Modelling and Analysing Neural Network Dynamics

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I hereby declare that all work presented in this thesis was performed by me or was referenced otherwise.

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Abstract

Neurons are often considered as the basic functional units of the brain. Our brain contains about 100 billions of neurons, of many different types and connected among themselves in a multitude of different ways. Yet, from this overwhelming complexity, order can emerge in the form of neural dynamics, when cohorts of neurons show synchronous activity. For example, oscillations of neural activity can be observed in many brain regions and are thought to be associated with cognitive processes such as information transfer or memory consolidation. However, too much oscillation can be detrimental, as during epilepsy crisis. Therefore, there must be mechanisms regulating the dynamics of neural networks. Our aim in this thesis is to further our understanding of neural networks dynamics. First, we modelled a network of cortical neurons known to exhibit oscillations. In this network, GABAergic interneurons are connected via chemical and electrical synapses (also called gap junctions), which promote synchronisation of neural assemblies. We implemented a novel model of gap junction plasticity, based on recent experimental evidence that they alter their strength in an activity-dependent manner. We hypothesised that gap junction plasticity can regulate network-wide neural dynamics and we investigated functional implications on information transmission in cortex. We then considered a brain region rich in neuronal gap junctions, the thalamic reticular nucleus (TRN). The TRN is thought to be the source of patterns of waxing-and-waning oscillations called spindles. We hypothesised that gap junction plasticity could lead to spindles and we simulated their pharmacological manipulation. Finally, we analysed and modelled the relationship between neural activity and hemodynamic response from in vivo recordings. We hypothesised that this relationship can be modelled with a transfer function. We then investigated the transfer function dependency of location and brain states. At last, we studied the prediction of neural activity from hemodynamic response.
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Chapter 1

Introduction

Our brain contains about 100 billion neurons, which represent the basic units of the nervous system. There are many different types of neurons, and even neurons from the same type show heterogeneities, inherent to any biological system. Neurons are connected by synapses and we estimate their number up to a quadrillion ($10^{15}$). However, from what could be complete chaos, functions emerge to the extent that we barely assess all the cognitive abilities of our brains. This raise a question that fascinates neuroscientists: From all this complexity, how does order and function emerge? Understanding the dynamics of neural networks is fundamental to better understand how our brain functions, or why it dysfunctions. Over the past decades, much progress has been made on understanding the inner workings of the brain. However, an important gap remains between macroscopic and microscopic descriptions. The field of theoretical neuroscience aims to provide a better understanding from the microscopic to the macroscopic scale, thanks to mathematical and computational techniques. Models, based on experimental observations offer a way to investigate and understand various mechanisms that may be difficult to research experimentally.

Synapses.

Neurons connect and communicate with each other via synapses, to form networks. In the mammalian brain, there exist two basic forms of synaptic transmission between neurons: chemical and electrical.

With chemical synapses, signals are propagated from a presynaptic neuron to a postsynaptic neuron using the release of chemical neurotransmitters in the space that separates both neuron membranes (synaptic cleft). The release of the neurotransmitter by the presynaptic neuron happens following a large depolarisation of the presynaptic neuron (spike) which causes the opening of channels permeable to calcium ions. The influx of calcium ions in the presynaptic neuron increases the calcium concentration which triggers the fusion of vesicles containing neurotransmitters with the presynaptic cell membrane, which is followed by their release in the synaptic cleft. The neurotransmitters diffuse across the synaptic cleft and bind to chemical receptors located on the postsynaptic
neuron. The binding triggers the activation of the receptors, which selectively allow ions to enter or exit the postsynaptic neuron. Depending on the change of the voltage across the postsynaptic membrane, presynaptic neurons are classified in two general groups: they are called *excitatory*, if they induce a depolarisation of the postsynaptic neurons and *inhibitory* if they induce an hyperpolarisation.

![Figure 1.1. Chemical and electrical synapses.](image)

**(A)** With chemical synapses, there is no cellular continuity between pre- and postsynaptic cells. During an action potential, the presynaptic neuron releases neurotransmitters in the presynaptic cleft. The neurotransmitters then bind on the specific postsynaptic receptors, which triggers the opening of ion channels. Ions can now flow in or out of the postsynaptic neuron, which changes its membrane potential and its probability to spike. **(B)** With electrical synapses, ions can flow directly between coupled neurons. The current contribution is proportional to the difference of membrane potentials between the neurons. Modified with permissions from Pereda et al. (2014).

Chemical synapses are the most common among vertebrates and are therefore more extensively studied. However, electrical synapses, also called gap junctions, are drawing interest. Indeed, it was recently shown that they exhibit important properties. In particular, they are thought to promote synchronous activity within networks of neurons and, like chemical synapses (Hebb (1949b)), their strength can modified by activity of coupled neurons.
Electrical synapses.

Ending decades of controversy about their existence (Golgi (1906)), Robertson, Furshpan, Potter and Watanabe were among the first to observe compelling evidence that neurons can communicate not only chemically, but also electrically. They found electrical synapses in invertebrates cells such as crayfish nerves and shrimp neurons (Robertson (1953); Furshpan and Potter (1957); Watanabe (1958)). Electrical synapses in the mammalian brain appeared significantly harder to observe (Connors and Long (2004)). The first strong evidence for mammalian electrical synapses came from single-cell recording in the mesencephalic nucleus of cranial nerves of adult rats (Hinrichsen (1970)), the vestibular nucleus (Wylie (1973); Korn et al. (1972)), and the inferior olivary nucleus (Llinas et al. (1974)).

The task to find and demonstrate electrical coupling was particularly difficult to achieve because it necessitates the ability to record intracellularly from two neighbouring cells simultaneously in the intact brain. The difficulty of this experiment explains why it took longer to study electrical synapses in the mammalian brain. However, recent technical breakthroughs in cell imaging, molecular cloning and transgenics made the study of gap junctions easier and they are now intensively examined.

Electrical synapses have different properties from those of chemical synapses (Bennett (1977)). While chemical synapses are polarised structurally and functionally, electrical synapses are bidirectional and often symmetrical. The ion current flows directly from one cell to the other. This process makes also the synaptic transmission with electrical synapses faster, with almost no synaptic delay. Thanks to those properties, electrical synapses are involved in activity synchronisation where chemical synapses are more specific and do point-to-point communication. In the following section we will see how the structure of electrical synapses is related to their function.

Gap junction structure.

Electrical synapses are made from gap junctions between two cell membranes that are very close to each other. At the synapse, the intercellular space is only between 2 and 4 nm (Maeda et al. (2009)). In vertebrates, gap junctions are made from connexins (Cx). Six connexin proteins form a connexon (also called hemichannel) and two connexons form a gap junction. For mammals, over eleven connexins are expressed, mostly found in glial cells. Among the neuronal connexins, Cx36 seems to be the most predominant, but additional neuronal connexins can be found, such as Cx45, Cx50, Cx57 and possibly Cx30.2 and Cx31.1 (Belluardo et al. (2000); Venance et al. (2000); Rash et al. (2012); Pereda et al. (2014)). This precisely aligned channel structure allows ions to flow directly.
Gap junctions allow the transfer of ions and molecules to transfer between cells. They are made from connexin protein. Six connexins form a connexon and two connexons form a gap junction. Gap junctions have been reported to be of three different kinds: (1) homotypic, when both connexons are made from the same connexins; (2) heteromeric, when connexons are made from different connexins; (3) heterotypic, when each connexon is made from a single connexin type, but they can differ between connexons. Modified with permissions from Söhl et al. (2005).

from one cell to the other. Because the pore of a gap junction is larger than the pores of the voltage-gated ion channels, relatively large molecules, such as ATP can be transferred between neurons (Purves (2004)). Cx36 gap junctions can be formed at the dendro-dendritic, dendro-somatic levels, or directly between axons (Hamzei-Sichani et al. (2007)). In the mature central nervous system (CNS), neuronal gap junctions are mostly found between neurons of the same type (Galarreta and Hestrin (1999); Gibson et al. (1999); Chu et al. (2003)).

The structure of the electrical synapses allow their transmission to be bidirectional and very fast, without delay. Those properties can explain the several functions that they promote and their presence in central and peripheral nervous system of both invertebrates and vertebrates.

**Functions and distribution of the gap junctions.**

Because of their lack of synaptic delay (in comparison to chemical synapses), gap junctions are particularly relevant when a fast reaction time between stimuli and motor action is needed. This may explain why they are found in escape networks of vertebrates (Antonsen and Edwards (2003); Phelan et al. (1996)); because there is almost no delay between the presynaptic and postsynaptic electrical signals, the very fast propagation of the action potentials minimise the time between the detection of a threatening stimulus and a potentially life-saving motor response (Faber et al. (1989)).
Furthermore, there is evidence that electrical synapses promote network synchrony and they are thought to be part of mechanisms of lateral excitation in sensory system (Pereda et al. (1995)). In mammals, gap junctions are found in the inferior olivary nucleus where evidence suggest that they promote large synchronous subthreshold fluctuations of membrane voltage at 2-8 Hz (Sotelo et al. (1974); Llinas et al. (1974); Benardo and Foster (1986)), in the thalamic reticular nucleus where they may coordinate local groups of TRN neurons (Landisman et al. (2002); Long et al. (2004)), in the hippocampus, where they are thought to participate in the modulation or generation of synchronous oscillations at gamma-frequency rhythm (Jefferys (1995); Hormuzdi et al. (2001)). In the cortex (Sloper (1972); Sloper and Powell (1978)), gap junctions between interneurons may play a role in promoting synchrony of large population of spatially distributed interneurons. Gap junctions occur also in the retina (Vaney and Taylor (2002)), in the olfactory bulb (Zhang and Sulzer (2003)), in the locus coeruleus (Christie et al. (1989)), where there are strong evidence involving gap junctions in generating subthreshold oscillations. Electrical synapses are present at all levels of the mammalian motor system, where they may enhance synchronous neural activity. For example they may be involved in generating respiratory rhythm in the brainstem (Rekling et al. (2000)).

In most cases, electrical synapses are known to promote coordinated neural activity but in cerebellar network they are also shown to promote desynchronisation (Vervaeke et al. (2010)).

In networks of neurons with electrical and chemical synapses, Tchumatchenko and Clopath demonstrated that both subthreshold resonance and gap junctions together promote oscillations Tchumatchenko and Clopath (2014). From a fluctuation-driven state, in which neurons fire asynchronously, increasing the gap junction strength drives the network to a synchronous regime of global oscillations, as can been observed in the barrel cortex in vivo (Cardin et al. (2009)).

In addition to promoting synchrony, gap junctions are also thought to assure robustness in the network output by providing alternative pathways through which a presynaptic neuron can affect the output of a postsynaptic neuron. Their modification can serve as a switch between multiple competing oscillators, as demonstrated with a simplified model of the crab stomatogastric ganglion (Gutierrez et al. (2013)).

**Bi-directionality of electrical synapses.**

Often, gap junctions are observed to be symmetrical, meaning the current flows as easily in both directions between the two connected neurons (pre- and post-synaptic naming is not relevant anymore). However, gap junctions can also be asymmetrical
as found in invertebrates (Furshpan and Potter (1959); Phelan et al. (2008)) and in vertebrates (Nolan et al. (1999); Vervaeke et al. (2010); Wang et al. (2014)). In a recent study, Sevetson and Haas (Sevetson et al. (2014)) show that coupling asymmetry can expand the output properties of pairs of electrically coupled neurons.

**Gap junction plasticity.**

(a) Factors of the electrical transmission strength.

(b) Activity-dependent induced LTD, after 5min of high frequency bursts

![Figure 1.3. Gap junction coupling and its plasticity.](image)

(a) In this example, at steady state, when $C_1$ is the presynaptic cell and $C_2$ the postsynaptic cell, the coupling coefficient is $CC_1 = \frac{V_2}{V_1} = \frac{R_2}{R_2 + R_C}$; similarly we obtain $CC_2 = \frac{V_1}{V_2} = \frac{R_1}{R_1 + R_C}$. Modified with permissions from Pereda et al. (2014); b) Coupled pair of TRN neuron: either they are driven to burst simultaneously (A) or only one is driven to burst (C) by current injection. Scale bars 20mV, 50ms. (B) and (D) In both cases, their normalised coupling coefficient $cc$ and their normalised synaptic conductance $G_C$ is decreased by about 15% after 5min of protocol. Modified with permissions from Haas et al. (2011a).

Unlike chemical synapses, electrical synapses were originally thought to lack dynamical properties. However recent studies show that the strength of their electrical coupling is modifiable (Cachope et al. (2007); Wang et al. (2015b); Turecek et al. (2014, 2016); Coulon and Landisman (2017)). In the retina, the conductance of gap junctions can vary from 50 pS to 450 pS between day and night cycles (Jin and Ribelayga (2016)).

To evaluate the strength of electrical transmission, it is important to consider the conductance of the gap junctions but also the passive properties of the coupled neurons determined by their capacitance and resistance. To quantify the strength of coupling, the coupling coefficient $(cc)$ is defined as the ratio between voltage deflections in “post”- and “pre-synaptic” cells during injection of current pulses (Figure 1.3a). Thus, the strength
of electrical coupling can be affected by gap-junctional factors and non-junctional factors (neuron properties).

Regarding non-junctional factors, electrical coupling can be amplified by voltage-dependant conductances, which add an additional depolarisation (Haas and Landisman (2012)). Because the resistance of the post-synaptic cell affects the electrical coupling, modification of the resistance will change the electrical coupling. This has been especially observed in the inferior olive glomerulus during the shunting effect of chemical inhibitory transmission, when the inhibitory synaptic conductance short-circuits the adjacent electrical synapses (Llinas et al. (1974); Best and Regehr (2009)). The input resistance is then locally reduced and following Ohm’s law, the post-synaptic potential is also reduced.

Gap junctional conductance has been observed to be dynamically modulated by neurotransmitter in both invertebrates and vertebrates, for example with dopamine in Cx36 gap junctions of AII amacrine cells (Kothmann et al. (2009)) or noradrenaline in hippocampal inhibitory interneurons (Zsiros and Maccaferri (2008)).

Although extensively described at chemical synapses, activity dependent plasticity of electrical synapses was not investigated until recently. In 2011, Haas et al. investigated the relationship between activity and strength at electrical synapses in thalamic reticular neurons of mice. After injecting pulse of current for 50 ms every 500 ms, leading to high frequency bursts, they observed long-term depression (gLTD) of the coupling coefficient, either the stimulation was to one or both neurons from pair of electrically coupled neurons (Haas et al. (2011a)). Other studies show that gap junctions exhibit activity-dependent long-term plasticity (Cachope and Pereda (2012); Turecek et al. (2014); Haas et al. (2016)).

There is no experimental data yet on activity-dependent long-term potentiation of gap junctions (gLTP) in mammals. However, there must be a potentiation mechanism to compensate the depression. Interestingly, the pathways leading to gLTD appear to be calcium-dependent which suggest that gLTP could also be the result of an activity-dependent mechanism (Sevetson et al. (2017)). Passive mechanisms, such as gap junction connexin turnover could compensate for long-term depression as well (Beardslee et al. (1998); Gaietta et al. (2002); Boassa et al. (2010); Carette et al. (2015); Wang et al. (2015a); Szoboszlay et al. (2016)).
Neural network dynamics.

If you position few sensitive electrodes on your head, and measure the variations of the electric potential over time, you could observe interesting patterns on the electroencephalogram (EEG). This is because the neural circuits of the brain can generate complex dynamics, which create patterns of activity in the local field potentials. For example, it is possible during sleep to observer waxing and waning patterns of oscillations that are thought to be associated with memory formation (Steriade et al. (1993); McCormick and Bal (1997a); Rosanova (2005a); Latchoumane et al. (2017); Xia et al. (2017)). Or during attention, it is possible to observe fast oscillations (over 40 Hz) during the few hundreds of milliseconds following the presentation of a stimulus (Fries (2001); Gregoriou et al. (2009); Vinck et al. (2013); Roubinen et al. (2013)). In this thesis we will focus on three types of network dynamics: 1) Transient response to a sustained stimulus - for example imagine how you notice a strong smell when you enter a room, but you quickly stop noticing it after few minutes. The stimulus is still there but you brain stopped paying attention to it; 2) Oscillatory network activity - when large cohorts of neurons become active simultaneously in a periodic fashion; 3) Chaotic activity - when the system shows absence of predictability, such as when a small change to initial conditions causes significantly different outcomes (Strogatz et al. (1994); Vogels et al. (2005)).

Aims.

The aims of this thesis are twofold. Firstly, we aimed to understand how neural network dynamics can emerge from the neuron properties and their connectivity. Secondly, we look at neural activity in vivo and aim to develop a model that could facilitate and improve measures of neural network dynamics.

Given the ubiquity of gap junctions, the experimental reports of gap junction plasticity and their potential role in synchronisation of neural assemblies, we wished to understand how gap junction plasticity might influence the neural network dynamics. In particular, we investigated the potential role of gap junction plasticity at the network level in two brain regions rich in gap junctions and with interesting network dynamics, the cortex and the thalamic reticular nucleus (TRN). To that end, we developed a computational model of neural networks with plastic gap junctions, consistent with recent studies. We showed that gap junction plasticity can regulate oscillations and allows for rich network dynamics, such as transient oscillations, sustained oscillations, or what seems to be chaotic activity. Moreover, we aimed to investigate the potential functional implications of gap junction plasticity. In particular, we wondered about its potential role in information transfer between populations of neurons.
There is currently no technology available to measure precisely the activity of large population of neurons in deep regions of the brain *in vivo*. However, on one hand the recent development of genetically encoded voltage indicators (GEVI) can allow tracking of voltage signals from surfaces up to 2 µm² and with sub-millisecond temporal resolution in living animals ([Hochbaum et al. (2014)])]. Notably, it allows the imaging of the whole surface of cortical layers 2/3. On the other hand, since the 90s ([Ogawa et al. (1990a, 1993)])], functional magnetic resonance imaging (fMRI) gives access to measures of the oxygen consumption in the brain, deeply and non-invasively. This measure is currently used as a proxy of the neural activity, nonetheless the need of a better understanding of the coupling between neural activity and blood-oxygen level remains.

While imaging with GEVI, it is possible to simultaneously record neural activity and hemodynamic response at the same spatial and temporal resolution. Therefore, our aim was to investigate the relationship between hemodynamic response and neural dynamics. With this in mind, we developed a mathematical model of the neurovascular coupling. Then, we investigated the dependency of the coupling on the brain states and location. Our model could be used to facilitate and further the understanding of neural network dynamics obtained from non-invasive fMRI.
Chapter 2

Gap junction plasticity can regulate oscillations in cortical networks

Despite the ubiquity of electrical synapses in the mammalian brain (Connors and Long (2004)), they initially did not receive the same amount of interest as their counterparts, chemical synapses. Fewer studies attempted the analysis of the potential functional implications of gap junction coupling both at the experimental and theoretical levels. At the experimental level, this can be explained by the technical challenges associated to their observation. However, important findings where recently uncovered: Gap junctions are plastic and their plasticity can be activity-dependent (Haas et al. (2011a); Sevetson et al. (2017)). This is particularly interesting, as gap junctions are thought to be involved in the synchronisation of populations of neurons. Indeed gap junctions create a passage between coupled neurons allowing ions to flow from one cell to another, which tends to reduce the difference between their membrane potentials. Furthermore, gap junctions can be found between fast spiking interneurons (Hatch et al. (2017)), which are reported to be involved in cortical neural dynamics (Cardin et al. (2009); Sohal et al. (2009); Whittington et al. (2011)).

In this chapter, we design a novel model of gap junction plasticity based on recent experimental literature (Haas et al. (2011a); Sevetson et al. (2017)). First, we show that gap junction plasticity may regulate cortical oscillations. Then we sought to research the functional implications of gap junction plasticity between cortical GABAergic neurons. We found that, by forcing the network dynamics to stay close to the transition between synchronous and asynchronous regime, gap junction plasticity may allow for information transfer. We would like to mention to the reader that the layout of the presented work is in an article format, as it has been submitted for publication. We thank Wilten Nicola and Claudia Clopath for their comments on earlier versions of the manuscript.
Gap junction plasticity as a mechanism to regulate network-wide oscillations

Abstract

Cortical oscillations are thought to be involved in many cognitive functions and processes. Several mechanisms have been proposed to regulate oscillations. One prominent but understudied mechanism is gap junction coupling. Gap junctions are ubiquitous in cortex between GABAergic interneurons. Moreover, recent experiments indicate their strength can be modified in an activity-dependent manner, similar to chemical synapses. We hypothesised that activity-dependent gap junction plasticity acts as a mechanism to regulate oscillations in the cortex. We developed a computational model of gap junction plasticity in a recurrent cortical network based on recent experimental findings. We showed that gap junction plasticity could serve as a homeostatic mechanism for oscillations by maintaining a tight balance between two network states: asynchronous irregular activity and synchronised oscillations. This homeostatic mechanism allows for robust communication between neuronal assemblies through two different mechanisms: transient oscillations and frequency modulation. This implies a direct functional role for gap junction plasticity in information transmission in cortex.

