Modélisation de l’intégration des entrées synaptiques excitatrices chez les cellules thalamocorticales

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Résumé

Abstract

Thalamocortical (TC) cells from the ventroposterolateral (VPL) nucleus of the thalamus relay the somatosensory inputs (excitatory lemniscal synapses at proximal dendrites) to the corresponding cortical area, but also receive feedback excitatory inputs from the cortex (corticothalamic synapses at distal dendrites). The goal of this study was to compare the synaptic integration of inputs coming to proximal vs. distal dendrites. A multicompartmental model was drawn from fully reconstructed cells of the VPL nucleus. Dendrites were spatially discretized in multiple segments associated to interconnected RC circuits. We were able to characterize the impact of neuronal size and dendritic diameter on the amplitude and on the time course of the somatic response. We also compared the synaptic integration for different distributions of proximal or distal inputs under different conditions of membrane potential and active properties. In all cases, the summation of proximal inputs was independent of their distribution, while the response induced by distal inputs saturated when those inputs were located at the same branches. The results obtained in this study suggest a physiological explanation of the synaptic pattern at TC cells.
Foreword

The following thesis contains the most important results obtained during my Master degree, which began in May 2009, as well as a detailed introduction and a brief conclusion. The first part of the introduction contains basic notions of neurobiology that are necessary for a full understanding of the study. It is written for the physicist that would present some interest in neuroscience. To put the outcome of the study into an interesting perspective, a description of the thalamocortical system and of thalamocortical cells themselves is included. The next part of the introduction describes the model used. Finally, a brief overview of the numerical techniques underlying the simulations is given.

The results presented in this thesis are grouped into an article that is not yet submitted to a journal. It is the product of a collaboration with my two supervisors, the Dr. Helmut Kröger, my principal supervisor, and the Dr. Igor Timofeev, my cosupervisor. Since I was the main investigator in this study, my name appears first on the article. I worked on the modeling and the programming parts and I achieved all the simulations and analyzed the data. Along with Dr. Timofeev, I participated in the writing of the article. My two supervisors provided the direction of the project and fruitful advice during the study. They were able to identify weaknesses in my work and to help me to solve the problems encountered. Note that part of those results or other results have been presented in numerous local, national or international conferences. Results and their implications are summarized in the conclusion.

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built indestructible friendships. I am glad to continue my Ph. D. studies under the supervision of Dr. Timofeev and to work in such a great scientific environment.

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Last but not least, I would like to thank my close friends and the members of my family for their endless support during this finite, but long process. Most of them do not work in science and I believe that the interaction with such good friends and family members is crucial for the sanity of a scientist.

Finally, I wish full recovery to my supervisor, Dr. Helmut Kröger, who suffered from a severe stroke last summer. He is a great physicist and teacher, but is also open minded to other fields of science, especially neuroscience. For those reasons he has all my admiration.
To beloved friends and family
and our long-lasting relationship

What I cannot create,
I do not understand.
-Richard P. Feynman
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List of abbreviations

AMPA  $\alpha$-amino-hydroxy-5-methyl-4-isoxazolepropionic acid
CNS  Central nervous system
EPSP  Excitatory postsynaptic potential
FPP  fast pre-potential
FWHM  Full width at half maximum
GABA  $\gamma$-aminobutyric acid
GHK  Goldman-Hodgkin-Katz
GR  Geometrical ratio
IN  Interneuron
IPSP  Inhibitory postsynaptic potential
LTS  Low-threshold spike
NMDA  $N$-methyl-D-aspartate
ODE  Ordinary differential equation
PDE  Partial differential equation
PNS  Peripheral nervous system
PSC  Postsynaptic current
PSP  Postsynaptic potential
PY  Pyramidal
RE  Reticular
TC  Thalamocortical
VL  Ventral lateral
VP  Ventral posterior
VPL  Ventroposterolateral
Chapter 1

Introduction

1.1 The physiological context

1.1.1 Some basic concepts

The brain is one of the two components of the central nervous system (CNS), the other being the spinal cord. The CNS integrates the information coming from the peripheral nervous system (PNS). The nervous system contains two types of cells: neurons and glial cells. 100 billion neurons are present in the human brain. They are electrically excitable due to various complex ionic channels, ion pumps and synaptic receptors embedded in their plasma membrane. In contrast, glial cells are not electrically excitable, but are extremely important in maintaining the brain homeostasis and regulating the synaptic transmission. Some of them, the Schwann cells in the PNS and the oligodendrocytes in the CNS, also ensure a fast propagation of action potentials by forming myelin sheaths insulating the axon of neurons.

Neurons consist in three main parts (Fig. 1.1A). The dendrites receive chemical or electrical signals from other neuronal cells. The cell body or soma is the center of integration of information. Finally, the axon transmits this information to other cells. This transmission is achieved by the action potential, a fast high-voltage signal produced at the soma when the cell is excited above a threshold called the firing threshold. The action potential propagates into the axon toward the synaptic contacts. Synapses constitute the connections between neurons and thus underlie all neuronal communications. In other words, a synapse is the junction between the axon of a presynaptic cell, or more precisely a synaptic button at the end of the axon, and a dendrite of a post-
synaptic cell (Fig. 1.1B). Connections at the postsynaptic cell are typically established at protrusions emerging from the dendritic shaft called dendritic spines. The space between the presynaptic button and the postsynaptic membrane is called the synaptic cleft. Neurotransmitters are released in that cleft via the release sites of the presynaptic neuron. They are captured by receptors at the postsynaptic neuron and a postsynaptic response is induced. The plasma membrane of a neuron consists of a phospholipid bilayer, i.e. two layers of counteroriented lipid molecules. The intracellular medium or the cytoplasm is negatively charged compared to the extracellular medium. The difference in potential between the intracellular and extracellular media is simply called the membrane potential \( V_m \). Various proteins establishing multiple types of channels that control in part the flow of ions and regulate the membrane potential are embedded in the phospholipid bilayer (Fig. 1.1C). Particularly important ions are \( K^+ \), \( Na^+ \), \( Cl^- \) and \( Ca^{2+} \). Most channels are said to be specific. For example, \( Ca^{2+} \) ions flow across channels that are permeable to \( Ca^{2+} \) ions, but not across channels only permeable to \( K^+ \). Ions tend to move down their concentration gradient, but this movement changes the distribution of charges and causes a voltage gradient or an electrostatic force that can act against the initial flow. When a channel is open, ions specific to that channel are allowed to flow from one side of the membrane to the other, the direction depending on the concentration and voltage gradients. When both phenomena are balanced, the net current across the membrane is zero and ions are in a dynamic equilibrium. The membrane potential value at which it occurs is the equilibrium membrane potential \( E_{ion} \). It thus depends on intracellular \([ion]_{in}\) and extracellular \([ion]_{ext}\) concentrations, but also on the temperature \( T \) of the environment and on the valence \( z \) of ions. For a channel permeable to only one specific ion, \( E_{ion} \) can be evaluated according to thermodynamics by the Nernst equation:

\[
e_{ion} = \frac{RT}{zF} \ln([{ion}]_{in}/[{ion}]_{ext}),
\]

where \( R \) is the gas constant (8.314 J/K·mol) and \( F \) the Faraday’s constant (96 485 C/mol). This voltage level is also referred to as the ionic reversal potential. For \( V_m > E_{ion} \), positive ions flow from the inside of the cell to the extracellular space, while for \( V_m < E_{ion} \), the direction is reversed. When different species of ions are present in the membrane, Eq. (1.1) can be generalized to the Goldman-Hodgkin-Katz (GHK) equation:

\[
V_{rest} = \frac{RT}{F} \ln \left( \frac{P_{K^+}[K^+]_{ext} + P_{Na^+}[Na^+]_{ext} + P_{Cl^-}[Cl^-]_{in}}{P_{K^+}[K^+]_{in} + P_{Na^+}[Na^+]_{in} + P_{Cl^-}[Cl^-]_{ext}} \right),
\]

where \( P_{ion} \) is the permeability associated to a specific ion (usually in cm/s). The \( Cl^- \) concentrations are inverted in Eq. (1.2) compared to \( K^+ \) and \( Na^+ \) concentrations because of the negative valence of \( Cl^- \) ions. This expression provides the steady state value of \( V_m \) or the resting membrane potential \( V_{rest} \). \( V_{rest} \) lies between -40 and -90 mV but has typically a value around -65 mV. However, note that in the brain, \( V_m \) is never
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Figure 1.1: Basic concepts. A, Schematic representation of a neuron. B, Synapse. C, Phospholipid bilayer with embedded channels.
Figure 1.2: Current-voltage relationships. A, Current-voltage relationship of a single nicotinic ACh-activated ionic channel for NH$_4^+$ (▽) and Li$^+$ (△). The recordings were obtained from voltage-clamp experiments on clonal BC3H-1 mouse muscle cells [2]. B, Current-voltage relationship for a single Ca$^{2+}$-dependent K$^+$ channel. The recordings were obtained from voltage-clamp experiments on bovine chromaffin cells [1]. Vertical axis: current, 8 pA per box. Horizontal axis: membrane potential (mV).

completely at rest due to constantly active neurons. The amplitude of the different currents taken into account in Eq. (1.2) can be described by Ohm’s law:

\[ i_{ion} = g_{ion}(V_m - E_{ion}), \]  

(1.3)

where \( g_{ion} \) is the ionic conductance density (usually in mS/cm$^2$) and is a measure of the channel density at the membrane. For ionic currents, \( i_{ion} \) and \( g_{ion} \) are simply referred to as the ionic current and conductance, respectively, by keeping in mind that they represent the density of those quantities. Eq. (1.3) implies a linear current-voltage relationship for an open channel (Fig. 1.2A).

The GHK equation could technically include more than three different species of ions. However, other ions like Ca$^{2+}$, despite a possibly crucial role in neuronal functions,
have intracellular and extracellular concentrations that are much lower than $K^+$, $Na^+$ and $Cl^-$ concentrations and can thus be neglected in Eq. (1.2). Furthermore, for highly unbalanced intracellular vs. extracellular concentrations, Nernst, GHK and Ohm’s law equations are not accurate. In such case and for large variations of $V_m$, ions hardly move against their concentration gradient. As a result, instead of being linear, the current-voltage relationship saturates for large variations of $V_m$ (Fig. 1.2B). This is particularly true for $Ca^{2+}$ currents, the intracellular concentration being $\sim 10000$ times weaker than the extracellular concentration.

Channels possess sensors that react either to voltage variations for voltage-gated channels or to the presence of specific molecules in their environment for ligand-gated channels. Note that these classes are not exclusive. For a channel to open, sensors must react to their environment. For that reason, the openings and closings are stochastic processes. However, considering the whole population of channels at the membrane, one can describe the transition from one state to another as a smooth process. Note that most channels are also time-dependent. A particular type of ionic channels are the leakage channels that mediate the leak current. This current is considered as a passive property of the membrane since the channels opening does not depend on $V_m$ or on binding molecules. It is mainly responsible for the value of $V_{rest}$. Other types of current are considered as active properties.

Channels are pores in the membrane that have one or two kinds of gates that are either activated, deactivated, inactivated or deinactivated. To let the current flow through it, a channel described by the two gates model must have both its activation and inactivation gates open. In such case the channel is activated and deinactivated. Some types of channels are only described by activation gates and do not inactivate or deinactivate. They allow ions to move across the membrane if they are activated, and block ions if they are deactivated. Consider the most important set of currents, i.e. the $Na^+$ and $K^+$ currents responsible for the generation of action potentials. When the membrane at the soma is sufficiently depolarized by cooperating effects of synaptic events and/or intrinsic currents, $V_m$ reaches a threshold value ($V_{th}$) where specific $Na^+$ channels are activated. $V_{th}$ is referred to as the firing threshold. The highly increased permeability to $Na^+$ ions and the high driving force due to a positive reversal potential of the $Na^+$ current produce a strong and fast depolarization (> 60 mV in amplitude). The generation of an action potential is an all-or-none process since its time course and its amplitude are independent on the stimulation, as long as it is strong enough to reach the firing threshold. However, this depolarization also activates channels of an outward persistent $K^+$ current that acts against the effect of $Na^+$ ions. In the meantime, $Na^+$ channels are also inactivated. Given those two mechanisms, the membrane quickly hyperpolarizes back toward its rest value. This is the repolarization phase. The different
states of Na\(^+\) and K\(^+\) channels during the action potential are shown in Fig. 1.3. Note that because K\(^+\) channels are slowly deactivated when the membrane is repolarized, \(V_m\) goes slightly below \(V_{\text{rest}}\) for some time after an action potential has been generated. This is the afterhyperpolarization phase. Note also that due to both the slowly deactivating K\(^+\) and the slowly deinactivating Na\(^+\) channels, there is a refractory period during which another action potential cannot be generated.

When the propagating action potential reaches the end of the axon where are localized synaptic buttons, the high depolarization applied on the membrane activates high-threshold Ca\(^{2+}\) channels. The Ca\(^{2+}\) ions crossing the membrane interact with synaptic vesicles that contains neurotransmitters. The vesicles merge with the membrane at the synaptic buttons and neurotransmitters are released in the synaptic cleft. Those neurotransmitters eventually bind to postsynaptic receptors. Receptors are another type of proteins embedded in the plasma membrane. When neurotransmitters bind to these receptors, channels open, the membrane permeability is increased and specific ions are allowed to enter channels. This current produces a synaptic response, i.e. a transient change in the local \(V_m\) or a postsynaptic potential (PSP). Receptors that bear their own channels are called ionotropic receptors. They are thus ligand-gated channels. Another family of receptors is the family of metabotropic receptors. They do not include ionic channels in their structure, but act indirectly on neighboring channels via intermediate molecules called G-proteins.

Neurotransmitters bind to specific receptors. Most common neurotransmitters or at least the most pertinent for the present study are the glutamate and the \(\gamma\)-aminobutyric acid (GABA) that binds to glutamatergic and GABAergic receptors, respectively. Synapses can be either excitatory or inhibitory, so they can depolarize or hyperpolarize the postsynaptic cell, respectively. Synapses that depolarize the postsynaptic cell and increase the probability of generating an action potential trigger excitatory postsynaptic potentials (EPSPs), while synapses that hyperpolarize the cell trigger inhibitory postsynaptic potentials (IPSPs). The \(\alpha\)-amino-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and the \(N\)-methyl-\(D\)-aspartate (NMDA) receptors are glutamatergic receptors and mediate EPSPs. GABAergic receptors such as GABA\(_a\) and GABA\(_b\) receptors induce IPSPs at the postsynaptic membrane.

The amplitude of the postsynaptic current (PSC) \(i_{\text{syn}}\) can be described by an ohmic relation:

\[
i_{\text{syn}} = g_{\text{syn}}(t)(V_m - E_{\text{syn}}),
\]

where \(g_{\text{syn}}(t)\) is the synaptic conductance and \(E_{\text{syn}}\) is the reversal potential of the synaptic current. Note that the conductance depends on time. Typically, ionotropic receptors promote a fast time course for PSCs or PSPs (e.g. AMPA-, NMDA- and
Figure 1.3: Different states of Na\(^+\) and K\(^+\) channels for action potential generation. **A,** At rest, both the Na\(^+\) and the K\(^+\) channels are deactivated. The inactivation gates of Na\(^+\) channels are open. **B,** When the soma is depolarized to the firing threshold, the activation gates of Na\(^+\) channels open and Na\(^+\) ions can cross the membrane from the outside of the cell to the inside. **C,** In the meantime, K\(^+\) channels are activated and an outward K\(^+\) current is induced. **D,** Na\(^+\) channels are then inactivated. The combined effect of the outward K\(^+\) current and the inactivation of Na\(^+\) channels produces a fast repolarization toward the resting value of the membrane potential. **E,** The K\(^+\) channels slowly deactivate after the repolarization, i.e. the channels stay open for some time. This slow deactivation causes the membrane potential to go slightly below its resting value for some time. This is the afterhyperpolarization phase.
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GABA\(_{\alpha}\)-receptor-mediated PSPs) while a slow time course of the postsynaptic response is associated to metabotropic receptors (e.g. GABA\(_{\beta}\)-receptor-mediated IPSPs) due to the indirect channel activation. However, due to different intrinsic kinetics, the NMDA-receptor-mediated current has a much slower time course than the AMPA type. The reversal potential is around 0 mV for typical excitatory synapses like AMPA- and NMDA-receptor-mediated synapses. Relation (1.4) already points out an important characteristic of the synaptic current. In the case of excitatory synapses, an already depolarized membrane at the time of a synaptic event implies a reduced driving potential (\(V_m - E_{syn}\)) and thus a reduced synaptic current. This effect will have a major impact on the synaptic integration since closely localized events will destructively interfere in that they will reduce each other’s driving potential for the synaptic current.

