictory"* (page 289). Moreover, in addition to the critics, Helmholtz left unexplored the details of how previous experiences could shape perception,

making difficult for his thesis to gain followers. However, this condition was about to change.

By deliberately ignoring the nature (conscious or subconscious) of the inference, but explicitly referring to Helmholtz, Kenneth Craik, in his 1943 book “The Nature of Explanation”, equated the function of the brain to that of building an inner **model** of its environment, a model being *“any physical or chemical system which has a similar relation-structure to that of the process it imitates”* (Craik 1943, page 51), with the purpose of drawing useful conclusions. This provided a clear base **function** (in Marr’s terms) to Helmholtz inductive approach.

It also constituted the right prerequisite for Marr’s **algorithmic level**. Leveraging on Craik hypothesis (while working in the same lab), and focusing on perception, Horace B. Barlow (1959) answered a specific question: *“The barrage of nervous impulses reaching the nervous system seems to be unmanageably large; how should a selection of this activity be made for current display and future reference?”* (Barlow 1959, page 9). The answer, according to Barlow, lied in the statistical properties of the past sensory impulses, considered in terms of messages passed between nodes (or ‘stages’) of the nervous system network. His hypothesis had, at its core, a repeating process: *“the sensory messages are submitted to a succession of re-coding operations which result in reduction of redundancy [...] of the message that get through”* (Barlow 1959, page 10). This algorithmic process was imagined to build an optimal code, carrying as much information and little redundancy as possible, with the same purpose of Helmholtz and Craik: letting the higher stages of the mind to ‘conclude’ about the best course of action to survive. The construction of an optimal code implied also that, at each stage in the nervous system, in order to operate the redundancy reduction, some of the sensory information was stored. And the storage concerned the orderly characteristics of the environment, which were provided by the stimuli, eventually producing a distributed model of the environment (Barlow 1985). By introducing redundancy reduction in the

study of perception, Barlow provided the foundation for Marr's algorithmic level.

A solution for Marr's **physical** level was introduced by Mac Kay (1962). He noted that, functionally, perception is part of an organism's answer to environmental events. In order to put into action adaptive responses to these events, the redundancy reduction in the flux of perception has to be matched by a reduction of redundancy in the actions responding to those events. Therefore, Mac Key hypothesized that one likely method of profiting of the redundancy reduction is to consider perception itself as an activity, more specifically, that the brain is trying to **predict** the incoming sensory stimulation. The prediction may concern samples extrapolated in *time* or in *space*.

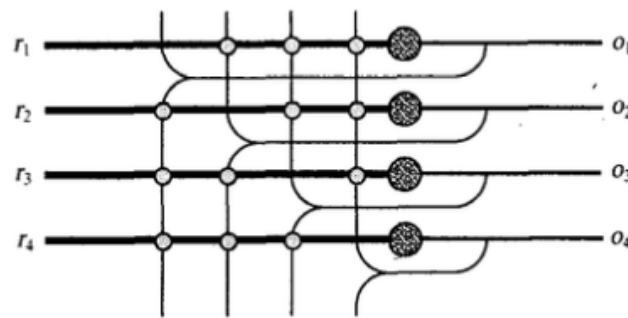


Figure 2.5. How a model of reality might be built in time. The model network with inputs r_i and outputs o_i feeding laterally to others o through modifiable inhibitory connections. The strength of inhibition increases when outputs are positively correlated. In matrix notation $o=r+Wo$. The strengths $W=w_{ij}$ of the synapses change according to a symmetric anti-Hebbian rule: $\Delta w_{ij}=-\alpha O_i O_j$ if $i \neq j$, otherwise $\Delta w_{ij}=0$, where α is a positive constant determining the rate of adaptation (Barlow and Földiák 1989).

Barlow and Földiák 1989 illustrate the extrapolation in time. By exploring the implications of having simple feature detectors in V1 for the global task of vision, they proposed a model similar to the novelty detector proposed by Kohonen and Oja 1976, characterized by lateral inhibition. The model consisted of linear units with inputs, outputs, and modifiable inhibitory lateral connections between units, whose strength increased for positively

correlated outputs (see Figure 2.5). Such network implements a decorrelation obtained by mutual inhibitory (anti-Hebbian) interactions. Barlow and Földiák proposed that these units, and this arrangement of connections, would be part of a system that store pairwise associations in past sensory experience to detect new causal factors in the world. Neurobiological evidence from their time was scarce, but following experiments confirmed the plausibility of anti-Hebbian rules (Bell et al. 1993, Bell 2001, Frégnac 2002).

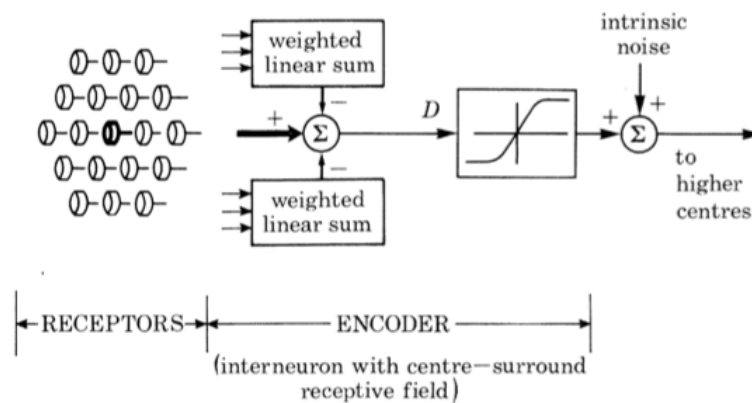


Figure 2.6. How a model of reality might be built in space. The signal produced by the central receptor (bold) is compared with the statistical prediction resulting from a weighted linear sum of signals from the nearby receptors. The encoded difference (D) is filtered, some arbitrary ('physiological') noise is added, and transmitted by the neuron to the brain.

Srinivasan et al. 1982 provided a specification of the extrapolation in space. By investigating the functional role of lateral inhibition in the retina under the assumption of redundancy reduction, they adopted a linear predictive coding procedure, which is a way to estimate future values of a discrete-time signal as linear function of previous samples (Makhoul 1975). The linear function exploits the correlations existing in the signal history to give a statistical estimate of the next values. The encoding advantage is that, by subtracting the estimate from the actual incoming signal, it is possible to send a minimized signal, assuming that encoder and decoder share the same parameters for the linear function. The minimized (or 'error') signal is actually the mismatch between the known statistical properties, stored as parameters of the linear combination, and the incoming signal. Srinivasan et

al. (1982) suggested that lateral inhibition in the retina could provide this substrate by minimizing the input range of a retinal neuron, and exploiting the correlations existing between neighboring points in an image. In their example, which uses still images, the intensity values from an area surrounding a point were linearly combined to generate an estimate of the intensity expected at a center point (see figure 2.6).

Mumford 1992 (and recently Bastos et al. 2013) added a proposal for Marr's third, physical, **neural substrate** level for cortex. Based on some anatomical evidence (Felleman and Van Essen 1991), Mumford proposed that cortico-cortical loops implement some kind of a prediction machine:

"the bulk of the computational work of the cortex is not carried out by one area at a time, but by information going back and forth over reciprocal pathways connecting pairs of areas: in doing this, each such pair of areas is trying to reconcile their constructs by some kind of relaxation algorithm"
(Mumford 1992, page 242).

In an iterative scheme, which represents the interactions between cortical areas in top/bottom pairs (Figure 2.7), the activity of layer V-VI pyramidal cells in one area, higher in the hierarchy, represents the source of the top-down feedback coming to the lower cortical area. This feedback is estimated using previous knowledge or "prior" stored as synaptic weights. Travelling through **top-down** connections, this feedback affects the supragranular cells integration in the lower area that send feedforward ascending input through the cortical hierarchy. The interaction between ascending inputs and top-down estimates produces a mismatch error signal, which is sent through **bottom-up** connections to the layer IV of the higher area. Here it induces the update of local synapses to change the representation of causes. In turn, this will affect the next generation of probable causes.

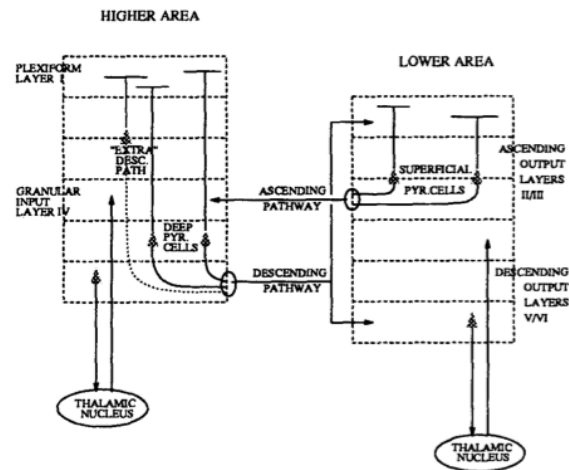


Figure 2.7. Cortico-cortical prediction machine (Mumford 1992). A top/bottom pair of areas with their connectivity. The descending pathway - bringing the prediction about incoming stimuli - is set by the deep pyramidal cells in layer V of the higher area terminating mainly in layers I and VI of the lower area. The ascending pathways - bringing the mismatch between predicted and actual stimuli - is set up by the axons of superficial pyramidal cells of the lower area terminating in layer IV of the higher area.

Three problems with this framework are presented here, the first two affecting the identification of cells for predictions and errors (advanced by Kogo and Trengove 2015), and the last casting a doubt over the necessity of prediction transmission altogether (Barlow and Foldiak 1989).

The first problem with this prediction schema is how the subtraction between the lower level incoming input and the top-down prediction is implemented. To propagate the prediction, the predictive coding framework (Mumford 1992) used layer V-VI pyramidal cells, which are glutamatergic and thus exert excitation on the layer IV spiny stellate cells. Since only inhibitory neurons could bear the negative prediction signal, one possible solution would be to have selective innervation of inhibitory neurons, but there is scarce evidence for such top-down specific connectivity (Usrey and Fitzpatrick 1996, Thomson and Bannister 2003). Another solution would be to assume that there is a baseline level of activity in both the higher and lower area neurons and the negativity is expressed by the decrease of the signals below the baseline (Bringuier et al. 1999, Fried et al. 2002). But also

this solution requires selective inhibition and suffers of scarce evidence as the previous.

The second problem concerns the ambiguous use of error-encoding signals, since error itself may carry ambivalent signals. Considering a single pair of one higher and one lower area, the error signals are supposed to influence the higher area activities to update the representation of the input. However, considering a cascade of areas (as suggested by the framework), some neurons would end up signaling at the same time mismatches to be sent bottom-up, but also local representation of input, ultimately affecting predictions to be sent top-down. For example, as reported by Kogo and Trengove 2015, V1 end-stopped cells (Hubel and Wiesel 1965, Pack et al. 2003) can be seen as "error-signaling" cells because they signal by their firing suppression the termination of a line segment while increase of their firing is observed when the bar length increase does not yet reach the inhibitory end-zone. At the same time, there is evidence (Kapadia et al. 1995, Bringuier, 1999; Chavane et al. 2000, Gerard-Mercier et al. 2016) that other classes of cells increase their firing when collinear line segments (along the orientation preference axis) are presented outside of their classic receptive field. The coincidence of both (higher) predictions and (lower) representations may result in the inability to choose whether a neuron is encoding the error or the representation. This situation could possibly generate inconsistency in the explanations provided by the predictive coding schema. However, recent evidence in support of selective pyramidal axon projections, together with advances in the understanding of the role of interneurons diversity in the cortical microcircuitry, has mitigated the risk of inconsistencies (Shipp 2016).

Another problem has been raised over the recorded reduction of activity, supposedly due to predictions suppressing incoming expected signals. The problem is that such suppression might simply be due to stimulus-specific adaptation. It has been shown that neurons in the visual cortex of cats, presented with a high contrast stimulus of a given orientation for several seconds — called 'adapting' stimulus — later show decreased response for

that orientation (Müller et al. 1999) due to short-term depression of the previously affected synapses (Dragoi et al. 2000) or change in resting potential (Haider et al. 2013). Instead of supposing a whole mechanism to send top-down signals containing the expected statistical structure of the environment, neuronal adaptation offers a compelling alternative to predictive coding, where neurons can adapt to those statistics without instructions from above. And, more importantly, neurons could still retain the functional role of maximizing the information transfer because they still respond to rare events. A conceptual reconjunction has been advanced, where predictive signals facilitate decorrelation through adaptation (Barlow and Foldiak 1989, Nirenberg et al. 2010).

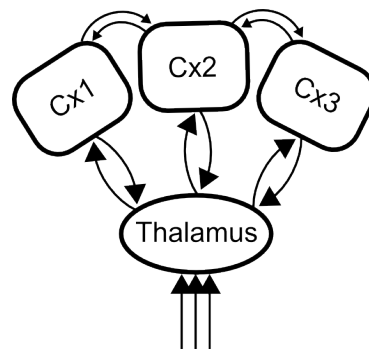


Figure 2.8. Thalamus as a blackboard (Mumford 1991). Cortical areas (Cx1, Cx2, Cx3) interact through lateral connections (small arrows) producing each multiple – and potentially conflicting – hypotheses. Corticothalamic connections (descending thick arrows) bring to thalamus all hypotheses, which are compared to incoming stimuli, and the thalamocortical inputs (ascending thick arrows) help settling which hypothesis is most plausible given the stimulus.

Mumford (1991) advanced a completely different proposal to corticothalamic function, possessing both inductive and also deductive elements. In his proposal (partially similar to Harth et al. 1987), the activities of the visual cortex are compatible with the predictive coding framework. V1 would still learn the features recurring in its sensory stimuli and, at every moment, it would still try to factor the causes of its current stimuli in terms of those features. By doing so, visual cortex would generate multiple hypotheses, almost certainly conflicting. Here comes the main difference and the specific

purpose of thalamus and corticothalamic connections. Instead of being as the cortico-cortical ones, shuttling back and forth predictions and errors, the corticothalamic connections would bring down to the thalamus all the hypotheses. The LGN would then act as a **blackboard** (a term coined for expert systems, see Corkill 1991), where all visual cortical ‘experts’ could interact, together with the sensory inputs (Figure 2.8). Over a few iterations of the recurrent processing, a consensus could be reached and then be broadcasted back to each visual cortical area as an *“improved view from an inner retina”* (Mumford 1991). At the physical level, this functional proposal takes into account the large amount of modulating corticothalamic connections and gives them a role that actually requires their numbers, their level of convergence, and their preservation of topology. In addition, it implies that thalamic activities may be maintained for brief periods (up to 100 ms), through calcium channels, like the T-type described before (in the section “Geniculate cells and their properties”).

In addition, the blackboard theory would solve the major critique against the inference approach — the ambiguous mapping of error-encoding signals onto same cells representing top-down and bottom up unit in a hierarchy of cortical areas — because, for the corticogeniculate feedback, the ambiguity is resolved by the driving nature of thalamocortical synapses, as opposed to the modulatory nature of cortical feedback. Such modulation could still affect enough thalamic activities to be said to bring down to thalamus several, possibly conflicting, stimulus representations inferred by the cortical neurons.

2.3.2 Theory 2: the corticothalamic loop implements higher-order feature integration

A long-standing controversy is that between synthetic and analytic theories of perception. The **synthetic** approach (heralded by William James, 1890) claims that the experience of complex sensory objects is built by combining elementary sensations. The **analytic** approach (bested by the Gestalt school,

Koffka 1935) claims that we initially form an immediate perception of unitary objects, and only later analyze them into more elementary components. Evidence from physiology would support the associationist approach, suggesting that, for example, along the visual pathway, a first analysis pass of the visual scene is made in terms of contrasts, orientations, colors, movements, managed in different areas of the brain, and only later fused into a unitary perception.

This idea provides the start for a Marr's **functional level** alternative to the inference proposed in the previous section. In 1980, Anne Treisman and Garry Gelade presented "A feature-integration theory of attention" where, on the basis of physiological and psychophysical experiments, they detailed the associationist approach: *"features are registered early, automatically, and in parallel across the visual field, while objects are identified separately and only at a later stage, which requires focused attention"* (Treisman and Gelade 1980). According to this framework, a visual scene is coded by receptors and neurons along the early visual pathway into separable features. It is only **focal attention**, serially maintaining the gaze onto stimulus locations, which triggers the integration ('binding') of the separate features pertaining to a location into a perceptual object. The most striking evidence for such a mechanism, was provided by psychophysical experiments.

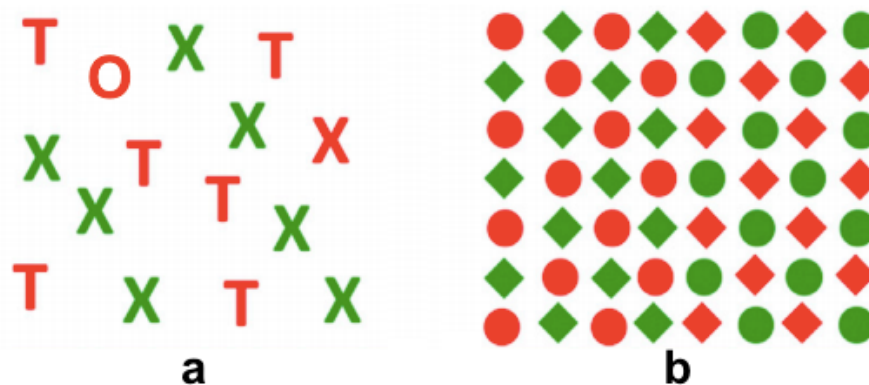


Figure 2.9. Feature integration. (a) It is easy to find the 'O' for its unique feature in comparison to the many mixed 'X's and 'T's sharing red and green textures. (b) It is required an attentional effort to recognize that the apparently uniform texture is

actually composed of two patterns pre-attentively undistinguishable (reproduced from Wolfe 2018).

Treisman showed that searching for a unique feature, like the 'O' shape in Figure 2.9a, takes a systematically shorter response time compared to searching for a conjunction of two features, like the red or green color *and* 'X' or 'T' form. Moreover, she showed how the discrimination of basic feature conjunctions (like color and shape) requires a deliberate act of attentional binding. A conscious attentional effort is needed to realize that Figure 2.9b is not a single homogeneous texture but that there are two textures, one on the left with red circles and green diamonds, and one on the right half with green circles and red diamonds. These results were taken as evidence to consider attention like a resource singularly and serially allocated, in a similar way to an internal searchlight that scans one visual object at the time and then passes to the next.

The biologist and Nobel laureate Gerald Edelman, in "The Mindful Brain" (with Vernon Mountcastle, 1978), later extended in "Neural Darwinism" (1987), proposed a theory for the **algorithmic level** of associationism. The theory moves in a way somewhat opposite to the predictive one described in the previous section. Whereas the inductive brain theory started from the theoretical positions of Bacon and Helmholtz and moved onto the search for cell matching predictive coding functions, the Neural Darwinism starts with the variability of cell morphologies and connectivity.

Experiments involving the repetition of the same stimulus across multiple trials revealed that cells might vary their activity level across trials (Shadlen and Newsome, 1998; Pouget et al. 2000, Carandini 2004, Harris 2005). Variability, expressed as ratio of variance and mean spike count over trials (called Fano factor), could in principle interfere with the transmission of information by impacting on spike timing precision and correlations among neuronal populations (Dayan Abbott 2001; Ferster and Spruston 1995, Averbeck et al. 2006). Variability concerns both neuron and population dynamics, in different parts of the brain and to different degrees (Softky and

Koch 1993, Fujii et al. 1996, Arieli et al. 1996, Kisley and Gerstein 1999, Scholvinck et al. 2015). Unexpectedly, though, the degree of variability is neither reduced nor expanded along the processing hierarchy (Shadlen and Newsome 1998). Cortical response variability is not the primary factor, affecting sensory discriminations whereas finer processes of temporal integration of “evidence” are needed in higher cortical areas (Britten et al. 1992, Shadlen and Newsome 1994, Huk and Shadlen 2005). Within each processing stage, considering the temporal evolution, after an initial variability increase triggered almost systematically upon stimulus presentation (Borg-Graham et al, 1998; Kara, 2000; Churchland et al, 2010), variability appears highly stimulus context dependent and decreases for input statistics to which the cortex is best adapted, specially for naturalistic images (Baudot et al, 2013) similar to those seen during early development (Gur and Snodderly 2006,). These facts hint towards the presence of some kind of neural adaptive solution against variability escalation.

In fact, variability exists not only for cell responses but also for cell morphology and connectivity. Over large populations, this leads to hypothesize the co-existence of multiple neuronal groups coding for the same stimulus feature (Finkel and Edelman 1985, Edelman 1993, Harris and Mrsic-Flogel 2013). Edelman applied such redundancy to describe how, during pre- and post-natal development, differences in synaptic connectivity and cell morphology produce different repertoires of neuronal groups (figure 2.10). These repertoires undergo three levels of selection.

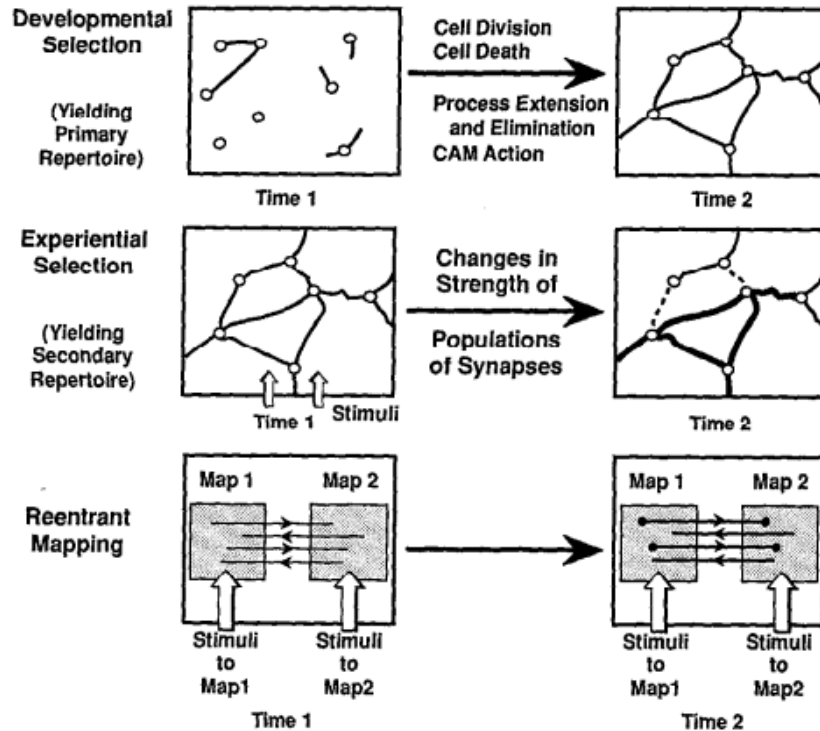


Figure 2.10. Neural Darwinism (Edelman 1987). The three levels of neuronal selection. On top row, the *developmental selection* uses molecules like nerve growth factor and cell death to get from single cells (top left) to different anatomical networks (top right), labeled as *primary repertoires*. In the middle row, *experiential selection* strengthens on weakens populations of synapses as a result of behavioral interactions, leading to the formation of *secondary repertoires* (middle right, with strengthen path in bold and weakened paths in dashed). In the last row, *reentrant mapping* temporarily strengthens – binds – functionally segregated repertoires (or *maps*) having correlated activity (bottom right, with strengthen directed functional connections in bold).

Primary repertoires are formed by selection-based self-organizing processes occurring during development (called “functional epigenesis” by Changeux and Danchin 1976), while the brain is being formed. At this stage, neurons are constrained by genetic and neurotropic factors, making them compete for their placement and to form the brain’s basic connectivity maps. After birth, **secondary repertoires** slowly take over, through an experience-dependent selection process during the critical period (review in Fregnac and Imbert, 1984). In this form of selection, the connections that provide more proficient results in the interaction with the world are strengthened, while others are weakened until withdrawal (Hebb 1949; Stent 1973, review in Frégnac 2002). This competition among neuronal groups uses mainly two mechanisms:

confinement and correlation. Confinement is the spatial integrative result of excitatory and inhibitory connections: upon stimulation, an initial spatial spread of excitation is followed by a contraction of neuronal activity. Correlation in the input addresses the temporal dimension and tight correlation elicits a larger response in a neuronal group, triggering synaptic modification, which in turn stabilizes the activation of one neuronal group in defiance of others. But these mechanisms do not reduce to a single repertoire each sensory pathway. Many neuronal groups are able to map the same stimulus and provide functional continuity in spite of cell depletion and sparse activity (Edelman 1993, Izhikevich and Edelman 2004). Therefore the activation of neural maps must be coordinated during a behavior. Edelman proposed that different neuronal groups can coordinate with each other through a higher order form of selection, called **reentry** or **reentrant mapping** (Edelman 1993). Reentry is a form of ongoing parallel signaling between separate neuronal groups, occurring along (cortico-cortical, corticothalamic, thalamocortical, cortico-basal, etc.) connections in a bidirectional and recursive fashion. The simultaneous activation of neuronal groups in different brain regions by a given stimulus, together with the effects of previous reentrant activity, dynamically selects and strengthens (for a short time duration) some of the connections between those groups. This coordinated dynamic interaction provided an algorithm to solve the binding of separate feature representations into percepts and actions.

This theory was largely inspired from the theory of selective stabilization of Changeux and colleagues on the one hand, and on the dynamic principles of parasynchronization of Milner and Delage on the other hand (review and references in Frégnac, 2002). Over time, this theory, attracted several criticisms. We will report the main two, one from Horace Barlow and another from Francis Crick.

Barlow (1988) criticized the definition of neuronal group. He pointed out that this concept did not specify clearly whether a single cell could take part into multiple groups or not. If it did, the number of neuronal groups could be virtually unlimited and have the combinatorial power required to bridge the gap between physiology and psychology, between many but finite cells and infinite behaviors and thoughts. Otherwise, the theory would be limited by the number of neurons and groups they could form. Edelman initial formulation did not imply the freedom wished by Barlow. But following works have tried to include this important “re-use” property. Izhikevich and Edelman 2004 showed that a large thalamocortical network, which included realistic conduction delays and spike-timing dependent plasticity (STDP), supported the formation of neuronal groups (defined by the time-locked temporal structure of their firing patterns). This first attempt did not however demonstrate the participation of a single neuron to multiple groups. In 2006, though, Izhikevich presented another, reduced, spiking network model in which the number of coexisting neuronal groups exceeded the number of neurons in the network. Note that a similar ambiguity was found in the concept of synfire chains of Moshe Abeles (Abeles 1982), where the same neurons could be recruited at several times in the same synchrony chain.

Also Francis Crick (1989) readdressed this critic, by looking in detail at the theoretical simulation provided in his 1987 book and in previous publications (Reeke and Edelman 1984, Pearson et al. 1987). Crick stressed that Edelman, having won a Nobel prize for his selectionist theory in immunology, where antibodies undergo a process of “evolution within the body” in order to match novel antigens, was very well aware of the difference between 'selectionist' and 'instructionist' theories. In an instructionist framework, a repertoire is produced by the interaction of the system under study with the environment. In a selectionist framework, the repertoire exists before that interaction (the “blue-print” synaptic envelope in Changeux et al (1976)), and the environment only selects relevant members of the repertoire

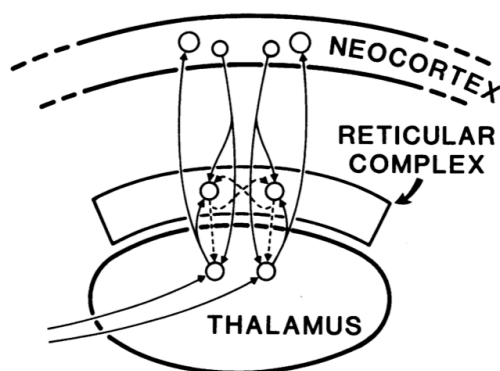
(this latter hypothesis is equivalent to the "functional verification" hypothesis of David Hubel and Torsten Wiesel. But, according to Crick, Edelman mixed these different models (as Changeux and colleagues also did). The connections formed a pre-existing repertoire, but the neuronal groups were constructed during the exposure to stimuli by obeying a quasi-Hebbian plasticity rule (based on membrane depolarization events instead of postsynaptic ones). In this respect, the neuronal groups were instructed and shared more properties with single neurons than with groups. Given these specificities, Crick proposed that it would be more reasonable to talk of '*Theory of Synaptic Selection*', although "*almost everybody's theory could be called a theory of synaptic selection*".

Crick's second critic concerned the concept of "re-entry". He accepted the fact that the brain has "many re-entrant pathways, for which at the moment we have no accepted explanation". But the expectations on explanation about the re-entrant pathways were unmet in Edelman's argumentation. For example, the purpose of the Darwin II simulation, detailed in the book, was to describe the reentry interaction inside a so-called 'classification couple', with the apparent aim of performing character recognition. The simulated model had two main sections, labeled 'Darwin' and 'Wallace'. Darwin is a two-level detector, whose basic features (like lines, angles) are hard-coded at the first level of integration. The second level is supposed to label the classification output. In a way similar to the first (lower) level, the second level requires some hidden instruction in order to produce a classification. The instructions come from the other half of the model. According to Crick: "*Wallace, in effect, is a cheat. It learns to recognize a letter in any position (or orientation) by some obscure scanning mechanism*". Although Edelman insisted on the unsupervised nature of the model, the only purpose of Wallace is to pass its recognition to Darwin as a teaching signal. The final problem raised by Crick was that the supposed reentrant connections in the model were reciprocating representations at the same (high) levels of Darwin and Wallace. But, in the brain, only a fraction of the connections follow this scheme, for example

those between MT and V4, or between different patches in the same cortical area. But the majority of reciprocal connections concern different levels, for example between thalamus and V1, or V1 and V2. The Darwin II model left these latter connections functionally unexplored. Note that the internal schema hypothesized by Edelman is very similar to the (now classical) Ballard cross-supervision model (De Sa and Ballard 1998).

Notwithstanding these critics, reflecting perhaps too strongly an ego's battle, the idea of reentry can be adopted as an algorithm for binding separate feature representations. However, a neural substrate is required to complete all Marr's explanatory levels. By providing clear functional roles for the corticothalamic feedback and intra-thalamic interactions in (re-entrant) looped corticothalamic maps, Francis Crick (1984) advanced the first neurobiological proposal for the **physical implementation level** of the associationist approach. Crick started by asking what would be the requirements of a searchlight mechanism: (i) *"It should be able to sample the activity in the cortex and/or the thalamus and decide 'where the action is'"*, (ii) *"It should then be able to intensify the thalamic input to that region of the cortex, probably by making the active thalamic neurons in that region fire more rapidly than usual"*, and finally (iii) *"It must then be able to turn off its beam, move to the next place demanding attention, and repeat the process"* (Crick 1984, page 4588). Based on the tonic/bursting firing modes in thalamus, and the thalamo-cortico-thalamic topological maps, Crick advanced the hypothesis that the reticular complex (PGN for vision) surrounding the thalamus might meet those requirements (Figure 2.11). The sampling of thalamic and cortical activity (i) could be indeed performed by the PGN, receiving excitatory projections from both LGN and V1, in a topological orderly fashion. Thanks to its inhibitory lateral connections PGN could solve "where the action is", by selecting the most active thalamo-cortical map in a winner-takes-all fashion. Crick suggested that the enhancement (ii) of thalamic activity, intensifying its input to cortex, could be performed by PGN triggering bursts volleys from the LGN. Finally, to address the turning of the

searchlight beam (iii), Crick neatly used the bursting mode property of being responsive only to the stimulus onset and then no longer respond. The previously bursting patch of LGN would then be silent, and the process would restart in another location.



Crick 1984

Figure 2.11. Searchlight hypothesis (Treisman 1969, Crick 1984). The position of the reticular complex (PGN for vision) is remarkable. All axons from the thalamus to the cerebral cortex pass through it, as do all of the reverse projections from the cortex to the thalamus. In addition, the reticular complex connections spread extensively in the plane of the nucleus and they are inhibitory. Therefore they are able to implement a winner-take-all architecture to put into competition the thalamo-cortical maps. Solid lines represent excitatory axons. Dashed lines show GABAergic (inhibitory) axons.

One mechanism would be central to generate the attentional focus: short-term synaptic potentiation, the ability of some synapses to increase their efficacy in triggering post-synaptic potentials following their activation (von der Malsburg 1982). This mechanism would operate onto existing **cell assemblies** (Hebb 1949). A cell assembly is a group of cells that fire together (without entering the debate of how much temporally close the firing should be, see for a perspective Harris 2005, Frégnac and Bienenstock 1998), a concept that can be mapped onto neuronal groups (Buzáki 2010, Lopes-dos-Santos e al. 2011). Crick distinguished **horizontal** cell assemblies — formed by “*neurons of a similar type, receiving input, in most cases, from similar sources and sending their output mainly to similar places*” — and **vertical** cell assemblies — formed by “*a cell at a higher level [which] is associated with one at a lower level (we are here ignoring the direction of the connection), and these, in turn, may be associated with those at a still lower level*” (Crick 1984,

page 4589). These transient — due to short-term synaptic potentiation, a fast reversible version of Hebb — vertical assemblies would solve the physical level of the associationist problem of how several separated features might come together under the searchlight beam of attention.

Apart from Crick's merit of using recent, for the time, results like intricate thalamic mechanisms and short-term potentiation, its reductionist account of one crucial property of consciousness — attention — granted a large and deserved success to his searchlight hypothesis, which is still used as a valid framework to understand the change in activity of LGN and PGN during attention tasks (McAlonan et al. 2006, 2008). However, also several critiques can be raised to his hypothesis. Two of them deserve special attention.

The first — and to my best knowledge not put forth before — concerns the crucial mechanism implemented by the reticular complex, in particular its ability to make thalamic neurons burst in the most active way. The problem is that thalamic neurons need a period of inhibition (~100 ms, Sherman 2004) in order to de-inactivate their T-channels and switch into bursting mode. Thus, the searchlight focus would need to be depolarized, as part of an active thalamo-cortical vertical cell assembly (among others), but also hyperpolarized, in order to burst. The only way through which this could happen is that the initial volley of LGN regular spiking due to the stimulus onset would reach both the reticular complex and cortex, where it would elicit a response and a following additional excitation of the reticular complex. Thanks to both LGN and cortical excitation, the PGN would in return strongly inhibit the LGN portion of the thalamo-cortical map, which could be then able to burst. But this process presents timing problems because during the rather long inhibition period (~100 ms!) some other LGN locations could win the searchlight competition. Koch 1987 proposed a mechanism, different from Crick's, but still in adhesion with the searchlight hypothesis, and which is based on the activation properties of N-methyl-D-aspartate (NMDA) receptors, abundant in the apical dendrites of LGN and PGN cells (Sherman and Guillery 2001, Salt 2002). In fact, in order to activate

these receptors the synaptic depolarizing input must be paired with an ongoing membrane depolarization. This nonlinear current-voltage property might push the NMDA receptors to behave like short-term temporal integrators, controlled by the corticogeniculate feedback, where temporally close retinal and cortical (co-)activations would transiently enhance the geniculate response.

While presenting his seminal blackboard hypothesis, Mumford (1991) fired another critique to the original Crick formulation. His skepticism was rooted on two points. First, considering only an information point of view, data transmission requires more bandwidth than data selection, so why would the management of attention focus require the rather non-specific recruitment of massive corticothalamic projection? Second: *“this theory ignores the fact that the cortex needs to write most of this data on the non-sensory nuclei of the thalamus before it can read it, and the data doesn't automatically stay around, i.e. the thalamus doesn't have loops so that it can maintain a state of excitation. Why go to all this trouble to send data down to the thalamus, as well as sending the gating signals, so that a subset of this data will echo back?”* (Mumford 1991, page 142). Koch's mechanism described above could address the first issue because the massive corticothalamic projection would serve a detailed one-to-one gating.

2.3.3 Cross-links between theories

The two theories presented above — inference and associationism — do not exclude each other. At the functional and algorithmic levels, they are quite different because they stress different aspects: Barlow, Craik, and Mumford focused their interest in the powers of analysis, abstraction, modeling and prediction, while Treisman, Edelman, and Crick focused on synthesis, selection and binding. However, the closer one scrutinizes the neurobiological evidence the more one sees aspects of both theories. In this following I will discuss these common aspects of the physical implementation levels of the frameworks presented above.

2.3.3.1 The functional result is a “vertical” cell assembly

Cell assemblies were the key foundation of Donald O. Hebb theory, in explaining the transition from cells to cognition, and from behaviorism to cognitivism (Hebb 1949). Today, they represent an underlying tenet of neuroscience (Milner 1993, Frégnac and Bienenstock 1998, Harris 2005). In particular, as reported above, Crick (1984) identified, as a requirement for his searchlight hypothesis, the “vertical” cell assembly — one encompassing different areas, close to Hebb original definition of *“a diffuse structure comprising cells in the cortex and diencephalon [...] capable of acting briefly as a closed system, delivering facilitation to other such systems and usually having a specific motor facilitation”* (Hebb 1949, page xix). In order to close an arc between sensation and action, the cell assembly is characterized by having a relaxation time — an activity duration that extends beyond those of the single cells constituting it (Braitenberg 1978). Such duration (in the order of hundreds of milliseconds), spanning a full sensation-action arc enables the cell assembly to be the correlate of percepts and related cognitive processes (Varela 1999, page 117). And recently, Buzsáki (2010) proposed an updated version of this concept — that he called synapsemble — extremely close to Crick’s mechanisms. He stressed how the variable sparse activation (Olshausen and Field 1997, Olshausen 2013) of redundant and spatially segregate (Edelman 1984, Izhikevich and Edelman 2004) sets of cells can be transiently integrated via short-term synaptic plasticity (von der Malsburg 1982, 1987), ultimately “read” by downstream structures with functionally equivalent results.

2.3.3.2 The functional mechanisms are competition and collaborative synergy

The two theories presented before offer different circumstances and mechanisms for the transient integration of cells into a vertical cell assembly. Given the abundance of potentially active cell assemblies, the “vertical cell assembly” hypothesis needs to be accompanied by additional hypotheses regarding how this transient integration is accomplished. Crick (1984)

basically proposed competition between thalamocortical maps, while Mumford (1991) proposed collaborative synergy.

Two known mechanisms might allow the coexistence of those two seemingly opposite properties, which can be implemented by the thalamo-cortico-thalamic loop, yielding a transient vertical cell assembly: (i) the *egocentric selection* (Suga et al. 1997, Suga and Ma 2003) provides evidence on how competition could be implemented in a topologically organized thalamocortical loop, and (ii) the *stochastic resonance* (Moss et al. 1993, Simonotto et al. 1997) provides an elegant mechanism to take benefit from common noisy background and induce correlated activities into anatomically segregated thalamocortical cells.

First, for the competition component, cortical “egocentric selection” is a mechanism proposed by Suga et al. 1997 (reissued by Alitto and Usrey 2003, Hasse and Briggs 2017), where cortical neurons, by making use of the feedback connections to thalamus, selectively control the activity of their own input sources — hence the “egocentric” label. Cortical cell responses are specific to certain features of the stimulus, due at least in part to the topological arrangement of thalamocortical inputs (Alonso et al. 1996, 2001). However, the topological arrangement of the corticothalamic feedback could also play an important role. Suga and colleagues found that neurons in the auditory cortex of the mustached bat, which are organized into iso-best frequency domains (equivalent to the visual iso-orientation cortical domains of other carnivore mammals), are able to augment and sharpen the auditory responses of thalamic neurons tuned to their same frequency (in the medial geniculate body). At the same time, they are able to reduce the response of thalamic neurons tuned to other frequencies. This is accomplished through a focused direct positive corticogeniculate feedback (Yan and Suga 1996), together with widespread indirect lateral inhibition through the thalamic reticular nucleus (Suga et al. 1995). This mechanism, initially identified by Suga and colleagues in the early auditory system, has been confirmed in the early somatosensory system (Krupa et al. 1999, Ghazanfar et al. 2001, Li and

Ebner 2007, Wu and Yan 2007, Temereanca et al. 2008, Zhang and Yan 2008). Similar evidence, although scarcer, has been reported in the early visual system, where the group of Adam Sillito found a specific center-excitation / surround-inhibition enhancement effect of cortical feedback projections (Andolina et al. 2007, Jones et al. 2012). By simultaneously enhancing a preferred thalamocortical map, while suppressing the topologically represented surround (either auditory, somatosensory, or visual), this mechanism results in the dynamic and transient confinement and strengthening of one vertical (thalamocortical) cell assembly at the expense of others.

The second mechanism may be instrumental in building collective synergy: stochastic resonance is a phenomenon that occurs in many systems, geophysical as well as biological, characterized by non-linear transfer functions (e.g. threshold based) when the presence of a non-zero level of stochastic input noise maximizes the transfer of a weak or noisy signal by lowering the response threshold (Moss et al. 1993, Simonotto et al. 1997). For example, an appropriate measure of information transfer (such as signal-to-noise ratio) shows that the addition of white noise to a weak periodic signal will amplify it because the (low) amplitude of the signal's frequency will sum (resonate) with the corresponding frequency in the white noise, leading to threshold crossings which will follow the peaks of the input signal. However, in systems characterized by intrinsic noise in addition to noisy inputs, such as biological neural systems, a better strategy seems that of adaptively tuning spike thresholds for taking advantage of stochastic resonance (Collins et al. 1995). In fact, if stimuli are noisy but generally within a certain range of magnitudes, it would seem more efficient to change the threshold of the neuron to match stimulus amplitude instead of adding noise to the input itself. Indeed, Behuret et al. (2013, 2015) in our lab showed that in vitro simulation of cortically controlled stochastic facilitation lowers the threshold (through changes of the levels of intrinsic variance) of thalamocortical projecting cells selectively both in space (across the neural population) and

time (with respect to the stimulus), realizing a form of dynamical gain control (Funke et al. 1996, Wolfart et al. 2005). They also showed that stochastic facilitation was controlled not only by the statistics of the simulated corticothalamic synaptic bombardment (in a top-down fashion), which imposed correlations across thalamocortical cells membrane potential fluctuations, but also by the convergence ratio, i.e. the number of thalamocortical cells converging simultaneously onto their cortical targets (in a bottom-up fashion). This stochastic control of the loop efficiency has been shown to induce coherent responses in otherwise unrelated cells (Bahar and Moss 2003, Neiman et al. 1999). Since the corticothalamic contributions are operating sub-threshold, this form of stochastic resonance, in association with the partial topological overlap of corticothalamic projections, could provide a realistic mechanism to stack multiple contributions onto the thalamus, as hypothesized by Mumford's blackboard.

2.4 Summary

The thalamus is an evolutionary old structure forming recurrent connection with every portion of cortex. Early sensory pathways are the ones more frequently explored experimentally, and within these, the early visual loop between the lateral geniculate and the primary visual cortex. Although a partial understanding of the function of the feedforward pathways from thalamus to cortex has been achieved, the function of the corticothalamic feedback is still unclear. Two main hypotheses constitute the theoretical framework in which experimental tests of the functional role of cortical feedback in low-level visual perception have been devised so far.

One hypothesis claims that the early stages of perception may constitute a form of unconscious inference. The function of the corticothalamic feedback would then be that of propagating cortical inferences back to the thalamus to be verified against external inputs. The algorithm realizing such function would learn a redundancy-free model of the visual world in cortex based on

the statistical properties of past sensory stimuli. The activity of the brain would use that cortical model to create predictions of incoming sensory stimuli. At the physical implementation level, cortical predictions would be sent to the thalamus through the corticothalamic feedback. Thalamus would act as a functional blackboard, where predictions and real input would overlap and be buffered for long enough to reach a consensus on a single most-probable representation, before being then broadcasted to all cortical areas.

The other hypothesis claims that the function of the corticothalamic feedback would be to contribute to the binding of separate features into unified perceived objects. Parallel streams of neurons, along the sensory pathways, would independently code for stimulus features (like orientated contours, colors, etc.). An algorithm would be thus required to select and bind these separate feature representations into transient cell assemblies. The repeated recurrent activation of anatomically different but functionally equivalent cell assemblies (the global process being called “reentry”) would ensure functional continuity, and represent the substrate for cell assembly selection. At the physical (lower) level, the binding would be implemented by short-term synaptic potentiation, transiently strengthening and selecting one vertical cell assembly, polling it through lateral inhibition provided by the reticular nucleus.

The concept of “vertical cell assembly” — encompassing cells across multiple areas (here thalamus and cortex) — is common to the low-level implementation of both frameworks. In order to be realized, it requires a specification of how to select and merge cells dynamically. Egocentric selection and stochastic resonance may provide two additional mechanisms for cortical experts to concurrently write and merge onto the thalamic blackboard. They would do so by providing a function for the corticothalamic modulatory connections, but not just any modulation. Each cortical expert would project back to the thalamus its own attuned selectivity, in a topologically organized fashion. But there is a lot of overlap, and each

projection is twofold: narrowly positive and broadly negative. In this manner an expert can inject its contribution (labeled as “noise” in the stochastic resonance) such that some input-output correlations are enhanced while others are diminished. If the stacked correlations brought by cortical feedback match those brought by the external input, the cell assembly including both cortical cells and their thalamic counterpart will increase their activity levels and correlation.