Author summary

Oscillations of neural activity emerge when many neurons repeatedly activate together and are observed in many brain regions, particularly during sleep and attention. Their functional role is still debated, but could be associated with normal cognitive processes such as memory formation or with pathologies such as schizophrenia and autism. Powerful oscillations are also a hallmark of epileptic seizures. Therefore, we wondered what mechanism could regulate oscillations. A type of neuronal coupling, called gap junctions, has been shown to promote synchronisation between inhibitory neurons. Computational models show that when gap junctions are strong, neurons synchronise together. Moreover recent investigations show that the gap junction coupling strength is not static but plastic and dependent on the firing properties of the neurons. Thus, we developed a model of gap junction plasticity in a network of inhibitory and excitatory neurons. We show that gap junction plasticity can
maintain the right amount of oscillations to prevent pathologies from emerging. Finally, we show that gap junction plasticity serves an additional functional role and allows for efficient and robust information transfer.

Introduction

Oscillatory patterns of neuronal activity are reported in many brains regions with frequencies ranging from less than one Hertz to hundreds of Hertz. These oscillations are often associated with cognitive phenomena such as sleep or attention. Local field potential measurements in the neocortex and thalamus show the prevalence of delta oscillations (0.5-4Hz) and spindle oscillations (7-15Hz) during sleep (Timofeev et al. (2012)). Theta oscillations (4-10Hz) are also reported in hippocampus and other brain regions (Buzsáki (2002)). Gamma oscillations (30-100Hz) observed in the cortex are thought to be involved in attention (Fries (2001); Gregoriou et al. (2009); Vinck et al. (2013); Rouhinen et al. (2013)), perception (Rodriguez et al. (1999); Melloni et al. (2007)) and coordinated motor output (Baker (2007); Omlor et al. (2007)). Thus, at the minimum, oscillations are present during the normal functioning of neural circuits.

However, oscillations are also associated with pathological circuit dynamics, such as hyper-synchronous activity during epileptic seizures (Fisher et al. (2005)). Altered gamma-frequency synchronisations may also be involved in cognitive abnormalities such as autism (Orekhova et al. (2007)) or schizophrenia (Lewis et al. (2005)). Thus, given both the functional and pathological effects of oscillations, a homeostatic mechanism is necessary to regulate oscillatory behaviour.

Several mechanisms can lead to the emergence of oscillations. They can arise in homogeneous population of excitatory neurons, where the positive feedback loop of excitation is only limited by the refractoriness of the neurons (Brunel (2000)). Alternatively, oscillations can also arise in a coupled network of excitatory and inhibitory neurons, where the excitatory and inhibitory neurons burst in opposing phase. (Sanchez-Vives and McCormick (2000); Haider et al. (2006); McCormick et al. (2015); Buzsáki and Freeman (2015); Veit et al. (2017)). Finally, gap junctions between inhibitory neurons promote synchronous oscillatory patterns (Traub et al. (2001); Pfeuty et al. (2003); Kopell and Ermentrout (2004); Connors and Long (2004); Tchumatchenko and Clopath (2014)).

The inhibitory network oscillations primarily involve fast-spiking interneurons. These neurons represent a large proportion of GABAergic interneurons (Kawaguchi and Kubota (1997)). They are the main cells targeted by thalamocortical synapses transmitting sensory information to the cortex (Gibson et al. (1999)). They are coupled via chemical synapses and gap junctions. Gap junctions are mostly found between neurons of the same class
(Galarreta and Hestrin 1999; Gibson et al. 1999; Chu et al. 2003) but they can also connect different subtypes, such as fast-spiking and regular spiking cells (Gibson et al. 1999; Caputi et al. 2009; Hatch et al. 2017). Moreover, there is evidence of the critical role of fast-spiking parvalbulmin (FS) interneurons in the emergence of cortical gamma activity in the cortex of rodents in response to sensory stimuli (Whittington et al. 2011; Bartos et al. 2007; Cardin et al. 2009; Sohal et al. 2009).

Two main properties of FS interneurons have been found critical in the existence of gamma oscillations. Firstly, FS interneurons selectively amplify gamma frequencies through subthreshold resonance (Cardin et al. 2009). Secondly, gap junctions between inhibitory interneurons (Galarreta and Hestrin 1999) have been shown to enhance synchrony (Gibson et al. 1999; Tamás et al. 2000; Hormuzdi et al. 2001; Buhl et al. 2003; Traub et al. 2004; Ostojic et al. 2009; Wang et al. 2014; Tchumatchenko and Clopath 2014; Robinson et al. 2017). A computational model with both properties, inhibitory neurons with subthreshold resonance, connected by gap junctions, has been shown to support gamma oscillations (Hutcheon and Yarom 2000; Pike et al. 2000; Fellous et al. 2001; Tateno 2004; Manor et al. 1997; Tchumatchenko and Clopath 2014).

Recently, gap junction plasticity has been experimentally demonstrated (Cachope et al. 2007; Wang et al. 2015b; Turecek et al. 2014, 2016; Coulon and Landisman 2017). For example, the gap junctions between rod cells in the retina can vary their conductance during day and night cycles (Jin and Ribelayga 2016). Moreover, they can experience bidirectional long-term plasticity in an activity-dependent manner (Cachope and Pereda 2012; Turecek et al. 2014; Haas et al. 2016). High frequency stimulation of a coupled pair of thalamic reticular nucleus (TRN) neurons induces gap junction long-term depression (gLTD) (Haas et al. 2011b). This occurs only when the TRN neurons burst. There is no data yet on the long-term potentiation of cortical gap junctions. However, Sevetson et al. (2017) show that the pathways leading to gLTD are calcium-dependent which suggest that gap junction long-term potentiation (gLTP) could also be the result of an activity-dependent mechanism. Other passive mechanisms, such as gap junction connexin turnover could compensate for long-term depression as well (Beardslee et al. 1998; Gaietta et al. 2002; Boassa et al. 2010; Carette et al. 2015; Wang et al. 2015a; Szoboszlay et al. 2016).

Given the existence of gap junction plasticity and the omnipresence of oscillations in cortex, we wondered whether gap junction plasticity can regulate network-wide gamma oscillations in cortex. To that end, we developed a computational model of a network of excitatory and FS inhibitory neurons. As demonstrated analytically by Tchumatchenko and Clopath (2014), we observed two different network behaviours depending on the gap junction strength. For weak gap junction strength, the network exhibits an asynchronous regime,
whereas for strong gap junctions, the network synchronises into coherent gamma oscillations with bursting activity. We then modelled the gap junction plasticity observed by Haas et al. (2011b) showing that bursting activity leads to gLTD. The plastic network sets itself at the transition between the asynchronous regime, where sparse spiking dominates, and the synchronous regime, where network oscillations dominate and burst firing prevails. Thus, our model shows that gap junction plasticity maintains the balance between the asynchronous and synchronous network states. This is robust to different possible gLTP rules. We then show that the network allows for transient oscillations driven by external drive. This demonstrates that transient, plasticity regulated oscillations can efficiently transfer information to downstream networks. Finally we show that gap junction plasticity mediates cross-network synchronisation and allows for robust information transfer trough frequency modulation. Critically, gap junction plasticity allows for the recovery of oscillation mediated information transfer in the event of partial gap junction loss.

Results

Network synchrony depends on gap junctions strength.

To study the effect of gap junction plasticity, we developed a network of coupled inhibitory and excitatory neurons in the fluctuation-driven state (Figure 2.2A). The Izhikevich model was used for the inhibitory neuron population to fit the fast-spiking inhibitory neuron firing pattern (Izhikevich (2007)). Excitatory neurons are modelled by leaky integrate-and-fire models. As in Tchumatchenko and Clopath (2014), the excitatory neurons act as low pass-filters for their inputs while the FS neurons have a sub-threshold resonance in the gamma range (Hutcheon and Yarom (2000); Pike et al. (2000); Fellous et al. (2001); Tateno (2004); Manor et al. (1997)). To demonstrate this, we injected an oscillatory current of small amplitude in a single cell and recorded the amplitude response for different oscillatory frequencies. Excitatory neurons better respond to low frequency inputs, while FS neurons respond maximally for gamma inputs (Figure 2.1B). This is in line with the experimental evidence of Cardin et al. showing that FS-specific light stimulation amplifies gamma-frequencies (Cardin et al. (2009)).

All neurons have chemical synapses but only inhibitory neurons are also coupled via gap junctions (Figure 2.1A). The gap junctions are modelled such that a voltage hyperpolarisation (depolarisation) in one neuron induces a voltage hyperpolarisation (depolarisation) in the connected neuron. The current contribution of gap junction coupling is proportional to the difference of voltages between the coupled neurons, multiplied by the gap junction strength $\gamma$ (Figure 2.1C). Moreover, when one neuron spikes, it emits a spikelet in the
coupled neuron. We model this by a positive inhibitory to inhibitory electrical coupling, which we add on top of the negative inhibitory to inhibitory chemical coupling (see Materials and Methods).

In order to understand the effects of gap junction plasticity, we initially considered the network without plasticity. We first explored the network behaviour for different values of the mean gap junction strengths $\gamma$ and mean external drive to the inhibitory neurons $\nu_I$. As demonstrated by Tchumatchenko and Clopath (2014), our network exhibits two regimes (Figure 2.1D): an asynchronous irregular (AI) regime and a synchronous regular regime (SR). The AI regime occurs for networks with weak external drive and weak gap junctions. In this regime the network is in the fluctuation driven regime so that the neurons spike due to variations in their input. The SR regime occurs for strong external drive and strong gap junctions. This regime leads to the emergence of gamma oscillations. Mathematically, the network undergoes a Hopf bifurcation (Ostojic et al. (2009); Tchumatchenko and Clopath (2014)). The oscillations arise as the network directly inherits the resonance properties of the individual neurons. This is mediated through the gap junction coupling, which effectively allows positive coupling through their spikelets. Moreover, the gap junctions reduce sub-threshold voltage differences between neurons, which promotes synchrony. The excitatory neurons are not necessary for the oscillations but they amplify the dynamics (see Tchumatchenko and Clopath (2014) for mathematical derivations). When placed in the SR regime, the network oscillates in the gamma-range at a frequency near the single neuron resonance frequency (Figures 2.1E-F). In addition, we observe that the spiking activity is characteristic to the network regime, with bursting activity in the synchronous regime and spikes in the asynchronous regime (Figures 2.1G-I).

To summarise, increased gap junction coupling and input drive into the network promotes gamma oscillations. To explain the relationship between network activity and gap junction plasticity, we first model the simplest case of plasticity between a pair of electrically coupled neurons. We then apply the plasticity rule to a population of neurons and investigate the effects on the network dynamics.

**Model of gap junction plasticity: bursting induces gLTD, spiking gLTP.**

To determine how gap junction plasticity can alter network dynamics, we developed a model of the plasticity based on experimental observations. Haas et al. (2011b) have shown that bursts in one or both neurons in an electrically coupled pair lead to long-term depression (gLTD). Therefore, we modelled gLTD as a decrease in the gap junction strength that is proportional to the amount of bursting. The constant of proportionality, $\alpha_{gLTD}$ serves as the learning rate. To infer $\alpha_{gLTD}$, we reproduced the bursting protocol in Haas et al., where
a neuron bursting for a few milliseconds, 600 times for 5 minutes, leads to 13% decrease (Figure 2.2A).

Activity-dependent gap junction long-term potentiation (gLTP) has not been reported experimentally yet in the mammalian brain. There is evidence for activity dependent short-term potentiation in vertebrates Pereda and Faber (1996); Cachope and Pereda (2012). However, without potentiation, all gap junctions would likely become zero with time. To address this concern, we hypothesise that gap junctions can undergo gLTP and we modelled it such that single spikes induce gLTP by a constant amount given by the potentiation learning rate $\alpha_{gLTP}$ (Figure 2.2B, first half). Furthermore, we considered activity-independent gLTP rules in the supplementary materials (Figure 2.6).

**Gap junction plasticity regulates network-wide oscillations.**

Our plasticity model therefore potentiates gap junctions under spiking activity and depresses under bursting activity. Therefore, we wondered how gap junction plasticity can alter network dynamics. We previously quantified the amount of spiking versus bursting in our network for different levels of fixed gap junction strength and mean drive. For low levels of both, the network is spiking whereas for high levels of both the network is bursting. The spiking to bursting transition (Figure 2.1G) corresponds to the bifurcation (Figure 2.1D) from asynchronous irregular to synchronous oscillations at gamma frequency. When inhibitory neurons are oscillating, they fire a burst of spikes at the peak of the oscillations (Figure 2.1I, $\gamma = 5$). Therefore, when gap junctions are plastic, the network steady state can be found on the side of the bifurcation that balances the amount of potentiation due to spiking activity with the amount of depression due to bursting activity. The depression learning rate is inferred from Haas et al., while the potentiation learning rate is left as a free parameter.

We found that a strong relationship exists between gap junction plasticity and network synchrony. When the network is in the AI regime, characterised by low prevalence of bursting activity, gap junction potentiation dominates. However, for a strong mean coupling strength, the emergence of oscillations is associated by high bursting activity, which leads to depression of the gap junctions. Therefore gap junction plasticity in our network maintains a tight balance between asynchronous and synchronous activity. Depending on the value of $\alpha_{gLTP}$, the position of the plasticity fixed point lies either in the asynchronous regime (low $\alpha_{gLTP}$, Figure 2.2C) or in the synchronous regime (high $\alpha_{gLTP}$). For high values of $\alpha_{gLTP}$, potentiation is fast while for low values, the potentiation is slow.
Gap junction plasticity allows for sparse but salient information transfer.

We wondered how gap junction plasticity would interact with time-varying inputs. For the following experiment we consider slow gLTP. First, we let the network reach its steady state with a low level of drive (Figure 2.2E, beginning). As previously observed, the mean gap junction strength reaches a value that sets the network near the AI/SR transition. Then, we proceeded by injecting an additional constant current to the network. This new current baseline induces network level oscillations (Figure 2.2E, transition). However, over time the mean gap junction strength decays due to the gap junction plasticity mechanism. This gap junction depression is followed by a loss of synchrony and the network reaches its new steady state (Figure 2.2E, end), again near the border of asynchronous and synchronous regimes.

We measured the response of read-out neurons that receive projections from the excitatory and inhibitory neurons in our network (Figure 2.2D). At the onset of the current step, the network undergoes transient oscillations. When the gap junctions are plastic, the downstream neurons increase their spiking activity only for a few hundred milliseconds during the transient oscillations and then became almost quiescent again (Figure 2.2F, second panel). This contrasts with the simulation of a static network where the downstream keep a high firing rate (Figure 2.2F, third panel).

These results suggest that synchronous activity is a powerful signal to provoke spiking in downstream neurons. But oscillations and high firing rates of downstream neurons are also metabolically costly (Kann (2011)). With transient oscillations however, the downstream neurons only sparsely fire when the stimulus changes but not when it is predictable. Thus, the regulation of oscillations mediated by gap junction plasticity allows for sparse but salient information transfer.

Gap junction plasticity enhances the ability of sub-populations of neurons to synchronise.

We now sought to study what could be the functional implications of fast gLTP. As stated before, this synchronises the network into gamma oscillations (Figure 2.11). Synchronisation between networks is considered to be one possible mechanism of information transfer (Salinas and Sejnowski (2001); Tiesinga et al. (2001); Fries (2005, 2015)). We wondered whether gap junction coupling could mediate cross-network synchronisation, and how gap junction plasticity would regulate this synchronisation. To test this hypothesis, we considered two subnetworks having different oscillation frequencies and coupled by gap junctions (Figure 2.3A). A fast network oscillates at a gamma frequency and therefore is called the gamma-network. Then, a slow-network oscillates at a slower frequency as the membrane time
constant of its inhibitory neurons is chosen to have a larger value. Indeed, previous analyses show that the network frequency in our model is inherited from the single neuron resonance frequency of inhibitory neurons (Tchumatchenko and Clopath (2014); Chen et al. (2016)). As a result, increasing the membrane time constant of the inhibitory neurons results in a decrease of the network oscillation frequency (Figure 2.3B-D). Cross-network gap junctions reduces the frequency difference between the gamma- and slow-network (Figures 2.3E and 2.3I) and larger differences of subnetwork resonant frequencies require a larger number of cross-network gap junctions for the networks to oscillate in harmony (Figures 2.3F and 2.3G). Their common frequency lies between the resonant frequencies of the decoupled networks. Importantly, cross-network synchronisation requires the subnetworks to be in phase. If the gamma- and slow-network do not share enough gap junctions, there is no correlation in their population activities (Figure 2.3H), despite having a common oscillation frequency in some cases ([Δf_{res} = 0; number of shared GJs = 0] on Figure 2.3I). However, for small differences in the subnetworks resonant frequency Δf_{res}, increasing the number of shared gap junctions induces the oscillations to lock together. The networks oscillate in phase (Figure 2.3H, end of first row) as reflected in their correlation (Figure 2.3I, dark red area). In summary, two networks in the SR regime with different resonance frequencies and/or out-of-phase can synchronise if they are coupled by gap junctions. Furthermore, a large number of shared gap junctions is required for large differences of resonant frequency.

As gap junctions can synchronise two oscillating populations of neurons, we wondered whether the same synchronisation would occur with one population in the AI regime. First, we initialised the gamma-network in the AI regime while the slow-network was initialised in the SR regime (Figure 2.4A). After coupling the gamma- and slow-network together, we found that, while the oscillation frequency of the gamma- and slow-network matched (Figure 2.4B), the two networks could not synchronise. The networks were always out-of-phase with very weak correlation between the population activities (Figure 2.4C, 4D). The results were similar if the gamma- and the slow-network were initialised in the reverse synchronous and asynchronous parameter regimes, respectively (not shown). Cross-network synchronisation is not robust when one network is not oscillatory.

Given these constraints on cross-network synchronisation, we wondered if gap junction plasticity could remedy the situation and allow for robust cross-network synchronisation. To test this hypothesis, we repeated the simulation protocols with the gamma- and slow-network initialised in the asynchronous and synchronous regimes (respectively) and with plastic gap junctions. Here we considered the case where the gLTP rates were slow. As shown previously, gap junction plasticity regulates oscillations such that the network in the asynchronous irregular regime transitions to the oscillatory regime (Figure 2.4E). The
oscillation frequencies of these two networks match (Figure 2.4F). Strikingly, even with a large resonant frequency difference, the gamma- and slow-network now synchronise with through a small number of shared gap junctions (4G, 4H). This indicates that gap junction plasticity allows for cross-network synchronisation that is robust to the underlying neuronal parameters for small numbers of shared gap junctions.

**Gap junction plasticity allows for robust information transfer.**

We hypothesised that cross-network synchronisation mediated by plasticity allows information transfer. To investigate this, we considered a similar network architecture as previously studied, with two networks, an input-network and an output-network. The input-network receives an input projected by random weights to its neurons. The output-network is connected to the input-network with a small number of gap junctions and inhibitory chemical synapses.

First, to demonstrate the information transfer capability of the network, we consider static gap junctions with oscillatory inputs to the input-network. The stimulus information is transmitted to the output-network via the frequency modulation of the synchronised oscillations and not by spike transmission nor amplitude modulation (Figures 2.5A-D). When sharing gap junctions, the input- and output-network synchronise together (Figure 2.5A) and their spiking activity is locked (Figure 2.5B). As the amplitude of the input signal increases, the spiking activity increases in the input-network but not in the output-network (Figure 2.5C). For a network in the SR, there is a positive correlation between the signal amplitude and the network oscillation frequency (Figures 2.1E and 2.5D). This frequency modulation is transferred from the input- to the output-network. Thus, the input amplitude can be estimated from the oscillation frequency of the output-network, despite the absence of chemical synapses between the input-network and the output-network (Figure 2.5E). However, this synchrony code is only possible for signals below a certain frequency (Figures 2.5F-G). Indeed, the instantaneous oscillation frequency is estimated by measuring the period between consecutive peaks of the population activity. For example, oscillations at 50 Hz have a period of 20 ms. Variations happening within those 20 ms are compressed to a single period value and thus are not transferred via frequency modulation. Mechanisms for estimating the input value from the oscillation frequency of the output-network are discussed further in the methods section. Finally, we tested if this synchrony code was valid for non-oscillatory signals (Figure 2.5H). We found that non-oscillatory, slowly varying random signals could also be robustly transmitted from the input- to the output-network with gap junction coupling (Figure 2.5I).
As gap junction plasticity can regulate oscillations, we tested whether the plasticity can make this synchrony code robust to parameter variations or potential gap junction loss. First, as previously shown, gap junction plasticity enhances the ability of networks to synchronise. If initialised in the AI regime and with static gap junctions, there is no information transfer via frequency modulation (Figure 2.5J, left panel). However, with plasticity and fast gLTP, the oscillations are regulated and the network synchrony is recovered which results in successful information transfer (Figure 2.5J left panel). A critical amount of oscillation power and a critical number of shared gap junctions are required for information transfer, after which increasing each of them does not yield significant improvement (Figure 2.5J). Furthermore, we studied whether gap junction plasticity could restore information transfer if gap junctions were deleted. While there is loss in the quality of the transfer when static gap junction are removed, plastic gap junctions maintain the quality of the transfer by increasing the strength of the remaining gap junctions. This mechanism compensates for the missing gap junctions (Figures 2.5J-K).

To summarise, gap junction plasticity expands the necessary conditions for information transfer. It regulates oscillations, and by promoting phase-locking of oscillations, it contributes to the propagation of information to downstream networks. Finally, if some gap junctions are failing, due to protein turnover perhaps, the remaining ones can increase their strength through plasticity. This helps to maintain accurate information transfer.

