Far in space and yet in synchrony: neuronal mechanisms for zero-lag long-range synchronization

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Abstract Distant neuronal populations are observed to synchronize their activity patterns at zero-lag during certain stages of cognitive acts. This chapter provides an overview of the problem of large-scale synchrony and some of the solutions that have been proposed for attaining long-range coherence in the nervous system despite long conduction delays. We also review in detail the synchronizing properties of a canonical neuronal micro-circuit that naturally enhances the isochronous discharge of remote neuronal resources. The basic idea behind this mechanism is that when two neuronal populations relay their activities onto a third mediating population, the redistribution of the dynamics performed by the latter leads to a self-organized and lag-free synchronization among the pools of neurons being relayed. Exploring the physiological relevance of this mechanism, we discuss the role of associative thalamic nuclei and its bidirectional interaction with the neocortex as a relevant physiological structure in which the network module under study is densely embedded. These results are further supported by the recently proposed role of thalamocortical interactions as a substrate for the trans-areal cortical coordination.

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1 Introduction

The development of multi-electrode recordings was a major breakthrough in the history of systems neuroscience [1]. The simultaneous monitoring of the extracellular electrical activity of several neurons provided a solid experimental basis for electrophysiologists to test the emergence of neuronal assemblies [2]. Specifically, the parallel registration of spike events resulting from different cells permitted the evaluation of temporal relationships among their trains of action potentials, an eventual signature of assembly organization. Modern multi-electrode techniques have now the capacity to simultaneously listen to a few hundreds of cells and, in contrast to serial single cell recordings, to reveal temporally coordinated firing among different neurons that is not linked to any external stimulus but rather to internal neuronal interactions. Only equipped with such class of technology it was possible to unveil one of the most interesting scenarios of structured timing among neurons, namely the consistent and precise simultaneous firing of several nerve cells, a process referred to as neuronal synchrony [3].

Neuronal synchronization has been hypothesized to underly the emergence of cell assemblies and to provide an important mechanism for the large-scale integration of distributed brain activity [3, 4]. One of the basic ideas in the field is called the binding by synchrony theory which exploits the dimension that temporal domain offers for coding [3, 5, 6, 7, 8]. Essentially, it states that synchrony can be instrumental for temporally bringing together the processing output of different functionally specialized areas in order to give rise to coherent percepts and behavior. The differential effect that synchronous versus temporally dispersed inputs can exert onto a downstream neuron indicates how the temporal coherence of a set of neurons can become a flexible and potentially information-carrier variable that can modulate subsequent stages of processing [3, 9, 10]. Despite an ongoing debate about its functional role in neuronal processing is still open, the last two decades have seen the accumulation of large amount of data which show evidence, at least in a correlative manner, for a role of synchrony and the oscillatory activity that often accompanies it in a variety of cognitive processes ranging from perceptual grouping or stimulus saliency to selective attention or working memory [7, 11, 12, 13, 14].

Interestingly, neuronal synchrony is not restricted to the local environment of a single cortical column or area. Rather, long-range synchrony across multiple brain regions, even across inter-hemispheric domains, has been reported in several species including the cat and primate cortex [15, 16, 17, 18, 19, 20]. However, the zero-lag correlated activity of remote neuronal populations seems to challenge a basic intuition. Namely, one tends to tacitly assume that since the interaction among distant systems is retarded by the conduction delays (and therefore, that it is the past dynamics of one system what is influencing the other one at present) it is not possible that such interaction alone can induce the isochronous covariation of the dynamics of two remote systems. Actually, the latencies associated with conducting nerve impulses down axonal processes can amount to several tens of milliseconds for a typical long-range fiber in species with medium or large sized brains [21, 22, 23]. These ranges of conduction delays are comparable with the time-scale in which

neuronal processing unfolds and therefore they cannot be simply discarded without further justification. Furthermore, profound effects in the structure and dynamics of the nervous system might have arisen just as a consequence of the communication conditions imposed by the time delays [24, 25]. As an example, several proposals of the origin of the lateralization of brain functions are based on the temporal penalty to maintaining information transferring across both hemispheres [26, 27].

The aim of this chapter is to illustrate that appropriate neuronal circuitries can circumvent the phase-shifts associated with conduction delays and give rise to isochronous oscillations even for remote locations. The chapter begins with a brief review of some theories that have been proposed to sustain long-range synchrony in the nervous system. Then we explore a novel and simple mechanism able to account for zero-lag neuronal synchronization for a wide range of conduction delays [28, 29, 30]. For that purpose, we shall investigate the synchronizing properties of a specific network motif which is highly expressed in the cortico-thalamo-cortical loop and in the cortex itself [31, 32, 33]. Such circuitry consists of the relaying of two pools of neurons onto a third mediating population which indirectly connects them. The chapter goes on by presenting the results of numerical simulations of the dynamics of this circuit with two classes of models: first using Hodgkin and Huxley (HH) type of cells and second building large-scale networks of Integrate And Fire (IAF) neurons. Finally, and after a detailed characterization of the influence of long-conduction delays in the synchrony of this neural module, we discuss our results in the light of the current theories about coherent cortical interactions.

2 How can zero-lag long-range synchrony emerge despite of conduction delays?

Before discussing different mechanisms proposed to cope with the long-range synchrony problem, it is first necessary to understand the origin of the delay that arises in neuronal interactions. As a rule, it is possible to dissect in at least five different contributions the latency in the communication between two neurons via a prototypical axo-dendritic chemical synapse. For illustration purposes here we follow the time excursion of an action potential generated in a presynaptic cell up to becoming a triggering source for a new spike in a postsynaptic cell.