3 Experimental constraints in modeling strategies

3.1 How to approach the study of corticothalamic loop functions?

Even if one focuses on the question of cortical feedback, and hypothesizes its general functional roles (see previous chapter), it is difficult to recompose the sparse functional evidence into a single coherent picture. Over the past decades few teams have embarked the arduous task of accessing the visual thalamus to test *in-vivo* hypotheses regarding functional roles of the cortical feedback and its mechanisms, often adopting very different experimental approaches, and frequently reporting contradictory results. One of the reasons for these oddities (and experimental discrepancies) may be the fact that thalamic function depends on the interaction of distinct circuits recruited by the corticothalamic feedback, operating through distinct mechanisms and whose balance is highly context-dependent (Ghodrati et al. 2017). However, as a whole, the thalamus remains a convenient way to control the flow of information through a very strategically organized structure (Sherman 2009), therefore a general functional role for the corticothalamic feedback and the contextual dependency of its expression need still be a major scientific concern. Over time, this concern has been addressed through modeling studies, each focusing on different aspects of the loop, from global dynamics to more functional spatial and temporal response properties.

The aim of this chapter is first to review the different contexts in which the corticothalamic function has been studied and assess the different

techniques of sub-circuit dissection in order to identify the key state variables characterizing the corticothalamic feedback that need to be emulated. The second aim is to recapitulate the different modeling approaches used to implement realistically the cortical feedback and clarify the potential roles that it could play in low-level vision.

3.2 The concepts of “closed” and “open” loop

The concept of feedback loop is ubiquitous:

“A dynamical system is a system whose behavior changes over time, often in response to external stimulation or forcing. The term feedback refers to a situation in which two (or more) dynamical systems are connected together such that each system influences the other and their dynamics are thus strongly coupled. Simple causal reasoning about a feedback system is difficult because the first system influences the second and the second system influences the first, leading to a circular argument. This makes reasoning based on cause and effect tricky, and it is necessary to analyze the system as a whole.” (Astrom and Murray 2012, page 1)

The condition in which two (or more) systems are connected in a cycle is called **closed** loop. It is also the normal condition of the thalamo-cortico-thalamic loop in an intact living animal. If the cycle is somehow broken — such as to form a purely catenary or feedforward multistage integrative process — the condition is called **open** loop (figure 3.1). In engineering, the study of feedback goes under the label “control theory” because a system is designed to be controlled by introducing a second system, called controller, which samples the operation of the first, compares it against a desired functioning, computes actions based on an internal model of the responses to external inputs of the first system, and acts on it to achieve the desired change. The loop is made for several reasons: to achieve stability against disturbances and errors, to make changes in a regulated manner, to provide additional behaviors like responsiveness to changes in both the environment and the system operations.

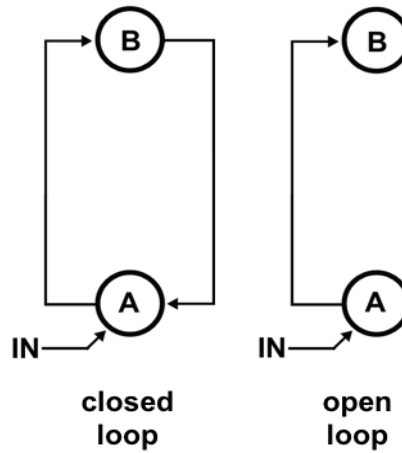


Figure 3.1. Closed and Open loop systems. *Left:* A closed-loop system is made of a dynamical system (A) whose activities, partially driven by external inputs (IN), are sampled by a second “controller” system (B) through feedforward connection (upward arrow). The controller B is able to act on A through its feedback connection (downward arrow). *Right:* the open-loop version of the system only retains the feedforward connection, without the possibility for the controller to act on A.

All these uses might also well serve the proposed functional roles described in the previous chapter. Therefore the strategy of opening the loop has been adopted in the studies regarding the thalamo-cortico-thalamic loop. However, one caveat in this description is that the “feedback” circuit definition depends on the actors in the loop and which view point the model addresses: if the question is to understand thalamic integration, the cortical input can be tested as a feedforward influence, although its information content will be altered by a more global loop between thalamus and cortex. In the following section, we will consider the whole early visual system as the functional system under study and cortico-thalamic projections defined as feedback loops internal to the system.

3.3 Experimental manipulation of the corticothalamic loop

Various experimental investigations of the corticothalamic loop are assessed in this section, grouped by which sub-circuits are being manipulated.

3.3.1 *In-vitro*: Isolation of the thalamo-cortico-thalamic loop in the dish

In-vitro slice preparation is an electrophysiology technique easing the access to the corticothalamic loop. For some animal species (mouse, rat, ferret, guinea pig) but not all it is possible to find an anatomical slicing plane angle that preserves (at least partially) the thalamo-cortical and corticothalamic projections (Agmon 1991, MacLean et al. 2006). Recordings and stimulation protocols are then performed on the slice while immersed in artificial cerebrospinal fluid (aCSF).

The advantages of this technique are multiple: (i) that it allows experimental control of the physiological conditions of cell and neurotransmitter activities through perfusion in the aCSF of chemical compounds (like membrane channels agonists and antagonists). (ii) it also becomes possible to impose artificial patterns of activity in the cortical layers that project back to thalamus or inactivate them pharmacologically. Other advantages include: being low in price, extended length of recording, exact placement of recording electrodes under microscope, partial preservation of local circuits. However, several drawbacks are introduced by the slicing procedure. Overall, the increase in control is opposed by the reduced range of application to realistic conditions. For example, the elimination of effects due to the background activity during rest, allows only for examination of the circuit under less physiological conditions, when the circuit is devoid of its usual inputs it. In addition, a variable portion of connections is severed during the slicing procedure, introducing significant inter-experiment variability.

In particular, for the thalamo-cortico-thalamic loop, the work of Bal and McCormick (1996) can be taken as example of the procedure and type of experimental aim. In order to study the role of low-threshold Ca^{2+} current in the genesis of thalamocortical oscillations, they cut sagittal slices (400 μm thick) preserving PGN and LGN, easing the access to LGN laminae and recording from a slice depth of 100-150 μm . The circuit dissection technique was particularly helpful in disentangling the particular intracellular

mechanism they were investigating, by easing the identification of and access to LGN principal cells, the control over the extracellular medium to study the Ca^{2+} channels in a range of cellular hyperpolarization and depolarization regimes.

3.3.2 *In-vivo*: Suppression of the cortico-thalamic feedback

3.3.2.1 by cortical ablation/inactivation

Removal of the cortico-thalamic feedback can be carried out by surgical ablation, chemicals (chemoablation), or by cooling (leading to transient inactivation) or even irreversible freezing (cryoablation) of the deep layers of visual cortex. The main advantage of the inactivation/ablation technique for the study of corticothalamic feedback is that it enables the comparison of open vs closed loop conditions during the presentation of stimuli in the intact or lesioned animal (either in the behaving or anaesthetized state). There are, though, several drawbacks in using this technique. In order to ensure the complete removal of feedback, large portions of cortex need to be removed, causing elimination of the usual inputs the thalamus receives. This procedure is often irreversible, preventing the possibility to check that restoring closed loop activities also restores the experimentally controlled functionalities. Finally the major trauma due to removal of large parts of cortex can have unexpected brain-wide physiological repercussions, that might be miss-interpreted as the actual consequences specifically due to the thalamo-cortical loop interruption.

The laboratory of Adam Sillito mastered cortical ablation techniques for the visual thalamocortical loop in cat and monkey. Ablating primary and secondary visual cortices (Brodmann areas 17, 18, and 19), they were the first to investigate the generation of length tuning in LGN cells as a result of cortical feedback (Murphy and Sillito 1987, Jones and Sillito 1991). Using the same technique, they later expanded these findings also to the PGN (Jones and Sillito 1994), for spatial frequency (Cudeiro and Sillito 1996), temporal precision (Andolina et al. 2007), and stimulus-induced cross-correlations in

the response of LGN cells (Sillito et al. 1994). In 1982, Vidyasagar and Urbas also used this technique to compare the orientation sensitivity of cat LGN principal cells with and without inputs from primary and secondary cortices. The functional impact of their primary observations will be discussed later in the text.

3.3.2.2 by *in-vivo* cryogenic blockade

In 1968, Skinner and Lindsley described a method for reversible cryogenic blockade of neural systems in the brain of unrestrained animals by local application of cooling probes (called ‘cryoprobes’) on the cortical surface or more in depth brain tissues. The cryoprobes were two concentric double cannulae, in which cooled alcohol was circulated from the internal to external cannula, producing an overall cylindric probe. These rather bulky probes were superseded by the “cryoloop” system introduced by Lomber et al. 1999, which proposed a system based on a single cannula (bendable to create various shapes) into which cooled methanol was circulated. In both systems the electrophysiological effects of the cooling were measured up to a few millimeters from the tip of the cooling device.

The main advantage of the cooling technique for the study of corticothalamic feedback is that it enables the reversible comparison of closed vs open loop conditions during the presentation of stimuli in living animals as for the ablation, with the major benefit of being able to restore the control condition. As for the ablation, the main drawback of this technique is the extension, in the order of millimeters of the target area. In addition, cortical cooling has hyper-excitability effects at the edges of the cooled zones (Volgushev et al. 2000), while several cooling rounds induce the death of increasingly large portions of the affected cells (Sillito et al. 1993).

The use of cortical cooling proved its usefulness by settling a long held debate regarding the main hypothesis of Hubel and Wiesel (1962): that the LGN afferents to V1 simple cells were organized to form oriented rows thus providing orientation selectivity to cortical cells. Successive experiments

casted doubts onto this hypothesis, reporting no conclusive orientation specificity of thalamic afferents. Ferster et al. 1996 tested the initial Hubel and Wiesel hypothesis in anesthetized cats while showing oriented stimuli and using cryoblockade of V1 cortex, thus recording the activity coming only from thalamic afferents. The authors reported that the initial hypothesis was correct: afferents from LGN are indeed organized in oriented rows. However, some authors still disputed the efficiency of the cooling, which might have spared deep cortical layers.

Baker and Malpeli (1977) performed the cooling of the primary visual cortex in the (rhesus) monkey to assess the effects of corticothalamic fibers blockade on the responses of LGN neurons. They reported that only a fraction (28%) of the LGN neurons projecting to cortex showed an overall increase in spontaneous and evoked activity, without changing the spike timing characteristics for stimuli such as bars, edges, and flashing spots. A few years later, Geisert et al. (1981) tried a similar procedure on cats, reversibly cooling primary and secondary visual cortices while recording the spontaneous and evoked activities (using spots, bars, and drifting square-wave gratings) from identified X and Y cells, with results differing from those reported by Baker and Malpeli 1977. They found that the influence of the cortico-geniculate pathway was both excitatory and inhibitory, affecting the center-surround structure of LGN receptive fields. When Funke and Eysel (1992) performed similar experiments in the cat, they reported again different results, an overall reduction of visual response amplitudes characterized, upon stimulation (light spots of increasing contrast), and more phasic responses due to a stronger reduction of the tonic response component during cooling. Yet other contradictory results were reported by Wörgötter et al. 1998, who used light spots to test LGN activities, while cooling primary and secondary cortices. In contrast to what was previously reported, they found that cooling affected mainly the spike timing pattern of evoked responses. Among the last to adopt this technique, using similar stimuli (random presentation of light spots to assess the center-surround

extents of the RF), Waleszczyk et al. 2005 reported that evoked responses were reduced and the central domain of the RF shrank.

3.3.3 *In-vivo*: Pharmacological control of the corticothalamic feedback gain

Another way of studying the corticothalamic loop is to change the gain in a gradual fashion (in contrast to the all-or-none methods presented above). The use of synthetic compounds enabled the experimental study of neurotransmitter-receptors interactions specific for neuron type (Lovinger 2008). Considering the effect of their binding on a specific receptor, pharmacological compounds are labeled as either **agonists**, which cause the activation of the receptor, or **antagonists**, which prevent its activation, in a direct on-site “competitive” or indirect “non-competitive” way. This technique includes two main forms of application: one covering millimeters of cortex (called “diffuse”), implying the use of specifically designed absorbent gels placed between the dura mater and cortex surface and then injected with the desired compound (Andolina et al. 2013), and another more targeted application implying micro-iontophoretic techniques, in which the compounds are conveyed by an electrical gradient, releasing small quantities to affect small volumes of brain tissues (down to ~50 μm diameter, Jones et al. 2012).

In particular for the study of the corticothalamic loop, these techniques present two advantages over ablation and cryogenic blockade: they are specific for channel type activation, and reversible without drawbacks on cell integrity. On the other hand, though, the channel specificity constitutes also their main limitation: they are not targeting specifically cell types (excitatory or inhibitory) or signaling pathway but affecting all cells expressing the targeted channel. For the present purposes, we will restrict our review to only the GABA-A agonist muscimol and Glutamate (there are three types of GABA receptor, and the affinity specificity varies between agonists).

In 1968, David Curtis, Arthur Duggan, and Chet deGroat used muscimol, a molecule extracted from mushrooms of the genus *Amanita* and having a

structure analogue to GABA, to inhibit spinal cord neurons. In addition in 1978, Curtis, David Lodge, and Hugh McLennan found that bicuculline — another compound antagonist of GABA action — blocked muscimol, making it a perfect compound to the functional study of GABA-a inhibition in a controlled manner (Squire 2006, page 193). The group of Adam Sillito was among the first to perform the infusion of bicuculline over the primary and secondary visual cortex of cats to record the activity of LGN (and PGN) cells in the open loop condition. The details regarding the functional results of Sillito's team experiments will be discussed in next chapters. The group of Michael Stryker used muscimol to block cortical activity during monocular deprivation (Reiter and Stryker, 1988). Here it suffice to say that this technique, in association with several stimulus protocols, yielded consistent results indicating an effective role for corticothalamic feedback in the modulation of thalamic activities.

Tsumoto et al. 1978 used iontophoretic techniques to study the functional impact of the corticofugal projection from the primary visual cortex to the LGN of cats, by forcing its recruitment through glutamate application. They found that rise of activity in the infragranular (layer 6) cortex had excitatory or inhibitory effects on LGN principal cells, depending on the overlap between the RF centers of cortical and LGN neurons. They observed enhanced excitation of the LGN neurons upon cortical electrophoretic Glutamate application if the distance between RF centers was within 2.3° of visual space. If the distance between RF centers was beyond 2.3° and up to 3.1° , then suppressive effects were observed.

3.3.4. In-vivo: Optogenetic control of the cortico-geniculate loop

Cortical ablation is irreversible, and neuropharmacological techniques are not specific enough to dissect the thalamocortical loop at the circuit level. A more recent technique — **optogenetics** — holds the promise to overcome those limits. Optogenetics relies on the combination of genetic and optical techniques to control by light emission the opening and closure of artificially

expressed channels on the membrane of genetically selected neurons of living animals. Specific (microbial opsin) genes that confer light responsiveness are inserted in the genome of living animals (though benign viral transfection), then light is delivered to the genetically modified cells, and the effects of this optical control on the firing of neurons are recorded and analyzed. The crucial advantages of optogenetics are that it enables neuroscientists to target the cell type (via virus specificity), and it also gives control over the spatial (micrometers) and temporal (milliseconds) extents of the stimulation events (Deisseroth 2010; Emiliani et al. 2015).

However, optogenetics presents also three main drawbacks. The first concerns the expression of opsin. Transgenic mouse lines are available, expressing opsin-controlled channels in a cell type-specific manner (Zeng and Madisen 2012). But transgenic techniques are still not able to be as selective as some research studies need. In these cases, virus injection enables to selectively target cell types. Yet, using viral transfection each cell may differ in the amount of opsin channels expressed, making the technique unreliable at population level. In addition, at the single cell morphology level, the location of the expressed opsin channels may vary (on the soma or dendrites) making it difficult to effectively dissect the circuitry (Zalocusky and Deisseroth 2013). The second problem concerns the spread of light in *in vivo* preparations. The implanted optical fibers used to deliver light at a defined wavelength suffer from an exponential drop of illumination intensity at increasing distance from the fiber tip, reducing the ability of the experimenter to control the number of affected cells and their level of activation (Sohal et al. 2009). The third problem concerns the type and timing of response induced by optogenetic stimulation. On the one hand, the cells expressing opsin channels change their dynamic behavior. When optogenetically stimulated, fast-spiking parvalbumin-expressing inhibitory neurons have been shown to alter their dynamics from type I (integrators) to type II (resonator) excitability, inducing the paradoxical coexistence of propagating waves (a type I indicator) and small amplitude oscillation onset

(a type II indicator) in the same population (Sohal et al. 2009). On the other hand, the optogenetic stimulation activates synchronously all cells expressing the opsin channels, irrespective of their possible phase differences and individual cell properties, making it difficult to dissect the underlying circuitry (Lu et al. 2016, Heitmann et al. 2017).

In particular for the study of the corticothalamic loop, several attempts have been published using optogenetics. In some cases, this new technique was used simply to replicate known results. For one example, Jurgens et al. 2012 expressed opsin channels in corticothalamic (layer 6) neurons of mouse (slices) and recorded thalamic responses to 10 Hz optogenetic stimulation. They found facilitating responses in both LGN principal cells and TRN. These findings echo those already presented by Lindstrom and Wrobel (1990) in anaesthetized cats, in which they found that electrical stimulation of corticothalamic neurons (at 10 to 20 Hz) led to an increased facilitation of thalamic principal cell responses. Such finding was replicated by Granseth et al. 2002, in thalamic rat slices, which showed that already with only paired pulses of intervals similar to Jurgens et al. 2012 (10 to 20 ms) facilitation could be consistently induced. Another example is provided by the cortical origin of thalamocortical oscillations. Stroh et al. 2013, using anaesthetized mice expressing Ca^{2+} opsin channel (ChR2), demonstrated that localized brief stimulations (3–20 ms) of layer 5 cortical neurons was sufficient to induce Ca^{2+} oscillatory waves (<1 Hz), which propagated initially through cortex and then to thalamus. These results recapitulated several studies. Starting from the results presented by Steriade et al. 1993, in which they showed by means of electrolytic or kainate lesions and corpus callosum transection in anaesthetized cats that slow (<1 Hz) oscillatory rhythms survived thalamic destruction, it was already clear the cortical origin of slow thalamocortical oscillations. The cortical origin hypothesis was further strengthened by Timofeev and Steriade 1996, which were able to abolish thalamic slow oscillation by decortication. Sanchez-Vives and McCormick 2000 identified in the cortical layer 5 the source of such oscillations (in

ferrets). At the same time, optogenetics kept its promise and was also able to elucidate basic roles of the thalamocortical loop that were still unsuspected. For example, self-sustained activity was thought to be a hallmark feature of cortical networks but, using a combination of optogenetic techniques in cortex and thalamus, Reinhold et al. 2015 demonstrated that the primary visual cortex of awake mice cannot self-sustain activity for more than a few tens of milliseconds without the support of thalamic input.

However, especially for the field of vision, the widespread use of mice, due to the ability of genetically encode the expression in them of optogenetic tools, precludes a range of experiments that would more meaningfully address questions specific to higher mammals. For example, Denman and McCormick 2015 used drifting grating visual stimuli, together with the optogenetic enhancing or silencing of corticogeniculate layer 6 neurons, to test the primary visual cortex influence on LGN. They reported a variety of effects, which included contrast-dependent enhancement and suppression of thalamic responses, but they were not able to find any effect that could be clearly indicating a modification of thalamic receptive fields. But vision in rodents cannot be directly compared with previous findings in carnivore species where acute binocular vision is required to hunt (like owls, ferrets, cats, and also primates; see, for example, Jones et al. 2012). Rather than a problem in the technique, there is a species-specific inability to be effectively driven by visual stimuli. In fact, Hasse and Briggs (2017) used optogenetic enhancement of corticothalamic neurons and stimulation protocols similar to Denman and McCormick 2015, but this time in the ferret, and reported consistently unidirectional changes in LGN activities during cortical optogenetic drive. In particular, they reported the enhancement of Y cells spatial and temporal frequency tuning selectivity (and limited selectivity improvement in X cells), and overall a reduction of visually evoked response latencies, an increase of spike-timing precision, and a reduction of the classical receptive field size.

3.4 *In-computo* simulation of the cortico-thalamic loop

The central task of computational neuroscience is that of reuniting different levels of description based on a diversity of data sets gathered by distinct labs working with different research focuses (Gerstner et al. 2012). From a descriptive standpoint, the task of building such multi-sided bridge could be ideally pursued in two different ways. First, **hypothesis-led** (a.k.a. top-down) models start from known theoretical principles and functions of the brain (e.g. reinforcement learning or sparse coding) and deduce how to implement them (in the Marr's sense) using neurons and synapses as components. Although such models are able to describe specific circuits and the role of subsystems of the brain, a similar approach is probably unfeasible for entire systems and, ultimately, the whole brain. A second, complementary approach is that of **integrative** (bottom-up) models, which use the knowledge at a microscopic level (e.g., molecular level: ion channels) to explain facts observed at a higher level (e.g., electrophysiology: action potentials). This approach enables to test whether individual properties are consistent with each other, and helps to reconcile conflicting experimental results. There are two main pitfalls in developing integrative models. One is the number of free parameters, whose growth may lead to over-fitting and consequent lack of explanatory power. Another is the choice of anatomical and functional features to be used/explained in the model, which can be (cherry) picked to get an optimal arrangement. However, a remedy to both caveats is the practice of building models relying heavily on experimental data and validating the model against a large number of experimental studies. Such tight adherence to experimental findings reduce the number of free parameters remaining in the model, while the extensive testing of the model against wide range of experimentally identified functional properties of the circuitry under study reduces the chance of overfitting. It is the latter approach we took in this work.

In order to position our work in the current computational landscape, here I describe briefly previous modeling efforts, classifying models according to their focus on functional properties of the corticothalamic feedback loop.

3.4.1 Impact of the thalamo-cortico-thalamic loop on cortical dynamics and oscillatory rhythm generation

The experimental work of Steriade, McCormick and Llinas has shown the importance of state-dependency on the functional expression of intrinsic excitability and conductance repertoire in the thalamus. These cellular data have provided almost ideal parametric benchmarks for computational scientists interested in the global dynamics of the cortico-thalamo-cortical loop. Alain Destexhe proposed a model, in which the corticothalamic feedback serves a state-dependent regulative purpose. An initial open-loop model (without cortical feedback) of thalamocortical oscillations (Destexhe and Babloyantz 1991) was based on the hypothesis that thalamus generated slow-wave oscillations (<1 Hz) acting as peacemaker for cortical activities (Andersen and Andersson 1968). The model was able to reproduce different levels of spatiotemporal coherence present in human electroencephalography (EEG) studies. But mounting evidence from multisite recordings in vivo (Contreras et al. 1996, Destexhe et al. 2001) showed that oscillation coherence across large cortical and thalamic areas was lost following removal or inactivation of the cortex, suggesting an opposite hypothesis in which the source of slow-wave oscillations was to be searched in the cortex while the thalamus, and the corticothalamic feedback, had a broadcasting role. Moreover, the experimental findings could be reproduced only in closed-loop models in which the corticothalamic feedback had a dominant inhibitory role on thalamocortical cells (Destexhe et al. 1998). This model-driven hypothesis was later confirmed experimentally (Destexhe et al. 1999). These modeling and experimental studies resulted in a comprehensive framework that took into account several properties of the thalamocortical system (Destexhe 2000, Destexhe 2009).

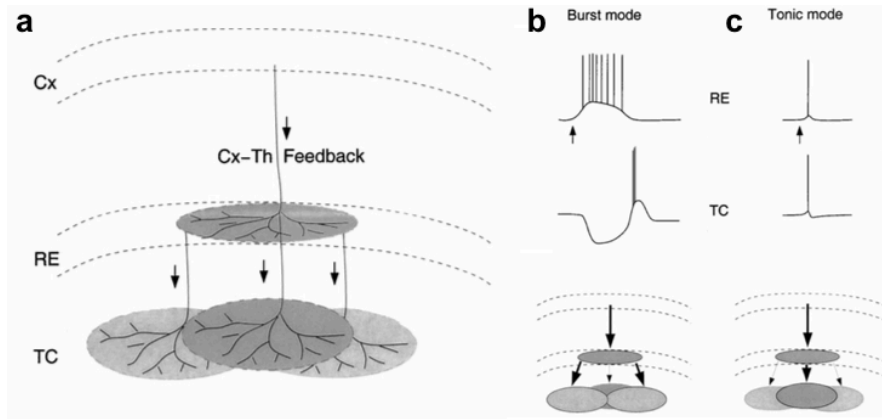


Figure 3.2. Cortical control of thalamic functions (Destexhe 2000). (a) Graphical representation of corticothalamic feedback on reticular complex (RE) and thalamo-cortical projecting cells (TC). The cortico-thalamic excitatory fibers (dark gray) branch to contact both RE and TC cells in a delimited area. RE cells' projections affect a much larger area of the thalamus (light gray). This arrangement has two dynamical implications. (b) When thalamic (both RE and TC) cells are in bursting mode, the inhibition from RE has a strong and diffuse effect on the thalamus, which enables spatiotemporally coherent oscillations. (c) When in tonic mode, RE inhibition has a limited effect compared to the excitation coming from cortex, which triggers fast locally coherent oscillations.

In the proposed framework (figure 3.2), the corticothalamic feedback controls thalamic relay cells in a state-dependent fashion. Corticothalamic fibers (dark grey) innervate both thalamic reticular (RE) nucleus and thalamic relay nuclei (TC). In turn, RE fibers innervate TC (light grey). During deep-sleep or barbiturate anesthesia, the activity of brainstem nuclei is reduced (Ozaki and Kaplan 2006, Jones 2008), and thalamic cells are lacking a constant source of excitation (Hasselmo and Giacomo 2006), which puts them in bursting mode (Sherman and Guillery 2001). In this state, cortical volleys trigger large burst discharges in RE cells, with the effect of widespread strong inhibition of TC cells. On the contrary, during wakefulness (or REM sleep), brainstem nuclei set thalamic neurons in tonic firing mode. In this state, cortical volleys evoke few spikes in RE cells, not enough to inhibit TC cells. The same network is then capable of two different functional responses. During deep-sleep, the widespread suppression provides slow-wave oscillations with diffuse spatiotemporal coherence, while

during wakefulness, cortical excitation is focused triggering fast oscillations that are coherent only within narrow cortical and thalamic sites, while RE inhibition would suppress the surrounding TC responses. This framework is not intended to provide functional predictions for specific sensory modalities, rather a series of guidelines that more focused studies could follow, for example the role of focused cortical excitation and broad RE inhibition onto TC relay functions.

3.4.2 Hypothesis of feedback kernel as negative mirror image of the feed-forward kernel

According to Köhn and Wörgötter (1996), the corticothalamic feedback serves a performance purpose. The authors proposed a hypothetical intrathalamic and corticothalamic connection scheme (that they called “paradoxical” because it went beyond the experimentally proved consensus). In order to test their proposal, they built a large-scale model of the early visual system (based on cat experimental data and extending an open-loop model presented in Wörgötter and Koch 1991). The model architecture included a preprocessing retinal layer with ON- and OFF-center receptive fields, modeled as a Difference-of-Gaussian kernel whose convolution with visual stimuli predicted the retinal spiking response. Each retinal unit projected to a group of four LGN Integrate-and-Fire cells. The intrathalamic paradoxical connection scheme prescribed that each LGN cell within an ON-center (or OFF-center) group directly inhibited two LGN cells of opponent RF organization. All four cells of an LGN group projected in turn to a corresponding ON (or OFF) cortical simple cell, where a similar mutual inhibitory connection scheme was assumed. Importantly, the authors proposed a precise negative mirror image scheme for the paradoxical feedback connectivity: each cortical cell excited the four LGN units with the same receptive field location but with a opponent RF organization.

This choice was justified by latency response considerations in natural visual environments. In these conditions, at each retinal location, transitions

between a bright to a dark stimulus — a negative contrast transition — and between a dark to a bright stimulus — a positive contrast transition — occur often. However, at retinal level, this takeover would take time, especially in small absolute contrast value conditions, which would lead to weak LGN excitation. The paradoxical intrathalamic and corticothalamic connectivity would overcome this limitation. When the presence of a stimulus would engage one pathway (ON- or OFF-center), the local inhibition of the opponent pathway would enhance its contribution to the corresponding cortical units, and *"At the moment of a contrast reversal the effect of the paradoxical connection pattern comes into play and the depolarization of the previously silent channel [ON or OFF] is accelerated, leading to a latency reduction of up to 4 ms using moderate synaptic weights"* (Köhn and Wörgötter 1996, page 199). In addition, this connection scheme was self-regulating because the balance between intrathalamic inhibition and corticothalamic excitation was determined by the input, driving directly the intrathalamic inhibition, but counterbalanced by the paradoxical excitation.

The importance of such paradoxical connection scheme, with its implications for latency, lies in the effects it can exert on the efficacy of LGN spikes on cortical targets, as noted by Funke and Wörgötter 1997 (Figure 3.3).

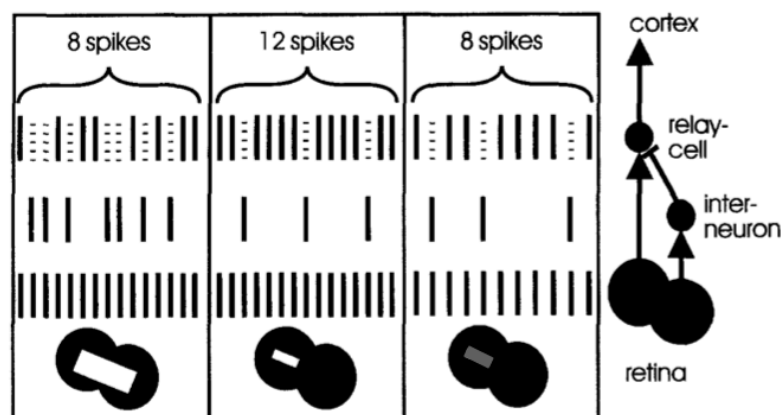


Figure 3.3 Conflicting stimuli can be resolved by considering interval patterns (Funke and Wörgötter 1997). *Right.* The receptive fields of retinal cells are drawn as disks. Feedforward excitation (arrows) and inhibition (T-shaped ends) to relay cells is also considered. *Left.* Sustained stimulation with light bars (rectangles) induces regular firing

in retinal cells (bottom row, black bars represent single spikes). The mean firing rate of the ganglion cell changes little with decreasing bar size. For relay cell firing, a one-to-one transmission of retinal spikes would be assumed (top row). But for each inhibitory input (middle row), relay cell spikes are blanked out (dashed lines in top row). The middle panel depicts the response (12 spikes) of the relay cell to a small bar (bottom). In the left and right panels, a cortical cell cannot distinguish the stimulus simply from the mean rate (8 spikes) because it is identical. But the interval structure in the left and right situations is different.

Two stimulus parameters affect LGN firing rate: contrast and spatial extent. Considering the center-surround organization of retinal input and antagonism in spatial summation, a large high contrast bar covering both opponent center and surround of the retinal receptive field (Figure 3.3, left) could, in principle, elicit a reduced mean firing rate similar to that evoked by a small low contrast bar, covering only the center (Figure 3.3, right). These two stimulus configurations (of different geometry and contrast) cannot be distinguished by the output LGN mean rate alone. However, taking into account the interval structure in the left and right situation, it is possible to distinguish them. The large bar, due to the strong inhibition, produces many second- and third-order intervals, whereas the small bar would mainly lead to fundamental intervals in the response, with the difference that these latter intervals are longer than the fundamental intervals elicited with the large bar. Similar considerations may be applied to oriented bars of varying contrast and how they differently affect the firing temporal structure of rows of LGN relay cells. The introduction of a similar temporal code could improve the performance of cortical cells orientation detection, even in the absence of intracortical mutual inhibition.

The idea of a temporal code, controlled by corticothalamic feedback was interesting, and actually anticipating themes of predictive coding that would be later stressed (Bastos et al. 2012). However, Köhn and Wörgötter could not provide experimental evidence in favor of such a specific arrangement. In fact, due to the lack of further supporting evidence, Wörgötter subsequently dropped such a selective connectivity, adopting an un-selective one (Wörgötter et al. 1998).

3.4.3 Functional impact of cortical input on LGN synchronization and group selection

According to the model of Kirkland and Gerstein (1998), the corticothalamic feedback serves the purpose of synchronizing the activity of geniculate cells responding to the same stimulus. Their work aimed at reproducing the data published by Sillito et al. (1994) concerning high values of cross-correlation in the spike trains of distant pairs of cat LGN cells (stimulated by drifting bars), supposedly synchronized by the cortical feedback because in the absence of cortex no correlation was reported. Kirkland and Gerstein made the hypothesis that the correlations were caused by cortical common input to spatially separated LGN cells. In particular, they focused their model onto two properties of the corticogeniculate feedback: (i) the effect of feed-back on LGN cell low-threshold calcium channels, which would induce bursts of action potentials and increase the probability of correlated firing in distant cells, (ii) a center-surround organization of corticogeniculate connections, with an excitatory center and an inhibitory surround. *“The principal rationale for this connectivity pattern is heuristic: we reasoned that corticogeniculate excitation, being direct, will be limited to the projection field of cortical cells, while the indirect inhibition will be further displayed out by the inhibitory neuron projections”* (Kirkland and Gerstein 1998, page 2011). The structure and importance they assigned to the feedback inhibition is an element that will be explored again later by other authors and also in our model. Guided by these hypotheses, the model of Kirkland and Gerstein reproduced Sillito’s experimental data in nearly every detail.

However, Carlos Brody (1998) reanalyzed Sillito’s data and showed how high values of cross-correlation could be dependent upon three sources: (a) spike timing, where the timing of occurrence of spikes in one train are matched by those in the other spike train (synchrony), which is usually presumed to cause high values of cross-correlation; (b) latency, where the timing of occurrence of spikes in one train are not matching those of the other train, but both have a an overall latency of response varying together over trials; (c)

excitability, where again the timing of occurrence of spikes in one train are not matching those of the other train, but the total number of spikes varies together over trials. Instead of type (a), Brody identified the correlations found by Sillito as type (c), slow resting potential correlations that can be induced by metabotropic channels controlled by cortex (McCormick and von Krosigk 1992, Godwin et al. 1996), or by the brainstem (Uhlrich et al. 1995). In response to this revised interpretation, Kirkland et al. (2000) published a novel analysis of their 1998 model, taking into account the induction of slow resting potential correlations and showing how cortical feedback inhibition in the model produced long-term correlation of LGN membrane potentials when LGN cells were in an oscillating regime. They provided no particular mechanistic explanation for the realization of the correlations identified by Brody 1998, noting only that *“the periodic nature of the stimulus, in conjunction with the cortical inhibitory input to the LGN, creates a sort of resonance phenomenon in which the geniculocortical network weakly oscillates”* (Kirkland et al. 2000, page 1867). Again, an important role was assigned to cortical inhibition. In the model proposed by Kirkland and Gerstein (1998) there were direct cortical inhibitory connections to LGN cells. But there is no anatomical evidence for such direct connections. Cortical excitatory connections are known to target both PGN cells and LGN interneurons (Sherman and Guillery 2001), which in turn are inhibitors of LGN principal cells. Therefore, Kirkland and Gerstein (1998) made a simplification that left out these thalamic sources of inhibition, which however represent the first loop intrinsic to the thalamus.

Funke and Wörgötter 1997 stressed the importance of cortical feedback for the selective role it could potentially have in synchronizing portions of the LGN, hence having a stronger effect on their cortical targets. In order to study this hypothesis, they took under consideration experimental data regarding the different temporal dispersion of retinal prepotentials and the corresponding spikes elicited in cat X-ON LGN target cells (measured using the inter-spike interval, ISI). The dispersion of the evoked activities of LGN

cells was lower than that of the corresponding retinal prepotentials and higher order peaks were observed only for the LGN. These authors hypothesized that the corticothalamic feedback could reduce the temporal dispersion of spike intervals for LGN, and predicted that the LGN spike interval dispersion would be higher in open loop than in the closed loop condition. They built a model of the corticothalamic loop in which retinal ganglion cells projected one-to-one to a LGN relay cells, which also received inhibitory input from LGN interneurons. The corticothalamic feedback from each cortical cell targeted (6) topographically aligned LGN relay cells. In their simulations, Funke and Wörgötter observed a reduction of the temporal dispersion of LGN spiking comparable to the experimental data. In addition, neighboring LGN cells synchronized their activity only during active corticofugal feedback in the closed loop condition.

Hillenbrand and van Hemmen (2002) proposed a more articulated hypothesis: the visual cortex would control the spatiotemporal structure of its own receptive fields through the corticothalamic feedback. They took an incremental approach, developing first a closed-loop model of intrathalamic circuitry, then studying its input to cortical cells in an open-loop arrangement, and finally closing this second loop with corticothalamic feedback to the LGN. They proposed a causal link between the fact that cortical feedback to the LGN can modulate the spike timing of principal cells by shifting their membrane potentials (Sherman and Guillery 2001) and the fact that cortical simple cells have variable tuning for the speed of moving stimuli (DeAngelis et al. 1995, Jagadeesh et al. 1997). More specifically, they proposed that the corticothalamic system produces a control mechanism for speed tuning by dynamically modulating LGN responses, and exemplified the hypothesized control mechanism with a model of the corticogeniculate loop that performed object segmentation based on motion cues.

The first closed-loop model was composed of an RGC layer of Poisson generators providing input to LGN principal cells and interneurons, which inhibited the principal cells. All neurons, except for the RGCs, were modeled

as conductance-based multi-channel spiking cells with adaptation (Gerstner and van Hemmen 1992). Differences in the parameters of retinthalamic feedforward excitation and inhibition generated two populations of LGN cells: non-lagged cells – where the excitation due to retinal spikes preceded the inhibition due to local interneurons, leading to an immediate response – and lagged cells – where retinal excitation was preceded by inhibition, leading to responses characterized by variable lags (Humphrey and Weller 1988).

The model was then extended to detail the input to cortex in an open-loop condition. The two groups of LGN cells projected to a layer of PGN cells and cortical simple cells of Layer 4. These latter are known (McLean and Palmer 1989, DeAngelis et al. 1995, Jagadeesh et al. 1997) to have stronger responses for stimuli having a particular direction and speed. Such preference derives from the sub-regions composing their spatio-temporal receptive fields, receiving geniculate inputs alternating between lagged and non-lagged cells (Saul and Humphrey 1990, DeAngelis et al. 1995, Jagadeesh et al. 1997). In the model, a specific direction and speed preference was given to a cortical simple cell by selecting its LGN afferents such that the lagged cells sub-region received the retinal input before the non-lagged cells sub-region. In addition, the authors showed how it was possible to change the preferred speed of a cortical cell by modulating the membrane potential of its afferent LGN cells. During presentation of a bar-stimulus shifting through their RF, membrane hyperpolarization shifted non-lagged cells response peak to earlier times and lagged cells response peak to later times, while membrane depolarization shifted non-lagged towards later times and lagged cells to earlier times. This resulted in the total maximum geniculate input to a cortical simple cell to shift towards lower velocities as the membrane potential hyperpolarized, due to the time needed for lagged cells to meet non-lagged ones, and towards higher velocities as the membrane potential depolarized. Therefore, a plausible gating mechanism was provided by the alteration of LGN membrane potentials.

The proposed effect of cortical feedback was to control the gating. A full closed-loop model was then designed to validate the functional impact of this hypothesis in an object segmentation task. The full model was included cortical interneurons in layer 4, and layer 6 cells, which projected to layer 4 interneurons, and also sent diverging projections to PGN, and LGN. Following the experimental evidence on metabotropic channels (Sherman and Guillery 2001), the gating control consisted of corticothalamic-driven K^+ leak conductance changes in LGN cells leading to variations of LGN cells resting membrane potential. This mechanism was exploited in the following manner. The open-loop model above showed that the velocity producing the maximal convergent input to a cortical cell was that yielding coincident lagged and non-lagged responses. Considering the divergence of corticothalamic pathway, each LGN cell received modulatory input from cortical cells representing an extended visual field, being excitatory from cortical cells with identical speed tuning and inhibitory from cortical cells with differing speed tuning (through PGN). The result was an adaptation of lagged and non-lagged LGN response timings, leading to stronger input to the cortical cells representing a stimulus velocity coherent with other nearby representations. Given the coherent movement of object borders, the cortical cells representing an object increased their response while the non-coherently stimulated ones were reduced.

Although being experimentally informed in many respects, this proposal also presented two assumptions not supported by experimental evidence (hence could be considered as predictions of the model): the precise spatial distribution of corticothalamic excitation to LGN and PGN, and the separate connectivity from PGN to LGN lagged / non-lagged subgroups.

3.4.4 Constructing a context-dependent feedback kernel

The impact of retinal feedforward, local interneurons, and cortical feedback on LGN principal cells has been Gaute Einevoll's subject of study for several years. Einevoll extended a data-driven model, formulated initially by

Heggelund's team (Ruksenas et al. 2000) where the receptive field of a LGN principal cell would be due to the spatial organization of its feedforward monosynaptic excitation and disynaptic inhibition. Few retinal ganglion cells (RGCs) would excite an LGN principal cell directly, while a group of RGCs, having RF centers near or overlapping those exciting directly the principal cell, would excite nearby local interneurons which in turn would inhibit the LGN principal cell. The RF properties of the LGN principal cell would then be the sum of these contributions, resulting in a RF itself composed of an excitatory center and an inhibitory surround (as its RGC sources, see Rodieck 1965).

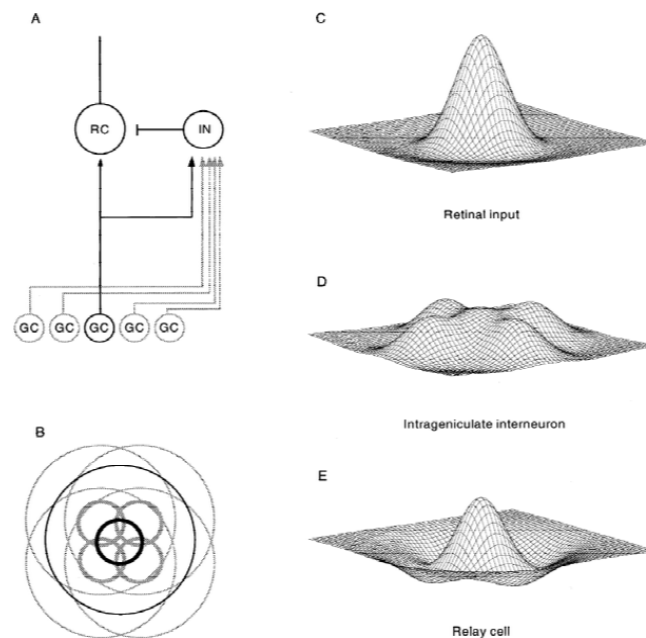


Figure 3.4. Retino-thalamic feedforward excitation and inhibition (Ruksenas et al. 2000). (A) Schematic model illustrating the direct retinal input (bold arrow) from a ganglion cell (GC) to a relay cell (RC) as well as the indirect input (bold T-arrow) through one inhibitory interneuron (IN). The inter-neuron also receives input from GCs surrounding the one projecting to the same RC. (B) The receptive field (small circle for center and large circle for surround) of the RC is a result of the direct input (bold) and the indirect inputs summing via the interneuron (gray). (C) The spatial receptive field profile of each GC is represented by the difference of one center excitatory and one surround inhibitory Gaussian (as in Rodieck 1965). (D) The spatial receptive field profile of the intrageniculate inhibitory interneuron is the sum of all its input GC profiles. (E) The resulting spatial receptive field profile for the RC is the difference between the retinal input in C and the interneuron in D.

Following Ruksenas et al. 2000 proposal, Einevoll and Heggelund 2000 proposed a mechanistic mathematical model. The model included direct excitatory input from a single RGC and indirect inhibitory input from a pool of intrageniculate interneurons. The advantage of this model was to take into account the geniculate circuitry, with direct physiological mapping of its parameters. The parameters of this model, and its follower (Einevoll and Plesser 2002) were fitted against Ruksenas et al. 2000 data-base of spot-diameter response curves of dLGN cells, which also included the retinal input reconstruction made from the S-potentials simultaneously recorded in the thalamic cells under study.

In 2005, Einevoll and Plesser took under scrutiny the most widely used model of LGN responses: the Difference-of-Gaussian (DOG) model (Hochstein and Shapley 1975, So and Shapley 1981, Mukherjee and Kaplan 1995, DeAngelis et al. 1997). Initially developed to account for RGC responses (Rodieck 1965), the DOG models the spatial receptive field as the difference of two circularly symmetric and concentric Gaussians. The analytical solution in the case of bars (Rodieck 1965) and full-field drifting gratings (Enroth-Cugell and Robson 1966) corresponded to the convolution of the DOG kernel with the stimulus signal.

Over time, the importance of using drifting gratings stimuli varying in size to study the feedback from cortex to thalamus became clear through a series of works (Sillito et al. 1993, Cudeiro and Sillito 1996, Jones et al. 2000). An important result of Sillito was already showing that a simple DOG model succeeded in reproducing LGN responses to size varying drifting gratings stimuli in preparations where the cortical feedback to thalamus was blocked (open-loop), but failed in reproducing LGN responses in intact (closed-loop) preparations.