Chemical synapses formed between presynaptic axons and postsynaptic dendrites are stereotypical. However, one should note that synapses may also be formed between dendrites of presynaptic and postsynaptic neurons, as encountered between mitral and granule cells in the olfactory bulb, but also between axons. We will not discuss those dendro-dendritic and axo-axonic synapses here and will consider this issue as an exception. Because they are much less present than chemical synapses, electrical synapses will also be ignored for the purpose of this study. Finally, other molecules embedded in the membrane form active transporters for ions called ion pumps. Their role is mainly to regulate the concentration and voltage gradients by acting directly against electrical and chemical forces. The information contained in this subsection and more can be found in textbooks [3,6].

1.1.2 The thalamocortical network

Located near the center of the brain (Fig. 1.4A), the thalamus relays the sensory information from the periphery to the neocortex via the TC cells, as well as the descending motor information to the neocortex. TC cells are also called thalamic relay neurons due to this relay function. The thalamus is thus the last station of the peripheral information before it reaches the cortex. For that reason it also plays a gating role for the sensory evoked inputs for the different states of vigilance encountered during wake and sleep. During sleep, the thalamus strongly reduces the relay of peripheral inputs to the cortex [7–10]. This is the consequence of a hyperpolarized membrane which is then far from the firing threshold [11]. This hyperpolarization is itself due to a reduced effect of the cholinergic inputs during sleep [12–14].

The thalamus can be divided in the dorsal thalamus and the ventral thalamus. The dorsal thalamus contains the TC cells, as well as some GABAergic interneurons
(INs) that inhibits TC cells. INs typically account for 25-30% of the population of the dorsal thalamus in cats, monkeys and humans brains [15–24], but are nearly absent in rodents [25–28]. The ventral thalamus forms a shell-like structure above the dorsal thalamus and is mainly composed of the thalamic reticular nucleus, which exclusively contains GABAergic reticular (RE) cells that inhibit thalamic relay nuclei. The zona incerta, the ventral lateral geniculate nucleus and the nucleus of the field of Forel are also a part of the ventral thalamus and may contain TC cells, but this is rather an exception. We can divide the dorsal thalamus in different nuclei, the majority of these nuclei being specific to a given sensory system and projecting to its corresponding cortical region (Fig. 1.4B, C). For example, visual stimuli are transmitted to the thalamus via the optic tract that connects to the dorsal lateral geniculate nucleus (first order) and the pulvinar (higher order). That visual information is then sent to the primary visual cortex in the occipital lobe. The only sensory system that does not require a thalamic gating is the olfactory system, which is also known to be the oldest sensory system. Some thalamocortical projections are non-specific, i.e. there are thalamic nuclei that send axons to different cortical fields. This is the case for intralaminar nuclei [29]. Subthalamic inputs of a common tract may also innervate various nuclei, like the spinothalamic tract that projects to both the ventral posterior (VP, sensory inputs) nucleus and the ventral lateral (VL, motor inputs) nucleus [30]. However, the lemniscal and the cerebellothalamic fibers connect exclusively to the VP and the VL nuclei, respectively.

The thalamocortical system consists of the thalamus and the cortex interconnected into a loop (Fig. 1.5). A glutamatergic TC neuron innervates numerous neocortical neurons (mainly from the layer IV), but also receives feedback excitatory inputs from descending corticothalamic fibers arising from the corresponding cortical region (mainly from the layer VI). The main target of TC neurons are the spiny stellate neurons, but they also innervate cortical pyramidal (PY) neurons and in much lesser extent the aspiny interneurons (reviewed in [31]). Cortical projections to TC cells are made by PY neurons. Both thalamocortical and corticothalamic axons send collaterals to the reticular nucleus thus including RE cells in the recurrent thalamocortical network and establishing an excitation-inhibition loop between the dorsal and the ventral thalamus. The multiple thalamic relay nuclei of the dorsal thalamus constitutes the main gate to the cortex to specific ascending sensory inputs from the medial lemniscus, the optic tract, the brachium of the interior collicus, the ansa lenticularis and the brachium conjunctivum. TC neurons, as well as RE neurons, also receive non-specific inputs from the brainstem modulatory systems (noradrenergic, serotonergic, cholinergic, etc.), which are important in modulating and regulating the different states of vigilance. More precisely, those inputs are mainly responsible of the blockade of K+ channels during the waking state, and are thus responsible for a relatively depolarized membrane at that
Figure 1.4: Structures and specific pathways of sensory systems. 

A, Central position of the thalamus. 
B, Topological arrangement of the neocortex. 
C, Specific pathways of different sensory systems. 

Modified from [3].
state (reviewed in [13]). The gating function of TC cells and the recurrent organization of the thalamocortical system enable it to generate and to sustain spontaneous activity in the network during sleep, i.e. when the system is closed to peripheral information.

In the present study, we used 8 three-dimensional reconstructions of TC cells to build a model (Fig. 1.6). The reconstructed cells were from the VPL nucleus of the cat, which conveys the peripheral sensory inputs coming by the medial lemniscal pathway to the layer IV of the somatosensory cortex (Fig. 1.7A). This is the pathway for mechanoreception such as the sensations of touch and vibration at the body and the proprioception (body position). The VPL nucleus also receives in part the information from the body relative to nociception (pain) and thermoreception (temperature) via the spinothalamic tract of the anterolateral system (Fig. 1.7B). For further details on the VPL nucleus or on the whole thalamocortical circuitry, see reference [31].

1.1.3 The thalamocortical unit

In cats, between 5500 and 8800 synapses are formed at a typical TC neuron in the VP nucleus [31, 32]. A density of 0.6-0.9 synapse per µm has been estimated [32]. Corticothalamic fibers connect to distal dendrites via small terminals (0.2-0.5 µm in diameter), while lemniscal synapses are formed at the proximal part of the dendritic arborization and are characterized by large terminals (2-4 µm in diameter) [32]. How-
Figure 1.6: 8 reconstructed neurons from the VPL nucleus.
Figure 1.7: Ascending somatosensory pathways. **A**, Dorsal column-medial lemniscal system. **B**, Anterolateral system. Modified from [3].
ever, corticothalamic axons form more synapses on TC cells than sensory ascending fibers. Large excitatory terminals that arise from the medial lemniscal tract (and some from the spinothalamic tract) constitute 12-29% of the total number while small excitatory terminals arising from the cortex (or in some cases from brainstem afferents) form 23-53% of the synaptic population [32]. We do not know actually what are the spatiotemporal activation patterns of those synaptic contacts, i.e. if multiple lemniscal and/or corticothalamic synapses can be simultaneously activated and if they are colocalized in a dendritic region or are rather sparsely distributed. Note also that inhibitory terminals arising from INs and RE cells and mainly established at proximal dendrites and at soma constitute 29-44% of the total population [32]. Finally, some dendro-dendritic connections with INs account for 2-7% of the total number of terminals at the typical cat TC neuron [32]. Similar ratios of the different types of synapses were obtained for the lateral geniculate nucleus [33].

TC cells are characterized by an important set of intrinsic currents that enables them to participate to or to trigger multiple patterns of oscillation. Besides the currents responsible for the generation of action potentials, most notable are the low-threshold Ca\(^{2+}\) (\(I_T\)) and the hyperpolarization-activated cation (\(I_h\)) currents. Both currents operate from a hyperpolarized level of \(V_m\). The former is a transient inward current mediated by channels called T-channels that can be activated/deactivated and inactivated/deinactivated. The dynamics is thus described by two kinds of voltage gates. Activation gates are open at a depolarized level of \(V_m\), while inactivation gates are open at a hyperpolarized level. Near \(V_{rest}\) and at more depolarized values of \(V_m\), T-channels are activated, but are also mostly inactivated, so Ca\(^{2+}\) ions cannot flow across them. To deinactivate the channels the membrane must be hyperpolarized (< -70 mV). Since those gates close slowly, stimulating from that level and up to the activation threshold of the channels leads to a Ca\(^{2+}\) influx that triggers a strong depolarization called a low-threshold spike (LTS) [34]. After a time of the order of a hundred milliseconds, the inactivation gates close and the membrane repolarizes toward \(V_{rest}\). The mechanisms are similar to those of the Na\(^+\) current underlying the generation of action potentials, but the kinetics are much slower. If the amplitude of the LTS is sufficient to reach the firing threshold, a burst of high frequency action potentials will be generated. Note that exciting the hyperpolarized cell is not a necessity to trigger an LTS. At the offset of a hyperpolarizing current, it is very likely that the TC neuron will trigger a spontaneous LTS crowned with Na\(^+\) spikes since \(V_m\) tends to return to its resting state, which implies crossing the activation threshold of \(I_T\) (Fig. 1.8(middle)). The specific range of action of \(I_T\) enables TC cells to operate in two different modes (Fig. 1.8(left and right)). At a depolarized level of \(V_m\), cells are in a tonic-firing mode and a sufficient stimulus triggers one or several unitary action potentials. Under hyperpolarization, however, TC cells operate in a bursting mode since they have that ability to generate
bursts of high-frequency action potentials. This firing mode suggests the crucial role of $I_{T}$ in thalamocortical oscillations during sleep, i.e. when modulatory (e.g. cholinergic) inputs are inactivated and cells are hyperpolarized [12–14].

$I_{h}$ is a mixed Na$^{+}$ and K$^{+}$ current that is activated under hyperpolarization of the membrane (half-activation at $V_m = -75$ mV) and that is almost completely deactivated at $V_m = -60$ mV [35]. As a consequence, when a TC cell is hyperpolarized from $V_{rest}$, $I_{h}$ is activated and produces a slow depolarization of the membrane. We refer to this slow apparent voltage change in time as the “depolarizing sag” (Fig. 1.8(right)). Since this depolarization may cross the activation threshold of $I_{T}$, it may contribute indirectly to the generation of an LTS by activating T-channels. Note also that despite its Na$^{+}$/K$^{+}$ nature, it has been demonstrated that $I_{h}$ has a Ca$^{2+}$ dependence [36]. This Ca$^{2+}$ dependence would induce a shift in its activation curve and increase the conductance of the channels underlying this current.

### 1.1.4 Thalamocortical oscillations

The thalamocortical system has a tendency to oscillate, and to different frequencies depending on the state of vigilance (reviewed in [4]). The various oscillations include the slow (<1 Hz), the delta (1-4 Hz), the spindle (7-15 Hz), the beta (15-30 Hz) and
the gamma (30-80 Hz) oscillations, as well as ripples (>100 Hz). Experimental studies have demonstrated the existence of the delta oscillation (1-4 Hz) during slow wave sleep. This activity can be induced independently in both thalamic and cortical structures. An enhancement of the neocortical delta activity has been observed in neocortical slabs, i.e. in a small and isolated part of cortex, and after the surgical removal of the thalamus [37,38]. Thalamic delta oscillations can be intrinsically generated in TC neurons during sleep by an interplay between $I_T$ and $I_h$ [35,39–41]. A long-lasting hyperpolarization of the membrane simultaneously deinactivates $I_T$ and activates $I_h$. The depolarizing sag recruits $I_T$ by opening the activation gates of T-channels before the closing of the inactivation gates. It results in a burst of action potentials. The inactivation and the deactivation of $I_T$ and $I_h$, respectively, at the depolarized level of $V_m$ induced by the burst results in a hyperpolarization of the membrane so a new cycle can start (Fig. 1.9).

However, the disappearance of synchrony between TC neurons at those frequencies in decorticated cats [42] indicates a minor role of the thalamic delta activity on cortical delta oscillations. In contrast, cortical delta oscillations could bring back the synchrony in TC neurons via the corticothalamic feedback projections.

Another type of thalamocortical oscillation is the sleep spindle oscillation (7-14 Hz). It results from both intrinsic and network mechanisms during early stages of sleep or during active phases of the slow sleep oscillation. The presence of thalamic spindle oscillations in decorticated cats points out a thalamic origin of this activity [42–45]. In vivo, in vitro and computational studies showed that such activity can be generated by an interaction between the reticular nucleus and relay nuclei of the thalamus [45–49]. Bursting RE cells induce IPSPs at TC neurons. At the offset of this inhibition, TC neurons generate a rebound burst of action potentials that induces EPSPs at RE cells, thus giving rise to a new cycle of spindle oscillation (Fig. 1.8B). However, it has been shown that TC cells may not fire at every cycle and that RE cells alone can generate these oscillations at their early phase [45,47]. Gap junctions between RE cells [50] is one possible mechanism underlying this independent activity [51]. The second phase results from interactions between RE and TC cells with a contribution of the cortical feedback to these two types of thalamic neuron. The last phase is referred to as the waning phase and is the consequence of a desynchronization of the network [45]. The $\text{Ca}^{2+}$ dependence of $I_h$ may also contribute to the termination of spindle oscillations by depolarizing TC cells and preventing rebound spikes to occur [52–54]. Given those mechanisms, spindle oscillations display a “waxing-and-waning” fashion (Fig. 1.8A). This 7-14 Hz activity thus lasts 1-3 seconds, but recurs every 5-15 seconds.
Figure 1.9: Thalamic delta oscillation.  

**A, In vivo** recordings from the lateral posterior nucleus of a decorticated cat.  
Top, Waxing and waning delta activity (2.2 Hz).  
Bottom, Left, Magnification of three segments of the top panel. LTSs vary in amplitude and do not trigger a burst at every cycles.  
Bottom, Right, Topographical plot of the delta activity indicates a stable frequency regardless of the amplitude of LTSs.  

**B, Model**, A model of a single TC neuron shows that the delta oscillation can be generated intrinsically [4].
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Figure 1.10: Spindle activity. A, *In vivo* recordings of cortical (area 4) and TC (ventral lateral nucleus) neurons of a cat showing the three phases of a spindle sequence. B, Computational model of two RE and two TC neurons showing intrathalamic spindle oscillations [4].
1.2 Modeling biophysical processes

1.2.1 The cable theory

The approach taken in the present study is exclusively a modeling one. This is an usual choice since electrophysiological recordings can rarely be carried out at dendrites or practically never be carried out at thin distal dendrites (~ 0.5-1 µm in diameter). Modeling biological mechanisms implies a transposition of a physiological description into physical and mathematical terms by making a reasonable number of assumptions and simplifications. Because neurons are electrically excitable cells, their transposition into a mathematical formulation comes naturally from the electrostatic theory. In the present subsection is introduced the cable theory, in order to obtain the cable equation, an equation well-known by scientists in the field of computational neuroscience. Some important axioms obtained from simple considerations, but that are crucial for an intuitive understanding of the voltage propagation in neurons are finally discussed. This model has been widely described in scientific literature and it has been largely used for both single cell and network modeling studies (see references [55, 56]).

The phospholipid bilayer that composes the plasma membrane is very thin (30-50 Å), so charges that are on one side of the bilayer may attract or repulse charges on the other side and vice versa via electrostatic forces. As a result charges accumulate at the membrane and a capacitance $C_m$ is established across it. $C_m$ is defined by capacitance per area, typically in $\mu$F/cm$^2$. Furthermore, as mentioned in section 1.1.1, the plasma membrane is not completely impermeable and different ions can move from one side to the other via leakage conductances or more complex types of channels. Different finite values of resistance or non-zero conductance can be assigned to the different types of channels. A constant resistance times units of area is assigned to the leak current and is referred to as the passive membrane resistance $R_m$, usually expressed in $\Omega$·cm$^2$. We may also refer simply to this quantity as the membrane resistance, since active properties are more conveniently described by conductances. Those variable conductances for active channels will be introduced later. The cytoplasm that fills the intracellular space also presents an axial resistance to the charges flowing in dendrites. However, at a given point in a branch, the axial resistance perceived is much lower than the membrane resistance, so charges preferentially move toward the cell body during forward propagation instead of flowing across the membrane. To describe this resistive effect of the intracellular medium, the axial resistivity $R_a$ is commonly used and is generally expressed in $\Omega$·cm. If we consider a dendritic branch or a segment of a dendritic branch as a cable of length $l$ and constant diameter $D$, the total cytoplasmic
resistance $r_a$ associated to this cable is given by

$$r_a = \frac{4R_a l}{\pi D^2}. \quad (1.5)$$

The resistance of a dendritic cable to the axial current thus decreases as the cable increases in diameter.

