The Combined Effects of Inhibitory and Electrical Synapses in Synchrony

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Recent experimental results have shown that GABAergic interneurons in the central nervous system are frequently connected via electrical synapses. Hence, depending on the area or the subpopulation, interneurons interact via inhibitory synapses or electrical synapses alone or via both types of interactions. The theoretical work presented here addresses the significance of these different modes of interactions for the interneuron networks dynamics. We consider the simplest system in which this issue can be investigated in models or in experiments: a pair of neurons, interacting via electrical synapses, inhibitory synapses, or both, and activated by the injection of a noisy external current. Assuming that the couplings and the noise are weak, we derive an analytical expression relating the cross-correlation (CC) of the activity of the two neurons to the phase response function of the neurons. When electrical and inhibitory interactions are not too strong, they combine their effect in a linear manner. In this regime, the effect of electrical and inhibitory interactions when combined can be deduced knowing the effects of each of the interactions separately. As a consequence, depending on intrinsic neuronal proper-
ties, electrical and inhibitory synapses may cooperate, both promoting synchrony, or may compete, with one promoting synchrony while the other impedes it. In contrast, for sufficiently strong couplings, the two types of synapses combine in a nonlinear fashion. Remarkably, we find that in this regime, combining electrical synapses with inhibition amplifies synchrony, whereas electrical synapses alone would desynchronize the activity of the neurons. We apply our theory to predict how the shape of the CC of two neurons changes as a function of ionic channel conductances, focusing on the effect of persistent sodium conductance, of the firing rate of the neurons and the nature and the strength of their interactions. These predictions may be tested using dynamic clamp techniques.

1 Introduction

Electrical synapses have long been known to exist in invertebrates (Watanabe, 1958; Furshpan & Potter, 1959), but only recently has evidence of their ubiquity been unequivocally found in the mammalian brain. Remarkably, electrical synapses in the CNS are frequently found to connect GABAergic interneurons. This is, for instance, the case in the striatum (Kita, Kosaka, & Heizmann, 1990), the hippocampus (Venance et al., 2000), the cerebellum (Mann-Metzer & Yarom, 1999), the reticular thalamic nucleus (Landisman et al., 2002), and the neocortex (Gibson, Beierlein, & Connors, 1999; Galarreta & Hestrin, 1999; Fukuda & Kosaka, 2000). In the neocortex, electrical as well as inhibitory synapses exist between fast spiking (FS) interneurons (Gibson et al., 1999; Galarreta & Hestrin, 2002) or between multipolar bursting neurons (Blatow et al., 2003). In contrast, low threshold spiking (LTS) interneurons interact mostly via electrical synapses, the inhibitory synapses between them being sparse (Gibson et al., 1999; Amitai et al., 2002). FS and LTS neurons are interacting reciprocally via inhibition but not via electrical synapses.

Recent experiments have shown that electrical synapses may be involved in synchronizing neural activity. Blocking of inhibition and excitation does not reduce the synchronization of interneurons in the molecular layer of the cerebellum between which electrical synapses have been identified (Mann-Metzer & Yarom, 1999). In slices of neocortex, in which LTS cells are activated by ACPD, the synchronous activity of LTS remains after blocking inhibition (Beierlein, Gibson, & Connors, 2000). Reciprocally, blockade of gap junctions through pharmacological agent (Draguhn et al., 1998; Perez-Velazquez, Valiante, & Carlen, 1994; Traub et al., 2001; Friedman & Strowbridge, 2003) or genetic manipulations (Deans, Gibson, Sellitto, Connors, & Paul, 2001; Hormuzdi et al., 2001; Blatow et al., 2003) reduces the synchronized activity in cortex or in hippocampus. Other studies suggest that electrical synapses alone are not sufficient for getting synchronous activity but that they are necessary. This has been shown in preparations of cortical slices where electrical synapses or inhibitory ones are not able to synchro-
nize neuronal activity (Tamas, Buhl, Lorincz, & Somogyi, 2000; Blatow et al., 2003). In contrast with these results, it has been recently reported that in inspiratory motoneurons, synchronous activity depends on inhibition and is strongly enhanced in the presence of CBX, a blocker of electrical synapses (Bou-Flores & Berger, 2001). Therefore, electrical synapses desynchronize neural activity, in this case.