- The first component is due to the propagation of an action potential from the axon hillock to the synaptic terminal. The limited axonal conduction velocity imposes a delay ranging from a few to tens of milliseconds depending on the caliber, myelination, internodal distance, length of the axonal process, and even the past history of impulse conduction along the axon [23, 34, 35].
- A second element of brief latency occurs due to the synaptic transmission. After the action potential has reached the presynaptic ending several processes contribute to different degree to the so-called synaptic delay. These include the exocytosis of neurotransmitters triggered by calcium influx, the diffusion of the

transmitters across the synaptic cleft, and their binding to the postsynaptic specializations. Altogether the complete process from the release to the binding to specialized channels can typically span from 0.3 ms to even 4 ms [36].
- Another source of delay is the rise time of the postsynaptic potential. Different ionic channels show different time-scales in producing a change in the membrane conductance which eventually induces the building-up of a significant potential. For fast ionotropic AMPA or $GABA_A$ receptors it can take a time of the order of half a millisecond for such a process to rise a postsynaptic potential [37].
- Dendritic propagation toward the soma by either passive or active conduction is also a source of a small lag which value depends on the dendritic morphology.
- Finally, the postsynaptic neuron can exploit several mechanisms, such as membrane potential fluctuations, to control to some degree an intrinsic latency in triggering a new action potential [38].

For long-distance fibers the most important contribution of delay typically comes from the axonal conduction. In human, an averaged-sized callosal axon connecting the temporal lobes of both hemispheres is reported to accumulate a delay of 25 milliseconds [26]. Definitely not a negligible quantity.

Nevertheless, a fiber connecting two brain regions is inevitably composed of non-identical axons, which give rise to a broad spectrum of axonal delays rather than a single latency value [26, 39]. This is one of the possible substrates for the establishment long-range synchrony, i.e., the systematic presence (within such a spectrum) of very fast axons reciprocally interconnecting all possible areas susceptible of expressing sync. Within this framework the combination of a hypothetical extensive network of very fast conducting axons with the phase resetting properties of some class of neurons could in principle sustain an almost zero-lag long-range synchrony process. GABAergic neurons have been indicated to meet the second of such requirements. Via a powerful perisomatic control this type of cells can exert a strong shunting and hyperpolarizing inhibition which can result in the resetting of oscillations at their target cells [40, 41, 42]. Their critical role in generating several local rhythms has been well described [43, 44]. However, their implication in the establishment of long distance synchrony is heavily compromised because the expression of fast long-range projections by interneurons is more the exception than the rule [42, 44]. Another important consideration is that long-range connections in a brain do not come for free. Even a small fraction of long-distance wiring can occupy a considerably portion of brain volume, an important factor that severely restricts the use of fast large-diameter fibers [26, 44].

Electrical synapses, and in special gap junctions, have also been involved in explaining spread neuronal synchrony [45]. Gap junctions consist of clusters of specialized membrane channels that interconnect the intracellular media of two cells and mediate a direct electrical coupling and the transferring of small molecules between them [46]. Evidence for gap junctions role in giving rise to fast rhythmic activity has been put forward by observations that fast oscillations can be generated in conditions where chemical synaptic transmission was blocked [47]. Gap junctions also present two clear advantages over chemical synapses for the induction of

zero-lag synchrony. First, they are not affected by synaptic delays since no neurotransmitters are used. Second, the electrotonic coupling between cells mainly acts via diffusion mechanisms and therefore, it tends to homogenize the membrane potential of the cells involved. Thus, gap junctions can be considered of synchronizing nature rather than excitatory or inhibitory class [45]. However, as we have pointed out before for long-distance fibers the axonal delay is the largest component of latency and the saving corresponding the elimination of the synaptic delay can just correspond to a small fraction of the total. In any case, electrical synapses are believed to underly homogenization of firing among neurons and to foster synchrony in moderately distributed networks [45, 48, 49].

Proposals for explaining the observed long-range synchronous fast dynamics in the cortex have also been inspired by the study of coupling distant oscillations. In this context R. Traub and others investigated the effect of applying dual tetanic stimulation in hippocampal slices [50]. The authors of Ref. [50] observed that a strong simultaneous tetanic stimulation at two distant sites in a slice preparation induced gamma-frequency oscillations that were synchronous. The concomitant firing of spike duplets by some interneurons with such double stimulation condition plus modeling support, led the authors to infer that a causal relationship between the interneuron duplet and the establishment of long-range synchrony should hold [50, 51].

From other perspective, it is important to remind that neuronal plasticity is a key element in determining the structural skeleton upon which dynamical states such as synchrony can be built. Therefore, the experience-driven process of shaping neuronal connectivity can considerably impact the ability and characteristics of synchronization of a given neuronal structure. Interestingly, this interaction can go in both directions and correlated input activity can also influence the connectivity stabilization via certain plasticity processes [52]. With respect to the specific issue of the influence of axonal delays in long-range coherence, modeling studies have shown that spike-timing-dependent plasticity rules can stabilize synchronous gamma oscillations between distant cortical areas by reinforcing the connections the delay of which matches the period of the oscillatory activity [53].