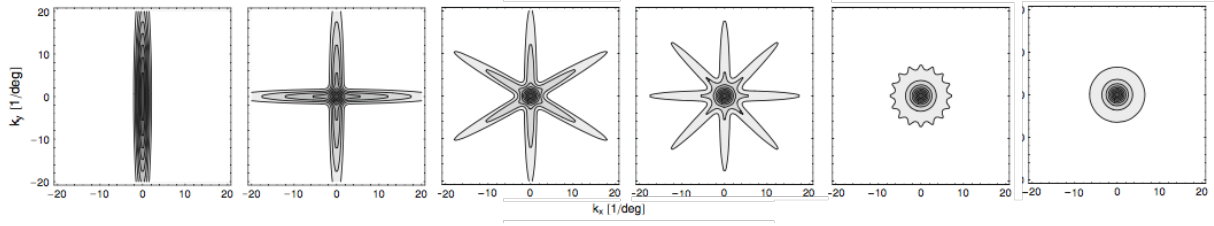


Figure 3.5. Cortico-thalamic contribution to LGN receptive field (Eienevoll and Plesser 2012). Six example of spatial loop kernels including increasingly more (respectively, $N=1, 2, 3, 4, 8, \text{inf}$) cortical feedbacks (horizontal and vertical dimensions are arbitrary) are reproduced from the original paper.

Building on the original DOG model, Eienevoll and Plesser (2012) presented an extended Difference of Gaussian (eDOG) model capable of reproducing the responses of LGN cells to several stimuli, including size-varying patches of drifting gratings in the closed-loop condition (as in Sillito and Jones 2002). The extension consisted in incorporating equations representing the influence of the corticothalamic feedback from a set of orientation-selective cortical cells. Their main hypothesis was that the cortical feedback to thalamus brings in the cortical orientation tuning, therefore the global feedback should be estimated from the superposition of orientation-selective cortical kernels. Each cortical cell being selective for a different orientation of the stimulus, the global feedback kernel resulting from the summation of all cortical contribution was a circular Gaussian kernel. The same approach was later used to show the validity of using firing rate models to reproduce early visual system responses (Heiberg et al. 2013).

More recently, Martinez et al. 2018 simulated a small size network with biologically detailed spiking units, that included LGN principal cell, LGN interneurons, and cortical cells and studies the functional impact of the excitatory and inhibitory input to LGN principal cells, driven by cortical feedback. The network RGC input layer was modeled as two DOG filter arrays of antagonistic center-surround (ON- and OFF-center) arrangement. LGN cells (both principal and interneurons) received input from only one of these arrays. The thalamic afferents to cortex was arranged in such a way to induce phase-opponent Gabor-like ON- and OFF- simple cells, whose spiking was fed

back to the thalamic cells in a configuration that resulted for LGN principal cells into a spatially widespread inhibitory feedback combined with spatially narrow excitatory feedback. Also phase properties of the cortical units were taken into account in the arrangement of feedback contributions, providing selective corticothalamic inputs to LGN cells. In particular, two feedback connectivity schemes were tested. One phase-matched scheme, in which ON-cortical cells projected to ON-thalamic cells (and OFF-cortical cells projected to OFF-thalamic cells), and a phase-reversed scheme, in which ON-cortical cells projected to OFF-thalamic cells (and vice-versa). Flashing spots and size-varying patches of drifting sinusoidal gratings were used as visual stimuli. The comparison of the two feedback projection schemes against the available literature showed that a phase-reversed feed-back kernel provided an increased center-surround antagonism in LGN responses to patch gratings, in accordance to the experimental findings of Wang et al. 2006, who also speculated a phase-reversed selective corticothalamic connectivity in agreement with the initial proposal of Köhn and Wörgötter (1996).

However, although the phase specificity of the cortical feedback connections to the LGN interneurons and principal cells was a pivotal prediction of this study, a pragmatic solution to bring the model closer to the known architecture of the visual thalamus, especially for the wider spread of inhibition, in line with the known facts of the thalamus, could have been to incorporate in the model the corticothalamic projection to the PGN and its wider projection to LGN principal cells.

3.5 Summary

Several sets of experimental evidence constrain *in-computo* approaches in the study of the cortico-thalamic feedback loop. In fact, the several available *in-vitro* and *in-vivo* experimental manipulations of the cortico-thalamic loop available to the modeler (isolation of the loop components, complete suppression of the feedback, pharmacological or optogenetic control of the

feedback) can offer only partial answers regarding functional roles of the feedback. Correspondingly, the already achieved *in-computo* simulations of the cortico-thalamic loop focused too narrowly on specific aspects of cortico-thalamic computation, single or at most few at a time, which necessarily lead to partial interpretative frameworks.

The existing *in-computo* literature regarding the corticothalamic loop functions outlines two broad lines of research:

- i. One focusing on functional specificity, depending on the **type of sensory stimulus** provided to the system: the loop enables the control of the amount, content, and temporal structure of the information transmitted to the rest of the brain.
- ii. One focusing on dynamic behavior (rather than functions) depending on the **state** of the system: the loop contributes to the generation and spread of different rhythmic activities.

The majority of *in-computo* works that I chose to present in the previous sections adopted point-like Integrate-and-Fire units (Lapique 1907, Dayan and Abbott 2001) to model the spiking behavior of cells across the early visual system. This modeling choice enables the overlap between the above two lines of research because (i) it enables the construction of models having both a functional specificity comparable to in *in-vivo* measurements (e.g. spike trains statistics, as well as membrane potential, conductance, and current). In addition, (ii) the structural details necessary to functionally specific models also support the generation and spread of rhythmic activities.

The uniformity of modeling choice will allow me to summarize several notable points from the models above:

- Distance-dependent connectivity for both the feedforward and feedback pathways is a common experimentally derived assumption

for all functionally oriented studies, but not for the study of rhythms (see Destexhe 2000 statistical wiring vs all other models).

- Several stimulus parameters affect the response of cells in the early visual system (the work of Funke and Wörgötter 1997 highlighted the interaction between two of them: contrast and size; Hillenbrand and van Hemmen 2002 for orientation and direction of motion).
- The ratio of excitatory and inhibitory inputs in the thalamus is a crucial free parameter to all models above. The cortical feedback is usually used to control the balance between excitation and inhibition (at least in Köhn and Wörgötter 1996, Funke and Wörgötter 1997, Hillenbrand and van Hemmen 2002, Martinez et al. 2018).
- The exact source of thalamic inhibition is not clearly dissected, leaving some ambiguity between local interneurons in the LGN or PGN. Destexhe (2000) clearly adopted PGN for its wide reach into the LGN, whereas Hillenbrand and van Hemmen (2002) adopted interneurons for feedforward inhibition and PGN for feedback inhibition.
- The feedback kernel is assigned an explicit functional hypothesis — the cortical feedback brings to thalamus the superposition of orientation-selective cortical kernels. This schema is explicit only in Einevoll and Plesser 2012 (which is also the most theoretical work). For all other works a more subtle (and less explicit) control is assigned, impacting on membrane potential, gain, excitatory-inhibitory balance, stimulus-induced correlations.

Considering the cross-links between theories of the previous chapter, and following the analysis points above, the hypothesized function of the feedback kernel that I tested in the simulations can be summarized in the following way:

“The cortical feedback to thalamus serves a dual — collaborative and competitive — functional role: collaborative through the superposition of selectivity for multiple stimulus features (contrast, size, orientation, spatial frequency, etc.), competitive through the set

of topologically organized connections which bring a narrowly positive and broadly negative image of cortical kernels”

The first element — the superposition of selectivity for multiple stimulus features in the corticothalamic kernel — that underlies Mumford’s blackboard collaborative approach was explicit in Einevoll and Plesser 2012, although only considering the superposition of multiple cortical orientation selectivity. Here, I intend a less explicit definition, in which the kernel is resulting from the cortical selectivity for a variety of stimulus features (caused by RF properties but also intracortical computation).

The second element — the opposition of topologically organized narrowly positive and broadly negative cortical feedback projections — known from morphology studies and the evidence from Suga’s egocentric selection experiments, was explicitly used as mechanism for stability by Destexhe 2000, Kirkland and Gerstein 1998, Hillenbrand and van Hemmen 2002. Here, while acknowledging such stability role, I follow more closely Suga’s functional role, assigning to narrowly positive connections the role of conveying the cortical kernel, and to broadly negative (via perigeniculate) connections a role of lateral competition.

4 Methods

4.1 Model Structure

Here I provide the description of the principles used to construct the simulated cortical and thalamic regions, the various connection pathways within and between these regions, and the cellular and synaptic properties, the experimental protocols, the procedures for the collection and analysis of data, and the software stack used to develop and simulate the model. The full code listing and parameters are also available on the project page on GitHub (<https://github.com/dguarino/T2>).

Our model was based on a previous model of V1 (Antolik et al. 2018) that has been modified for the purpose of this PhD thesis to allow focusing on the thalamus and the corticothalamic feedback loop. It consisted of: (i) a region of visual field, (ii) two retinotopically congruent regions of the dorsal thalamus, namely the lateral geniculate nucleus (LGN) and perigeniculate nucleus (PGN), and (iii) a retinotopically congruent region of the cat primary visual cortex (V1). The model covered 7x7 degrees of visual field centered at ~5 degrees of eccentricity around the area centralis. This corresponded to 1.4 mm² of LGN and PGN tissue (Sanderson 1971), and to 3.5x3.5 mm patch of cat primary visual cortex.

RETINA. We used a simple model of the transduction from luminance stimuli to retinal ganglion cell (RGC) spikes that included a phenomenological model of RGC receptive field (as in Rodieck 1965, Cai et al. 1997). This model has

two space-time separable components, one for the center and one for the surround of the RGC receptive field (RF) response:

$$RF = S_c T_c - S_s T_s \quad (1)$$

The spatial components was modeled as a Gaussian functions of the visual stimulus position (x), according to the model of Rodieck 1965:

$$S_{c,s}(x) = A_{c,s} \cdot e^{-\frac{(x-x_{c,s})^2}{\sigma_{c,s}^2}} \quad (2)$$

with A being the amplitude of response, and σ the radius of the RF component. These parameters were chosen according to the literature for cat RGCs at ~ 5 degrees of eccentricity from the area centralis, to be $\sigma_c = 0.2$ deg, $\sigma_s = 0.7$ deg (Linsenmeier et al. 1982, Marrocco et al. 1982) and $A_c = 1.0$, $A_s = 0.05$ (Cai et al. 1997). The time components were modeled as sums of Gamma functions (Cai et al. 1997):

$$T_{c,s}(t) = K_1 \times \frac{[c_1(t-t_1)]^{n_1} e^{-c_1(t-t_1)}}{n_1^{n_1} e^{-n_1}} - K_2 \times \frac{[c_2(t-t_2)]^{n_2} e^{-c_2(t-t_2)}}{n_2^{n_2} e^{-n_2}} \quad (3)$$

the parameters were taken from Nirenberg et al. 2010 ($K_1 = 1.05$, $K_2 = 0.7$, $c_1 = 0.14$, $c_2 = 0.12$, $t_1 = -6.0$, $t_2 = -6.0$, $n_1 = 7.0$, $n_2 = 8.0$).

The visual transduction, for each RGC, was computed as follows. Stimulus S , a set of luminance values pertaining to a cell RF area, was convoluted with a RF:

$$r(t) = (RF \times S)[t] = \alpha_1 \sum_0^t RF(t) \cdot view(t - \tau) / \alpha_2 \quad (4)$$

where both RF and $view$ were 3D arrays (2D for the space component and a third dimension for the time component), $\tau = 7$ ms was the duration of the RF temporal component, and $\alpha_1 = 380000$ and $\alpha_2 = 150$, were dimensionless linear luminance gain parameters. This response $r(t)$ represented the absolute mean luminance convolution of RF kernel and stimulus view, therefore it was unbound. We adopted an additional saturation term, similar to Bonin et al. 2005, to saturate the luminance response with a contrast response, obtained

convolving the standard deviation of the spatial component (here simply represented by the variable x) of the stimulus $S(t)$ with the response $r(t)$:

$$z(t) = (r \times S)[t] = \beta_1 \sum_0^t r(t) \cdot std(S(x)) / \beta_2 \quad (5)$$

where $\beta_1=200000$ and $\beta_2=.00001$, were dimensionless linear contrast gain parameters. This saturation term represented an abstraction of the RGC firing rate, as if already weighted by the triadic dendro-dendritic contribution coming from LGN interneurons (as suggested by Sherman 2004), which we did not model explicitly.

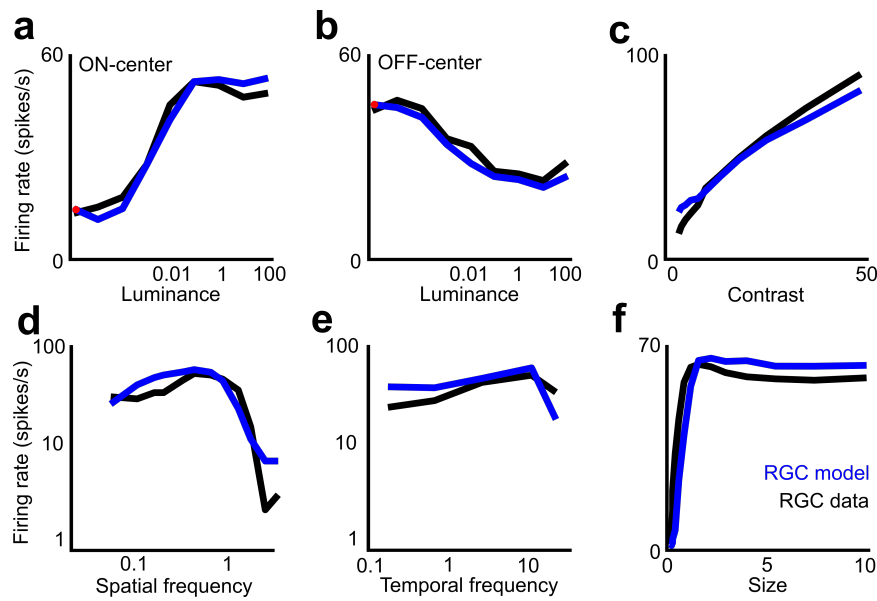


Figure 4.1. Model RGC qualitative fitting. Responses of our RGC phenomenological model (in blue) overlaid onto experimentally measured responses of cat RGC (in black). **a-b.** Model (**a:** On-center cells, **b:** Off-center cells) and *in-vivo* (Barlow and Levick 1969, respectively their figures 2 and 3) responses to increasing uniform luminance levels (cd/m^2). The red circles show the spontaneous activity (dark discharge) that we modeled with white noise injection. **c.** Model and *in-vivo* (Derrington and Lennie 1982, their figure 3B) responses to full-field drifting gratings (2.5 cycles/deg, 12 cd/m^2 , 5.2 cycles/second). **d.** Model and *in-vivo* (Derrington and Lennie 1982, their figure 4) responses to full-field drifting gratings varying in spatial frequency (from 0.06 to 2 cycles/deg, 12 cd/m^2 , 2.6 cycles/second, 200 cd/m^2 , 60% contrast). **e.** Model and *in-vivo* (Derrington and Lennie 1982, their figure 6) responses to full-field drifting gratings varying in temporal frequency (from 0.2 to 20 cycles/sec, 12 cd/m^2 , 200 cd/m^2 , 60% contrast). **f.** Model and *in-vivo* (Alitto and Usrey 2015, their figures 3 and 4) responses to patches of drifting gratings varying in diameter (from 0.1 to 10 degrees).

The sum of response $r(t)$ and saturation term $z(t)$, in units of luminance (cd/m^2) assuming the kernel values as dimensionless, was injected as current (nA) in an Integrate-and-Fire model, together with an amount of white noise used to mimic the response variability and average firing rate of RGCs (for On- and Off-center cells, see Figure 4.1, a and b). The parameters of the luminance and contrast saturation term, and noise were chosen to match the literature available for luminance (Barlow and Levick 1969) and contrast (Derrington and Lennie 1982) of RGC responses (Rathbun et al. 2010) and S-potential inputs to LGN (Weyand 2007). All relevant stimuli, later tested in the full model, were used here to tune RGC responses to fit the available *in-vivo* intracellular data from cat RGC (Figure 4.1).

LATERAL GENICULATE AND PERIGENICULATE NUCLEI. The lateral geniculate nucleus (LGN) of cats has three laminae of alternating ocularity (see Sherman Guillery 2001, p.48). Given that we do not explored any aspect related to binocularity, we modeled only the superficial lamina A, containing X cells, further divided into X-On and X-Off cell groups according to their contrast phase preference (Enroth-Cugell et al. 1977). We chose to not model the Y pathway of cat since its cells present a non-linear spatio-temporal RF, and we chose to restrict ourselves to the X pathway having a linear response to stimuli (Sherman Guillery 2001, p.48). Given the limited computational resources we chose to model 100 principal cells per deg^2 , which represents down-sampling by a factor of about 20 (Sherman and Koch 1986, Budd 2004, Tömböl 1967, Sanderson 1971), with a total 12800 principal cells in the LGN, divided into two 6400 sets for On- and Off-center cells. We applied the same reasoning for PGN, using the same cell density, magnification factor (Sanderson 1971), and receptive field size overlap observed in the literature (Lam and Sherman 2005, Soto-Sanchez et al. 2017).

PRIMARY VISUAL CORTEX. The cortex corresponded to a 3.5×3.5 mm patch of cat primary visual cortex. It contained 10800 excitatory and 2700 inhibitory neurons, in the ratio 4:1 (Beaulieu et al. 1992, Markram et al. 2004), and ~10 million synapses, with a significant down-sampling (~10%) of the actual

density of neurons present in a corresponding portion of cat cortex (Beaulieu and Colonnier 1989) to make the simulations computationally feasible.

4.1.1 Model Neurons

All excitatory and inhibitory neurons were modeled as point-like spiking neurons. All sub-cortical neurons were conductance-based Leaky Integrate-and-Fire (LIF, Lapique 1907, in Brunel and VanRossum 2007). We adapted LIF unit parameters for the different cell types from in-vivo and in-vitro measurements of neurons in the cat visual system and classically modeled in the literature (Freed and Sterling 1988, Wörgötter and Koch 1991, Destexhe et al. 1996, Destexhe et al. 1998, Huertas et al. 2005, Budd 2004). The neurons in cortex were modeled as Adaptive Exponential Integrate-and-Fire units (Brette and Gerstner 2005, see Antolik et al. 2018 for motivation and justification). All neuron model details are re-reported in Table 4.1.

Parameter	Value		Source
Retinal Ganglion Cell			
Threshold	-50.0	mV	Greenberg et al. 1999
Resting potential	-63.0	mV	Lankheet et al. 1989
Reset potential	-55.0	mV	Margolis and Detwiler 2007
Refractory period	0.5	ms	Lankheet et al. 1989
Membrane time constant	10.0	ms	Freed and Sterling 1988
Membrane capacitance	0.1	nF	Freed and Sterling 1988, Weiner 2012
On-center mean noise (std)	0.0 (± 2)	nA	to make corresponding LGN firing as in Levick and Williams 1964
Off-center mean noise (std)	0.0 (± 5)	nA	"
On/Off-center radius	0.2	deg	Linsenmeier et al. 1982, Marrocco et al. 1982
On/Off-surround radius	0.7	deg	"
LGN			
Threshold	-45.0	mV	Worgotter and Koch 1991
Resting potential	-65.0	mV	Worgotter and Koch 1991, McCormick and Huguenard 1992
Reset potential	-55.0	mV	Huertas et al. 2005
Refractory period	2.0	ms	Huertas et al. 2005
Membrane time constant	10.0	ms	Huertas et al. 2005
Membrane capacitance	0.2	nF	Destexhe et al. 1998
Excitatory reversal potential	0.0	mV	Worgotter and Koch 1991
Inhibitory reversal potential	-80.0	mV	Huertas et al. 2005
Excitatory synaptic constant	1.5	ms	Huertas et al. 2005
Inhibitory synaptic constant	5	ms	Huertas et al. 2005
PGN			
Threshold	-50.0	mV	Destexhe et al. 1996
Resting potential	-70.0	mV	Destexhe et al. 1996
Reset potential	-55.0	mV	Huertas et al. 2005
Refractory period	5.0	ms	Huertas et al. 2005
Membrane time constant	10.0	ms	Destexhe et al. 1996
Membrane capacitance	0.2	nF	Destexhe et al. 1996
Excitatory reversal potential	0.0	mV	Huertas et al. 2005
Inhibitory reversal potential	-80.0	mV	Huertas et al. 2005
Excitatory synaptic constant	1.5	ms	Huertas et al. 2005
Inhibitory synaptic constant	5	ms	Huertas et al. 2005
Cortical excitatory			
Threshold	-53.0	mV	derived from Monier et al. 2008
Resting potential	-80.0	mV	"
Afterpotential reset	-54.0	mV	"

Refractory time constant	2.0	ms	"
Membrane time constant	10.0	ms	"
Membrane capacitance	0.05	nF	"
Excitatory reversal potential	0.0	mV	"
Inhibitory reversal potential	-80.0	mV	"
Excitatory synaptic time const.	7.8	ms	"
Inhibitory synaptic time const.	15.0	ms	"
Subthreshold adaptation (a)	-5.2	nS	"
Spike-triggered adaptation (b)	0.08	nA	"
Slope factor (Δ_p)	2.0	mV	Naud et al. 2008
Adaptation time constant (τ_w)	88.0	ms	"
Cortical inhibitory			
Threshold	-53.0	mV	derived from Monier et al. 2008, McCormick et al. 1985
Resting potential	-80.0	mV	"
Afterpotential reset	-53.0	mV	"
Refractory time constant	0.5	ms	"
Membrane time constant	10.0	ms	"
Membrane capacitance	0.05	nF	"
Excitatory reversal potential	0.0	mV	"
Inhibitory reversal potential	-80.0	mV	"
Excitatory synaptic time const.	7.8	ms	"
Inhibitory synaptic time const.	15.0	ms	"
Subthreshold adaptation (a)	-5.2	nS	"
Spike-triggered adaptation (b)	0.08	nA	"
Slope factor (Δ_p)	2.0	mV	Naud et al. 2008
Adaptation time constant (τ_w)	88.0	ms	"
Thalamic Connectivity			
Retina → LGN			
Synaptic efficacy	6	nS	Blitz and Regehr 2003, 2005, Lam and Sherman 2013
Delay	1.0	ms	Lindstrom 1982
LGN → PGN			
# synapses per receiver	60		Sherman and Guillery 2001, Murphy et al. 2000, Jones 2002, Sillito and Jones 2002
Synaptic efficacy	1.5	nS	Liu et al. 2001
Radius of arborisation	75	μm	Friedlander et al. 1979, Alonso et al. 2006
Delay	1.0	ms	Lindstrom 1982, Funke and Eysel 1998, Rogala et al. 2013
PGN → PGN			
# synapses per receiver	20		Golshani et al. 2001, Jones 2002 page 1659
Synaptic efficacy	0.1	nS	Ulrich and Huguenard 1996
Radius of arborisation	70	μm	Cucchiari et al. 1991, Sanchez-Vives et al. 1997, FitzGibbon 2006
Delay	1.0	ms	Rogala et al. 2013, Bragg et al. 2017
PGN → LGN			
# synapses per receiver	110		Golshani et al. 2001, Jones 2002 page 1659
Synaptic efficacy	0.5	nS	Sanchez-Vives et al. 1997, Lam and Sherman 2011
Radius of arborisation	150	μm	Cucchiari et al. 1991, Cox et al. 1996, Sanchez-Vives et al. 1997
Delay	1.0	ms	Lindstrom 1982, Funke and Eysel 1998, Rogala et al. 2013
LGN → V1 (exc/inh)			
# synapses per receiver	45		Sherman Guillery 2001, Budd 2004, daCosta and Martin 2011
Synaptic efficacy	1.3	nS	Banitt et al. 2007, daCosta and Martin 2011
Radius of arborisation	250	μm	Antolik and Bednar 2011
Delay	2.0	ms	Rogala et al. 2013
V1 → PGN			
# synapses per receiver	40		Murphy et al. 2000
Synaptic efficacy	0.6	nS	Golshani et al. 2001, Liu et al. 2001, Deleuze and Huguenard 2006
Radius of arborisation	90	μm	Deleuze and Huguenard 2006, FitzGibbon 2000
Delay	5.0	ms	Rogala et al. 2013
V1 → LGN			
# synapses per receiver	250		Murphy and Sillito 1996, Murphy et al. 2000
Synaptic efficacy	0.4	nS	Golshani et al. 2001
Radius of arborisation	60	μm	Murphy et al. 1996, 1999, FitzGibbon et al. 1999, daCosta et al. 2009
Delay	5.0	ms	Ahlens et al. 1982, Rogala et al. 2013
Cortical Connectivity			
excitatory → excitatory			
# structured synapses	2000		Beaulieu and Colonnier 1985, Stepanyants et al. 2009
% random synapses	40		Buzás et al. 2006
Synaptic efficacy	0.5	nS	Cruikshank et al. 2007, Hoffmann et al. 2015, Markram et al. 1998
Radius of arborisation	200	μm	Budd and Kisvárdy 2001, Stepanyants et al. 2009
Delay	0.2	ms	Ohana et al. 2012

excitatory → inhibitory				
# structured synapses	2000			Beaulieu and Colonnier 1985, Stepanyants et al. 2009
% random synapses	40			Buzás et al. 2006
Synaptic efficacy	0.75	nS		Cruikshank et al. 2007, Hoffmann et al. 2015, Markram et al. 1998
Radius of arborisation	190	μm		Budd and Kisvárdy 2001, Stepanyants et al. 2009
Delay	0.3	ms		Ohana et al. 2012
inhibitory → inhibitory				
# structured synapses	500			Beaulieu and Colonnier 1985, Stepanyants et al. 2009
% random synapses	40			Buzás et al. 2006
Synaptic efficacy	0.2	nS		Cruikshank et al. 2007, Hoffmann et al. 2015, Markram et al. 1998
Radius of arborisation	250	μm		Budd and Kisvárdy 2001, Stepanyants et al. 2009
Delay	0.2	ms		Ohana et al. 2012
inhibitory → excitatory				
# structured synapses	500			Beaulieu and Colonnier 1985, Stepanyants et al. 2009
% random synapses	40			Buzás et al. 2006
Synaptic efficacy	0.26	nS		Cruikshank et al. 2007, Hoffmann et al. 2015, Markram et al. 1998
Radius of arborisation	230	μm		Budd and Kisvárdy 2001, Stepanyants et al. 2009
Delay	0.3	ms		Ohana et al. 2012

Table 4.1. Model parameters.

4.1.2 Connectivity

In constructing the model, we included realistic network properties, such as the spread and relative proportions of the various sets of connections composing the intra-, inter-thalamic, and thalamocortical circuitry. The synaptic connections were probabilistically drawn with replacement, and number of synapses given in the table above. The extents of axonal and dendritic arborization reported in the literature usually refer to the terminal extents of labeled cells; we took these measures as representing three standard deviations (3σ) of the Gaussian distribution of connection probability. Another important consideration in designing the connectivity was the reliability of synaptic transmission. Both in cortex and thalamus, it has been shown that a small portion of presynaptic action potential succeeds in evoking postsynaptic potentials (Allen and Stevens 1994, Stratford et al. 1996, Weyand 2007). However, it would be computationally expensive to model explicitly synaptic failures, therefore we have decided to account for synaptic transmission failures in the number of simulated synapses per neuron, adopting a 50% factor (unless otherwise stated in the following text) with respect to the input counts reported in the literature.

THALAMIC CONNECTIONS. To determine the likelihood of intra-thalamic connections between pairs of neurons (LGN-to-PGN and PGN-to-LGN), we used a Gaussian probability distribution centered on the pre-synaptic neuron:

$$g_1(x, \sigma) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{x^2}{2\sigma^2}} \quad (6)$$

with standard deviation specified in Table 4.1. The total number of synapses per LGN cell is reported to be between 5000 and 8000 (Sherman and Guillery 2001, Murphy et al. 2000, Jones 2002 p.1661, Sillito and Jones 2002). Of the total, 16% of these connections are from RGCs but, considering that Sherman and Guillery 2001 reported the majority of them are not able to trigger an action potential in the LGN cell and only 1 to 5 can, we further simplified our model by having only one connection between an RGC and one LGN principal cell, that represents the combined influence of the retino-thalamics synapses.

Then, 36% come from PGN (therefore 1800-2880, mean ~2200, which we down-sampled to 220). The total number of synapses per PGN cell is reported to be around 6000 (Golshani et al. 2001, Jones 2002 p.1659: 6771±1018) of which: 20% is from LGN (therefore ~1200, downsampled to 120), 15% from other PGN cells (therefore ~900, downsampled to 90). Measures of the mean arborization distance of LGN axons into PGN are obtained from both morphological (Friedlander et al. 1979, Alonso et al. 2006) and functional (Lam and Sherman 2005, 2011) studies, and report radius range between 50 and 150 μm . For our Gaussian distributions, we used a 3σ radius of 75 μm . Morphological studies (Cucchiaro et al. 1991, Sanchez-Vivez et al. 1997, FitzGibbon 2000, 2006) give a 50-300 μm radius for PGN to PGN connections, either dendro-dendritic or axon collaterals, we used 70 μm . Morphological (Cucchiaro et al. 1991, Cox et al. 1996, Sanchez-Vivez et al. 1997) and functional (Lam and Sherman 2005) studies give 100-300 μm radius for the axonal arborizations of PGN to LGN, we adopted 150 μm radius (3σ).

THALAMO-CORTICAL CONNECTIONS. According to the literature (Sherman and Guillery 2001, Budd 2004), each cortical neuron receives connections from ~45 LGN cells. Each neuron in V1 received connections from both On- and Off-center LGN populations. The spatial thalamo-cortical connectivity was determined by a Gabor distribution, as reported by Troyer et al. 1998:

$$g_2(x, y, \lambda, \theta, \varphi, \sigma, \gamma) = e^{\frac{x'^2 + y'^2 \gamma^2}{2\sigma^2}} \cdot e^{i(2\pi x' \lambda + \varphi)} \quad (7)$$

where $x' = x \cos \theta + y \sin \theta$ and $y' = -x \sin \theta + y \cos \theta$. For individual neurons the orientation θ , phase φ , size σ , frequency λ , and aspect ratio γ of the Gabor distribution were selected as follows. To obtain a functional organization in the cortex, we pre-computed an orientation map corresponding to 3.5×3.5 mm of cortical area (Antolik and Bednar 2011), and this map was used to assign an orientation preference θ to each cortical neuron. The phase φ of the Gabor distribution was randomly assigned (Ziskind 2013). Remaining parameters were set to constant values, following the average values reported by Jones and Palmer 1987 for cat V1 RFs located in the parafoveal area (size $\sigma = 0.25$ degrees of visual field, the spatial frequency $\lambda = 0.8$ Hz and the aspect ratio $\gamma = 0.57$).

INTRACORTICAL CONNECTIONS. According to Beaulieu and Colonnier 1985, the number of synaptic inputs per single neuron in cat V1 is ~ 5800 . A large portion of these connections comes from other cortical areas (Budd 1998), with recent estimates for cat reporting as many as 76% of them coming from outside V1 (Stepanyants et al. 2007). In our model, cortical synapses were formed taking into account the proportion of excitatory and inhibitory cortical cell type densities, the average number of synaptic inputs, the proportion of extra-area input and the failure rates of synaptic transmission. In total, each excitatory cortical cell received 800 synaptic inputs, while inhibitory neurons received 520 inputs, to account for their smaller size. The probability of connection between two neurons in the network was distance-dependent, based on Gaussian decay. Cortico-cortical connectivity was determined by the zero-mean hyperbolic probability density function:

$$pdf(x) = e^{-\alpha \sqrt{\theta^2 + x^2}} \quad (8)$$

with α being a distance parameter, and the other parameters as above. The parameters for this *pdf* incorporated four known principles: (i) connection probability decays with increasing cortical distance between neurons (Budd

and Kisvarday 2001, Stepanyants et al. 2007); (ii) connections have a functionally specific bias (Buzas et al. 2006, Ko et al. 2011); (iii) excitatory neurons have the weak tendency towards connecting nearby neurons of similar receptive field properties, and this tendency increases for more distant post-synaptic neurons (Buzás et al. 2006); (iv) the anti-phase relationship between excitatory and inhibitory conductances in cat V1 simple cells suggests a push-pull connectivity (Hirsch et al. 2003, Lauritzen and Miller 2003, Baudot et al. 2013).

CORTICOTHALAMIC CONNECTIONS. Of the total 5000-8000 synapses per LGN cell (Sherman and Guillery 2001, Murphy et al. 2000, Jones 2002, Sillito and Jones 2002) 44% come from cortex (therefore 2200-3520, with a mean 2800, that we down-sampled to 280). The number of synapses per PGN cell coming from cortex is 60% (therefore ~ 3600) but, in this case, a different down-sampling reasoning applied. The feedback connections from primary visual cortex to PGN have been measured only by few morphological studies and reported to form en-passant boutons, in the order of tens, within a radius below 25 μm (Ahlsen and Lindstrom 1983, Boyapati and Henry 1984, FitzGibbon et al. 1999, FitzGibbon 2000). However, PGN cells form a dense dendro-dendritic network that is capable of spreading excitation laterally within the PGN population in a range of 50-150 μm radius (Deleuze and Huguenard 2006, their figures 3 and 4), we have used a value of 90 μm radius (3σ).

Cortical inputs to LGN have been measured mainly by morphological studies (Murphy and Sillito 1996, Murphy et al. 1999, FitzGibbon et al. 1999, daCosta and Martin 2009) and re-ported to have irregular circular shapes with apical radius varying between 50 and 100 μm , we used 60 μm radius (3σ). We drew all cortico-thalamic connections probabilistically from a Gaussian distribution (as in eq. 1, above). Recent studies indicated the possibility of a more functionally specific connectivity schema (Jones et al. 2013), but these findings will need more investigation to solidify the evidence.

4.1.3 Synapses

Synaptic inputs were modeled as transient conductance changes. A presynaptic event caused a step increase with an exponential decay of the postsynaptic conductance change. Retino-geniculate synaptic strength has been measured *in-vitro* (Blitz and Regehr 2003, 2005, Lam and Sherman 2013) giving changes in conductance in the range 5-40 nS, mediated by AMPA synapses; we used 6 nS with 1.5 ms decay time constant for the excitatory synaptic conductance (see Table 4.1). LGN to PGN synaptic strength, mediated by AMPA synapses, has been measured by Liu et al. 2001 on a per synapse basis leading to a mean value of 1.914 ± 1.814 nS, we used 1.5 nS, with 1.5 ms decay time constant. Recurrent PGN synaptic strength, mediated by GABA synapses, was reported to be in the range 0.03-0.83 nS (Ulrich and Huguenard 1996); we used 0.1 nS with 5 ms decay time constant for the inhibitory synaptic conductance. The synaptic conductance of inhibitory connections from PGN to LGN, mediated by GABA synapses, has been reported to be in the range 0.4-0.6 nS (Sanchez-Vivez and McCormick 1997, Lam and Sherman 2011), we used 0.5 nS with 5 ms decay time constant. In cortex postsynaptic conductance change is modeled in the same way. LGN to V1 synaptic strength, mediated by AMPA synapses, has been measured by Banitt et al. 2007, and we adopted their values: 1.3 nS with a 7.8 ms decay time constant. The cortical feedback synaptic efficacy onto LGN cells is mediated by AMPA synapses, 0.2-0.8 nS (Lam and Sherman 2013), we used 0.2 nS with 1.5 ms decay time constant. To our best knowledge, the synaptic efficacy of cortical feedback onto PGN cells has not been measured in cat, we used 0.4 nS with 1.5 ms decay time constant of the excitatory synaptic conductance, as most thalamic and cortical synapses, since it secured sufficient excitability of the model while preventing instability. This value is also in agreement with the ranges measured in mouse (0.400 ± 0.257 nS, by Golshani et al. 2001, Liu et al. 2001).

4.1.4 Delays

The transmission delays between processing layers we adopted were taken from several converging experimental reports: 1 ms from LGN to PGN, 1 ms PGN to PGN (Rogala et al. 2013), and 1 ms PGN to LGN (Lindstrom 1982, Funke and Eysel 1998, Rogala et al. 2013). The transmission delay between LGN layers to cortex is 2 ms (Lindstrom 1982). While feedback transmission delays between cortex and LGN or PGN are between ~5 ms (Lindstrom 1982, Budd 2008, Rogala et al. 2013), we used 5 ms.

4.2 Inactivation

Several virtual inactivation experiments were conducted, to compare the model's output with experimental results from the literature. Here we considered three main conditions: (i) full system (*full* condition), (ii) whole cortex removal (*without-cortex* condition), (iii) inactivation of a small portion of cortex, (iv) inactivation of only the feedback connections (open loop or *feedforward-only* condition), see figure 5.1 for a summary. In condition (iii), a point in cortex was chosen having the same (or orthogonal) orientation with respect to the orientation domain in the center of the cortical sheet, and a negative current (-0.5 nA), sufficient to prevent spiking, was injected into all neurons within a circular disk area. Jones et al. 2012 reported an area of cortical focal iontophoretic inactivation of approximately 600 μm , corresponding to ~0.5 degrees considering V1 magnification factor around the area centralis (we adopted the same 600 μm radius). The relative spatial position of cortical and thalamic receptive field was also taken into account, identifying overlapping and non-overlapping cortical and thalamic receptive fields. For the inactivation of cortical areas non-overlapping with thalamic RFs, these authors reported a thalamic distance between receptive field centers of approximately 2.5 degrees of visual field, which we chose accordingly in our model.

4.4 Stimuli

We performed our study by comparing network activity for several classes of visual stimulus. Each test trial consisted of a series of visual stimuli that were interleaved with a blank field of uniform luminance (50 cd/m²) presented for 150ms. The model was tested with respect to 6 stimulus parameter variations: (a) changes of ambient luminance of the blank, (b) changes of contrast level in a sinusoidal drifting grating (DG), (c) changes of spatial frequency, (d) changes of temporal frequency, (e) changes of size of the DG patch, (f) changes of orientation. The model responses have been tuned using iteratively all stimuli. This was due to the fact that some model parameters were not exactly constrained by the available literature and thus have been determined to fit functional data. Stimuli (c), (d), (e), (f) were used to test the model in both full (i) and experimentally altered feedback (ii) conditions, while stimulus (e) was also tested with partially inactivated cortex (iii). All stimuli were created using the Mozaik framework (Antolik and Davison 2013).

LUMINANCE. The model was stimulated with five levels of ambient luminance: complete darkness, 0.085, 0.85, 8.5, 85 cd/m², as in Barlow and Levick 1969 and Papaioannou and White 1972. The average (background) level of luminance for all other simulated experiments was 30 cd/m².

CONTRAST. We used Michelson contrast, as the difference between the cd/m² luminance peak (L_{max}) and trough (L_{min}) values, divided by twice the average (background) luminance, $C = \frac{L_{max} - L_{min}}{L_{max} + L_{min}}$. Being normalized by the background luminance, the contrast is usually expressed as percentage. Nine contrast levels were used: 0, 2, 4, 8, 18, 36, 50, 80, 100%, as in Kaplan et al. 1987. The contrast level of all the following experiments was fixed at 80%.

SPATIAL FREQUENCY. Patterns of full-field sinusoidal drifting gratings were supplied to the model. Eight different frequencies were chosen for the

sinusoidal gratings: 0.07, 0.1, 0.2, 0.3, 0.5, 0.8, 1, 1.5, 2, 8 cycles/degree (with temporal frequency of 2 Hz), as in Bisti et al. 1977, Maunsell et al. 1999.

TEMPORAL FREQUENCY. Patterns of full-field sinusoidal drifting gratings were supplied to the model. Eight different temporal frequencies: 0.05, 0.2, 1.2, 3.0, 6.4, 8, 12, 30 were chosen for the drifting movement of the gratings (having 0.5 cycles/degree of spatial frequency), as in Marrocco and McClurkin 1985, Marrocco et al. 1996, Alitto and Usrey 2004.

ORIENTATION. Patterns of full-field sinusoidal drifting gratings were presented to the model, with eight different orientations uniformly chosen between 0 and 90 degrees (having 0.5 cycles/degree of spatial frequency and 2 Hz of temporal frequency), as in Daniels et al. 1977, Vidyasagar and Urbas 1982.

SIZE. Patterns differing in the radius of a circular patch of sinusoidal (with 0.5 cycles/degree frequency) drifting (8 Hz) gratings were presented to the model. Ten radiuses were chosen: 0.125, 0.19, 0.29, 0.44, 0.67, 1.02, 1.55, 2.36, 3.59, 5.46 degrees, as in Murphy et al. 1987, Sillito and Jones 1991, DeAngelis et al. 1994, Jones et al. 2012.

4.5 Iterative procedure to find a single parameter set

Optimization of the full parametric identification search cannot be done easily when using so many parameters. Many biological ranges of parameters were present in the literature, and a systematic fitting would be too much time-consuming. Therefore, the concomitant fitting of selected experimentally recorded functional responses was our guide. We identified as key parameters to match the available data the arborization radius of LGN→PGN and PGN→LGN, for the LGN responses to sized stimuli in the *without-cortex* condition, and the arborization radius of V1→PGN, for the LGN responses to sized stimuli in the *full* condition. We heuristically found parameters fitting both condition, and then searched the surrounding

parameter spaces to assess stability. As reference parameter value for the parameter search, we took the index of end-inhibition.

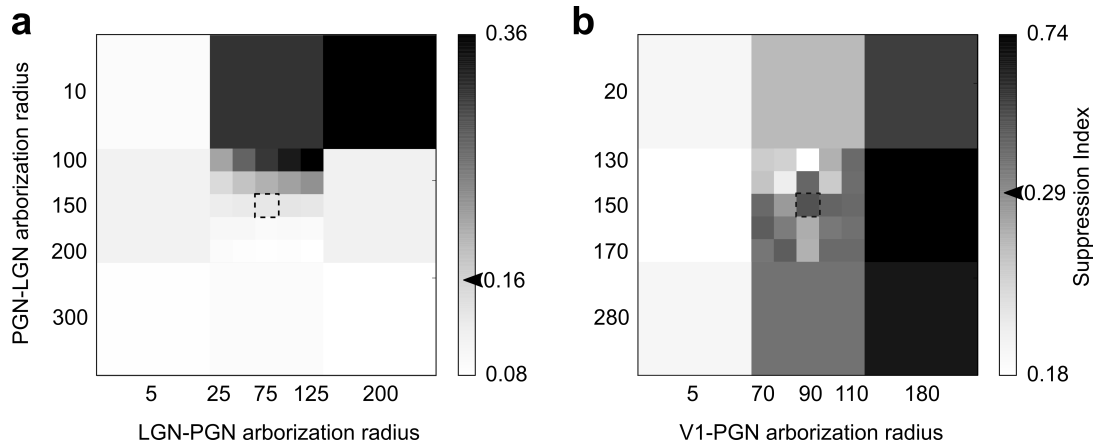


Figure 4.2 LGN, PGN, and V1 connection parameter space. (a) Suppression indexes measured in the parameter space of PGN-LGN arborization radiuses (vertical axis) and LGN-PGN arborization radiuses (horizontal axis). The parameter space around the chosen value (dashed square) has a finer scale. (b) Suppression indexes measured in the parameter space of PGN-LGN arborization radiuses (vertical axis) and V1-PGN arborization radiuses (horizontal axis). In both figures, the arrowheads on the color bars are the values from the dashed squares.

We show the results of the parameter space exploration in Figure 4.2. The heuristically found values for the parameters are LGN→PGN: 75 μm , PGN→LGN: 150 μm , V1→PGN: 90 μm . These values produce the suppression index values closest to those measured *in-vivo* by Alitto and Usrey (2015) in the intact cat LGN, using patches of sinusoidal drifting gratings, which scored 0.43 (± 0.02). And also, they fit proportionally those measured by Murphy and Sillito (1987), which reported a significant reduction (35.5%) of the average suppression index between the control (0.71 ± 0.02) and ablated cortex (0.43 ± 0.02). We will discuss in detail these results and those of our model in chapter 6.

4.6 Simulation recording and Analysis

We presented the above stimuli to the model for several trials (varying from 6 to 12, depending on the simulated duration, which in turn depended on the type of stimulus and reference experimental conditions) and recorded the spike timing and synaptic conductances of simulated units from the LGN, PGN, and V1 populations, chosen either randomly or selectively depending on the type of experiment. For the experiments having stimuli (a-f) with conditions (i-ii) we recorded randomly from ~100 cells in both LGN and PGN for the experiments having stimulus (e) with conditions (i-iii) we also recorded from a grid of 20x20 cells (100 μm side, spacing 5 μm) in both LGN and PGN, centered on the 0,0 coordinate of visual space. We recorded spikes, membrane potential, excitatory and inhibitory conductances in all selected neurons.

TRIAL AVERAGED FIRING RATE. The first 100 ms from stimulus onset were discarded in order to get rid of the onset flashing transient effect (which would justify another study, and which are often omitted for non stationarity reasons in the experimental literature). Then the firing rate was calculated as the average number of spikes over trials per neuron for each stimulus. When a population measure is provided in the text, the average over neurons was also performed.

LOW-PASS INDEX. We used the index defined by Kimura et al. 2013 to describe the degree of spatial frequency tuning of firing rates to low spatial frequencies. It is computed as the ratio of the response magnitude at the lowest spatial frequency eliciting a response to that at maximal response.

END-INHIBITION INDEX. We used the index defined by Murphy and Sillito 1987 to describe the degree of size tuning in LGN cells, it is given by the percentage difference between the peak and the plateau of the size tuning curve, divided into bins from 1 (low suppression) to 10 (high).