Discussion

Our modelling study tested whether gap junction plasticity can regulate gamma oscillations in cortical network models. Our findings suggest that gap junction plasticity can maintain a balance between synchronous regular and asynchronous irregular regimes. For strong electrical coupling, the network is in the oscillatory regime. The oscillations consist of synchronised bursting mediated by the inhibitory neuron network. These bursts trigger depression of the gap junctions (Haas et al. (2011b)) allowing the network to leave the oscillatory regime and spike asynchronously. However, the irregular asynchronous regime is dominated by sparse firing. Either this sparse firing, or constant protein connexin turnover may be a source of gap junction potentiation (Wang et al. (2015b); Sevetson et al. (2017); Beardslee et al. (1998); Gaietta et al. (2002); Boassa et al. (2010); Carette et al. (2015); Wang et al. (2015a)). Thus, the asynchronous irregular regime tends to potentiate gap junctions. Therefore, the network behaviour critically depends on the plasticity learning rate. Fast gLTP leads to synchronous activity while slow gLTP leads to asynchronous states. We demonstrate the functional role of plasticity in both cases. In the AI regime, the network can respond to changes in input drives through transient oscillations. Those
transient oscillations could serve as an energetically efficient way to transfer information to a downstream neuron. In the SR regime, the network oscillations can serve as the substrate for information routing between networks. These results demonstrate how gap junction plasticity can regulate oscillations to mediate information transfer between cortical populations of neurons.

**Gap junction coupling between interneurons affects network synchrony.** Despite being less common than chemical synapses, gap junctions are ubiquitous in the central nervous system. Example includes the inferior olivary nucleus (Sotelo et al. (1974); Llinas et al. (1974); Benardo and Foster (1986)), the thalamic reticular nucleus (Landisman et al. (2002); Long et al. (2004)), the hippocampus (Jefferys (1995); Hormuzdi et al. (2001)), the retina (Vaney and Taylor (2002); Jin and Ribelayga (2016)), the olfactory bulb (Zhang and Sulzer (2003)), the locus coeruleus (Christie et al. (1989)), or also the neocortex (Sloper (1972); Sloper and Powell (1978)). Moreover, they drastically alter the firing activity of their connecting neurons (Haas (2015); van Welie et al. (2016)), as well as the network dynamics (Traub et al. (2001); Pfeuty et al. (2003); Kopell and Ermentrout (2004); Connors and Long (2004); Tchumatchenko and Clopath (2014)). Furthermore, gap junctions between inhibitory interneurons are reported in many cortical regions where global oscillations of neural activity are observed (Galarreta and Hestrin (1999); Deans et al. (2001); Pfeuty et al. (2003); Gibson et al. (2005)). These inhibitory neurons exhibit sub-threshold resonance that amplifies a specific frequency range (Cardin et al. (2009)). Therefore, gap junction induced synchrony and inhibitory neurons frequency preference are a possible substrate for global oscillations in these cortical regions. Our work is consistent with results of Tchumatchenko and Clopath (2014); Chen et al. (2016) showing that together gap junction strength and sub-threshold resonance of inhibitory neuron promote oscillations of neuronal activity.

**Previous models of gap junction plasticity.** There has been a recent interest in modelling gap junction plasticity. Snipas et al. (2017) developed of model of gap junction coupling that would exhibit short-term plasticity. By combining a 36-state model of gap junction channel gating with Hodgkin-Huxley equations (Hodgkin and Huxley (1990)), they show that gap junction channel gating, induced by bursting activity, could lead to short term depression. In future work, it would be interesting to combine this model of gap junction short-term plasticity with our model. Chakravartula et al. (2017) introduced a new type of adaptive diffusive coupling in a network of Hindmarsh-Rose neurons (Hindmarsh and Rose (1982, 1984)). They assumed that connections between pairs of neurons would follow a Hebb’s law (Hebb (1949a)), where neurons with simultaneous activity would strengthen their connection, while others with dissimilar activity would weaken their coupling. They observe the emergence of locally synchronised groups of neurons, whose synchronisation could be
transient or permanent. Their results are consistent with ours showing synchronisation of subnetworks coupled with gap junctions.

**Model of gap junction plasticity: bursts induce gLTD, spikes induce gLTP.** Recently, Haas et al. (2011b) reported the first experimental evidence of activity-dependent gLTD of gap junctions of interneurons in the thalamic reticular nucleus, even though the mechanism remains to be investigated (Szoboszlay et al. (2016)). Also Sevetson et al. (2017) found that calcium-regulated mechanisms support gap junction gLTD in the thalamic reticular nucleus. The mechanisms are similar to those observed for the plasticity of chemical synapses. We designed a rule for activity-dependent gLTD consistent with those results. We assumed that a cortical fast-spiking interneuron would exhibit the same plasticity properties as a thalamic reticular neuron because gap junctions are mostly made from the connexin Cx36 throughout the central nervous system (Landisman et al. (2002); Rouach et al. (2002)). To our knowledge, there is no study yet on activity-dependent gLTP of gap junctions. However recent studies (Wang et al. (2015b); Sevetson et al. (2017)) suggest that gLTD and gLTP share a common pathway. Therefore, we propose a rule for activity dependent gLTP, assuming that low frequency spiking activity leads to gap junction potentiation. However, our results do not depend on the exact formulation of gLTP. As we have shown, an activity-independent rule yields similar behaviour (supplementary material, Figure 2.6). Moreover, we did not observe significant changes by modelling asymmetrical gap junctions (supplementary material, Figures 2.7 and 2.8). In particular, we observed that gap junctions tend to become symmetrical after learning (Figure 2.8E). Experimentally, high frequency stimulation of just one of the coupled pair of neurons lead to asymmetrical results, which could indicate that the asymmetrical model is more relevant (Figure 5 of Haas et al. (2011b) - where the inbound and outbound coupling coefficients varies differently). We observed that the steady-states, for each rule, falls on similar lines, parallel to the bifurcation between the asynchronous irregular and the synchronous regular regime. The position of those lines depends on the speed of the gLTP and on the plasticity rule. In our simulations, there is a factor 10 of difference between the ratios of potentation and depression learning rates, between the spiking gLTP rule and the passive gLTP rule (see Table 2). Maybe new experimental evidence on the biological values of this ratio could help predict if one of those rules is more relevant than the other.

In our model, chemical synapses are static. If they were plastic, we could imagine that, uncorrelated spiking during the asynchronous irregular regime would lead to long-term depression of the chemical synapses, while on the contrary, correlated bursting during the synchronous regime would lead to long-term potentiation (Markram et al. (1997); Bi and Poo (1998); Sjöström et al. (2001); Clopath et al. (2010)). However, our model seems to
exhibit similar behavior for a large range of parameters and we could expect that the findings from this study would hold in the presence of plastic chemical synapses (Figures 2.9 and 2.10).

**Gap junction plasticity regulates oscillations and propagates transient information.** Our model demonstrates that the regulation of oscillations is mediated by gap junction plasticity. Fast potentiation leads to bursting activity while slow potentiation leads to asynchronous irregular activity. Our first hypothesis assumed that the potentiation is slow and the network is in the AI regime. Thus, at the steady-state, gamma power is weak or non-existent. Evidence from (Tallon-Baudry and Bertrand (1999); Ray and Maunsell (2015)) is consistent with our results. When no stimulus is provided or task required, electroencephalogram recordings show that power in the gamma-band is weak. After the onset of a sensory stimulus, gamma oscillations can be detected in cortical areas. This has been reported for example with visual stimuli triggering gamma oscillations in the mouse visual cortex (Saleem et al. (2017)). In our model, the neurons oscillate transiently when receiving a constant external stimulation. This mechanism operates by crossing the bifurcation boundary between the AI and SR regime. However, over time the mean gap junction strength decays due to the additional bursting activity. The gap junction depression leads to a loss of synchrony and the network returns to the AI regime. Therefore we predict a loss in gamma power for sustained stimulus. A similar mechanism may be involved in the reduction of gamma oscillation induced by slow smooth movements (Kruse and Eckhorn (1996); Tallon-Baudry et al. (1999)).

We wondered what could be the functional role of this transient oscillatory regime. Projecting the excitatory activity of our network model to downstream neurons revealed that they fire sparsely, for a short duration after stimulus onset, and are quiescent otherwise. Thus, gap junction plasticity could efficiently encode the change in incoming stimuli. This could allow for energy conservation, as oscillations are energetically expensive (Kann (2011)). Moreover, Palmigiano et al. (2017) show that cortical circuits near the onset of oscillations could promote flexible information routing by transient synchrony.

**Plastic gap junction coupling for robust information routing.** The role of gamma oscillations is highly debated (Ray and Maunsell (2015)). They could play no role and simply be a marker of the excitation-inhibition interaction. However others studies suggest they could be involved in information transfer. It is thought that retinal oscillations carry information to the visual cortex (Koepsell et al. (2009)). Moreover they could serve as inter-area communication by promoting coherence in neural assemblies, which would align their windows of excitation. This would allow for effective spike transmission (Ray and Maunsell (2015); Fries (2005); Bosman et al. (2012)). Furthermore, Roberts et al.
observed high gamma coherence between layers 1 and 2 of macaque’s visual cortex by dynamic frequency matching. Here, we demonstrate one potential mechanism for information transmission through gamma oscillations. Our networks make use of gamma frequency modulation to transmit information in a robust manner, similar to the principle used for FM radio broadcasting. The amplitude of the input signal modulates the oscillation frequency, which increases almost linearly with the amplitude. Our model demonstrates that gap junction plasticity robustly mediates network oscillations and cross-network synchronisation. If some gap junctions are removed, the remaining gap junctions become stronger and compensate for the missing ones. Thus, gap junction plasticity insures the phase-locking of the coupled network and it allows for information routing. In particular, there is evidence suggesting that gap junctions could promote long-distance signaling by implementing frequency modulation of calcium waves in astrocytes (Goldberg et al. (2010)). Moreover, correlation was found during gamma activity between amplitude and frequency modulation of local field potential of CA3 pyramidal neurons of anesthetised rats (Atallah and Scanziani (2009)). In addition, our network models could also represent the subnetworks of the TRN, with each connected to a separate excitatory neuron of thalamus (Lee et al. (2014)). However, TRN inhibitory neurons exhibit longer bursts than those of cortical fast-spiking neurons, due to long lasting T-current (about 50ms) and further work is necessary to make predictions on this brain region behaviour (Huguenard and Prince (1992)).

Failure to regulate oscillations could be the origin of several cognitive pathologies. Disruption of brain synchrony in the inferior olive is thought to contribute to autism due to the loss of coherence in brain rhythms (Welsh et al. (2005)). Excess of high frequency network wide oscillations in the cortex have been observed to also correlate with autism in young boys (Orekhova et al. (2007)). The inferior olive differs for its density of gap junction being the highest in the adult brain (Llinas et al. (1974); Sotelo et al. (1974)). It may be involved in the generation of tremors in Parkinson’s disease, however the severity of induced tremors in Cx36 knockout mice remained the same as in wild-type mice (Nakase and Naus (2004); Long et al. (2002)). This could be due to gap junctions made from other connexins (such as Cx43) taking over for the knocked-out ones.

Recent studies highlight the critical role of gap junctions and their plasticity in efficient cognitive processing (Liu et al. (2016)). As experimental and computational techniques improve, new efforts can further unveil their properties and expand our understanding of cortical functions. Our computational model shows that gap junction activity-dependent plasticity may play an important role in network-wide synchrony regulation.
Methods

We consider a network with $N_I$ inhibitory neurons (20%) and $N_E$ excitatory neurons (80%) with all-to-all connectivity (Figure 2.2A). Inhibitory neurons are modelled by an Izhikevich model and excitatory neurons by a leaky integrated-and-fire model (LIF) (Izhikevich (2003, 2007)). The simulation time-step is $dt = 0.1$ ms. Inhibitory neurons are connected by both electrical and chemical synapses, whereas excitatory neurons have only chemical synapses. We designed a novel plasticity model for activity dependent plasticity of gap junctions and we investigated its impact on network dynamics and function. We then investigated the dynamics of two networks coupled by chemical and electrical synapses. We use a decoder to quantify the effects of gap junction plasticity on information transfer. The model is written in Python and takes advantage of the tensorflow library that leverages GPU parallel processing capabilities (Abadi et al. (2016)). It is available on github (https://github.com/gpernelle/gap-junction-plasticity-cortex).

Neuron model.

We model Fast Spiking (FS) interneurons with Izhikevich type neuron models (Izhikevich (2007)). This model offers the advantage to reproduce different firing patterns as well as a low computational cost (Izhikevich (2004)). The voltage $v$ follows

$$\tau_v \dot{v} = (v - v_{ra})(v - v_{rb}) - k_u u + RI, \quad (1)$$

$$\tau_u \dot{u} = a(v - v_{rc}) - u, \quad (2)$$

combined with the spiking conditions,

$$\text{if } v \geq v_{threshFS}, \text{ then } \begin{cases} v \leftarrow v_{resetFS} \\ u \leftarrow u + b. \end{cases} \quad (3)$$

where $\tau_v$ is the membrane time constant, $v_{ra}$ is the membrane resting potential, $v_{rb}$ is the membrane threshold potential, $k_u$ is the coupling parameter to the adaptation variable $u$, $R$ is the resistance and $I$ is the current. The adaptation variable $u$ represents a membrane recovery variable, accounting for the activation of K$^+$ ionic currents and inactivation of Na$^+$ ionic currents. It increases by a discrete amount $b$ every time the neuron is spiking and its membrane potential crosses the threshold $v_{threshFS}$. It provides a negative feedback to the voltage $v$. The recovery time constant is $\tau_u$, $a$ is a coupling parameter, $v_{resetFS}$, $b$ and $v_{rc}$ are voltage constants.
For the FS neurons, we chose the membrane potential reset $v_{\text{resetFS}}$ and the spike-triggered adaptation variable $b$ to account for the onset bursting activity observed in vivo. Modifying $k_u$, $v_{ra}$, $v_{rb}$ and $v_{rc}$ was sufficient to observe the emergence of a resonance frequency. We set the time constant $\tau_u$ to obtain a resonance frequency of 45 Hz, which is in the same range as observed in vivo by Cardin et al. (2009) (Figure 2.2B). To measure the sub-threshold resonant property (Figures 2.1B, 2.3B and 2.3D), we recorded the amplitude of the neuronal membrane potential $V_E$ in response to different oscillation frequencies $f$ of low level sinusoidal currents $I(t) = I_0 \cos(2\pi ft)$ (with $I_0 = 0.01 \text{ pA}$). We then normalised the amplitude response as follow

$$R_E(f) = \frac{||V_E(I_0 \cos(2\pi ft))||}{\max_f(||V_E(I_0 \cos(2\pi ft))||)},$$

for frequencies between 0 and 1 kHz. The $|| ||$ denotes the maximum absolute value observed over time.

To model regular spiking excitatory neurons, we chose a leaky integrate-and-fire model,

$$\tau_m \dot{v} = -v + R_m I,$$

where $\tau_m$ is the membrane time constant, $v$ the membrane potential, $I$ the current and $R_m$ the resistance. Spikes are characterised by a firing time $t_f$ which corresponds to the time when $v$ reaches the threshold $v_{\text{threshRS}}$. Immediately after a spike, the potential is reset to the reset potential $v_{\text{resetRS}}$.

**Network.**

In the single network model (Figures 2.1 and 2.2), each neuron is connected to all others by chemical synapses, but in addition, inhibitory neurons are connected via electrical synapses to all other inhibitory neurons, as in Tchumatchenko and Clopath (2014). Thus, the current each individual neuron $i$ receives can be decomposed in four components

$$I_i(t) = I_{i,\text{spike}}(t) + I_{i,\text{gap}}(t) + I_{i,\text{noise}}(t) + I_{i,\text{ext}}(t),$$

where $I_{i,\text{spike}} = I_{i,\text{chem}} + I_{i,\text{elec}}$ is the current coming from the transmission of a spike via electrical (i.e. spikelet) and chemical synapses, $I_{i,\text{gap}}$ is the sub-threshold current from electrical synapses (for inhibitory neurons only), $I_{i,\text{noise}}$ is the noisy background current and $I_{i,\text{ext}}$ characterises the external current. The current due to spiking $I_{i,\text{spike}}$ on excitatory
neurons is given by

\[ I_{i}^{\text{spike}}(t) = W^{IE} \sum_{j=1}^{N_I} \sum_{j \neq i} \exp \left( -\frac{t - t_{jk}}{\tau_I} \right) + W^{EE} \sum_{j=1}^{N_E} \sum_{j \neq i} \exp \left( -\frac{t - t_{jk}}{\tau_E} \right). \] (7)

The current \( I_{i}^{\text{spike}} \) into inhibitory neurons are

\[ I_{i}^{\text{spike}}(t) = \sum_{j=1}^{N_I} \sum_{j \neq i} W_{ij}^{II} \exp \left( -\frac{t - t_{jk}}{\tau_I} \right) + W^{EI} \sum_{j=1}^{N_E} \sum_{j \neq i} \exp \left( -\frac{t - t_{jk}}{\tau_E} \right), \] (8)

where \( W^{\alpha\beta} \) is the coupling strength from population \( \alpha \) to population \( \beta \) with \( \{\alpha, \beta\} = \{E, I\} \).

Finally, \( W_{ij}^{II} = W_{ij}^{II,c} + W_{ij}^{II,e} \) is the inhibitory to inhibitory coupling between neuron \( i \) and \( j \), consisting of the chemical synaptic strength \( W_{ij}^{II,c} \) and \( W_{ij}^{II,e} \) the electrical coupling for supra-threshold current, also called the spikelet. There is no experimental data yet on the change of the spikelet as function of the strength of the gap junctions. We hypothesize that the contribution of the spikelet is proportional to the gap junction coupling \( W_{ij}^{II,e} = k_{\text{spikelet}} \gamma_{ij} \), where \( \gamma_{ij} \) is the gap junction coupling between neurons \( i \) and \( j \). This spikelet term is necessary due to the fact that our neuron model does not explicitly have a spike kernel in the voltage dynamics (Tchumatchenko and Clopath (2014)). Note that \( W^{EE}, W^{EI}, W^{IE}, W^{II,c} \) are identical among neurons, but \( W_{ij}^{II,e} \) varies as the spikelet contribution depends on the coupling strengths \( \gamma_{ij} \), which can be plastic. We also modeled the network with chemical weights following a log-normal distribution, which yielded similar results (data not shown).

We represent the post-synaptic potential response to a chemical or electrical spike with an exponential of the form \( \exp \left( -\frac{t - t_{jk}}{\tau_{\alpha}} \right) \) for \( t > t_{jk} \). The excitatory and inhibitory synaptic time constants are \( \tau_E \) and \( \tau_I \) respectively and \( t_{jk} \) represents the \( k \)th firing time of neuron \( j \).

In between spikes, for every pair of inhibitory neurons \( i, j \), the gap junction mediated sub-threshold current \( I_{i}^{\text{gap}} \) is characterized by

\[ I_{i}^{\text{gap}}(t) = \sum_{j=1}^{N_I} \sum_{j \neq i} \gamma_{ij} \left( V_j(t) - V_i(t) \right), \] (9)

where \( \gamma_{ij} \) is the gap junction coupling between inhibitory neurons \( i \) and \( j \) of respective membrane potential \( V_i \) and \( V_j \). In our model, we suppose that gap junctions are symmetric with \( \gamma_{ij} = \gamma_{ji} \). Gap junctions are initialised following a log-normal distribution with the location parameter \( \mu_{\text{gap}} = 1 + \ln(\gamma/N_I) \) and the scale parameter \( \sigma_{\text{gap}} = 1 \).
Neurons also receive the current $I_{\text{noise}}$ which is a coloured Gaussian noise with mean $\nu_I$, standard deviation $\sigma_I$ and $\tau_{\text{noise}}$ the time constant of the low-pass filtering

$$\tau_{\text{noise}} \dot{s}(t) = -s(t) + \xi(t)$$

and

$$I_{\text{noise}}(t) = \sqrt{2\tau_{\text{noise}} s(t)}\sigma_I + \nu_I,$$

with $\xi$ is drawn from a Gaussian distribution with unit standard deviation and zero mean.

**Plasticity model of gap junctions.**

Our plasticity model is decomposed into a depression $\gamma^-$ and a potentiation term $\gamma^+$. 

**gLTD: depression of the electrical synapses for high frequency activity.**

*Haas et al. (2011b)* showed that bursting activity of both neurons or one of the two neurons leads to long-term depression (gLTD) of the electrical synapses. To capture this effect in our model, we first defined a variable $b_i$ which is a low-pass filter of the spikes of neuron $i$

$$\tau_b \dot{b}_i(t) = -b_i(t) + \tau_b \sum_{t_{ik} \leq t} \delta(t - t_{ik}),$$

where $\delta$ is the Dirac function and $\tau_b = 8$ ms is the time constant. When $b_i$ reaches a value of $\theta_{\text{burst}} = 1.3$, this indicates that two or more spikes happened within a short time interval. Therefore, the burstiness of neuron $i$ is characterised by $H(b_i(t) - \theta_{\text{burst}})$ where $H$ is the Heaviside function that returns 1 for positive arguments and 0 otherwise.

In our simplified model, we consider that the individual electrical coupling coefficient $\gamma$ between neurons are non-directional. Every time the interneurons burst, the gap junctions undergo depression,

$$\dot{\gamma}_{ij}(t) = \dot{\gamma}_{ji}(t) = -\alpha_{\text{gLTD}}[H(b_i(t) - \theta_{\text{burst}}) + H(b_j(t) - \theta_{\text{burst}})],$$

where $\alpha_{\text{gLTD}}$ is the depression learning rate.