In summary, there are a number of factors and mechanisms that have been put forward to explain certain aspects of the long-range synchronization of nerve cells. Synchronization is a process or tendency toward the establishment of a dynamical order with many possible participating sources, and as a result it is not strange that several mechanisms can simultaneously contribute or influence it. Thus, neural systems might use distinct strategies for the emergence of coherent activity at different levels depending on the spatial scale (local or long-range), dynamical origin (intracortical or subcortical oscillations), and physiological state (sleep or awake), among others. Nevertheless, one should notice that a significant long-range synchronization is observed across different species with different brain sizes and at different stages of the developmental growth of brain structures. This point strongly suggests that any robust mechanism for generating zero time-lag long-distance cortical synchrony maintains its functionality for a wide range of axonal lengths. While it is possible

that developmental mechanisms compensate for the resulting delay variations [54] it is still difficult to explain all the phenomenology of long-distance synchronization without a mechanism that inherently allows for zero-lag synchronization for a broad range of conduction delays and cell types. In the following parts of this chapter we focus our attention on a recently proposed scheme named dynamical relaying which might contribute to such mechanism [28, 29, 30].

3 Zero-lag long-range neuronal synchrony via dynamical relaying

In this section we explore a simple network module that naturally accounts for the zero-lag synchrony among two arbitrarily separated neuronal populations. The basic idea that we shall further develop later, is that when two neuronal populations relay their activities onto a mediating population, the redistribution of the dynamics performed by this unit can lead to a robust and self-organized zero-lag synchrony among the outer populations [28, 29, 30].

At this point it is important to remind the separation of processes generating local rhythms or oscillations in a brain structure from the mechanisms responsible for their mutual synchronization. The model and simulations that are presented below provide a proof of principle for a synchronizing mechanism among remote neuronal resources despite long axonal delays. No particular brain structure or physiological condition is intended to be faithfully reproduced, rather the main objective is the demonstration that under quite general conditions an appropriate connectivity can circumvent the phase lags associated to conduction delays and induce a zero-lag long-range synchrony among remote neuronal populations. In any case, it is worth mentioning that the diffused reciprocal connectivity which dynamical consequences we study below is characteristic of the interaction of the neocortex with several thalamic nuclei [31, 32]. Connectivity studies in primate cortex have also identified the pattern of connections investigated here as the most frequently repeated network motif at the level of cortico-cortical connections [33, 55, 56].

3.1 Illustration of dynamical relaying in a module of three HH cells

The most simple configuration to illustrate the effects of dynamical relaying corresponds to the study of the activities of two neurons that interact by mutually relaying their dynamics onto a third one. We begin then by investigating a circuit composed of three Hodgkin & Huxley cells with reciprocal delayed synaptic connections (see top panel in Figure 1 for an schematic representation of the network architecture). We first consider a condition in which the isolated neurons already operate in an intrinsic spiking state and observe how the synaptic activity modifies the timing of

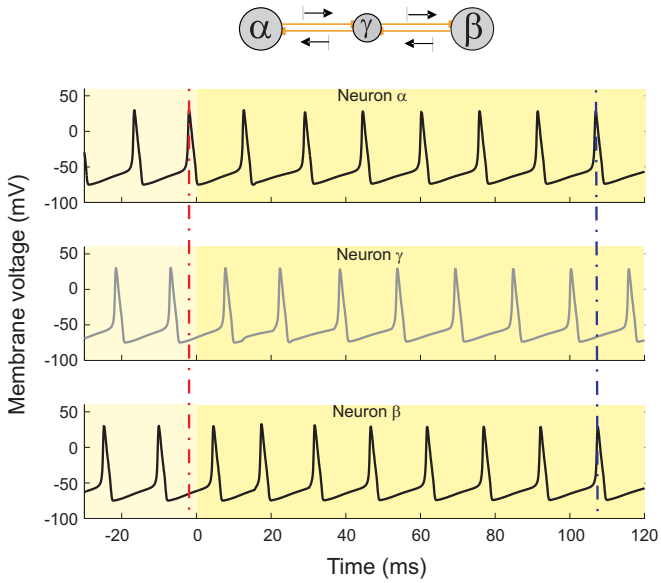

Fig. 1 Time series of the membrane voltage of three coupled HH cells $N_\alpha - N_\gamma - N_\beta$. At time $t = 0$ the excitatory synapses were activated. Conduction delay $\tau = 8$ ms. Vertical lines help the eye to compare the spike coherence before and after the interaction takes place.

their action potentials. To this end we add an intracellular constant current stimulation (10 μA/cm^2) so that each isolated neuron develops a tonic firing mode with a natural period of 14.7 ms. The initial phase of the oscillations of each cell is randomly chosen to exclude any trivial coherent effect. Finally, we also set all axonal conduction delays in the communication between neurons to a considerably long value of 8 ms to mimic the long-range nature of the synaptic interactions. Further details about the methodology used in the following simulations can be found at Refs. [29, 30]. In Figure 1 we show the evolution of the membrane potentials under such conditions before and after an excitatory synaptic coupling among the cells is activated.

Previously to the switch-on of the synaptic coupling between the cells we can observe how the three neurons fire out of phase as indicated by the left vertical guide to the eye in Figure 1. However, once the interaction becomes effective at $t = 0$ and synaptic activity is allowed to propagate, a self-organized process, in which the outer neurons synchronize their periodic spikes at zero-phase even in the presence of long conducting delays, is observed. It is important to notice that no external agent or influence is responsible for the setting of the synchronous state but this is entirely negotiated by the network itself. Furthermore, we checked that the present synchrony is not just a phase condition between purely periodic oscillators but a true temporal relationship. To that end, we added independent noisy membrane fluctuations to each neuron that resulted in a non-perfectly deterministic firing of the three

neurons. In this case, the circuit maintained an approximated zero-lag synchrony between the outer neurons, reflecting both the robustness of the synchrony mechanism to moderate noise perturbations and showing that the synchrony process can be generalized beyond a phase relation.