SUPPRESSION INDEX. A measure similar to the above end-inhibition index, computed as follows:

$$SI = 1 - \frac{\text{Response to large gratings}}{\text{Response to optimal size grating}}$$

ORIENTATION BIAS. We used the index defined by Vidyasagar and Urbas 1982 to describe the degree of orientation tuning of LGN cells: it is measured, for each cell, by the ratio of the peak response to the optimal orientation relative to the response evoked in the non-optimal orientation. The results for all cells are grouped into bins from 1 (low bias) to 10 (high).

SIZE TUNING COMPARISON. This protocol is similar to that in Jones et al. 2012, see their methods for further details. The aim of this procedure is to compare the responses of LGN cells recorded when retinotopically overlapping and non-overlapping portions of cortex were intact or locally inactivated. The null-hypothesis is that the local inactivation of cortex does not change the activity of spatially identified (by having their RF overlapping or not with cortical cells in the inactivated portion) LGN cells. A different result in the inactivated-cortex condition will tell us that the inactivation DOES something. Therefore, we want to have a population measure of the affected LGN cells with and without inactivation. We performed the trial averaged firing rate for all recorded LGN cells. Then, we considered as null-hypothesis data the LGN responses obtained in the intact condition. If in the inactivated cortex condition some LGN cells significantly changed their response (non-parametric two-tailed Wilcoxon test, see below), then we inspected for which stimulus radius the change was happening: changes for the smallest radius eliciting the smallest response, changes for the radius eliciting the peak response, and changes for an average of the responses to large radii. The (mean over the cells) percentage amount of each change type was then reported.

STATISTICAL SIGNIFICANCE ASSESSMENTS. The biological question we are asking is whether the LGN activities are changed by the cortical feedback. Given that

we distinguished the experimental procedures into two conditions, control and variously inactivated feedback, we can formulate a null-hypothesis: “the LGN activities in the control and feedback-inactivated conditions are the same” and its corresponding alternate hypothesis. The experiments performed in the literature (that we replicated in our *in-computo* simulations) utilize two types of statistical tests depending on the kind of variable measured. For the ongoing activity and low-pass index of spatial frequency, we are dealing with a comparison of cells’ firing rates as measurement variable, therefore one-way ANOVA (or Wilcoxon, for non normal distributions with skewness test not passed) is used. For all other experiments, where the firing rate is measured at different step changes of a stimulus value, the results are grouped into two categories therefore two-sample t-test (or Welch, for non normal distributions with different standard deviations) is used, often because of small sample size and possibility of unequal variance. For the overlapping / non-overlapping surround suppression experiments, a non-parametric two-tailed test (Wilcoxon) is used, as in Jones et al. 2012. On the trial averaged firing rates, we also performed a statistical test for the null hypothesis “two related samples have identical average values” (as in Jones et al. 2012). In this case, the standard error of the mean was also computed.

4.7 Software stack

We modeled the thalamo-cortical loop using Mozaik (Antolik and Davison 2013, see code at <https://github.com/antolikjan/mozaik>). Mozaik is an integrated workflow framework for large scale neural simulations, intended to relieve users from writing boilerplate code for projects involving complex heterogeneous neural network models, complex stimuli and experimental protocols and subsequent analysis and plotting. It is built on top of the following tools:

- imagen (for stimuli generation)

- PyNN 0.8.0 (for simulator independent neural network model definition, see <http://neuralensemble.org/PyNN/>)
- NEST simulator 2.1.0
- Neo (for exchange and internal representation of data)
- matplotlib (for plotting)

Additional analysis code was written using the scipy library (<https://www.scipy.org/>). All the code is available online (see <https://github.com/dguarino/T2>). Experimental data were digitized by scraping the original published material using WebPlotDigitizer 3.11 (<http://arohatgi.info/WebPlotDigitizer>).

5 Results — overview

5.1 The model and its flavors

To gain insight into the function of the corticothalamic loop, it is important to bridge the gaps in our knowledge, by consolidating the experimental findings into a single coherent whole. In pursuit of this goal, we have built a large-scale, biologically detailed model of the cat thalamo-cortico-thalamic loop that accounts for an unprecedentedly broad range of experimental findings, provides mechanistic understanding of this neural system, and informs future experiments.

The model was constrained by connectivity statistics determined in anatomical studies, single cell electrophysiological properties *in vitro* and *in vivo*, and functional measures of the evoked firing statistics in the intact and lesioned early visual system (Figure 1a). During development of the model and its validation, we have adopted an iterative approach that gradually incorporates the available experimental findings into a pluripotent model with a single parameter set, following similar integrative strategies to those pursued in Antolik et al. (2018) in modeling V1. This approach enabled us to iteratively increase the experimental constraints on the parameters of the model, reducing the risk of overfitting with its consequent loss of explanatory power.

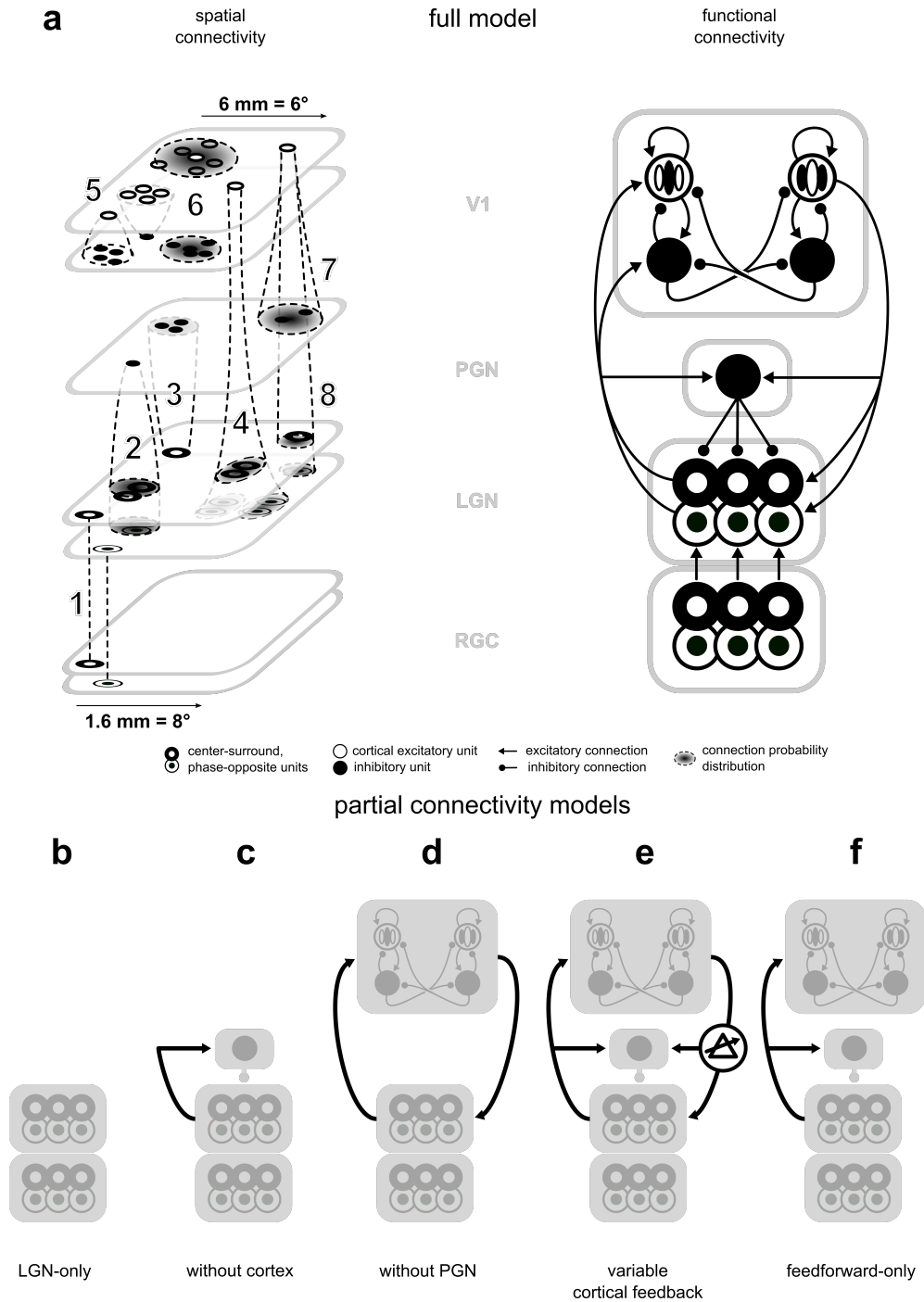


Figure 5.1 The model and its flavors. (a) Model components and connectivity, spatial (left, retinotopically organized) and functional (right). From the bottom: A phenomenological model of X retinal ganglion cell (RGC) sends its outputs to thalamus for two response subgroups with distinct center-surround phase opponency (ON-center (white/empty inner disk), OFF-center (dark/filled inner disk), represented by center-surround phase-opponent circles and annuli. Each RGC output excites (ascending arrows, right) a responsive LGN principal cell with the same phase opponency (1, left). Each PGN inhibitory cell (filled circle) afferent RF is formed by sampling connections

from a probability distribution defined by a Gaussian function overlaid on both ON- and OFF-center LGN cells (2). LGN afferents from PGN are formed by sampling connections from a similar Gaussian-defined distribution overlaid on PGN (3). Primary visual cortex (V1) excitatory (empty circle) and inhibitory (filled circle) cells afferent RFs are formed by sampling connections from a Gabor-defined probability distribution overlaid on the ON- and OFF-center LGN cells (4), with positive parts of the Gabor function overlaid on ON-center and negative on OFF-center sheets (and vice-versa for the opposite phase preference). V1 excitatory-to-inhibitory and inhibitory-to-excitatory connections (5) realize a push-pull connectivity, with each excitatory cell being the target of inhibitory cells of opposite phase (top right), and with distance-dependent lateral connections formed by sampling connections from a probability distribution defined by a hyperbolic function (6). Cortical feedback connections to the thalamus (excitatory, descending arrows on the right) are formed by sampling connections from Gaussian-defined probability distributions overlaid on PGN (7) and LGN (8) populations (see Chapter 4 - Methods for details on the parameter set). (b-e) Partial connectivity models. Only the connections between layers are affected by changes in, grayed elements were untouched. (b) *LGN-only*, where LGN was driven only by RGCs. (c) *Without cortex*, corresponding to the open-loop condition from a thalamus-centered viewpoint, where LGN was driven by both RGCs and PGN cells. (d) *Without PGN*, where only the feedback from PGN to LGN was inactivated. (e) *Variable cortical feedback*, where the cortical activity was spatially modulated (represented by a variable amplifier symbol). (f) *Feedforward-only*, open-loop condition from a cortical-centered viewpoint, where there was no feedback from cortex to thalamus.

We probed the model with six different types of stimulus, in five experimental configurations, each corresponding to a specific subset of connectivity patterns, which account for the majority of stimulation protocols and preparations used in experimental studies of the cortico-thalamic loop. All the experimental studies we considered compared the responses of neurons in the early visual system recorded in a control condition (Figure 5.1a) — where the visual pathway and its embedded loops are left intact — against various open-loop and altered-feedback configurations (Figure 5.1b-e).

To maintain consistency with the literature, our analysis reiterated, *in-computo*, the experimental comparison between intact and lesioned pathways, using conditions and stimuli as in the original studies. However, we also followed what we could label as a “constructionist” approach to

appreciate, both at the thalamic and cortical level, how receptive field features and global functional organizations were shaped or modified by adding feedback loops, up to the level of functional specificity of the intact early visual system.

5.2 The “constructionist” approach

The choice of a label — “constructionist” — for our approach, which is part of integrative computational neuroscience (Gerstner et al. 2012), is used here to underline the acquisition of additional knowledge during the process of inserting incrementally new feedback loops until the complexity of the intact system is fully implemented. At a more conceptual level, this “constructionist” approach can be seen as, rooted in the works of Piaget (1964) and Papert (Papert and Harel 1991). In our case, each configurational step (see Figure 5.1b-f, partial connectivity models: LGN-only, without cortex, etc.) is interacting with and leveraging on the knowledge acquired previously to yield additional explanations.

Building on the experience gained in previous approaches in the lab, engineered by Jan Antolik (Antolik et al. 2018), this “constructionist” approach is also meant to refine the strategy of increasing the constraints on model parameters. In the process of building a model, the modeler is faced with the question of why a new parameter should be added. The genesis of a novel functional feature, which was not apparent before adding this parameter, may be taken as a sufficient reason. This approach might be justified by stating that it is a documented biological feature and therefore should be added. But, this iterative approach does not fulfill one of the purposes of modeling, which is to provide a parsimonious explanation for the presence of experimentally observed features. Hence one should add a parameter/feature to a model only when the initial model cannot reproduce the experimental result it is made to account for. In our work, here, we apply this piecewise iterative process, dissecting what circuits do by taking the

simplest model and showing how each new parameter (in our case each new 'loop') builds and interacts with previous ones.

5.3 Thalamus-centered and Cortex-centered viewpoints

Along the visual pathway the first stage of integration after the eye is the thalamus therefore, in the next chapter, we adopted a *thalamic-centered point of view*. Feedforward information from the retina is processed by the LGN principal cells (Figure 5.1b: *LGN-only* configuration). Then, step-by-step, we introduced feedback loops, starting from that intrinsic to the thalamic level (LGN→PGN→LGN, Figure 1c: *without-cortex* configuration), followed by those proceeding from cortex to thalamus (LGN→V1→LGN, Figure 5.1d: *without-PGN* configuration, and LGN→V1→PGN/LGN, Figure 1e: *variable cortical feedback* configuration). At each step we compare the model performance with that observed for the full closed loop configuration (Figure 5.1a).

The second stage of integration concerns the impact of the corticothalamic feedback on the mesoscopic functional organisation of the cortical network. Therefore in the following chapter we will switch to a cortex-centered viewpoint. We will compare a cortical open-loop condition, lacking only the feedback from cortex to thalamus (Figure 5.1f: *feedforward-only* configuration), and the *full* configuration (Figure 5.1a).

Our results provide both phenomenological and mechanistic explanations for specific functional features and offer testable predictions for further exploration of the role of thalamo-cortical loop in low-level perception.

6 Thalamus-centered viewpoint

Using a thalamus-centered viewpoint, we analyze the role of intrathalamic feedback, and then add the cortical feedback to discern its functional contribution to the already existing thalamic computations.

First, to showcase our “constructionist” approach, we present how LGN spatial frequency selectivity changes across connectivity patterns of incremental complexity. (i) In the LGN-only configuration, LGN responses inherit retinal spatial selectivity (Figure 5.1b). (ii) In the without-cortex configuration, the addition of intrathalamic inhibition from PGN increases LGN tuning selectivity, (Figure 5.1c). (iii) In the full configuration, the cortical feedback smooths such selectivity, (Figure 5.1a). (iv) In the without-PGN configuration, the increased selectivity is lost when only the intrathalamic inhibition is removed (Figure 5.1d).

Second, following the same approach, we present how LGN extra-classical surround suppression changes across models. (i) In the *LGN-only* configuration, LGN responses show no surround suppression when driven by retina. (ii) With the addition of PGN, in the *without-cortex* configuration, we provide a mechanistic explanation of how the spatial structure of LGN→PGN→LGN interactions produces a small degree of extra-classical surround suppression of LGN responses, even in the absence of any cortical feedback. (iii) The comparison of *without-cortex* and *full* configurations, which is an approach commonly seen in the experimental literature, shows how cortical feedback enhances LGN surround suppression. (iv) By selectively

suppressing spatially identified portions of cortex in the *variable-cortical-feedback* configuration (Figure 5.1e), we deepen our understanding of how the contribution of corticothalamic feedback enhances thalamic center-surround opponency.

Third, we present how LGN contrast sensitivity changes between models: (i) In the *without-cortex* configuration, the intrathalamic LGN-PGN interplay confers to thalamic responses a range of contrast sensitivity; (ii) In the *full* configuration, cortical feedback changes the balance of excitation, extending the LGN dynamic range of contrast sensitivity.

Fourth, we present how LGN acquires sensitivity to stimulus orientation: (i) In the *without-cortex* configuration, the thalamus alone presents no orientation selectivity; (ii) In the *full* model, the corticothalamic feedback introduces an orientation preference in the responses in both LGN and PGN.

Finally, we analyze more complex dependencies on cortical feedback of the thalamic response to two stimulus features: mean luminance of uniform background and temporal frequency of drifting gratings.

6.1 Role of PGN in LGN spatial frequency tuning

Most neurons along the early visual pathway respond best when a sinusoidal grating of a particular — preferred — spatial frequency is presented in their receptive field (Enroth-Cugell and Robson 1966, Bisti et al. 1977, Linsenmeier et al. 1982). For LGN X cells, spatial preference is inherited from RGC afferents, with response amplitude both frequency- and stimulus-dependent. At high spatial frequencies the transfer ratio (ratio of input and output spikes) is high (Cheng et al. 1995), but at low spatial frequencies (below 0.5 cycles/deg) the transfer ratio is low (Cudeiro and Sillito 1996). To date, it is not clear what is the mechanism that LGN neurons adopt to perform such signal transfer modulation.

In order to dissect how the thalamocortical network structure and its embedded loops affect the response to stimuli varying in spatial frequency, we compared the responses of our *LGN-only* (Figure 5.1b), *without-cortex* (Figure 5.1c), *without-PGN* (Figure 5.1d), and *full* (Figure 5.1a) configurations. For all configurations, we used full-field drifting grating of varying spatial frequency (10 stimuli, logarithmically spaced, from 0.07 to 8 degrees, see Chapter 4 - Methods, spatial frequency protocol), and we recorded from LGN cells (n=243, 110 X-Off and 133 X-On), sampled across a grid spanning a disk of 300 μm radius. The activity of PGN cells (n=55, same recording grid) was also recorded in the *without-cortex* and *full* configurations.

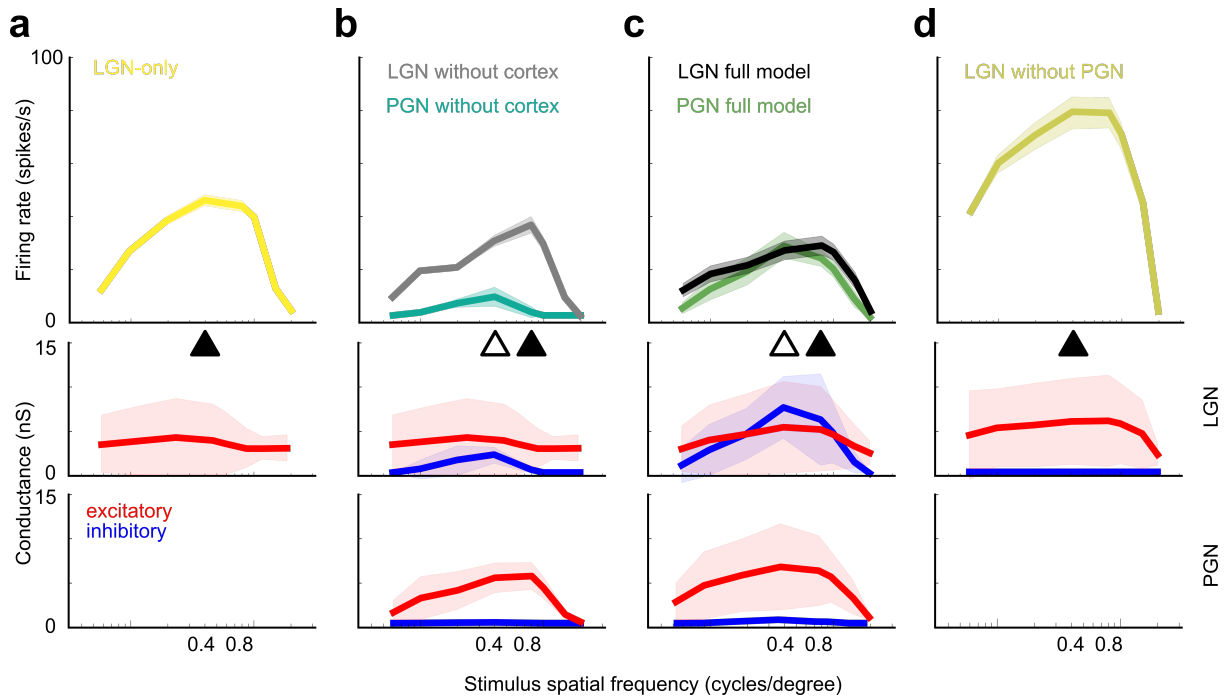


Figure 6.1. Role of PGN in LGN spatial frequency tuning. (a-d) Top row, population firing rates for several LGN models, averaged over trials (the error bars capture only the trial-to-trial variability). Bottom rows, excitatory (red) and inhibitory (blue) conductances for LGN (second row from the top) and PGN cells (bottom row). We show only the results for On-center cells, Off-center responses being qualitatively the same. In the *LGN-only* configuration (a), the preferred spatial frequency is 0.4 cycles/degree (black empty arrowhead). In both *without-cortex* (b) and *full* (c) configurations, the peak response in PGN is also observed at that same frequency (grey empty arrowhead) but the peak in LGN shifts to a higher 0.8 cycles/degree (black empty arrowhead). This shift is absent in the *without-PGN* configuration (d). The trial averaged conductances show that, in the *without-cortex* configuration (b), PGN→LGN inhibition peaks at 0.4 cycles/degree, as PGN

firing rate. It reduces LGN firing from its overall higher levels of the *LGN-only* configuration, leaving a larger response for spatial frequencies between 0.4 and 0.8 cycles/degree. The cortical feedback, in the *full* configuration (c), raises directly LGN excitatory conductances and indirectly LGN inhibitory conductances through PGN, without changing their peaks. The removal of LGN inhibitory conductances, in the *without-PGN* configuration (d), releases again the LGN response for frequencies around the 0.4 cycles/degree peak.

The *LGN-only* configuration response (Figure 6.1a, yellow mean line and shaded SEM) peaked at 0.4 cycles/degree, with cut-off for frequencies above 0.8 cycles/deg, as expected from the RF properties of RGCs and the absence of any LGN recurrence. In the *without-cortex* configuration (Figure 6.1b), when the loop between PGN and LGN was closed, PGN cells inherited LGN firing rate response properties (green mean line and shaded SEM), with optimal response at 0.4 cycles/deg. As an effect of PGN feedback inhibition, the LGN peak response shifted to 0.8 cycles/deg. Similarly, in the *full* model (Figure 6.1c), PGN peaked at 0.4 cycles/deg and LGN peaked at 0.8 cycles/deg. Such a shift must result from the PGN feedback because it did not appear in the *without-PGN* configuration (Figure 6.1d), where the LGN response peaked at 0.4 cycles/deg, as in the *LGN-only*. The firing rate tuning curves indicated that the LGN mean response to spatial frequency-modulated stimuli (28 ± 10 spikes/s) was initially inherited from the afferent RGCs. LGN above-mean responses operated a band-pass of only the 0.2-1.0 spatial frequency interval. Once connected, PGN received LGN responses for that frequency band and fed back its corresponding response as inhibition to LGN, with its mean response raised but not shifted by cortical feedback. The result was that LGN peak responses were shifted towards higher frequencies.

This interpretation is supported by comparing the trial averaged excitatory and inhibitory conductance tuning curves (Figure 6.1, corresponding panels below each firing rate tuning curve). In the *LGN-only* configuration, the RGC-driven total excitatory synaptic conductance peaked at 0.4 cycles/deg. The introduction of PGN, in the *without-cortex* configuration, provided the LGN with inhibitory conductances peaking similarly at 0.4 cycles/deg, which did

not affect the excitatory conductances for higher frequencies, resulting in the shift of preferred spatial frequency. The introduction of cortical feedback, in the *full* configuration, did not change frequency selectivity in either LGN or PGN. It rose, however, the level of both excitatory and inhibitory mean input conductances for the LGN.

The *LGN-only* configuration did not allow a direct comparison to LGN electrophysiological data, given that there is no available in-vivo preparation to record the LGN cell responses to only retinal spikes. However, we used the overall retinogeniculate spiking transmission reliability estimated by Weyand 2007 (see Chapter 4, Methods) and recorded retinal drive to LGN (consisting of S-potentials from the optic tract, Cheng et al. 1995, Kocbach et al. 2001) to set model responses for spatial frequency modulated stimuli.

A possible role for PGN feedback to LGN in spatial frequency tuning was proposed by Kimura et al. 2013, based on the effects of iontophoretic application of GABA_A receptor antagonists (Bicuculline and Gabazine). These antagonists inactivate PGN inhibitory inputs to LGN, a condition we reproduced in our without-PGN configuration, Figure 6.1d. Kimura et al recorded responses to full-field drifting gratings of varying spatial frequency and compared the responses of (n=39) LGN cells in the presence or absence of PGN inhibition by using a low-pass index, i.e. ratio of responses to the lowest spatial frequency to responses at the optimal spatial frequency. The low-pass index was significantly higher in their PGN inactivated condition (control 0.59 ± 0.04 vs PGN inactivated 0.75 ± 0.04 , ANOVA $p < 0.001$), with 84.6% experimental data points above the identity line. The same cells showed no significant change at the spatial frequency eliciting their maximal response (control 0.35 ± 0.03 vs PGN inactivated 0.34 ± 0.03 , $p = 0.61$) nor in spatial frequencies above peak (control 0.96 ± 0.07 vs PGN inactivated 0.98 ± 0.07 , $p = 0.87$). In comparing our full and without-PGN configurations, we found in our simulations a similarly significant effect in the low-pass index, with 76.5% of model data points above the unity line (full 0.69 ± 0.007 vs without-PGN 0.73 ± 0.002), while no change was observed both at the peak

frequency (full 0.49 ± 0.05 vs without-PGN 0.48 ± 0.02 , $p=0.91$) or above (full model 0.34 ± 0.07 vs without-PGN 0.4 ± 0.01 , $p=0.78$). In their discussion, Kimura et al. 2013 proposed that these results could be due to a PGN preference for low frequencies. With our modeling results, we give a more quantified interpretation: PGN overall preference is inherited from LGN input but, by mirroring back to LGN its own preference, PGN reduces the transfer of some frequencies, resulting in a shift of LGN peak.

Note that our simulations exhibited significantly less neuron-to-neuron variability in the low-pass index than the experimental data. This was however expected given the numerous sources of variability present in biological networks and lacking in our model, such as neuron-to-neuron variability in the total synaptic strength from individual pathways (which was kept constant in the model), neuron-to-neuron variability of the intra-cellular properties, and potential active sources of noise along the whole thalamo-cortical pathway.

6.2 Extra-classical surround suppression is caused by intra-thalamic inhibition

The spatial extent of the receptive fields found in the early visual pathway are generally non-monotonous functions of the stimulus size. For small sizes, responses increase as excitation is dominant. Beyond a critical size, responses saturate and then decrease because of larger recruitment of antagonistic inhibition. Unexpectedly, though, increased suppression is expressed beyond the classical surround of LGN neurons (Cleland et al. 1983). The origin of this additional suppression is still a matter of debate. It has been attributed by some authors to cortical feedback (Murphy and Sillito 1987, Jones and Sillito 1994, Jones et al. 2000, de Labra et al. 2007). Other authors proposed a retinal origin, further amplified by the thalamus (Alitto and Usrey 2008, 2015). To study this phenomenon, we compared the responses of the LGN when driven only by retinal feedforward excitatory

inputs (*LGN-only* configuration) to those when receiving in addition the feedback of inhibitory inputs from the PGN (*without-cortex* configuration). For both models, we used as stimuli circular patches of drifting gratings of varying radius (logarithmically spaced from 0.12 to 4.7 degrees, see Chapter 4 - Methods, size tuning protocol), and we recorded the activity of LGN cells ($n=243$, 110 X-Off and 133 X-On), in a circular grid of 300 μm radius, centered on the stimulus. The activity of PGN cells ($n=57$, same recording grid) was also recorded in the *without-cortex* configuration.

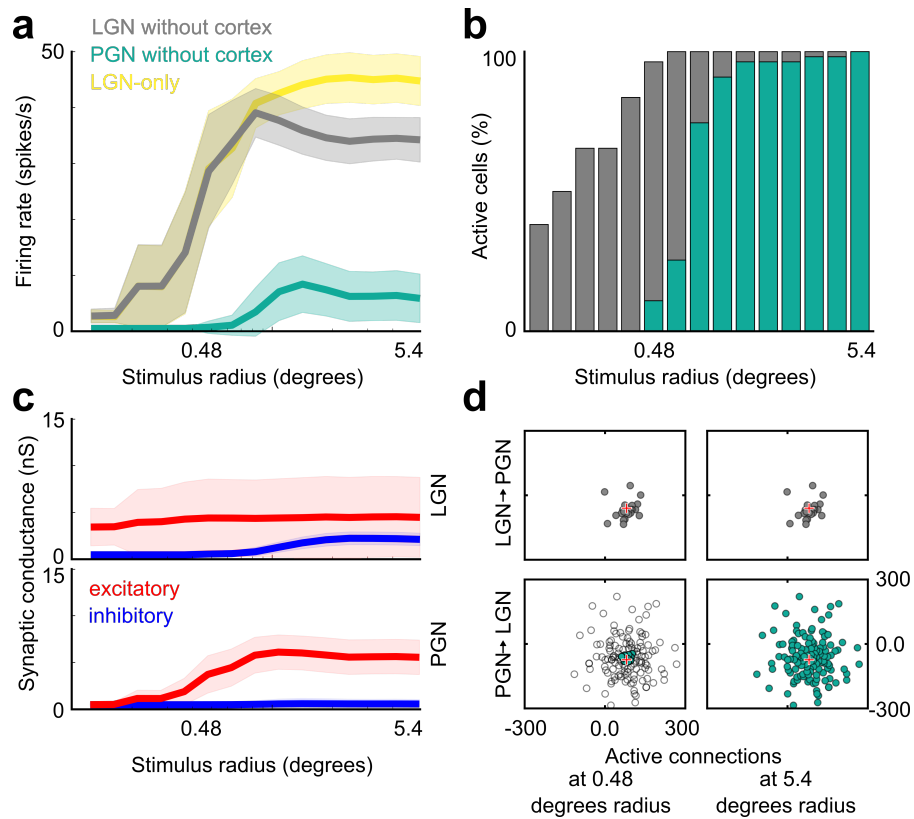


Figure 6.2. Surround suppression in the thalamus in the absence of cortical feedback. (a) Population trial-averaged size tuning curves (with shaded SEM) for the LGN-only model (yellow), without-cortex model (grey), and PGN driven only by LGN (green). (b) Percentage of responsive LGN and PGN cells increasing stimulus radii (same color-coding as panel a). Mean spontaneous activity levels in the simulations were respectively 1.63 ± 1.2 spikes/s for LGN and 1.12 ± 0.8 spikes/sec for PGN. Note the difference between LGN and PGN in the minimum size eliciting the response. (c) Size tuning of excitatory (red) and inhibitory (blue) conductances (with shaded SEM) in the LGN (X-OFF) and PGN. In the LGN, the excitatory conductance dominated for all stimulus sizes. However, the inhibitory conductance increased beyond a 0.48° radius corresponding to the PGN increase in excitatory inputs from the LGN. (d) Active

connections, with their spatial relationships (in μm) for a representative LGN X-OFF cell (red cross) at 0.48° and 5.4° stimulus radii. Upper row, the cell was active at 0.48° therefore all ($n=22$) its LGN→PGN connections were active. Lower row, out of all ($n=123$) PGN→LGN connections to the reference cell, a 0.48° stimulus recruited few ($n=11$, green dots) PGN connections. Only a stimulus of 5.4° radius recruited the totality of PGN cells connected to the reference LGN cell.

The comparison between the response of the LGN-only (Figure 6.2a, yellow curve) and the without-cortex configurations (Figure 6.2a, grey curve) showed a significant reduction (28.5%, Welch t-test, $p<0.001$) of the average response of the LGN cells for large stimulus sizes, which could only be attributed to impact of the PGN feedback (Figure 6.2a, green curve). By measuring the percentage of LGN and PGN cells progressively recruited with the increase of stimulus size, we found that the percentage of LGN cells firing above ongoing activity increased with stimulus size (8.5 ± 7.9 growth rate, Figure 6.2b). The percentage of active PGN cells also increased with stimulus size but its recruitment threshold was found for sizes above 0.5 deg radius and its growth rate was steeper (11.0 ± 18.8 , Figure 6.2c).

The differential increase in the number of cells in LGN and PGN recruited by increasing stimulus sizes, led us to hypothesize that the balance of LGN excitation and inhibition could shift from an excitation-prevalent regime at small sizes, where the retinothalamic drive was the main component of LGN responses, to a more balanced regime at large sizes, where the inhibition from PGN counter-balanced direct excitation. Our simulations supported this hypothesis. By plotting the excitatory and inhibitory synaptic conductances against stimulus size (Figure 6.2c), we observed that LGN excitatory conductance grew with the stimulus size up to a plateau, while LGN inhibitory conductance started to grow only with larger stimuli, but also grew faster, in correspondence with the increase in firing of PGN cells. These results resulted from the experimental constraints we introduced in modeling intra-thalamic connectivity. Based on morphological and functional studies (Friedlander et al. 1979, Alonso et al. 2006, Lam and Sherman 2005), the spatial spread of LGN→PGN excitatory connections was set to $75 \mu\text{m}$

(radius). The spatial spread of PGN→LGN inhibitory connections was set to 150 μm (Cucchiaro et al. 1991, Sanchez-Vives et al. 1997). At the physiological level, synaptic efficacy was higher for LGN→PGN connections (1.9 ± 1.8 nS, Golshani et al. 2001) than for the feedback LGN→PGN connections (0.5 ± 0.1 nS, Cox et al., 1996, Lam and Sherman, 2011). Thus, LGN→PGN excitatory connections were narrower and stronger than the broader and weaker PGN→LGN inhibitory connections. This arrangement resulted in a dynamical shift from excitation-driven responses at small sizes (Figure 6.2d, top row) to inhibitory-balanced responses at large sizes (Figure 6.2d, bottom row).

Taken together, the mechanistic explanation provided by our *without-cortex* configuration was that when progressively increasing the stimulus size, the recruitment of antagonistic inhibition from PGN cells was first weak, since the active LGN cells were below or close to PGN spatial integration threshold. But, once the stimulus was activating enough LGN cells and the PGN recruitment threshold was sufficiently trespassed, the overall responsiveness gain of PGN grew stronger than that of LGN, such that the inhibitory PGN feedback contribution overcame the excitatory LGN drive.

With respect to experimental evidence, the *LGN-only* configuration stands aside because of its over-simplified instructive purpose, as in the previous section. However, we took experimental measures of RGC suppression index — ratio of larger-than-optimal to optimal stimuli responses — and we compared them with those resulting from our model. In cat, Fisher et al. (2017) reported an RGC suppression index of 0.14 ± 0.02 ($n=1$ X-cell, and $n=14$ Y-cell), similar to that reported by Alitto and Usrey (2008) in primate (0.15 ± 0.06 , $n=3$ parvo-cellular and $n=9$ magno-cellular cells). Our *LGN-only* configuration produced a lower suppression index of 0.06 ± 0.03 . However, there are two considerations to take into account, one regarding our model and the other regarding the experimental measures. First, our modeling efforts were focused on the X pathway, and to model the response of RGCs, we used the classical Difference of Gaussians (DoG) model, with two

Gaussian functions, one for the excitatory center opposed to one for the inhibitory surround (Rodieck, 1965, Cai et al., 1997). This model produces an X-like reduced surround suppression in response to large patches of sinusoidal drifting gratings (Einevoll and Plesser, 2005). Second, the experimental studies are faced with the relative paucity of cells for which all stimulation protocols could be performed, which often leads experimenters into pooling together RGC X- and Y-cells. However, Y-cells have greater nonlinear surround suppression than X-cells (Barlow et al. 1977, Shapley and Victor 1979, Enroth-Cugell and Jakiela 1980, Passaglia et al. 2001; similarly in primate, Solomon et al. 2006). In addition, the X- and Y-RGCs have segregated projections to cells in the thalamus, which also differ in morphology (both body size and dendritic arbors, Sherman and Guillery 2001, pages 34-41). Therefore those experimental measures of surround suppression should be considered with care since more Y- than X-cells were recorded.

The results of our *without-cortex* configuration will be discussed and compared with the available literature in the next section.

6.3 Extra-classical surround suppression in LGN cells is enhanced by cortical feedback

LGN cells, recorded when primary visual cortices (areas 17, 18, and 19) are ablated or pharmacologically inhibited, have a lower suppression index than those having an intact cortical feedback to thalamus (Murphy and Sillito 1987). The apparent role of cortical feedback seems therefore to enhance the existing intra-thalamic selectivity presented in the previous section.

In order to assess the presence and amount of cortical enhancement of thalamic suppression, we compared the responses of our *without-cortex* and *full* configuration. As above, we stimulated both model configurations with circular patches of drifting gratings of varying radius, and recorded the

activities of LGN (n=243, 110 X-Off and 133 X-On), and PGN cells (n=57, same recording grids as above).

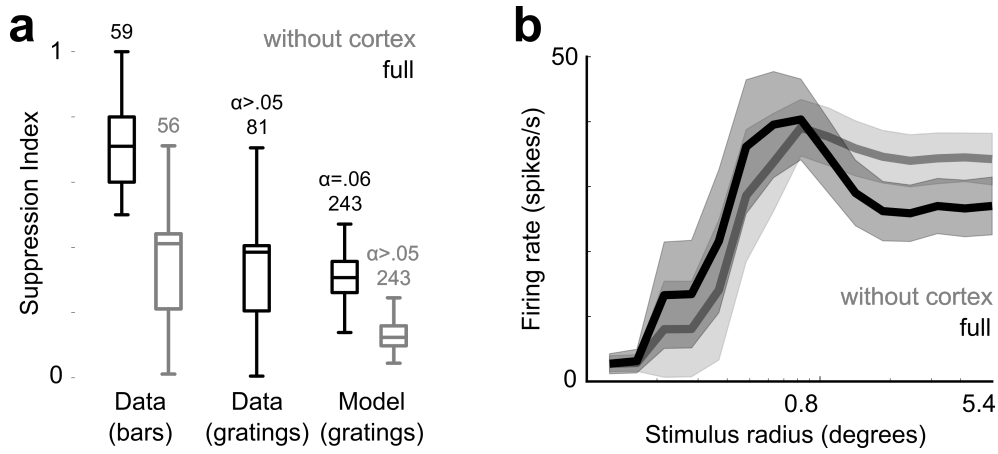


Figure 6.3. Surround suppression of LGN responses. (a) Suppression indices in the literature (left and middle) and our model (right). The experimental data for drifting bars (left, control, in black, vs ablated cortex, in grey) from Murphy and Sillito 1987 shows a reduction of suppression when cortex is ablated. The experimental data for drifting gratings (middle, control, in black) come from the study of Alitto and Usrey 2015. Model data (right, *full*, in black, vs *without-cortex*, in grey) show a reduction which is both in line with the gratings data and qualitatively comparable to the available experimental data. On top of each box, the number of recorded cells. For the control gratings data and both conditions of the model, also the index of normality (α) is reported. (b) LGN trial averaged size tuning curves for the *full* (black curve, with shaded SEM) and *without-cortex* model configuration (grey, with shaded SEM). Notice, in the *full* model, the shift in LGN optimal stimulus size, together with significantly higher peak and lower plateau.

We measured a significant reduction (43.3%) of average suppression index between *full* and *without-cortex* configurations (from 0.29 ± 0.01 to 0.16 ± 0.01 , Welch t-test, $p < 0.001$, Figure 6.3a, right black and grey boxes respectively).

Looking at the responses in more detail, adding cortical feedback changed the response in a stimulus-size-dependent manner (Figure 6.3b, respectively black and grey curve with shaded SEM). We observed that the *full* model showed a significant increase in mean response at optimal sizes (+16.1%, Welch t-test $p < 0.001$), whereas it produced a significant decrease of mean response for larger-than-optimal sizes (-18.3%, Welch t-test, $p < 0.001$).

Comparing our results with the available literature is straightforward. The reduction of suppression index scores measured in our *without-cortex* configuration was in qualitative agreement with the in-vivo experimental results reported by Murphy and Sillito (1987) who recorded (n=56) LGN X cells from cats with either intact or ablated cortical areas 17 and 18. They found a significant reduction (35.5%) of the average suppression index between control and ablated cortex conditions (from 0.71 ± 0.02 to 0.43 ± 0.02 , t-test, $p < 0.001$), as shown in Figure 6.3a (left black and grey bars for control and ablated cortex respectively).

The suppression index measured in our *full* model was also in agreement with the suppression index (0.43 ± 0.02) measured in the control condition (Figure 6.3a) and reported by Alitto and Usrey (2015, for cat, but also similar to that reported in an earlier study by Alitto and Usrey 2008, for macaque). In addition, the normality of our distribution of suppression index values fitted with their own report based on n=81 cells..

Our models predicted the same qualitative difference between the *full* and *without-cortex* configurations as Murphy and Sillito (1987), while matching the absolute magnitude of the inhibition reported by Alitto and Usrey (2015). The difference between experimental studies can be partially attributed (as in the previous section) to the fact that Murphy and Sillito (1987) included in their study both X- and Y-cells (unfortunately the exact number of each cell type was not reported), while Alitto and Usrey pooled a population largely dominated by X-cells (X-: n=61,; Y-:n=15, unclassified: n=5). Unfortunately the latter study did not include a condition where cortical feedback was inactivated. In addition, such experimental variability could also be due to differences in responses evoked by different stimuli (bars vs gratings).

The overall size tuning selectivity of LGN firing responses of both *without-cortex* and *full* model configurations is also in line with the available literature. By using muscimol infusion over cat visual cortical areas (17, 18, and 19), Andolina et al. (2012) reported a significant reduction of mean LGN

responses for drifting grating stimuli of preferred size (-20.9%, t-test $p=0.017$), together with a significant increase of mean response for larger-than-optimal stimuli (+31.6%, $p<0.001$) (see also Fisher et al. 2017). Similarly, comparing our *full* vs *without-cortex* model configurations, we found that the absence of corticothalamic feedback significantly lowered LGN peak responses at preferred size, while also not suppressing larger-than-optimal stimuli (Figure 6.3b).

These studies also pointed to the possibility that the influence of an individual corticofugal cell onto its thalamic target could depend on the spatial relationship between their receptive fields. We investigated this phenomenon in the next section.

6.4 Center-surround opponency in LGN cells is enhanced by cortical feedback

When studied at single cell level, the effects of cortical feedback onto thalamus are not homogeneous. The seminal work by Tsumoto et al. (1978) showed that spatial relationships between the RFs of V1 cells and their target LGN cells determined the sign of the corticothalamic modulatory effect on LGN responses. By boosting V1 cell responses (to moving bars) with local release of glutamate, they observed response enhancement in LGN cells having spatially overlapping receptive fields with the boosted V1, while response suppression for spatially non-overlapping receptive fields. Other studies have reported similar results, but the underlying mechanism for such opponency is still unresolved.

We studied this phenomenon by comparing the responses of our *full* and *variable-cortical-feedback* configurations (Figure 5.1e). As before, we stimulated our model with circular patches of drifting gratings of varying radius, and recorded the activity of LGN cells ($n=39$, 20 X-Off and 19 X-On), and PGN cells ($n=15$). In addition, we mimicked in our simulations an

experimental strategy implemented by Jones et al. 2012 by removing in a spatially controlled manner the cortical feedback from recorded LGN cells. For this purpose, we focally inactivated sets of cortical excitatory cells (covering a circular area of $\sim 600\ \mu\text{m}$ diameter, by directly injecting negative rectangular currents steps of $-0.5\ \text{nA}$, for the whole duration of the stimulation). Cortical cell responses were grouped, according to their RFs center positions with respect to LGN RFs positions, in two categories: *overlapping* — when cortical RFs subtended an area of visual space containing that of the recorded LGN cells — or *non-overlapping* — when their RF subtended nearby (within $\sim 400\ \mu\text{m}$) but different areas of visual space than those sampled by the recorded LGN cells.