Weak electrical gradients in a homogeneous extracellular space are assumed. It implies a constant potential and an infinite conductance for the extracellular medium [5]. Since we are interested in the difference in potential $V_m$ across the membrane, we set $V_{ext} = 0$. Note that since the voltage spread is more important along the axis of a dendritic branch than in its transverse directions [57], both the radial ($\rho$) and the azimuthal ($\theta$) coordinates in the intracellular medium are neglected. The initial three spatial dimensions problem thus becomes a one spatial dimension problem, i.e. we set $V_m(\rho, \theta, x, t) = V_m(x, t)$.

We consider a simple cable with constant geometry and passive properties $C_m$, $R_m$ and $R_a$. The axis of this cable is along the $x$ axis (Fig. 1.11A). By taking an infinitesimal segment of length $\Delta x$ and building its equivalent electrical circuit (Fig. 1.11B), we can extract the spatiotemporal flow of charges. This small RC circuit is composed of a capacitance in parallel to a resistor in order to reproduce the effect of a permeable thin
plasma membrane on the membrane current. The resistor is in series with a battery establishing the reversal potential $V_{\text{rest}}$. The whole circuit connects to ground outside the membrane, since the extracellular medium is assumed to be homogeneous and to have an infinite conductance. This circuit is connected to two neighboring small RC circuits via axial resistors mimicking the impact of the cytoplasm on the current in the intracellular medium. According to Eq. (1.5), the total axial resistance associated to a segment of length $\Delta x$ and diameter $D$ is $4R_a\Delta x/\pi D^2$. Similarly, the total membrane resistance and the total membrane conductance are respectively given by $R_m/\pi D\Delta x$ and $\pi D\Delta x C_m$. Consider the figure 1.11. $V_m(x, t)$ is the membrane potential at point P1 at time $t$ and $V_m(x + \Delta x, t)$ is the membrane potential at P2 at time $t$. The difference between those voltages is given by Ohm’s law:

$$\Delta V_m(x,t) \equiv V_m(x + \Delta x,t) - V_m(x,t) = -\frac{4R_a\Delta x}{\pi D^2} i_a(x,t),$$  \hspace{1cm} (1.6)$$

where $i_a(x,t)$ is the axial current flowing in the intracellular segment of length $\Delta x$, from point P1 to P2. In the limit $\Delta x \to 0$ we obtain

$$\frac{\partial V_m}{\partial x}(x,t) = -\frac{4R_a}{\pi D^2} i_a(x,t).$$ \hspace{1cm} (1.7)$$

We define $i_m(x,t)$ as the current flowing across the membrane from P1. A part of that current flows in the capacitance and another part flows in the resistance of the membrane circuit. We can express $i_m$ as follows:

$$i_m(x,t) = \frac{V_m(x,t) - V_{\text{rest}}}{R_m/\pi D\Delta x} + \pi D\Delta x C_m \frac{\partial V_m}{\partial t}(x,t).$$ \hspace{1cm} (1.8)$$

In the absence of active properties, the membrane potential $V_{\text{rest}}$ equals the reversal potential for the leak current $E_{\text{leak}}$. Applying Kirchhoff’s current law at point P1 gives

$$i_a(x - \Delta x,t) - i_a(x,t) - i_m(x,t) = 0.$$ \hspace{1cm} (1.9)$$

Since $i_a(x - \Delta x,t) - i_a(x,t) = i_a(x,t) - i_a(x + \Delta x,t)$, Eq. (1.9) can be rewritten in the following way:

$$i_m(x,t) = i_a(x,t) - i_a(x + \Delta x,t).$$ \hspace{1cm} (1.10)$$

Substituting this expression for $i_m(x,t)$ in Eq. (1.8) and taking the limit $\Delta x \to 0$, we obtain

$$-\frac{\partial i_a}{\partial x}(x,t) = \frac{\pi D}{R_m}(V_m(x,t) - V_{\text{rest}}) + \pi D C_m \frac{\partial V_m}{\partial t}(x,t).$$ \hspace{1cm} (1.11)$$

Taking the spatial derivative of Eq. (1.7) and reorganizing it gives

$$\frac{\partial i_a}{\partial x}(x,t) = -\frac{\pi D^2}{4R_a} \frac{\partial^2 V_m}{\partial x^2}(x,t).$$ \hspace{1cm} (1.12)$$
The substitution of the right-hand side of this last expression into the left-hand side of Eq. (1.11) gives
\[
\frac{D R_m}{4 R_a} \frac{\partial^2 V_m(x, t)}{\partial x^2} = V_m(x, t) - V_{\text{rest}} + R_m C_m \frac{\partial V_m(x, t)}{\partial t}.
\] (1.13)

This partial differential equation (PDE) is a form of the linear cable equation.

Two quantities called the time and length constants can be defined. They are respectively expressed as
\[
\tau_m = R_m C_m,
\] (1.14)
in units of time, and
\[
\lambda = \left(\frac{D R_m}{4 R_a}\right)^{1/2},
\] (1.15)
in units of length. For simplicity, we define the electrotonic potential \(V\) as the deviation from the resting potential, i.e. \(V = V_m - V_{\text{rest}}\). Eq. (1.13) can thus be reexpressed as
\[
\lambda^2 \frac{\partial^2 V}{\partial x^2}(x, t) = V(x, t) + \tau_m \frac{\partial V}{\partial t}(x, t).
\] (1.16)

For steady state conditions, i.e. for \(\partial V/\partial t = 0\), Eq. (1.16) reduces to an ordinary differential equation (ODE) and its general solution is
\[
V(x) = A_1 e^{x/\lambda} + A_2 e^{-x/\lambda}
\] (1.17)
or
\[
V(x) = B_1 \cosh(x/\lambda) + B_2 \sinh(x/\lambda).
\] (1.18)

Two boundary conditions are needed to identify constants \(A_1\) and \(A_2\). Suppose a semi-infinite cable. The finite end corresponds to \(x = 0\) and is voltage-clamped at \(V = V_0\). The voltage where \(x \to \infty\) implies that \(V\) tends to zero when approaching infinity. The unique solution to Eq. (1.17) is thus
\[
V(x) = V_0 e^{-x/\lambda}.
\] (1.19)

This expression brings a physical meaning to the length constant. In a semi-infinite cable, \(\lambda\) is the distance over which a steady state voltage is reduced to \(1/e \simeq 0.368\) times its value at \(x = 0\) or anywhere along the cable. A semi-infinite cable might appear as an impossible condition to fulfill. However, this description of an electrotonic attenuation of the voltage that provides \(\lambda\) applies very well to branches of more than \(4\lambda\) in length. It can thus be used to treat long-lasting responses in long dendrites.

An equivalent interpretation of the time constant can also be obtained. If we consider a cable clamped to \(V = V_0\) over all its length, the decay in potential at the offset
of the voltage-clamp will be described by \( \tau_m \). Taking \( \frac{\partial^2 V}{\partial x^2} = 0 \) in Eq. (1.16) and solving the resulting first order differential equation with \( V = V_0 \) at \( t = 0 \), we obtain \( V(t) = V_0 \exp[-t/\tau_m] \). At the offset of the voltage-clamp, the electrotonic potential will therefore decay to 0.368\( V_0 \) after a time \( t = \tau_m \). However, the definition Eq. (1.14) stands when the voltage mainly decays via a current flow across the membrane. It hardly applies for thin distal dendrites of neurons, where voltage transients rise and decay quickly in distance and time. Even for large sections, like the soma and its near perisomatic region, which are close to isopotentiality, \( \tau_m \) does not faithfully describe the time course of typical responses. This fact previously led to a misevaluation of the time constant in cat motoneurons (see a description of the problem by Rall [58]). Furthermore, it was shown that for fast excitatory synaptic currents, the time course of EPSPs is independent of \( R_m \) and thus Eq. (1.14) is certainly not accurate [59]. On the other hand, one can safely say that anywhere in a cell, the time constant is always smaller or equal to the value provided by Eq. (1.14).

Consider now a finite cable of length \( l \) instead of an infinite cable, but that still has the extremity \( x = 0 \) clamped to \( V = V_0 \). If the other extremity at \( x = l \) is a sealed end, the new boundary condition for this extremity is \( \frac{dV}{dx} = 0 \) since the voltage spread or the current flow stops at that impermeable end. Using Eq. (1.18) for simplicity, the unique solution in such condition can be expressed as

\[
V(x) = V_0 \left[ \frac{\cosh(l/\lambda) \cosh(x/\lambda) - \sinh(l/\lambda) \sinh(x/\lambda)}{\cosh(l/\lambda)} \right]
\]  
(1.20)

or, using the propriety of hyperbolic functions \( \cosh(a-b) = \cosh(a) \cosh(b) - \sinh(a) \sinh(b) \),

\[
V(x) = \frac{V_0 \cosh \left( \frac{l-x}{\lambda} \right)}{\cosh(l/\lambda)}.
\]  
(1.21)

Another special case of a finite cable \( l \) is the “open end” condition. The extremity at \( x = 0 \) is still clamped at \( V = V_0 \), while the open extremity at \( x = l \) will be assigned an electrotonic potential \( V = 0 \). Since \( V = V_m - V_{\text{rest}} \), we say that the cable is clamped at its resting potential at \( x = l \). Using a similar approach as for the sealed end, the unique solution can be obtained:

\[
V(x) = \frac{V_0 \sinh \left( \frac{l-x}{\lambda} \right)}{\cosh(l/\lambda)}.
\]  
(1.22)

Different voltage spreads for different boundary conditions are shown in figure 1.12. The voltage spread within the cable is largely reduced at shorter distances for cables with an open end than for cables with a sealed end, due to a shunting effect at the open
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Figure 1.12: Voltage spread in cables for different boundary conditions. Curve a corresponds to a semi-infinite cable. Curves b, c and d correspond to the “open end” condition for different cable lengths. There is a shunting effect of the voltage spread due to the open end. Curves e, f and g correspond to the “sealed end” condition. The resistance along the cable is higher than for an open end. As a consequence, the current flow toward the end is weaker and the voltage is higher. For small cable lengths, the membrane tends to become isopotential along the cable. The curve a for a semi-infinite cable is the limit between the “open” and “sealed end” cases. Modified from [5].

end and a reduced resistance along the cable. The case of a semi-infinite cable is at the limit between those two cases.

It is clear from previous results that different responses might be obtained at different positions in a cable or in a neuron depending on boundary conditions. It would also be the case for a transient current instead of a constant current. The response obtained from a current injection may be highly variable at the site of stimulation given different sets of geometrical parameters. Of major interest in this study is the amplitude of the response. An important quantity is the input resistance, which can be measured experimentally at the soma by taking the ratio of the steady voltage to the steady current \( I_{\text{inj}} \) applied by an electrode. It is an easy measure to carry out and it provides an idea of the degree of excitability of a cell. The higher is the input resistance, the higher is the response to an applied current. For a semi-infinite cable, the input resistance \( R_{\infty} \) at the extremity \( x = 0 \) is noted \( R_{\infty} \) in the literature and can be expressed as

\[
R_{\infty} = (R_m R_a)^{1/2} \pi D^{3/2} \frac{2}{2}.
\]  

(1.23)

In that case the electrotonic voltage at \( x = 0 \) would be

\[
V(x = 0) = R_{\infty} I_{\text{inj}}.
\]  

(1.24)

Since the axial resistance increases as the diameter decreases, it is clear from Eq.
that the input resistance is higher for both higher membrane and axial resistances. For a finite cable of length \( l \) in the “open end” condition, \( R_{\text{in}} < R_\infty \) at \( x = 0 \), while \( R_{\text{in}} > R_\infty \) for the same cable in the “sealed end” condition. Note also that \( R_\infty \) is higher for a finite cable of length \( l \) than for a cable of length \( 2l \). From this simple fact, one could expect a cell with extensive dendritic trees to trigger smaller responses at their cell body than a more compact cell. This is what Rall predicted when he studied the voltage spread in branched dendrites [5]. At tested conditions, he even found that the dendritic input resistance \( R_{\text{dend}} \) at the connecting point between the soma and a primary branch reaches the value obtained for an infinite cable when dendrites get sufficiently extensive. \( R_{\text{dend}} \) depended only on the first few branching orders and did not change much whether higher orders were included or not in the model. On the other hand, this statement does not apply for events arising at distal branches since they are electrically isolated. Note also that since \( R_{\text{dend}} \) decreases when the amount of branching in trees increases, the current flow from the soma to dendrites is enhanced for extensive dendrites and smaller and rapidly decaying somatic responses are to be expected. Furthermore, \( R_{\text{in}} \) is typically a measure of excitability under the application of a steady current and one could question the reliability of these facts for a highly transient response, as for an AMPA-receptor-mediated EPSP.

What happens for transient responses? Softky previously obtained an elegant expression from the cable theory describing, after making a few assumptions, the amplitude of an EPSP evoked by a fast current input [59]:

\[
V_{\text{peak}} \approx 1.5 \frac{R_a^{1/2} I_{\text{peak}}}{(\pi D)^{3/2} C_m^{1/2}} \sqrt{t_{\text{peak}}},
\]

(1.25)

In this expression, \( I_{\text{peak}} \) is the amplitude of the current applied and \( t_{\text{peak}} \) is the time taken to reach its peak from the onset of the current. In contrast to what provide Eqs. (1.23) and (1.24) for a steady voltage, the amplitude of a fast EPSP given by Eq. (1.25) does not depend on the membrane resistance \( R_m \), but is dependent on the capacitance. This is an important result. It predicts that the amplitude of an EPSP will grow considerably as the diameter of the targeted branch decreases, but also that it will depend on the membrane capacitance, which would not be really the case for a steady voltage. However, Eq. (1.25) is limited by the fact that the amplitude of an EPSP should depend on the driving potential. The depolarization induced by an EPSP stops to increase when its amplitude gets closer to the reversal potential \( E_{\text{syn}} \) of the synaptic current (\( \sim 0 \) mV, typically). This effect is not taken into account in Eq. (1.25). Note that high in amplitude transient responses are largely attenuated during their propagation to soma, and much more than for the spreading of steady voltage. The reason is that the axial resistance and the membrane capacitance are organized in a distributed low-pass filter. For the same reason, one can expect a fast EPSP to get broadened during its propagation to soma [60–63].
1.2.2 The compartmental model

In the previous subsection we found solutions of the cable equation for a steady state voltage in different simple conditions. Since the current delivered at a synapse is highly transient, we would like to calculate the response induced at the postsynaptic membrane for a transient current. However, evaluating $V_m$ and the propagation of potentials in highly complex arborizations increases rapidly in difficulty. Including nonlinear membrane properties such as intrinsic currents and ionic pumps makes an analytical approach impossible to achieve and makes numerical calculations long to carry out. The best strategy to adopt to solve those problems is the compartmental modeling, a method first developed by Rall [64].

To obtain the cable equation (1.13), we used infinitesimal RC circuits. In fact, one can spatially discretize a complete neuron into a given number of equivalents circuits connected by resistors mimicking the effect of the cytoplasm on the intracellular current
flow. The neuron is thus “compartmentalized” in multiple isopotential segments (Fig. 1.13). A compartment must be small enough so that spatial differences in \( V_m \) within the compartment can be neglected. In the limit of an infinite number of compartments, the solution of the system would approach the exact solution for a continuous cable. However, a relatively low number of segments is needed to reduce the numerical error to a more than acceptable level. Compartments do not need to have all the same size, and the equivalent passive properties \( c_m, r_m \) and \( r_a \) can be determined easily. By integrating \( C_m (\mu F/cm^2) \) and the membrane leakage conductance \( g_{\text{leak}} (S/cm^2) \) over the surface area, the total membrane capacitance \( c_m \) and the total membrane resistance \( r_m \) can be calculated. Similarly, the axial resistance \( r_a \) connecting to the previous and the next compartments is calculated by taking the integral of \( R_a (\Omega \cdot \text{cm}) \) over the first extremity to the middle of the segment and over the middle to the last extremity. In the compartmental model, the spatial derivatives of the cable equation (1.13) can be removed. Instead of solving iteratively a continuous PDE for each compartment with proper boundary conditions, we solve a system of coupled ODEs.

Adding various currents to an initially passive model is an easy task in a compartmental formalism. Consider a single compartment as shown in figure 1.14. Each synaptic or active intrinsic current \( j \) can be inserted via an additional parallel conductance \( g_j \) in series with a battery \( E_j \) that fixes the reversal potential of the new current. Note that \( g_{\text{leak}} = 1/R_m \) by convention. However, \( g_j \) is usually not constant and depends specifically on time \( t \) and on \( V_m \). This is why it is represented as a variable conductance in figure 1.14. The total membrane current can be expressed as

\[
i_m = C_m \frac{dV_m}{dt}(t) + g_{\text{leak}}(V_m - E_{\text{leak}}) + \sum_j g_j(V_m - E_j) \quad (1.26)
\]

or, at equilibrium,

\[
C_m \frac{dV_m}{dt}(t) = -g_{\text{leak}}(V_m - E_{\text{leak}}) - \sum_j g_j(V_m - E_j). \quad (1.27)
\]

Note also that each current in Eqs (1.26) and (1.27) is in fact a density of current per unit of area, since \( C_m \) and the different conductances are respectively in units of capacitance and conductance per units of area. However, \( V_m \) is the absolute membrane potential.