We fit $\alpha_{\text{gLTD}}$ to the data by implementing the stimulation protocol used in *Haas et al. (2011b)*. We applied a constant current injection of 300 pA for 50 ms every 0.5 s (2 Hz) and of -80 pA the rest of the time, to maintain the membrane potential at -70 mV. This protocol lasts for 5 minutes. We estimate $\alpha_{\text{gLTD}} = 15.69 \text{ nS} \cdot \text{ms}^{-1}$ by such that it leads to a depression of 13% of the gap junction strength at the end of the stimulation protocol, as reported by Haas et al.
**gLTP:** potentiation of the electrical synapses for low frequency activity.

If gap junctions were only depressed, they would decay to zero after some time. Therefore, there is a need for gap junction potentiation. However, no activity dependent mechanisms was reported yet in the experimental literature, but Cachope and Pereda (2012); Wang et al. (2015b); Sevetson et al. (2017); Debanne and Russier (2017) suggest that the calcium-regulated mechanisms leading to long-term depression could be involved in potentiation as well.

We consider two gLTP rules. The first has a soft bound, i.e. the magnitude of modification is proportional to the difference between the gap junction value and a baseline coupling strength $\gamma_b$

$$\hat{\gamma}_{ij}^+(t) = \hat{\gamma}_{ji}^+(t) = \alpha_{gLTP} \left( \frac{\gamma_b - \gamma_{ij}(t)}{\gamma_b} \right) \left[ sp_i(t) + sp_j(t) \right].$$

(14)

where $\alpha_{gLTP}$ is the potentiation learning rate and $sp_i(t) = \sum_{t_{ik} \leq t} \delta(t - t_{ik})$.

The second gLTP rule we consider has no maximum bounds

$$\hat{\gamma}_{ij}^+(t) = \hat{\gamma}_{ji}^+(t) = \alpha_{gLTP} [sp_i(t) + sp_j(t)].$$

(15)

Moreover, to show that our results do not depend on the specific gLTP rule, we also consider a different gLTP rule where the update is passive and therefore does not depend on neural activity. This alternative rule yields similar results (supplementary material, Figure 2.6).

**Coupling coefficient.**

The coupling coefficient is the ratio of voltage deflections when a step current was injected to one neuron of a coupled pair, which were maintained at a baseline voltage of -69 mV. During current injection, the injected neuron is hyperpolarized at -75 mV

$$cc_{12} = \frac{\Delta V_2}{\Delta V_1},$$

(16)

when 1 is the index of the injected neuron. The gap junction conductance used for measuring the coupling coefficient was obtained from the mean value of the gap junction coupling at steady-state. The coupling coefficient is about 5% for a network of 200 inhibitory neurons. Please note that the gap junction conductance and the coupling coefficient scale inversely to the network size in our model. We chose to use the mean value, as there is very little variance (4 orders of magnitude lower that the mean value) in the gap junction coupling strength at
steady state. For reference, the coupling coefficient was measured around 12% ± 8% averaged for 313 pairs in the TRN (Haas et al. (2011b)). Moreover, for adult rats, for 91 paired recordings of adjacent IO neurons, the coupling coefficient varies from 1% to 8% (Hoge et al. (2011)), and for 14 pairs of fast-spiking cortical neurons, the coupling coefficient was around 1.5% (Galarreta and Hestrin (2002)).

Quantification of network spiking activity.

To estimate the plasticity direction for different values of external input \( \nu \) and gap junction strength \( \gamma \), we observe the activity of the network (without plasticity) in a steady state over a duration \( T = 6 \) s. For a chosen tuple \((\nu; \gamma)\), we average over time and over neurons the bursting and spiking activity

\[
A_{\text{bursting}} = \frac{1}{T} \int_0^T \frac{1}{N_I} \sum_{i=1}^{N_I} [H(b_i(t) - \theta_{\text{burst}})] dt
\]

and

\[
A_{\text{spiking}} = \frac{1}{T} \int_0^T \frac{1}{N_I} \sum_{i=1}^{N_I} s_{p_i}(t) dt.
\]

Then, we explore the values of the ratio of bursting over spiking activity

\[
\text{ratio} = \frac{A_{\text{bursting}}}{A_{\text{spiking}}}
\]

as function of the coupling coefficient \( \gamma \) and of the mean external input \( \nu \) over the parameter space \( P_1 = [0; \gamma_{\text{max}}] \times [0; \nu_{\text{max}}] \).

Quantification of oscillation power and frequency.

To quantify the frequency and the power of the oscillations in the neuronal activity, we perform a Fourier analysis of the population activity \( r \) which we define as the sum of neuron spikes within a population, during the time step \( dt \)

\[
r(t) = \frac{1}{dt} \frac{1}{N_I} \int_t^{t+dt} \sum_{i=1}^{N_I} \sum_{i_k \leq t} \delta(u - t_{ik}) du.
\]

We compute a Discrete Time Fourier Transform (DFT) and extract the power and the frequency of the most represented frequency in the Fourier domain. The formula defining
the DFT is
\[ \hat{r}_k = \sum_{n=0}^{N-1} r_n \exp \left( -i2\pi k \frac{n}{N} \right) \quad k = 0, \ldots, N - 1. \] (21)
where the \( r_n \) sequence represents \( N \) uniformly spaced time-samples of the population activities. We measure the amplitude of the Fourier components \( \hat{r}_k \) for \( k = 1..N/2 \) (because the Fourier signal is symmetric from \( N/2 \) to \( N \)). We identify the maximal one, its associated frequency \( f_{\text{max}} = \frac{k}{N} \) and its power \( P = (|\hat{r}_k|/N)^2 \).

**Downstream read-out neurons.**

To simulate the projection of a cortical layer onto another layer, we model downstream read-out neurons with the same regular spiking neuron model as the first cortical layer. The input \( I_j \) received by each downstream neuron is the projected activity of all excitatory and inhibitory neurons of the first cortical layer, multiplied by the coefficients \( W^{\text{ERON}} \) and \( W^{\text{IRON}} \) respectively:

\[ I_j(t) = W^{\text{ERON}} \sum_{i=1}^{N_E} \sum_{t_{ik} \leq t} \exp \left( -\frac{t - t_{ik}}{\tau_E} \right) + W^{\text{IRON}} \sum_{i=1}^{N_I} \sum_{t_{ik} \leq t} \exp \left( -\frac{t - t_{ik}}{\tau_E} \right). \] (22)

When delivering the step current \( I_{\text{step}} \) to the network (Figure 2.2D), the time at which the neurons receive \( I_{\text{step}} \) follows a normal distribution centered on the transition time, with variance 10 ms. This variability avoids the confound of transient and unstable synchronisation of the network due to a strong input delivered to all neurons simultaneously.

**Cross-network synchronisation.**

We investigate the role of gap junction coupling and its plasticity in synchronising networks having different oscillation frequency preferences. We design a network consisting of two subnetworks having the same topology as described in *Network*: Each subnetwork has 800 excitatory neurons and 200 inhibitory neurons. There are all-to-all chemical synapses within each subnetwork (their strengths are reported in Table 1). There are no cross-network chemical synapses. The intra-network gap junctions are all-to-all. In addition, we vary the number of sparse cross-network gap junctions from 0 to 50. The gap junction strengths are initialised following a log-normal distribution as described in *Network*. We take \( \gamma = 3 \) which yields AI behaviour in the network and we take \( \gamma = 5.5 \) which yields bursting behaviour in the SR regime.

One of the subnetworks is called the Slow Network (SN) and we change the value of the membrane time constant of its inhibitory neurons \( \tau_{vS} \) from 17 ms to 55 ms. This
decreases the neuron sub-threshold resonance frequency, which also lowers the frequency of the subnetwork oscillation when it is in the synchronous regime. The second subnetwork has its neuron membrane time constant fixed at 17 ms and is called the gamma-network because it oscillates at gamma frequency. The simulations last 10 seconds, which is long enough for the gap junction coupling to reach its steady state when the gap junctions are plastic.

To quantify the similarity between population activities from both subnetworks, we evaluate the Pearson’s correlation coefficient between their population activities $r_{GN}$ and $r_{SN}$ from the gamma- and slow-network respectively. The firing rates, $r_{GN}$ and $r_{SN}$ are defined as in equation (20).

For each subnetwork, we evaluate the frequency and power of their oscillations as described in the section *Quantification of oscillation power and frequency*. When the difference of oscillation frequency between both subnetworks is less than 1 Hz, we measure the cross-correlation of their population activities $r_{GN}$ and $r_{SN}$

$$ (r_{GN} \star r_{SN})(\tau) \overset{\text{def}}{=} \int_{-\infty}^{\infty} r_{GN}(t) r_{SN}(t + \tau) \, dt. $$  \hspace{1cm} (23)

The phase difference is measured as the time delay relative to the oscillation period

$$ \Delta \phi = \arg \max_t \left( (r_{GN} \star r_{SN})(\tau) \right) \frac{T_{\text{period}}}{T_{\text{period}}}, $$  \hspace{1cm} (24)

where $\star$ is the convolution operator and $T_{\text{period}}$ is the oscillation period.

**Information routing.**

We investigate whether gap junction coupling and its plasticity play a role in routing information between networks. We consider the same system as described in the previous section, with two subnetworks coupled with gap junctions, except here all the inhibitory neurons have the same membrane time constant $\tau_v = 17$ ms (e.g. corresponding to resonance frequency at gamma). The first network, called the Input Network (IN) receives an input projected to its $N_{IN}$ neurons ($N_{IN} = 1000$) by $N_{IN}$ weights drawn from a uniform distribution between 0 and 1. The second network is called the Output Network (ON, $N_{ON} = 1000$).

To examine if there is successful transfer of information between both networks, we attempt to reconstruct the input signal from the ON’s population activity $r_{ON}$. First, we
obtain the low-pass filtered population activity of ON, \( r_{fil} \), with

\[
\tau_r \dot r_{fil}(t) = -r_{fil}(t) + r_{ON}(t),
\]

(25)

with \( \tau_r = 3 \) ms. Then we detect the rising and falling times of the filtered population activity by detecting when it crosses a threshold \( \theta_r = 2 \). This gives us rising times \( t^*_k \), when it crosses the threshold from below, and falling times, when it crosses the threshold from above. We obtain the peak intervals \( T_k \) by measuring the time difference between consecutive rising times \( T_k = t^*_{k+1} - t^*_k \).

For Figure 2.5D, we plot \( \bar{x}_k \), the mean values of the input signal \( x \) between the rising times \( t^*_k \) and \( t^*_{k+1} \) as function of their corresponding peak intervals \( T_k \)

\[
\bar{x}_k(t) = \frac{1}{T_k} \int_{t^*_k}^{t^*_{k+1}} x(t)dt.
\]

(26)

We reconstruct the network input (Figure 2.5 E,H) by doing a linear interpolation of the inverse of those peak intervals \( T_k \), so that the input signal and reconstructed input have the same length.

\[
\hat{x}(t) = \left( \frac{1/T_{k+1} - 1/T_k}{t^*_{k+1} - t^*_k} \right) (t - t^*_k) + \frac{1}{T_k}, \forall t \in [t^*_k; t^*_{k+1}].
\]

(27)

Finally to estimate the quality of the reconstruction, we measure the Pearson’s correlation coefficient (which is invariant by affine transformation) between the input and the reconstructed input.

In order to test the robustness of the system we measure the quality of the reconstruction for an oscillatory input signal of which we vary the frequency \( f \) (Figure 2.5F) and amplitude \( A \) (Figure 2.5G).

\[
x(t) = A[\cos(2\pi ft) + 1]
\]

(28)

Then we measure the routing of random signals \( x(t) = \nu_{IN} + \sigma_{IN} \cdot \eta_{IN}(t) \), where \( \nu_{IN} \) is the signal mean, \( \sigma_{IN} \) is the signal standard deviation, \( \eta_{IN} \) is an Ornstein Uhlenbeck fluctuation with correlation time \( \tau_x = 100 \) ms and unit variance. We build a dataset of 10 input signals and then we measure the Pearson’s correlation coefficients between the input \( x(t) \) and the reconstructed input \( \hat{x}(t) \) for those 10 inputs respectively. For Figure 2.5I, we scale the log-normal distribution of the gap junction strength (see Network) with \( \gamma = 3 \) to set the network in the asynchronous, with \( \gamma = 5.5 \) to set the gap junction near their plasticity fix point, and \( \gamma = 8 \) for a regime with strong oscillations.

To study the robustness of the information routing to gap junction deletion, we randomly
delete an increasing number of gap junctions and measure the evolution of the Pearson’s correlation between $x$ and $\hat{x}$. We also measure the change in the mean gap junction coupling, if there is plasticity, between the initialisation (with $\gamma = 5.5$) and the steady-state (after 6 s of simulation).

All parameters are listed in Table 1 unless otherwise specified in a figure.
Parameters.

We list in Table 1 the parameters used for our simulations.

**Table 1. Model parameters**

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<th>Cortical Fast Spiking Interneurons</th>
<th>Cortical Regular Spiking Neurons</th>
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<tr>
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<tr>
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<tr>
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<tr>
<td>$\tau_{noise}$</td>
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**Information routing - Figure 2.5**

| $T_{sim}$ | 10 s |
| $\tau_{filt}$ | 3 ms |
| $\tau_x$ | 100 ms |
| $\mu_{IN}$ | 0.5 |
| $\sigma_{IN}$ | 1/200 |
| $\nu_I$ | 200 pA |
| $\theta_r$ | 2 |
| $A$ (Fig. 2.5D) | [0-2000] pA |
| $A$ (Fig. 2.5G) | [0-10000] pA |
| $A$ (Fig. 2.5, all others) | 400 pA |
| $f$ (Fig. 2.5B,C,D,E) | 4 Hz |
Figures.

(A) E-I recurrent network w/ GJs

(B) Subthreshold Resonance

(C) Gap Junction Coupling

(D) Oscillation Power

(E) Oscillation Frequency

(F) Frequency Histogram

(G) Bursting/Spiking Ratio

(H) Raster plots of 100 FS neurons (blue) and 100 pyramidal neurons (red) for two values of the gap junction coupling, where dots represents spiking times and each line represents a neuron (note that the network E/I proportion is actually 80%/20%). Top raster plot shows asynchronous activity for low gap junction coupling and bottom raster plot shows synchronous activity in inhibitory and excitatory neuron populations, for strong gap junction coupling. (I) Membrane voltage traces of individual inhibitory neurons (dark blue) and population average (light blue, down-shifted) for different values of the gap junction coupling. Bursts appear for strong gap junction coupling on the peaks of the membrane voltage oscillations.

Figure 2.1. Network synchrony depends on gap junction strength.

(A) The network consists of excitatory (E) and inhibitory (I) neurons. The neurons are coupled in an all-to-all fashion with chemical synapses. The inhibitory neurons are also connected by gap junctions (jagged green line). (B) Voltage response of one single excitatory (red line) / inhibitory (blue line) neuron to a sub-threshold oscillatory input current (see Methods). Excitatory neurons act as low-pass filters, whereas the inhibitory neurons show a resonance frequency in the gamma range. This resonance is in agreement with the network wide response observed by Cardin et al. 2009, when FS neurons are stimulated in the gamma range (black line, figure redrawn from [32] Figure 3d). (C) Simulation of a pair of electrically coupled neurons N1 and N2, where N1 is voltage-clamped (red) such that it is hyperpolarised (light blue) and the potential of N2 is measured for different value of gap junction strength (γ = 3 and γ = 5). (D) Power of the main frequency component in the Fourier domain of the population activity (PA) of inhibitory neurons. The blue area denotes the lack of oscillations AI whereas the red area SR shows periodic oscillations in the spiking activity of inhibitory neurons. (E) Oscillation frequency of the network activity. The white area represents a region where the network is not oscillating and has no oscillation frequency. (F) Histogram of the oscillation frequency of population spiking activity. The values are contained in the γ range, from 30 to 60 Hz. (G) Ratio of bursting \( A_{\text{bursting}} \) over spiking \( A_{\text{spiking}} \) activity, averaged over 2 seconds. Bursting activity prevails in the light region and sparse firing dominates in the dark region. For the following figures 2.1H and 2.1I, 100 ms of data is represented. (H) Raster plots of 100 FS neurons (blue) and 100 pyramidal neurons (red) for two values of the gap junction coupling, where dots represents spiking times and each line represents a neuron (note that the network E/I proportion is actually 80%/20%). Top raster plot shows asynchronous activity for low gap junction coupling and bottom raster plot shows synchronous activity in inhibitory and excitatory neuron populations, for strong gap junction coupling. (I) Membrane voltage traces of individual inhibitory neurons (dark blue) and population average (light blue, down-shifted) for different values of the gap junction coupling. Bursts appear for strong gap junction coupling on the peaks of the membrane voltage oscillations.
Figure 2.2. Model of gap junction plasticity. Bursting induces gLTD, spiking gLTP.

(A) Bursting protocol replicated from Haas et al. [16]. A current (red line, top panel) of 300 pA for 50 ms at 2 Hz and of -80 pA otherwise is injected into a pair of coupled neurons induces repeated bursting (blue line, middle panel, voltage trace). To quantify the amount of bursting, we low-pass filtered ($b_i$) the voltage trace, threshold it at $\theta_{burst} = 1.3$ (discontinued dark line), and integrate. Light blue areas represent the periods during which bursts are detected and therefore gap junctions are depressed. (B) When neurons N1 and N2 spike sparsely (top panel, dark blue, first part of the stimulus), gap junctions are potentiated (bottom panel, green line, first part of the simulation), whereas when they are bursting, gap junctions are depressed (second part of the simulation). (C) Green dots show steady-state values of the mean gap junction coupling for the gLTP with soft bounds, for different values of the network drive along the y-axis. For slow gLTP, the steady-state can be found in the A1 regime, where the power of the oscillations of the population spiking activity is low (blue area). (D) Network architecture: A step excitatory drive is fed to the network of E and I neurons (same network detailed on Figure 2, with plastic gap junctions) inducing gamma oscillations. The activity of the network is read out by a downstream population of 200 regular spiking cells. (E) Top panel, step excitatory drive fed to the networks. Second panel, evolution of the mean gap junction coupling. As the excitatory drive is delivered, a gamma oscillation appears, leading to an increase in bursting activity which is followed by a depression of the gap junctions, until the new fixed point is reached. Bottom panels, raster plots of the inhibitory neurons (blue, I1), excitatory neurons (red, E1) and read-out neurons (red, RON). 6 s of data is represented. (F) Top panel, step excitatory drive. Other panels, population activity of the read-out neurons in red, evolution of the mean gap junction coupling in light blue. Second panel, simulation with plastic gap junctions. The read-out neurons are the most active during the transient oscillations. Third panel, static gap junction coupling. The read-out neurons are active as long as the excitatory drive is high. Bottom panel, no gap junction coupling. The read-out neurons are not active. 10 s of data is represented.
Figure 2.3. Subnetworks having different frequency preferences can synchronise their activity if they share gap junctions.

(A) Both subnetworks have the same topology with all-to-all connected inhibitory and excitatory neurons. Inhibitory neurons have static gap junctions (GJs). The Gamma Network (GN) is connected to the Slow Network (SN) with a varying number of gap junctions. The time constant of the SN inhibitory neuron membranes is varied. (B) Frequency-transfer characteristics of a single inhibitory neuron to a sub-threshold oscillatory input current (see Methods) for different values of its membrane time constant $\tau_v$. The sub-threshold resonance frequency decreases as $\tau_v$ increases. Data of Cardin et al. 2009 is also represented (black line, figure redrawn from [32] Figure 3d). (C) Changing the single neuron sub-threshold resonance modifies the network oscillation frequency. Mean inhibitory membrane potential for each population. When no gap junctions are shared (bottom row), both networks do not synchronise and are out-of-phase. With 40 shared gap junctions (top row), the networks synchronise and are in phase for small values of $\Delta f_{res}$. 100 ms of data is represented. (D) Relationship between single neuron resonance (black line) and network oscillation frequency (gray line). For panels E, F, H, I, the x-axis represents the number of cross-network gap junctions between the GN and SN. The y-axis represents the difference of resonance frequency $\Delta f_{res}$ between the GN and the SN. For panels E and F, for each tuple ($\Delta f_{res}$; Number of shared GJs), the upper (lower) triangle represents the value in the SN (GN), in a similar configuration as represented on panel A. (E) Oscillation frequencies. We observe that the GN and the SN adopt the same oscillation frequency for low $\Delta f_{res}$ and high number of shared gap junctions. (F) Oscillation power. Only increasing $\Delta f_{res}$ seems to have an impact of the power of the SN. (G) Raster plots, where dots represent spiking times and each line represent a neuron, for small (first column) and large (second column) differences in $\Delta f_{res}$. For all raster plots, from top to bottom are represented excitatory and inhibitory neurons from the SN, then inhibitory and excitatory neurons from the GN. 100 neurons are shown for each population. When no gap junctions are shared (bottom row), both networks do not synchronise and are out-of-phase. With 40 shared gap junctions (top row), the networks synchronise and are in phase for small values of $\Delta f_{res}$. 100 ms of data is represented. (H) Phase differences between population activities of the GN and the SN, when they share the same frequency. Lighter squares denote parameters for which the phase difference is lower. The GN and the SN are considered in phase when the phase difference is zero. Dark blue squares describe a region that is excluded because the GN and the SN do not oscillate at the same frequency, therefore cannot be in phase. (I) Pearson’s correlation of the PAs of the GN and SN. Comparing with panel H, there is high correlation when the GN and the SN are in phase.
Figure 2.4. Gap junction plasticity lets networks recover synchronisation.