The mechanism responsible for synchronization depends on the ability of an EPSP to modify the firing latencies of a postsynaptic neuron in a consistent manner. It further relies on the symmetric relay that the central neuron provides for the indirect communication between the outer neurons. The key idea is that the network motif under study allows for the outer neurons to exert an influence on each other via the intermediate relay cell. Thus, the reciprocal connections from the relay cell assure that the same influence that is propagating from one extreme of the network to the other is also fed-back into the neuron which originated the perturbation and therefore, promoting the synchronous state.

It must be noticed, however, that the effect of a postsynaptic potential on a neuron strongly depends on the internal state of the receiving cell, and more specifically on the phase of its spiking cycle at which a postsynaptic potential (PSP) arrives [57, 58]. Since the neurons of the module are in general at different phases of their oscillatory cycles (at least initially) the effects of the PSPs are different for the three cells. The magnitude and direction of the phase-shifts induced by PSPs can be characterized by phase response curves. The important point here is that the accumulation of such corrections to the interspike intervals of the outer neurons is such that after receiving a few PSPs they compensate the initial phase difference and both cells end up discharging isochronously, representing a stable state. Simulations predict that a millisecond-precise locking of spikes can be achieved already after the exchange of only a few spikes in the network (in a period as short as 100 ms). This value is found to be a function of the maximal synaptic conductivity and can be even shorter for stronger synapses.

A key issue of the synchronization properties exhibited by such network architecture is whether the zero-lag correlation can be maintained for different axonal lengths or whether it is specific to a narrow range of axonal delays. To resolve this issue we need to test the robustness of the synchronous solution for other values of the conduction delays. In Figure 2 we show the quality of the zero-lag synchronization for two HH cells as a function of the conduction delay. In that graph we plot the results for two different scenarios: one in which the neurons are directly coupled via excitatory synapses (dashed line) and a second one in which the two neurons interact through a relay cell also in an excitatory manner (solid line). A quick comparison already reveals that while the direct excitatory coupling exhibits large regions of axonal conduction delays where the zero-lag synchrony is not achieved, the relay-mediated interaction leads to zero time-lag synchrony in 28 out of the 30 delay values explored, $(1-30)$ ms. Only for the cases of $\tau = 3$ ms and $\tau = 10$ ms the network motif under study does not converge to the isochronous discharge for the outer neurons. For such latencies the three cells entered into a chaotic firing mode in which the neurons neither oscillate with a stable frequency nor exhibit a consistent

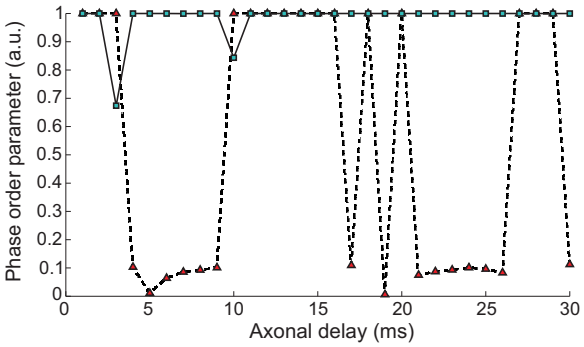

Fig. 2 Dependence of zero time-lag synchronization as a function of the axonal delay for a scheme of two coupled cells (dashed line) and three coupled cells (solid line). In the case of the three interacting cells only the synchrony between the outer neurons is plotted here.

relative lag between their respective spike trains.

Robust zero-lag synchrony among the outer neurons is also observed when the synaptic interaction between the cells is inhibitory instead of excitatory. Different synaptic rise and decay times within the typical range of fast AMPA and $GABA_A$ mediated transmission were tested with identical results as those reported above. These results indicate that the network motif of two neurons relaying their activities through a third neuron leads to a robust zero-lag synchrony almost independently of the delay times and type of synaptic interactions. We have also conducted simulations to test the robustness of this type of synchrony with respect to the nature of the relay cell. The results indicate that when a relay cell is operating in a parameter regime different from the outer ones (such as different firing rate or conductances), the zero-lag synchrony is not disturbed. Remarkably, even in the case where the relay cell is operating in a subthreshold regime, and thus only spiking due to the excitatory input from any of the outer neurons, the process of self-organization toward the zero-lag synchrony is still observed. It is also worth mentioning that in all cases such firing coherence is achieved through small shifts in the spiking latencies which leave the mean frequency of discharges (or rate) almost unchanged.

3.2 Effect of a broad distribution of conduction delays

Axons show a significant dispersion in properties such as diameter, myelin thickness, internodal distance, and past history of nerve conduction. Within a fiber bundle the variability from one axon to another of these characteristics is directly related to the speed of propagation of action potentials along them and eventually trans-

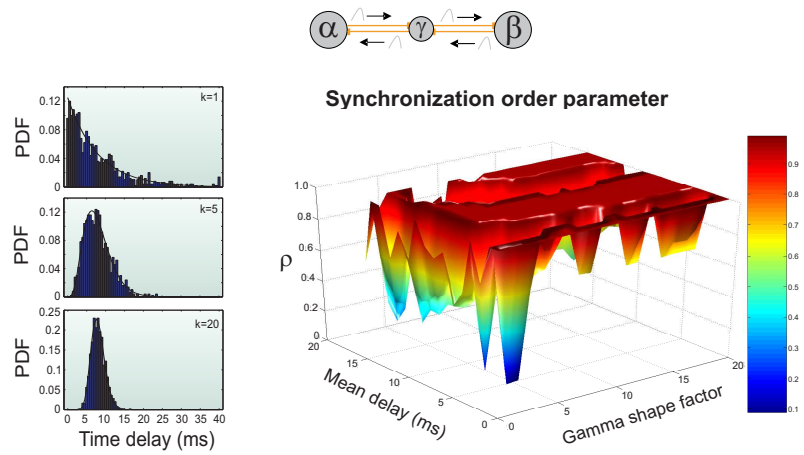

Fig. 3 Left panels: gamma distribution of delays with different shape factors (k=1, 5, and 20) and the same mean ($\tau = 8$ ms). Right panel: synchronization index at zero-lag of the outer neurons as a function of the shape factor and mean of the distribution of delays.