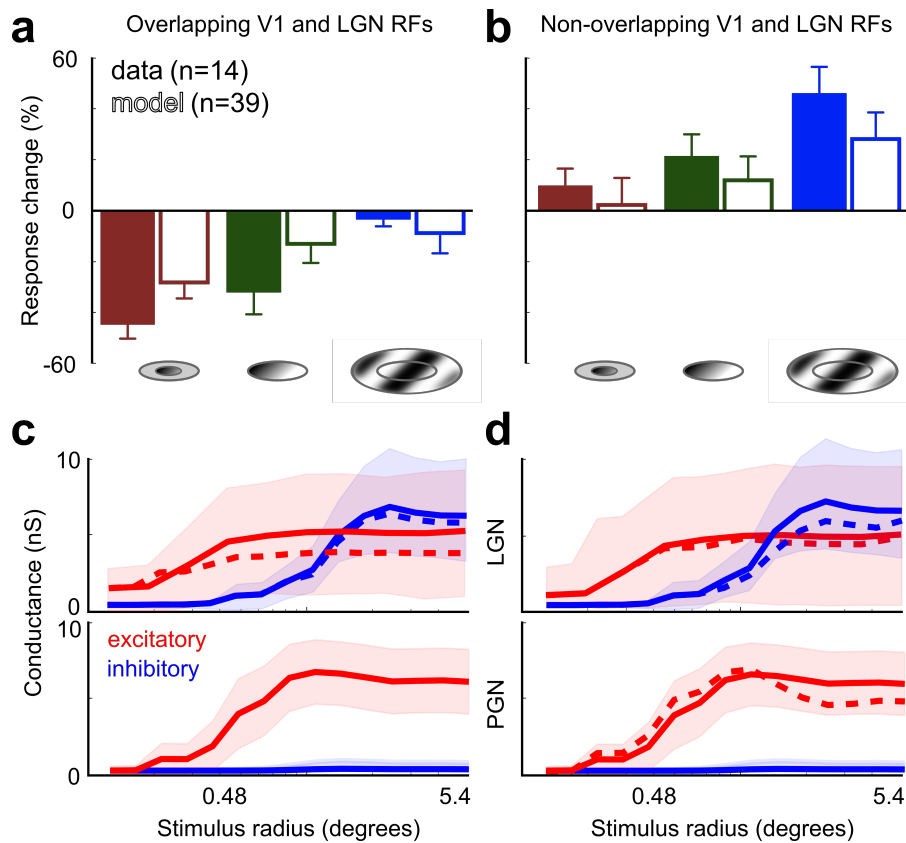


Figure 6.4. Dependence of size tuned LGN responses on the degree of retinotopic overlap between cortical and LGN receptive fields. (a,b) Population summary histogram of the mean percentage change in LGN cell responses between *full* and *variable-cortical-feedback* configurations (empty bars), and between intact and locally-inactivated cortex as in Jones et al. 2012 (filled bars). When V1 and LGN RFs are overlapping (a) a large negative change is observed for smaller-than-optimal stimuli

(brown), while the change is limited for optimal (green), and larger-than-optimal (blue) stimuli. For non-overlapping V1 and LGN RFs (**b**) the trend is opposite, with the largest change occurring at larger-than-optimal sized stimuli. (**c,d**) Trial averaged excitatory (red) and inhibitory (blue) synaptic conductance tuning curves for model LGN cells for two categories of receptive fields: overlapping (**c**; left column) and non-overlapping (**d**; right column) with V1 inactivated sites. Mean and SEM values of control tuning responses are represented by solid curves and shaded envelopes. The *variable-cortical-feedback* configuration is represented by dotted curves. When the overlapping cortical sites are inactivated (**c**), only the excitatory conductance is reduced appreciably, whereas no or minimal change is observed in the evoked inhibitory conductance. When non-overlapping cortical sites are inactivated (**d**), the model prediction is reversed: the inhibitory conductance is lower while the excitatory conductance profile is essentially unchanged.

As in Jones et al. 2012, we compared the LGN responses obtained in the *full* model to those recorded in the *variable-cortical-feedback* model configuration, when the cortical cells were inhibited for both the overlapping and non-overlapping subsets. We measured the percentage change of response in the LGN cells based on three stimulus size ranges: (i) smaller-than-optimal stimuli, (ii) optimal stimuli, and (iii) larger-than-optimal stimuli.

When we inactivated the overlapping cortical group, the recorded LGN responses (Figure 6.4a) showed a significant decrease (-29.3%) for less-than-optimal sizes (brown bars; Wilcoxon matched pair test, $p=0.001$), together with smaller decreases for optimal (-16.7%, green bars) and for larger-than-optimal sizes (-9.1%, blue bars).

When we inactivated the non-overlapping cortical group, the recorded LGN cells (Figure 6.4b) resulted in a significant increase (+6.5%) for larger-than-optimal sizes (blue filled bar; Wilcoxon matched pair test, $p=0.002$), together with smaller increase for optimal (+13.2%, green filled bar) and smaller-than-optimal sizes (+2.4%, brown filled bar).

We used our model to gain a mechanistic understanding of the experimental results for the overlapping and non-overlapping conditions. Considering the connectivity constraints we adopted (the larger footprint of $V1 \rightarrow PGN$ compared to $V1 \rightarrow LGN$ connections, together with their relative synaptic

efficacy), we hypothesized that the corticothalamic feedback had an excitatory center and an inhibitory surround organization. Hence the effective functional impact of the disynaptic inhibitory pathway combining V1→PGN→LGN was broader than the direct monosynaptic excitation mediated by the V1→LGN connections. Consequently, each time a stimulus engaged overlapping cortical and thalamic receptive fields, a corticothalamic enhancement of LGN center responses was generated through the direct excitatory pathway, together with an enhancement of suppressive surround through the broader indirect inhibitory pathway.

This hypothesis was supported by the size-selectivity curves of the excitatory and inhibitory input conductances. Our simulations showed indeed that, when suppressing cortical activation in regions in register with the activated thalamic receptive fields (Figure 6.4c), the withdrawal of cortical feedback excitation led to a reduced thalamic response at small/optimal stimulus sizes, while at large sizes the inhibition was still dominant (in line with Figure 6.2c). In contrast, in non-overlapping receptive field regions, suppression of cortical feedback (Figure 6.4d) resulted in a withdrawal of indirect additional inhibition coming disynaptically from cortex, which consequently led to an enhanced response at large stimulus sizes, while at small sizes both the feedforward and feedback inhibitions were less engaged.

Our *variable-cortical-feedback* configuration was explicitly shaped and tested to recreate virtually the experimental work of Jones et al. (2012), therefore the comparison is straightforward (although it should be noted that they performed their experiments with macaque monkeys not cats). They reversibly inactivated small regions (~600 μm diameter) of V1 by iontophoretic application of GABA, while presenting patches of drifting sinusoidal gratings of varying diameter. Local inactivation of cortical cells having RF centers in overlap with LGN RF centers (Figure 6.4a, n=14, full color) resulted in a significant decrease of LGN responses (-45.8%) below control levels for less-than-optimal sizes (Wilcoxon matched pair test, p=0.003). We found a smaller decrease for optimal, and non-significant

change for larger-than-optimally sized. Local inactivation of cortical cells having RFs non-overlapping LGN ones (Figure 6.4b, $n=12$) resulted in a significant increase (+46.3%) above control levels in larger-than-optimal sizes (Wilcoxon matched pair test, $p=0.003$), together with a smaller increase for optimal and for smaller-than-optimal sizes. These results, with which our model's results are in qualitative agreement, confirm that cortical feedback exerts opposite effects depending on the relative spatial co-registration of cortical and thalamic receptive fields, and further refine the sign of the functional influence: feedback is excitatory for spatially overlapping receptive fields, but mainly at small or optimal sizes, while feedback is inhibitory for non-overlapping receptive fields, but mainly at larger-than-optimal sizes.

6.5 Dynamic range of contrast sensitivity in LGN cells is enhanced by cortical feedback

The statistics of visual stimuli in the natural world are extremely variable in terms of contrast and spatiotemporal frequency content, but the dynamic range of input firing rate that they can reliably transmit is limited due to efficient gain control mechanisms (Tadmor and Tolhurst 2000, Simoncelli and Olshausen 2001). In particular, LGN neurons show stronger contrast gain control than retinal ganglion cells in the intact system (Rathbun et al. 2016). However, the mechanisms of this thalamic enhancement, and the role played by cortical feedback are still unresolved.

We explored this phenomenon by comparing the responses of our *without-cortex* and *full* configurations. We stimulated both models with full-field drifting gratings of varying contrast (values between 0 and 100 Weber contrast, 30 cd/m² background luminance), and we recorded from LGN cells ($n=243$, 110 X-Off and 133 X-On), and PGN cells ($n=57$, same recording grids as above).

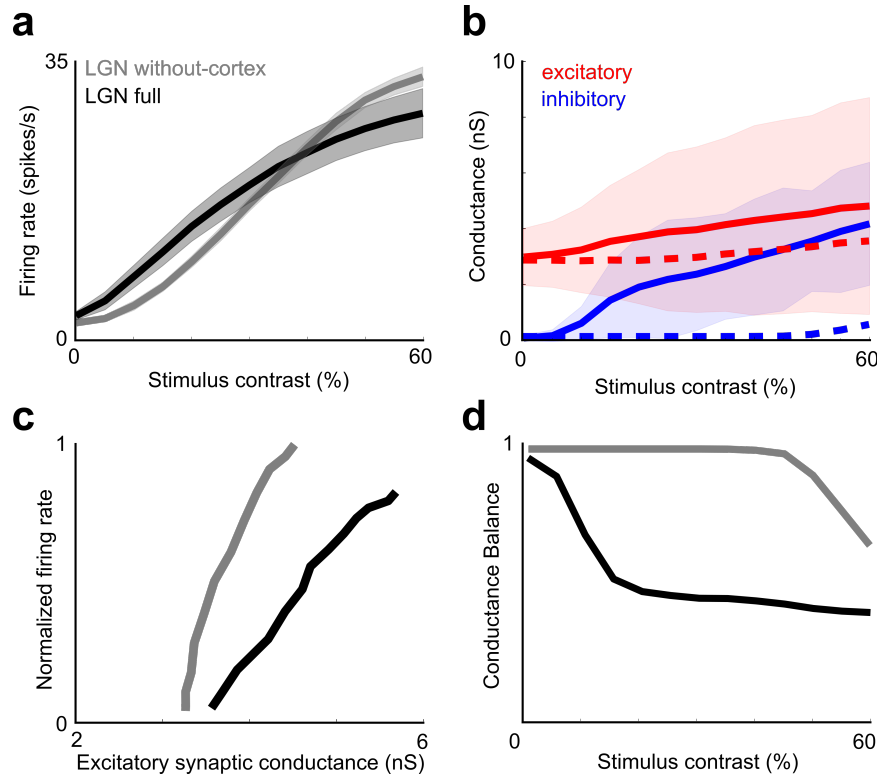


Figure 6.5. Cortical feedback changes the contrast sensitivity of LGN cells. (a) Contrast tuning curves based on trial averaged firing rates for the On-center LGN population (Off-center follows the same trend and has been omitted for clarity). The comparison between the *full* (black mean lines and shaded SEM) and *without-cortex* (grey mean line and shaded SEM) configurations show that cortical feedback significantly increases trial averaged firing rate for low-contrast stimuli (stimulus contrast <35%, Welch t-test $p < 0.001$) and reduces it for high-contrast stimuli (contrast >50%, Welch t-test $p < 0.001$) (b) Trial-averaged excitatory (red) and inhibitory (blue) conductance tuning curves for On-center LGN cells (Off-center cells shared the same properties) in the full (solid) and without-cortex (dashed) models. Both excitatory and inhibitory conductances are increased by the cortical feedback but the inhibitory gain increases more than the excitatory. (c) Input-output ratio for LGN On-center cells computed using trial-averaged conductances and trial-averaged firing rates. In the without-cortex model (grey) the dynamic range is significantly reduced compared to the full model (black). (d) The contrast dependence for the balance between excitation and inhibition is translated to the right in the *full* model compared to the *without-cortex* configuration, indicating a drastic increase in the evoked spiking threshold.

We found (Figure 6.5a) that the contrast tuning curves for both X-On and X-Off cells were significantly different between *full* and *without-cortex* configurations (Welch t-test, $p < 0.001$). We noted, for both types of cells, a reduction in response gain — as slopes of firing rate regression lines — from

without-cortex (On: 0.57, Off: 0.18) to full (On: 0.43, Off: 0.15) models. This resulted in higher responses for low contrasts and lower responses for high contrasts in the *full* model compared to *without-cortex* configuration.

To understand the mechanism behind these changes, we used population trial-averaged conductance tuning curves of LGN cells (Figure 6.5b). We found that the cortical feedback increased both inhibitory (blue) and excitatory (red) gain — slope of the conductance curve regression line — over the contrast domain, equally for both X-On and X-Off LGN cells (we will report only X-On for brevity). The inhibitory gain changed from almost flat (0.05 Hz/nS) in the *without-cortex* configuration to 0.23 Hz/nS in the *full* model. Also the excitatory gain changed from almost flat (0.07 Hz/nS) in the *without-cortex* configuration, to 0.14 Hz/nS, in the *full* model. At low contrast, the total inhibitory synaptic conductance was larger but still low compared to the excitatory conductance. At high contrast, the increase in inhibitory conductance surpassed that in excitatory conductance. This explained the stronger responses for low contrasts and weaker responses for high contrasts in the *full* model.

To better visualize how the cortical feedback affected the gain amplification, we computed the input-output ratio (Figure 6.5c) — ratio of LGN excitatory synaptic conductances and normalized trial-averaged population firing rate (Chance et al. 2002). For both X On- and Off-center cells, we found a steeper gain in the *without-cortex* configuration compared to a more gentle gain.

In order to deepen our understanding of how the cortical feedback affected the gain amplification, we looked at the excitatory-to-inhibitory conductance balance (Figure 6.5d) — computed as the ratio of excitatory to total input conductances ($\frac{excitation}{excitation+inhibition}$), where values close to 0 represent inhibitory-dominated regimes, values close to 0.5 balanced regimes, and values of 1 excitatory-dominated regimes. This measure showed the dependency of gain amplification to the balance between excitatory and inhibitory conductances in the two (*full* vs *without-cortex*) configurations. The *without-cortex*

configuration was dominated by the excitatory conductance for stimulus contrast values up to 50% (in agreement with the dashed curves of panel **b**). The *full* model shifted to a balanced regime for a lower contrast value (at ~20% contrast). It therefore passed from a relatively reduced sensitivity, probably due to noise-like degradation, to a marked increase in sensitivity.

Not all experimental studies agree on the role of cortical feedback on the contrast sensitivity of LGN cells. However, when the largest amount of cells from these studies are taken into account — without the authors' selection for the specific purposes of the studies — there is a trend, in the absence of cortical feedback, toward a reduction of overall response and contrast gain, as we found comparing our model configurations results. For example, in primates, for (n=44) LGN cells tested with full-field sinusoidal drifting gratings, Przybyszewski et al. 2000 reported a non-significant decrease of response in the absence of cortical feedback (cooling V1 - control: -2.76 ± 8.16 spikes/s, their Figure 1b). They reported no response gain change (regression slope control: 0.609 ± 0.09 vs cooling: 0.649 ± 0.12 ; t-test, $p > 0.5$). Again in primates, for (n=19) LGN cells tested as above, Webb et al. 2002 also reported an overall response decrease in the absence of cortical feedback (cooling V1 - control: -29.8 ± 31.2 spikes/s, their Figure 3CI). Webb et al. also compared the response gain between control and cortex ablated, reporting a modest (but significant) decrease for the whole set of recorded LGN neurons (-0.9 , t-test, $p < 0.001$). In cats, Kwon et al. 1992 presented spots of varying luminance (with respect to the fixed luminance background), in a control condition vs a condition where iontophoretic application of the NMDA antagonist d-APV, while recording from both (n=24) LGN X and Y cells. They reported a significant reduction of saturation response (-26.9 ± 5.8 , t-test, $p = 0.0001$) and also a reduction of response gain (regression slope: -98.2 ± 24.2 , t-test, $p = 0.0005$).

6.6 Orientation selectivity bias in thalamus is determined by cortical feedback

Weak orientation tuning — the sensitivity of cell responses to stimulus orientation — has been reported for cat LGN cells (Daniels et al. 1977, Creutzfeldt and Nothdurft 1978, Lee et al. 1979) and a possible tuning role has been assigned to cortical feedback (Krug et al. 2001, Sedigh et al. 2017).

We set out to explore orientation tuning in the thalamus by comparing the responses of our *without-cortex* and *full* model configurations. As stimuli we used full-field drifting gratings of varying orientations (10 orientations, equally spaced between 0 and 90 degrees). Guided by the hypothesis that the local cortical orientation preference could differently bias thalamic responses, we recorded from two separate groups of LGN cells (for a total of $n=52$, 28 X-On and 24 X-Off). The two groups were chosen such that, in the corresponding cortical location, the majority of cortical cells belonged to the same iso-orientation preference domain (Payne and Peters 2002), i.e. shared for instance an orientation preference for horizontal (i.e. center of orientation domain) or expressed a mixture of preferences (i.e. pinwheel; see Figure 6.6a for details).

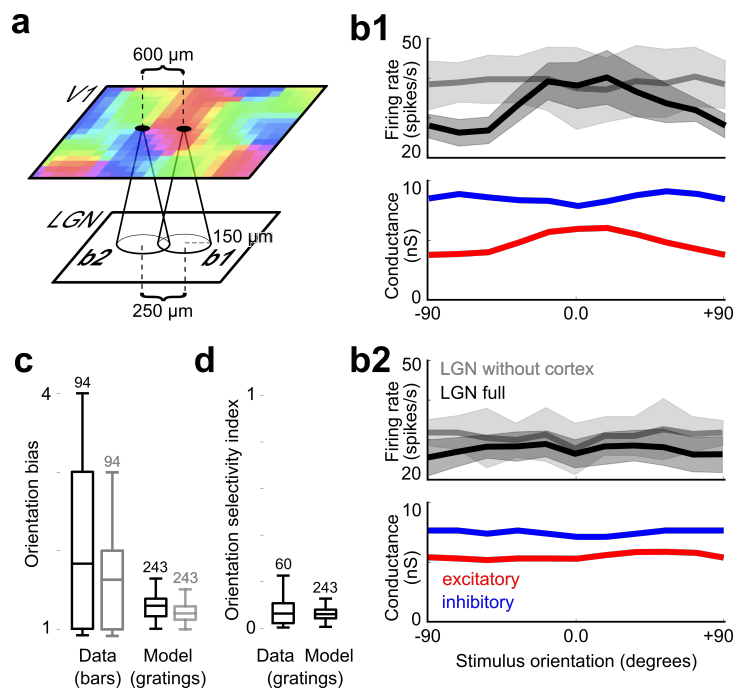


Figure 6.6 Cortical feedback determines the orientation bias of LGN responses. (a) Setup of the virtual experiment. Two groups of LGN cells (b1 and b2) were selected to have, in the corresponding cortical location, different cortical orientation preference domains. For the LGN group b1 was chosen a location with a majority of cortical cells having an horizontal orientation preference, in the middle of a cortical iso-orientation domain. For the LGN group b2 was chosen a location corresponding to a cortical mixture of preferences, in the middle of a cortical pinwheel. The LGN groups included cells from an area of 150 μm radius each, and partially overlapping (areas centers were $\sim 250 \mu\text{m}$ apart, which corresponded to a cortical separation of $\sim 600 \mu\text{m}$). (b1, top) Orientation tuning curves of trial averaged firing rate responses in the LGN group b1, in the full model (black, with shaded SEM), and without-cortex model (grey, with shaded SEM). (b1, bottom) Trial averaged synaptic conductance tuning curves for the *full* model. Note the substantially larger LGN inhibitory conductance, which decreases for the preferred orientation, and the lower excitatory conductance, with an increase corresponding to the preferred orientation. (b2) Same as b1, for the LGN group b2. Note the absence of orientation bias in the *full* model configuration. (c) Orientation bias ratio in the full (black) and without-cortex (grey) conditions, for each recorded LGN cell. Experimental data from Vidyasagar and Urbas 1982 shows a significant mean reduction, as reproduced by our model (see text for detailed values). (d) Orientation selectivity indexes measuring the normalized circular distance between stimuli and responses, only for the control condition. Experimental data from Naito et al. 2012 and our full model results have comparable means.

In the *without-cortex* model configuration there was no significant response preference towards any orientation in either LGN groups (Figure 6.6, panels b1 and b2, grey curves). However, the two groups responded differently to the orientation protocol in the *full* model. A significant orientation preference emerged (Welsh t-test, $p < 0.01$) in the LGN group targeting in the corresponding cortical map a majority of cortical cells preferring horizontal (Figure 6.6 b1, black). In contrast, no significant tuning change due to cortical feedback was found in the LGN group targeting the pinwheel (Figure 6.6 b2, black).

A mechanistic intuition for these results was provided by comparing the excitatory (red) and inhibitory (blue) conductance tuning curves of the two LGN cell groups in the *full* model (Figure 6.6, b1 and b2, lower panels). In the LGN group b1 a significant orientation preference of response emerged towards stimuli oriented at 0 degrees (Welsh t-test, $p < 0.001$), by raising the

excitatory conductance at 0 degrees while also raising more the inhibitory conductance at higher (>50) degrees. Such preference was not present in the conductances recorded in the LGN group with mixed cortical preference.

The selection of cells we performed was made possible by our *in-computo* approach, whereas a similar sampling is difficult to achieve in the available experimental literature. However, Vidyasagar and Urbas (1982) tested orientation selectivity in (lesioned areas 17 and 18) cat LGN cells, using drifting extended bars (15 x 0.1 deg, moving at 5 deg/s). They ranked LGN cell firing rate responses according to an orientation bias — calculated as ratio of preferred to non-preferred orientations responses (0 for non selective, or totipotent, tuning and higher numbers for selective responses). The reported biases (see Figure 6.6c, black for control and grey for lesioned cortex conditions respectively) of LGN X-cells (n=94) changed significantly between the two conditions, with a 14.5% decrease of mean orientation bias from 1.83 ± 0.55 to 1.74 ± 0.62 (paired t-test, $p < 0.001$). Comparing the *full* and *without-cortex* responses of the totality of recorded LGN cells (see Figure 6.6c, black and grey respectively), we found a significant 15.7% decrease of mean orientation bias from 1.27 ± 0.14 to 1.13 ± 0.07 (paired t-test, $p < 0.001$). More recently, the orientation tuning of cat LGN cells has been tested also with sinusoidal drifting gratings (Naito et al. 2007, 2013, Suematsu et al. 2012, Scholl et al. 2013, Osaki et al. 2017), unfortunately without testing for its cortical origin. All studies reported low orientation selectivity indexes (OSI) — the normalized circular distance between stimuli and responses. In particular, Suematsu et al. 2012 reported for LGN X cells a mean OSI=0.07 (Figure 6.6e, black), which was in agreement with analogous measure in the *full* model (OSI=0.06).

Vidyasagar and Urbas (1982) also reported that the cortical lesion resulted in an orientation preference bias at the LGN level favoring the representation of the cardinal meridians (horizontal and vertical), which has been attributed to corticofugal shaping of the thalamic network for these most common features of visual stimuli (Krug et al. 2001). However, rather than

corticofugal, the residual bias reported in the experimental recordings was possibly reflecting anisotropies in receptor density along the horizontal streak, which may be species-dependent. In the cat, the work of Thompson et al. 1994 argued for some polar foveo-centric bias at the retinal and thalamic levels (see also Levick and Thibos 1980, reviewed in Frégnac and Imbert 1984, Shou et al. 1986, Vidyasagar 1987).

6.7 Ongoing activity of LGN cells is increased by cortical feedback

Another possible role attributed to cortical feedback has been that cortical feedback controls the tonic activation of thalamic cells, which may contribute to their functional operating range by setting their "resting state" (Webb 1976, Tsodyks et al. 1999, Ringach 2009). However, cat experiments *in-vivo* measuring the so-called "ongoing" activity of LGN principal cells, i.e. the activity recorded in the presence of only background illumination and also labeled "background" or "spontaneous" activity, have shown little influence of cortical feedback on spontaneous spiking thalamic responses (Funke and Eysel 1992, 1998, Cudeiro et al. 2000, Waleszczyk et al. 2005, Andolina et al. 2007, 2012).

We compared the responses of LGN cells in our *full* and *without-cortex* configurations, while stimulating them with a uniform luminance background (1 cd/m²), and we recorded from (n=243) LGN cells.

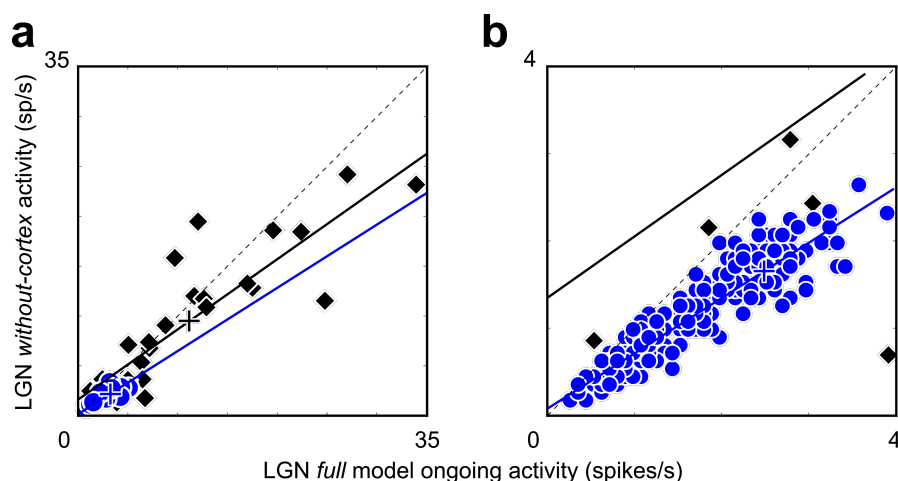


Figure 6.7. Cortical feedback increases ongoing activity in the model LGN. (a) Comparison of LGN ongoing activity in the *without-cortex* (vertical axis) vs *full* (horizontal axis) configurations. Model data (blue circles) follows a slope similar to the experimental data from Waleszczyk et al. 2005 (black diamonds). This decrease is found significant in the simulation case (Kruskal-Wallis $p < 0.001$). Linear regressions are plotted for data in black, and for model in blue. The dotted line represents identity (no change between conditions). (b) Zoomed portion of the same data as in (a) to better appreciate model datapoints distribution.

In our *without-cortex* configuration (Figure 6.7, white circles), the absence of cortical feedback significantly decreased by -23% the ongoing activity of the LGN cells (from *full* model mean 3.8 ± 0.4 to *without-cortex* mean 2.9 ± 0.3 spikes/s, Kruskal-Wallis $p < 0.001$).

Waleszczyk et al. 2005 measured the mean firing rate of LGN cells in the presence of a uniform luminance background ($0.5\text{--}1.0\text{ cd/m}^2$) while the temperature of cortex was either left intact or cooled down. Comparing the two conditions (Figure 6.7, black diamonds, $n=23$), Waleszczyk et al. 2005 reported that during cortical cooling the ongoing firing rate of LGN X cells decreased from 9.8 ± 1.3 to 8.3 ± 1.2 spikes/s. However, in spite of the change in mean (-15%), the two rate distributions were not statistically significantly different (Kruskal-Wallis $p=0.57$).

In comparing the results of our simulations and the experimental data, we observed an overall lower mean ongoing activity in the models compared to in vivo reports, and a significant difference between model configurations. The lower mean ongoing activity of the models might be due, as described before, to the absence of any other source of noise except for the retinal drive, which was also the reason for the lower variability, resulting also in slightly higher levels of correlation between model cell responses (experimental Pearson's $r=0.876$ vs model $r=0.924$). In fact, in experimental conditions of intact feedback, Kaplan et al. 1987 reported the ongoing activity of cat LGN X cells ($n=45$) at 14.12 ± 13.1 spikes/s for a uniform screen luminance of 100 cd/m^2 .

6.8 Temporal tuning of LGN cells is not affected by cortical feedback

To the best of our knowledge, systematically manipulating the temporal frequency of drifting sinusoidal gratings to measure the response change of LGN X-cells in control vs altered conditions has not been performed in the cat. In the macaque monkey, only Marrocco et al. 1996 performed such experiments, with inconclusive results.

Marrocco et al. 1996 studied the response of macaque LGN cells to sinusoidal drifting grating stimuli varying in temporal frequency while the temperature of cortex was either left at control level or reversibly cooled. The authors compared the firing rate of 32 cells in the two conditions and grouped the responses (Figure 6.8, black bars) into three classes: those that showed an increase in the altered condition ($n=14/32$, 44%), those that showed a decrease in the same condition ($n=7/32$, 20%), and cells that showed no significant change between conditions ($n=9/32$, 36%). The significance was assessed with a one-way ANOVA test (with the significance level set at $p=0.05$). They reported a change in the firing rate of approximately 10-20 spikes/s, and the majority of cells had the same peak response in the control and cortex-off conditions.

We explored the cortical influence on LGN responses to full-field sinusoidal drifting gratings varying in temporal frequency (0.5 cycles/deg, drifting at eight speeds, from 0.1 to 8 Hz) in our *without-cortex* and *full* configurations, while recording from ($n=110$, randomly sampled) LGN cells.

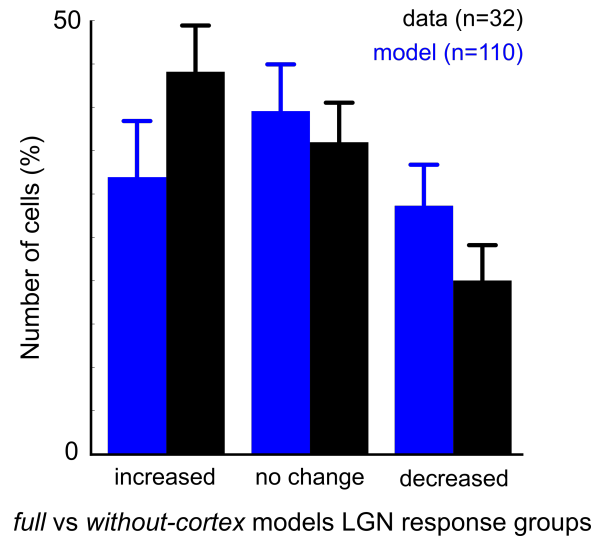


Figure 6.8. Temporal tuning is not affected by cortical feedback. Percentage of cells changing their firing rate between control and altered conditions in response to stimuli varying in temporal frequency, grouped by rate increase, no change, and decrease groups. In black, results from Marrocco et al. 1996, in blue model data.

We report no statistically significant differences between firing rate tuning curves between configurations (Welch t-test, $p=0.91$). The trial-averaged temporal frequency tuning curve of firing rates were virtually equal between models (with a difference of ± 3 spikes/s) and we did not show them.

We grouped the change in response for the LGN cells we recorded from in the two models (Figure 6.8, blue bars) and we found qualitatively similar proportions (increase: $n=32/110$, 29.1%; no change: $n=29/110$, 26.3%; decrease: $n=39/110$, 35.4%). In addition to no statistically significant difference between firing rate tuning curves, we also report no significant difference between the two configurations.

7 Results — Cortex-centered viewpoint

Based on the assumption that the cortico-thalamo-cortical loop makes the thalamus and primary visual cortex behave as a single dynamical system (Jones 1985, Potter et al. 2014), this chapter turns towards formulating possible functional roles of the corticothalamic loop from a cortical viewpoint.

Cortical activity exerts its influence onto cortical and thalamic structures through the cortico-thalamo-cortical loop (embedded in our modeling effort) and cortico-cortical connectivity (outside the range of our models). However, another component is the intrinsic horizontal connectivity of V1, which is also impacted by the loop and, therefore, may participate in a non-explicit way to the integrative functions of the thalamo-cortical system.

The focus of this chapter is on a realistic description of the direct (feedforward) and indirect (local intracortical, horizontal) visual projections recruited by stimulation of a restricted location in the thalamus, in the absence or presence of cortico-thalamic feedback. This comparative description between the “open-loop” (*feedforward-only*) and the “closed-loop” (*full*) configurations demonstrates the functional impact of the modulatory role of the feedback and its interplay with horizontal connectivity.

In particular, in this chapter, we explore the hypothesis that particular stimulus configurations may recruit the corticothalamic pathway, which, due to its divergence, may in turn modulate the contextual influence of

horizontal connectivity, and consequently up- or down-regulate the functional selectivity encoded cortically.

As main stimulus configuration, we choose circular patches of drifting gratings of increasing radius. At small radii, the focalized stimulus in the retina, inducing through the thalamic relay a feedforward activity hot spot in the cortical map, creates a “center” of cortical activity. This also creates, when the stimuli grow in size, a corresponding “surround”, and a center-surround opposition.

In our virtual experiments, we explored the relationship between the “center” and “surround” by partitioning, during the analysis, the recorded cortical cells into two (“center” and “surround”) domains with additional sub-domains defined by the orientation preference relative to that of the test grating (“iso-oriented” and “cross-oriented”).

By comparing the responses of these cortical sub-domains in the *feedforward-only* (Figure 5.1f) vs *full* (Figure 5.1a) configurations, we found that the introduction of the cortico-thalamo-cortical loop yielded additional suppression for non-preferred stimulus orientations, which strengthened the tuning selectivity of the orientation preference map of cortical cells. Similarly, we found additional suppression for larger-than-preferred stimulus sizes, strengthening the surround suppression of cortical cells in the center.

Looking for possible synaptic mechanisms for such a strengthening, we analyzed the contextual changes in the size-dependent tuning curves of excitatory and inhibitory conductances. In the *feedforward-only* configuration, we found an overall inhibition-dominated regime of conductances for all cortical sub-domains in both center and surround, with no significant surround suppression. In the *full* model, the excitatory and inhibitory conductances were overall more balanced but the excitatory cells were still in an inhibition-driven prevalent regime, especially at large stimulus sizes, while the inhibitory cells were in an excitation-driven prevalent regime, with significant surround suppression.

In order to search for causal relationships in the circuit, we inspected the coherence between spiking in one location (either center or surround) and the integrated postsynaptic effect recorded through LFP. In the *feedforward-only* configuration, we found a monotonic increase of coherence for growing stimulus sizes. In the *full* model, we found substantially lower levels of coherence at large sizes.

Overall, these results indicate, from a cortex-centered viewpoint, the cortico-thalamo-cortical loop has an important role in selective amplification of suppression and strengthening of cortical selectivity.

7.1 The loop strengthens the tuning selectivity of cortical orientation preference map with stimulus size increase

It is known from a series of electrophysiology studies in the primary visual cortex (of cats, ferrets, and primates) that the LGN afferents to V1 preserve size tuning (Nolt et al. 2004, Sceniak et al. 2006), and there they undergo additional surround suppression (cat: Hubel and Wiesel 1965, Blakemore and Tobin 1972, Sillito et al. 1995; monkey: Kapadia et al. 1999, Sceniak et al. 1999). It is also known that stellate cells (in Layer 4) and pyramidal cells (in Layer 2/3, 5 and 6) are also selective for stimulus orientation (Hubel and Wiesel 1964, Somers et al. 2002). In this section, we explore the dynamical interaction between these functional preferences and the cortico-thalamo-cortical loop.

In the primary visual cortex there is an overlay of functional preference maps (orientation, size, direction, etc.), whose interaction is still a matter of debate (Swindale et al. 2000, Ribot et al. 2016). For example, Ohana et al. 2012 proposed a mechanism for intracortical surround suppression: that the excitatory input received by neurons centered on the stimulus is antagonized by an inhibitory input, whose strength grows proportionally to the surround area recruited by the stimulus. Triggered by horizontal connections,

inhibitory neurons from a localized neighborhood (within $\sim 1000\ \mu\text{m}$ radius) would increase their firing for large sized stimuli. At the same time, such local modulatory network is also bearing orientation selectivity (Cattaneo et al. 1982), with preferential connectivity between excitatory cells having similar orientation, and inhibitory cells preferentially targeting excitatory cell of cross-oriented orientation preference (Hirsch 2003). As a matter of fact, our lab has demonstrated in the cat — using *in-vivo* current clamp and voltage clamp intracellular techniques — a diversity of interactions between excitatory and inhibitory orientation-tuned conductances much richer than expected from the orthodox literature: 1) cells may receive both excitatory and inhibitory inputs tuned for the same preferred orientation; 2) cells may receive the excitatory input tuned for the preferred stimulus but the inhibition tuned for non-preferred stimulus, and 3) even cells receiving excitatory and inhibitory inputs tuned for a stimulus preference different from that expressed at the spike level (Monier et al. 2003, Monier et al. 2008, Fournier et al. 2014).

Here, we explored the idea that the recruitment of the cortico-thalamo-cortical pathway by large stimuli increases both orientation and size tuning selectivity in the cortical region target by the feedforward thalamic input, by increasing suppression of center neurons at non-preferred stimuli. To test this hypothesis, we presented to our model full-field and size-varying patches of drifting gratings (see Chapter 4 - Methods), and we compared cortical cell responses in two configurations: *full* model, and *feedforward-only*, where cortico-thalamic connections were absent, corresponding to an *in-vivo* preparation in which the corticothalamic pathway would be inactivated (for example by inactivating V1 Layer 6 neurons with muscimol, as in Jones et al. 2012, or using optogenetics, as in Hasse and Briggs 2017).

To measure the topological impact of the cortico-thalamo-cortical feedback loop in more functional terms, we monitored the visual responses of cortical cells in a circular grid of 6 mm diameter centered on the retinotopic feedforward representation of the grating stimulus center (covering 6

degrees of visual field for parafoveal vision, see Chapter 4 - Methods). We then analyzed two topologically defined domains, “center” and “surround” (Figure 7.1, middle panels) and partitioned cells into four sub-domains according to their orientation preference relative to that of the test grating stimulus. The first cortical domain contained cortical cells whose RF centers sampled the center of the stimulus, and whose feedforward activation impacted a circular area of 700 μm radius (roughly the scale of a hypercolumn). Within this domain, the *iso-center* cell sub-domain contained cells with orientation preference matching the stimulus orientation (Figure 7.1a, $n=32$), and the *cross-center* sub-domain grouped cells with orthogonal (or cross-) orientation preference (Figure 7.1c, $n=42$). The other domain contained cells whose RF centers sampled a surrounding annulus of the visual space (inner circle of 1 degree radius and outer circle of 1.8 degrees radius), and whose cortical positions were beyond 1000 μm from the center (thus sampling across hypercolumns distinct from the center). Similarly to the “center” groups, cells were partitioned into an *iso-surround* sub-domain, containing cells with preferred orientation as in the stimulus (Figure 7.1b, top, $n=561$), and a *cross-surround* sub-domain, containing cells with preferred orientation orthogonal to the stimulus (Figure 7.1d, bottom, $n=591$).

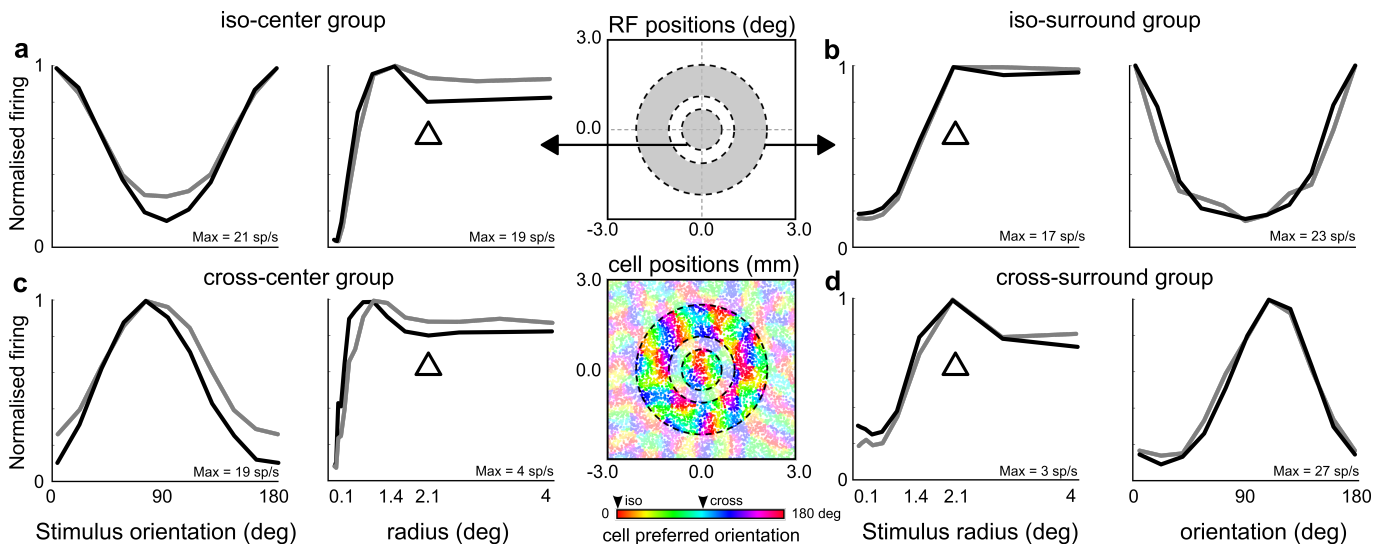


Figure 7.1. Corticothalamic loop increases suppression for non-preferred stimuli. In the middle panel, concentric cortical areas from which the groups are sampled. **Top**

middle, all sampled cells had their RF centers in either a center area (0.7 degree radius) or a surround annulus (from 1.0 to 1.7 degrees). **Bottom middle**, within each area, an iso group was made of cells having preferred orientation matching the stimulus (0 degrees, red domains), and an cross-group was made of cells having the orthogonal preferred orientation (~90 degrees, cyan domains). (a) Orientation- and size-normalized tuning curves for the “iso-center” group (the maximal firing rate is reported in each panel; no SEM is reported to ease curve reading). (Left) The iso-center mean responses were lower for stimuli of orientation orthogonal to the preferred orientation in the full model (black curve) vs the feedforward-only model (grey). (Right) The iso-center mean responses to size varying stimuli were more suppressed for larger-than-optimal sizes (>1.5 deg) in the full model (black curve) compared to the *feedforward-only* configuration (grey). (b) Size and orientation normalized tuning curves for the “iso-surround” group (same color and plot coding as in a). No significant reduction was measured for either stimulus. Note that, in the full model, the sizes at which the response reaches its peak in the surround were the same at which in the center there were surround suppression troughs (marked by an arrowhead in both panels). (c) Orientation and size normalized tuning curves for the “cross-center” group. The mean response to cross-oriented stimuli by the cross-oriented cell group was lower for larger-than-optimal sizes in the full vs *feedforward-only* configurations. Cross-center mean responses to size varying stimuli were lower for larger-than-optimal sizes in the full vs *feedforward-only* configurations. (d) Size and orientation normalized tuning curves for the “cross-surround”. No significant change was measured for either stimulus.

In Figure 7.1 we present the results relative to each cell group. By convention, the grating test orientation was set at the preferred orientation (0 degrees), and cross-oriented cells had consequently very low response rate. In order to compare the responses of all groups, we report the normalized firing rate in the *feedforward-only* (grey mean curve) and *full* (black mean curve) model configurations. As reference, we show the peak firing rate in the *full* model.

Overall, we found that (i) when tested with full-field sinusoidal drifting grating varying in orientation, the presence of cortico-thalamo-cortical feedback was associated with enhanced suppression at stimulus orientations cross-oriented to the one preferred by the identified cell groups; (ii) when tested with patches of sinusoidal drifting gratings, the cortico-thalamo-cortical loop increased the local tuning contrast of the orientation map. Both these specific tuning effects were absent in the surround-domain.

In the center (Figure 7.1 a and c), with respect to orientation tuning (left), in the *feed-forward-only* configuration the suppression at non-preferred stimuli was significantly lower than in the *full* model (a: -8.8%, Welch t-test $p=0.0031$; c: -10.3%, Welch t-test $p=0.0044$). Regarding size tuning (right), in the *feedforward-only* configuration the suppression index was low (iso-center group SI: 0.11 ± 0.13 ; cross-center group SI: 0.22 ± 0.1). In the *full* model, the presence of the cortico-thalamo-cortical feedback pathway resulted in significantly higher values of the suppression index (iso-center group SI: 0.32 ± 0.12 , Welch t-test, $p=0.0022$; cross-center group SI: 0.64 ± 0.21 , Welch t-test, $p=0.0041$).

In the surround (Figure 7.1 b and d), with respect to orientation tuning (left), in the *feedforward-only* configuration the suppression at cross-oriented stimuli was not significantly different than in the *full* model. Regarding size tuning (right), in the *feedforward-only* configuration there was surround suppression at large stimulus sizes, although not significantly different between models (Welch t-test, $p>0.05$). The presence of the cortico-thalamo-cortical feedback pathway resulted in higher values of the suppression index (iso-center group SI: 0.32 ± 0.2 ; cross-center group SI: 0.64 ± 0.1).

Two points about these results are consistent with a surround contribution to center suppression mediated by the cortico-thalamo-cortical loop. First, in both the *full* and *feedforward-only* configurations, the strongest suppression (troughs in the size tuning curves for the center groups) corresponded to the peaks in the surround groups (marked by arrowheads), not surprisingly placed at 2.1 degrees stimulus radius, given the average RF location of surround-cells. Second, even if the stimuli optimally oriented for the iso-group caused, not surprisingly, weak response rates in the cross-oriented groups, the cross-center responses were also affected by the surround, and by the presence or absence of cortico-thalamo-cortical feedback, in the same way as the iso-groups (cross-center peaks *full*: 5.4 ± 0.5 spikes/s, *feedforward-only*: 4.2 ± 0.2 ; cross-surround peaks *full*: 3.5 ± 0.5 spikes/s, *feedforward-only*: 2.2 ± 0.2). In the remainder of this chapter, we address the first set of results

because it relies on larger response amplitudes and also because the second result appears to share similar features, with a possibly similar mechanism.

To better visualize the relationship between the orientation domains with respect to the increase in stimulus size, we looked at the tuning contrast of the orientation map — given by the normalized ratio between activities (R) in iso/preferred (p) and cross/non-preferred (np) orientation domains ($\frac{R_p - R_{np}}{R_p + R_{np}}$). The results (Figure 7.2) show that cortical feedback increased the local tuning contrast of the orientation map for stimuli of size larger than 0.5° for cells located in the center domain. This specific size-tuning effect is lost in the surround-domain.