For all panels, the x-axis represents the number of cross-network gap junctions between GN and SN. The y-axis represents the difference of resonance frequency $\Delta f_{res}$ between the GN and the SN. The gap junctions are static from panels A to D and plastic from panels E to H. Values for the SN (resp. GN) are represented by the upper (resp. lower) triangles in a similar configuration as represented on Figure 2.3A. The GN (SN) has weak (strong) initial mean GJ coupling. Shared GJs are initialised with mean coupling strength in the middle between those of the GN and the SN. (A) Oscillation power. The GN, with weak GJ coupling, shows weak oscillations. (B) Oscillation frequency. We observe that the GN and the SN oscillate at the same frequency only for high number of shared GJs. (C) Phase differences between PAs of the GN and the SN (as for Figure 2.3H). The GN and the SN stay mostly out-of-phase. (D) Correlation of the PAs of the GN and the SN. Except for the particular case where $\Delta f_{res} = 0$ and the number of shared GJs is high, the PAs of the GN and the SN show no correlation. (E) Oscillation power. Comparing with panel A, we observe that the oscillation power seems to match in both networks, with mostly the oscillation power of the GN (initially weak) increasing to the SN’s levels (initially strong). (F) Oscillation frequency. Comparing with panel B, we observe an extension of the region where the GN and the SN oscillate at the same frequency. (G) Phase differences between PAs of the GN and the SN. We observe here a large region where the GN and SN are in-phase. (H) Correlation of the PAs of the GN and the SN. Comparing with panel D, we observe a large extension of the region where both networks are synchronised.
Figure 2.5. Gap junction coupling allows networks to transmit information and gap junction plasticity improves robustness of the transfer.

(A) Voltages traces of inhibitory neurons in the input-network (IN) in light blue and in the output-network (ON) in purple, when networks share no GJs (first rows) or 40 GJs (bottom rows). Despite not directly receiving the input signal, the ON synchronises its activity with the IN. For panels B to I, the networks share 40 GJs. 50 ms of data is represented. For the following figures 2.5B, 2.5C and 2.5H, 1 s of data is represented. (B) Input signal in red, number of spiking events of inhibitory neurons of the IN in light blue and of the ON in purple, for time bins of 0.1 ms. (C) Input signal in red, number of spiking events of inhibitory neurons of the IN in light blue and the ON in purple, for time bins of 25 ms. (D) Input signal amplitude $A_i$ as function of the corresponding PA peak interval $T_i$ for input signals oscillation at 4 Hz with mean varying from 0 to 1000 (See Methods). (E) Input signal in red and decoded input signal in purple. The PA peak interval $T_i$ is used to estimate the input amplitude. (F) Correlation between input signal and decoded input signal. The amplitude of the input is 400 pA, its frequency goes from 0 to 100 Hz. (G) Correlation between input signal and decoded input signal. The amplitude of the input goes from 0 to 10000 pA, its frequency goes from 0 to 100 Hz. (H) Example of 1 s of coloured noise input signal ($A = 800$ pA, mean = 400 pA, $\tau_{\text{filter}} = 100$ ms) in red and decoded input in purple (correlation 0.8). (I) Pearson’s correlation coefficient between input and decoded input for static (plastic) network in black (gray) for different values of the mean initial GJ coupling strength, as function of the number of shared GJs. The simulation is repeated for 10 different inputs. (J) Pearson’s correlation coefficient between input and decoded input for static (resp. plastic) network in black (resp. gray) as function of the proportion of GJs removed. The simulation is repeated for 10 different inputs. (K) Mean gap junction change between the steady-state value obtained with all the gap junctions, and the steady-state value obtained after gap junction removal. The remaining gap junctions compensate for the missing ones as they become stronger in strength.
Supplementary Methods

Passive rules as gap junction long term potentiation.

We consider two additional gap junction long term potentiation (gLTP) rules, which are passive as opposed to activity-dependent in the main article. In the passive case, the gap junction coupling increases constantly by a small amount. We consider a soft bound, i.e. the magnitude of increase is proportional to the difference between the gap junction value and a baseline coupling strength $\gamma_b$.

$$\dot{\gamma}_{ij}^+(t) = \dot{\gamma}_{ji}^+(t) = \alpha_{LTP} \left( \frac{\gamma_b - \dot{\gamma}_{ij}(t)}{\gamma_b} \right).$$  \hspace{1cm} (29)

Second, we consider a gLTP rule with no bounds, written as

$$\dot{\gamma}_{ij}^+(t) = \dot{\gamma}_{ji}^+(t) = \alpha_{LTP}.$$ \hspace{1cm} (30)

Asymmetrical gap junction plasticity.

We consider plasticity rules where the change is directional, and not symmetrical as previously described. After the bursting protocol, Haas et al. (2011b) (Figure 2.4C) measured a larger coupling change for the outbound coupling, i.e. when the coupling is measured with current injection in the cell that was quiet during the pairing protocol. In light of this observation, we consider the following gap junction long term depression (gLTD) rule

$$\dot{\gamma}_{ij}^-(t) = -\alpha_{gLTD}^* [H(b_j(t) - \theta_{burst})],$$ \hspace{1cm} (31)

where $\alpha_{gLTD}^*$ is the learning rate, $H$ is the Heavyside that returns 1 for positive arguments, $b_j$ is the same low-pass filter of the neuron activity as described in equation (12) in the main text and $\theta_{burst}$ is a bursting threshold. To compare this rule with the symmetrical rule, we set $\alpha_{gLTD}^* = 2 \cdot \alpha_{LTD}$, as overall there is twice less activity driving plasticity. As for the main text, the parameters are fit by implementing the stimulation protocol used by Haas et al.

The activity-dependent gLTP rules becomes

$$\dot{\gamma}_{ij}^+(t) = \alpha_{LTP} \left( \frac{\gamma_b - \gamma_{ij}(t)}{\gamma_b} \right) [sp_j(t)],$$ \hspace{1cm} (32)
where $\alpha_{gLTP}$ is the learning rate and $sp_i(t) = \sum_{t_{ik} \leq t} \delta(t - t_{ik})$ and $\delta$ is the Dirac function.

The unbounded gLTP rule becomes

$$\dot{\gamma}_{ij}^+(t) = \alpha_{gLTP}[sp_j(t)].$$

We measure the symmetry index of the gap junction coupling, such as described in Vasilaki and Giugliano (2014)

$$s(W) = 1 - (0.5N(N-1) - M)^{-1} \sum_{i=1}^{N_I} \sum_{j=i+1}^{N_I} |\gamma_{i,j} - \gamma_{j,i}|,$$

where $N_I$ is the number of inhibitory neurons, and $M$ represents the number of null pairs $\{\gamma_{i,j}, \gamma_{j,i}\} = \{0,0\}$. The symmetry index varies in the range $[0;1]$, where 1 means all the pairs are identical, and 0 means that none is.

**Additional parameters.**

We list in Table 2 the parameters used for our simulations in the supplementary material. Other parameters, except those described in the figure captions, remained unchanged. The symmetrical and asymmetrical rules have the same parameters, except for $\alpha_{gLTD}$ becoming $\alpha_{gLTD}^*$ for asymmetrical gap junctions. As reported in the main text, $\alpha_{gLTD} = 15.69 \text{ nS} \cdot \text{ms}^{-1}$.

**Table 2.** Gap junction potentiation learning rates.

<table>
<thead>
<tr>
<th>Type</th>
<th>$\gamma_b$</th>
<th>$\frac{\alpha_{gLTP}}{{\alpha_{gLTD}, \alpha_{gLTD}^*}}$</th>
</tr>
</thead>
<tbody>
<tr>
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<td>20</td>
<td>2</td>
</tr>
<tr>
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<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Passive bounded</td>
<td>20</td>
<td>0.03</td>
</tr>
<tr>
<td>Passive unbounded</td>
<td>-</td>
<td>0.015</td>
</tr>
</tbody>
</table>
Supplementary Figures

Figure 2.6. Evolution of the mean gap junction strength for different plasticity rules.

Four gLTP rules are considered: potentiation is either soft-bounded (A, B) or unbounded (C, D) and the rule is activity-dependent (A, C) or passive (B, D). The evolution of the mean gap junction coupling is represented over time, for different initial values ($\gamma_m(0) = \{2, 6\}$) and mean network drive $\nu$. The network drive is a coloured noise current $I_{noise}$ described in equation (11) in the main text. The value taken by $\nu$ are 50, 100, 150 or 200 pA. Lighter colours represent smaller values of $\nu$. We observe that the value of the steady-state do not depend on the initial value of the mean gap junction coupling. (E) Power of the main frequency component in the Fourier domain of the population activity of inhibitory neurons for 2 seconds of simulation. The blue area denotes the lack of oscillations. Labels show the steady-state of the simulations designed by the same labels. Note that only the steady-states of simulations initialised with $\gamma_m(0) = 2$ are shown. We observed that the steady-states falls on lines parallel to the bifurcation between the asynchronous irregular and the synchronous regular regime. The position of those lines depends on the speed of the gLTP and on the plasticity rule.
Figure 2.7. Evolution of the mean gap junction strength for different plasticity rules, for asymmetrical gap junctions.

Same caption as figure 2.6, but for asymmetrical gap junction plasticity.

Four gLTP rules are considered: potentiation is either soft-bounded (A, B) or unbounded (C, D) and the rule is activity-dependent (A, C) or passive (B, D). The evolution of the mean gap junction coupling is represented over time, for different initial values ($\gamma_m(0) = \{2, 6\}$) and mean network drive $\nu$. The network drive is a coloured noise current $I_{\text{noise}}$ described in equation (11) in the main text. The value taken by $\nu$ are 50, 100, 150 or 200 pA. Lighter colours represent smaller values of $\nu$. We observe that the value of the steady-state do not depend on the initial value of the mean gap junction coupling. (E) Power of the main frequency component in the Fourier domain of the population activity of inhibitory neurons for 2 seconds of simulation. The blue area denotes the lack of oscillations. Labels show the steady-state of the simulations designed by the same labels. Note that only the steady-states of simulations initialised with $\gamma_m(0) = 2$ are shown. We observed that the steady-states falls on lines parallel to the bifurcation between the asynchronous irregular and the synchronous regular regime. The position of those lines depends on the speed of the gLTP and on the plasticity rule.
**Figure 2.8. Comparison of symmetrical and asymmetrical gap junction coupling.**

(A) Evolution of the mean gap junction strength when gap junctions are symmetrical (blue continuous lines, same simulations as for panel A of figure 2.6) or asymmetrical (red dashed lines, same simulations as for panel A of figure 2.7). Lighter colours represent lower values of the mean network drive, going from 50 pA to 200 pA. The results shown are for the activity-dependent, soft-bounded gLTP rule. The results are identical for the passive gLTP rules. The initial conditions (network drive and initial mean coupling) are the same as described for figures 2.6 and 2.7. (B,C) Weight matrix for 10 gap junctions once the mean gap junction coupling has reached its steady state, for symmetrical gap junctions (B) and asymmetrical gap junctions (C). Lighter colours represent stronger values of the gap junction coupling. (D) Histogram of the individual gap junction coupling at steady state, for symmetrical gap junctions (blue), and asymmetrical gap junctions (red). (E) Evolution over time of the symmetry index of the gap junction coupling, for asymmetrical gap junctions. We observed that at steady-state the gap junction become symmetrical.
Figure 2.9. Phase diagrams as function of the chemical coupling.

First column (A,D,G,J): Power of the main frequency component in the Fourier domain of the population activity (PA) of inhibitory neurons. Second column (B,E,H,K): Oscillation frequency of the network activity. The white area represents a region where the network is not oscillating and has no oscillation frequency. Third column (C,F,I,L): Ratio of bursting $A_{bursting}$ over spiking $A_{spiking}$ activity, averaged over 2 seconds. Bursting activity prevails in the light region and sparse firing dominates in the dark region. First row (A,B,C): There is no chemical synapses. Second row (D,E,F): The strength of chemical synapses is half of the weights used for this study. Third row (G,H,I): The strength of chemical synapses is doubled. Last row (J,K,L): There is no inhibitory to inhibitory chemical synapses, but the rest of the chemical synapses have the standard strength.
Figure 2.10. Plasticity steady-state as function of the strength of the chemical synapses. (A) Evolution of the mean gap junction strength during 30 seconds, when there is no chemical synapses (purple lines), or when the strength of the chemical synapses is halved (green lines) or doubled (red lines) in reference to the value used for this study (blue lines). The convergence of the plasticity steady-state is observed for 2 different values of the initial mean gap junction conductance which correspond to a network initialised in the synchronous or in the asynchronous regime.
Figure 2.11. With fast gLTP, transition from the asynchronous irregular regime to the synchronous regular regime

The simulation was initialized in the AI regime ($\gamma = 2$) and we observed the transition to the steady-state in the SR regime ($\gamma \sim 6$), due to the fast gTLP ($\alpha_{gLTP}/\alpha_{gLTD} = 7$). (A) Evolution of the mean gap junction coupling strength (first row), mean bursting activity (second row, averaged over windows of 400 ms), mean spiking activity (third row, averaged over windows of 400 ms), and ratio of the window averaged mean bursting activity over the window averaged mean spiking activity (last row). The leftest grey rectangle shows the time at which variables have been observed for panels B, C. The middle grey rectangle shows the time at which variables have been observed for panels D, E. The rightest grey rectangle shows the time at which variables have been observed for panels F, G. Panels B, D, F show raster plots of 100 FS neurons (blue) and 100 pyramidal neurons (red) at the times represented by grey rectangles on panel A. Dots represent spiking times and each line represents a neuron (note that the network E/I proportion is actually 80%/20%). Top raster plot shows asynchronous activity for low gap junction coupling. Bottom raster plot shows synchronous activity in inhibitory neuron populations, for the steady-state which correspond to strong gap junction coupling. Panels C, E, G show voltage traces of a single inhibitory neuron (dark blue) and the mean inhibitory voltage (light blue) at the times represented by the grey rectangles on panel A. We observed, on panel G, that for the steady-state in the SR regime, neurons are bursting, while they are mostly spiking in the AI regime (panels C, E).
Figure 2.12. Influence of the speed of the gap junction potentiation on the network steady-state.
Panels A, B, C, D show the evolution of the mean gap junction coupling over time, for different parameters: for panel A and C, the mean gap junction is initialised in the AI regime; for panels B and D, it is initialised in the SR regime. For the simulations in blue (panels A and B), the mean external current is 100 pA, while it is 200 pA for the simulations in red (panels C and D). The darkness of each curve depends on the corresponding $\alpha_{gLTP}/\alpha_{gLTD}$ ratio, represented on panel E. (E) Values of the steady-states as function of the $\alpha_{gLTP}/\alpha_{gLTD}$ ratio. Each marker represent the steady-state of the corresponding simulations represented on panels A, B, C, D. (F, G, H, I) Raster plots during steady-states described by the green italic letters F, G, H, and I. For F and H, the network is in the AI regime. For G and I, the network is in the SR regime. The blue (resp. red) dots represent spikes of 100 inhibitory (resp. excitatory) neurons during 200 ms. We note on panels C and D that if the gLTP is too slow (low ratio $\alpha_{gLTP}/\alpha_{gLTD}$), the gap junctions are eventually totally depressed.
Chapter 3

Gap junction plasticity can lead to spindle oscillations

In the previous chapter, we introduced a novel model of gap junction plasticity, based on experimental data from Julie Haas’ group (Haas et al. (2011a)). They provided the first evidence of activity-dependent plasticity of gap junction of thalamic reticular nucleus (TRN) neurons. Interestingly, the TRN is thought to be the origin of a specific type of network dynamics, namely spindle oscillations (also simply called spindles). Spindle oscillations are patterns of waxing and waning oscillations observed during sleep and have been recently linked to memory formation (Rosanova (2005a); Latchoumane et al. (2017); Xia et al. (2017)). Despite potentially knowing their source for over 30 years, their generation is not yet fully understood. The TRN shows interesting properties that have been overlooked by modelling studies so far: it contains mostly inhibitory neurons coupled by gap junctions, the neurons exhibit tonic and bursting firing modes, and the TRN gap junctions alter their strength in an activity dependent manner.

Therefore, after considering the implications of gap junction plasticity on the dynamics of cortical networks, in this chapter we sought to determine the potential role of gap junction plasticity in the spindle generation in thalamo-cortical network. Our main result is that activity-dependent plasticity of gap junctions can lead to the emergence of spindles in inhibitory interneuron circuits alone. At its core, the mechanism operates by transitioning between the asynchronous irregular and synchronous regular firing regimes repetitively. Gap junction potentiation induces a transition to synchronized oscillations while gap junction depression induces a transition into the asynchronous irregular regime. This creates waxing and waning patterns characterizing spindle oscillations. Finally, we test the consistency of our model with experimental perturbation studies. We would like to mention to the reader that the layout of the presented work is in an article format, as it has been submitted for publication. We are thankful to Wilten Nicola and Claudia Clopath for their comments on earlier versions of the manuscript.
Gap Junction Plasticity can Lead to Spindle Oscillations.

Abstract

Patterns of waxing and waning oscillations, called spindles, are observed in multiple brain regions during sleep. Spindles are thought to be involved in memory consolidation. The origin of spindle oscillations is ongoing work but experimental results point towards the thalamic reticular nucleus (TRN) as a likely candidate. The TRN is rich in electrical synapses, also called gap junctions, which promote synchrony in neural activity. Moreover, gap junctions undergo activity-dependent long-term plasticity. We hypothesised that gap junction plasticity can modulate spindle oscillations. We developed a computational model of gap junction plasticity in recurrent networks of TRN and thalamocortical neurons (TC). We showed that gap junction coupling can modulate the TRN-TC network synchrony and that gap junction plasticity is a plausible mechanism for the generation of sleep-spindles. Finally, our results are robust to the simulation of pharmacological manipulation of spindles, such as the administration of propofol, an anaesthetic known to generate spindles in humans.

Author summary.

During non-rapid-eye-movement sleep, neurons tend to become active together for about one second, before desynchronising. This waxing and waning pattern of neuronal activity is called spindle oscillations and is thought to be important for memory formation. Spindle oscillations travel throughout the cortex and are thought to originate from a small region within the thalamus, the thalamic reticular nucleus (TRN). The TRN has singular characteristics: it contains only inhibitory neurons and they are coupled with electrical synapses. Many studies highlight the role of electrical synapses between inhibitory neurons to generate oscillations. Moreover, they have been shown to be plastic, their strength can be altered by the neuronal activity. Therefore, the plasticity in electrical synapses could act as a mechanism to generate spindle oscillations. We developed a computational model of plasticity of electrical synapses in a network of thalamic neurons. We first show that electrical synapses can be a lead
factor of oscillations within the thalamus. Then, we show that spindle oscillations can be generated by the gap junction plasticity.

**Introduction.**

Spindle oscillations are waxing and waning patterns which are characterised by field potentials oscillating at 7-15 Hz and occurring every 5-15 seconds (Steriade et al. (1993); McCormick and Bal (1997b)). They can be observed during sleep and their absence can be a marker of schizophrenia (Ferrarelli et al. (2010)).

The thalamic reticular nucleus (TRN) is thought to be involved in the genesis of sleep spindles (von Krosigk et al. (1993); Lee et al. (2013); Halassa et al. (2014)). The TRN consists of inhibitory neurons and surrounds the dorsal thalamus like a shell (Houser et al. (1980); Pinault (2004)). Interestingly, spindle oscillations are observed in thalamus after decortication (Morison and Bassett (1945); Timofeev and Steriade (1996)) or cortical deafferentation Steriade et al. (1987); Lemieux et al. (2014) and they are not observed in the isolated cortex (Fuentesalba et al. (2004)). Moreover, they are also observed in isolated TRN in vitro (Deschênes et al. (1985)).

The 'classical' model postulates that sleep spindles arise from the interactions between feedfoward inhibition from the TRN onto thalamo-cortical (TC) neurons and feeback excitation from the TC to the TRN (Bal et al. (1995); Cox et al. (1996); Timofeev et al. (2001); Timofeev and Chauvette (2013)). Computational models also suggest that the mutual inhibition from TRN and TC neurons could generate spindle activity in the TRN (Wang and Rinzel (1993); Destexhe et al. (1994)). Another possible factor in the existence of thalamic sleep spindles is the two distinctive firing patterns that TRN and TC neurons exhibit: sequences of tonic action potentials and high frequency bursts of action potentials (Jahnsen and Llinás (1984); Mulle et al. (1986); Avanzini et al. (1989); Contreras et al. (1992, 1993); Bazhenov et al. (2000); Murray Sherman (2001); Sun et al. (2012)). The tonic firing mode can be observed during wakeful states (McCormick and Feeser (1990)) while burst firing mode can be observed during spindles (Halassa et al. (2011)). Modelling studies suggest that the transition from tonic to bursting firing mode can be associated with the transition from asynchronous to synchronous network regime (Postnova et al. (2007); Shaffer et al. (2017)).