Compartments need to be connected together. Suppose that \( \hat{i}_{m_k} \) is the total current flowing across the membrane of total capacitance \( c_m \) at the compartment \( k \). By Kirchhoff’s current law, \( \hat{i}_{m_k} \) equals the axial current flowing out of the compartment \( k - 1 \) toward \( k \) minus the current flowing out of \( k \) toward the compartment \( k + 1 \):

\[
\hat{i}_{m_k} = \hat{i}_{a_{k-1,k}} - \hat{i}_{a_{k,k+1}}, \quad (1.28)
\]
where $\dot{i}_{ak-1,k}$ and $\dot{i}_{ak,k+1}$ denote the axial currents. This can be reexpressed as

$$c_{mk} \frac{dV_m(t)}{dt} + \sum_j i_j = \frac{V_{k-1} - V_k}{r_{ak-1,k}} - \frac{V_k - V_{k+1}}{r_{ak,k+1}},$$

(1.29)

where $r_{ak-1,k}$ and $r_{ak,k+1}$ are the total axial resistances between adjacent compartments. At bifurcation points, the current flow in daughter branches is taken into account by adding another two terms at the right-hand side of Eq. (1.29) with appropriate indexes. Both daughter branches have the same $k - 1$ compartment.

If we consider a morphologically complex cell model with $N$ compartments, we end up with a system of $N$ differential equations to solve. It can be written in a matrix formulation:

$$\dot{\bar{V}} = A\bar{V} + \bar{b},$$

(1.30)

where $\dot{\bar{V}}$ is a $N$ components column vector containing the time derivatives and $\bar{V}$ is a column vector of unknown membrane potentials. $A$ is a $N \times N$ matrix containing the coefficients of $V_1$, $V_2$, ..., $V_{N-1}$ and $V_N$ and $\bar{b}$ is a column vector containing products of conductances with their corresponding reversal potential values. Note that $A$ is a sparse matrix, i.e. it mainly contains zeros since one dendritic compartment is generally not connected to more than 2 or 3 neighboring compartments. For a sufficiently fine spatial discretization, the multicompartment model provides good solutions with efficient calculations since the second-order spatial derivatives have been removed from our differential equations.
1.2.3 Modeling active membrane properties of thalamocortical cells

The existence of active and specific channels was demonstrated by Hodgkin and Huxley in the early 50s. Using voltage-clamp experiments in a squid giant axon, they were able to describe the mechanisms underlying the generation of action potentials. The prolific pair of scientists then established an elegant mathematical formalism for the description of channels kinetics [65]. An intrinsic or a synaptic current $j$ can be modeled using an ohmic relation:

$$i_j = g_j(V_m - E_j), \quad (1.31)$$

where $g_j$ and $E_j$ are respectively the conductance and the reversal potential for the current $j$. However, $g_j$ is usually not a constant factor in Eq. (1.31) and may depend on time $t$, on the membrane potential $V_m$ or on other variables. Eq. (1.31) can be reexpressed in the following way:

$$i_j = \overline{g}_j m^M h^N (V_m - E_j), \quad (1.32)$$

where $\overline{g}_j$ is the peak conductance, typically in S/cm$^2$ for intrinsic currents, and $m$ and $h$ are respectively the activation and inactivation variables and are generally functions of $t$ and $V_m$. The $m$ variable conceptually represents the ratio of open activation gates, while $h$ is the ratio of open inactivation gates. Both $m$ and $h$ thus have a value between 0 and 1 and can also be thought of as the probability of finding a gate in its “open” state. The values of $M$ and $N$ are determined from the fitting to experimental recordings. They represent more or less the number of ions of type $j$ needed to open the gate or the number of gates. The functions of $m$ and $h$ are obtained empirically from real electrophysiological recordings in order to reproduce the intrinsic activity of real cells. The passage from an open to a closed state of gates or from a closed to an open state is described by rate equations:

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m \quad (1.33)$$

$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h, \quad (1.34)$$

where the $\alpha$ and $\beta$ constants are called rate constants and are functions of $V_m$, but not $t$. By setting Eqs. (1.33) and (1.34) equal to zero, we obtain the steady state values of rate equations:

$$m_\infty = \frac{\alpha_m}{\alpha_m + \beta_m}, \quad (1.35)$$

$$h_\infty = \frac{\alpha_h}{\alpha_h + \beta_h}. \quad (1.36)$$
Expressions (1.35) and (1.36) describe the voltage dependence of the activation and inactivation processes and can be determined by fitting experimental data. It provides the range of action of a given current in terms of $V_m$. The remaining information to obtain is the time dependence of those processes. Time constants can be determined from voltage-clamp experiments. A time constant can be defined for each type of gate:

$$\tau_m = \frac{1}{\alpha_m + \beta_m} \quad (1.37)$$

$$\tau_h = \frac{1}{\alpha_h + \beta_h} \quad (1.38)$$

Rate constants can then be evaluated from experimental data of $m_\infty$, $h_\infty$, $\tau_m$ and $\tau_h$, and a function for rate constants can be constructed. The solutions for the activation and inactivation variables are

$$m = m_\infty - (m_\infty - m_0) \exp(-t/\tau_m) \quad (1.39)$$

$$h = h_\infty - (h_\infty - h_0) \exp(-t/\tau_h). \quad (1.40)$$

Again the constants $m_0$ and $n_0$ can be obtained empirically. To model currents, one can use either time constants with steady state values of $m$ and $n$ as in Eqs. (1.39) and (1.40) or Eqs. (1.33) and (1.34) with proper rate constants.

As for all excitable cells, TC neurons possess Na$^+$ and K$^+$ channels that allow them to generate action potentials. In all simulations we used a model established in a past study on hippocampal PY neurons [66] and that was later used in several modeling studies on TC cells [49, 67, 68] or on other types of cells [69, 70]. The K$^+$ conductance is expressed as

$$g_K = \overline{g}_K n^4. \quad (1.41)$$

Those channels do not inactivate and are only described by an activation variable $n$. The rate constants are given by

$$\alpha_n = \frac{0.032(67 - V_m)}{\exp\left(\frac{67 - V_m}{5}\right) - 1} \quad (1.42)$$

$$\beta_n = 0.5 \exp\left(\frac{62 - V_m}{40}\right). \quad (1.43)$$

Similarly, the Na$^+$ conductance is described by

$$g_{Na} = \overline{g}_{Na} m^3 h. \quad (1.44)$$
The rate constants for that transient current are

\[
\alpha_m = \frac{0.32(65 - V_m)}{\exp\left(\frac{65 - V_m}{4}\right) - 1}
\]

(1.45)

\[
\beta_m = \frac{0.28(V_m + 12)}{\exp\left(\frac{V_m + 12}{5}\right) - 1}
\]

(1.46)

\[
\alpha_h = 0.128 \exp\left(\frac{69 - V_m}{18}\right)
\]

(1.47)

\[
\beta_h = \frac{4}{1 + \exp\left(\frac{92 - V_m}{5}\right)}.
\]

(1.48)

As mentioned in section 1.1.3, the low-threshold calcium \((I_T)\) and the hyperpolarization-activated cation \((I_h)\) currents are crucial for thalamocortical oscillations during sleep. In some simulations we used one or both of these currents. The model of \(I_T\) was described in a previous study \([71]\) and is based on voltage-clamp data \([72]\). The kinetics of activation and inactivation were later updated \([73]\). Typically, intracellular and extracellular Ca\(^{2+}\) concentrations are respectively of the order of 0.1 µM and 1 mM, which is low compared to K\(^+\), Na\(^+\) and Cl\(^-\) concentrations (~10-100 mM). The respective Ca\(^{2+}\) concentrations inside and outside the cell are also highly unbalanced. This imbalance causes the outward current to be nearly absent since Ca\(^{2+}\) ions hardly move against their concentration gradient, and thus a reversal potential cannot be deduced from usual considerations. The current-voltage relationship for an open channel is nonlinear and Ohm’s law cannot be used. To describe Ca\(^{2+}\) currents another form of the GHK equation called the Goldman-Hodgkin-Katz constant-field equation is required. It is dependent on \(V_m\) and on the extracellular \([Ca^{2+}]_{\text{ext}}\) and intracellular \([Ca^{2+}]_{\text{in}}\) calcium concentrations. It is denoted as \(G(V_m, [Ca^{2+}]_{\text{ext}}, [Ca^{2+}]_{\text{in}})\) and is expressed as follows:

\[
G(V_m, [Ca^{2+}]_{\text{ext}}, [Ca^{2+}]_{\text{in}}) = \frac{4F^2V_m[Ca^{2+}]_{\text{in}} - [Ca^{2+}]_{\text{ext}} \exp(-2FV_m/RT)}{1 - \exp(-2FV_m/RT)}.
\]

(1.49)

\(I_T\) is formulated as

\[
I_T = \overline{P}_\text{Ca}m^2hG(V_m, [Ca^{2+}]_{\text{ext}}, [Ca^{2+}]_{\text{in}}),
\]

(1.50)

where \(\overline{P}_\text{Ca}\) is the maximum permeability of T-channels, typically in cm/s. Activation and inactivation parameters were obtained from experimental data:

\[
m_\infty = \frac{1}{1 + \exp\left(-\frac{V_m + 59}{6.2}\right)}
\]

(1.51)

\[
h_\infty = \frac{1}{1 + \exp\left(-\frac{V_m + 83}{4}\right)}
\]

(1.52)
\[ \tau_m = \frac{1}{\phi_m} \left[ 0.612 + \frac{1}{\exp\left(\frac{-V_m + 134}{16.7}\right) + \exp\left(\frac{-V_m + 18.8}{18.2}\right)} \right] \]  

\[ \tau_h = \begin{cases} \frac{1}{\phi_h} \left[ \exp\left(\frac{V_m + 469}{66.6}\right) \right] & \text{if } V_m < -82 \text{ mV} \\ \frac{1}{\phi_h} \left[ 2.8 + \exp\left(\frac{-V_m + 24}{10.5}\right) \right] & \text{if } V_m \geq -82 \text{ mV}, \end{cases} \]  

where \( \phi_m = 5^{(T-24)/10} \) and \( \phi_h = 3^{(T-24)/10} \) are corrections for the temperature \( T \) at the activation and inactivation time courses, since the recordings were carried out at \( T = 24^\circ \text{C} \).

The kinetics of \( I_h \) are slightly different from the kinetics of the other currents described here. We used a model based on voltage-clamp experiments [35] that was developed to study the oscillatory activity in TC cells [71]. Another version was developed to take into account the dependence of \( I_h \) on intracellular Ca\(^{2+} \) [52]. Ca\(^{2+} \) ions bind directly to h-channels. However, the binding may not be direct [74]. A modified version was later introduced [49] to match with data obtained in sino-atrial node cells [36]. In this model, Ca\(^{2+} \) ions bind to a regulating factor (\( P \)) that in turn binds to h-channels in their open state (\( O \)) and blocks their transition to a closed state (\( C \)):

\[ C \overset{\alpha}{\underset{\beta}{\rightleftharpoons}} O \]  

\[ P_0 + 2\text{Ca}^{2+} \overset{k_1}{\underset{k_2}{\rightleftharpoons}} P_1 \]  

\[ O + P_1 \overset{k_3}{\underset{k_4}{\rightleftharpoons}} O_L. \]

This model would explain the phase shift of the activation curve of \( I_h \) toward more depolarized values of \( V_m \) in presence of a higher concentration of intracellular Ca\(^{2+} \) [36,52]. In Eq. (1.55), transitions of h-channels from one state to another are described by rate constants \( \alpha \) and \( \beta \):

\[ \alpha = [O]_{\infty}/\tau_{[O]} \]  

\[ \beta = (1 - [O]_{\infty})/\tau_{[O]} \]

with

\[ [O]_{\infty} = \frac{1}{1 + \exp\left(\frac{V_m + 75}{5.5}\right)} \]  

and

\[ \tau_{[O]} = \frac{1}{\phi_{[O]}} \left[ 20 + \frac{1000}{\exp\left(\frac{V_m + 71.5}{14.2}\right) + \exp\left(\frac{-V_m + 89}{11.6}\right)} \right]. \]
where $[O]$ and $[O]_{\infty}$ denote respectively the ratio and the steady state ratio of open channels in the unbound state and $\phi[O] = 3(T^{36})^{1/10}$ is a correction for the temperature. Ratios $[C]$, $[O]$, $[P_0]$, $[P_1]$ and $[O_L]$ for the different states are dimensionless and are equivalent to the activation variable $m$ in (1.32). Note that $[C]+[O]+[O_L]=1$. Eq. (1.56) expresses the Ca$^{2+}$ binding to an unknown regulating factor $P$. Its unbound and bound states are respectively denoted as $P_0$ and $P_1$. The unbinding rate is $k_2 = 4 \times 10^{-4}$ ms$^{-1}$, while the binding rate is described as follows:

\[ k_1 = k_2 \left( \frac{[\text{Ca}]_{\text{in}}}{[\text{Ca}]_{1/2}} \right)^4. \]  

(1.62)

$[\text{Ca}]_{1/2} = 0.002$ mM is the Ca$^{2+}$ concentration at half-activation of the Ca$^{2+}$ dependence. The exponent 4 to the right-hand side of Eq. (1.62) corresponds to the number of binding sites at $P$. Finally, $P_1$ binds to h-channels as in Eq. (1.57) and put them into a “locked” state ($O_L$) at a rate $k_3$. This rate has been estimated by the following expression:

\[ k_3 = 100k_4[P_1]. \]  

(1.63)

The h-channels unlock at a rate $k_4 = 0.001$ ms$^{-1}$. $[P_1]$ is the ratio of molecules $P$ in their bound state. In other words, $[P_0]+[P_1]=1$. Ratios $[P_0]$, $[P_1]$ and $[O_L]$ for the different states at each time $t$ can be obtained from rate equations similar to Eqs. (1.33) and (1.34) with rate constants $k_1$, $k_2$, $k_3$ and $k_4$. The Ca$^{2+}$ dependence of $I_h$ is included in $k_1$. The amplitude of $I_h$ is then simply described by an ohmic relation of the form

\[ I_h = g_h([O] + g_{inc}[O_L])(V_m - E_h), \]  

(1.64)

where $g_{inc} = 2$ is a factor for an increased conductance of locked channels due to the indirect Ca$^{2+}$ binding. It was estimated from experimental observations [36]. In absence of Ca$^{2+}$ dependence, the kinetics of $I_h$ would be given by Eq. (1.55) only, using rate constants of Eqs. (1.58) and (1.59). The variable $[O_L]$ would not appear in Eq. (1.64).

Instead of being entirely free to diffuse once they entered the cell, Ca$^{2+}$ ions quickly interact with numerous molecules. Pumps and buffers mechanisms that mediate the Ca$^{2+}$ extrusion from the inside of the cell or its binding to different molecules were included in the model [75]. A linear model of diffusion was adopted. Parameters were taken from a previous modeling study on TC neurons [73]. An intracellular Ca$^{2+}$ concentration at equilibrium $[\text{Ca}]_{\infty} = 0.24$ $\mu$M was assumed and a thin shell of depth $s = 0.1$ $\mu$m beneath the membrane was considered in concentration calculations. The Ca$^{2+}$ handling obeyed the following first-order ODE:

\[ \frac{d[\text{Ca}]_{\text{in}}}{dt} = -\frac{i_{\text{Ca}}}{2Fs} + \frac{[\text{Ca}]_{\infty} - [\text{Ca}]_{\text{in}}}{\tau_{\text{Ca}}}, \]  

(1.65)

where $i_{\text{Ca}}$ is the Ca$^{2+}$ current density and $\tau_{\text{Ca}} = 5$ ms is the time constant for a fast Ca$^{2+}$ retrieval.

In the present study, different active properties were individually or simultaneously added to the model. At most, all the mechanisms described in this subsection were included at
somatic compartments (Fig. 1.15A). All mechanisms may also be included in dendritic compartments, except for sodium and potassium channels, which were restricted to the soma (Fig. 1.15B).