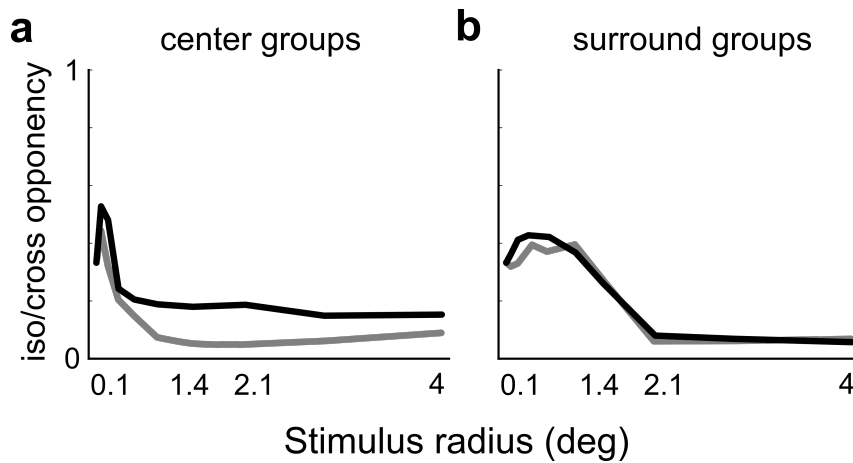


Figure 7.2. Contrast of the orientation tuning map. The ratio of iso- over cross- domain activities is different in the center and surround, depending on the stimulus size. (a) The center groups, in the *feedforward-only* configuration showed low tuning contrast, but in the *full* model configuration they showed significantly more contrast (Welch t-test, $p=0.003$). (b) In the surround groups, the tuning contrast levels were not significantly different in either configuration.

Given the explorative and predictive nature of these virtual experiments, we could not find in the literature a direct comparison for all our results. However, our *full* model results for the iso-center group were in agreement with the available data regarding cat V1 size-tuning responses (for cells having RFs close to parafoveal, ~5 degrees of eccentricity, DeAngelis et al. 1994, SI: 0.52 ± 0.4 ; Walker et al. 1999, SI: 0.35 ± 0.9). And the radius sizes for the tuned responses of center and surround corresponded to the measures

reported in the literature (cat: Sillito et al. 1995, monkey: Cavanaugh et al. 2002).

In addition, the reduction of suppression index measured for our iso-center *feedforward-only* vs *full* configurations was in agreement with the only available experimental data (to the best of our knowledge) in the cat about the size-tuning of cortical cell responses in the absence of cortical feedback to thalamus, provided by Bolz and Gilbert (1986). They inactivated Layer 6 of cat V1 with GABA injections, while presenting stimuli varying in size, and reported a reduced suppression index in Layer 4 (SI changed from 0.54 to 0.1). However, Layer 6 is known to also be a source of direct input to Layer 4 (Douglas and Martin 1991) therefore their results could not be unequivocally attributed to the cortico-thalamo-cortical feedback loop. In our model, the only external source of input to cortical neurons came from thalamus, therefore our results could be unequivocally attributed to the cortico-thalamo-cortical feedback.

7.2 Cortically-mediated surround suppression is strengthened by the cortico-thalamic loop

Given the stronger effects obtained in the previous section for the cortico-thalamo-cortical strengthening of surround suppression, we decided to explore it further. Virtual experiments allowed us to monitor the conductance balance between synaptic excitation and inhibition and compare it between model configurations. Our aim was to search for a possible mechanism in the cortico-thalamic pathway that would be working synergistically with the V1 horizontal lateral connectivity to amplify surround suppression.

In the same setup presented in the previous section, we compared the excitatory and inhibitory synaptic conductance size-tuning curves recorded in the *feedforward-only* and *full* models, for the V1 excitatory iso (n=32) and

cross (n=85) groups, and for the inhibitory iso (n=10) and cross (n=19) groups.

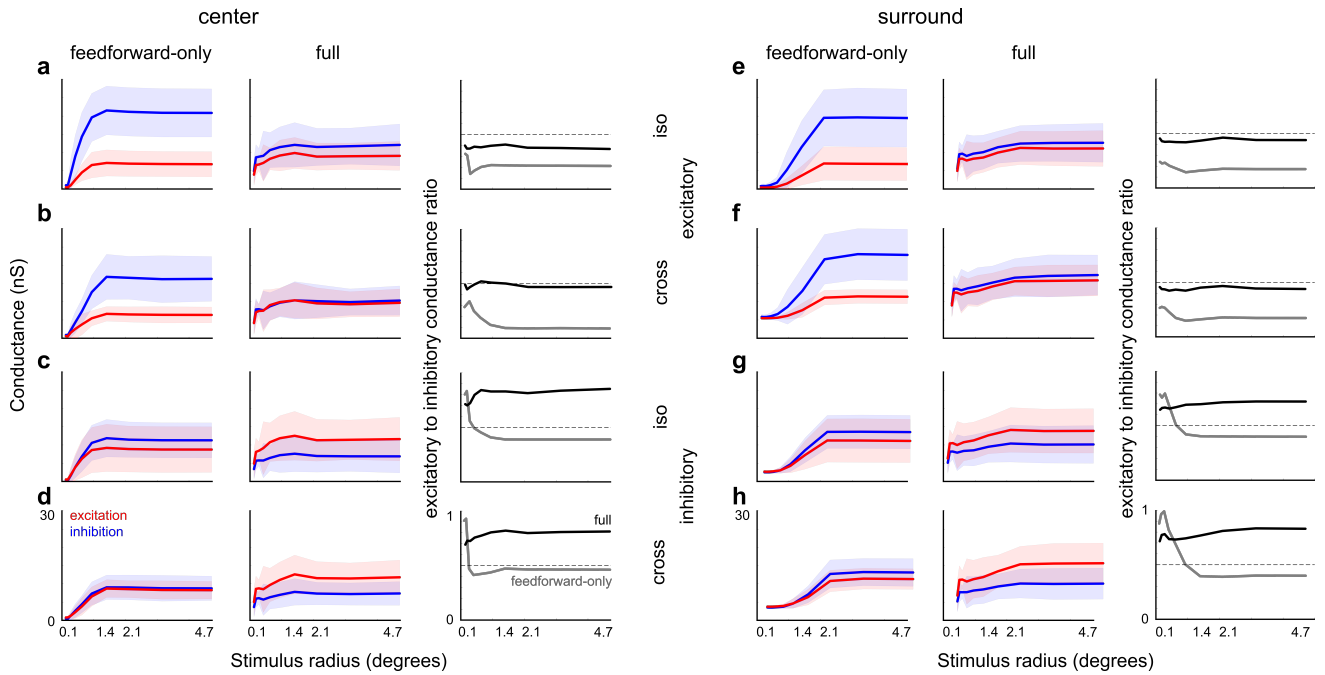


Figure 7.3. Synaptic conductance size-tuning curves across cortical groups. The conductance size-tuning curves for all groups of cells are shown for center (left half) and surround (right half) regions, in the *feedforward-only* and *full* model configurations (first two columns in each half). Their excitatory-to-inhibitory conductance ratio is the last column in both halves. For the excitatory cells of both center (a and b) and surround (e and f) the presence of the *full* loop changed the excitatory/inhibitory balance from inhibition-dominated to a still inhibition-dominated but more balanced regime, as confirmed by the corresponding <1 ratios. For the inhibitory cells of both center (c and d) and surround (g and h) the introduction of the full loop inverted the excitatory/inhibitory balance from inhibition-dominated to excitation-dominated, as confirmed by the corresponding >1 ratios.

Overall, two main results emerged from the comparison of the size tuning curves of excitatory (red curve and shaded SEM) and inhibitory (blue curve and shaded SEM) conductances, in the *feedforward-only* (open-loop) and *full* (closed-loop) model configurations.

First (Figure 7.3, panels a-d), in the center, only the conductances of both excitatory and inhibitory cells showed surround suppression (see Table 7.1).

In the surround, the conductances of both excitatory and inhibitory cells showed no suppression at large sizes (with all SIs < 0.01).

		<i>Feedforward-only</i>		<i>Full</i>	
		Conductance SI		Conductance SI	
		excitatory	inhibitory	excitatory	inhibitory
Excitatory cells	iso	0.09±0.02	0.08±0.05	0.15±0.05	0.12±0.06
	cross	0.11±0.03	0.09±0.06	0.21±0.08	0.20±0.04
Inhibitory cells	iso	0.07±0.05	0.08±0.02	0.23±0.05	0.18±0.06
	cross	0.06±0.03	0.07±0.01	0.17±0.06	0.18±0.05

Table 7.1: Suppression Index of the conductance tuning curves for all center classes of recorded cells, in the feedforward-only and full models.

Second, cortical excitatory and inhibitory cells presented an opposite trend between models. In the center, in the *feedforward-only* configuration, excitatory cells were dominated by inhibitory conductances (58.3% higher than excitatory at large sizes, Figure 7.3, a and b), while inhibitory cells were more balanced (inhibition 28.6% higher than excitation, Figure 7.3, c and d). In the *full* model, cortical excitatory cells had more balanced excitatory and inhibitory conductances (see Figure 7.3, a and b), while inhibitory cells were dominated by excitatory conductances (45.2% higher than inhibition, see Figure 7.3 c and d). The surround presented a similar trend (see Figure 7.3, e and f for the excitatory cells, and g and h, for the inhibitory cells). These results were comforted by the excitatory-to-inhibitory conductance ratio — a measure of contrast between excitation and inhibition ($\frac{excitation}{excitation+inhibition}$) — where values close to 0 represent inhibitory-dominated regimes, values close to 0.5 balanced regimes, and values of 1 excitatory-dominated regimes (see rightmost columns for both center and surround panels in Figure 7.3). In the

center, the cortico-thalamo-cortical loop shifted the conductance regime of excitatory cells from inhibitory-dominated in the *feedforward-only* configuration (iso ratio: 0.23, cross ratio: 0.12), to a more balanced conductance regime in the *full* model (iso: 0.41, cross: 0.48). For the inhibitory cells, which had a balanced conductance regime in the *feedforward-only* configuration (iso: 0.43, cross: 0.47), the cortico-thalamo-cortical loop in the *full* model shifted their conductance regime to an excitatory-dominated one (iso: 0.74, cross: 0.69). In the surround, in the *feedforward-only* (*ffw*) vs *full* configurations, there was a similar difference between excitatory (*ffw* iso: 0.20, cross: 0.21, and *full* iso: 0.45, cross: 0.46) and inhibitory cells (*ffw* iso: 0.42, cross: 0.43, and *full* iso: 0.72, cross: 0.81).

Again, the exploratory nature of these virtual experiments did not allow a direct comparison with *in-vivo* electrophysiological measurements. However, in the full model, the suppression indexes recorded for excitatory cells were qualitatively in accordance with Ozeki et al. 2009 (their Figure 4, excitatory SI: 0.55 ± 0.3 , inhibitory SI: 0.47 ± 0.7). The overall higher inhibitory conductances were in accordance with data from the cat: Anderson et al. 2001 (4 to 5 times higher, their Figure 4DF), Ozeki et al. 2009 (+20%, their Figure 2H), which might also be related to the phase of the stimulus (Taylor et al. 2018, their Figure 6).

In our results above, nothing seemed to indicate a straightforward cortico-cortical horizontal influence from the iso- or cross-surround on the center. But both center and surround inhibitory cells underwent the inversion of excitatory to inhibitory balance mediated by the loop. To follow the cortico-thalamo-cortical loop, we inspected the thalamic targets of cortical excitatory cells, in the same *feedforward-only* and *full* model configurations as above, by recording the conductances of (n=91) cells from LGN and (n=33) cells from PGN, within a region covering 2 degrees of visual field centered on the stimulus (Figure 7.3).

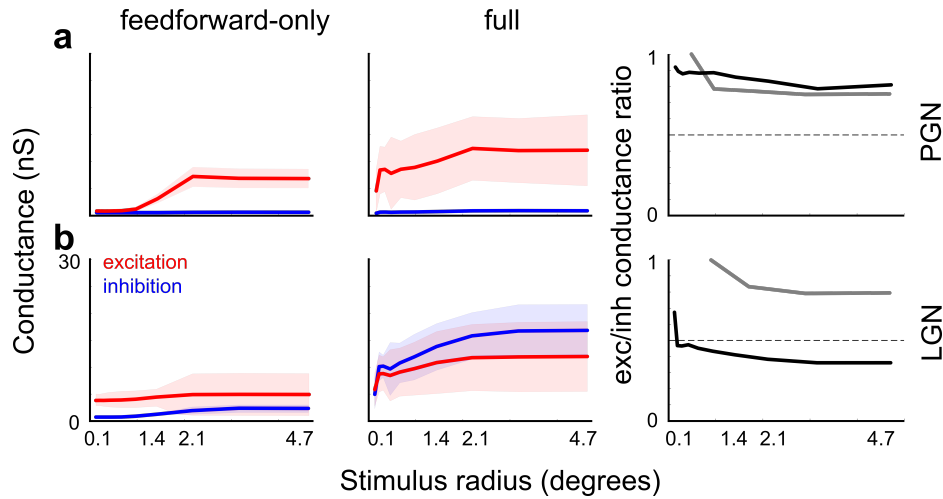


Figure 7.3. Conductance size tuning curves in thalamus. The conductances size tuning curves of PGN (a) and LGN (b), in the *feedforward-only* and *full* model configurations are plotted, with their contrast ratio as last column. For the PGN (a), the corticothalamic feedback raised an already excitatory-dominated regime, as confirmed by the corresponding ~ 1 ratio (upper right panel). For the LGN (b) the cortico-thalamic feedback changed the excitatory/inhibitory balance from excitatory-dominated to an inhibitory-dominated and more balanced regime, as confirmed by the corresponding shift of conductance balance ratio towards lower values (<0.5) (bottom right panel).

The comparison of PGN population conductance tuning curves in *feedforward-only* and *full* model configurations (Figure 7.3 a) showed a significant increase in excitatory synaptic conductance at the same stimulus sizes of the peak in cortical iso-surround excitatory cells, only in the control condition (with SI: 0.11 ± 0.2 , Welch t-test, $p=0.0027$), which argues in favor of a cortical origin, either direct or mediated through additional excitation of the LGN. This was also confirmed by the excitation-dominated conductance ratio in both the *feedforward-only* and *full* model configurations.

An inversion similar to the ones recorded in cortex, but of opposite sign, was found in the comparison of LGN population conductance tuning curves (Figure 7.3 b), where LGN conductances shifted from an excitation-dominated regime, in the *feedforward-only* configuration, to an inhibition-dominated regime, in the *full* model. The dependence on PGN inhibition for such a shift was visible in the LGN inhibitory conductance tuning curve, as demonstrated by the analysis of conductance balance (right column, Figure 7).

In summary, in the *feedforward-only* configuration, the LGN was in an unbalanced — excitation-dominated — conductance regime, which strongly drove cortex. In our model (constrained by the available data, see Chapter 4 - Methods), there was a higher thalamic impact on cortical inhibitory cells (~20% more: 1.3 nS for each thalamic synapse onto an excitatory cortical cell, 1.6 nS for an inhibitory cortical cell). This explained why the inhibitory conductances were higher for all cortical cells in the *feedforward-only* configuration. But the sole impact of the thalamo-cortical pathway was not enough to explain why only the cortical inhibitory cells underwent an inversion of conductance balance in the *full* model. In the *full* model, where the loop between cortex and thalamus was closed, the cortical excitation coming to LGN and PGN increased with the size of the stimulus, recruiting proportionally larger portions of the visual system, thus increasing LGN and PGN responses (see Figures 6.3, 6.4, and 7.3). For small/optimal stimulus sizes, this resulted in strong excitation in the cortical center cell classes (see Figure 7.1 and 7.3). But for larger stimuli, the proportionally larger surround acted both on thalamus and cortex, by increasing inhibitory neuron responses.

The structural organization of the cortical orientation preference map may provide a good mechanistic substrate for this excitation/inhibition balance inversion, as a form of functional antagonism in the orientation domain (see Figure 4F in Frégnac and Bathellier 2015). Such an organization, if deterministically fixed, could be an obstacle to the genesis of inhibition-driven horizontal intra-cortical surround suppression because, once excited by large stimuli, iso-oriented excitatory neurons in the surround would only excite iso-oriented excitatory and inhibitory neurons in the center, according to the push-pull hypothesis of Hirsch, resulting in further excitation in the center. However, this hypothesis may be largely overstated and not supported by the probabilistic nature of cortico-cortical connectivity (Chavane et al. 2011, Ohana et al. 2012). This probabilistic nature requires additional work to further explore the different conductances acting on the

response of center cells. In particular, a way to dissect the excitatory and inhibitory interactions between center and surround would imply at least the selective silencing of surround excitatory to center inhibitory (both iso- and cross-oriented) connections, center excitatory to center inhibitory (both iso- and cross-oriented) connections. Such a silencing (or, equally interesting, imposed activity boosting) is laborious but achievable in a living preparation, for example using muscimol (Crook et al. 1992, Jones et al. 2012), glutamate iontophoresis (Tsumoto et al. 1978), or, more recently, optogenetics (Hasse and Briggs 2017).

7.3 Spike-to-field coherence of the cortico-thalamic center is damped by the activation of the loop during surround suppression

In the previous section, the conductance tuning curves, with their ratios, showed the existence of a cortico-thalamo-cortical modulation of cortical horizontal functional connectivity. A common tool to characterize functional connectivity is the relationship between the spikes of individual neurons recorded in a given location and the local field potential (LFP) — an extracellular electric potential integrating contributions from all active cellular processes within a relatively localized volume of brain tissue (Creutzfeldt et al. 1966, Katzner et al. 2009, Buszáki et al. 2012) — recorded at locations displaced from the site where spikes are recorded. Such relationship is assessed using the spike-triggered average of the LFP (stLFP), also called spike-field coherence (Eckhorn et al. 1988, Jin et al. 2008, Nauhaus et al. 2009), which yields a measure of the dynamical functional connectivity between the spiking activity at the source location — where spikes are recorded — and the postsynaptic response at a target location — where the LFP is recorded (Einevoll et al. 2013).

Our intuition for the source of modulation of cortical excitation and inhibition balance inversions was that the excitatory iso-surround group (n=38) would be producing in the center a stronger spike-field coherence in

the *full* model (thanks to the cortico-thalamo-cortical loop) compared to the *feedforward-only* configuration.

To test this intuition, we measured the spike-field coherence between the spiking activity at the source location — center or surround — and the spike-triggered average of LFP response at the target location. To do so, we monitored the spikes from iso- (n=9) and cross-oriented (n=16) surround cell groups, together with representative samples of the synaptic currents and cell voltage traces of (n=31) iso-oriented cells in the center, in both models. We generated a synthetic LFP from the conductances and membrane potential recorded from the sample of cells (according to the forward method described in Destexhe et al. 1998, Pettersen and Einevoll 2008) for each of the 10 stimulus sizes, in the *feedforward-only* and *full* model configurations. We then computed the spike-triggered average of LFP (as in Arieli et al. 1999). For each stimulus size, each spike in the source cell group was used to trigger the average of (n=12) trials LFP, producing segments of fixed duration (600 ms), centered according to the spike timing of each single neuron in each group. This averaging was necessary to extract the coherent activity in the LFP to build up and average-out uncorrelated sources of variance. Finally, a spike-field coherence tuning curve was assembled from the stLFPs computed for each stimulus size.

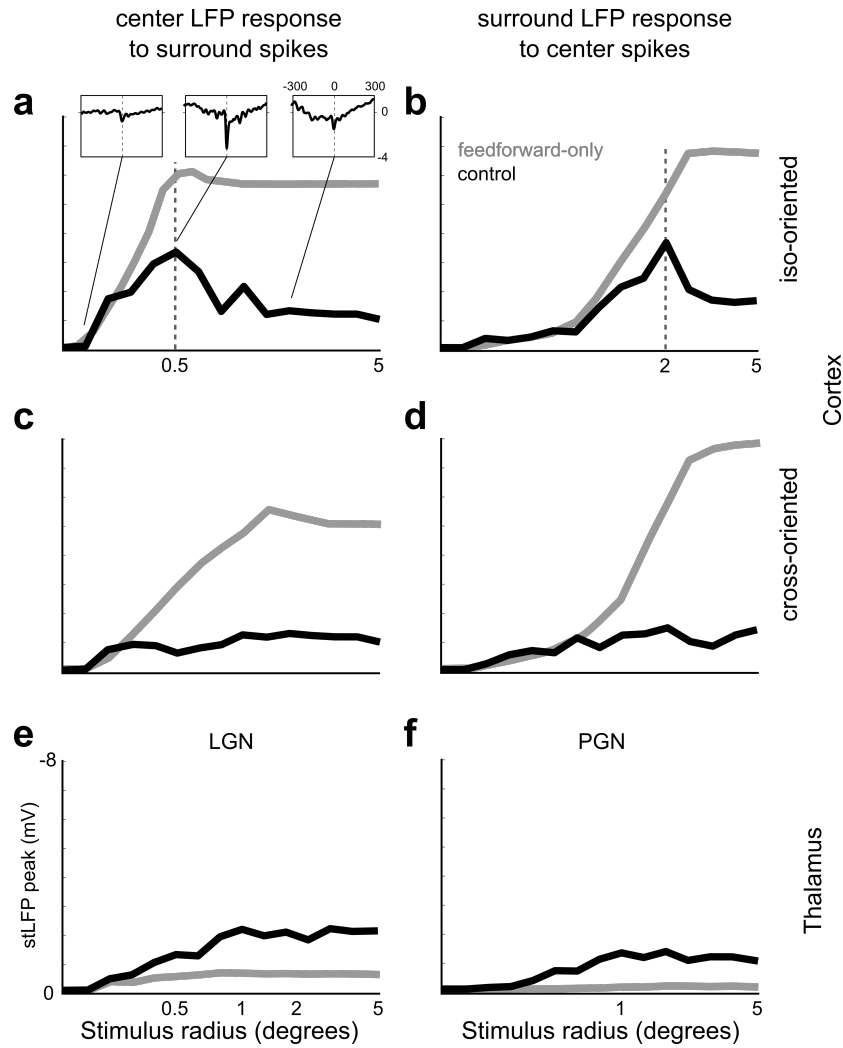


Figure 7.5. Spike-field coherence tuning curves of center and surround groups. Spike-triggered LFP (stLFP) size tuning curves for center and surround, iso and cross-oriented cell groups in cortex (respectively, a and c, b and d), in log-scale. **(a)** The cortical LFP response of iso-oriented cells in the center to spikes in the surround. In the *feedforward-only* configuration (grey curve), the coherence is rising to a peak at 0.5 deg of stimulus radius. For larger stimuli, the coherence is still high. In the *full* model (black curve), the coherence is overall lower, with a corresponding peak at 0.5 deg stimulus radius, but also reduced for larger stimuli. In the insets, trial-averaged LFPs recorded at the marked stimulus sizes, exemplifying the process creating the tuning curve. **(b)** The surround LFP response of iso-oriented cells to center spikes follows a similar trend, with only a peak shifted to larger (2.1 deg radius) stimuli. **(c-d)** The cross-oriented cells in both the center and surround did not follow the same trend of iso-oriented cells. The introduction of the cortico-thalamo-cortical loop only reduced the recorded levels of coherence. **(e-f)** In the thalamus, both LGN **(e)** and PGN **(f)** increased their LFP coherence in the presence of corticothalamic feedback.

In the *feedforward-only* configuration (Figure 7.4a, grey curves), the stLFP showed a monotonic increase of coherence between spikes of the excitatory iso-surround and LFP of all cell classes in the center. In contrast, in the *full* model (Figure 7.4a, black curves), the stLFP showed, at sizes near the optimal firing rate response of Figure 7.1, an increase of coherence between spikes of the excitatory iso-surround and LFP of all cell classes in the center, while, for stimuli larger than optimal, the stLFP dropped (see inlets in Figure 7.4a). Correspondingly, in the surround iso-oriented group (Figure 7.4b), the highest spike-field coherence between local firing and center LFP was reached at 2 degrees radius. In contrast, in the cross-oriented groups (Figure 7.4 c and d) the spike-field coherence in the full model was overall low, showing no particular peaks.

In the thalamus, we found the opposite pattern of LFP coherence. In the LGN (Figure 7.4e) and PGN (Figure 7.4f), the coherence with cortical center LFP was higher in the full model compared to the feedforward-only, but neither showed size-tuning.

These results showed that our initial intuition was oversimplified: an intact cortico-thalamo-cortical loop (compared to an open-loop condition) produced an overall drop of coherence between center and surround excitatory iso-groups (contradicting our initial prediction) but selectively raised the coherence between center and surround spikes, only for preferred stimulus sizes (see above sections). In parallel, it raised the surround coherence to center spikes for larger than preferred stimulus sizes. However, in order to invoke a direct causal role (Einevoll et al. 2013) for the surround suppression of center responses, the way the spike-triggered LFP average is built has to be taken into consideration, especially when looking at Figure 7.5a. The figure shows the level of center LFP coherence to surround spikes, with a rise in coherence for stimuli of 0.5 degree radius. But at that size, the stimulus is not hitting directly the surround cortical cells (although it has to be considered that thalamo-cortical divergence partially propagates thalamic activity also to the cortical surround). Therefore, for small stimuli, surround

spikes cannot cause the raise in center coherence. Few spikes from the surround ongoing activity (also partially driven by thalamocortical divergence) triggered the summing up of center LFPs, which were already coherent for local intracortical and stimulus-induced correlations. A completely different interpretation of the coherence levels can be applied for the center results at large sizes (Figure 7.5a, beyond 1 degree stimulus radius) and for the surround results (Figure 7.5b). The (many more) spikes fired by the surround for large stimuli are not making the center and surround more coherent, actually the opposite (for stimulus radiuses >1 degree). In contrast, the spikes fired by the center for large stimuli are making the center and surround more coherent (Figure 7.5b, around 2 degrees stimulus radius) but not for stimuli beyond the surround area (> 2 degrees).

To the best of our knowledge, the measure of spike-field coherence has never been performed experimentally in the *feedforward-only* (or similarly inactivated loop) condition. However, the shape and overall time-course of our stLFPs resembled those reported in the (similarly few) studies where they were recorded in the intact visual cortex of cat (Gray and Singer 1989, Arieli et al. 1995). In particular, Gray and Singer 1989 performed inter-columnar recordings between cat area 17 and 18 during full-field drifting gratings stimulation and reported correspondence between the tuning curves obtained from multi-unit activity (MUA) and LFP, confirmed by their spike-field coherence measurements.

In summary, in the previous section we obtained indications that the cortico-thalamo-cortical contribution from the cortical surround is changing the conductance balance of both excitatory and inhibitory cells in the cortical center. Here we refined this observation, by specifying that a bi-directional (surround-to-center and center-to-surround) reduction of coherence for larger than optimal stimuli, is observed only in the full model, and that closed loop connectivity is needed for the emergence of size-tuning selectivity in cortical cells.

8 Discussion and Conclusions

The aim of this thesis was to provide a better understanding of the functional role of the corticothalamic feedback loop by using a detailed and biologically plausible model of the different subcircuits composing the mammalian early visual system and dissecting their functional impact by appropriate computational paradigms.

I approached this task by reviewing and synthesizing the current published knowledge (in chapter 2). I selected experimental and modeling strategies, together with corresponding analysis workflows (in chapter 3 and 4). I summarized the model structure and various versions of it (in chapter 5), and then I presented the modeling results, divided in two complementary points of view: a *thalamic-centered viewpoint* (in chapter 6), where I looked at the functional role of cortical feedback for thalamic integration, and a *cortical-centered viewpoint* (in chapter 7), where I looked at the functional role of cortico-thalamo-cortical loop for cortical integration.

I analyzed the recurrent nature of the early visual system, and the information flow between the feedforward pathway and the various embedded loops from cortex and PGN by a systematic approach: (i) incrementally adding loops to the feedforward skeleton such as to reach the full connectivity model; (ii) reproducing in-vivo experimental studies by using virtual recordings in my simulations, and (iii) venturing into the proposition of new experiments. By adopting such a “constructionist” approach, I attempted to extract the relevance of these different sets of loops, for visual

processing. This was made possible by the ease of turning on or off each of the visual system sub-elements in the in-computo approach.

Here I will recapitulate my findings, presenting how they relate to the initial aim of the thesis, highlight their links with the background chapters, placing them within the context of the field, while also acknowledging limitations. In conclusion, I suggest ways to improve them, and indicating how they could help other researches in the field.

8.1 Developing an virtual experimental strategy

In the corticothalamic feedback scenario, the *in-vivo* thalamic function depends on the interaction of distinct circuits operated by distinct mechanisms, and the cortico-thalamic feedback recruits them in a highly context-dependent manner. Not surprisingly, over the past decades, only few teams have embarked on the challenging task of studying the cortical feedback to visual thalamus, often reporting contradictory results, depending on the type of experimental technique which was used and on which circuit was under examination.

I approached the task of reuniting different levels of description, based on a diversity of data sets gathered by separate labs, having different research focuses, by using an integrative large-scale spiking model of the cat thalamo-cortico-thalamic loop. This model was constrained by anatomical studies for connectivity statistics, single cell electrophysiology studies for cell parameters, and functional population studies for the firing statistics of evoked responses. By iterating through the reproduction of experimentally recorded responses to six stimuli configurations (uniform luminance background, sinusoidal drifting gratings modulated in contrast, spatial and temporal frequencies, orientation and size) presented in conditions where the corticothalamic loop was either intact, variously inactivated or totally suppressed, we converged on a single parameter set that enabled us to

reconcile a number of experimental observations. The parametric validation process followed a “constructionist” step-by-step strategy that started from the simplest open-loop model and incrementally complexified it in a more realistic closed-loop system. At each integrative step, I showed how each new embedded loop interacted with previous ones and how it changed the functional representation of the sensory input in thalamus or cortex.

8.2 How cortex modulates its own thalamic input

In chapter 6, I started by showing that the LGN-PGN system is capable of response selectivity for stimulus features in the absence of cortical feedback, inheriting and further refining retinal selectivity. Then, I presented how the corticothalamic feedback modulates the existing thalamic discriminative sensitivity by enhancing focused excitation and broad inhibition. Here, I will discuss these results, grouping them by common themes.

8.2.1 The LGN response tuning to spatial and temporal frequency is almost entirely inherited from retina

In the absence of both PGN and cortical feedback (LGN-only condition), the spatial frequency selectivity expressed in the LGN is inherited from retinal inputs (Figure 6.1a). PGN feedback refines such selectivity (Figure 6.1 b and d). The introduction of cortico-thalamic feedback does not change response selectivity but only its amplitude (Figure 6.1 c and d). Similar considerations apply for LGN temporal frequency response: local inhibitory contributions, either from interneurons or PGN, are the source of non-linear filtering of the LGN transfer function (Hamamoto et al. 1994); they have a strong influence on cortical integration (Alitto and Usrey 2004) but are virtually not affected by cortical feedback (Marrocco et al. 1996).

These findings emphasize how strongly some aspects — here spatial frequency — of the signal coming from retina are able to determine basic response properties of thalamus and cortex. Such retinal dominance can have

evolutionary origins, in capturing visual environment statistics (Sakmann and Creutzfeldt 1969, Dan et al. 1996, Mante et al. 2005) so that the early visual system responds almost entirely to the behaviorally relevant range. Within this range, cells in the visual cortex can encode for additional stimulus features, such as oriented contours of various sizes in V1 (Creutzfeldt and Nothdurft 1978), or for cross-scale, cross-orientation, and cross-position combinations of features, as shown in V2 (Freeman et al. 2013). Only stimuli within the right range of spatial and temporal frequencies, but also selective to new features (such as orientation or size tuning) better engage cortex and better show the different responses of thalamus.

8.1.2 The cortical feedback controls thalamic excitability and the dynamic range of evoked responses

Before considering functional effects specific for higher-order stimulus features, cortical feedback controls two very basic properties of thalamic response: (i) overall excitability, and (ii) response dynamic range.

First, with a spatially uniform stimulation (background luminance), the cortical feedback increases the ongoing activity of LGN (Figure 6.7), contributing to the idea of a generic cortical modulation of thalamic response by the corticofugal synaptic bombardment. The introduction of cortical feedback does not change how the LGN-PGN system responds to luminance increases, except for the overall amplitude of response.

This result is linked to those of the previous section (§8.2.1), stressing the importance for the thalamocortical system to be probed using stimuli capable of engaging a selective cortical response.

As evident in the protocol, the absence of additional sources of variability in the model represents one major limitation in tightly matching the experimental results for ongoing activity. A straightforward solution — but non-realistic, although used in other models (e.g. Diesmann et al. 1999, Vogels and Abbott 2005) — would have been to add an external controllable

source of variability, like a generator of (white or colored) noise. However, our main goal was to study the mechanism of such a system in the cleanest possible, though rich enough, setup, therefore we did not add any ad-hoc additive noise source into the model, which would have propagated and amplify throughout the modeled circuitry due to the presence of strong recurrence.

Second, with a contrast-modulated stimulus (sinusoidal drifting gratings), it is possible to look at how the cortical feedback modulates the LGN transfer function. It controls LGN functional sensitivity by lowering the input/output gain (Figure 6.5b), while also controlling LGN response threshold (Figure 6.5d).

Considering three options described in the literature (Figure 8.1), our modeling results, by consistently reproducing existing experimental evidence, show how known thalamocortical circuitry can implement a global cortical gain control through changes in response threshold with similar input/output gain (panel c). This set of results shows how varying the difference between maximal and minimal luminance of a sinusoidal drifting grating is a simple yet powerful protocol to uncover a general cortical ability to modulate the LGN transfer function.

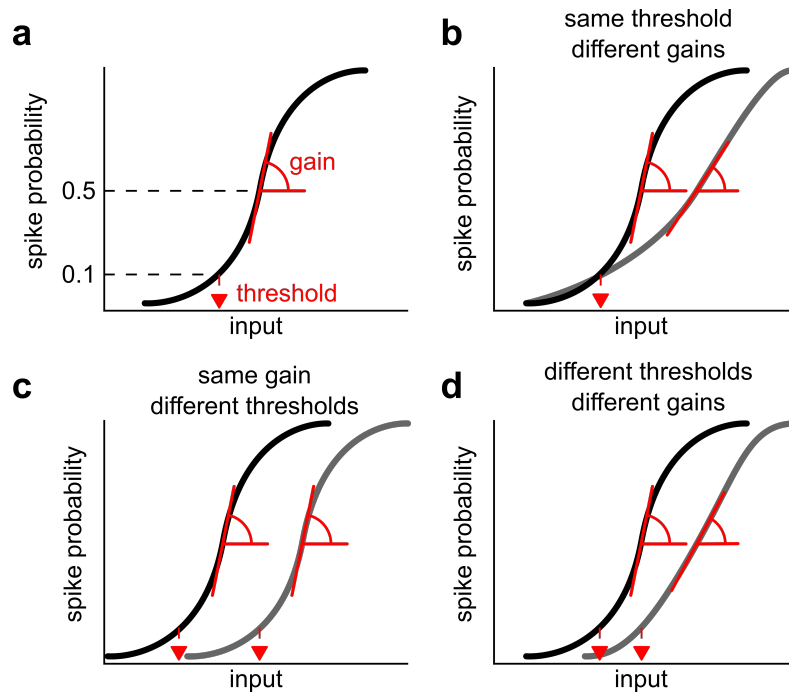


Figure 8.1 Generic models of gain control. Experimental and theoretical studies identify three possible forms of control over the neural transfer function. (a) The transfer function is characterized by its *gain* — slope of the tangent at 0.5 spiking probability — and its *threshold* — abscissa at 0.1 spiking probability. The transfer function represents the dependence of the response probability (ordinates) with the input current or input conductance amplitude, or some feature-selective drive. Three hypothetical scenarios could explain how the cortex might exert its control over thalamus by controlling differentially gain and threshold : (b) only changes of gain (as in Chance et al. 2002), (c) only changes of threshold (Wolfart et al. 2005, Behuret et al. 2013, and ours), (d) changes of both gain and threshold.

Gain modulation performed by corticothalamic projections regards how it might also serve the genesis of contrast-invariant responses at the cortical level. Simple cells in primary visual cortex respond in a contrast-invariant manner to drifting gratings varying in their orientation (Skottun et al. 1987, Anderson et al. 2000). The contrast-invariant tuned response of simple cortical cells has been initially ascribed (Troyer et al. 1998, Miller 2003) to strong indirect feedforward inhibition, from LGN-driven cortical interneurons, dominating a weaker direct feedforward excitation from LGN. Later, a property of feedforward excitatory thalamocortical synapses has been suggested to provide on its own the mechanism required for generating contrast invariance (Banitt et al. 2007): irrespective to stimulus orientation,

the thalamocortical synapses are rapidly depressed by train of stimuli (Boudreau and Ferster 2005). Considering such depression together with stimulus orientation and the converging thalamocortical afferents, a stimulus cross-oriented with the preferred orientation of a simple cell would invest and activate only roughly half of the projecting thalamocortical cells, resulting in less and uncorrelated synaptic activity, compared to an iso-oriented stimulus. Here, based on the above gain modulation result (Figure 8.1), I can speculate that contrast-invariant cortical response might also be enhanced by the cortical modulation of LGN transfer function, where the LGN response is raised at low contrasts and saturates at high contrasts, only when the feedback is present.

8.2.3 The intrathalamic connectivity participates to extra-classical RF computations

The LGN thalamocortical cell shows a dependence on stimulus size beyond its classical discharge field, which results in the spatial confinement of LGN responses.

In line with experimental data, our model thalamus (LGN and PGN) probed in isolation from cortex (*without-cortex* configuration) is expressing selectivity for stimulus size, with a small but significant degree of extra-classical surround suppression (Figure 6.2a). This is due to an increase of PGN inhibition onto LGN (Figure 6.2c), which is only expressed for large sizes (Figure 6.2b).

How is it built a preference for stimulus size in the response of an LGN cell in the absence of cortical feedback and retinothalamic selectivity? Such preference is a result of balance between LGN excitation and PGN inhibition. This balance is established by the LGN-PGN connectivity. More in detail, the extent of LGN axonal arborizations into PGN is narrow, while the extent of PGN axonal arborization into LGN is wide. Therefore, for an LGN cell, the spatial profile of excitation is focused while that of inhibition is broad, much like the RF structure that it inherits from retina but, in its case, it goes

beyond the classical discharge field. This arrangement results in two LGN response regimes. Driven by its retinal afferents, the LGN responds already to small-sized stimuli, but the reduced summated excitation coming from few LGN cells is not enough to elicit a significant response from PGN (left of Figure 6.2 a and b). When exposed to large-sized stimuli, many more LGN cells drive more PGN cells, whose combined inhibition is stronger onto their LGN targets (right of Figure 6.2 a and b). The stimulus size that elicits just the largest possible response from an LGN cell, without engaging too many PGN cells, will yield the preferred size for that LGN cell. Larger stimuli will induce extra-classical surround suppression of that LGN cell responses.

Such extra-classical, beyond-RF, selectivity of LGN responses has been long known (Cleland et al. 1983, Murphy and Sillito 1987). However, the proposed explanation has been ascribed either to properties of the retinal afferents, or to cortical feedback. For the retinal origin, the Y-type does show extra-classical suppression but the RGC X-type (that we chose to model) shows little if any (Barlow et al. 1977, Passaglia et al. 2001, 2009). It is only considering together the two afferents, as it is often done for practical but not so rigorous reasons (see discussion at the end of §6.2), that extra-classical effects are reported in the X pathway. For the cortical origin, Hubel and Wiesel (1965) already reported end-stopping (which they called “stopped edge”) hypercomplex cells in both V1 and V2 (see also Pack et al. 2003), and hinted to interactions with the length-tuning of V1 cells, which could be back-propagated to thalamus. In addition, Murphy and Sillito 1987 reported that, without feedback, LGN cells were still retaining a degree of surround suppression. However, confounds cannot be ruled out for several reasons: for their experimental procedure (ablation), for feedback from even higher visual cortical areas (they removed only areas 17 and 18), for the inclusion of Y-type LGN cells. It could therefore be maintained that, in an in-vivo preparation, it is difficult to decide between the many possible sources of extra-classical suppression.

In our *in-computo* simulation, we can choose what to include. The retinal RF is represented by a Difference-of-Gaussians, with no built-in retinal long-range connectivity, and the cortical feedback can be disconnected completely. And when this is done, the thalamus is still capable of extra-classical surround suppression. Considering also how stable the parameter space appears from the search we have performed around the mean values taken from the literature for the LGN→PGN and PGN→LGN axonal arborizations (see Methods), our conclusion is that thalamic circuitry without cortex is capable to express surround suppression.

In summary, I showed that, for growing stimulus size, first there is a growing excitation of LGN responses, up to stimuli large enough to also trigger a strong PGN response. I expect that this response will produce a halo of LGN response suppression in region retinotopically corresponding to the edges of the stimulus. In fact, these cells will not receive retinal excitation but will reticular inhibition due to PGN→LGN spread. A computational confirmation of this prediction can be found in Martinez et al. 2018 (Figure 7), where they show the topographic representation of responses of LGN cells in to both flashed spots and drifting gratings, and both stimuli induced the halo. This will introduce an enhanced spatial confinement of LGN population activities, with an excited center and a suppressed surround that extends beyond the stimulus. As I will argue in the next section, this property can be further utilized by the corticothalamic feedback to induce an even stronger spatial confinement.

8.2.4 The visual cortex projects its own preference to thalamus

In this section, I will argue that the organization of corticothalamic feedback connections is similar to the intrathalamic one, and that it exploits the intrathalamic functional connectivity (and its stimulus-dependent response variation), resulting in LGN responses biased towards the cortical preference of their feedforward targets.

In the previous section, I discussed results from the available literature and our model, arguing that the thalamic center-surround opposition is achieved by strong, spatially focused, LGN→PGN and weak, spatially diffuse, PGN→LGN connectivity. From our results, the corticothalamic connectivity is similar: the extent of V1→LGN axonal arborizations is narrow, with stronger synaptic efficacy, compared to the wider extent of V1→PGN axonal arborization, with weaker synaptic efficacy.

Three sets of evidence from both experimental and modeling results support my argumentation:

- i. When the LGN responses are tested with stimuli of variable size, in the *full* model compared to *without-cortex* configuration, there is a significant increase of response at the preferred size together with an increase of surround suppression (Figure 6.3b).
- ii. The cortex exerts its control by varying the LGN balance of excitation and inhibition through differential corticogeniculate and corticoreticulate spread of connections (Figure 6.4). The extent of V1 axonal arborizations into LGN is narrow, with stronger synaptic efficacy, compared to the wider extent of V1 axonal arborization, with weaker synaptic efficacy. This arrangement results in an increased LGN response for the optimal size, and further LGN suppression for larger-than-optimal stimuli.
- iii. LGN cells corticotopically placed under a pinwheel of the cortical orientation map present less orientation bias with respect to LGN cells placed under the middle of iso-domains (Figure 6.6).

Three more notes should be made regarding these results.

First, as a general consideration, this arrangement is not surprising, given that a focused excitatory center paired with a broad inhibitory surround provides stability both theoretically and experimentally (Kirkland and Gerstein 1998, Chance et al. 2002). It is interesting to note that both

peripheral-to-central and central-to-peripheral connections adopt the same stability-ensuring solution.

Second, in our model, the spread of corticogeniculate connections follows a Gaussian distribution. Corticofugal axon arborizations in the LGN have been measured mainly by morphological studies, which reported irregular circular shapes (Murphy and Sillito 1996, Murphy et al. 1999, FitzGibbon et al. 1999, daCosta and Martin 2009). A single morpho-functional study (Murphy et al. 1999, 2000), mapping the orientation preference of the cortical origin cell for each corticothalamic axon in the LGN, reported more elongated axonal spread either iso- or cross- oriented with respect to the orientation of their source cortical cell. This triggered speculations on the possible functional role of this morphological specificity (Sillito and Jones 2000). However, a study exploring this role in relation with cortico-cortical and corticothalamic feedback did not provide clear-cut functional conclusions (Jones et al. 2013). We chose an isomorphic Gaussian feedback spread in the present work, and this arrangement already shows a discrete functional impact, but it would be interesting to replicate it using Gabor-shaped distributions for the sampling of corticogeniculate connections, to further explore their functional impact.

Third, in our model, the spread of corticoreticulate connections is a simplification, based on our understanding of the experimental literature. We set V1→PGN connections to have a larger spread than V1→LGN. But the experimental literature gives an opposite picture. In particular, morphological studies reported only en-passant boutons of corticofugal axons in the PGN (Ahlsen and Lindstrom 1983, Boyapati and Henry 1984, FitzGibbon et al. 1999, FitzGibbon 2000). However, PGN cells form a dense dendro-dendritic network (using gap-junctions) that is capable of rapidly spreading excitation laterally within the PGN population (Deleuze and Huguenard 2006). Instead of modeling the gap-junctions we decided to simply have direct corticoreticulate excitatory connections that roughly matched the reported spread of PGN-PGN excitation. A due improvement to

the model would be to implement a model having the gap-junctions and compare its responses against those obtained with the present one.

The last result of this section regards different expressions of cortical bias on thalamic computations in different locations of thalamus, depending on the structure of the target area of the feedforward projection in the V1 orientation map (Figure 6.6a).

In the *without-cortex* configuration, there was no significant orientation bias for any LGN cell (Figure 6.6, gray curves). In the *full* model, though, for cells of the LGN targeted mainly by cortical cells well grouped within an iso-domain of the orientation map, there was a bias increase (although non-significant) of LGN preference towards the orientation of the target cortical iso-domain (Figure 6.6 b1, black curve). No bias was found for LGN cells reciprocally connected to cortical cells situated within a pinwheel of the orientation map (Figure 6.6 b2, black curve).