lates into the existence of a whole range of latencies in the neuronal communication between two separated brain areas. Thus, conduction times along fibers are more suitably considered as a spectrum or distribution rather than a single latency value [26, 39].

A crucial question is therefore whether the synchronization transition that we have described in the former section is restricted to single latency synaptic pathways or preserved also for broad distributions of axonal delays. To answer this issue we model the dispersion of axonal latencies by assuming that individual temporal delays of the arrivals of presynaptic potentials (i.e., latency times) are spread according to a given distribution. This intends to mimic the variability among the different axons within a fiber bundle connecting two neuronal resources. Since data about axonal distributions of conduction velocities in long-range fibers is limited, specially in the case of humans [26, 39], and there is probably not a unique prototypical form of such distributions we explore a whole family of gamma distributions with different shapes. The left panels shown in Figure 3 illustrate different gamma distributions of axonal delays for three different shape factors.

Our numerical simulations indicate that for a large region of mean delays (between 3 and 10 ms) the outer neurons synchronize independently of the shape of the distribution. These results can be observed in the right panel of Figure 3 where we plot the zero-lag synchronization index of the outer neurons of the network motif as a function of the shape of the gamma distribution of axonal delays and its mean value. Only distributions with unrealistic small shape factor (i.e., exponentially decaying distributions) prevent synchrony irrespective of the average delay of the synaptic connections. For more realistic distributions, there is a large region of

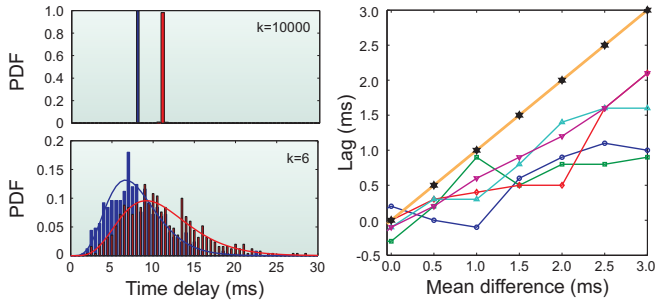

Fig. 4 Left panels: different gamma distributions of delays used for the two dissimilar branches of the network module. Upper left panel shows distributions with shape factor k=10000 (quasi-delta) and means of 8 and 11 ms. Bottom left panel shows distributions with shape factor k=6 and means of 8 and 11 ms. Right panel: lag between the discharges of the outer neurons as a function of the difference in the mean of the distributions of delays for the two branches. Shape factors k=6 (squares), k=8 (circles), k=10 (diamonds), k=12 (up-triangles), k=14 (down-triangles), and k=10000 (stars) were tested.

axonal delays that gives rise to the zero-lag synchrony among the outer neurons. As in the case of single latencies, we find a drop in the sync quality for distributions with a mean value around $\hat{\tau} \sim (10-12)$ ms, where chaotic firing is observed. The isochronous spiking coherence is in general recovered for larger mean delay values.

So far we have considered a rather symmetric situation in which similar distributions of axonal delays are present in each of the two branches that connect the relay neuron to the outer units. This assumption can only hold when the relay cell is approximately equidistant from the outer ones. In the final section of this chapter we refer to several results pointing to the thalamic nuclei and their circuitry as ideal relay centers of cortical communication which approximately satisfy this condition. It is nevertheless advisable to investigate the situation in which the axonal delays of each of the two pathways of the network motif are described by dissimilar distributions. In this case, we find that if the distributions of delays for each branch have different mean values then a nonzero phase-lag appears between the dynamics of the outer neurons. This effect is illustrated for gamma distributions of different shape factors in Figure 4. For delta distributions of delays (which is equivalent to the single latency case) the lag amounts to the difference in mean values. Thus, if one of the pathways is described by a delta distribution of delays centered at $\tau_a = 5$ ms while the other is represented by a latency of $\tau_b = 7$ ms, then after some transient the neuron closer to the relay cell consistently fires 2 ms (i.e., $\tau_b - \tau_a$) in advance to the other outer neuron. It is worth to note that such value it is still much smaller than the total delay accumulated to communicate both neurons ($\tau_a + \tau_b = 12$ ms). When studying the effect of broader distributions of delays we observed that outer cells tend to fire with a lag even smaller than the difference in the mean values of

the distributions. Thus, our results suggest that broader distributions of delays can help distant neurons to fire almost isochronously.

3.3 Dynamical relaying in large-scale neuronal networks

A further key step in demonstrating the feasibility of synchronizing widely separated neurons via dynamical relaying is the extension of the previous results to the level of neuronal populations, the scale at which neuronal micro-circuits develop their function [59]. Far from being independent, the dynamical response of any neuron is massively affected by the activity of the local neighborhood and by the long-range afferents originating in distant populations. It is also important to consider the random-like influences usually referred to as background noise, a term that collects a variety of processes from spontaneous release of neurotransmitters to fluctuations of unspecific inputs [60, 61]. In such a scenario, we explore whether long-range fibers supporting dynamical relaying, and thus indirectly connecting pools of neurons, are suitable to promote remote interpopulation synchrony in the presence of local interactions and noise sources.