1.3 Numerical simulations under the NEURON simulation environment

1.3.1 Temporal discretization

Over the past 60 years or so, extensive work has been achieved in order to model the electrical activity of neuronal cells or networks (for an overview see references [55, 56]). To fill the constantly increasing needs in a theoretical formulation of the neuronal mechanisms and in numerical techniques, simulation environments have been developed. The most widely used simulation environments specific to computational neuroscience are NEURON [76, 77] and GENESIS [78]. In the present study we used the NEURON simulation environment [76]
to perform numerical simulations. Two main reasons justified that choice. First of all, the morphology can be easily taken into account, and second, the algorithms built in NEURON automatically solve the system of differential equations (1.30). However, the apparent simplicity should not overwhelm the major concerns present in every numerical studies: the stability, the accuracy and the efficiency. The stability ensures that the solution provided by an algorithm does not diverge from the analytical solution with the number of time steps, the accuracy ensures that the solution quickly converges to a small numerical error with a decreasing size of time steps and the efficiency implies a fine balance between a low numerical error and fast calculations.

To solve the ODEs with respect to time, we used NEURON’s default integration method, i.e. a backward Euler method. It is an implicit integrator since it considers future values in its calculations. It is a quite accurate method for small time steps $\Delta t$, but more importantly it is very stable. For a ODE of the form

$$\frac{dV}{dt} = f(V, t),$$

the solution $V(t + \Delta t)$ can be approximated by

$$V(t + \Delta t) \approx V(t) + f(V(t + \Delta t), t + \Delta t) \Delta t.$$ (1.67)

The method has a first order accuracy, i.e. the local error is proportional to $\Delta t$ and always converges toward a steady state value for a progressively increasing time. A sufficiently small time step $\Delta t = 0.025$ ms was used in all simulations. For details on other integration methods implemented in NEURON, see reference [77].

### 1.3.2 Spatial discretization

NEURON is based on the method of compartmental modeling. Compartments need to be created. The geometry of each segment is either specified by the user for completely designed cell models, or is automatically calculated by NEURON when the morphological and geometrical information of a real cell reconstruction is given in input. Biophysical properties and distributed mechanisms are defined by the user. Membrane capacitance and current conductances are defined as densities, so NEURON can calculate for each particular compartment its total capacitance and conductances, as described in section 1.2.2. Active transporters such as $\text{Ca}^{2+}$ pumps are only virtually present in the model. According to the geometry of segments, ionic concentrations are taken into account and extrusion or intrusion of ions can be described by a simple relation between intracellular and extracellular concentrations, as in the case of $\text{Ca}^{2+}$ ions. Synaptic currents are point processes, i.e. each stimulation site is associated to a point on the dendrite. Since a given compartment is in fact an isopotential segment in the model, the site of stimulation is assigned to the middle of the segment. This middle point is referred to as the node of the segment. If one wants to inject a synaptic current at a very
precise place, he will probably have to decrease the compartment’s length. Note that NEU- RON’s solutions are second-order accurate in space, i.e. the error will be reduced by a factor of 4 if the number of compartments is doubled.

In this study, the number of compartments assigned to each section was defined using the d-lambda rule [79]. This rule provides a spatial grid sufficiently precise to take into account the impact of the diameter, the membrane capacitance and the axial resistivity on the propagation of fast responses in a dendritic arborization. Neurons, or particularly their dendrites, are believed to process fast information with high temporal reliability [80]. Eq. (1.25) showed that for fast EPSPs, or equivalently at high stimulation frequencies, the amplitude of induced responses is mainly capacitive and is thus mostly independent of the membrane resistance. The time course is also nearly independent of the membrane resistance. Since the reliability of fast inputs is a paradigm for neuronal processing, the spatial grid chosen in cell models should be accurate for such inputs. Fast EPSPs are dramatically attenuated during their propagation toward the cell body due to the low-pass filtering caused by the axial resistance and the membrane capacitance. For those enumerated reasons, the classical length and time constants are irrelevant. A more accurate length constant for inputs at a frequency $f$ can be calculated from the following expression:

$$
\lambda_f \approx \frac{1}{2} \sqrt{\frac{D}{\pi f R_a C_m}}.
$$

(1.68)

Hines and Carnevale suggested that the segments length should be at least smaller than a fraction of $\lambda_{100}$, i.e. the frequency-dependent length constant for $f = 100$ Hz [79]. This fraction of $\lambda_{100}$ is called d-lambda. It must be specified by the user. In the present study, d-lambda was assigned the common value of 0.1. The number of compartments could be locally increased for more precise positions of distributed stimulation sites, without any notable impact on the somatic response evoked by a stimulus.
Chapter 2

Integration of excitatory synaptic inputs in dendritic trees of thalamocortical neurons

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Title in French: Intégration des entrées synaptiques excitatrices chez les cellules thalamocorticales
2.1 Résumé

Les cellules thalamocorticales du noyau ventro-postérolatéral (VPL) du thalamus relaient l’information sensorielle au cortex somatosensoriel. Les fibres sensorielles ascendantes forment des synapses excitatrices principalement aux dendrites proximaux des cellules TC, mais des connections excitatrices en provenance des cellules pyramidales (PY) du cortex sont également formées aux dendrites distaux. Généralement, les entrées sensorielles induisent des réponses rapides et de courte durée alors que les entrées corticothalamiques induisent des réponses lentes et de longue durée. Dans cette étude, nous avons questionné la façon avec laquelle diverses distributions de synapses excitatrices aux différents compartiments de la cellule TC contribuent à la génération de potentiels synaptiques au soma. Nous avons utilisé un modèle multi-compartmental tiré de reconstructions complètes de cellules TC. Différents niveaux du potentiel membranaire ($V_m$) ont été considérés: un niveau dépolarisé où les cellules déchargent de manière tonique et un niveau hyperpolarisé où elles déchargent en bouffées de potentiels d’action grâce à l’interaction du courant de cations activé sous hyperpolarization ($I_h$) et du courant de calcium à seuil bas ($I_T$). L’étude a révélé que la sommation des signaux synaptiques induits aux dendrites proximaux est indépendante du type de distribution des sites de stimulation, alors que la stimulation des mêmes branches aux dendrites distaux provoque une forte saturation de la réponse au corps cellulaire avec le nombre d’entrées. Dans les cas où il y avait absence de saturation, l’interaction de $I_h$ et $I_T$ à des niveaux hyperpolarisés de $V_m$ a généré une forte amplification des réponses somatiques. Les simulations ont également révélé des réponses plus lentes dans le cas de stimuli distaux. On conclut que la position des synapses aux cellules TC est suffisante pour expliquer les différences observées dans la durée des réponses somatiques aux entrées sensorielles et corticothalamiques. Dépendamment du type de distribution des synapses aux dendrites, l’influence corticothalamique au soma est comparable ou plus faible que celle des fibres sensorielles ascendantes.

2.2 Abstract

Thalamocortical (TC) neurons of the ventroposterolateral (VPL) nucleus relay the sensory information to the somatosensory cortex. Ascending sensory fibers form excitatory synapses mainly at proximal dendrites of TC cells, but cortical pyramidal (PY) neurons also establish excitatory connections at TC cells, principally at distal dendrites. Generally, sensory inputs induce fast-rising and short-lasting EPSPs and corticothalamic inputs induce slow-rising and long-lasting EPSPs. In this study we investigated how the distribution of excitatory synapses on different compartments of TC neurons contributes to the generation of synaptic potentials at the soma. We used a multicompartmental model based on fully reconstructed TC neurons. We considered different levels of the membrane potential ($V_m$), i.e. a depolarized level where cells operate in a tonic-firing mode and a hyperpolarized level where they fire in a bursting
mode mediated by the interplay of the hyperpolarization-activated cation current ($I_h$) with the low-threshold calcium current ($I_T$). We found that the summation of synaptic signals evoked at proximal dendrites was independent of the type of distribution of stimulation sites, while targeting the same branches at distal dendrites induced a strong saturation of the somatic response with the number of inputs. In nonsaturating cases, the interplay of $I_h$ and $I_T$ at hyperpolarized levels of $V_m$ strongly increased the amplitude of somatic responses. Simulations also revealed slow-rising and long-lasting somatic responses to distal stimuli. We conclude that the location of synapses on TC neurons is sufficient to explain the differences in the shape of somatic responses to peripheral vs. cortical sources. Depending on the distribution of synapses over dendrites, corticothalamic influences on the soma may be comparable or lower than ascending sensory influences.

2.3 Introduction

The central nervous system displays a high diversity of cell morphologies and intrinsic currents, each type of neurons being seemingly adapted to perform its own tasks. Of particular interest are the TC neurons of the thalamus that relay sensory information to the cortex and modulate its flow [31, 81]. How the particular spherical geometry and the complex morphology [82, 83] of those neurons enable them to achieve efficiently their neuronal functions is still unclear. It is now recognized that dendrites hold an important role in the processing of information [84, 85], but the way it is done given a particular set of active properties and patterns of the dendritic arborization still lacks explanations.

In the ventrobasal complex of the thalamus of mammals, large terminals arising from ascending sensory pathways (e.g. medial lemniscal tract) establish several contacts with thick proximal dendrites of TC cells [32, 86]. In contrast, corticofugal axons typically connect to thin distal dendrites via small terminals [32, 87]. However, giant corticothalamic terminals similar to sensory ascending terminals have been found at TC cells, mainly on primary branches near a bifurcation point [87, 88], and described in various nuclei and through different species [89]. These data indicate that large terminals arriving to TC neurons from any source are located on proximal dendrites.

Theoretical, computational and in vitro work shows that EPSPs may sum sublinearly when synapses are clustered at the same branches in absence of amplifying active properties due to a reduced driving potential or a shunting effect of highly active dendrites, while the somatic response would increase linearly with the number of inputs when they rather come to different branches [64, 90, 91]. In vitro studies in hippocampal and cortical PY cells as well as in striatal medium spiny neurons suggest the importance of having multiple closely spaced synapses for the generation of NMDA, calcium or sodium spikes, which would rescue a sublinear summation to a linear or a supralinear one, hence favoring a configuration of
clustered inputs [91–94]. However, a recent in vivo study on the primary visual cortex of mice demonstrated that terminals sharing the same orientation preference contact different branches [96]. It is then unclear if summation occurs when synchronous inputs come to the same or different dendritic branches and if the same arithmetic rules apply in all neuronal structures.

In the study presented here we investigated in a morphologically realistic multicompartmental model the impact of different distributions of synaptic sites at both proximal and distal dendrites on the somatic response in TC cells and the effect that may have the main intrinsic currents $I_T$ and $I_h$ on the summation of EPSPs. The results were also obtained with cells of distinct neuronal sizes, pointing out differences in excitability and EPSP kinetics due to the compactness of the cell, but the arithmetic rules were similar in all tested cells.

2.4 Methods

2.4.1 Multicompartmental model

In order to take into account the complex morphology of TC cells, a multicompartmental model was built from three-dimensional reconstructions of 8 real TC neurons of the VPL nucleus. Reconstructions were carefully performed for a minimal shrinkage of neuronal sections. Full details on both cells labeling and reconstruction, as well as the main morphological features of the studied cells can be found in a previous paper [83]. The identification numbers of the cells (1 to 8) are the same between the two articles. Simulations were run on the NEURON simulation environment [76]. The number of compartments was estimated using the d-lambda rule [79]. On some occasions the number of compartments was increased locally in order to obtain the synaptic distribution with precise locations and separations of the synaptic sites, but the individual effect of each single synaptic current injection on the soma was not affected by this increased number of compartments. The mean amplitude, the time to peak and the full width at half maximum (FWHM) of the somatic response to a single EPSP evoked at the proximal or the distal part were quantified for all 8 reconstructed neurons. The FWHM was used to measure the global kinetics or shape of a response, while the time to peak more appropriately described the impact of dendritic filtering of passive properties on the rising phase of the voltage [60–63]. The time to peak was measured from the foot of the EPSP to its peak amplitude. The complete study was done on four cells of different sizes: the smallest (cell 4), the largest (cell 6) and the two cells of median sizes (cells 1 and 2), in terms of their total surface area.

Passive properties were considered constant over all compartments and cells. The membrane capacitance ($C_m$), the leak conductance ($g_{leak}$) and its associated reversal potential
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$(E_{\text{leak}})$ were assigned respective values of 0.878 $\mu$F/cm$^2$, 0.0379 mS/cm$^2$ and -69.85 mV \cite{68,73}. The axial resistivity was defined as $R_a = 173 \Omega$-cm \cite{73}. In all performed simulations, potassium and sodium channels were included in the somatic compartments, the kinetics being drawn from a previous model of fast action potentials in hippocampal PY cells \cite{66}, with a resting membrane potential of $V_T = -52$ mV. The corresponding peak conductance and reversal potential for both the sodium and the potassium currents were respectively set to $g_{Na} = 200$ mS/cm$^2$, $E_{Na} = 50$ mV, $g_K = 200$ mS/cm$^2$ and $E_K = -100$ mV.

For most of the simulations, $I_T$ was included in all compartments. This typical current of the TC neuron was modeled via Hodgkin-Huxley-like equations, based on a well established model \cite{71}. However, the kinetics were taken from a more recent study \cite{73}. The T-channels associated with that current were distributed over all sections, but based on previous experimental and computational studies \cite{68,97,98}, a highest density was assigned to the proximal part of dendrites:

$$P_{Ca} = \begin{cases} 
20.6 \times 10^{-5} \text{cm/s} & \text{in soma} \\
41.2 \times 10^{-5} \text{cm/s} & \text{if } x < 40 \mu m \\
5 \times 10^{-5} \text{cm/s} & \text{otherwise} 
\end{cases} \quad (2.1)$$

where $x$ is the distance to the cell body. Control experiments were made with a constant density of T-channels over the dendritic and somatic compartments. As long as the total number of T-channels was kept constant, the results of the experiments differed to a minor extent (data not shown). The impact of the T-channels distribution was more prominent when the membrane was highly dynamically active or subject to synaptic bombardment, i.e. if the cell was generating a sustained firing pattern \cite{68}.

When specified, $I_h$ ($g_h = 20$ mS/cm$^2$, $E_h = -40$ mV) was also included in all compartments as previously described \cite{49,52,71}, the voltage dependence being drawn from voltage-clamp experiments \cite{35}. We also considered the Ca$^{2+}$ dependence of $I_h$ \cite{36}.

Finally, we modeled Ca$^{2+}$ extrusion and buffering within a shell of thickness $s = 0.1 \mu m$ beneath the membrane with a first-order differential equation \cite{75}. The intracellular Ca$^{2+}$ concentration at equilibrium was set to 240 mM and for fast Ca$^{2+}$ handling, a time constant $\tau_{Ca} = 5$ ms was assumed \cite{73}.

### 2.4.2 Mean dendritic diameter

To estimate how the diameter of dendrites changes with the distance to soma, we measured the dendritic diameter ($D$), using bins of 1 $\mu m$ as a function of the distance $x$ to the cell body for every possible path from the soma to a dendritic tip. The mean diameter at a point $x$ was
then given by the following equation:

\[
\langle D(x) \rangle = \frac{1}{N(x)} \sum_{k=1}^{N(x)} D(x),
\]

(2.2)

where \( N(x) \) is the number of paths reaching the point \( x \). Primary branches of prominently branched trees were then assessed a higher weight in the calculations than in trees containing a few dendritic sections.

This mean dendritic diameter is given for each distance \( x \) to the soma. Later in the study we will refer to the mean path diameter. A path is a possible route for EPSPs propagation within the dendritic arborization. We define the mean path diameter as the average diameter of the path joining two points of interest, e.g. the mean diameter between the soma and a site of stimulation.

### 2.4.3 Synaptic current and distributions of synaptic sites

A realistic fast excitatory postsynaptic current \( i_{syn} \) was modeled as a point process using standard equations for the synaptic conductance \( g_{syn} \):

\[
i_{syn} = g_{syn}(V_m - E_{syn})
\]

(2.3)

\[
g_{syn} = \begin{cases} 
0 & \text{if } t < t_{stim} \\
\frac{a}{\tau_1} & \text{otherwise,}
\end{cases}
\]

(2.4)

where \( E_{syn} = 0 \text{ mV}, \tau_1 = 0.1 \text{ ms} \) and \( \tau_2 = 1.4 \text{ ms} \) are the reversal potential of the synaptic current and two time constants, respectively. We defined \( t \) as the running time of the simulation and \( t_{stim} \) as the onset time of \( i_{syn} \). For a sufficient somatic depolarization following distal injections of synaptic current, we fixed the coefficient \( a \) to 2.5 nS, leading to a maximal synaptic conductance of \( \approx 2 \text{ nS} \).