The reason for these results can be ascribed to the fact that corticothalamic projections overlap extensively but up to a limit roughly established by the cortical “hypercolumn”. LGN cells well under an orientation iso-domain, are far enough from the projections of cortical cells pertaining to another iso-domain, leading to the presence of an orientation bias similar to their corresponding cortical iso-domain. They also will be less affected by non-preferred cortical stimuli. On the contrary, LGN cells under a pinwheel receive concurrent direct excitation and indirect inhibition (through PGN) fed back by all orientation-tuned cells composing the cortical “hypercolumn” (Hubel and Wiesel 1965), which cancel each other out, consequently not expressing any particular tuning.

8.3 How cortex affects its own computations by modulating thalamus

In chapter 7, I explored with virtual experiments how the cortico-thalamo-cortical loop modifies cortical computations. I examined how the loop strengthens the tuning contrast between cross-oriented domains of the cortical orientation preference map. I found that the corticothalamic loop increases cortical surround suppression by changing the balance of excitation and inhibition in thalamic and cortical cells. Then, I examined how the corticothalamic loop modulates selectively the spike-to-field coherence in cortex, dampening more the surround than the center.

8.3.1 The loop regulates the cortical spread of excitation

In this section I will argue that the cortico-thalamo-cortical loop regulates the cortical spread of excitation by enhancing response suppression.

Four sets of evidence from the results support my argumentation:

- i. When tested with full-field sinusoidal drifting grating varying in orientation, an intact cortico-thalamo-cortical loop significantly enhanced the response suppression for cross-oriented stimuli (Figure 7.1 a and c, left).
- ii. When tested with size-varying patches of sinusoidal drifting gratings, the intact cortico-thalamo-cortical loop significantly increased the local tuning contrast of the orientation map selectively for stimulus sizes and only for cells located in the center domain (Figure 7.1 a and c, right, and Figure 7.2).
- iii. Only in the center domain, the cortico-thalamo-cortical loop significantly enhanced the surround suppression of both excitatory and inhibitory cells conductances (Figure 7.3, panels a-d, and Table 7.1) by changing the excitatory/inhibitory conductance balance of excitatory cells and increasing the excitatory conductance of inhibitory cells.

- iv. In the thalamus, the cortico-thalamo-cortical loop changed in a similar manner the conductance tuning curves of PGN and LGN (respectively Figure 7.4 a and b), at stimulus sizes corresponding to those engaging the cortical surround.

The model results identify two main roles for the cortico-thalamic loop: (i) it strengthens the tuning contrast of the cortical orientation map through horizontal inhibition in cortex and through corticothalamic enhancement of the excitatory/inhibitory balance; (ii) it dynamically and selectively modulates the activity coherence between iso-oriented cortical cells. The first is due to an increase of cortically mediated surround suppression to the cortical center, making the ratio of excitation-to-inhibition more balanced for iso-center excitatory cells while shifting the ratio towards more excitatory dominated regimes for inhibitory cells. The second is due to selectivity of coherence control over cell type (only apparent for iso-center excitatory cells) and stimulus features (size).

8.3.2 The loop selectively controls corticothalamic coherence

In this section I will argue that the cortico-thalamo-cortical loop selectively manages cortical and thalamic coherence, characterized by the spike-triggered LFP — a measure of functional connectivity between the spiking activity at a source location and the postsynaptic response at a target location.

Evidence from three results support my argumentation:

- i. In cortex, an intact cortico-thalamo-cortical loop lowers on average the coherence between center and surround, with respect to an open-loop condition, where the coherence is high over the whole stimulus domain (comparison of respectively grey and black curves in Figure 7.5 a-d).
- ii. However, an intact cortico-thalamo-cortical loop raises selectively the coherence between center and surround only for the iso-oriented excitatory cells; in the center, coherence is high for small stimuli but

low for large ones (Figure 7.5a), while in the surround it is low for small stimuli and high for large ones (Figure 7.5b).

- iii. Contrarily to cortex, in the thalamus an intact cortico-thalamo-cortical loop uniformly raises the thalamic coherence only to the cortical center (Figure 7.6).

Two considerations represent the starting point for further (*in-vivo* and *in-computo*) experiments: (i) the causal relationship between center and surround needs more measures to be completely established, and similarly (ii) thalamocortical coherence need more measures to better assess the impact of corticothalamic feedback.

First, as mentioned in the discussion of §7.3, the way the spike-triggered LFP average is built has to be taken into consideration, especially when looking at Figure 7.5a, where the coherence levels for the cortical center iso-group cannot be imputed to the surround but to local coherence. The source of such coherence should be further investigated. Measuring the local intracortical cross-correlation, together with the thalamocortical cross-correlation, is probably the best way to proceed, and we are currently working on it. Again, the prediction, partially confirmed by preliminary results (unpublished), is that the cortico-thalamo-cortical loop will increase the levels of cross-correlation both in cortex and between cortex and thalamus.

In addition, another doubt can be cast on the coherence between cortical center and surround. The assumed causal relation between spikes in one location and LFP in another, at the core of the coherence measure (spike-triggered LFP), holds well for monosynaptic connections but less for highly recurrent networks like cortex (Einevoll et al. 2013). However, the two configurations (feedforward-only and full) considered here are specifically targeting the monosynaptic thalamus-to-cortex and cortex-to-thalamus connections. Therefore, the responses of the recurrent cortex are compared in two conditions that are partially breaking that recurrence.

Second, the loop is increasing the coherence between the whole thalamic assembly (LGN and PGN) to the cortex region representing the stimulus center. This result potentially contradicts Behuret et al. 2015 (Figure 9 and its description), where it is proposed that cortico-thalamic feedback controls the coherence of LGN thalamo-cortical projecting cells in order to focus the spotlight of attention. More specifically, they proposed that, in order to have a functional (attentional) role, the cortico-thalamic feedback is selectively decorrelated for retinotopically relevant portions of LGN — boosting the sensory transfer through disruption of thalamic spontaneous oscillations — while correlated towards other, irrelevant, portions of the LGN — boosting their oscillation and preventing sensory transmission. I reported that the whole recorded LGN and PGN, in the *full* model, were coherent with the cortical center, over the whole set of stimulus sizes. This would be in contradiction with the special arrangement described above. However, it has to be noted that the whole recorded LGN and PGN are taken here to perform the coherence measure. That measure should be repeated exploring topologically defined extents of these populations to see whether during sensory processing spatially non-homogenous differences in strength of thalamocortical coherence emerge locally, probably adopting also information theory measures, as it was done in Behuret et al. 2013. My expectation, in line with Behuret et al. 2015, is that the portion of LGN directly beneath the cortical center should score better for a thalamocortical coherence measures, and be more locally decorrelated, than the LGN portion beneath the cortical surround, which should be more engaged in thalamic-only oscillations.

8.4 Limits and perspectives

In building the present model, the ultimate goal was not to match a single set of experimental results, rather to reflect an extensive compilation of the available literature. However, it is not possible to be exhaustive in the

timeframe of a PhD thesis, given the volume of the relevant literature, both with respect to what has already been done in previous models, and regarding the implementation choices. A few notes on both aspects can help identifying future direction of development.

8.4.1 Comparison with previous models

I already discussed previous modeling efforts in chapter 3. Here I will consider two principal directions that seem better aligned with the present results and type of modeling.

Cross-correlation. As mentioned in the previous section (§8.4.2), there are questions that would be better addressed by considering the correlation between thalamic populations (LGN and PGN) and those between cortical and thalamic populations. The experimental work done by Sillito et al. 1994, where the cross-correlation between LGN cells was studied with and without cortical feedback, could be approached *in-computo* while avoiding the problems raised by the *in-vivo* preparation (underscored by Brody 1998). That study triggered a series of models aiming at the replication of those results (Orzo et al. 1997, Kirkland and Gerstein 1998, Kirkland 2000). All models confirmed the ability for the cortical feedback to induce correlations in thalamic activity both temporally and spatially selective with respect to the stimuli used. However, as mentioned in chapter 3, all models were lacking the PGN, receiving direct inhibition from cortex, but the results presented in this thesis point towards a relevant role for the PGN, even in the absence of cortico-reticulate feedback. In any case, a more elaborate interpretation would require — in our present model — additional *in-computo* experiments to look at the correlations induced in the whole system by the cortico-thalamic recurrence. As mentioned before, we are already working in this direction.

Temporal structure of thalamic response. The study of how the cortical feedback affects LGN inter-spike interval and temporal response kernel is directly related to the previous topic. Wörgötter et al. 1998 built a model

after their experimental study involving intra-cellular recording in the LGN performed while cortex was inactivated (by cooling or application of GABA) or stimulated (by application of Glutamate in layer VI). They found significant modifications in the LGN cells for both inter-spike intervals (ISI) and temporal response kernel. In particular, they reported a reduction and broadening of ISI peaks during inactivation, and an increase and narrowing of the ISI peaks during stimulation, compared to the control condition. Not surprisingly for the type of phenomena under scrutiny, taken into account the considerations of chapters 2 and 4 regarding the control on temporal responses by feedforward inhibition, their model included local LGN interneurons targeted by both cortical feedback and retina. It would be interesting to add feedforward retinothalamic (especially RGC to interneurons) modulation of LGN response, in the first place to compare it with the phenomenological model we implemented, but also to assess the modulatory power that the corticothalamic feedback can exert on this earlier activity, compared to that of LGN-PGN interaction.

8.4.2 Implementation choices

I already discussed the modeling choices in the Methods (chapter 4). However, some choices deserve some additional comments.

Early vs higher-order vision. A general consideration is due on the choice of studying the cortico-thalamic feedback from a early visual system point of view. Topological organization is one of the most salient properties of the early stages of vision, but the higher the processing stage is, the looser the retinotopic organization becomes. Therefore, the strategy based on specific stimuli and a clear open/closed loop opposition will probably become unreliable for higher-order corticothalamic relationships (Sherman and Guillery 2002, 2011, Crick and Koch 1998). How to carry on the study there? At least two alleys can be taken to keep studying the thalamocortical relationship. One, close to the present modeling efforts, implies using (and probably adapting) coherence and information theory measures to the flow

of information through the visual streams (as suggested in Sherman and Guillery 2011, and modeled by Cortes and van Vreeswijk 2010 with respect to Pulvinar). The other, less close to the present modeling efforts, implies behavioral efficiency cues to assess the functional role of the thalamocortical loop. For example, experiments involving behavioral responses (such as saccades and reaction times) could be used to assess how the thalamocortical loop can speed up and make more accurate the process of converging onto a motor response.

Simple retina. We considered a simple model of retina composed of a Difference of Gaussians with extra components (Naka-Rushton and suppressive field). However, more complex anatomical and functional features are present in the retina. The use of more rich, biologically plausible, models such as Virtual Retina (from INRIA, Wohrer and Kornprobst 2009) could be explored to obtain more realistic input spike trains, although the detailed correlation structure between ganglion cells in the INRIA model may not be biologically relevant. Using a better retinal model is certainly not a limitation since we adopted the Mozaik framework, where replacing the input layer with any chosen alternative is straightforward. This improvement would be particularly important should one choose to study more detailed temporal and correlational properties of the thalamic and cortical response.

Monosynaptic retinothalamic connections. We chose to model the retinothalamic pathway as a monosynaptic topological relationship. Although it captures the clear retinotopic feature preserved up to the primary visual cortex (Hubel and Wiesel 1965, Alonso et al. 2006) it also leaves behind interesting questions on the spread of retinothalamic connections and how they affect thalamic computation (Ruksenas et al. 2000, Wang et al. 2011, Martinez et al. 2014, Litvina and Chen 2017). Future version of the model could overcome this limitation, but they also need specific ways to assess the outcomes of such an improvement.

LGN interneurons vs PGN. LGN interneurons were not included in the present model. This is because their role is not clear. There is some evidence of functionally similar ON- and OFF-center organization of their receptive field (Wang et al. 2011), but it is not established (Hanes et al. 2011). The functional hypothesis taken into consideration in the present model is contrast gain control through triadic synapses (Famiglietti and Peters 1972, Sherman 2004), which has been implemented in the phenomenological model of the retinothalamic system by the Naka-Rushton component.

Asymmetry between OFF- and ON-center pathways. One major limitation in the model is the absence of built-in reference to the asymmetry between OFF- and ON-center pathways; which has been quantified in depth recently (Jin et al. 2008, Yeh et al. 2009, Kremkow et al. 2014). In the cat, such asymmetry has been ascribed to the fact that off-center responses dominate the cortical representation of the area centralis, while in the thalamus ON- and OFF-center afferents are balanced in number (Jin et al. 2008). We could implement such asymmetry in our model, by varying the geniculate afferent convergence to cortical domains (and it would be interesting to explore how much asymmetry is tolerated by the system). However, our simplistic ON/OFF balanced model still captures the essential features of the system at the cells' eccentricities of all experimental studies we took under consideration (usually around 5 degrees (but sometimes beyond) from the area centralis).

8.5 Defining a functional role for the corticothalamic loop

When searching for hypotheses to shape a functional understanding of the anatomical elements present in the early visual system (in chapter 2), I focused on two classical perspectives which constitute the current consensus and adopted the hierarchical schema of three levels of analysis proposed by David Marr (1982) — (i) What is the functional goal (the "computation")? (ii) What are the generic algorithms used to achieve the goal? (iii) What is the

physical (neural) substrate implementing the algorithms? Here, I will summarize them to produce a comprehensive view of the functional role of cortical feedback in low-level visual perception, and discuss how the present results fit this view.

The first theory claims that the early stages of cortical-based perception may constitute a form of unconscious inference (Helmholtz 1866, Shulz and Frégnac 2012). It attributes a clear functional goal to the corticothalamic feedback, particularly that of bearing cortical inferences to the thalamus to be verified against external inputs. The algorithm realizing the goal would (i) learn a redundancy-free model of the visual world based on the statistical properties of past sensory stimuli (Craik 1943, Barlow 1959), and (ii), considering perception as an inferential activity (Mac Kay 1962), use the model to predict incoming sensory stimuli (Barlow and Földiák 1989). In particular, at the physical/neural level, an elementary example of static spatial redundancy reduction was suggested (Pece 1992, Daugman 1995), where cortical (V1) predictions would be brought to thalamus (LGN) to help cortex extract the contours from incoming retinal images. Mumford (1991) suggested a more articulated, dynamic, view, where the thalamus would act as a blackboard for cortical representations. The corticothalamic feedback would bring feature representations of cortical cells to the thalamus, where they would overlap and be buffered (through iterations over the thalamocortical loop) for as long as hundreds of milliseconds, enough to reach a consensus on a single most-probable representation, which would be then broadcast to all (connected) cortical areas.

The second theory, taking a synthetic approach to perception (James 1890), claims that the functional goal of cortico-thalamic feedback would be instrumental in binding of separate features into unified perceived objects. Edelman's reentry principle offers a possible algorithm, and the searchlight hypothesis of Crick could be used to implement the physical level of this framework. I merged these two approaches because they assume the same premises: (i) the functional phenomenology of psychological entities is best

captured by the concept of transient (fast and reversible) Hebbian cell assembly (Milner 1945, von der Malsburg 1982, Frégnac and Bienenstock 1998, Frégnac 2002), (ii) parallel streams of neurons, along the sensory pathways, independently code for stimulus features (like orientated contours, colors, etc.), and (iii) a mechanism is required to select and bind these separate feature representations into dynamic cell assemblies.

Edelman (1978, 1987) proposed the "reentry" algorithm by viewing the genetic and epigenetic variability in morphology and connectivity of neurons as a form of redundancy suitable for a selectionist approach. Through the recurrences imposed by the thalamo-cortico-thalamic loop, the reiterate activation of anatomically different but functionally equivalent cell assemblies (called "reentry" process) would both (i) ensure functional continuity, in spite of cell energy depletion and sparse activity, and (ii) represent the substrate for cell assembly selection. Francis Crick refined the set of known mechanisms operating on cell assemblies (Crick 1987). He suggested that (i) the binding would be implemented by short-term synaptic potentiation, transiently strengthening vertical (i.e. across stages of integration, thalamo-cortical and cortico-cortical) cell assemblies, and (ii) the selection of one vertical cell assembly would be implemented by the reticular nucleus of thalamus, polling the most active thalamocortical assemblies.

Two additional mechanisms can contribute to the formation of a transient vertical cell assembly: the egocentric selection, and the stochastic resonance.

First, *cortical egocentric selection* is a mechanism proposed by Suga et al. 1997, where cortical neurons selectively control the activity of their own thalamic input sources, through focused direct excitatory and widespread indirect inhibitory cortico-thalamic feedback. By simultaneously enhancing a preferred thalamo-cortical map, while suppressing the topologically represented surround, this mechanism would result in the dynamic confinement and strengthening of one "vertical" (thalamocortical) cell assembly at the expense of others.

Second, *stochastic resonance* in neural networks is a phenomenon that occurs in threshold-based systems where the presence of a tuned level of additive input noise facilitates the transfer of a weak signal by lowering the response threshold (Moss et al. 1993). This mechanism smooths the precise topology required by the previous mechanism. By imposing top-down correlations — whose content can represent cortically identified features — this mechanism would induce coherent responses in otherwise unrelated cells, promoting the creation of cell assemblies through functional correlation.

By taking into account the physiological knowledge of the corticothalamic system, and by merging the hypotheses above, I would conclude that:

The corticogeniculate feedback is a sensory-driven control loop, whose goal is to support the formation of dynamical and transient thalamocortical cell assemblies. The build-up and selection of such cell assemblies, is enabled by several features: (i) short-term correlation-based synaptic facilitation/potentiation; (ii) no direct lateral connectivity in the LGN; (iii) cortical "egocentric" selection of thalamic inputs (through direct focused cortico-geniculate and cortico-reticulate excitation, and indirect broad reticulo-geniculate inhibition); (iv) cortico-thalamic stochastic resonance acting at the level of principal thalamic cells of the LGN, inducing coherence in otherwise unrelated cells.

The dynamic formation and competition of cell assemblies enacted by these thalamo-cortical mechanisms implements a form of blackboard for cortical representations, whereby not only overlay and buffer them, but also enable their competition and mutual dynamical strengthening. This latter property could underlie higher-level visual processing such as figure-ground detection (Mumford et al. 1987, Lamme 1995) or contour integration (Kapadia et al. 1995, Gilbert et al. 1996, Gilad et al. 2012).

The results that I discussed above are not enough to validate this composite hypothesis, but each one, while specifically addressing questions related to

the corticothalamic feedback in the early visual system, also contributes to the consolidation of this global explanatory picture. Here, I will list the modeling results of this thesis that support (or relate to) the four features of the hypothesis I am proposing.

The first two features (i) *short-term correlation-based synaptic facilitation*, and (ii) *no direct lateral connectivity in the LGN*, are constitutive physiological and anatomical details. We have built the model including them, and discussing them in early chapters (2 — Background, and 4 — Methods).

Regarding the feature (iii) *cortical "egocentric" selection of thalamic inputs*, this thesis acknowledges the classical interpretation, and goes beyond it, recognizing two viewpoints under which it has to be intended. From a *thalamic-centered viewpoint*, most of the results of this thesis support (directly or indirectly) the classical interpretation. I have shown an intrathalamic mechanism that results in the confinement of LGN responses, depending on stimulus size, already active in the absence of cortical feedback (Figure 6.2). Then I have shown how such mechanism is directly played by the visual cortex, through strong, focused, corticogeniculate and weak, diffuse, corticoreticulate connectivity — anatomical hallmarks of cortical egocentricity (Yan and Suga 1996, Suga et al. 1995). This results in enhanced selectivity for stimulus size (Figure 6.3), which is also sensitive to the topological alignment of cortical response (Figure 6.4) — functional hallmarks of cortical egocentricity (Suga et al. 1997). This cortical egocentricity can also be noted, indirectly, in how LGN cells corticotopically placed under a pinwheel of the cortical orientation map present less orientation bias with respect to LGN cells placed under the middle of iso-domains (Figure 6.6). And, from a *cortical-centered viewpoint*, this thesis introduces an effect of cortical egocentricity for cortex itself. In fact, I have shown that the cortico-thalamo-cortical loop enhances the local tuning contrast of the orientation map selectively for stimulus sizes, only for cells located in the center domain (Figures 7.1, 7.2, and 7.3).

The fourth feature, regarding (iv) *cortico-thalamic stochastic resonance inducing coherence in otherwise unrelated LGN cells*, is less represented in the results of this thesis. However, its two components (stochastic resonance and coherence) are separately and partially addressed. With respect to stochastic resonance, I have shown how the LGN-PGN circuitry can implement thalamocortical gain control through changes in response threshold, and how this can be under cortical control (Figure 6.5). This control of thalamic response threshold might represent the substrate for stochastic resonance (compare with Figure 1c and Figure 2a in Wolfart et al. 2005, Behuret et al. 2015). And, with respect to coherence, I have shown that an intact cortico-thalamo-cortical loop raises, selectively for stimulus size, the coherence between cortical center and surround (Figure 7.5), while also raising the thalamic coherence to the cortical center (Figure 7.6).

One additional note regards the stacking of cortical representations, central for Mumford's blackboard theory. I have shown how, in our model that does not have retinal selectivity for stimulus orientation or (extra-classical) stimulus size, the cortex induces its own preference for stimulus orientations in otherwise unselective thalamic responses (Figure 6.6). These two selectivities are summed without additional specialized LGN cells or circuits, and this could be interpreted as a 'correlate' of the blackboard, especially considering that other selectivities could be projected from cortex (such as in the model of Hillenbrand and van Hemmen 2002).

Ultimately, more advanced stimulation protocols will have to be analyzed in the model, such as those involving more complex integration of multiple visual features (e.g. various version of contour integration), and more advanced measures of cell assembly detection and analysis will have to be performed, in order to demonstrate how the proposed hypothesis of corticothalamic loop could be implemented in the living brain. However, to that end, the presented work represents the most advanced computational framework, which allows the pursuit of such goals.

8.6 Summary and conclusions

In this thesis I tried to synthesize the current knowledge about the corticothalamic feedback loop using a systematic detailed modeling approach. I built a large-scale biologically detailed model of the early visual system, which includes three known neural features critical for building transient vertical cell assemblies: (i) topological thalamocortical mapping, (ii) short-term synaptic plasticity, (iii) intrathalamic (LGN→PGN, PGN→LGN) and corticothalamic (V1→PGN, V1→LGN) connectivity. In addition, I took a constructionist approach to investigate the role of intrathalamic and corticothalamic loops, incrementally revealing their impact on early visual processing.

First, taking a *thalamus-centered viewpoint*, I showed how the cortex modulates its own thalamic input. LGN inherits from retina several features of response (e.g. spatial and temporal frequency tuning). It develops, thanks to the LGN-PGN loop, computational capabilities that go beyond the retinal receptive field (e.g. extra-classical surround suppression). The cortical feedback modulates thalamic computations, overall through a control on thalamic excitability and dynamic range, in particular, through a form of egocentric selection in which cortex selectively enhances retinotopically corresponding thalamic locations while also suppressing retinotopically unrelated locations. The cortical feedback not only modulates existing thalamic features (such as size-tuning), but also imposes onto thalamus a bias towards cortical features that are not present in the isolated thalamic computations (such as orientation tuning), realizing a form of blackboard for cortex.

Second, taking a *cortex-centered viewpoint*, I showed how the cortex affects its own computations by modulating thalamus. The cortico-thalamo-cortical loop implements a form of cortical egocentricity, by increasing the local tuning contrast of the orientation map, selectively in the center domain. In

addition, for stimuli of a preferred size, it strengthens the coherence of the center domain, in both cortex and thalamus, while lowering it for large-sized stimuli.

Taken together, these results show how a portion of the early visual system, through the cortico-thalamo-cortical loop, could form a transiently coherent whole — a vertical cell assembly — selective for some features of the stimulus, which can potentiate its processing and transfer probabilities to downstream “reader” structures.

Appendix

Scientific contributions:

- Domenico Guarino, Jan Antolík, Andrew P. Davison, Yves Frègnac, (2017), “An integrative model explaining many functions of corticothalamic feedback”, BMC Neuroscience 18(1):59 (doi: 10.1186/s12868-017-0371-2)
- Assunta Pelosi, Domenico Guarino, (2015), “Striatal cholinergic interneurons modulate action selection and reinforcement learning”, Frontiers in Neural Circuits 9(15) (doi: 10.3389/fncir.2015.00015)
- Domenico Guarino, (2018), “Krauzlis’ strange inversion of reasoning”, Frontiers in Systems Neuroscience 12(34) (doi: 10.3389/fnsys.2018.00034)

Tooling development:

- Samuel Garcia, Domenico Guarino, Florent Jaillet, Todd R Jennings, Robert Pröpper, Philipp L Rautenberg, Chris Rodgers, Andrey Sobolev, Thomas Wachtler, Pierre Yger, Andrew P Davison, (2014), “Neo: an object model for handling electrophysiology data in multiple formats”, Frontiers in Neuroinformatics 20 (doi: 10.3389/fninf.2014.00010)
- Andrew P. Davison, Yves Frègnac, Thierry Brizzi, Domenico Guarino, Olivier Manette, Cyril Monier, Yves Frègnac, (2013), “Helmholtz: a customizable framework for neurophysiology data management”, Frontiers in Neuroinformatics 25 (doi: 10.3389/conf.fninf.2013.09.00025)

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An integrative model explaining many functions of corticothalamic feedback

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In the early visual system of the cat, the feedforward pathway going from the lateral geniculate nucleus (LGN) to the primary visual cortex (V1) is well characterized both anatomically and functionally. On the other hand, despite a large amount of experimental work, there is poor agreement about functional roles of the feedback pathway from V1 to LGN. The common experimental approach compares system responses taken in the *open-loop* condition - probing thalamus in isolation from cortex - and in the *closed-loop* condition - probing the intact system. In the literature to date this approach has yielded inconsistent results. Open- and closed-loop results for some stimuli differ only by an additive factor, while for other stimuli there is a marked qualitative difference in the results.

In this computational study, we investigated the thalamocortical loop with reference to an unprecedentedly broad set of experimental studies. We took published data for six types of experiments (with stimuli varying in luminance, contrast, spatial frequency, temporal frequency, size, and orientation) involving both open- and closed-loop conditions. We explored each condition with an integrative large-scale spiking model of the cat early visual system that includes LGN, perigeniculate nucleus (PGN), and V1. The model is heavily constrained by the available literature at multiple levels: anatomical, functional, and statistical. The model is developed using the Mozaik workflow engine [1] with NEST [2] as the backend simulator.

The experimental constraints enabled us to find a single parameter set that qualitatively and quantitatively accounts for the published responses to all stimuli in both open- and closed-loop conditions. We report that in our model the feedback has additive effects on: spontaneous activity, in agreement with [3], contrast tuning response [4], and temporal frequency tuning [5]. On the other hand, in our model the feedback changes the shape of responses for: spatial frequency tuning, as in [6], size tuning response [7], and orientation tuning [8].

We identify two main mechanisms supporting our results: the reciprocal spatial distribution of cortical and thalamic receptive fields, as in [9], and the topological mirroring of cortical response profiles onto thalamus, as in [10].

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A commentary on: “Cortical and thalamic excitation mediate the multiphasic responses of striatal cholinergic interneurons to motivationally salient stimuli”

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A commentary on

Cortical and thalamic excitation mediate the multiphasic responses of striatal cholinergic interneurons to motivationally salient stimuli

by Doig, N. M., Magill, P. J., Apicella, P., Bolam, J. P., and Sharott, A. (2014). *J. Neurosci.* 34, 3101–3117. doi: 10.1523/JNEUROSCI.4627-13.2014

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Each time there is an interaction with the environment, we select one among many, equally possible, actions. How is it done? In the classical view, to access motor resources, many cortical action plans compete in the basal ganglia: a set of subcortical neuron populations, whose output constantly inhibits specific thalamic targets. In the basal ganglia, one cortical plan is selected, the corresponding thalamic inhibition is disabled, finally producing the action (Albin et al., 1989). The classical view of action selection is now extended, including thalamic afferents. And, in the current view, a key role as modulators of action selection has been assigned to cholinergic interneurons of the striatum, the largest basal ganglia structure (Ding et al., 2010).

Striatum is divided in two major populations of GABAergic medium spiny neurons (MSNs) according to different expression of D1 and D2 dopamine receptors. These two populations and their downstream pathways are respectively addressed as direct and indirect, for their connections with output basal structures (Tepper and Bolam, 2004). More than 90% of striatal neurons are MSNs while the remaining 5–10% are two types of interneurons, cholinergic, and GABAergic. These are providing the lateral inhibition that can actually implement the competition among cortical plans and therefore are a key to understand action selection.

Cholinergic interneurons are known as tonically active neurons (TANs) for their spontaneous activity (>4 Hz). They receive glutamatergic afferents from cortex and thalamus, forming more synapses with thalamic than cortical terminals (Doig et al., 2014), and dopaminergic afferents from substantia nigra pars compacta. Locally, they branch dendritic arborization up to a millimeter in diameter, and they innervate GABAergic interneurons, other TANs and MSNs (Tepper and Bolam, 2004).

Under resting conditions, MSNs are hyperpolarized by TANs spontaneous tonic firing (Tepper and Bolam, 2004). Morris et al. (2004) showed that increased cortical activity makes TANs respond with a brief burst, an afterhyperpolarization pause in their firing, and a rebound burst.

In addition, Ding et al. (2010) have shown, *in vitro*, that also thalamic stimuli elicit TAN burst-pause pattern response.

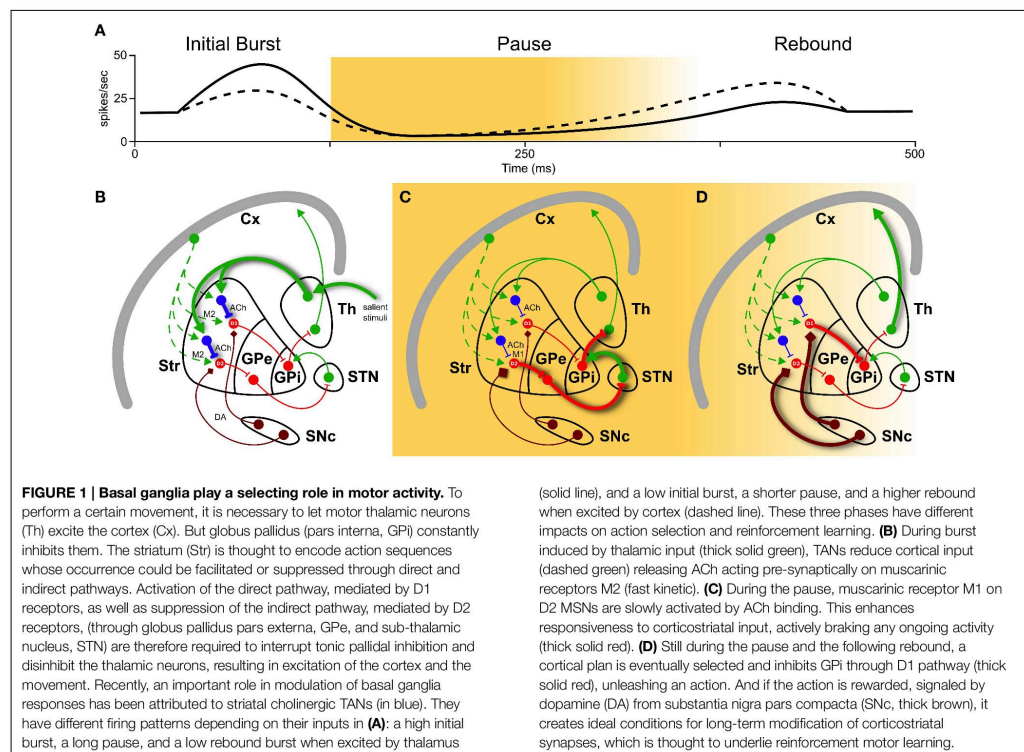
The work of Doig et al. (2014) aims at functionally distinguish thalamic and cortical contributions to action selection. Using different stimuli (single-, paired-pulse, and pulse trains) selectively delivered in the cortex and thalamus of rats, they were able to identify two temporal TAN response patterns. As in Morris et al. (2004), they used peri-stimulus time histogram (PSTH) analysis to identify the three main phases in TAN response: burst, pause and rebound. Applying pulse trains, which mimic the timing of motivationally salient stimuli (Ding et al., 2010), they were able to discriminate cortical and thalamic stimuli, predicting the whole TAN response based only on the initial phase. In fact, the number of spikes in the burst correlated positively with pause length and negatively with the magnitude of rebound: thalamic source was identified by high initial phase, long pause and low rebound, while cortical source was marked by lower initial phase, short pause, and higher rebound (Figure 1A).

To explore the contribution to action selection of these two different TANs responses, Doig et al. (2014) performed experiment in primates. The authors referred to the effect on striatum of salient stimuli, which are known to shift attention and

suppress ongoing motor activity by engaging thalamostriatal-evoked pause in TANs (Desimone and Duncan, 1995). A reward-conditioning task was performed with macaque monkeys. Two conditions were used: reward-predicting visual stimulus, followed by juice delivery, and reward-only, in which juice was delivered randomly without any predictive stimulus. Although in these experiments the authors could not determine the (cortical or thalamic) origin of inputs, using their PSTH characterization, they found in monkeys a correlation similar to that seen in rats for thalamic-induced pattern and, more importantly, it was present only after reward-predicting stimuli and weak or absent after reward-only.

Taking into count these and other results in current literature, we might point a mechanism linking action selection (1) and salient stimuli (2) (see also Figure 1). The link is in the interplay of acetylcholine (ACh) and dopamine (DA) release, induced by thalamic-mediated salient stimuli.

(1) TANs “thalamic” response pattern prepares the condition for action selection. In fact, after release, ACh binds to muscarinic receptors M2 (fast kinetic) and M1 (slow kinetic). M2 activation transiently reduces glutamate release from cortical terminals during the initial phase (Figure 1B). More



effectively, M1 activation on D2 MSNs enhances their responsiveness to corticostriatal input throughout the pause (Ding et al., 2010, and **Figure 1C**). Hence MSNs located in proximity of pausing TANs will transiently become much more responsive to cortical input (Pakhotin and Bracci, 2007).

- (2) The same “thalamic” response pattern reinforces rewarded cortical actions. Its longer pause creates a window for a cascade of events: ACh, while suppressing the ongoing actions exciting D2 MSNs, induces local DA release from dopaminergic axons acting on ACh nicotinic receptors (Threlfell et al., 2012, **Figure 1C**). In addition, ascending dopamine neurons

activity due to rewarded actions further increases DA levels (**Figure 1D**). Increase in DA will thus create ideal conditions for long-term modification of corticostriatal synapses, which is thought to underlie reinforcement motor learning (Pakhotin and Bracci, 2007).

In conclusion, Doig et al. (2014) contribute in clarifying the importance of cholinergic interneurons as modulators of action selection. With their work *in vivo*, they support the current view—hypothesized with *in vitro* data (Ding et al., 2010; Threlfell et al., 2012)—that ACh and DA work in synergy to select actions and reinforce learning.

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Krauzlis' Strange Inversion of Reasoning

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Keywords: attention, multiple-draft model, homunculus, cell assembly, basal ganglia, superior colliculus

"Attention" is a central faculty of the mind (Baars, 1988; Minsky, 1988). It has been early proposed that it is a process selecting some of the available information to focus on enhanced processing (Deutsch and Deutsch, 1963; Treisman and Gelade, 1980). Contrasting this approach, Richard J. Krauzlis recently (2014; 2017) proposed that attention is an *effect* of selection processes instead of being their *cause*. In this article, I will argue that Krauzlis' view realizes what Dennett (2009) calls a "strange inversion of reasoning," in which the competence of selecting behaviors does not need the comprehension of any attentive homunculus. In order to make the equivalence, I will detail an interface mapping between a philosophical position (Dennett's Multiple-Draft model, 1991) and a neuroscientific position (Krauzlis' attention as an effect). Such a mapping is meant to encourage a scientifically grounded dialogue between the two disciplines.

According to the original feature-integration theory of visual attention, "features are registered early, automatically, and in parallel across the visual field, while objects are identified separately and only at a later stage, which requires focused attention" (Treisman and Gelade, 1980, p. 98).

The selection mechanism of attention, and its corresponding neural correlates, have been henceforth the target of further research. Crick (1984) proposed, with his "searchlight" hypothesis, that the thalamic reticular nucleus controls the focus of attention, whose content is represented at the cortical level. In fact, reticular cells receive connections from both feedforward thalamic and feedback cortical pathways, and they also inhibit each other, thus having the necessary circuitry to implement competition among their afferents (Sherman and Guillery, 2001). Over time, several other brain areas have been implicated in attentive behavior (Krauzlis et al., 2013): sensory and parietal cortex, frontal cortices like the frontal eye field, with a growing role for the superior colliculus (SC). Recently, Lovejoy and Krauzlis (2010) locally and reversibly suppressed the SC of monkeys performing a visual detection task. For stimuli placed in the affected part of SC, monkeys' performance was drastically reduced. Using the searchlight hypothesis, the conclusion would be that SC selects which part of the visual field has to be the target of attention, by supplying the ascending pathway to cortex with a saliency map (Koch and Ullman, 1987). Thus, the next step (Zénon and Krauzlis, 2012) consisted in transiently inactivating the SC during a detection task and measuring responses in corresponding visual cortical areas, with the prediction that cortical activity would be reduced due to SC inactivation. Surprisingly, the inactivation of SC did impair task performance but did not reduce cortical activity, challenging the idea that SC selects the target of visual attention.

Instead of searching for another correlate center of attention, Krauzlis and colleagues proposed a different model: *attention is an effect rather than a cause*. It would be the functional consequence of competition between "interpretations of the current state by the basal ganglia rather than competition to determine how sensory data is represented in the neocortex" (Krauzlis et al., 2014, p. 458). Such a reversal of how attention is intended realizes a "strange inversion of reasoning" (Dennett, 2009), where processes that do not have comprehension can nonetheless show competence. In Krauzlis case, attentive behaviors would not result from the comprehension of a homunculus selecting which sensory data is represented in neocortex. They would instead result from the competence of selective processes in the basal ganglia.

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Further exploring this link prompts the identification of an interface—revolving around the concept of cell assembly (Hebb, 1949)—yielding a synergistic mapping between Dennett's Multiple-Drafts model (MDM) and Krauzlis' model regarding attention.

Dennett's MDM fundamental thesis is: "There is no single stream of consciousness, no place where 'it all comes together' for a Central Meaner. There are multiple drafts, separate channels in which specialist circuits try to do their various things. Most of these fragmentary drafts of narrative play short-lived roles in the modulation of activity but some get promoted to further functional roles, in swift succession. The seriality of this process is not a hard-wired design feature, but rather the upshot of a succession of coalitions of these specialists" (Dennett, 1991, p. 253). These four sentences are the core building blocks of Dennett's explanation of consciousness. By analyzing each sentence, I will now build the interface and use it to map the two models (see Table 1 for a direct comparison).

The first sentence rejects the homunculus, and Krauzlis shares it: "Viewing attention as an effect rather than a cause has the advantage of eliminating the need to find the homunculus that aims the spotlight of attention. Instead, we should be able to explain the functional circuits that give rise to the phenomenology of attention without using the word 'attention'" (Krauzlis et al., 2014, p. 461).

In the second sentence, Dennett was intentionally vague using the term "draft." A possible denotation for draft, however, may be the Hebbian cell assembly: "a diffuse structure comprising cells in the cortex and diencephalon (and also, perhaps, in the basal ganglia of the cerebrum), capable of acting briefly as a closed system, delivering facilitation to other such systems and usually having a specific motor facilitation" (Hebb, 1949, p. xix). As explicitly put in Hebb's definition, the concept of cell assembly identifies sets of cells, spanning the whole sensation-action arc. However, over time, two overlapping versions of the same concept emerged. *Object-action cell assemblies*, representing potential associations between sensory objects and actions (Humphreys and Riddoch, 2000), and (generic) *cell assemblies*, with a broader sense of "set[s] of neurons among which excitatory connections have been potentiated" (Harris, 2005). Therefore, if we denote Dennett's "specialist circuit" by a set of functionally related areas (e.g., visual: lateral geniculate nucleus, striate and extrastriate cortices, SC, ..., as in Akins, 1996), then a "draft" can be denoted by an active (generic) cell assembly—one out of many that could be active at any given moment in the "specialist."

The third sentence fits the proposed interface well, highlighting the fluidity of cell assemblies, and introducing a selection process involving them: "some get promoted to further functional roles, in swift succession." But how, exactly?

This question is crucial for the MDM, and the interface may offer an answer, provided it succeeds in the terminology mapping. Krauzlis considers that "Good decision making depends crucially on properly identifying the current state of the animal and its environment" (Krauzlis et al., 2014, p. 457). This wording implies a "state" that has to be recognized. The concept of "state" has its root at the beginning of cybernetics, where every physical system (including an organism, its nervous system, and its environment) can be described by a finite set of states and state transitions (Ashby, 1961, p. 10). However, this powerful abstraction has been subsequently challenged because many relations between an organism and its environment, or "affordances" (Gibson (2013), are equally possible in the same environmental state. The neural components of such relations have been mapped onto object-action cell assemblies (Humphreys and Riddoch, 2000; Cisek, 2007). Therefore, a distinction has to be made between Krauzlis' "candidate state"—denoted by any object-action cell assembly that can be potentially enacted—and his "current state" that should be denoted by an object-action cell assembly which has been selected, among many, to be actually enacted.

According to Krauzlis, the "current state" is evaluated by the basal ganglia. In fact, they receive sensory patterns (Voorn et al., 2004) and action plans (Jin et al., 2014) from cortex, threat detections from the amygdala (LeDoux, 2014), memories of action sequences from hippocampus (Jai and Frank, 2015) with their possible outcomes from prefrontal cortex (Donoso et al., 2014), and stimulus saliency from thalamic intralaminar nuclei (Ding et al., 2010; Doig et al., 2014). Each of these areas, in MDM terms, is a specialist producing a temporary draft. Within the basal ganglia, the striatum has the circuitry to implement competition among them (Tepper and Bolam, 2004; Cisek, 2007). However, "Because different sensory inputs and types of knowledge contribute unequally to different states, their influence on perception and action will be limited by the strength of their contribution to the state that currently dominates the competition" (Krauzlis et al., 2014, p. 458). This point is central to build the interface and realize the terminology mapping, thus it requires further unpacking.

The intrinsic recurrent connections between cells of an assembly stabilize their firing through mutual excitation (Harris, 2005) while also suppressing other assemblies through inhibition

TABLE 1 | Interface providing a mapping between philosophical and neuroscientific terminology.

Dennett terms	Interface	Krauzlis terms
"Specialist"	Set of brain areas	
"Draft"	(specialist's) cell assembly	
"Affordance" (Gibson)	(object-action) cell assembly	"Candidate state"
"Coalition of specialists"	Dynamic mutual strengthening between (specialist's) cell assemblies, eventually leading to an (object-action) cell assembly	Strength of "different sensory inputs and types of knowledge contributions to the current state"
"Winning coalition"	Strengthened (object-action) cell assembly currently dominating the selection process	"Current state"
"Succession of coalitions"	Sequence of (object-action) cell assemblies (or phase sequence)	"Linked chain of states"

(Zenke et al., 2015). The occurrence of a specific assembly in one area both raises the probability of occurrence for some assemblies and quenches the probability of occurrence for some other assemblies in the same or other areas at some later time (Ponzi and Wickens, 2009; Truccolo et al., 2010) by means of short-term synaptic plasticity (von der Malsburg, 1994). Now, two or more specialists, each producing temporary drafts / cell assemblies, can interact through direct or striato-thalamo-cortical connections (Hikosaka et al., 2000; Sommer and Wurtz, 2004, 2006). These interactions, dynamically raising or lowering the probability of occurrence of an assembly given the occurrence of another, are the required mechanism for having dynamic coalitions of specialists' drafts, denoted by mutually strengthening assemblies. Eventually, one of these coalitions temporarily wins the competition in the striatum, and its entailed action is performed. The outcome for the organism is signaled, at the nervous system level, as dopaminergic reward (Threlfell et al., 2012) instrumental in selecting the synapses that will be targeted for growth (Li et al., 2003; Howe et al., 2013; Pelosi and Guarino, 2015), which will shape cell assemblies, and which will turn into (possibly better) behaviors (Montague et al., 1996).

With "state that currently dominates the competition" being the object-action cell assembly currently dominating the selection process in the basal ganglia (Dennett's winning coalition), we may now proceed to the fourth sentence, regarding the seriality and succession of coalitions. The proposed interface still matches: "As circumstances change, a candidate state that provides a poor match in one round of competition could emerge as predominant just moments later. This results in a linked chain of states, where the transition from one to the next is precipitated by some event or change in an internal variable, that gives the new state more support than the preceding one and carries along with a new decision policy" (Krauzlis et al., 2014, p. 458). Here, "candidate state" is denoted, as proposed earlier, by no more than an object-action cell assembly competing with all the others in the striatum. These candidate states, with their associated potential actions, represent different decision policies. Hence, a succession of selected states — comprehension-less but competence-full, thanks to a reinforcement learning process—steers the policy making that we label as "attentional" behavior. The reinforcement behind this succession of states, and its link to attentional behavior, is also fitting the Hebbian "phase sequence" (Hebb, 1949, p. 87).

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To summarize (see **Table 1**), several cell assemblies (Dennett's "short-lived," "coalitions of specialists," "drafts," or Krauzlis' "candidate states") are dynamically strengthened and compete in the striatum. At every moment, one object-action cell assembly is temporarily dominating the selection process in the striatum (Dennett's winning "coalition," or Krauzlis' "current state"), getting enacted. In time, a series of winning assemblies (Dennett's "succession of coalitions of specialists," or Krauzlis' "linked chain of states") gets selected to be pursued with actions, leading (or not) to rewards for the organism, ultimately promoting the formation, dissolution, and change of cell assemblies. Hence it is not a homunculus, rather learned associations that drive the production of "attentional" behaviors."