These experimental facts raise the following issues. How do intrinsic cellular properties affect synchrony of neurons coupled via inhibitory or electrical synapses? What is the significance of the combination of electrical and inhibitory couplings for neuronal dynamics? The goal of this work is to address these issues in the simplest system in which they can be answered in models or in experiments: a pair of neurons, interacting via electrical synapses, inhibitory synapses, or both, and activated by the injection of a noisy external current.

The pattern of firing of a pair of model neurons can be characterized by the cross-correlations (CCs) of their activity, which measure the probability that the two neurons fire with some given time delay. Of particular interest are the locations and the width of the peaks and the troughs of the CCs. The main limitation in measuring CCs in experiments is the stationarity of the data. This puts constraints on the number of spikes one must accumulate. Simulations of neuronal models can be useful to estimate how long the recordings should be to get reliable estimate of the CCs. Exploring in a systematic way the space of parameters of a model using only numerical simulations is not the best way to discover the general rules underlying the dependence of the CCs on neuronal properties. Here, we derive an analytical expression for the CC of a pair of spiking neurons under the assumptions of weak interactions and weak noise. It provides valuable information about the way noise and intrinsic and synaptic properties affect the shape of the CCs. To our knowledge, this is the first time such an analytical expression has been obtained.

Only a few theoretical works have been devoted to neurons coupled via electrical synapses (Sherman & Rinzel, 1992; Chow & Kopell, 2000; Pfeuty, Mato, Golomb, & Hansel, 2003). Recently we combined analytical and numerical studies to investigate how cellular properties affect synchronization of activity of neurons coupled via electrical synapses (Pfeuty et al., 2003). We showed that the stability of the asynchronous state in a large network of tonically firing neurons and the way it is affected by the average neuronal firing rate depend crucially on the shape of the neuronal phase response function (for the definition of the PRF, see section 2). Our theory predicts that sodium or calcium currents impede synchrony of neurons coupled via electrical synapses, whereas potassium currents promote it. This study also shows that predictions for experiments derived in the framework of the leaky integrate-and-fire (LIF) model should be considered with caution. Indeed, we found that large networks of electrically coupled LIF neurons and conductance-based neurons behave in qualitatively different
ways unless strong potassium conductances are involved in the dynamics of the conductance-based model. This previous work focused on the conditions for antisynchronous states in pairs of neurons and for stability of asynchronous states in large networks. The analysis was also restricted to a single model. In this article, we complement that study by investigating in detail how the features of the CCs of a pair of electrically coupled neurons depend on their intrinsic properties. We also study in a two-compartment model how the location of the synapses, on the soma or on the dendrite, affects the CCs.

In contrast to the case of electrically coupled neurons, synchrony of neurons coupled via chemical synapses has been extensively studied. Many of the results that have shaped our concepts regarding this issue have been obtained in the framework of the LIF model (Abbott & van Vreeswijk, 1993; van Vreeswijk, Abbott, & Ermentrout, 1994; Hansel, Mato, & Meunier, 1995; Brunel & Hakim, 1999) or of a modified version of it, the spike response model (Gerstner & Kistler, 2002). Several works have also considered neuronal models with more realistic biophysics (Wang & Rinzel, 1992; Hansel, Mato, & Meunier, 1983; Hansel et al., 1995; van Vreeswijk et al., 1994; Wang & Buzsáki 1996; Ermentrout, 1996; Crook, Ermentrout, & Bower, 1998a, 1998b; Golomb, Hansel, & Mato, 2001; Ermentrout, Pascal, & Gutkin, 2001; Acker, Kopell, & White, 2003). However, few general results relate intrinsic properties and synchronization behavior. Moreover, these results deal mostly with the stability of fully synchronized states and not the stability of asynchronous state in large networks or antiphase locking of a pair of neurons. In this article, we provide new results regarding how intrinsic properties affect antiphase locking and bistability between in-phase and antiphase locking for a pair of reciprocally coupled inhibitory neurons.