From 8 reconstructed cells used in this study, one was recorded intracellularly (cell 6, see examples of recordings in Fig. 1A in [83]). The shape of the simulated EPSPs elicited by the stimulation of proximal dendrites was very similar to responses of neurons induced by the medial lemniscal stimulation.

We refer to a synapse or a synaptic site as any dendritic site where a synaptic current was injected. Summation of responses to dendritic stimuli was investigated using a centripetal distribution of synapses (2-10 release sites aligned along the dendritic path from 60 \( \mu \text{m} \) to 15 \( \mu \text{m} \) or 150 \( \mu \text{m} \) to 105 \( \mu \text{m} \) to the soma for the proximal or the distal part of dendritic trees, respectively), a radial distribution (all simulation sites were equally distant to the soma, at 60
µm or 150 µm for the proximal or distal part, respectively [synapses distributed on different branches]), and more realistic random patterns of distribution (see Fig. 2.11).

2.4.4 Statistical analysis

For statistical comparison, we used a two-sample $t$-test assuming unequal variances between samples. The tests were performed in MATLAB (The MathWorks, Natick, MA) with the $ttest2$ algorithm of the standard statistical toolbox. $P$-values $< 0.01$ were considered significant. Other analysis (amplitude, time to peak and FWHM of responses) were also calculated using the MATLAB environment.

2.5 Results

2.5.1 Basic electrophysiological features

For all reconstructed TC cells, we stimulated with a synaptic current all possible branches at distances of 60 and 150 µm to the cell body in order to compare somatic responses between cells and between proximal and distal inputs (Table 2.1-2.2). The membrane potential at the time of the stimulation ($V_m(t_{stim})$) was fixed at -70 mV via current injection. The model contained $I_T$ that could slightly influence the time course of responses. By plotting the mean amplitude of synaptic responses recorded at the soma as a function of cell size, we observed larger responses in smaller cells and smaller responses in larger cells (Fig. 2.1D). That was true for responses elicited by both proximal and distal stimuli. This occurs because the somatic input resistance depends on the volume of dendritic trees. Cell 6, which has the largest total surface area, gave a mean response of 39% the amplitude of that obtained for cell 4, the smallest cell. In contrast, the standard deviation of amplitudes within each neuron was not very large. The amplitude of somatic responses was not dramatically different for stimuli applied to proximal vs. distal dendrites (Fig. 2.1D). The mean somatic amplitude for a stimulus at distal dendrites was between 78% (cell 4) and 85% (cell 7) of the amplitude obtained for proximal stimuli, despite a highly significant difference ($P < 1 \times 10^{-14}$ in all cases).

To quantify the impact of the dendritic filtering on the rising phase of voltage responses, we measured the time to peak. We found that stimuli applied to the distal part of dendritic trees induced responses with a significantly longer latency to peak ($P < 1 \times 10^{-5}$ in all cases) as compared to somatic responses elicited by the stimulation of proximal dendrites.

To quantify global kinetics or shape of responses we used the FWHM. A striking result
Figure 2.1: Propagation of an evoked EPSP. A, Reconstructed dendrite from cell 2. A synaptic current was injected at a proximal (arrowhead 1, 15 µm from soma) or a distal (arrowhead 2, 150 µm from soma) branch of the dendritic tree. B, Same as A, but for a dendrite from cell 6. C, Voltage attenuation during propagation of the signal toward soma. Left, Voltage transients at different parts of the dendritic tree and at soma induced by the stimulus at point 1, as indicated. The local and somatic responses were sharper in cell 6 (green, see arrow) than in cell 2 (brown), even if the dendrites had similar diameters. Right, Same as left, but for a stimulus applied at point 2. D, Amplitude of somatic responses as a function of the total membrane area of 8 investigated neurons.
obtained from our simulations was the marked difference in voltage transients kinetics between neurons, especially for proximal stimuli. FWHM reveals that somatic responses evoked in large cells have in the mean faster kinetics than in smaller neurons. In Fig. 2.1 we illustrated this point by stimulating at distances of 15 µm and 150 µm to the cell body a dendrite from a neuron of median size (Fig. 2.1A, cell 2) and a dendrite from the largest neuron (Fig. 2.1B, cell 6). We recorded voltage responses at 15, 10, 5 and 0 µm and at the soma for the proximal stimulus and at 150, 100, 50 and 0 µm and at the soma for the distal stimulus (Fig. 2.1C). Due to the high input impedance of distal dendrites, the local responses were of high amplitude (order of 20 mV vs. about 1 mV when proximal dendrites were stimulated). Their time to peak was very short and they attenuated dramatically when propagated to soma (Fig. 2.1C). Fast local responses in distal dendrites are due to a small local membrane capacitance to charge (fast and high depolarization) and a large remaining portion of the cell toward which charges diffuse (fast decay of the EPSP at the site of stimulation). Despite a strong initial response, EPSPs are largely attenuated and filtered during propagation, giving a somatic voltage transient characterized by a relatively low amplitude and a slower time course [63, 99, 100].

The repolarization of the somatic response evoked in a large cell (Fig. 2.1C, green) was faster than for a neuron of median size (Fig. 2.1C, brown). This is a consequence of the extensive branching of cell 6 promoting a lower dendritic input impedance from the soma to dendrites and thus a more important flow of charges toward the remaining portion of the cell, as well as a smaller somatic voltage transient [5]. Due to high values of the geometrical ratio [101] in TC neurons for signals propagating from distal dendrites toward soma [83], the main attenuation occurred in the region of branching points. Another important factor is the thickness of the dendritic path (see below). EPSPs evoked at proximal branches attenuate much less due to this proximity to the soma and the thickness of the dendrites but have smaller amplitudes at the site of stimulation since the targeted branches are thick and weakly electrically isolated from the large cell body. The fact that we obtained the same responses at the connecting point between the primary branch and the cell body and at the soma itself (Fig. 2.1C, 0 µm and soma) is a consequence of the continuity of the cable equation at boundaries between dendritic sections, or in other words the continuity of the current and the voltage. Note the quasi-isopotentiality between proximal dendrites and that soma.

The somatic response elicited by proximal stimuli of a large neuron often revealed fast pre-potentials or FPPs (see arrow in Fig. 2.1C), which previously were thought to be a somatic deflection of dendritic spike [102–105]. Here, however, the FPP-like responses were only a consequence of passive cell properties.
### Integration of synaptic inputs in dendritic trees of TC neurons

#### Table 2.1: Electrophysiological features. Proximal stimulus (60 µm).

<table>
<thead>
<tr>
<th>Cell</th>
<th>Amplitude (mV)</th>
<th>Time to peak (ms)</th>
<th>FWHM (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.455 ± 0.020</td>
<td>4.835 ± 0.366</td>
<td>34.930 ± 0.166</td>
</tr>
<tr>
<td>2</td>
<td>0.466 ± 0.023</td>
<td>4.690 ± 0.661</td>
<td>34.609 ± 0.384</td>
</tr>
<tr>
<td>3</td>
<td>0.426 ± 0.021</td>
<td>4.675 ± 0.526</td>
<td>34.532 ± 0.265</td>
</tr>
<tr>
<td>4</td>
<td>0.902 ± 0.092</td>
<td>5.425 ± 1.454</td>
<td>36.818 ± 0.573</td>
</tr>
<tr>
<td>5</td>
<td>0.664 ± 0.037</td>
<td>4.738 ± 1.139</td>
<td>34.205 ± 0.750</td>
</tr>
<tr>
<td>6</td>
<td>0.349 ± 0.051</td>
<td>3.039 ± 2.928</td>
<td>29.155 ± 4.134</td>
</tr>
<tr>
<td>7</td>
<td>0.395 ± 0.019</td>
<td>4.432 ± 0.524</td>
<td>34.024 ± 0.310</td>
</tr>
<tr>
<td>8</td>
<td>0.569 ± 0.027</td>
<td>4.646 ± 0.946</td>
<td>33.814 ± 0.779</td>
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</tbody>
</table>

#### Table 2.2: Electrophysiological features. Distal stimulus (150 µm).

<table>
<thead>
<tr>
<th>Cell</th>
<th>Amplitude (mV)</th>
<th>Time to peak (ms)</th>
<th>FWHM (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.374 ± 0.034</td>
<td>5.954 ± 0.500</td>
<td>35.040 ± 0.193</td>
</tr>
<tr>
<td>2</td>
<td>0.378 ± 0.037</td>
<td>6.044 ± 0.824</td>
<td>34.787 ± 0.349</td>
</tr>
<tr>
<td>3</td>
<td>0.357 ± 0.029</td>
<td>5.959 ± 0.709</td>
<td>34.735 ± 0.264</td>
</tr>
<tr>
<td>4</td>
<td>0.704 ± 0.063</td>
<td>6.693 ± 1.1376</td>
<td>36.695 ± 0.407</td>
</tr>
<tr>
<td>5</td>
<td>0.526 ± 0.042</td>
<td>6.305 ± 1.037</td>
<td>34.518 ± 0.545</td>
</tr>
<tr>
<td>6</td>
<td>0.278 ± 0.029</td>
<td>6.263 ± 2.393</td>
<td>32.142 ± 2.625</td>
</tr>
<tr>
<td>7</td>
<td>0.334 ± 0.025</td>
<td>5.903 ± 0.680</td>
<td>34.361 ± 0.342</td>
</tr>
<tr>
<td>8</td>
<td>0.447 ± 0.026</td>
<td>6.319 ± 1.200</td>
<td>34.311 ± 0.730</td>
</tr>
</tbody>
</table>
Integration of synaptic inputs in dendritic trees of TC neurons

Figure 2.2: Mean diameter vs. distance to the cell body in 4 thalamocortical cells. The neurons studied show similar profiles in their dendritic diameters as a function of the distance to soma. The diameter of individual dendrites initially drops with distance to soma and then reaches an asymptotic level. The mean of the curves was properly fitted by a decaying exponential function. The vertical dashed line defines the domain of the strongly decaying part (large diameters) of the arborization ($\leq 60 \, \mu m$) as the proximal part, while the distal branches were associated to the tail of the curves ($> 60 \, \mu m$).

2.5.2 Impact of the dendritic diameter on neuronal responses

Voltage signals that propagate in the dendritic arborization of neurons are subject to modulation. First, the thickness of the path determines total axial and membrane resistances and thus the electrotonic attenuation in the dendritic cables defining that path. In uniform semi-infinite cables, this is properly described by the length constant, generally denoted $\lambda$ [5]. The thinner is the path, the stronger is the electrotonic voltage attenuation. Second, the particular geometry of dendritic trees imposes specific input impedances at branching points. For branches of several $\lambda$ in length connected together, the behavior of signals approaching a junction can be properly described by Rall’s geometrical ratio [101]. This relation also stands when only two sections or segments of different diameters are connected together. For a thin segment receiving a synaptic input and connecting to a much thicker one, which is generally the case in forward propagation, there is a low input impedance at the connecting point, causing the voltage transient to attenuate when spreading from the thin segment to the thick one, despite a high current flow toward that expanse.

We plotted the mean dendritic diameter as a function of the distance to the cell body for the 4 cells studied (Fig. 2.2). There is a quick initial drop with distance in diameter values, and an asymptotic level of dendritic diameter farther from the soma. The mean dendritic diameter could be appropriately fitted by a decaying exponential function. We defined the domain of the strongly decaying part of the arborization ($\leq 60 \, \mu m$) as the proximal part,
while thin distal branches were chosen to correspond to the tail of the curves (> 60 µm). We will keep those definitions through the paper.

We investigated the dependence of somatic voltage transients to the mean path diameter in 4 TC cells (Fig. 2.3). A synaptic current was injected at 60 or 150 µm from the soma on all possible branches and the amplitude of all somatic voltage responses recorded was plotted as a function of the average value of the dendritic diameter from the stimulation site to the soma (Fig. 2.3A1, B1, C1 and D1). The somatic responses were higher in amplitude for thick dendrites than for thin dendrites. This increase in amplitude as a function of the diameter was not linear. Starting at small values of path diameter, the amplitude increased quickly when the thickness increased, due to a reduced attenuation. This increase in amplitude progressively faded because the input impedance at the site of injection drops when the global diameter of the path increases. However, no peak seemed to be reached for all 4 cells. Thus, in TC cells, thicker dendritic branches lead to more successful EPSPs, i.e. more efficient in reaching and depolarizing the somatic compartment. Neglecting the impact of a complex branching is a coarse approximation, but it provides a global understanding of that dependence of the somatic amplitude on dendrites geometry. In average, the amplitude measured at the soma was smaller for EPSPs evoked at distal branches than for EPSPs evoked nearer the soma. Nevertheless, the data obtained from stimuli applied to both proximal and distal parts of the dendritic arborization largely overlapped.

When injecting simultaneously a synaptic current at 10 sites separated by a distance of 5 µm, from 60 to 15 µm for proximal inputs and 150 to 105 µm for distal inputs (centripetal distribution, see Methods), a different dependence in diameter of the amplitude of somatic responses was found compared to the case of the single site stimulation (Fig. 2.3A2, B2, C2 and D2). In this experiment, the mean path diameter was calculated as the average value of the diameter from the soma to the farthest stimulation from the cell body, i.e. the site of injection at 60 or 150 µm. For multisite stimulations, the somatic EPSPs’ amplitudes elicited by proximal vs. distal stimuli were now clearly distinct. Due to a high input impedance in distal dendrites, the summed stimuli induced a major depolarization of dendrites with values close to the reversal potential for EPSPs. The reduced driving potential under the summation of large amplitude distal EPSPs is responsible for such separation in data. As \( \Delta V_m \) approaches \( E_{syn} \), \( i_{syn} \) progressively vanishes [64].

### 2.5.3 Linear vs. sublinear summation of fast excitatory synaptic potentials

Next, we investigated how EPSPs are summed and how the dendrites influence voltage transients recorded at the cell body. We stimulated branches using the centripetal distribution (see Methods), i.e. we added sites of stimulation one by one, starting with the most distal position, i.e. 60 µm for proximal or 150 µm for distal dendritic stimuli. Every branch en-
Figure 2.3: Dependence of somatic responses on the dendritic diameter in 4 thalamocortical cells.

**A1**, Amplitude of somatic responses to a proximal (60 µm, blue, \( n = 74 \)) or a distal (150 µm, red, \( n = 110 \)) stimulus vs. the average diameter of the dendritic path from the stimulation site to the soma in cell 1. **A2**, Same as **A1**, but for the simultaneous activation of 10 proximal (60 to 15 µm, blue) and 10 distal (150 to 105 µm, red) sites. There is 5 µm between the sites of stimulation. **B1-C1-D1**, Same as **A1**, but for cells 2 (\( n = 70 \) for blue markers; \( n = 120 \) for red markers), cell 4 (\( n = 47 \), blue; \( n = 59 \), red) and cell 6 (\( n = 56 \), blue; \( n = 131 \), red), respectively. **B2-C2-D2**, Same as **A2**, for cells 2, 4 and 6, respectively.
countered at 60 or 150 μm of distance to soma could bear the first synaptic site and thus provided a group of distributed sites. We recorded the induced response at the soma in each case \(V_m(t_{\text{stim}}) = -70 \text{ mV}\). The amplitude of somatic responses increased with the number of activated sites. Figures 2.4, 2.5 and 2.6 show examples of somatic responses and global results for cells 1, 4 and 6 respectively. Cell 2 displayed results very similar to cell 1 as they had a similar size (not shown).

In cell 1 and cell 2 an increase in the number of sites on proximal dendrites revealed a constant increase in the amplitude of the somatic response, while the sequence of distal stimuli lead to a progressively saturating response (Fig. 2.4B). Repeating the same experiment for all possible cases confirmed that proximally elicited EPSPs summed in an almost linear fashion, while distally elicited EPSPs summed sublinearly (Fig. 2.4C1 and C2, respectively). The normalized increase in the amplitude of the response with an increase in the number of stimuli was around 1 for stimulation of proximal dendrites and went to 0.4-0.5 for stimulation of distal dendrites (Fig. 2.4D). This nonlinearity was due to the decreasing driving potential of the synaptic current when the summation of distal EPSPs brought the peak of the combined local response close to \(E_{\text{syn}}\) at dendrites. Thinner dendrites lead to a stronger saturation due to larger local EPSPs. We conclude that because of the thickness of targeted branches, interacting proximal inputs are not strongly subject to synaptic saturation. A small initial saturation of somatic responses to the stimulation of the first 5 proximal dendritic sites occurred because we stimulated first the most distant sites of the proximal part (Fig. 2.4D, blue).