To check if zero-lag correlated firing is thus induced among neurons in different populations we built three large networks of sparsely connected excitatory and inhibitory Integrate And Fire neurons. We interconnect the three populations following the topology of the network motif under study, i.e. the mutual relaying of activities of two external populations onto an intermediate pool of relay neurons. Each network consists of 4175 neurons of which 80% are excitatory. The internal synaptic connectivity is chosen to be random, i.e. each neuron synapses with a 10% of randomly selected neurons within the same population, such that the total number of synapses in each network amounts to about 1,700,000. Additionally, to model background noise, each neuron is subjected to the influence of an external train of spikes with a Poissonian distribution. The inter-population synaptic links are arranged such that each neuron in any population receives input from 0.25% of the excitatory neurons in the neighboring population. This small number of inter-population connections, compared to the much larger number of intra-population contacts, allows us to consider the system as three weakly interacting networks of neurons rather than a single homogeneous network. Intra-population axonal delays are set to 1.5 ms, whereas the fibers connecting different populations are assumed to involve much longer latencies in order to mimic the long-range character of such links.

We first begin by initializing the three networks without the long-range inter-population connections. Thus only the recurrent local connections and the Poissonian external background are active and then responsible for any dynamics in the stand-alone networks. Consequently, each population initially exhibits incoherent spiking of their neurons with respect to neurons belonging to any of the other populations. Once the long-range synapses are activated at $t = 100$ ms, we observe

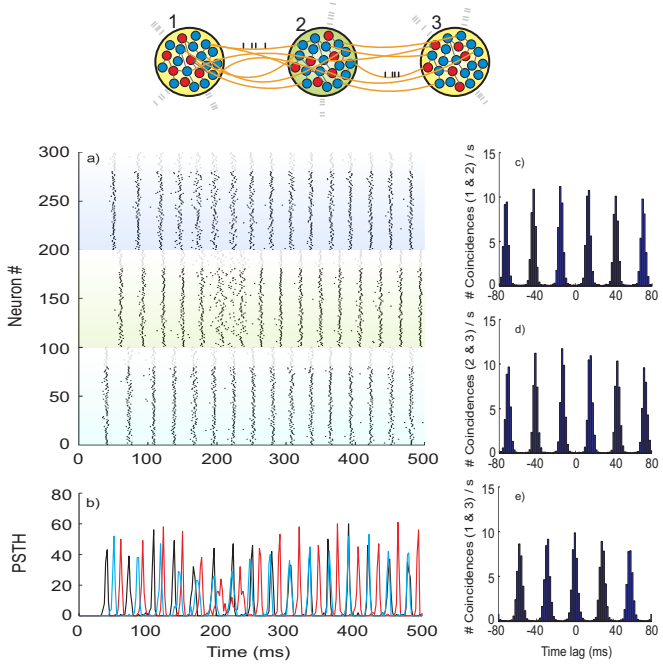

Fig. 5 Dynamics of three large-scale networks interacting through dynamical relaying. Panel a): raster plot of 300 neurons randomly selected among the three populations (Neurons 1-100 are from Pop. 1, 101-200 from Pop. 2, and 201-300 from Pop. 3). The top 20 neurons of each subpopulation (plotted in gray) are inhibitory, and the rest excitatory (black). Panel b): firing histogram of each subpopulation of 100 randomly selected neurons (black, red, and blue colors code for populations 1, 2, and 3, respecively). Panel c): averaged cross-correlogram between neurons of Pop. 1 and Pop. 2. Panel d): averaged cross-correlogram between neurons of Pop. 2 and Pop. 3. Panel e): averaged cross-correlogram between neurons of Pop. 1 and Pop. 3. At t=100 ms the external inter-population synapses become active. Bin sizes for the histogram and correlograms is set to 2 ms. Inter-population axonal delays are set to 12 ms.

how the firing of the neurons organize toward the collective synchrony of the outer populations. Thus, the firing cycles of the outer networks of neurons occur with decreasing phase lags until both populations discharge near simultaneously and exhibit almost zero-phase synchrony. Figure 5 illustrates the typical raster plots, firing histograms, and cross-correlograms of neurons among the three inter-connected networks for a long conduction delay of 12 ms. Similar results are observed when other axonal delays in the range of 2 to 20 ms are explored.

The effective coupling of the networks modifies the relative timing among their spikes yielding populations 1 and 3 to rapidly synchronize. However, the qualitative dynamics of each single neuron seems to be not so much altered by the interaction and periodic firing of comparable characteristics is found in both the coupled and uncoupled case (compare the firing of the central population in Fig. 5 and Fig.