Another issue investigated here is the interplay of inhibitory and electrical synapses. This issue has been studied analytically and numerically in the framework of the LIF model (Lewis & Rinzel, 2003) or in specific conductance-based models (Skinner, Zhang, Velazquez, & Carlen, 1999; Traub et al., 2001; Bartos et al., 2002; Nomura, Fukai, & Aoyagi, 2003; Bem & Rinzel, 2004). However, general principles governing this interplay are lacking. When the coupling strengths are not overly strong, the two types of synapses interact linearly when combined. As a consequence, we show that depending on cellular properties, they can cooperate or act antagonistically. We derive rules to predict these effects. We also show that in the strong coupling regime, the two types of synapses can interact in a nonlinear manner. Indeed, we find a regime in which synchrony promoted by inhibition is amplified by electrical synapses, although these synapses alone do not promote synchrony.

Finally, our work provides concrete predictions on the relationship between intrinsic properties and synchrony. We propose to test these predictions in experiments in which ionic currents or interactions are modified by
dynamic clamp (Sharp, O’Neil, Abbott, & Marder, 1993; Prinz, Abbott, & Marder, 2004).

The letter is organized as follows. In section 2, we describe the methods employed in this work. We describe the two models that are the framework of our study: the quadratic integrate-and-fire model (QIF) and a conductance-based model that involves sodium and potassium currents. We also derive a general formula for the CCs of weakly coupled spiking neurons. Section 3 is devoted to the results obtained in the framework of the QIF model. We first consider the situation of weak or moderate couplings, and we rely on our analytical formula for the CCs. We checked with numerical simulations that these results extend over a substantial range of coupling strength and noise level. The effects specific to strong coupling are subsequently analyzed. The theory developed in the first part of the article allows one to predict the effects of calcium, potassium, or sodium currents. For the sake of concreteness, we focus in section 4 on the effect of a persistent sodium current. The case of other currents is briefly considered in section 5.

2 Methods

2.1 The Models.

2.1.1 Single Neuron Dynamics. Two models are considered in this work: the quadratic integrate-and-fire (QIF) model and a two-compartment conductance-based model.

The QIF model is sufficiently simple that it can be studied with analytical calculations. In this model, the dynamical equation for the subthreshold membrane potential, \( v \), is (Latham, Richmond, Nelson, & Nirenberg, 2000; Hansel & Mato, 2003; Pfeuty et al., 2003)

\[
\tau_m \frac{dv}{dt} = A(v - V_s)^2 + I_{\text{ext}}(t) - I_c,
\]

where \( \tau_m = 10 \text{ ms} \), \( A = 0.25 \), and \( I_c = 0 \) are constant parameters and \( I_{\text{ext}}(t) \) is the total external current to the neuron. The parameter \( V_s \) is varied. The membrane potential is measured in mV. Hence, \( A \) is measured in mV\(^{-1}\) and the “current” in mV.

If \( I_{\text{ext}} \) is constant in time and smaller than \( I_c \), \( v \) converges to a fixed point at large time. In contrast, if \( I_{\text{ext}} > I_c \), the solutions to equation 2.1 diverge in finite time. We define action potential firing as \( v \) reaching some threshold value \( V_T \) from below. The membrane potential is then instantaneously reset to some value \( V_r < V_T \). In this article, we assume that \( V_r < V_s < V_T \). The membrane potential between two action potentials (\( I_{\text{ext}} > I_c \)) can be expressed analytically, solving equation 2.1 with the initial condition \( v(0) = \)}
\[ v(t) = \sqrt{\frac{I_{\text{ext}} - I_c}{A}} \tan \left( \frac{t \sqrt{A(I_{\text{ext}} - I_c)}}{\tau_m} + \alpha \right) + V_s \]  

(2.2)

where \( \alpha \) is an integration constant determined by the condition that at \( t = 0 \), the membrane potential of the neuron is at its reset value, \( V_r \):

\[ \alpha = \tan^{-1} \left( \frac{V_r - V_s}{\sqrt{(I_{\text{ext}} - I_c)/A}} \right) . \]  

(2.3)