Generally, similar results were obtained in simulations performed on cell 4 (smallest cell, Fig. 2.5) and cell 6 (largest cell, Fig. 2.6). However, because of the compactness of dendritic trees, the mean amplitude of induced responses at the cell body was higher for cell 4 as compared to cell 1. In some dendrites the amplitude of combined responses was sufficient to activate the T-channels. Since a small amount of \(I_T\) is needed in a compact TC neuron to generate amplification, small low-threshold spikes (LTSs) were apparent for proximal stimuli (Fig. 2.5B1 and B2). Such amplification produced a supralinear summation for proximal stimuli, but not for distal stimuli (Fig. 2.5C1, C2 and D). Activation of \(I_T\) resulted in a progressively increasing latency of the peak of voltage transients in neuronal soma (Fig. 2.5B2).

For the biggest cell (Fig. 2.6, cell 6), the differences were the following: (a) somatic responses to single or multiple stimulation sites were of smaller amplitude, (b) in most cases, somatic responses to stimulation of thinner proximal dendrites had FPP-like shape (see Fig. 2.6B1, blue). This occurs because the propagation to soma was not sufficient to attenuate the sharp dendritic responses, (c) due to low-pass filter effects of passive properties on propagated EPSPs, somatic responses had very slow time courses and were dramatically attenuated in some very thin dendrites encountered in cell 6 (Fig. 2.6B2).
Figure 2.4: Linear and sublinear summation of fast EPSPs in cell 1. **A**, One dendrite from the reconstructed cell 1. The 10 blue arrowheads indicate the position of the stimulation sites where a synaptic current is injected at the proximal part of the dendrite (p, 60 to 15 µm). Sites are separated by 5 µm. Red arrowheads indicate the same, but for distal stimuli (150 to 105 µm) for 6 different possibilities (d1 to d6). **B**, Summed somatic responses corresponding to the stimulated branches shown in **A**. In all cases, the lowest trace corresponds to the response induced by the activation of the most distant site to the soma (60 or 150 µm). The second lowest trace results from the simultaneous activation of the most distant site and the site 5 µm closer to the soma (60 and 55 µm or 150 and 145 µm), and so on. The top trace corresponds to the simultaneous activation of all 10 sites in the group. Note the variability of responses to distal stimuli due to different branch diameters. **C**, Curves depicting the somatic amplitude vs. the number of activated sites on the proximal (**C1, n = 74**) and distal (**C2, n = 110**) parts for all possibilities on cell 1. The black curves stand for the mean. **D**, Mean increment in the somatic response with an increasing number of activated sites. The increments were obtained from data shown in **C1** and **C2**, and then mean and standard deviation were calculated. The values were normalized to the first increment. A constant curve near the value 1 at the ordinates axis indicates a linear summation (proximal inputs, blue), while a curve decreasing below 1 points out a sublinear summation (distal inputs, red).
Figure 2.5: Linear and sublinear summation of fast EPSPs in cell 4. Same as Fig. 2.4, but for cell 4. The responses in B1 were obtained with the dendrite in A1 and the ones in B2 with the dendrite in A2. Note that in this cell the summed responses to proximal stimuli were amplified by LTSs because the amplitude of the combined EPSPs was sufficient to activate the T-channels in this compact neuron (B1-2). Note that the peak of the response is delayed when an LTS is produced (B2).
Figure 2.6: Linear and sublinear summation of fast EPSPs in cell 6. Same as Figs. 2.4-2.5, but for cell 6. Note the shape of transients in B1 induced by proximal stimuli (p1).
2.5.4 Centripetal vs. radial distributions of synaptic sites

The summation rules might be highly dependent of how synapses are distributed over dendrites. To test this hypothesis, we compared the somatic amplitudes obtained for a centripetal distribution of synaptic sites to amplitudes measured for a radial distribution of sites (See Methods). Here we stimulated only one dendritic tree for simplicity. Results obtained on cells 1 and 6 are shown (Figs. 2.7 and 2.8, respectively). Targeted branches and the order of activation of the radial synaptic sites in the sequence were chosen randomly (from dots a to j, Figs. 2.7-2.8B). The position of the first activated site in a centripetal distribution corresponded to the first activated site a of the radial configuration (Figs. 2.7-2.8B, arrowheads).

In all cases we recorded voltage transients at the position of the first input and at the cell body, for both the proximal and the distal parts. In order to make the active amplification clear, the simulations were carried out under the most efficient conditions of EPSP expression at the soma (both $I_T$ and $I_h$ activated [t_stim = −200 ms, see below]). The dendritic summed EPSPs obtained from those simulations appeared to be composed of two components (Figs. 2.7-2.8C1). The first one is fast and high in amplitude and comprises the rising phase and the first part of the decaying phase, while the second component takes place in the later part of the repolarization and is mainly a consequence of a Ca$_{2+}$ flow across T-channels. This second component usually became clearly present with a sufficient number of activated sites when radial distributions of synapses on distal or on proximal dendrites were stimulated or when a centripetal distribution of proximal synapses was stimulated (Figs. 2.7-2.8C1, C3 and C4).

The second component was nearly absent when closely spaced distal synapses were activated (Figs. 2.7-2.8C2). Therefore, when saturation of the local synaptic current occurred, both the first and the second components saturated and thus summed sublinearly (Figs. 2.7-2.8C2).

Consider figure 2.7. The second component of the response obtained for a centripetal distribution of proximal sites was amplified with an increasing number of activated sites, hence suggesting a supralinear summation, while the first component even seemed to saturate (Fig. 2.7C1). The supralinearity was obviously a consequence of the interaction of $I_T$ and $I_h$ and the transient amplification represents an LTS. The same conclusion can be drawn for the radial distribution of proximal sites (Fig. 2.7C3), despite a smaller first component, as expected.

The second components for both distributions were very similar. The situation is different for distal inputs. While the second component saturated quickly for distal inputs in a centripetal distribution (Fig. 2.7C2), it was progressively amplified for a radial distribution of inputs (Fig. 2.7C4). These traces point out an important result: since the time course of the first component is too fast, the LTS rises upon the second component.

Somatic voltage transients were very similar between distributions for proximal stimuli (Fig. 2.7D1, D3). For stimuli applied to distal dendrites, there was a marked difference in responses obtained from different distributions (Fig. 2.7D2, D4). The centripetal distribution produced highly saturating somatic voltage transients with the increase in the number of activated sites, while for synaptic sites radially distributed the somatic responses summed supralinearly. Interestingly, the amplification brought the somatic voltage transient close in
Figure 2.7: Dendritic integration in cell 1. A, Reconstructed dendrite from cell 1. B, Dendrogram showing the branching pattern of the dendrite in A. Arrowheads indicate the sites of stimulation in a centripetal distribution (from 1 to 10 simultaneously activated sites) for both proximal (blue) and distal (red) parts of the tree. Dots (blue, a to j, proximal; red, a’ to j’, distal) indicate the position of synaptic sites in a radial distribution. All stimulation sites were equally distant to the soma but were located on different branches. Letters correspond to the order of stimulation: a is the first place where a synaptic current was injected, then b was activated simultaneously to a, and so on, until sites a, b, ..., j were all activated. Pipettes 1 and 2 show the location of recording sites for intradendritic recordings. C, Dendritic transients induced by 1 to 10 inputs corresponding to the recording sites shown in B. C1, Centripetal distribution. C2, Same as C1, but for distal stimuli. C3, Same as C1, but for inputs in a radial distribution. C4, Same as C3, but for distal stimuli. D, Somatic responses corresponding to the distributions in B. The patterns of stimulation in D corresponds to the ones shown in C.
amplitude to the responses obtained with proximal stimuli. The time course was also similar. This is a consequence of slow intrinsic currents overwhelming the intrinsic kinetics of EPSPs. It was not the case in absence or in a weakly activated \( I_T \) (not shown). The generation of an LTS at the second component of voltage transients therefore induced a latency of the peak in the somatic depolarization (Fig. 2.7D1, bar).

Similar responses were obtained from the simulations achieved on cell 6 (Fig. 2.8). However, as stated in previous sections, the low excitability of this large cell prevented clear LTSs to occur. In absence of supralinear summations, we rather observed a linear summation of inputs for the stimulation of proximal and distal sites in a radial distribution and stimulation of proximal sites in a centripetal distribution, as shown by the constant space between traces at dendrites (Fig. 2.8C1, C3 and C4, second component) or at soma (Fig. 2.8D1, D3 and D4).
2.5.5 Effects of active dendrites and synaptic distributions on somatic responses

To quantify the effect of typical active properties of TC neurons on the synaptic integration, we tested different conditions in the model: passive membrane, presence of $I_h$, presence of $I_T$ and presence of both $I_h$ and $I_T$ in the model. Passive conditions refer to the absence of both $I_h$ and $I_T$ in the model, since sodium and potassium channels responsible for the generation of action potentials were kept in somatic compartments to keep electrical properties as constant as possible. In order to investigate the effects of intrinsic currents on synaptic responses, all simulations were achieved at a hyperpolarized level of the membrane potential ($V_m(t_{stim}) = -75$ mV) at which $I_h$ is activated and $I_T$ is deinactivated. A constant current was applied to control $V_m$. Since $I_h$ is activated under hyperpolarization, the membrane potential was unable to stabilize in those conditions. Therefore, neurons were hyperpolarized below -75 mV prior to stimulation when $I_h$ was present. In those conditions, different amounts of current gave different depths and slopes of $V_m$ in time and thus different time of stimulations. We thus tested the effect of $I_h$ in the $I_h/I_T$ conditions for two different delays of synaptic activation: $t_{stim} = 400$ ms and $t_{stim} = 200$ ms (Fig. 2.9C2, inset).

For cells 1, 2 and 6 we randomly selected 10 centripetal and 10 radial distributions with 10 positions of synaptic sites to be simultaneously activated. For cell 4 we only stimulated 5 sites, since under some conditions 6 sites were sufficient to elicit one or several somatic action potentials in that modeled neuron. We rejected these cases because it blurred the impact of $I_h$ and $I_T$. Amplitudes of somatic transients induced with 10 or 5 activated synaptic sites were collected and statistically compared between conditions and types of distribution (see Methods).

Two important conclusions could be drawn from that series of simulations. First of all, responses produced by proximal stimuli were not significantly dependent of the type of distribution of stimulated synapses (Fig. 2.9A1, B1, C1 and D1). A difference was however apparent for cell 4 (Fig. 2.9C1, $I_h/I_T$, $P = 0.025$). This was to be expected since we stimulated only 5 sites, the 5 sites farther from the cell body and thus more sensitive to synaptic saturation (see also Fig. 2.5D). The same experiment performed for distal stimuli lead to highly significant differences between the results obtained for centripetal vs. radial distributions of stimulated sites ($P < 0.0001$ in every case). EPSPs evoked when sites were organized in a centripetal distribution strongly saturated in amplitude, leading to small somatic voltage transients. Active properties were not sufficient to rescue those integrated responses to acceptable amplitudes, i.e. responses linearly dependent to the number of inputs. In contrast, in most of the times, events arising on different branches (radial distribution) led to amplitudes of the same order of magnitude as the ones produced by inputs delivered to proximal dendrites, but a little smaller.

The second important conclusion carried by our data is that the interaction of $I_T$ and $I_h$
Figure 2.9: Dependence of the amplitude of somatic responses on the distribution of synapses (centripetal vs. radial) and on the activity of intrinsic currents. A, B and D-10 synapses stimulated; C, (framed)-5 synapses stimulated. \([I_h/I_T 400 \text{ ms}]\) and \([I_h/I_T 200 \text{ ms}]\) denotes different time for synaptic stimulation. Inset in C2 shows examples of responses with \([I_h/I_T 400 \text{ ms}]\) and \([I_h/I_T 200 \text{ ms}]\). *-\(P < 0.0001\); **-\(P < 0.005\); NS-nonsignificant.
had a strong impact on the synaptic integration of EPSPs when neurons were hyperpolarized. In passive or $I_h$ conditions, the summation of synaptic potentials was linear or sublinear, depending on the type of distribution. In contrast, it is clear from figure 2.9 that combining $I_h$ and $I_T$ produced a strong amplification of EPSPs, while only a small increase in somatic responses due to $I_T$ could be visually notable when $I_h$ was blocked (Fig. 2.9A, B, C and D1). This cooperative effect was dependent on the slope of $V_m$ (Fig. 2.9C2, inset). The steeper was the slope, the more efficient was the amplification. This cooperative effect of $I_h$ and $I_T$ progressively disappeared with the decreasing slope of $V_m$ at more depolarized $V_m$ or at a stabilized value ($t > 1000$ ms, data not shown). Synaptic responses obtained when only $I_h$ was activated were not significantly different from responses induced at a passive membrane.

We mentioned that the first component of the local response may saturate (e.g. Fig. 2.8C1) but will still produce a linearly increasing response at the soma (e.g. Fig. 2.8D1). We investigated that intriguing observation. We found that this saturation progressively disappears as the combined EPSP moves toward the soma. The voltage transient induced at $60 \mu m$ (Fig. 2.10A1 and A2) from soma was highly saturated, while the corresponding transient at $20 \mu m$ and at the cell body increased linearly (Figs. 2.8D1 and 2.10A1 and A2). The local dendritic saturation is a consequence of a large amplitude of EPSPs evoked at $60 \mu m$. The current flow for backpropagating EPSPs from the branch at $20 \mu m$ to the one at $60 \mu m$ attenuates a little because the geometrical ratio (GR) at branching points is small (branching point 1, GR = 1.26, Fig. 2.10B). For forward propagating EPSPs from $60 \mu m$ to $20 \mu m$ the geometrical ratio is very high (branching point 1, GR = 7.47, Fig. 2.10B). It results in major attenuation of EPSPs. The membrane at $20 \mu m$ integrates responses of smaller amplitudes and thus does not saturate in its driving potential for synaptic currents. As a result, a signal that increases linearly with the number of proximal inputs to the cell was delivered to the soma (Fig. 2.8D1).

2.5.6 Patterns of organization of synaptic contacts

In this section we tested the effects of close to natural distributions of corticothalamic vs. lemniscal synapses on somatic responses of TC neurons. The hypothesis is that responses to stimulation of sensory ascending fibers, forming clusters of release sites that contact thick proximal dendrites [32,86] will not saturate, while corticothalamic fibers coming preferentially to thin distal dendrites and forming small synaptic buttons [32,87] will not induce saturation in a condition where they would come either to different dendrites or to different branches of the same dendrite.

To model synapses established by large lemniscal terminals, we positioned on a thick proximal dendrite a cluster of 8 release sites grouped within $5 \mu m$ of dendritic length. To run the simulations we simultaneously activated three of these clusters positioned on three different dendrites. For comparison purposes, we positioned the same type of multirelease site
Figure 2.10: Attenuation of synaptic responses propagating toward soma depends on dendritic path and branching point morphology. **A1**, Dendritic recordings were made at 60 (1), 40 (2) and 20 µm (3) from the cell body. **A2**, Magnification of framed parts in **A1**. **B**, Curves showing the membrane potential corresponding to the peak of the combined EPSPs for 1 to 10 simultaneously activated synapses (lower to upper curve). Positions of stimulated synaptic sites are indicated by arrowheads. Pipettes labeled 1, 2 and 3 indicate the position of recording sites corresponding to traces in **A**.
Integration of synaptic inputs in dendritic trees of TC neurons

synapses on distal dendrites (Fig. 2.11A). The exact distribution of corticothalamic synapses and the number of synapses formed by a single corticothalamic axon is unknown. To model the corticothalamic synaptic activation, we randomly distributed 24 single release site synapses (same number of release sites as for the lemniscal stimulation) to the distal portion of either one or three different dendrites. For comparison purposes we also randomly distributed 24 single release site synapses on either one or three proximal dendrites (Fig. 2.11A). Simulation were run at $V_m(t_{stim}) = -65$ mV (Fig. 2.11B1) and $V_m(t_{stim}) = -75$ mV (Fig. 2.11B2). All simulations were performed with both h- and T-channels included in the model ($t_{stim} = 400$ ms).

On proximal dendrites, any pattern of synaptic distribution induced similar responses that depended on $V_m$. At a depolarized level of the membrane potential ($V_m = -65$ mV), the summed responses induced by the activation of all release sites was almost identical to the arithmetic sum of responses induced by the stimulation of individual release sites (Fig. 2.11B1, left). At a hyperpolarized level of the membrane potential ($V_m = -75$ mV), the early components behaved similarly, but simultaneous activation of all release sites led to the activation of $I_T$, and as follows to the generation of LTSs (Fig. 2.11B2, left).