The TRN is particularly dense in interneurons coupled with electrical synapses (gap junctions) Landisman et al. (2002). Interestingly, gap junctions have been shown to promote activity synchronisation (Traub et al. (2001); Pfeuty et al. (2003); Kopell and Ermentrout (2004); Connors and Long (2004); Tchumatchenko and Clopath (2014)) and some models consider their involvement in spindle oscillations (Landisman et al. (2002); Lewis and Rinzel...
Experimental results show that administration of halothane, a gap junction blocker, in TRN of decorticated cats lead to a reduction of spindle activity (Fuentealba et al. 2004). Moreover, it has been show that gap junctions are plastic (Cachope et al. 2007; Wang et al. 2015b; Turecek et al. 2014, 2016; Coulon and Landisman 2017). High frequency stimulation of a pair of TRN inhibitory neurons coupled by gap junctions leads to long-term depression of the gap junctions (gLTD) (Haas et al. 2011a).

Given the probable involvement of gap junctions in the synchronous pattern of the TRN, and the existence of activity-dependent gap junction plasticity, we hypothesised that gap junction plasticity could act as a mechanism to generate spindle oscillations. To test this, we developed a model of TRN and TC neurons. Consistent with our previous work in cortex (Tchumatchenko and Clopath 2014; Pernelle et al. 2017), the gap junction coupling strength of TRN neurons modulates the TRN-TC network synchrony (Tchumatchenko and Clopath 2014; Pernelle et al. 2017). Then, we show that gap junction plasticity can lead to the emergence of waxing and waning oscillations that have the same characteristics as sleep spindles observed during stage 2 of non-rapid-eye-movement sleep (NREM). Finally, we show that our model allows for manipulation of spindles in agreement with experimental results.

Results

Gap junction coupling between TRN inhibitory neurons promotes synchrony in the TRN-TC network.

In order to understand the effect of gap junction plasticity on spindle activity, we consider first a static network of inhibitory TRN neurons, fully connected via chemical and electrical synapses (Figure 3.1A). The Izhikevich model of rat TRN neurons was used to reproduce the firing and bursting modes (Izhikevich 2007). As previously reported Tchumatchenko and Clopath (2014); Pernelle et al. (2017), we observed a synchronous regular (SR) regime for strong gap junction coupling and external network drive, and an asynchronous irregular (AI) regime for low levels of both (Figure 3.1B). With stronger gap junction coupling, the inhibitory neurons merge their electrical properties and synchronise together. This is due to the current contribution of the gap junction coupling which is proportional to the difference of voltages between the coupled neurons. Moreover, spiking inhibitory neurons emit an excitatory spikelet in the coupled inhibitory neurons, on top of the inhibition provided by the inhibitory chemical synapses. We observe that the TRN neurons exhibit the two firing modes characterising TRN neurons. Tonic firing mode is mostly observed in the AI regime,
while burst firing mode is mostly observed in the SR regime (Figures 3.1C and 2.6). To complete our thalamo-cortical model, we connect in an all-to-all fashion the TRN neurons to TC neurons that are excitatory (Figure 3.1D). We observe that the excitatory neurons follow the activity patterns generated by the TRN neurons (Figures 3.1E-I and 3.7).

To summarise, the synchrony of the TRN-TC network increases with the gap junction coupling strength and input drive. To understand the effect of gap junction plasticity on spindle activity, we model the plasticity, similarly as in *Pernelle et al. (2017)*.

**Gap junction plasticity dynamics drive spindle activity.**

*Haas et al. (2011a)* reported the first experimental evidence of gap junction activity-dependent long-term depression. After identifying pairs of neurons coupled by gap junctions, they repetitively provoked bursts during five minutes in one or both neurons and they observed long-term depression (gLTD) of the coupling coefficient. We therefore used a model of gap junction plasticity that is activity-dependent (developed in *Pernelle et al. (2017)*). The frequency of the spiking activity determines the direction of the plasticity. We hypothesise that sparse firing lead to gap junction long-term potentiation (gLTP), while repetitive burst firing leads to gLTD (Figure 3.2A). This rule allows for the emergence of spindle activity. From the AI regime, sparse firing leads to an increase in the gap junction coupling strength, which drives the TRN network in the SR regime (waxing phase, Figure 3.2B). Then, due to the sustained bursting of TRN neurons, depression of the gap junction follows and the network crosses back the bifurcation between AI and SR regime and enters the AI regime again (waning phase, Figure 3.2B). This network dynamic creates a waxing-and-waning mechanism that characterise sleep spindles.

**Gap junction coupling resembles a chaotic attractor.**

The network dynamic, previously observed for a single spindle event, repeats itself irregularly (5-10 seconds) and has an irregular duration (0.5-2 seconds) (Figures 3.3A and 3.8B-D). The spindle activity, driven by the gap junction coupling strength, is not purely periodic. We observe indeed a variation in the spindle duration, power and intervals between spindles. The delay-dimension embedded phase portrait bares a strong resemblance to a chaotic attractor (Figure 3.3B). Moreover, from identical initial conditions, small perturbations to the gap junction coupling will cause the dynamical system to diverge at an exponential rate before saturation, which is distinctive of a chaotic system (Figure 3.3C-D).
TRN activation suppresses spindle activity.

To test our model, we looked at the experimental literature for perturbation experiments, and then tested whether our model is consistent with the data. In particular, Lewis et al. (2015) observed a significant reduction of spindle activity during stimulation of the TRN. We wondered if our model would exhibit a similar effect. We started from conditions that allow spindle activity as previously described (Figure 3.4A). With a TRN external drive of 40 pA, repetitive patterns of waxing-and-waning oscillations are observed. When increasing the drive to the TRN to 50 pA, the TRN-TC network becomes asynchronous and the spindle activity is suppressed (Figure 3.4B). In order to understand this effect, we investigated the spiking activity and the oscillation power, which influence the gap junction plasticity. When superimposing lines of iso-power (Figure 3.4C) and iso-activity (Figure 3.4D), we observe that, while at 40 pA they coincide, they start to diverge when activating the TRN. When the drive $\nu$ is 50 pA, the amount of bursting activity, and therefore gLTD, is higher for the same level of network oscillation. This implies that it becomes more difficult for the gap junction coupling to reach values that are associated with the SR regime. Thus, the gap junction plasticity stabilizes at a fixed point outside the SR regime, which results in the absence of spindle oscillations. The spindle suppression for higher could be rescued by increasing the potentiation learning rate gLTP, as it would move the gap junction steady back in the SR regime (see Chapter 2, Figure 2.12 for the influence of the speed of the potentiation on the steady-state). We observed that spindles can be suppressed by increasing the amount of bursting and creating a plasticity fixed point in the AI regime. Similar conditions may be observed in awake animals, where no spindle activity is observed.

Manipulation of spindle activity with propofol.

As a second test, we wondered whether our model is consistent with the effects of propofol on spindles. Propofol is an anaesthetic that promotes spindle activity in humans (Murphy et al. (2011)). It targets $\text{GABA}_A$ receptors and prolongs the duration of GABAergic inhibitory postsynaptic currents (IPSCs) (MacIver et al. (1991); Orser et al. (1994); Bai et al. (1999)). To simulate this effect, we increase the time constant of chemical inhibitory synapses $\tau_I$. Starting from a network in the asynchronous regime (Figure 3.4B), once $\tau_I$ crosses a threshold, which depends on the external TRN drive (Figure 3.8A), the TRN exhibits spindle activity (Figure 3.5A). On the updated activity diagram ($\tau_I = 20$ ms), when superimposing the line of iso-power (obtained from a power diagram for $\tau_I = 20$ ms) to the line of iso-activity, we observed that the iso-activity line stays to the right of the iso-power line unlike for a smaller $\tau_I$ (Figures 3.4D and 3.5B). Increasing the duration of
GABAergic IPSCs leads to a decrease in bursting activity for the same level of network oscillation. Therefore, the gap junction coupling can reach values associated with the SR regime. The gap junction coupling oscillatory cycle through the bifurcation between the AI and SR regime is restored and spindle activity is observed. This effect increases with $\tau_I$ and the power, duration, and inter-spindle-interval increase with $\tau_I$ (Figures 3.5C-E). This effect is chaotic up to $\tau_I = 14$ ms, when the spindle power is low, as we observe large range of spindle intervals (Figure 3.5D, $\tau_I = 14$ ms). Then, as the spindle power increases, their behavior becomes less chaotic.

To summarise, mimicking the effect of propofol on the dynamic of inhibitory synapses can generate spindle activity through gap junction plasticity.
Discussion.

To summarise, our modelling study tested whether gap junction plasticity can generate spindle oscillations in the thalamus. Our findings suggest that gap junctions between TRN neurons can regulate the synchrony in both the TRN and TC. Moreover, we showed that, depending on the dynamics of inhibitory synapses, gap junction plasticity can generate spindle oscillations. Gap junctions generate patterns of waxing-and-waning spindle oscillations in the population activity, with their strength oscillating in a non purely periodic fashion around the bifurcation between asynchronous irregular (AI) and synchronous regular (SR) regimes. In the AI regime, sparse firing leads to potentiation of the gap junctions, which drives the network towards the SR regime. However, once in the SR regime, oscillations emerge, which lead to repetitive bursting of TRN neurons. This trigger gap junction depression and drives the network back to the AI regime. This alternation between AI and SR regimes can generate spindle like activity. This mechanism is robust to the dynamics of inhibitory synapses and the external drive to the network. For fast synapses or strong TRN activation, the gap junction plasticity reaches a steady-state in the AI regime and no spindles are observed. Slowing down the dynamics of inhibitory synapses or reducing the TRN activation promotes the emergence of spindle oscillations. Therefore, gap junction plasticity is a potential mechanism in generating spindle oscillations.

While there is no experimental data yet on activity-dependent LTP of gap junctions, recent studies suggest that gap junction gLTP and gLTD share similar calcium-regulated pathways (Wang et al. (2015a); Szoboszlay et al. (2016); Sevetson et al. (2017)). Therefore we designed a rule for activity-dependent gLTP consistent with Haas’ results (Haas et al. (2011a)). We assumed that sparse firing would lead to gLTP. Our results do not depend stricly on this assumption. Indeed, in a previous study we reported that passive gLTP mechanism would yield similar results (Pernelle et al. (2017)).

Our computational model shows that gap junction plasticity could be involved in the genesis of spindle oscillations. The spindle activity generated by our model bares the hallmark of chaotic activity. This corroborates modelling work of gap junction coupling, but between excitatory TC neurons (Hughes et al. (2004); Ermentrout (2006)). However, further numerics are required to characterise this system, which could be an interesting future work. Unfortunately, the dynamics of the plasticity mechanism makes these systems computationally intensive to simulate, requiring very long simulation times. Furthermore, Fuentealba et al. (2004) observed a reduction of the spindle activity in vivo when blocking gap junction with administration of halothane in TRN of decorticated cats. Those results are consistent with our model, where gap junctions are the leading factor in the the emergence of oscillations.
Alternative models for spindle generation have been proposed. For example, a classical model takes the minimal substrate for spindles to be the interaction between TRN and TC neurons. Bursts from TRN inhibitory neurons trigger bursts of excitatory thalamic relay cells, which then excite the TRN neurons and the cycle continues (Steriade and Deschenes (1984); Steriade et al. (1985); von Krosigk et al. (1993); Bal et al. (1995); Cox et al. (1996); Timofeev et al. (2001); Bonjean et al. (2011); Timofeev and Chauvette (2013)). With our model however, spindles can be generated from the gap junction plasticity in isolated TRN. This is consistent with observations in vitro from Deschênes et al. (1985) or the in vivo study from Steriade et al. (1987). Those mechanisms for spindle generation are not mutually exclusive, they could act in concordance and guarantee the robustness of this mechanism or they could promote different types of spindles, such as the slow and fast spindles (Andrillon et al. (2011)).

Spindle oscillations appear involved in memory formation and consolidation (Rosanova (2005b); Gais et al. (2000); Rosanova (2005c); Werk et al. (2005); Astori et al. (2013); Latchoumane et al. (2017); Xia et al. (2017)). Thus, better understanding the potential implications of gap junction plasticity in spindle generation could further our understanding on memory formation.

To conclude, we showed that gap junction plasticity could modulate the synchrony in the thalamus and generate spindle oscillations. Finally, our model is consistent with experimental perturbation studies.
Methods.

We consider a network with $N_I$ TRN inhibitory neurons and $N_E$ TC excitatory neurons with all-to-all connectivity (Figure 1). Inhibitory neurons are modelled by an Izhikevich model and excitatory neurons by a leaky integrated-and-fire model (LIF) (Izhikevich (2003, 2007)). Equations are integrated using Euler’s method with a time-step of 1 millisecond. This large time-step was used as numerical simulations of gap junction plasticity are very computationally intensive. However, we performed tests with smaller time-steps (up to 0.02 ms) and we observed similar neuron and network dynamics. Inhibitory neurons are connected by both electrical and chemical synapses, whereas excitatory neurons have only chemical synapses. The model is written in Python and is available on github: https://github.com/gpernelle/spindles_with_gap_junctions.

Neuron models.

We model TRN neurons with Izhikevich type neuron models for rat TRN neurons (Izhikevich (2004, 2007)). This model reproduces the tonic spiking and bursting that is typical of TRN neurons. The voltage $v$ follows

$$
\tau_v \dot{v} = k_v (v - v_{ra})(v - v_{rb}) - k_u u + RI, \tag{35}
$$

$$
\tau_u \dot{u} = a[c(v - v_{rc}) - u], \tag{36}
$$

combined with the following conditions,

$$
\begin{align*}
\text{if } v &\geq v_{peakTRN}, \text{ then } \left\{ \begin{array}{l}
v \leftarrow v_{resetTRN} \\
u \leftarrow u + b,
\end{array} \right. \\
\text{and if } v &\leq v_{switch}, \text{ then } c = 10 \text{ else } c = 2. \tag{37}
\end{align*}
$$

where $\tau_v$ is the membrane time constant, $v_{ra}$ is the membrane resting potential, $v_{rb}$ is the membrane threshold potential, $k_v$ is a voltage parameter, $k_u$ is the coupling parameter to the adaptation variable $u$, $R$ is the resistance and $I$ is the current. The adaptation variable $u$ represents a membrane recovery variable, accounting for the activation of K$^+$ ionic currents and inactivation of Na$^+$ ionic currents. It increases by a discrete amount $b$ every time the neuron is spiking and its membrane potential crosses the threshold $v_{peakTRN}$. It provides a negative feedback to the voltage $v$. $\tau_u$ is the recovery time constant, $a$ and $c$ are coupling parameters, $v_{resetTRN}$, $b$ and $v_{rc}$ are voltage constants. We slightly modified Izhikevich’s model. In our model, $v_{resetTRN}$ was reduced from -55 mV to -60 mV to decrease
the spontaneous bursting activity that could be observed in the asynchronous irregular regime. The parameter \( v_{\text{switch}} \) was reduced from -65 mV to -70 mV to slightly decrease the spindle oscillation frequency.

To model TC excitatory neurons, we chose a leaky integrate-and-fire model,

\[
\tau_m \dot{v} = -v + R_m I,
\]

where \( \tau_m \) is the membrane time constant, \( v \) the membrane potential, \( I \) the current and \( R_m \) the resistance. Spikes are characterised by a firing time \( t_f \) which corresponds to the time when \( v \) reaches the threshold \( v_{\text{threshTC}} \). Immediately after a spike, the potential is reset to the reset potential \( v_{\text{resetTC}} \).

Network.

In the single network model (Figures 1 and 2), each neuron is connected to all others by chemical synapses. Additionally, inhibitory neurons are connected via electrical synapses to all other inhibitory neurons, as in Tchumatchenko and Clopath (2014). Thus, the current each individual neuron \( i \) receives can be decomposed in four components

\[
I_i(t) = I_{\text{spike}}^i(t) + I_{\text{gap}}^i(t) + I_{\text{noise}}^i(t) + I_{\text{ext}}^i(t),
\]

where \( I_{\text{spike}}^i = I_{\text{chem}}^i + I_{\text{elec}}^i \) is the current coming from the transmission of a spike via electrical (i.e. spikelet) and chemical synapses, \( I_{\text{gap}}^i \) is the sub-threshold current from electrical synapses (for inhibitory neurons only), \( I_{\text{noise}}^i \) is the noisy background current and \( I_{\text{ext}}^i \) characterises the external current. The current due to spiking \( I_{\text{spike}}^i \) on excitatory neurons is given by

\[
I_{\text{spike}}^i(t) = W_{IE}^{\text{IE}} \sum_{j=1}^{N_E} \sum_{j \neq i \leq t} \exp \left( -\frac{t - t_{jk}}{\tau_I} \right) + W_{II}^{\text{IE}} \sum_{j=1}^{N_E} \sum_{j \neq i \leq t} \exp \left( -\frac{t - t_{jk}}{\tau_E} \right),
\]

The current \( I_{\text{spike}}^i \) into inhibitory neurons are

\[
I_{\text{spike}}^i(t) = \sum_{j=1}^{N_I} \sum_{j \neq i \leq t} W_{ij}^{\text{IE}} \exp \left( -\frac{t - t_{jk}}{\tau_I} \right) + W_{II}^{\text{IE}} \sum_{j=1}^{N_E} \sum_{j \neq i \leq t} \exp \left( -\frac{t - t_{jk}}{\tau_E} \right),
\]

where \( W_{\alpha\beta} \) is the coupling strength from population \( \alpha \) to population \( \beta \) with \( \{ \alpha, \beta \} = \{ E, I \} \). Finally, \( W_{ij}^{\text{II}} = W_{ij}^{\text{II},e} + W_{ij}^{\text{II},i} \) is the inhibitory to inhibitory coupling between neuron \( i \).
and $j$, consisting of the chemical synaptic strength $W_{II,c}$ and $W_{ij}^{II,e}$ the electrical coupling for supra-threshold current, also called the spikelet. We model the contribution of the spikelet as a linear function of the gap junction coupling $W_{ij}^{II,e} = k_{\text{spikelet}} \gamma_{ij}$, where $\gamma_{ij}$ is the gap junction coupling between neurons $i$ and $j$. Note that $W^{EE}, W^{EI}, W^{IE}, W^{II,c}$ are identical among neurons, but $W_{ij}^{II}$ varies as the spikelet contribution depends on the coupling strengths $\gamma_{ij}$, which can be plastic.

We represent the post-synaptic potential response to a chemical or electrical spike with an exponential of the form $\exp\left(-\frac{t-t_{jk}}{\tau}\right)$ for $t > t_{jk}$. The excitatory and inhibitory synaptic time constants are $\tau_E$ and $\tau_I$ respectively and $t_{jk}$ represents the $k^{th}$ firing time of neuron $j$.

In between spikes, for every pair of inhibitory neurons $i, j$, the gap junction mediated sub-threshold current $I_{i}^{gap}$ is characterised by

$$ I_{i}^{gap}(t) = \sum_{j=1}^{N_i} I_{ij}^{gap}(t) = \sum_{j=1}^{N_i} \gamma_{ij}(V_j(t) - V_i(t)), \quad (43) $$

where $\gamma_{ij}$ is the gap junction coupling between inhibitory neurons $i$ and $j$ of respective membrane potential $V_i$ and $V_j$. In our model, we suppose that gap junctions are symmetric with $\gamma_{ij} = \gamma_{ji}$. Gap junctions are initialised following a log-normal distribution with the location parameter $\mu_{gap} = 1 + \ln(\gamma/N_I)$ and the scale parameter $\sigma_{gap} = 1$.

Neurons also receive the current $I_{noise}$ which is a coloured Gaussian noise with mean $\nu_I$, standard deviation $\sigma_I$ and $\tau_{noise}$ the time constant of the low-pass filtering

$$ \tau_{noise} \dot{s}(t) = -s(t) + \xi(t) \quad (44) $$

and

$$ I_{noise}(t) = \sqrt{2 \tau_{noise} s(t) \sigma_I + \nu_I}. \quad (45) $$

with $\xi$ is drawn from a Gaussian distribution with unit standard deviation and zero mean.

**Plasticity model of gap junctions.**

Our plasticity model is decomposed into a depression $\gamma^-$ and a potentiation term $\gamma^+$, developed in Pernelle et al. (2017).

**gLTD: depression of the electrical synapses for high frequency activity.**

To model the gap junction long-term depression (gLTD) measured by Haas et al. (2011a) following high frequency activity in one or both neurons, we create a second order filter,
composed of two low-pass filters. We first defined a variable $b_i$ which is a low-pass filter of the spikes of neuron $i$

$$\tau_b \dot{b}_i(t) = -b_i(t) + \tau_b \sum_{t_{ik} \leq t} \delta(t - t_{ik}),$$  \hspace{1cm} (46)$$

where $\delta$ is the Dirac function and $\tau_b = 8$ ms is the time constant. Then we defined a variable $q_i$ which is a low-pass filter of $b_i$, that characterises if the bursting is sustained,

$$\tau_q \dot{q}_i(t) = -q_i(t) + p_i(t),$$ \hspace{1cm} (47)$$

where $\tau_q$ is the filter time constant. Then depression is applied when $q_i$ is over a threshold $\theta_q = 0.3$.

In our model, we consider that the individual electrical coupling coefficient $\gamma$ between neurons are non-directional. Therefore, when the interneurons show sustained bursting activity, the gap junctions undergo depression,

$$\dot{\gamma}_{ij} = -\alpha_{LTD} [H(q_i(t) - \theta_q) + H(q_j(t) - \theta_q)],$$ \hspace{1cm} (48)$$

where $\alpha_{LTD}$ is the learning rate and $H$ is the Heaviside function that returns 1 for positive arguments and 0 otherwise.

We fit $\alpha_{LTD}$ to the data by implementing the stimulation protocol used in Haas et al. (2011a), as reported in Pernelle et al. (2017).