The condition \( v(T) = V_T \) determines the firing period, and the firing frequency of the neuron is \( f = 1/T \). One finds

\[ T = \tau_m \frac{\tan^{-1} \left( \frac{V_T - V_r}{\sqrt{(I_{\text{ext}} - I_c)/A}} \right) - \tan^{-1} \left( \frac{V_r - V_s}{\sqrt{(I_{\text{ext}} - I_c)/A}} \right)}{\sqrt{A(I_{\text{ext}} - I_c)}} . \]  

(2.4)

Near firing onset, \( I_{\text{ext}} \approx I_c \), the frequency \( f \) behaves like \( f \propto \sqrt{I_{\text{ext}} - I_c} \), whereas \( f \) increases linearly with \( I_{\text{ext}} \) for large \( I_{\text{ext}} \).

The subthreshold dynamics needs to be supplemented with a model for the suprathreshold part of the membrane potential time course. Assuming that the width of the action potentials is much smaller than the interspike intervals, we represent them by a \( \delta \)-function at each time a spike is fired. Therefore, the membrane potential of the neuron can be written at time \( t \),

\[ V(t) = v(t) + \theta \sum_{\text{spikes}} \delta(t - t_{\text{spike}}), \]  

(2.5)

where \( \theta \) measures the integral over time of the suprathreshold part of action potentials.

For given \( V_r \) and \( V_T \), the membrane potential time course depends on the parameter \( V_s \). This is shown in Figure 1A, where \( V(t) \) is plotted for \( V_r = 0, V_T = 12 \) mV and different values of \( V_s \). In all these examples, the external current is such that the neurons fire at \( f = 50 \) Hz. It is clear that the concavity of the potential time course depends on \( V_s \). For \( V_s \approx V_r \), it is convex except right after a spike, whereas for \( V_s \approx V_T \), it is concave except right before a spike. For \( V_s = (V_T + V_r)/2 \), the membrane potential displays an inflexion point at half the firing period.

The conductance-based model used in this work has two compartments. The somatic compartment has a leak current, \( I_L \), a fast sodium current, \( I_{Na} \), a delayed rectifier potassium current, \( I_K \), and a persistent sodium current, \( I_{NaP} \). Details about these currents are given in appendix A. The second compartment, which corresponds to the dendrite, is passive. For simplicity, we assume that the two compartments have equal areas. Therefore, the
membrane potentials of the soma, $V$, and of the dendrite, $V_d$, follow the equations:

\begin{align}
C \frac{dV}{dt} &= -I_L - I_{Na} - I_{NaP} - I_K + I_{ext} - g_c(V - V_d), \\
C \frac{dV_d}{dt} &= -g_{ld}(V_d - V_{ld}) - g_c(V_d - V),
\end{align}

(2.6)

(2.7)

where $g_c$ is the coupling conductance between the two compartments, $g_{ld}$ is the leak conductance of the dendritic compartment, and $I_{ext}$ is an external current.

2.1.2 Inhibitory and Electrical Synaptic Couplings. Inhibitory interactions are taken into account in the QIF model by adding to the right-hand side of the dynamical equation for $v$, equation 2.1, an additional current of the
form

\[ I_{\text{inh}}(t) = g_{\text{inh}} s(t) \]  \hspace{1cm} (2.8)

Here, \( g_{\text{inh}} \) is a negative constant parameter measuring the strength of the inhibitory coupling. The function \( s(t) \) is defined by

\[ s(t) = \sum_{\text{spikes}} f(t - t_{\text{spike}}), \]  \hspace{1cm} (2.9)

where the summation extends over all the spikes fired by the presynaptic neuron at time \( t_{\text{spike}} \) prior to time \( t \) and

\[ f(t) = \frac{1}{\tau_1 - \tau_2} \left( e^{-t/\tau_1} - e^{-t/\tau_2} \right) \Theta(t) \]  \hspace{1cm} (2.10)

with \( \tau_1 \) and \( \tau_2 \), the rise and the decay time of the synapse, respectively, and \( \Theta \) the Heaviside function: \( \Theta(t) = 0 \) for \( t < 0 \) and \( \Theta(t) = 1 \) otherwise. Note that the integral of \( f(t) \) over time is normalized to 1. Each neuron receives \( s(t) \) from the other neuron.