The situation was different when distal dendrites were stimulated. When clusters of release sites were activated, the summation was sublinear and independently of $V_m$, the response to the activation of three clusters of 8 release sites each was much smaller than the arithmetic sum obtained from the activation of individual synapses (Fig. 2.11B, right, top). When synapses (release sites) were distributed randomly on a distal portion of a single dendrite, the attenuation of the response was small and it was nearly absent when synapses were randomly distributed on three different dendrites (Fig. 2.11B, right, middle and bottom). In addition, when the cell was hyperpolarized ($V_m = -75$ mV), an EPSP elicited by the simultaneous activation of distributed synapses generated a small LTS (Fig. 2.11B2, right, middle and bottom).

2.5.7 Threshold number of synaptic sites needed to elicit a somatic action potential

The thalamus acts as a gate for the sensory information flowing toward the cortex [106]. In order to understand that gating role we investigated the conditions under which TC neurons can elicit one or several action potentials. We randomly distributed synaptic sites over the proximal ($\leq 60 \mu m$) or the distal ($> 60 \mu m$) part of dendrites. All compartments in defined regions had the same chance to bear a synaptic site. Synaptic currents were all applied simultaneously at the different positions. The number of sites was increased at a given level of the membrane potential until the firing threshold was reached. We defined the number of required synapses as the threshold number ($N_{th}$) for one or several action potentials to be generated at the cell body. The number of sites needed to elicit at least one action potential
Figure 2.11: Somatic responses of TC neurons to the activation of synapses with different patterns of distribution. A, Portion of the reconstructed cell 6 showing the position of synaptic contacts in different configurations (different colors) for both proximal and distal parts. B, Somatic responses under the activation of 24 synaptic release sites for 3 different configurations. Somatic traces in color correspond to the simultaneous stimulation of synapses shown in A and the black traces show the arithmetic sum of responses obtained from each site activated individually. A somatic response similar to this arithmetic sum would indicate a linear summation. B1, Membrane potential of -65 mV at the time of the stimulation. B2, Membrane potential of -75 mV at the time of the stimulation. Note that, as expected, the EPSPs had a smaller amplitude when the membrane potential was more depolarized (B1).
Integration of synaptic inputs in dendritic trees of TC neurons

Figure 2.12: Minimal number of synapses required to elicit an action potential in TC neurons. A, Threshold number of synapses for the generation of at least one action potential as a function of the membrane potential for stimuli applied to proximal (A1) and distal (A2) parts of dendrites. Four traces correspond to four studied neurons. Note that the threshold number was lower for proximal inputs than for distal inputs when the membrane potential was within physiological range. However, under strong hyperpolarization (-90 mV), the threshold number of distal inputs was lower than for proximal inputs in all cells. B, Examples of somatic responses from points 1-4 indicated in upper panels. Note that when the membrane potential was much hyperpolarized (-80 mV), the threshold responses elicited bursts of action potentials.

depended on $V_m$ (Fig. 2.12). At depolarized voltages (above -50 mV), only a few synapses were needed to trigger an action potential. When the neuron was progressively hyperpolarized (till about -65 mV), $N_{th}$ increased near linearly with the hyperpolarization in voltage, but the slope of this increase depended on the cell size and was steeper for the smallest tested cell (Fig. 2.12A). In the voltage range from -65 mV to -75 mV, $N_{th}$ dramatically decreases, because of the activation of $I_T$. In this situation, the EPSPs elicited an LTS that led to the generation of action potentials (Fig. 2.12). At voltages between -75 mV and -80 mV, $N_{th}$ was nearly constant; however, LTSs led to the generation of bursts of action potentials and not single spikes (Fig. 2.12B). Below -80 mV, the number of sites needed to elicit a burst again started to increase. This experiment also demonstrated that in order to trigger an action potential in TC neurons, the excitation arriving to distal dendrites requires 25-30% more of synapses to be activated (compare Fig. 2.12A1 with Fig. 2.12A2).
2.6 Discussion

In this study we investigated the impact of neuronal size, dendritic diameter, active membrane properties and distributions of excitatory synapses on the integration of synaptic inputs in thalamic relay neurons. We show that local dendritic responses induced at thin distal dendrites are manifold higher than at thick proximal dendrites. If several closely located synapses are activated simultaneously on distal, but not proximal dendrites, the local response soon approaches the reversal potential for the EPSP leading to a saturation of the response. In contrast, the simultaneous activation of additional synapses on proximal dendrites results in a nearly linear summation of the individual responses. When propagating to the neuronal somata, the dendritic signals attenuate. The attenuation of EPSPs evoked at the proximal part of dendrites is much smaller compared to the major attenuation of propagated EPSPs elicited at distal dendrites. This occurs because distally generated responses travel long distances and go through multiple branching points of high geometrical ratio in forward propagation. Depending on the distribution of synaptic sites, the somatic responses induced by distal inputs are either comparable in amplitude or smaller than those obtained for proximal inputs. With the investigated number of simultaneously activated sites, synaptic responses were generally significantly enhanced by the activation of $I_h$ and $I_T$ at a hyperpolarized range of the membrane potential, but none of these currents was able to enhance unitary evoked responses.

Our study focused on the hypothetically different integration modes or arithmetic rules between proximal and distal parts of the dendritic arborization, since synapses formed at these respective regions arise from different afferents. The same unitary synaptic event generated either in proximal or in distal dendrites revealed differences in the time course of induced somatic voltage transients depending on the relative distance of the input to soma, as expected from the cable theory [60,61]. Amplitudes were however of the same order of magnitude, despite being significantly different, suggesting that failures of dendritic propagation might not be frequent, at least at an input distance of 150 µm. As suggested in a previous study [107], failures of the corticothalamic EPSPs encountered in experiments might result from the synaptic mechanisms and the stochastic nature underlying the release probability of neurotransmitters, and not from the propagation of potentials in dendrites.

Synaptic democracy between proximal and distal inputs has been suggested in other types of cells [108,109]. As we investigated here in modeled TC neurons, a single event originated in distal dendrites did not necessitate active properties or a stronger synaptic conductance to induce a somatic response of the same order of magnitude as the one induced by a proximal input. Similar results have been obtained in past modeling experiments on TC neurons [110,111]. We enlarged these studies by investigating the interaction of multiple synaptic events for various distributions of the sites of stimulation on different dendrites of different neurons. Neurons with more extensive dendrites displayed lower in amplitude and faster somatic responses than compact cells. This is a consequence of their lower somatic input resistance and the highest current flow toward their large dendritic trees. Nevertheless, despite
different degrees of excitability, the arithmetic rules of the synaptic integration were similar from one cell to another. In nearly passive conditions, when synaptic inputs were aligned along a proximal dendrite, somatic voltage transients increased linearly with the number of those inputs, while the summation was rather sublinear for inputs distributed in a similar fashion at the distal part. This was a consequence of the decrease in the driving potential of the synaptic current, a phenomenon called synaptic or dendritic saturation [112, 113]. This saturation was present for clustered distal synapses since local EPSPs are very high and thus closer to the reversal potential of the synaptic current. Spreading synaptic sites over the numerous branches induced at least a linearly increasing somatic response at the soma with the number of activated sites, for both proximal and distal parts. The highly branched structure of TC dendrites may thus be justified since it provides isolation of synapses and a reduced interaction or interference of synaptic events. However, proximal dendrites contain a much lower number of branches, reducing the possibilities of distributing the synapses or to separate them, but as shown in our results, the integration of those perisomatic inputs was not strongly dependent on the type of distribution.

Here we claim that in order to produce the most efficient depolarization of the cell body, corticothalamic distal synapses should be established by multiple single release site terminals contacting different dendritic branches and trees. In contrast, sensory ascending fibers may connect to the proximal part of TC cells via a few giant terminals carrying a large number of release sites. These results bring a physiological explanation of the organization of the excitatory synapses distribution in thalamic relay cells. However, it is important to note that several studies in PY neurons emphasized the importance of clustered inputs for the generation of dendritic spikes and the absence of sublinearity in such conditions [114]. The mechanisms included in the model in the present study were not sufficient to generate similar dendritic spikes for clustered inputs. Supplementary simulations with any other specific intrinsic current could provide more data on this point, but experimental results do not suggest the presence of such mechanisms in TC neurons. Furthermore, avoiding synaptic saturation might not be an important neuronal strategy and this phenomenon may achieve an important function itself, for instance noise filtering or gain modulation of the input-output relation of a neuron [69].

Experimental results demonstrate that responses of TC neurons to the stimulation of corticothalamic pathways grow linearly with stimuli strength, while responses of the same neurons to lemniscal stimuli show all-or-none features [115–118]. This suggests that corticothalamic influences are composed of a large number of small unitary events, but that lemniscal synaptic events are unitary. Our results confirm that this organization is efficient.

Rall’s pioneer theoretical work on dendritic physiology suggested that various time courses of somatic voltage transients corresponding to different dendritic locations imply different physiological functions at cells level [119]. Slow low-pass filtered somatic responses of small amplitude corresponding to local EPSPs evoked at distal dendrites may be integrated over a large time window before reaching the threshold for the generation of an action potential, while faster and larger in amplitude responses may trigger a spike if their respective peaks
coincide in time. This was later formalized as the temporal integration and coincidence detection modes, respectively (reviewed in [120]). Sharp somatic voltage transients induced by the stimulation of perisomatic synapses at depolarized levels of $V_m$ suggest a coincidence detection mode for proximal synaptic inputs. In contrast, slower transients obtained when stimulating the distal part point out a temporal integration of inputs. This would be especially true in presence of a strong but slow NMDA-receptor-mediated component at distal synapses, as reported for corticothalamic synapses [117]. The NMDA component was lacking in our simulations. We did not include it into the model because the role of NMDA receptors in shaping TC neurons responses in vivo is unclear. Our data are supported by previous studies suggesting that synapses formed at the TC neuron by corticofugal axons may have a role of modulation and regulation of the background level of $V_m$, while lemniscal synapses would act as drivers of the activity of thalamic relay cells during wake by integrating the information in a precise timing [121]. In vitro and in vivo studies showed that sensory activity will be transferred with reliability if the postsynaptic TC cell is sufficiently depolarized because lemniscal inputs at hyperpolarized levels of $V_m$ do not reach the firing threshold [9, 10, 116]. However, at hyperpolarized levels of $V_m$, temporally summed lemniscal responses may lead to the generation of LTSs crowned with action potentials [10, 104].

The interplay of $I_h$ and $I_T$ underlies thalamic delta oscillations [35]. $I_T$ also plays a major role in the generation of sleep spindle activities [45, 48, 122]. Our data provide information on how synaptic inputs are modulated by those intrinsic currents of TC cells. $I_h$ alone did not play a major role for all tested conditions of synapses distribution. Congruently to experimental data, $I_T$ can lead to an amplification of subthreshold synaptic signals when they are summed. However, a stronger synaptic boosting was found when $I_T$ was interacting with $I_h$. This amplification was observed in most cases. This is physiologically relevant for a paradigm of efficiency since the activation voltage range of $I_h$ lies in the voltage range where $I_T$ is deinactivated. Furthermore, previous work showed that channels underlying the $I_h$ current in TC cells might be colocalized with T-channels (Williams, personal communication).
Chapter 3

Conclusion

The exact strategy followed by neurons to process information is currently a point of debate. Several experimental studies addressing the question of synaptic integration in cortical and hippocampal PY cells and INs have been achieved [90–93, 95, 108, 123–127], but only a few were carried out on TC cells. Morphologically distinct cells with different sets of intrinsic currents from various regions and neural systems may not obey the same arithmetic rules of input integration. Furthermore, a clear understanding of the impact of geometrical and morphological features on signal propagation is still lacking. Due to different ranges of activation of intrinsic currents, it is very likely that inputs to a TC cell display nonlinear amplifications under hyperpolarization of the membrane, i.e. in the bursting mode of the cell, while a depolarized TC neuron in a tonic-firing mode would integrate its inputs in a linear manner. However, the role of the specific morphology of TC cells in synaptic integration remains unknown. The two main excitatory synapses formed at TC cells arise from sensory ascending fibers and descending corticothalamic fibers. Numerous contacts are formed by large sensory fiber terminals at thick proximal dendrites, while small corticothalamic terminals contact mainly the thin distal dendrites [32]. Due to the all-or-none nature of EPSPs under the stimulation of lemniscal fibers [115, 116], it is likely that only one sensory terminal contact a single TC cell, while one descending fiber may connect to multiple dendritic branches according to the variability of EPSPs amplitude under the stimulation of corticothalamic fibers [115, 117, 118].

In order to understand the impact of typical geometry and intrinsic currents of TC neurons on their integrative properties, we investigated the synaptic integration for their different modes of operation and for different distributions of excitatory synaptic inputs. Due to limited experimental techniques, we used a modeling approach to build a multicompartmental model from real reconstructed TC neurons from the VPL nucleus. We were particularly interested in comparing the somatic response induced by proximal vs. distal inputs, since synapses formed at these respective regions arise from different sources. Similar unitary synaptic events induced at both the proximal and the distal parts of the cells resulted in small somatic responses (0.2-
0.9 mV). The somatic responses obtained from distal inputs were significantly smaller in amplitude and longer than for proximal inputs. They were however of the same order of magnitude for both positions, meaning that the large depolarization induced at remote thin distal branches can counterbalance the attenuation of EPSPs during the propagation toward soma. However, thick dendritic paths provided stronger depolarization to the cell body than globally thin dendrites due to a reduced attenuation, despite a reduced impedance at the site of stimulation for thick dendrites. Simulations also revealed a significant difference between responses generated in different cells. Due to their extensive branching, large cells had a reduced dendritic input impedance from the point of view of the soma, and somatic voltage transients were smaller in amplitude and had a faster time course than for small TC cells.

By increasing the number of inputs to the cell, we found that the response induced at the soma by proximal inputs was nearly independent of their distribution over dendrites. Voltage transients recorded at the soma near resting membrane potential increased linearly with the number of stimulated sites, but could increase supralinearly for an initially hyperpolarized membrane due to $I_T$. In contrast, distributing sites of stimulation along a dendritic path at distal branches resulted in a saturating somatic response when the number of inputs increased progressively. This sublinearity in the summation is a consequence of the large amplitude of distal EPSPs that, when summed, gets closer to the reversal potential of the excitatory synaptic current and reduce the driving potential. On the other hand, when inputs were spread over different branches, the summation became linear or revealed amplification, depending of $V_m$ at the time of the stimulation.

We tested different sets of intrinsic properties: a passive membrane, a membrane with T-channels, with h-channels and with both types of channels included in the model. As already mentioned, the presence of $I_T$ in the model could boost the response and allow a supralinear summation. The presence of $I_h$ in the model always induced an inherent change of $V_m$ over time. In the case where $I_T$ was absent, the $I_h$ current did not change the amplitude of responses compared to the case of a passive membrane. However, depending on the time course induced by $I_h$, the supralinearity mediated by $I_T$ could be enhanced. It confirms previous studies showing that the interaction of $I_T$ and $I_h$ is important for the generation of bursts of action potentials in TC cells during delta oscillations [35,39–41]. Since this boost of the LTS depends on the time of stimulation and on the depth of the hyperpolarization, the frequency of oscillations and of stimulations at hyperpolarized levels of $V_m$ might be crucial for the generation of an LTS.

The present study allowed us to build a hypothesis on an efficient synaptic organization at TC cells and to bring a physiological meaning to what is currently known about typical distributions of excitatory synapses at those cells. According to our results, it is preferable for corticothalamic distal synapses to be dispersed over different dendritic branches and trees and to have locally a few contacts. This would be in agreement with previous findings [32, 115,117,118]. In contrast, sensory ascending fibers may connect to proximal dendrites via a few giant terminals carrying a large number of release sites without being strongly affected
by the synaptic saturation. This is what the large size of lemniscal synapses and the all-or-none nature of induced EPSPs suggest [32, 115, 116]. Other studies on PY cells carried out in slices suggested the crucial role of clustered inputs in generating dendritic $\text{Na}^+$, $\text{Ca}^{2+}$ or NMDA spikes (reviewed in [114]). In our study, the mechanisms included in the model were not sufficient to generate similar dendritic spikes. The spatiotemporal pattern of synaptic activation under natural conditions remains unknown. Furthermore, a recent *in vivo* study made in the visual cortex showed that inputs corresponding to the same orientation or the same sensory feature were induced at widely dispersed sites on the dendritic arborization [96]. A similar pattern of connections may apply to corticothalamic synapses. However, further simulations with different sets of intrinsic properties are needed to test new hypotheses. Calcium imaging experiments in *in vitro* preparations could also be done to test these results showing the nonlinearity mediated by $I_T$. 
Bibliography