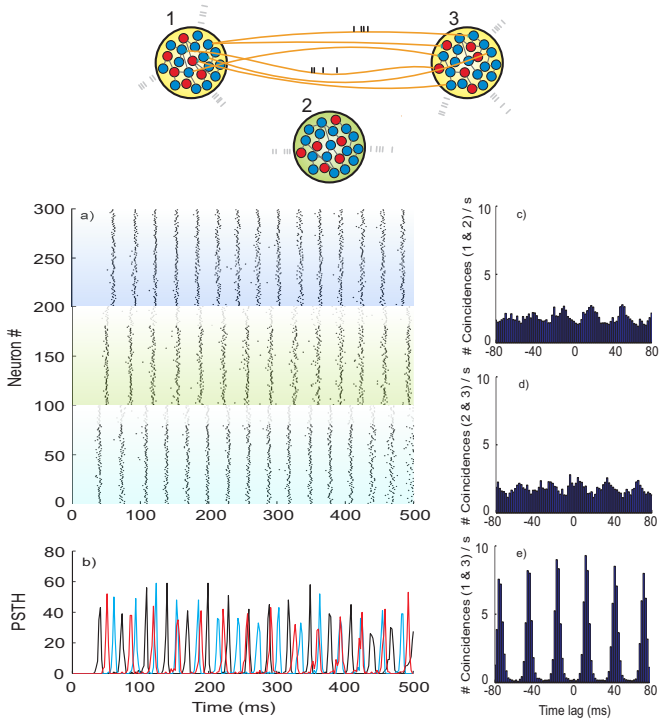

Fig. 6 Dynamics of two large-scale networks interacting directly. Population 2 is disconnected from other populations. Panel a): raster plot of 300 neurons randomly selected among the three populations (Neurons 1-100 are from Pop. 1, 101-200 from Pop. 2, and 201-300 from Pop. 3). The top 20 neurons of each subpopulation (plotted in gray) are inhibitory, and the rest excitatory (black). Panel b): firing histogram of each subpopulation of 100 randomly selected neurons (black, red, and blue colors code for populations 1, 2, and 3, respecively). Panel c): averaged cross-correlogram between neurons of Pop. 1 and Pop. 2. Panel d): averaged cross-correlogram between neurons of Pop. 2 and Pop. 3. Panel e): averaged cross-correlogram between neurons of Pop. 1 and Pop. 3. At t=100 ms the external inter-population synapses become active. Bin sizes for the histogram and correlograms is set to 2 ms. Inter-population axonal delays are set to 12 ms.

6 where in the latter the population 2 remains uncoupled from other populations). Indeed, the mean period of the coupled oscillatory activity ($\sim$32 ms) is found to be close to the local rhythm of an isolated network ($\sim$34 ms), and therefore the coupling has little effect on the frequency of oscillation. This indicates that zero-lag synchrony can be brought by this mechanism via small latency shifts without hardly affecting the nature of the neuronal dynamics. A different situation might appear when no prominent oscillatory activity is present in the isolated networks before they are functionally coupled. In that case (not illustrated here) we find that the reciprocal coupling among the networks can act as a generator of oscillations and zero-lag synchrony. In the latter case we find the period of the population os-

cillations strongly influenced by the conduction delay times and as a result by the coupling.

To better determine the role of the relay cells (Pop. 2) in shaping the synchronization among cells belonging to remote neuronal networks (Pop. 1 and Pop. 3), we designed the following control simulation. We investigated the neuronal dynamics obtained under exactly the same conditions as in the former approach with the only variation that this time the two outer networks interacted directly. The results are summarized in Figure 6. The solely change of the topology of the connections induces that the networks 1 and 3, even if engaged in oscillations with similar characteristics as before do no longer synchronize their spikes at zero-lag and highlighting the essential role of a relaying population.

So far we have focused on studying how a V-shaped network motif with reciprocal interactions determines the synchronization properties of the neurons composing it and compared them to the case of a direct reciprocal coupling between two populations. The results above indicate that the V-shaped structure can promote the zero-lag synchrony between their indirectly coupled outer populations for long delays, while just direct connections between two populations can sustain zero-lag synchrony only for limited amounts of axonal latencies. However, usually both situations are expected to occur simultaneously, this is neuronal populations that need to be coordinated might be linked by both direct (monosynaptic) and non-direct (multisynaptic) pathways. Therefore, we also conducted some numerical studies about how the addition of a direct bidirectional coupling between the populations 1 and 3 (and thus closing the open end of the sketch shown in top of Fig. 5 to form a ring) modified the synchronization properties formerly described, which were due only to their indirect communication via population 2. We observed that when the connectivity (or number of synapses) between the pools of neurons 1 and 3 is moderate and smaller than the connectivity between these populations and the relay population 2, then a zero-lag synchronous dynamics between the outer populations still emerges. This holds even for the case when the synapses linking Pop. 1 and Pop. 3 have a different delay than the ones linking these to the relay center. As expected, when the reciprocal connectivity between pools 1 and 3 is stronger then direct coupling dominates and, depending on the delay, it can impose a non-zero lag synchronous solution.

Among other relevant networks that might sustain the emergence zero-lag synchrony among some of its nodes stands the star topology. For such an arrangement, which in some sense can be understood as to be composed of several V-shaped motifs, numerical simulations show that the outer elements of the star that are bidirectionally connected to the central hub also tend to engage in zero-lag synchronous spiking.

4 General discussion, conclusions and perspectives

In this chapter we have dealt with the intriguing problem of explaining how long-range synchrony can emerge in the presence of extensive conduction delays. This challenging question that has arisen the attention of many researchers is still far from being fully clarified. Nevertheless, our main goal in the previous pages was to disseminate the idea that in addition to intrinsic cellular properties an appropriate neuronal circuitry can be essential in circumventing the phase shifts associated with conduction delays. In particular, here we have explored and shown how a simple network topology can naturally enhance the zero-lag synchronization of distant populations of neurons. The neuronal micro-circuit that we have considered consists of the relaying of two pools of neurons onto a third mediating population which indirectly connects them. Simulations of Hodgking & Huxley cells as well as large networks of Integrate And Fire neurons arranged in the mentioned configuration demonstrated a self-organized tendency toward the zero-lag synchronous state despite of large axonal delays. These results suggest that the presence of such connectivity pattern in neuronal circuits may contribute to the large-scale synchronization phenomena reported in a number of experiments in the last two decades [3, 4].