For simplicity, we limit our study of the conductance-based model to the case of inhibitory synapses located on the soma. Therefore, we incorporate inhibition in this model by adding to the right-hand side of the equation for \( V \) in equation 2.6 a current of the form

\[ I_{\text{inh}}(t) = -g_{\text{inh}} s(V(t) - V_{\text{inh}}), \]  \hspace{1cm} (2.11)

where \( g_{\text{inh}} > 0 \) is a constant conductance, \( V_{\text{inh}} \) is the reversal potential of the synapse, and \( s \) is the synaptic conductance dynamics defined in appendix A. The reversal potential of the inhibition is \( V_{\text{inh}} = -75 \text{ mV} \) throughout the article.

An electrical synapse between two neurons induces a synaptic current proportional to the difference of their membrane potential. In both the QIF and the conductance-based model, the effect on neuron \( i \) of an electrical synapse connecting neuron \( j \) and neuron \( i \) is taken into account by adding to the right-hand side of the dynamical equation of neuron \( i \) a current of the form

\[ I_{\text{gap}} = -g_{\text{gap}} (V_i - V_j), \]  \hspace{1cm} (2.12)

In the QIF model, \( V_i \) and \( V_j \) are the membrane potentials of the neurons defined by equations 2.1, and 2.5. In the conductance-based model, \( V_i \) and \( V_j \) stand for the potentials of the somatic or the dendritic compartments depending on the locations of the electrical synapses.
2.1.3 Noise. stochasticity is introduced in the dynamics of the QIF model by adding a gaussian white noise current, $I_{\text{noise}}$ (zero mean, standard deviation, $\sigma$), in the right-hand side of equation 2.1. In the conductance-based model, noise is incorporated in a similar way in the dynamics of the somatic compartment.

2.2 Cross-Correlations of Spike Trains. We characterize the synchrony properties of a pair of neurons by the CCs of their activity. Given the time series at which neuron $i = 1, 2$ fire action potentials, one can define a variable $S_i(t)$ by

$$S_i(t) = 1/\delta$$

if neuron $i$ has fired a spike in a time bin of size $\delta$ about time $t$ and $S_i(t) = 0$ otherwise. For a sufficiently small $\delta$, the time average of $S_i$, $\langle S_i(t) \rangle$, is the average firing rate of neuron $i$.

The normalized CC of the spike trains of the two neurons is defined as

$$C(\tau) = \frac{\langle S_1(t) S_2(t + \tau) \rangle}{\langle S_1(t) \rangle \langle S_2(t) \rangle}.$$  

(2.14)

It represents the density of probability that neuron 2 will fire a spike in some bin of size $\delta$ a delay $\tau$ after a spike of neuron 1.

2.2.1 Synchrony and Antisynchrony of a Pair of Neurons. A flat CC indicates that the two neurons fire independently, whereas a peak in the CC at some time shift indicates that the neurons have an increased probability to fire with some constant time delay. In particular, synchronous firing corresponds to an increased probability of the two neurons to fire simultaneously, that is, to a peak of the CC at $\tau = 0$ in the CC.

The model neurons considered in this article fire periodic trains of action potentials in response to constant input current. Noise in the input will decorrelate the periodic firing of action potentials. If the noise is not overly strong, this decorrelation requires several action potentials, and if the neurons fire with some correlation, the CCs will display a few oscillations with a period equal to the average firing period of the neurons, $T$. We will say that the two neurons tend to fire in antisynchrony if the CC of their activity displays a peak at $\tau = \pm T/2$.

2.3 Reduction to a Phase Model.

2.3.1 The Phase Dynamics of a Pair of Neurons. The study of the dynamics of a pair of interacting oscillatory neurons is greatly simplified if one assumes that their cellular properties are not too different, the noise they receive is small, and the coupling between them is weak. Under these assumptions, the dynamics of the neurons can be described in terms of two
phase variables—one for each neuron. In this reduced model, interactions between the neurons are taken into account by effective coupling functions that depend on their phase difference (Kuramoto, 1984; Ermentrout & Kopell, 1986; Hansel et al., 1993, 1995; van Vreeswijk et al., 1994) and the dynamics of the phases for the two neurons are given by the coupled differential equations,