**gLTP: potentiation of the electrical synapses for low frequency activity.**

If gap junctions were only depressed, they would decay to zero after some time. Therefore, there is a need for gap junction potentiation. However, no activity dependent mechanism has been reported yet in the experimental literature, but Cachope and Pereda (2012); Wang et al. (2015b); Sevetson et al. (2017); Debanne and Russier (2017) suggest that the calcium-regulated mechanisms leading to long-term depression could be involved in potentiation as well.

To model potentiation, we use the same soft-bound rule as presented in Pernelle et al. (2017),

$$\dot{\gamma}_{ij}^{+}(t) = \dot{\gamma}_{ji}^{+}(t) = \alpha_{LTP} \left( \frac{\gamma_b - \gamma_{ij}(t)}{\gamma_b} \right) [s_{p_i}(t) + s_{p_j}(t)].$$ \hspace{1cm} (49)$$

where $\alpha_{LTP}$ is the learning rate and $s_{p_i}(t) = \sum_{t_{ik} \leq t} \delta(t - t_{ik})$. 

72
Quantification of network spiking activity.

To estimate the plasticity direction for different values of external input $\nu$ and gap junction strength $\gamma$, we observe the activity of the network (without plasticity) in a steady state over a duration $T = 6$ s. For a chosen tuple $(\nu; \gamma)$, we average over time and over neurons the bursting and spiking activity

$$A_{bursting} = \frac{1}{T} \frac{1}{N_I} \sum_{i=1}^{N_I} [H(b_i(t) - \theta_{burst})]dt$$  \hspace{1cm} (50)

and

$$A_{spiking} = \frac{1}{T} \frac{1}{N_I} \sum_{i=1}^{N_I} sp_i(t)dt.$$  \hspace{1cm} (51)

Then, we explore the values of the ratio of bursting over spiking activity

$$\text{ratio} = \frac{A_{bursting}}{A_{spiking}}$$  \hspace{1cm} (52)

as function of the coupling coefficient $\gamma$ and of the mean external input $\nu$ over the parameter space $P_1 = [0; \gamma_{max}] \times [0; \nu_{max}]$.

Quantification of oscillation power and frequency.

To quantify the frequency and the power of the oscillations in the neuronal activity, we perform a Fourier analysis of the population activity $r$ which we define as the sum of neuron spikes within a population, during the time step $dt$

$$r(t) = \frac{1}{dt} \frac{1}{N_I} \int_{t}^{t+dt} \sum_{i=1}^{N_I} \sum_{t_{ik} \leq t} \delta(u - t_{ik})du.$$  \hspace{1cm} (53)

We compute a Discrete Time Fourier Transform (DFT) and extract the power and the frequency of the most represented frequency in the Fourier domain. The formula defining the DFT is

$$\hat{\gamma}_k = \sum_{n=0}^{N-1} r_n \exp \left(-i 2\pi k \frac{n}{N} \right) \quad k = 0, \ldots, N - 1.$$  \hspace{1cm} (54)

where the $r_n$ sequence represents $N$ uniformly spaced time-samples of the population activities. We measure the amplitude of the Fourier components $\hat{\gamma}_k$ for $k = 1..N/2$ (because the Fourier signal is symmetric from $N/2$ to $N$). We identify the maximal one, its associated frequency $f_{max} = \frac{k}{N}$ and its power $P = (|\hat{\gamma}_k|/N)^2$. 

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Spectrogram of the population activity.

To compute the spectrogram of the population activity, the data are split in \( NFFT \) length segments and the spectrum of each section is computed. The Hanning windowing function is applied to each segment, which overlap of the 1900 ms, and the mean is removed.

Quantification of spindle power, duration and inter-spindle intervals.

To quantify the spindle properties, we filter the spectrogram of population activity in the [5-15] Hz frequency band. The beginning \( B_i \) and end \( E_i \) of each spindle is determined by the rising slope and falling slope of the power crossing the threshold \( \theta_{\text{spindle}} \). The spindle duration is the difference between falling and rising times \( d_i = E_i - B_i \) and the intervals between spindles is the difference between consecutive rising time \( \Delta_i = E_{i+1} - E_i \).

Estimation of the largest Lyapunov’s exponent.

The largest Lyapunov’s exponent is a measure of the rate of divergence of a system after a perturbation. Once the spindle oscillations begin, we perturb the gap junctions. Between different realisations, only the perturbation differs, by setting a different random seed while drawing the perturbation matrix. The perturbation is drawn from a uniform distribution \( U(0; 0.1 * \gamma_m) \), where \( \gamma_m \) is the mean gap junction coupling strength at the time of the perturbation (\( t = 10 \) s).

We then proceed to estimate the rate of divergence between realisations from the perturbation time

\[
e(t) = \frac{1}{N(N-1)} \sum_{i \neq j} |\gamma_{m,i}(t) - \gamma_{m,j}(t)|
\]  

(55)

where \( \gamma_{m,i} \) and \( \gamma_{m,j} \) are the mean gap junction coupling of realisations \( i \) and \( j \).

We then perform a linear regression on the logarithm of the mean distance \( \log(e) \), from the perturbation time until the distance saturates, about 30 seconds after the perturbations. The slope \( \lambda \) gives us an estimate of the largest Lyapunov’s exponent.
Parameters.

We list in Table 3 the parameters used for our simulations.

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<th>TRN Interneurons</th>
<th>Thalamo-Cortical Neurons</th>
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**Figures.**

(A) The TRN network consists of inhibitory (I) neurons coupled in an all-to-all fashion with chemical synapses (black lines) and gap junctions (jagged green lines). For all the following activity diagrams, the x-axis represents the mean gap junction coupling strength $\gamma$ and the y-axis represents the mean value of the network external drive $\nu$. (B) Power in the Fourier domain of the strongest oscillation frequency of the population activity. The red area denotes oscillations characterising the synchronous regular regime (SR) and the blue area show the lack of oscillations characterising the asynchronous irregular regime (AI). (C) Ratio of bursting $A_{\text{bursting}}$ over spiking $A_{\text{spiking}}$ activity. Sparse spiking prevails in the dark region while bursting is dominating in the light region. (D) The thalamus network consists of excitatory neurons coupled with chemical synapses among them and with the TRN inhibitory neurons in an all-to-all fashion. (E) Same as B, but for the TRN inhibitory neurons of the TRN-TC network. (F) Same as B, but for the TC excitatory neurons of the TRN-TC network. (G) Strongest oscillation frequency of the population activity of the TRN inhibitory neurons. Most values are contained in the 7 - 15 Hz spindle frequency range. (H) Same as G, but for the TC excitatory neurons. (I) Same as C, but for the TRN inhibitory neurons of the TRN-TC network.

**Figure 3.1.** TRN-TC synchrony depends on gap junction strength in TRN. (A) The TRN network consists of inhibitory (I) neurons coupled in an all-to-all fashion with chemical synapses (black lines) and gap junctions (jagged green lines). For all the following activity diagrams, the x-axis represents the mean gap junction coupling $\gamma$ and the y-axis represents the mean value of the network external drive $\nu$. (B) Power in the Fourier domain of the strongest oscillation frequency of the population activity. The red area denotes oscillations characterising the synchronous regular regime (SR) and the blue area shows the lack of oscillations characterising the asynchronous irregular regime (AI). (C) Ratio of bursting $A_{\text{bursting}}$ over spiking $A_{\text{spiking}}$ activity. Sparse spiking prevails in the dark region while bursting is dominating in the light region. (D) The thalamus network consists of excitatory neurons coupled with chemical synapses among them and with the TRN inhibitory neurons in an all-to-all fashion. (E) Same as B, but for the TRN inhibitory neurons of the TRN-TC network. (F) Same as B, but for the TC excitatory neurons of the TRN-TC network. (G) Strongest oscillation frequency of the population activity of the TRN inhibitory neurons. Most values are contained in the 7 - 15 Hz spindle frequency range. (H) Same as G, but for the TC excitatory neurons. (I) Same as C, but for the TRN inhibitory neurons of the TRN-TC network.
Figure 3.2. Gap junction plasticity can generate spindle-like activity.

(A) The gap junction plasticity is activity-dependent, high-frequency activity leads to long-term depression of the gap junctions (gLTD), while sparse activity leads to long-term potentiation of the gap junctions (gLTP). (B) Plasticity mechanism leading to the generation of spindle-like events. The first row shows the population activity of inhibitory neurons, defined as the sum of action potentials, as a function of time. After a period of asynchronous activity, neurons synchronise in a waxing and waning fashion. The second row shows the voltage trace of a single neuron \( i \). The same neuron \( i \) is chosen for the following graphs. The vertical red bars show the neuron spiking times \( v_i \geq 0 \). The third row shows the low-pass filter of the spiking activity, quantifying the bursting activity of the neuron. The fourth row shows the second low-pass filter of the spiking activity, which measures sustained bursting activity. The dashed-line \( \theta_{LTD} = 0.3 \) represents the threshold above which gLTD (green region) is activated. The last row shows the mean value of all gap-junctions coupling neuron \( i \). The gap junctions are potentiated on the spike times (vertical red bars) and depressed when the LTD filter is above its threshold.
Figure 3.3. Gap junction plasticity induces irregular behaviour.
(A) Population activity, defined at the instant sum of action potentials of inhibitory neurons (top, 40 seconds) and mean gap junction coupling (bottom, 600 seconds) as a function of time. (B) 3D Phase portrait of the mean gap junction strength (x) as function of its delayed representation (y delayed by 100 ms and z delayed by 200 ms). 2D Phase portrait in (x,y), (y,z) and (z,x) phase space representation. (C) 10 realisations of the mean gap junction coupling. The same random seed is chosen for all 10 realisations, however at 10 s, a small random perturbation (with a different random seed between realisations) is added to the gap junction coupling, and the traces diverge. All simulations are done with the same frozen noise and the gap junction perturbations are the only source of variability between realisations. (D) Estimation of the largest Lyapunov’s exponent. The blue line represents the logarithm of the average of the L1 distance between pairs of realisations. The realisations diverge exponentially immediately after the perturbations. The dashed black line represents the results of a linear regression for the 30 seconds following the perturbations.
**Figure 3.4. TRN activation can suppress spindle activity.**

Panels A and B consist of the same sub-panels, but for different values of TRN external drive (left: $\nu = 40$ pA and right: $\nu = 50$ pA). The first row shows the population activity of inhibitory neurons as a function of time. The second row shows the local field potential, which is computed as the mean membrane voltage of inhibitory neurons. The third row shows the evolution of the mean gap junction coupling. The fourth row shows a spectrogram of the network spiking activity, red colour represents strong power of the corresponding frequency in the Fourier domain. The last row shows a frequency histogram over the same simulation time. (A) With $\nu = 40$ pA, there is spindle activity. The gap junction coupling oscillating which results in waxing and waning oscillations of around 9 Hz, as shown by the spectrogram and frequency histogram. (B) From (A), the TRN external is increased to $\nu = 50$ pA. The network is in the asynchronous irregular regime. The mean gap junction coupling (third row) is stable and the spectrogram and frequency histogram show no dominating frequency. (C) Same as Figure 3.1E, power in the Fourier domain of the strongest oscillation frequency of the population activity. The dashed line represents the iso-power line of 5 dB. (D) Same as Figure 3.1I, mean spiking activity type. The continuous line represents the iso-activity line of 0.002 and the dashed line represents the iso-power line of 5 dB, extracted from Figure 3.4C.
Figure 3.5. Potential action of propofol in the generation of spindle activity.

Panel A consists of the same sub-panels as Figure 3.3B ($\nu = 50$ pA) but for a larger value of the time constant of the inhibitory synapses ($\tau_I = 20$ ms instead of 10 ms). (A) With propofol, the time constants of inhibitory synapses is increased ($\tau_I = 20$ ms). There is the emergence of spindle activity with waxing and waning oscillations of around 8 Hz, as shown by the spectrogram and frequency histogram. (B) Similar activity type diagram as Figure 3.1E, but for $\tau_I = 20$ ms. The red dashed line represents an iso-power line of 5 dB, similarly as drawn on panel 3.4C. The continuous blue line represents an iso-activity line of 0.002. (C) Power of the oscillations during spindle events as function of the inhibitory synapse time constant $\tau_I$. (D) Duration of the spindles oscillations as function of $\tau_I$. (E) Intervals between spindle events as function of $\tau_I$. 

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Figure 3.6. Voltages traces and network activity during spindle events for the network with just the TRN inhibitory neurons.

(A) In grey, population activity during a spindle event. In blue, voltage traces of 3 different TRN interneurons during the same time. During the spindle, the neuron burst together, but are not synchronised otherwise. (B) Raster plot during the same spindle event as presented in (A). Each line corresponds to one neuron, and the dots represent the spiking times. (C) As for (A), but zoomed-in on only 1000 ms.
Figure 3.7. Voltages traces and network activity during spindle events for the TRN-TC network.  
(A) In grey, population activity during a spindle event. Below, voltage traces of different TRN interneurons (blue) and TC excitatory neurons (red) during the same time. During the spindle, the neuron burst together, but are not synchronised otherwise.  
(B) Raster plot during the same spindle event as presented in (A). The spiking times of 100 TRN interneurons are plotted in blue, and 100 TC neurons in red.  
(C) As for (A), but zoomed-in on only 1000 ms.
Figure 3.8. Propofol induces spindles through gap junction plasticity.
The x-axis represents the time constant of the TRN interneurons $\tau_I$ and the y-axis represents the external drive to the TRN $\nu$.
(A) Mean power of the spindles. Light colours denotes more power. There is spindle activity for high values of $\tau_I$ and $\nu_E$. (B) Mean duration of spindle events. (C) Mean time intervals between spindle events. (D) Variance in the intervals between spindle events.
Chapter 4

Predicting neural network dynamics from hemodynamic response

Hemodynamic response is often used to estimate neural activity in imaging approaches such as blood-oxygen-level dependent functional magnetic resonance imaging (BOLD fMRI), yet the need of a better understanding of the relationship between changes in hemodynamic response and neural activity remains. To address this, we investigate in this chapter the nature of the neurovascular coupling and we develop a computational model to estimate neuronal dynamics from its localized hemodynamic response. We obtained widefield mesoscopic in vivo optical imaging from transgenic mice expressing the genetically encoded voltage indicator (GEVI) VSFP Butterfly 1.2 in layer 2/3 pyramidal neurons. Our modelling approach assumes that the hemodynamic response signal is the result of the convolution of the neural activity signal with a transfer function, to be determined, using the separated voltage and hemodynamic signals in the form of changes in fluorescence intensity from these experiments. We first investigate the dependency of the transfer function to the brain state, and to the mouse vessel map. Then, we use our transfer function model to predict neural dynamics, knowing the hemodynamic response, and vice-versa. We would like to thank Chenchen Song and Thomas Knöpfel for providing the data and for their insight on the project.

Introduction.

Hemodynamic and metabolic processes accompanying neural activity result in dynamic alterations in cerebral blood flow. Despite the difference in temporal resolution, this hemodynamic response is routinely used as a proxy of neural activity in imaging approaches, such as blood-oxygen-level dependent functional magnetic resonance imaging and optical imaging of intrinsic signals, due to neurovascular coupling (Buxton and Frank (1997); Logothetis et al. (2001); Devor et al. (2003); Buxton et al. (2004); Jones et al. (2001); Berwick et al. (2003)).

However, the precise spatiotemporal relationship between hemodynamic response and neural activity remains insufficiently understood (Jones et al. (2004); Devonshire et al. (2001)).
The hemodynamic response is also intrinsically dynamic across different brain states (Mourao-Miranda et al. (2005)), and also comprised of distinct signal components (including both blood volume and blood oxygenation) that need to be separately considered (Bandettini et al. (1997); Buxton et al. (1998); Gu et al. (2005); Sirotin et al. (2009); Ma et al. (2016, 2017)). Increasing evidence are showing that spatially distributed cortical regions interact dynamically through different brain states (De Luca et al. (2006)), but the hemodynamic response and its relationship to neural activity are both unclear. The experimental access to neurovascular coupling had been technically limited, where large area monitoring of neural activity in fully intact brains was challenging.

Genetically encoded voltage indicators (GEVIs) including the voltage sensitive fluorescent protein (VSFP) family were developed to overcome this limitation, where its specific expression in identified cell classes allows mesoscopic monitoring of voltage activity (proxy of the neural activity) in restricted cell populations through a fully intact skull (Siegel and Isacoff (1997); Dimitrov et al. (2007); Akemann et al. (2010)). In particular, FRET-based ratiometric VSFPs (e.g. the VSFP Butterfly family) are capable of providing simultaneous optical readout of both hemodynamic and voltage activity, where the change in fluorescence of the pair of acceptor and donor fluorescent proteins is divergent for voltage activity, and positively correlated for hemodynamic responses (Akemann et al. (2010); Lam et al. (2012); Mutoh et al. (2012); St-Pierre et al. (2014)).

We obtained from Thomas Knöpfel’s lab wide-field mesoscopic optical voltage imaging in vivo, acquired using transgenic mice expressing VSFP Butterfly 1.2 in cortical layer 2/3 pyramidal neurons (Mishina et al. (2014); Knöpfel et al. (2015)). We first analysed the coupling between voltage and hemodynamic signals averaged over the whole cortical layer. Then, we developed a mathematical model of the neurovascular coupling using three free parameters. We investigated the evolution of those parameters across brain states and against the distance to blood vessels. Finally, we measured the prediction capability of our neurovascular coupling model, by predicting the neural activity from the hemodynamic signal and vice-versa.

Results

Modelling the neurovascular coupling.

To study the neurovascular coupling we obtained hemodynamic and voltage data from the Knöpfel’s lab (Song (2016)). The data was acquired as mice were exhibiting burst suppression, which is an alternation of latent activity and burst firing observed during the
transition from deep sleep to alertness. The recordings were then split into one-minute recordings, called repeats. We first investigate the relationship for the recordings averaged over a region of interest (ROI) describing the mouse cortex (Figure 4.1A). While the voltage signal shows sharp transitions between latent activity and high-frequency activity states (Figure 4.1B), the hemodynamic response shows smoother variations (Figure 4.1C) and seems correlated to the voltage activity. We hypothesize that the hemodynamic signal is the result of a convolution of the voltage signal with a filter $\alpha$, which we call transfer function. In the Fourier domain, the transfer function is the ratio of the Fourier transform of the hemodynamic signal to the Fourier transform of the voltage signal (neural activity). We note the sharp peak around 9 Hz in the real component of the Fourier transform, which is in the range of the heartbeat frequency of a mouse (Figure 4.1D). In the temporal domain, the transfer function has a particular shape: an initial offset, a trough and an exponential decay towards 0 (Figure 4.1E). Observing similar transfer function shapes for other recordings, we aim to model it with a simple model built with three free parameters $\tau_0$, $\tau_1$ and $\tau_2$. The parameter $\tau_0$ represents the initial offset, $\tau_1$ controls the depth of the trough and $\tau_2$ the decay towards 0 (Figure 4.1E, green trace). This model unveils some properties about the relationship between hemodynamic and voltage signals. It shows a delayed negative correlation between the hemodynamic and the voltage signal. Indeed, as spiking activity goes up, few hundreds of milliseconds later, the cortical blood flow increases in support to the neural activity, which in turn leads to an increase in the light absorbance and a decrease in the hemodynamic signal. The width of the trough, controlled by $\tau_2$, reflects the duration of the time window in which the voltage signal is correlated with the hemodynamic signal. We note that, initial offset values $\tau_0$ different than zero underlie an instant coupling between both signals. Indeed, the first part of the curve approximates a Dirac delta function, which is the identity for the convolution operator. This could results from a lack of separation between voltage signal and hemodynamic response (Carandini et al. (2015)).

To summarize, we can model the relationship between neural activity and cortical blood flow. We now wonder how this relationship evolves with the brain state.

**Brain state could modulate the neurovascular coupling.**

To investigate the change in neurovascular coupling with the brain state, we compute the transfer function when a mouse seems to transition from deeper sleep to a more alert state (Figure 4.2A). We note that, throughout the experiment, the width of the trough of the transfer function becomes smaller (Figure 4.2B-D), indicating faster responses of the hemodynamic signal. This evolution could be associated by a decrease in the anaesthetics concentration in the mouse blood, driving the mouse towards a more alert state. However,
we could not reliably repeat this analysis on other recordings. In the future, it could be interesting to directly study the evolution of the transfer function as function of the anaesthetics concentration. We observed that the neurovascular coupling could depend on the brain state, with faster coupling for more alert states. We now wonder if there is a spatial dependency of the coupling.

Spatial dependency of the transfer function.

After having studied the relationship between voltage and hemodynamic signals averaged over the mouse cortex, and observed that brain states may modulate this coupling, we investigate the spatial dependency of the neurovascular coupling. We could expect that neurons near arteries have an easier access to oxygen and therefore exhibit a faster hemodynamic response than those far away from arteries. Cortical blood flow recordings display the amount of light reflected, which is lower in regions where the blood is rich in oxygen, near the arteries for example, because more light is absorbed. We segment those regions of lower intensity and create a putative vessel map (Figure 4.3A). We fit our transfer function model for every position within the ROI and plot the values obtained for each three parameters (Figure 4.3D) and their respective standard deviation error (Figure 4.3C). Similar topographies appear in most of the maps and we note that they can relate to the vessel map. To validate our hypothesis that the transfer function changes as function of the distance to the arteries, we study the value of the parameters as function of the distance to the putative arteries (Figure 4.3D). We perform a linear regression for each parameter against the distance of this position to the closest putative vessel.