Is there in the brain any particular structure where such connectivity pattern is significantly common and one of its main building blocks? Within the brain complex network the thalamus and its bidirectional and radial connectivity with the neocortex form a key partnership. Several authors have indicated that the reciprocal coupling of cortical areas with the different thalamic nuclei may support mechanisms of distributed cortical processing and even form a substrate for the emergence of consciousness [62, 63, 64, 65]. It has also been explicitly proposed that diffuse cortical projections of matrix cells in the dorsal thalamus together layer V corticothalamic projections are an ideal circuitry to extend thalamocortical activity and sustain the synchronization of widespread cortical and thalamic cells [31, 32]. The resemblance of such circuitry with the topology studied here is evident once the identification of the associative nuclei of the thalamus as our relay population for cortical activity is done. Altogether, the results described in this chapter point to the direction that long axonal latencies associated with cortico-thalamo-cortical loops are still perfectly compatible with the isochronous cortical synchronization across large distances. Within this scheme the most important requirement for the occurrence of zero-lag synchronization is that the relay population of cells occupies a temporally equidistant location from the pools of neurons to be synchronized. It is then highly significant that recent studies have identified a constant temporal latency between thalamic nuclei and almost any area in the mammalian neocortex [66]. Remarkably, this occurs irrespectively of the very different distances that separate the thalamus and the different cortex regions involved and relies on the adjustment of conduction velocity by myelination. Thus, thalamic nuclei occupy a central position for the mediation of zero-phase solutions.

Coherent dynamics between remote cortical populations could of course be generated also by reciprocally coupling these areas to yet another cortical area or other subcortical structures. It is important to remark that connectivity studies in primate

cortex have identified the pattern of connections studied here as the most frequently repeated motif at the level of cortico-cortical connections in the visual and other cortical systems [33, 55, 56]. The functional relevance of this topology in cortical networks is unclear but according to our results is ideally suited to sustain coherent activity.

In general, it is quite possible that a variety of mechanisms are responsible for bringing synchrony at different levels (distinguishing for example, among local and long-distance synchrony) and different cerebral structures. The fact that each thalamus projects almost exclusively ipsilaterally (the massa intermedia is clearly inadequate for supporting the required interthalamic communication) is already an indication that the callosal commissure should play a prominent role in facilitating interhemispheric coherence. Lesion studies have since long confirmed this view [67]. However, within a single hemisphere the disruption of intra-cortical connectivity by a deep coronal cut through the suprasylvian gyrus in the cat cortex was observed to not disturb the synchrony of spindle oscillations across regions of cortex located at both sides of the lesion [68]. This suggests that subcortical, and in particular cortico-thalamic interactions, could be responsible not only for the generation of oscillations but also for maintaining both the long-range cortical and thalamic coherence found in such regimes. It is likely then that subcortical loops with widespread connectivity such as the associative or non-specific cortico-thalamo-cortical circuits could run in parallel as an alternative pathway for the large-scale integration of cortical activity within a single hemisphere [32, 59, 65]. As we have proven here, with such connectivity pattern even large axonal conduction delays would not represent an impediment for the observation of zero time-lag coherence.

We would like to stress here that conduction delays are an important variable to consider not only in synchrony but in any temporal coding strategy. They contribute with an intrinsic temporal latency to neuronal communication that adds to the precise temporal dynamics of the neurons. Thus, they may have an important implication in gating mechanisms based in temporal relationships. For instance, when assisted by membrane oscillations neurons undergo repetitive periods of interleaved high and low excitability and it has been reported that the impact of a volley of spikes bombarding one of such oscillatory neuron is strongly influenced by the phase of the cycle (variable influenced by conduction delays) at which the action potentials reach the targeting neuron [38]. Conduction delays along with the frequency and phase difference of two respective oscillatory processes determine the timing of the arrival of inputs and therefore can control whether the incoming signal will be relatively ignored (when coinciding the trough of excitability) or processed further away (when reaching the neuron at the peak of the fluctuating depolarization) [10, 69]. By this mechanism it has been hypothesized that a dynamically changing coherent activity pattern may ride on top of the anatomical structure to provide flexible neuronal communication pathways [69]. Based on the properties formerly reviewed subcortical structures such as some thalamic nuclei might be in an excellent situation to play a role in regulating such coherence and contribute to the large-scale cortical communication.

In summary, the network motif highlighted here has the characteristic of naturally inducing zero-lag synchrony among the firing of two separated neuronal populations. Interestingly, such property is found to hold for a wide range of conduction delays, a highly convenient trait not easily reproduced by other proposed mechanisms, which have a more restricted functionality in terms of axonal latencies. Regarding its physiological substrate, the associative thalamic nuclei have the cortex as their main input and output sources and seem to represent active relay centers of cortical activity with properties well suitable for enhancing cortical coherence [32]. The advantage of this approach in terms of axonal economy, specially compared to an extensive network of fast long-range cortical links, is overwhelming. Ongoing research is being directed to a detailed modeling of the interaction between cortex and such nuclei with an emphasis in investigating the role of axonal limited conduction velocity. From the experimental side the relatively well controlled conditions of thalamocortical slice experiments, allowing for the identification of synaptically coupled neurons and cell class, might be a first step for testing whether the topology investigated here provides a significant substrate for coherent spiking activity. An important issue related to the physical substrate of synchrony is how the dynamic selection of the areas that engage and disengage into synchrony can be achieved but that is a subject beyond the scope of the present chapter.

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