\[
\frac{d\phi_1}{dt} = f_1 + g_{\text{inh}} \Gamma_{\text{inh}}(\phi_1 - \phi_2) + g_{\text{gap}} \Gamma_{\text{gap}}(\phi_1 - \phi_2) + \eta_1(t) \tag{2.15}
\]

\[
\frac{d\phi_2}{dt} = f_2 + g_{\text{inh}} \Gamma_{\text{inh}}(\phi_2 - \phi_1) + g_{\text{gap}} \Gamma_{\text{gap}}(\phi_2 - \phi_1) + \eta_2(t), \tag{2.16}
\]

where \( f_1 \) and \( f_2 \) are the frequencies of the neurons when decoupled. In the following, we consider the homogeneous case: \( f_1 = f_2 = f \). The phase coupling \( \Gamma_{\text{inh}} \) and \( \Gamma_{\text{gap}} \), which corresponds to chemical and electrical interactions, respectively, depends on the phase response function (PRF) of the neuron, \( Z(\phi) \). These can be computed from the convolution integrals with \( \phi \) between 0 and 1:

\[
\Gamma_{\text{inh}}(\phi) = \int_0^1 Z(u) s(u - \phi) \, du \tag{2.17}
\]

\[
\Gamma_{\text{gap}}(\phi) = \int_0^1 Z(u) (V(u) - V(u - \phi)) \, du \tag{2.18}
\]

where

\[
s(\phi) = \frac{1}{\tau_1 - \tau_2} \left( e^{-\phi/(f\tau_1)} - e^{-\phi/(f\tau_2)} - \frac{1}{1 - e^{-1/(f\tau_1)}} - \frac{1}{1 - e^{-1/(f\tau_2)}} \right) \tag{2.19}
\]

and \( V(\phi) \) is the membrane potential expressed as a function of the phase variable. The functions \( \Gamma_{\text{gap}}(\phi), \Gamma_{\text{inh}}(\phi) \), and \( Z(\phi) \) are periodic with period 1. The terms \( \eta_1(t) \) and \( \eta_2(t) \) in equations 2.15 and 2.16 are the effective noise on the phase dynamics that corresponds to the noise in the input received by the neurons.

Assuming white and gaussian input noise with zero mean and standard deviation, \( \sigma \), and generalizing the approach developed by Kuramoto (1991) in the context of the LIF model, one can show that for the QIF model, \( \eta_1(t) \) and \( \eta_2(t) \) are white gaussian noise with zero mean and standard deviation \( \sigma_\phi \):

\[
\sigma_\phi^2 = \sigma^2 \int_0^1 [Z(u)]^2 \, du. \tag{2.20}
\]

Therefore, the effective noise in the phase dynamics of the QIF neuron is proportional to the average of its PRF over a period.
2.3.2 Analytical Expression for the CC of a Pair of Neurons in the Weak Coupling and Weak Noise Limit. In the weak coupling, weak noise limit, the time elapsed at time $t$ since the last spike fired by neuron $i$ is simply the firing period, $T$, multiplied by the phase, $\phi(t)$, computed modulo 1 ($\text{mod}(\phi_i(t), 1)$). Similarly, the time elapsed between the last spikes fired by neurons $i$ and $j$ is $\tau = T \text{mod}(\phi_i(t) - \phi_j(t), 1)$. In the weak coupling limit, the CC and the phase shifts’ probability distribution function, $P_0(\Delta)$, are related by

$$C(\tau) = P_0\left(\frac{\tau}{T}\right).$$

(2.21)

A more detailed proof of this equation is given in appendix B.