We observe that $\tau_2$, which controls the duration of the time window in which the voltage signal influences the hemodynamic signal, increases as the distance to the vessel increases. This positive correlation could mean that, for a position distant from arteries, the neurovascular coupling is slower and the hemodynamic signal is influenced for a longer time.

To summarize, we observed that the neurovascular coupling is spatially dependent, being faster close to the vessels.

Prediction of neural dynamics from the hemodynamic response.

Modelling the coupling between neural activity and hemodynamic signal not only offers insight about their relationship, it also allows us to predict one signal having the other. We computed a transfer function model $\alpha_{model}$ by fitting the raw transfer function of a repeat of mouse M1217F (Figure 4.4A). Using this model, we predict $\hat{v}$ and $\hat{h}$ for the other repeats of both mice M1217F and M1223M. We observe that the prediction seem to perform
well for low frequency variations while high frequency variations are filtered out. It also seems that there is not enough information in the hemodynamic signal to predict the high frequency components of the voltage signal, and the fast oscillations obtained are due to the heartbeats, found in the hemodynamic signal (Figure 4.4B).

We then proceed to measure the prediction performance. To that end we compute the correlation between the data and the predicted signal, for both hemodynamic and voltage signals, and we compare the correlation between hemodynamic and voltage signal as a baseline (Figure 4.4C). We observe that, while being modelled from a single repeat of mouse M1217F (isolated from the test data), the prediction for the neural activity (Figure 5D) and the hemodynamic signal (Figure 4.4E) are improved over the baseline levels. It also seems that the predictions for the repeats of M1217F are better overall than those of mouse M1223M, which might be due to some dependency of the transfer function to the specimen, and our model could be overfitting for mouse M1217F.

To summarize, we show that modelling the neurovascular coupling allows to predict neural activity from unseen hemodynamic data, with better accuracy than simply taking the hemodynamic signal as proxy.
Discussion.

This study investigated the nature of the neurovascular coupling for layer 2/3 pyramidal neurons. We first observed that some properties of this coupling are conserved between brain states of between specimens. It can be approximated by a transfer function such that the hemodynamic response is the result of the neural activity convolved by this transfer function. The transfer function highlights the delayed anti-correlation between neural activity and hemodynamic response, which we can understand as follows: surges in neural activity require increase in blood flow to provide the necessary oxygen in support to the active neurons. The oxygen-rich blood, which arrives with a delay, exhibits less hemodynamic signal due to the increased light absorbance resulting from the additional oxygen and larger blood volume. The neurovascular coupling can be approximated by a mathematical model with three free parameters. We study the evolution of this simple model regarding different conditions. We observed that the brain state can influence the neurovascular coupling. It seems that more alert states are associated with faster hemodynamic responses to the change of neural activity. However, more/better data could improve the characterisation this dynamic. First, as we observed in the result section (Figures 4.1E and 4.2B-C), the voltage and hemodynamic signals seem to lack separation, which could result in correlation being already present in the data and influence positively our predictions. Then, we develop our model of transfer function based a single experiment from one mouse, and tested it on both mice (excluding the experiment used for fitting the model). However with the low number of data points and specimen, it is difficult to prevent overfitting of our model and we cannot be sure how well it generalises on other specimen, let alone across species. Gathering more data seems crucial to further test the validity of our assumptions. We also observed that the neurovascular coupling is spatially dependent, with slower hemodynamic response for neurons more distant to vessels. However, the signal-to-noise ratio can be really poor for local values of the voltage or hemodynamic signal, which leads to difficult estimation of the local transfer functions and results in high variability of the model parameters. More sophisticated statistical analysis could isolate the most relevant data. Moreover, despite being robust the Levenberg-Marquardt (Levenberg (1944); Marquardt (1963)) algorithm for solving non-linear least squares problems only provides local minima, therefore it might be possible that better solutions for the transfer function model exist. Also, our vessel segmentation has not been proofed against expert manual segmentations. It would also be interesting to separate arteries from veins, as arteries might have a more relevant role in the neurovascular coupling.

Modelling the neurovascular coupling not only improves our understanding of the relationship between neural activity and cortical blood flow, it also allows us to predict one
quantity knowing another. Functional magnetic resonance imaging (fMRI) is a non-invasive imaging modality that provides a measure of the blood oxygen concentration in the brain (Ogawa et al. (1990a,b); Ogawa and Lee (1990)). It was long assumed that blood oxygen concentration is a correlate of neural activity (Roy and Sherrington (1890)). Therefore, fMRI can be used to identify the critical functions performed in different brain regions. Our model shows that the direct link between neural activity and hemodynamic response holds true for slow varying quantities, because of the slowness of the vascular response. However, as technology and techniques improve, fMRI spatial and temporal resolution increase, and this relationship can be refined. We could imagine that, for fast fMRI, our model could improve the prediction of the neural activity, and therefore the quality of the diagnostics based on this modality.
Materials and Methods.

Experimental data.

Data was acquired and preprocessed by the Knöpfel Lab (Song (2016)), in the form of video clips of neural activity and hemodynamic response, with binary masks defining the region of interest.

The neural activity was obtained from transgenic mice expressing GEVI VSFP Butterfly 1.2 in cortical layer 2/3 pyramidal neurons (Mishina et al. (2014); Knöpfel et al. (2015)). The data of two mice was used for the modelling, designated by M1217F and M1223M. During the acquisition, mice were maintained between deep anaesthesia and alertness through the administration of isoflurane. This was performed with the aim to observe burst suppression, which is a neural dynamic where neurons alternate between high frequency activity and latent periods. Data was recorded in sets of 4 minutes intervals, later split in 1 minute intervals called repeats. A set of 4 consecutive repeats is called an experiment.

Transfer function.

To model the transfer function between voltage signal (neural activity) and hemodynamic signal (cortical blood flow), we assume that the hemodynamic signal is the result of the voltage signal convolved by a filter $\alpha$,

$$(v * \alpha)(t) = h(t). \quad (56)$$

The convolution theorem lets us write that the Fourier transform of this convolution is equal to the point-wise product of the individual Fourier transforms $\mathcal{F}(v * \alpha) = \mathcal{F}(v) \cdot \mathcal{F}(\alpha)$ where $\mathcal{F}$ is the Fourier transform. Thus, having $v$ and $h$ we can estimate the transfer function in the Fourier domain, $\mathcal{F}(\alpha)$, with

$$\mathcal{F}(\alpha) = \frac{\mathcal{F}(h)}{\mathcal{F}(v)}, \text{ for } v \neq 0. \quad (57)$$

Note that we remove frequencies over 100 Hz from $\mathcal{F}(h)$ and $\mathcal{F}(v)$ to reduce the amount of noise in the data. Going back to the temporal domain, we obtain the transfer function $\alpha$ with

$$\alpha = \mathcal{F}^{-1}(\mathcal{F}(\alpha)). \quad (58)$$
Modelling the transfer function.

We model the transfer function with three free parameters $\tau_0, \tau_1$ and $\tau_2$ with the following equation

$$\alpha_{\text{model}}(t, \tau_0, \tau_1, \tau_2) = \frac{\tau_0}{t + \epsilon} - \frac{t}{\tau_1} e^{-\frac{t}{\tau_2}}, \text{ with } \tau_1, \tau_2 > 0,$$

where $\epsilon$ is chosen arbitrarily small ($\epsilon = 0.01$) such that the function $\alpha_{\text{model}}$ is defined in 0. $\tau_0$ controls the initial offset of the model, $\tau_1$ controls the depth of the trough and $\tau_2$ controls its width.

Fitting the transfer function model.

Parameters of the transfer function model are estimated by finding $\beta = (\tau_0, \tau_1, \tau_2)$ minimizing the sum of residuals

$$\hat{\beta} = \arg\min_{\beta} S(\beta),$$

with

$$S(\beta) = \sum_t |\alpha(t) - \alpha_{\text{model}}(t, \beta)|^2.$$

We use the Levenberg-Marquardt (LM) algorithm to solve this minimisation problem (Levenberg (1944); Marquardt (1963)). The LM algorithm, despite finding only local minima, is robust (Marquardt (1963); Ramsin and Wedin (1977)). In particular, we choose initial parameters close to what seems the global solution, with $\beta_0 = (0.04, 4, 5)$.

Using the transfer function as a predictive tool.

With the assumption that the transfer function is generalizable among mice and brain states, we can use it to predict one signal having another. Thus, we can predict the hemodynamic signal $\hat{h}$ with

$$\hat{h} = \mathcal{F}^{-1}(\mathcal{F}(v) \cdot \mathcal{F}(\alpha_{\text{model}})).$$

Similarly, knowing $h$, we can estimate the voltage $\hat{v}$ with

$$\hat{v} = \mathcal{F}^{-1}\left(\frac{\mathcal{F}(h)}{\mathcal{F}(\alpha_{\text{model}})}\right), \text{ with } \alpha_{\text{model}} \neq 0.$$ 

Performance of the prediction.

To measure the quality of the predicted signal, we evaluate the Spearman’s correlation coefficients between the original signals ($h$ or $v$) and their predictions ($\hat{h}$ or $\hat{v}$). The Spearman’s correlation coefficient is a non-parametric test which measures the strength of a
monotonic relationship between paired data. It ranges in [-1;1] where 0 means that there is no monotonic relationship between the variables, negative values denote an anti-correlation and values close to ±1 denote a very strong monotonic relationship. The Spearman’s correlation between \( h \) and \( \hat{h} \) is

\[
c_{h,\hat{h}} = \frac{\text{cov}(rg_h, rg_{\hat{h}})}{\sigma_{rg_h} \sigma_{rg_{\hat{h}}}}
\]

where \( rg \) denote that the variable is ranked, \( \text{cov} \) is the covariance and \( \sigma \) denotes the standard deviation. The Spearman’s correlation \( c_v,\hat{v} \) between \( v \) and \( \hat{v} \) is defined similarly by substituting \( h \) by \( v \).

**Vessel segmentation and vessel distance map.**

We perform the vessel segmentation in three steps. First, we measure the logarithm of the variance of the hemodynamic signal. The signal to noise ratio being low, we assume the variance comes mostly from noise and is lower close to the vessels, where the signal is better. Second, we equalize the histogram locally by performing a Contrast Limited Adaptive Histogram Equalisation (CLAHE) (Zuiderveld (1994)), with a filter size of (50 px,50 px). The CLAHE enhances the contrast but prevents the over-amplification of noise that can result from the application of adaptive histograms. Third, we binarise the image to segment what we assume to be the vessels. Values are first rescaled between 0 and 255, then only pixels with intensity below 60 are considered vessels, the rest is considered background.

Once we have a vessel map, we create a vessel distance map which calculates the Euclidian’s distance to the closest pixel belonging to the vessel class \( V \), with

\[
d(x,y) = \min_{(x',y') \in V} \sqrt{(x-x')^2 + (y-y')^2}.
\]

**Spatial dependency of the transfer function model.**

We wish to test the hypothesis that there is a linear relationship between the parameter values, and their distance to the closest vessel. Therefore, we perform a linear regression of the parameters values \( \tau_k(x,y) \) again the vessel distance map \( d(x,y) \)

\[
\tau_k(x,y) = A_k \cdot d(x,y) + b_k,
\]

with

\[
A_k = \frac{\sum_{x,y}(d(x,y) - \bar{d})(\tau_k(x,y) - \bar{\tau}_k)}{\sum_{x,y}(d(x,y) - \bar{d})^2}
\]

(67)
and

\[ b_k = \bar{\tau}_k - A_k \cdot \bar{d} \]  \hspace{1cm} (68)

with \( k = \{0, 1, 2\} \) and where a horizontal bar over a quantity denotes the average value of that quantity.
Figure 4.1. Modelling the relationship between hemodynamic and voltage signals.

(A) Binary mask used for mouse M1232M to define the Region of Interest (ROI) over the mouse cortex. Below is an example of a single frame of the voltage and hemodynamic signal respectively. B to D represent variables as function of time (x-axis). 

(B) The voltage signal is average over the ROI for the 2950 frames acquired at 50 Hz. (C) Same as B, for the hemodynamic signal. (D) Transfer function in the Fourier domain, $\mathcal{F}\alpha$. (E) In red, temporal representation of the transfer function $\alpha$ described in D. In green, model of the transfer function ($\tau_0 = 7.21 \cdot 10^{-2}$ s, $\tau_1 = 11.9$ s, $\tau_2 = 1.14$ s)
Figure 4.2. Brain state may modulate the coupling between hemodynamic and voltage signals. 

(A) 4 consecutive 1 minute recordings of hemodynamic (light blue) and voltage (dark blue) signals, from repeat $r_0$ to repeat $r_3$. Signals are normalized between 0 and 1.  

(B) In red, transfer function $\alpha$ in the temporal domain of the corresponding signals shown in A. In green, fitted models of the transfer function, $\alpha_{\text{model}}$. 

(C) The modelled transfer functions presented in B are superimposed and drawn with increased opacity going from $r_0$ to $r_3$. 

(D) Value of the parameter $\tau_2$ of the transfer function model, for the repeats 0 to 3 of the same recording displayed on panels A,B and C.
Figure 4.3. Spatial dependency of the coupling between hemodynamic and voltage signals.
Transfer functions and their models have been computed at each position within the ROI. (A) Segmentation of the vessels from the hemodynamic data to generate a map of the distance to the closest vessel. A time-average of the recording results in an image that is processed with a Contrast Limited Adaptive Histogram Equalisation (CLAHE) filter with a filter size of (50,50). Then a threshold is applied to generate the vessel segmentation, from which the distance transform is computed. (B) Parameter estimations for $\tau_0$, $\tau_1$, $\tau_2$ found in the 95th percentile. Lighter colours represent higher values. (C) Standard deviation error of the respective parameters in B. Lighter colours represent lower values. (D) Value of the parameters $\tau_0$, $\tau_1$, $\tau_2$ as function of the distance to the closest vessel.
Figure 4.4. Performance of signal prediction.
A model of the transfer function is chosen after fitting a transfer function of an experiment of mouse M1217F and is used to predict signals of other recordings of mouse M1217F and of the recordings of mouse M1223M. (A) The light blue curve is a model of the transfer function in the temporal domain, obtained after fitting the transfer function of mouse M1217F, experiment 4, repeat 1 (in red). For (A) and (B), 60 seconds of recordings are displayed. (B) Traces of hemodynamic data (light blue) and voltage (dark blue) of mouse M1223M, and their predicted models (orange) for experiments 31 and 33, obtained with the modelled transfer function presented on panel A. For the following panels C,D,E, box plots show a distribution of the data: each box spans the 25th and 75th percentile of the distribution, the middle line is the median, and the lower and upper whiskers indicate the minimum and maximum values. (C) Box plots of the Spearman’s correlation coefficients between hemodynamic and voltage data of each repeat, grouped by experiment. (D) Box plots of the Spearman’s correlation coefficients between voltage and predicted voltage data, of each repeat, grouped by experiment. (E) Box plots of the Spearman’s correlation coefficients between hemodynamic and predicted hemodynamic data, of each repeat, grouped by experiment.
Chapter 5

Conclusion

Summary of thesis.

In this thesis we aimed at modelling and analysing neural network dynamics, in order to further understand its inner mechanisms. We first developed computational models of neural networks with gap junction plasticity and observed the emergence of neural dynamics. From Haas et al. findings (Haas et al. (2011a)), we modelled a gap junction plasticity rule, which is homeostatic and, more specifically, regulates oscillations. On one hand, if the gap-junction long-term potentiation (gLTP) is too weak, oscillations do not occur. This is seems implausible as weak oscillations are usually reported in cortical networks during cognitive functions. On the other hand, if the gLTP is much stronger than the gap junction long-term depression (gLTD), the network exhibits only synchronized oscillations, which could be pathological. Outside of those extreme cases, the gap junction plasticity maintains the network near the transition between asynchronous irregular regime and synchronous regular regime. As a consequence, interesting network dynamics can emerge. From a constant stimulus, the network can exhibit transient oscillations, which allows for efficient transfer of salient information. In the oscillatory regime, gap junction plasticity could ensure robustness of information transfer between brain regions through frequency modulation. In some other cases, it is possible that equilibrium between gLTP and gLTD, and between asynchronous and synchronous regimes, are unstable and lead to what seems to be chaotic activity. By oscillating near the transition between asynchronous and synchronous regimes, the gap junction plasticity can lead to the emergence of spindle oscillations. Moreover our results are consistent with experimental studies of pharmacological spindle manipulation. Our results shows that gap junction plasticity could play a major role in the regulation of neural network dynamics. However, our models are based on sometimes critical assumptions, such as the potentiation rule and learning rate, as there is no data yet that about activity-dependent gLTP. Yet, our investigation indicates that different rules that the one mainly explored could lead to similar outcomes. We hope that, as technique and technology improve, so will the characterisation of gap junction plasticity.

Currently, there is no technology that allows the tracking of neural activity of large
populations of neurons at high spatial and temporal resolution *in vivo* in deep brain regions. Functional magnetic resonance imaging (fMRI), which can measure the blood-oxygen level non-invasively with increasingly better spatial and temporal resolution, is often used as a proxy of the neural dynamics. However, the relationship between hemodynamic response and neural activity can be refined. Here we have shown that, we can build a model that allows predictions of the slow component of the neural activity, given the hemodynamic response. This was possible due to the recent development of genetically encoded voltage indicators that allow the tracking of neural activity, simultaneously as recording of the hemodynamic response, and both at a high spatial and temporal resolution. Better voltage and hemodynamic signal separation and more data are necessary to improve our neurovascular coupling model and to better understand its dependency such as the brain state, or to better generalise between different individuals.

**Future Work.**

The work presented in this thesis approached the modelling and analysing of neural network dynamics from two perspectives. The first approach consisted in doing numerical simulations of mathematical models of neural networks, with plasticity rules derived from experimental studies. The second approach took on analysing experimental data and modelling the underlying relationship between hemodynamic response and neural activity. Extensions of the modelling work presented here can be pursed in the following directions:

- In our cortical and thalamo-cortical network models, chemical synapses are static. It would be interesting to investigate the implications of the plasticity of chemical synapses in concert with gap junction plasticity. In particular gap junctions are thought to be involved in circuit formation and maturation (*Hanganu et al.* (2009); *Maher et al.* (2009); *Belousov and Fontes* (2013)). Moreover, gap junctions could be involved in the plasticity of chemical synapses, as Cx36 knockout mice exhibit impairment of long-term potentiation of cortical and hippocampal chemical synapses (*Wang and Belousov* (2011); *Postma et al.* (2011)).

- modelling the modulation of gap junction coupling by neuromodulators, such as dopamine or nitric oxyde (*Roerig and Feller* (2000)). For example, gap junction coupling in the retina decreases in response to light activation, which triggers the release of dopamine and nitric oxyde (NO) (*Urschel et al.* (2006); *Bloomfield and Völgyi* (2009)). This could lead to additional insight on the effect of gap junction plasticity on neural network dynamics.
modelling the gap junction plasticity in different brain regions, such as the inferior olive, where gap junctions are involved in the synchronisation of neuronal ensemble activity (Leznik (2005)). Moreover gap junction coupling promotes millisecond precision-correlated activity among electrically coupled Golgi-cells, which could have implications on temporally precise motor control (van Welie et al. (2016)).

Gap junctions seem to play a fundamental role during development. In the postnatal days, the incidence of neuronal gap junction coupling can be over 60% in regions such as the cortex or hippocampus and is not restricted to cells of the same type (Meyer et al. (2002); Venance et al. (2004)). Then, development uncoupling occurs, during which the incidence and strength of the gap junction coupling decrease, except in some regions such as the TRN (Meyer et al. (2002)). Understanding the mechanism and consequences of the developmental regulation of gap junction coupling could provide useful knowledge, as a similar mechanism but on a shorter time-scale happens after brain injury and could be associated with cell death (Belousov and Fontes (2013)). A better understanding of the mechanisms involved could help to develop more protective actions following brain injuries.

There is currently no data on activity-dependent gap junction potentiation. We could expect that in the coming months or years, as techniques and technology improve, new experimental evidence could be used to refine our models. Moreover, most of the data on gap junctions in mammalian brains comes from the study of connexin Cx36, as it is the prevalent neuronal connexin, and Cx36 knockout models are often used to infer the role of gap junction coupling. However, other connexins could compensate for the Cx36 deficiency and future work on modelling other neuronal connexins and their interactions could be valuable.

As technology and techniques improve, so should the quality of the data obtained from genetically encoded voltage indicators or similar imaging methods. This could allow to refine the relationship between neural activity and hemodynamic response. Moreover, we could hope that new techniques would allow to track the specific activity of different neuron types independently, such as regular spiking excitatory neurons and fast spiking interneurons, which would offer helpful insight to further understand neural network dynamics.

**Conclusion.**

In this thesis, we have modelled and analysed of neural networks dynamics. We have observed how plasticity of electrical synapses could maintain the network in a non pathological regime, while allowing for information transfer. Additionally, our models suggest that gap junction
plasticity could lead to a specific type of dynamics observed during sleep, namely spindle oscillations. Then, we analysed neural dynamics in relation with hemodynamic response and we observed that our model of this relationship could predict the neural activity from the hemodynamic response alone. In summary, our work aimed to further our understanding of the regulation of neural network dynamics, through computational models based on recent findings and experimental data.
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Appendix

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