The interface I proposed, here, and the mapping between the terminology used by Dennett and that of Krauzlis is meant to encourage the exchange between philosophy of mind and neuroscience. In fact, on the one hand, it seems that the philosophical refinement of questions regarding the mind needs more scientific injections (Dennett, 2003). While, on the other hand, neuroscience is in danger of a technological stale-point because it is lacking more encompassing and purposeful views (Frégnac, 2017). If, and only if, a common terminology will be adopted such an exchange will take place and benefit both disciplines.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

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Neo: an object model for handling electrophysiology data in multiple formats

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Neuroscientists use many different software tools to acquire, analyze and visualize electrophysiological signals. However, incompatible data models and file formats make it difficult to exchange data between these tools. This reduces scientific productivity, renders potentially useful analysis methods inaccessible and impedes collaboration between labs. A common representation of the core data would improve interoperability and facilitate data-sharing. To that end, we propose here a language-independent object model, named “Neo,” suitable for representing data acquired from electroencephalographic, intracellular, or extracellular recordings, or generated from simulations. As a concrete instantiation of this object model we have developed an open source implementation in the Python programming language. In addition to representing electrophysiology data in memory for the purposes of analysis and visualization, the Python implementation provides a set of input/output (IO) modules for reading/writing the data from/to a variety of commonly used file formats. Support is included for formats produced by most of the major manufacturers of electrophysiology recording equipment and also for more generic formats such as MATLAB. Data representation and data analysis are conceptually separate: it is easier to write robust analysis code if it is focused on analysis and relies on an underlying package to handle data representation. For that reason, and also to be as lightweight as possible, the Neo object model and the associated Python package are deliberately limited to representation of data, with no functions for data analysis or visualization. Software for neurophysiology data analysis and visualization built on top of Neo automatically gains the benefits of interoperability, easier data sharing and automatic format conversion; there is already a burgeoning ecosystem of such tools. We intend that Neo should become the standard basis for Python tools in neurophysiology.

Keywords: electrophysiology, interoperability, Python, software, file formats

1. INTRODUCTION

Neuroscience research relies on specialized software to analyze and visualize data, but often no single piece of software is sufficient to meet all the needs of a particular study. The solution is either to extend the software or to transfer data between software tools. The former requires both programming skills and effort. If an entirely novel analysis method is needed, this effort is unavoidable, but if, as is often the case, the required functionality is already provided by a different software tool, transferring the data can in principle be much more efficient. Unfortunately, in neurophysiology there is a very wide variety of software in use, much of it proprietary and developed by recording hardware manufacturers, and with little in the way of common data formats. In practice, researchers spend a lot of time and effort converting data between different formats, and those with good programming

skills are strongly tempted to re-implement functionality that already exists elsewhere rather than go through a tedious conversion process. A reduction in the amount of effort required for neurophysiology data conversion could greatly enhance the productivity of the field and reduce duplication of effort.

Three approaches to reducing the effort of data conversion, and thereby increasing the interoperability of data analysis tools, can be envisioned. The first is to develop a common file format, capable of containing all data generated by all the different software tools in use. Having such a file format, the number of possible conversion pathways that must be implemented is greatly reduced. Ideally, hardware manufacturers would support exporting recorded data in this format. This approach has been tried with some success in the domain of clinical electroencephalography (EEG) (Kemp et al., 1992; Kemp and

Olivan, 2003; Schlögl, 2006), and the Program on Standards for Data Sharing of the International Neuroinformatics Coordinating Facility (INCF) is currently developing a standard file format for electrophysiology data (Teeters et al., 2013) based on the HDF5 file format. A comparison of 19 different biomedical data formats is provided by Schlögl (2010).

The second approach is to define a language that can describe the structure of data files in different formats, and then write descriptions of each of the formats of interest using this language. Conversion between data formats, or reading a data file into software, can then be fully automated. This approach was taken by Durka and Ircha (2004), who developed the SignalML markup language for describing biomedical time series.

The third approach is to define an application programming interface (API) that takes care of the data conversion, and implement this as a library which can be used by software developers to provide uniform access to data, independent of the file format. An advantage of this compared to the other two approaches mentioned above is that it encourages modularity in software development: the data-conversion library defines certain data structures which can then be used by developers of analysis and visualization tools, which thereby gain greater interoperability. A previous effort to define an API for electrophysiology data in neuroscience was undertaken by a consortium of recording hardware manufacturers, which in 2000 began development of the Neuroshare API (<http://neuroshare.org>). The Neuroshare API is available as a C library and as a MATLAB (The Mathworks Inc.) extension. These are distributed as compiled dynamic-link libraries (DLLs), one per manufacturer; the source code is generally not available, and most are only available for the Windows operating system. The API is rather low-level, consisting of a number of functions and low-level data structures such as numerical arrays. BioSig (<http://biosig.sourceforge.net/>) is a cross-platform open source library for biomedical signal processing (EEG, ECG, etc.), available for MATLAB/Octave and for C/C++ (with wrappers for Python), which includes support for a large number of biomedical file formats.

We have developed a novel, object-oriented API for representing electrophysiology data in memory and for reading/writing such data from/to multiple file formats. The Neo (from Neuroscience Electrophysiology Objects) API is defined as an object model, and is intended to be able to represent any electrophysiology dataset, from *in vitro* patch-clamp recordings through multi-electrode array recordings to EEG. We have implemented the Neo object model as a cross-platform, open-source Python package, but it should be possible to implement it in any object-oriented programming language. An object-oriented API is a natural fit for neuroscience data, and in particular makes it easier to encapsulate data and the associated metadata, hence preserving the information about the experimental context that is needed to correctly interpret and analyze the data.

The principal goal of developing Neo is to improve the interoperability of software for working with electrophysiology data. Such interoperability includes the exchange of data objects between software tools in memory as well as via the filesystem. The existence of a Neo implementation in a given language means, for example, that one scientist or research group can

develop a library for electrophysiology data analysis and another a library for visualization of such data, then a third scientist can easily combine both libraries in his/her own workflow, without having to worry about plumbing the tools together, taking care of correct metadata conversion, etc. By having an object model that is shared across programming languages, we hope to make conversion of data analysis routines between languages more straightforward.

In this article we describe the considerations which led to the design of the API, we describe the object model and its Python implementation, then give some examples of using the Neo Python package in real-world situations. Finally, we discuss the advantages and disadvantages of the Neo approach with respect to the other approaches to data sharing and software interoperability mentioned above, and outline possible future directions.

2. DESIGN CONSIDERATIONS

Starting with the basic requirement that the object model should allow the representation and manipulation of any electrophysiology dataset, we elaborated the design according to the following principles.

2.1. SCOPE

It was decided that the object model should contain only classes for representing electrophysiology data and for reading/writing such data from/to files or databases. Further, the behavior of these objects should allow only basic manipulations such as rearranging datasets or extracting sub-sets. In particular, we wished to specifically exclude visualization or analysis methods, even such simple ones as taking the mean. The motivation for this was to keep Neo as lightweight as possible. In our experience developing open-source software, small, focused libraries are much more likely to see widespread uptake. In future, we expect to extend the object model to support other data types closely-related to electrophysiology, such as calcium imaging and behavioral data, but these were not included in the initial design so as to avoid diluting our efforts.

2.2. METADATA

We distinguish *essential* metadata, which is required for the data to have even minimal meaning rather than just be arrays of numbers, *desirable* metadata, which is necessary to correctly analyze the data, and *additional* metadata. Examples of essential metadata are the sampling interval and the physical units of a recording. Desirable metadata might include identification of the neuron or brain area from which the recording was made, or the filter settings used. Additional metadata provide information that is specific to a particular user or software tool, such as which color to use when plotting the data in a graphical interface. The object model should make it impossible to create data objects without essential metadata. For desirable and additional metadata, it should be straightforward to annotate any object. Annotations should take the form either of key-value pairs or of subject-predicate-object triples as used in RDF (Manola and Miller, 2004). In our Python implementation, we chose key-value pairs for simplicity, but we are considering adding support for triples in future versions. For desirable metadata we add the further

requirement that the metadata must be preserved when writing to and then reading again from a file or database, whatever the format.

2.3. STRUCTURE

Experimental protocols in neuroscience are hugely diverse, and may be structured in many ways in terms of stimulus presentation, behavioral responses, and pharmacological interventions. The object model should allow at least the structure related to the electrophysiological recordings to be represented in the relationships between data objects rather than only as metadata. At least two levels of hierarchical organization are needed (e.g., a recording session consisting of multiple trials, or a multi-electrode recording with multiple channels), but non-hierarchical cross-links are also needed.

2.4. INTEROPERABILITY

Wherever possible, compatibility with other widely used scientific libraries in a given implementation language should be preserved.

2.5. EFFICIENCY

Electrophysiology datasets are often very large, either because recording lasts for a long time, hours or days, or because of recording from many channels. This means that both the object model and its implementation must provide memory- and computation-efficient representations.

3. OBJECT MODEL

The Neo object model consists of 14 classes, which may be divided into three types: data objects, container objects and grouping objects. **Figure 1** provides an overview of the Neo objects and their relationships. Data objects contain numerical data together with associated metadata. The data types that are represented are (i) sampled continuous, analog signals; (ii) action potentials

(“spikes”), characterized by their time of occurrence and, optionally, their waveforms; (iii) events, each of which consists of a time of occurrence and a textual label; and (iv) epochs, each of which consists of a start and end time together with a label. The full list of data objects is as follows:

- **AnalogSignal**: a record of a continuous, analog signal with a fixed sampling interval, for example the membrane potential recorded from an intracellular electrode using current clamp.
- **IrregularlySampledSignal**: a record of a continuous analog signal with a varying sampling interval. This is found, for example, in data from neuronal network simulations with a variable-time-step integration method.
- **AnalogSignalArray**: a record of a multichannel continuous analog signal with a fixed sampling interval, for example from an multi-electrode array or from an EEG recording.
- **Spike**: one action potential characterized by its time and waveform.
- **SpikeTrain**: a set of action potentials (spikes) emitted by the same unit in a period of time (with optional waveforms). Such data is generated by spike sorting from multi-electrode recordings, and directly by simulations.
- **Event** and **EventArray**: a time point representing an event in the data, or an array of such time points. Events may represent, for example, pharmacological interventions or triggers during behavioral experiments.
- **Epoch** and **EpochArray**: an interval of time representing a period of time in the data, or an array of such intervals. An example would be the time during which a stimulus is presented.

For each data type, the object model provides both a scalar representation (a single instance of a data item, for example, **AnalogSignal** and **Spike**) and an array representation (e.g., **AnalogSignalArray** and **SpikeTrain**) in order to provide a choice between simplicity and efficiency in data analysis. For example, when working with single-electrode data, using the scalar objects is simpler and produces code that is easier to understand, without having to deal with array indexing. For electrode-array or EEG data on the other hand, using NumPy-like arrays is much more efficient than using lists of objects.

Container objects provide a simple hierarchical grouping of data. A **Segment** may contain any of the data object types provided all the objects share a common clock, i.e., they represent data recorded at the same time, although the sampling interval, onset and duration of recording may differ between data objects. A **Block** is the top-level container, and contains **Segments** and **RecordingChannelGroups** (see below). To illustrate this further, in the common experimental paradigm of running multiple trials, i.e., presenting the same stimulus multiple times, the data from each trial would be stored in a **Segment**, and all the **Segments** stored in a single **Block**. Deeper or more complex hierarchies are not supported directly by Neo, but it would be straightforward for a user to define a higher-level object to contain multiple blocks. Some of the Neo input/output modules (see below) support storage of multiple **Block** objects.

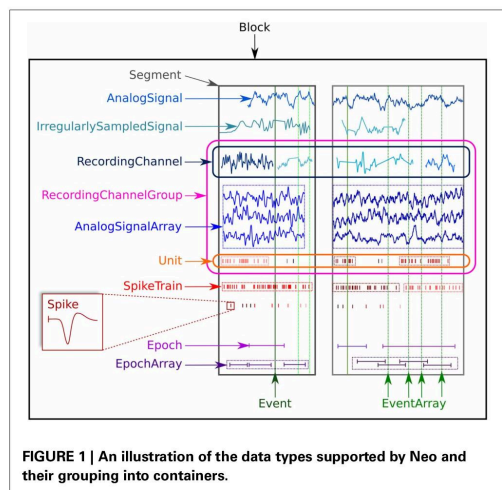


FIGURE 1 | An illustration of the data types supported by Neo and their grouping into containers.

Grouping objects express the relationships between data objects, such as which signals were recorded on which electrodes, which spike trains were obtained from which membrane potential signals, etc. They contain references to data objects that cut across the simple container hierarchy. Another way to think of this organization is that “container” objects group data that were acquired at the same time, while “grouping” objects group data that were recorded from the same channel, array, location, etc. The grouping objects are as follows:

- **Unit:** gathers all the `Spike` and `SpikeTrain` objects within a `Block`, possibly across several `Segments`, that were emitted by the same neuron.
- **RecordingChannel:** links `AnalogSignal` and `IrregularlySampledSignal` objects that come from the same logical and/or physical channel inside a `Block`, possibly across several `Segment` objects.
- **RecordingChannelGroup:** a group for associated `RecordingChannel` objects, for example all the channels from a single tetrode.

The `RecordingChannelGroup` has several uses. Firstly, for linking several `AnalogSignalArray` objects across several `Segment` objects, e.g., linking multi-electrode array recordings across trials. Secondly, to associate a `Unit` with the group of recording channels from which it was calculated (since with multi-electrode arrays, action potentials from the same neuron may be recorded on more than one recording channel); Thirdly, for grouping `RecordingChannel` objects by signal type (for example, with intracellular recording, it is common to record both membrane potentials and currents at the same time). Fourthly, for multi-electrode arrays, a `RecordingChannelGroup` is used to gather all `RecordingChannel` objects belonging to the same array.

3.1. OBJECT ATTRIBUTES

Most objects, and in particular all of the data objects, have a number of *required* attributes. These are essential metadata without which the numerical data values contained in the object cannot be interpreted. For example, in the case of `AnalogSignal`, the required attributes are the sampling interval (or, equivalently, the sampling rate), the time stamp of the first sample and the units of the signal, for example “millivolts” in the case of the membrane potential. All attributes that represent physical quantities must state the units, for example, the sampling rate could be given as “10 kHz.”

In addition to the required attributes, each object has a number of *suggested* attributes. These attributes are intended to contain desirable metadata that are not essential for working with the objects, but that are likely to be useful in developing analysis methods, automatic graph generation, tracking provenance, etc. Examples of such suggested attributes are `name`, `rec_datetime` (the date and time of the original recording) and `file_origin` (the filesystem path or URL of the original data file from which the data were read). The number of suggested attributes is likely to increase in future versions as structured terminologies and ontologies for neurophysiology are developed.

Full details about required and suggested attributes are available in the Neo documentation, online at <http://neuralensemble.org/neo/>.

Finally, any object may contain any number of additional attributes or annotations. Such annotations may be numerical or text values, arrays of such values, or dictionaries/hash tables containing such values. They are intended to contain any information that may be useful in subsequent processing of the data, for example metadata describing the experimental protocol.

3.2. RELATIONSHIPS BETWEEN OBJECTS

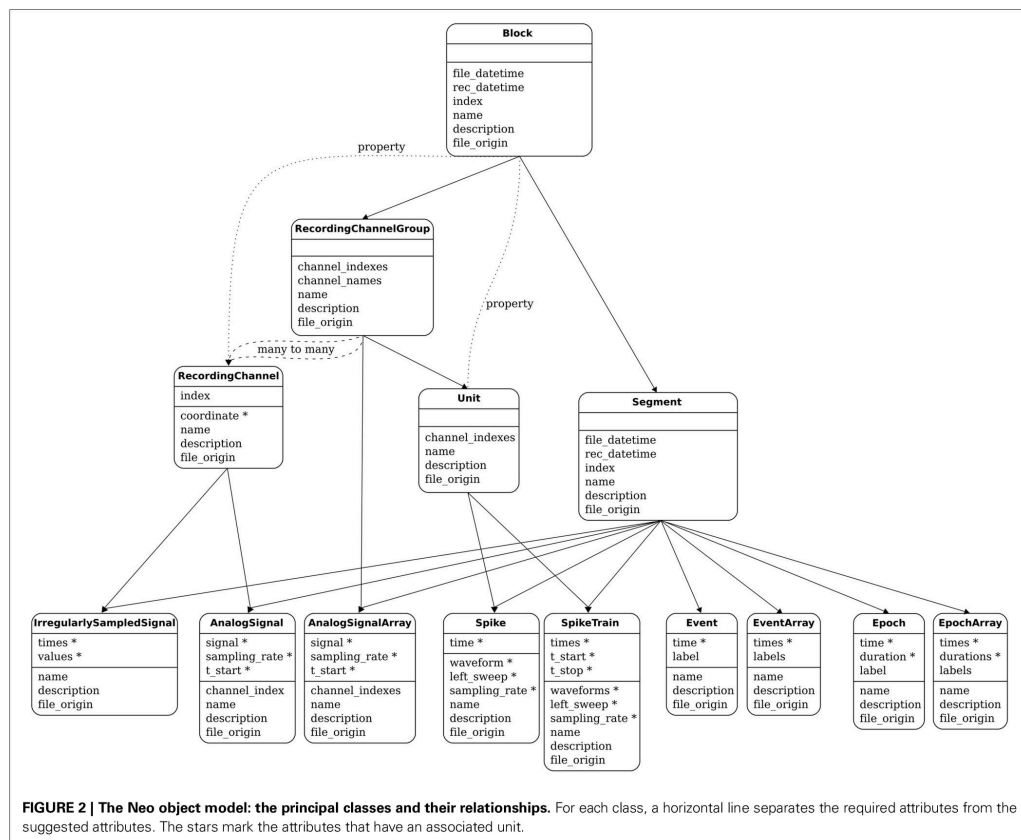
The functions of the container and grouping objects are based on lists of references to other objects. For example, `Block` has an attribute `segments`, which is a list of references to all the `Segment` objects contained in that `Block`. Such relationships are bi-directional, for example each `Segment` has an attribute `block` pointing to the `Block` within which it is contained. **Figure 2** shows all of these relationships. More detail is available in the online documentation.

3.3. IMPLEMENTATION IN PYTHON

When implementing the object model in a specific language, ease-of-use considerations come to the fore. If a package or library is to gain widespread adoption, it should be easy to build and install on different platforms, and should be interoperable, as much as possible, with existing tools and existing code for handling electrophysiology data in that language.

In the case of Python, the latter consideration dictates that a Neo implementation must be based on NumPy (Oliphant, 2007), the *de facto* standard for numerical computing in Python. NumPy provides a powerful, *N*-dimensional array object that can contain integers, floating point numbers, strings or other Python objects. A given numerical array can have any combination of precision and byte-order. Most array operations are implemented in C or Fortran for efficiency. The principal choice in implementing the Neo object model in Python is whether the classes for data objects should inherit from the NumPy `ndarray` class (a Neo class *is* a NumPy array) or whether to use composition (where the Neo class has a `data` attribute which is a NumPy array). Inheritance has two important advantages: (i) existing code that works with NumPy arrays will work with Neo data objects without modification; (ii) Neo objects gain most of the functionality of NumPy arrays “for free,” i.e., we do not have to re-implement this functionality. A number of operations on, and methods of, NumPy arrays have to be re-implemented or extended for Neo objects, in order to preserve the extra metadata carried by Neo objects, but these would in any case have to be implemented if taking the composition approach. The principal disadvantage of the inheritance approach is complexity: creation of subclasses is one of the more difficult parts of the NumPy API. After weighing up these considerations, we chose to use inheritance.

The second major choice was how to represent the measurement units of the data. Several Python packages are available for handling units and physical quantities in Python. The decision to use inheritance for NumPy support narrows down the choice. We chose to use the Quantities package (<http://pythonhosted.org/quantities/>), which provides a `Quantity` class that inherits



from the NumPy `ndarray` class and adds a concept of physical dimensions and units. This means that trying to add a `Quantity` array with dimensions of voltage to an array with dimensions of current will produce an exception, while adding an array in millivolts to an array in volts will perform scaling so as to give the correct result. The particular choice of `Quantities` is not limiting. It would be possible to replace it with another units package that subclasses `ndarray`, such as `Pint` (<http://pint.readthedocs.org/>), without changing the Neo interface.

In summary, the classes for the Neo data objects all inherit from `Quantity`, and so gain checks for dimensional consistency for free, in addition to the large amount of functionality inherited from `ndarray`. Neo objects add further checks (for example, trying to add together two `AnalogSignals` with different sampling rates produces an exception) and further operations (for example, it is possible to slice `AnalogSignals` and `SpikeTrains` according to time as well as according to index).

Other Python packages for working with time series data do not fill the niche that Neo does. The core function of Neo is data representation. The `Pandas` package (<http://pandas.pydata.org>) is

a general toolkit for working with heterogeneous data. Neo contains functionality specific for neural data analysis, such as grouping of channels by anatomical location. Another package, `nitime` (<http://nipy.org/nitime>), provides algorithms for time-series analysis that are tailored toward neuroimaging data. In contrast, the Neo package intentionally does not provide algorithms for data analysis since this will vary widely across users. Overall, Neo provides functionality that is specific to neuroscience data (unlike `Pandas`) but not specific to particular applications within neuroscience (unlike `nitime`). This means that Neo is ideally situated to be a common format for neuroscientists, who may then analyze the data using the tools provided by other packages as desired.

Because the primary function of Neo is neural data representation, the methods provided fall into two categories: (1) reading from the various formats used by hardware manufacturers; (2) linking the resulting objects in a neuroscientifically meaningful way. The first type of linkage is spatial: `AnalogSignal` objects may be added to `RecordingChannel` objects, and `RecordingChannel` objects added to spatially defined `RecordingChannelGroup` objects. The second type of

linkage is temporal: `AnalogSignal` objects also belong to a `Segment` object (representing a period of time), and `Segment` belongs to `Block` (representing an entire experiment). Typically the provided IO methods construct the linkages in this hierarchy automatically. The user may then iterate over the data in whichever way is most intuitive for the application: either temporally (trial by trial within a session) or spatially (channel by channel within the brain).

The Neo package is available from the Python Package Index (<https://pypi.python.org/pypi/neo/>) and as Debian and Ubuntu packages through NeuroDebian (Halchenko and Hanke, 2012). The core of Neo works with both Python 2 (version 2.6 or later) and Python 3 (version 3.2 or later). For some file formats, only Python 2 is currently supported. At the time of writing, the latest version is 0.3.1. Full documentation is available online at <http://neuralensemble.org/neo/>. There is an extensive test suite, and the project makes use of continuous integration (<https://travis-ci.org/NeuralEnsemble/python-neo>) to rapidly catch regressions.

4. READING AND WRITING DATA WITH MULTIPLE FILE FORMATS

In addition to implementing the Neo object model as a Python API, the Neo Python package also provides a set of input/output (IO) modules for various neurophysiology file formats, including proprietary formats (e.g., Plexon, Spike2, NeuroExplorer, Axon, AlphaOmega, Micromed and Tucker-Davis), the formats used by various open-source and/or freely distributed tools (e.g., Klustakwik, Elan, WinEdr) and generic file formats such as MATLAB, ASCII and HDF5. In most cases, the proprietary formats are read-only, while the more open and generic formats support both reading and writing. The Neo documentation provides guidelines for anyone wishing to add support for a new format.

The inclusion of support for multiple file formats in the Neo package has several benefits: (i) it demonstrates the universality of the object model, which is able to represent the data from all of these different formats; (ii) it is an important part of realizing our goal of improving interoperability of different tools and the ease of sharing data between different projects; (iii) it provides an immediate benefit to users, thus driving uptake of the Neo software; (iv) tool developers can use Neo as a basis and immediately gain the benefit of supporting multiple file formats, without them having to implement such support themselves.

For each file format there is a separate Python class, each of which implements the same interface. Reading data for a given format can be as simple as:

```
from neo.io import MyFormatIO
reader = MyFormatIO(filename="myfile.dat")
data = reader.read()
```

However, given the large size of many neurophysiology datasets, it is not always desirable to load all the data into memory at once. The full interface therefore offers more fine-grained control. All read functions have two optional parameters: `cascading` and `lazy`. When `cascading` is set to false, only a single object is loaded and none of its references to other

objects are populated. The `lazy` parameter does not influence whether linked objects are loaded, but determines the treatment of data objects: when `lazy` is true, the numerical data is not loaded, instead empty data objects are created including all properties and metadata. This allows examining the contents of files with a substantially smaller memory footprint. IO classes can implement a method to load the full version of a lazily loaded object once the numerical data is required.

The IO API also takes into account that a dataset does not necessarily come from a single file. Some software provides recordings in a directory or in a database. Such cases are taken into account through the attribute `mode` in each IO class. The behavior is changed only at instantiation:

```
from neo.io import MyFormat1IO, MyFormat2IO
reader1 = MyFormat1IO(filename="myfile.dat")
# MyFormat1IO.mode = 'file'
reader2 = MyFormat2IO(dirname="/path_to_dataset")
# MyFormat2IO.mode = 'dir'
```

Some file formats internally store arrays in a compact continuous way. In such cases, the class implementations use the NumPy “mmap” mechanism. This reduces the memory footprint and allows transparent access to files that do not fit into memory.

For the implementation of file readers, an early difficulty was collecting information about the specifications for proprietary file formats. This tedious task was accomplished using several approaches: (i) asking manufacturers to open the specifications; (ii) reading code from other packages; (iii) reading C header files; (iv) basic reverse engineering with hexadecimal editors. Nowadays, many manufacturers provide their file specifications in the user documentation. The main difficulty remains in the versioning of these specifications. In general, the internal file formats do not change much over time, but sometimes some problematic changes occur, making the classes non backward compatible. This has been taken into account for some file formats. The `AxonIO` implementation is a good example where two very different versions of the same file format can be read transparently. Unfortunately, this is not the case for all classes and the effort must continue.

5. USAGE EXAMPLES

5.1. RECORDING MULTIPLE TRIALS FROM MULTIPLE CHANNELS

In this example we suppose that we have recorded from an 8-channel probe, and that we have recorded three trials. We therefore have a total of $8 \times 3 = 24$ signals, each represented by an `AnalogSignal` object.

As shown in **Figure 3**, our dataset (contained in a single `Block`, not explicitly shown) contains:

- Three `Segment` objects, each representing data from a single trial,
- One `RecordingChannelGroup`, composed of eight `RecordingChannel` objects.

This information can be traversed or averaged in two different ways. The first is temporal traversal (by segment). For example, suppose you wish to correlate the overall neural response with the

stimulus that was delivered in each segment. In this example, we treat each segment in turn, averaging over the channels in each:

```
import numpy as np
from matplotlib import pyplot as plt

# We assume that the variable "block" has been
# previously loaded from file

for seg in block.segments:
    print("Analysing segment %d" % seg.index)

    siglist = seg.analogsignals
    time_points = siglist[0].times
    avg = np.mean(siglist, axis=0)
    # Average over signals of Segment

    plt.figure()
    plt.plot(time_points, avg)
    plt.title("Peak response in segment %d: %f"
              % (seg.index, avg.max()))
```

The second alternative is spatial traversal of the data (by channel), with averaging over trials. For example, perhaps you wish to see which physical location produces the strongest response, and each stimulus was the same:

```
# We assume that our block has only 1
# RecordingChannelGroup and each RecordingChannel
# only has 1 AnalogSignal.
rcg = block.recordingchannelgroups[0]
for rc in rcg.recordingchannels:
    print("Analysing channel %d: %s"
          % (rc.index, rc.name))

    siglist = rc.analogsignals
    time_points = siglist[0].times
    avg = np.mean(siglist, axis=0)
    # Average over signals of Recording Channel

    plt.figure()
    plt.plot(time_points, avg)
    plt.title("Average response on channel %d"
              % rc.index)
```

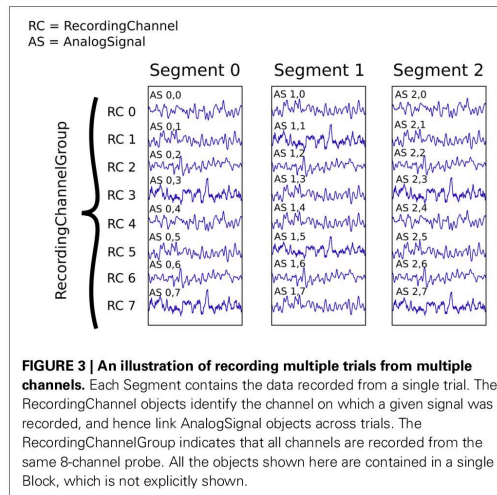
5.2. RECORDING SPIKES FROM MULTIPLE TETRODES

Here is a similar example in which we have recorded with two tetrodes and extracted spikes from the extra-cellular signals. The spike times are contained in `SpikeTrain` objects. As shown in **Figure 4**, our data set (again contained in a `Block`) contains:

- Three Segments (one per trial).
- Two `RecordingChannelGroups` (one per tetrode), which contain:
 - Four `RecordingChannels` each
 - Two `Unit` objects (= two neurons) for the first `RecordingChannelGroup`
 - Five `Units` for the second `RecordingChannelGroup`.

In total we have $3 \times 7 = 21$ `SpikeTrains` in this `Block`.

There are three ways to access the spike train data: by segment, by recording channel or by unit.



5.2.0.1. By Segment. In this example, each `Segment` represents data from one trial, and we want a peristimulus time histogram (PSTH) for each trial from all units combined:

```
for seg in block.segments:
    print("Analysing segment %d" % seg.index)
    stlist = [st - st.t_start
              for st in seg.spiketrains]
    count, bins = np.histogram(np.hstack(stlist))
    plt.figure()
    plt.bar(bins[:-1], count,
            width=bins[1] - bins[0])
    plt.title("PSTH in segment %d" % seg.index)
```

5.2.0.2. By Unit. Now we can calculate the PSTH averaged over trials for each unit:

```
for unit in block.list_units:
    stlist = [st - st.t_start
              for st in unit.spiketrains]
    count, bins = np.histogram(np.hstack(stlist))
    plt.figure()
    plt.bar(bins[:-1], count,
            width=bins[1] - bins[0])
    plt.title("PSTH of unit %s" % unit.name)
```

5.2.0.3. By RecordingChannelGroup. Here we calculate a PSTH averaged over trials by channel location, blending all units:

```
for rcg in block.recordingchannelgroups:
    stlist = []
    for unit in rcg.units:
        stlist.extend([st - st.t_start
                       for st in unit.spiketrains])
    count, bins = np.histogram(np.hstack(stlist))
    plt.figure()
    plt.bar(bins[:-1], count,
            width=bins[1] - bins[0])
    plt.title("PSTH blend of recording channel group
              %s" % rcg.name)
```


The code samples shown here are extracted from a complete example script available in the Neo source code distribution, see https://github.com/NeuralEnsemble/python-neo/blob/master/examples/generated_data.py.

6. DISCUSSION

We have presented here an object-oriented API for handling electrophysiology data in neuroscience, and an implementation of this API in the Python programming language. We have shown how this model is designed to allow for convenient and efficient representation of all kinds of electrophysiological data, from spikes to broadband continuous signals, with support for all common recording technologies, including multi-channel systems like tetrodes. Furthermore, we have illustrated the practical use of the Neo Python package through examples in typical real-world situations.

The generality of the Neo object model for the representation of electrophysiological data coupled with the availability of a large set of IO modules for common file formats in the Python package makes Neo a very convenient and powerful base package to build upon when developing software to manipulate, analyze or display electrophysiological data in Python. It thus fulfils our initial goal as a tool to facilitate data sharing and conversion, as well as software interoperability, with the hope that Neo will become the standard base package for the community of Python developers working with electrophysiological data.

6.1. PROJECTS USING NEO

The success of the Neo project and the suitability of the object model will be determined by whether other software tools for working with neurophysiology data adopt the Neo object model and whether they gain benefits from doing so. A number of projects and laboratories are already using Neo.

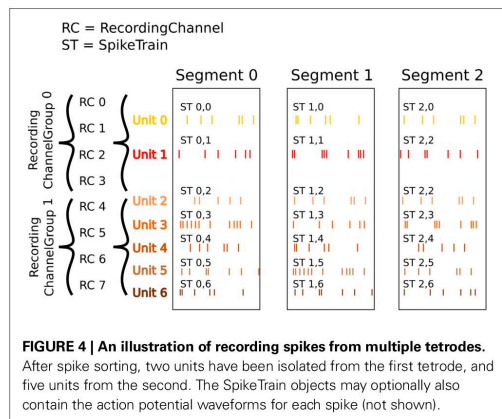
The German INCF Node (G-Node) has adopted the Neo model for the representation of electrophysiological data in its data management platform (<https://portal.g-node.org/data/>). The purpose of the platform is to provide a centralised system for

organising and sharing of electrophysiology data. A major obstacle to data sharing and re-use in the field of electrophysiology is the large variety of data formats. The G-Node platform provides a unified way of representing electrophysiological data according to the Neo object model, as well as automated format conversion utilizing the Neo IO modules. Being compliant with the Neo model, the system's API achieves interoperability with other tools that use the Neo objects and facilitates integration of data access and data analysis. G-Node offers a Python client tool that provides a front-end to the data hosted on the G-Node data platform in terms of the Neo Python objects (Sobolev et al., 2014). The G-Node platform complements the Neo data representation with meta-data storage using an unrestrictive format (Grewe et al., 2011), enabling extensive data annotation in a standardized way.

PyNN (Davison et al., 2009) is a Python API for simulator-independent neuronal network simulations. One aspect of simulator independence is reformatting the data produced by each simulator into a common format. Originally, this common format was based on NumPy arrays together with a small amount of metadata, which could be saved to file in a small number of non-standard formats. As of version 0.8, PyNN has adopted Neo as the common format for output data. This has had several benefits: (i) the hierarchical structure of Neo allows much more of the structure of the simulation experiment to be preserved; (ii) a much more complete set of metadata can easily be provided; (iii) a much wider range of file formats is now available; (iv) data recorded in biological experiments and data generated by simulations can now be analyzed and visualized with the same tools; (v) reduced development effort for the PyNN development community, since a large piece of functionality has been "out-sourced" to Neo.

Spyke Viewer (Pröpper and Obermayer, 2013) is a flexible and extensible graphical application for navigating, analysing and visualising electrophysiology data. The central features of Spyke Viewer are the navigation view, filter system, and plug-in architecture. Filters define data subsets of interest. Plug-ins implement data analysis algorithms or visualizations, and Spyke Viewer comes with a variety of plug-ins implementing common neuroscientific plots such as raster plots or correlograms. Spyke Viewer uses Neo as its object model as well as for loading and exporting data. The navigation view allows users to select Neo grouping and container objects, offering a common structure for the data independent of its source format. Filters use properties and annotations of Neo objects to define which objects are shown in the navigation view. Plug-ins operate on Neo data objects. Because of the standard data model provided by Neo, plug-ins work with data from many different formats. This enables Spyke Viewer users to conveniently share methods implemented in plug-ins.

OpenElectrophy (Garcia and Fourcaud-Trocmé, 2009) is a graphical user interface built on top of Neo. This software implements four independent components: (i) SQL database management for Neo objects; (ii) a fast viewer for Neo objects; (iii) a complete off-line spike sorting tool-chain; (iv) a time-frequency toolbox (fast multi-channel wavelet scalogram plotting and transient oscillation detection). The main difficulty when designing a spike sorting tool-chain is the management of data in various and complex situations: (i) the hardware setup may use a single electrode, several independent electrodes, several independent



N-trodes or electrode arrays; (ii) the protocol may involve one continuous recording or multiple chunks of recording; (iii) the nature of the recording may be full band signals, filtered signals or pre-detected spikes. Many spike sorting tools take into account only one combination of these situations because it is rather complex to support all the possible combinations. The Neo object model allows all these situations to be dealt with transparently in OpenElectrophy.

Datajongleur (<https://github.com/G-Node/Datajongleur>) is a collection of scientific data objects. It supports management of data objects with numerical behavior in combination with relational databases, like SQLite (<http://www.sqlite.org/>, file based), or PostgreSQL (<http://www.postgresql.org/>, server based). Datajongleur provides a Neo implementation that allows storing Neo objects in a relational database.

As a consequence of the common use of the Neo Python package, it is now straightforward to take recorded data from experiments or simulation data generated by PyNN, store them on the G-Node data platform or in a relational database using Datajongleur, then analyze and visualize them in Spyke Viewer or OpenElectrophy, in a seamless pipeline. Although we have focused in this section on the advantages of Neo for tool developers, the Neo Python package is equally suitable for use by individual scientists analysing their data with their own scripts.

6.2. FLEXIBILITY AND EXTENSIBILITY OF THE OBJECT MODEL

The Neo object model has been designed to be as general as possible while still retaining the ability to clearly represent data objects and express the relationships between them in a way that is natural for neuroscientists. Nevertheless, many experiments in neuroscience combine electrophysiology recordings with recording of other types of data, such as temperature and position in space, and with sensory stimuli. Many such data types are straightforward to represent using the Neo object model. For example, temperature, the angle of a trackball, or an auditory stimulus can all naturally be stored in an `AnalogSignal`, while a `SpikeTrain` could be adapted to represent transients (time of occurrence plus waveform) in calcium imaging data.

For data that don't naturally fit into the current objects, it is possible for users to define their own classes that interact with the Neo objects. For example, with calcium imaging data, a user could define their own class to represent the image series, then use `AnalogSignal` to represent the time course of activity within a region of interest. To store such mixed data, either two separate files can be used, or, with the HDF5 format, both data types can be stored in a single file, using the `NeoHDF5IO` class to automatically store the time-series data and using an HDF5 library directly to store the imaging data.

6.3. RELATED INTEROPERABILITY EFFORTS

As outlined in the Introduction, there have been a number of previous efforts to solve the problem of incompatible file formats in neurophysiology and related fields, such as clinical electrophysiology.

BioSig (<http://biosig.sourceforge.net/>) is a cross-platform open source library for biomedical signal processing, available

for MATLAB/Octave and for C/C++. Python bindings can be generated from the C/C++ library using SWIG. It includes support for a large number of file formats. Neuroshare (<http://neuroshare.sourceforge.net/>) is an API that must be implemented as a library by each equipment manufacturer that wishes to support it. The libraries are not in general open source and most of them are only available for Windows. NiBabel (<http://nipy.sourceforge.net/nibabel/>) is a Python library for accessing common neuroimaging and medical file formats – its goals are very similar to those of Neo, but in a different domain. In the biomedical domain there are a large number of file formats for storage of biomedical time series data (ECG, EEG, etc.; reviewed in Schlögl, 2010), some of which are international standards and others quasi-standards due to widespread uptake. An example of the latter is the European Data Format (EDF and EDF+) which was supported by about 50 companies as of 2004 (Kemp, 2004). The GDF format (Schlögl, 2006) is a more recent development that addresses many of the limitations of earlier formats. SignalML (Durka and Ircha, 2004) is an alternative approach, defining a markup language for describing file formats so as to allow automatic conversion. Kemp (2004) compares EDF+ and SignalML, concluding that the SignalML approach is more flexible but that this flexibility comes at a price in terms of stability and increased effort for users.

We expect that Neo will be interoperable with, and broadly complementary to these existing efforts. For example, the Neo Python package already offers a `NeuroshareIO` module for reading data files via the Neuroshare libraries, and it should be straightforward to add IO modules for EDF/EDF+, GDF and the HDF5-based standard file format being developed by the INCF. The particular advantages of the Neo Python package are (i) its rich object model can capture all of the complexity typically found in neurophysiology experimental protocols; (ii) it is written in pure Python without any C/C++ dependencies except the widely available NumPy package; as such it is easy to install and highly cross-platform; (iii) it focuses on neuroscience research, whereas most of the other tools cited above have a biomedical focus; (iv) by using the Python programming language, users of Neo gain all of the benefits associated with that language, such as readability, increased productivity, ease of use for system integration, and access to a powerful ecosystem for scientific computing.

6.4. SUSTAINABILITY

Neo is developed as an open, collaborative project at <http://neuralensemble.org/neo>, using GitHub for version control and issue tracking. Anyone is welcome to propose and implement changes, which will then be reviewed by one or more of the other contributors, and a decision on whether to accept the changes taken by consensus. 19 people from ten separate institutions have at some time contributed code or documentation to the Neo project; six people from five institutions have contributed within the past 12 months. This distributed development effort, in which the collaboration arises informally from shared needs and interests rather than formally through grant funding, gives us confidence that Neo development is sustainable.

6.5. FUTURE PLANS

The Neo object model was designed after discussion between a group of scientists and engineers, both developers and potential users, from several laboratories. We consider the essential elements of the object model to be stable. However, as users and developers gain experience with the software, some evolution is to be expected. It will be necessary to find a compromise between changes to enhance usability and support new use cases, and the stability needed for a low-level library on top of which other software is built.

Among the improvements already envisaged are the following: (i) some simplification of the object model, in particular merging of the scalar and array representations (e.g., `AnalogSignal` and `AnalogSignalArray`); (ii) addition of an image sequence object, to support calcium- and voltage-sensitive-dye imaging experiments, which are closely related to electrophysiology.

We also plan a number of improvements to the Python implementation: (i) improved memory management for IO. Despite the lazy/cascade mechanism, most Neo IO classes do not allow loading only a chunk or a subset of data; (ii) efficiency improvements. Some relationships are not efficient for querying (filtering) an object when the dataset is large. For instance, linking a `SpikeTrain` with its associated `AnalogSignal` is not currently straightforward.

The object model is intended to be implementable in other languages besides Python. We have concentrated our initial efforts on one language in order to build up a critical mass of code to support the object model. An important future direction will be reaching out to users of other languages, such as MATLAB, and providing support for the object model. To this end, we have created documentation for using Neo-structured data in MATLAB at <http://pythonhosted.org/neo/io.html#neo.io.NeoMatlabIO>.

The development of the Neo object model has so far focused on the representation of recorded data, as typically stored in data files during an electrophysiology experiment. For broader use it would be desirable to also support data resulting from the processing and analysis of such data. Ideally, the object model should enable representing the relationship between analysis results and the original data. Instead of leaving the definition of corresponding objects to each user, it would make sense to extend the Neo model by a minimal set of definitions for generic scientific data along with provenance information. Such developments should be coordinated with international standardization efforts, such as those of the INCF Data Sharing Program (Teeters et al., 2013).

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Helmholtz: a customizable framework for neurophysiology data management

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The benefits of capturing the output of neurophysiology laboratories in structured databases are potentially very large, both in improved data management within a laboratory and in easier and more effective sharing of data, whether with close collaborators or in public databases. However, at present the task of systematically annotating every experiment with sufficient metadata to enable the data to be correctly analysed and interpreted is typically an arduous one. Then, once the effort to create a laboratory database has been made, considerable further effort is needed, due to lack of software tool support, to make use of the database in the day-to-day life of the laboratory, and so realise the potential benefits.

To improve this poor cost-benefit ratio requires that both entering data/metadata into a database system and making use of it later in analyses, visualization etc. be made much easier. This in turn will require software tools that can either integrate with or replace the existing software for data acquisition and analysis used in the laboratory, and that provide a smooth and intuitive workflow to minimize the time required for the potentially tedious process of data annotation. Meeting these requirements in the highly heterogeneous fields of neurophysiology and systems neuroscience can be very difficult, since there is very little standardization of data formats, equipment, software platforms or experimental protocols between different labs.

In this presentation we review some general principles that we think should be followed in trying to address these difficulties, and present a specific solution we have developed: Helmholtz, an open-source framework for developing databases that are customized to the needs of an individual neurophysiology lab.

The Helmholtz framework is built on top of the Django web framework (<http://www.djangoproject.com/>); following the tradition in the web development community of naming Django-based projects after famous jazz musicians, we named our project after a famous physiologist.) Using Django as a basis brings several advantages: (i) it can be used both for a local database, using the simple, built-in webserver and for a centralized repository; (ii) an abstraction layer on top of the underlying relational database allows any of the widely-used database systems to be used interchangeably (e.g. MySQL, PostgreSQL, Oracle, or the built-in, configuration-free SQLite); (iii) the same abstraction layer makes it easier for non-programmers to extend and customize the database: no knowledge of SQL is required; (4) it is easy to build multiple interfaces to the same database, for example interfaces to acquisition or analysis software, using web technologies.

Helmholtz provides core components which handle elements that are common to all or many domains of neurophysiology. For example, information about data acquisition: metadata for experimental setups (equipment, etc.), subjects (species, weight, anaesthesia, surgery, etc.), stimulation and recording protocols, for electrophysiology (in vivo and in vitro), optical imaging and morphological reconstructions. Another component supports databasing of analysis results, linked to the original data on which they are based, and with descriptions of the analysis methods used. Extension components to support the specific needs of individual labs are straightforward to write, requiring minimal programming experience.

Helmholtz supports multiple interaction methods: via a web interface (with support for tablet computers); batch data import from spreadsheets; programmatic interaction via a web-services API. The API generates and accepts multiple data formats: XML, JSON, YAML and odML; RDF support is planned in the near future.

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Keywords: database, web-services, data management, Electrophysiology, metadata, ease-of-use, provenance, customization

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