Using equations 2.15 and 2.16, one finds that $\Delta = \phi_1 - \phi_2$ satisfies the Langevin equation,

$$\frac{d\Delta}{dt} = \Gamma_-(\Delta) + \eta(t),$$

(2.22)

where we have assumed that the two neurons fire at the same average firing rates. We have defined $\eta(t) \equiv \eta_1(t) - \eta_2(t)$ and $\Gamma_-(\Delta) \equiv (\Gamma(\Delta) - \Gamma(-\Delta))$ with

$$\Gamma(\Delta) = g_{inh} \Gamma_{inh}(\Delta) + g_{gap} \Gamma_{gap}(\Delta).$$

(2.23)

The noise $\eta(t)$ is the difference of two gaussian white noise, with zero average and standard deviation $\sigma_\phi$. Therefore, it is a gaussian white noise with zero average and standard deviation $\sqrt{2}\sigma_\phi$. Hence, the phase-shift distribution, $P(\Delta, t)$, satisfies a Fokker-Planck equation (van Kampen, 1981):

$$\frac{\partial P(\Delta, t)}{\partial t} = \sigma_\phi^2 \frac{\partial^2}{\partial \Delta^2} P(\Delta, t) - \frac{\partial}{\partial \Delta}[\Gamma_-(\Delta) P(\Delta, t)].$$

(2.24)

The stationary phase shifts distribution, $P_0$, is the solution of this equation, which satisfies the additional constraint

$$\frac{\partial P_0(\Delta, t)}{\partial t} = 0,$$

(2.25)

that is,

$$P_0(\Delta) = e^{G(\Delta)} \left[ A \int_0^\Delta e^{-G(\Delta')} d\Delta' + B \right].$$

(2.26)

where

$$G(\Delta) = \int_0^\Delta \frac{\Gamma_-(\Delta')}{\sigma_\phi^2} d\Delta'.$$

(2.27)
and A and B are two integration constants, which are determined by the periodicity of $P_0$, that is, $P_0(0) = P_0(1)$, and its normalization, $\int_0^1 P_0(\Delta) d\Delta = 1$. One finds

$$P_0(\Delta) = \frac{e^{G(\Delta)}}{\int_0^1 e^{G(\Delta')} d\Delta'}.$$  \hfill (2.28)

One can show that $P_0$ is extremum for phase shifts $\Delta$ solutions of

$$\Gamma_-(\Delta) = 0.$$  \hfill (2.29)

These solutions for which

$$\frac{d\Gamma_-}{d\phi}(\Delta) = \Gamma'(\Delta) < 0(\text{resp.} > 0)$$  \hfill (2.30)

are maxima (resp. minima) of $P_0$.

The function $\Gamma$ is periodic with period 1. Therefore, $\Delta = 0, \pm 1/2$ are always solutions of equation 2.29. Other solutions may also exist. Equations 2.29 and 2.30 can be easily interpreted. Indeed, in the absence of noise, when time goes to infinity, the two neurons phase-lock, and the possible phase shifts are the stable fixed point of equation 2.22 with $\eta = 0$. It is straightforward to see that these phase shifts are the solutions of equation 2.29 and that equation 2.30 is the condition for their stability. In the presence of noise, the phase shifts between the two neurons have an increase (resp. decrease) in probability density to be near the stable (resp. unstable) fixed points of the noiseless dynamics. In the limit $\sigma \to 0$, $P_0(\Delta)$ is nonnegligible only for values of $\Delta$ in the vicinity of the maxima of $G(\Delta)$. For chemical synapses, $G(\Delta)$ is continuously differentiable at least up to the second order. Expanding $G$ around its maxima, one finds that $P_0$ is a sum of gaussians centered around these points, with a width proportional to $1/\sqrt{-\Gamma'(\Delta)}$. Therefore, the greater is the stability of a fixed point in the absence of noise, the sharper is the probability distribution around when noise is present. This is also true for electrical synapses for $\Delta \neq 0$. For $\Delta = 0$, the phase-shift distribution of the QIF model has a cusp. This is because in the QIF model, the PRF is discontinuous at $\Delta = 0$ and because we have modeled the spikes as a $\delta$-function added to the subthreshold voltage.

Note that the phase shift distribution depends on the couplings and the noise via the ratios $g_{\text{gap}}/\sigma^2$ and $g_{\text{inh}}/\sigma^2$. However, the locations of the extrema of the phase shift distribution depend on only the coupling via the ratio $g_{\text{gap}}/g_{\text{syn}}$ and are independent of the noise.

3 Cross-Correlations in the Quadratic Integrate-and-Fire Model

The QIF model is defined in section 2. Its dynamics are one-dimensional, with a temporal evolution of the voltage in its subthreshold range given by
one first-order differential equation. This equation is supplemented with a reset condition whenever the voltage reaches a threshold. In response to a suprathreshold step of current, the neuron fire spikes periodically. The QIF model is reminiscent of the more standard LIF model. However, in contrast with this model, the QIF dynamics of the voltage between the spikes are nonlinear. As a consequence of the quadratic nonlinearity in the dynamics, the temporal second-order derivative of the voltage of the QIF neuron vanishes during the interspike at a time that depends on a parameter, $V_s$ (as shown in section 2). This parameter also controls the excitability of the neuron (see below). As we will see, this gives rise to a variety of synchronization regimes as $V_s$ varies that do not occur in the LIF model but do occur in a conductance-based model with dynamics that are more faithful to neuronal biophysics.

The goal of this section is to identify these regimes in the QIF model. We consider three situations: a pair of neurons interacting solely via inhibition, a pair of neurons interacting solely via electrical coupling, and dual coupling, in which the neurons interact via both types of synapses. We show that similar regimes are found in biophysically more realistic models.

Because of the simplicity of the QIF model, many aspects of the dynamics of QIF networks (Hansel & Mato, 2003; Pfeuty et al., 2003) can be investigated using analytical techniques. In the case of a pair of neurons, an analytical formula can be established for their CC, assuming weak coupling and weakly noisy inputs (see equation 2.28). Using this formula, we conducted a systematic study of the ways in which the CC of the activity of a pair of QIF neurons depends on $V_s$, the firing frequency, and the nature of the neuronal coupling on synchrony. We present the results in the form of phase diagrams for the various regimes of parameters corresponding to qualitatively different shapes of CCs. Subsequently, we use numerical simulations to show that the results thus established hold for a broad range of coupling strengths and investigate new behaviors that may occur beyond this range.

3.1 Weakly Coupled Quadratic Integrate-and-Fire Neurons.

3.1.1 The Phase Response Function. The PRF of the QIF model can be computed analytically. It is given by (Ermentrout, 1981; Kuramoto, 1991; Pfeuty et al., 2003)

$$Z(\phi) = \left( \frac{dv(\phi)}{d\phi} \right)^{-1},$$

(3.1)

where $\phi = t/T$ with $T$ given by equation 2.4 and

$$v(\phi) = \sqrt{(I_{\text{ext}} - I_c)/A} \tan \left( \frac{\phi T \sqrt{A(I_{\text{ext}} - I_c)}}{\tau_m + \alpha} \right) + V_s.$$

(3.2)
Using equation 2.1, one finds

\[
Z(\phi) = \frac{\tau_m}{A[v(\phi) - V_s]^2 + I_{\text{ext}} - I_c}.
\]

(3.3)

Clearly \(Z(\phi) > 0\) for all \(\phi\). It is nonmonotonic and has one maximum, \(Z(\phi_m)\) at some \(\phi_m\), which depends on the frequency \(f\) and on \(V_s\) (for fixed \(V_r\) and \(V_T\)). Examples of the PRF, \(Z(\phi)\), are plotted in Figure 1B for three values of \(V_s\). For \(V_s < (V_r + V_T)/2\), \(\phi_m\) is a decreasing function of \(f\) with \(\phi_m \rightarrow 1/2\) in the limit \(f \rightarrow 0\) and \(\phi_m \rightarrow 0\) in the limit \(f \rightarrow \infty\). For \(V_s > (V_T + V_r)/2\), \(\phi_m\) increases with \(f\). Still, in the limit \(f \rightarrow 0\), \(\phi_m \rightarrow 1/2\) but \(\phi_m \rightarrow 1\) for \(f \rightarrow \infty\). For \(V_s = (V_T + V_r)/2\), \(\phi_m = 1/2\), independently of \(f\). Examples of the PRF are plotted in Figure 1B for three values of \(V_s\).

An analytical formula for the CC of a pair of QIF, equation 2.28, can be derived assuming weak coupling and weak noise. The results presented in this section were derived using this formula to compute the CCs.

3.1.2 The Three Generic Shapes of the CC for Inhibitory Coupling. Three examples of CCs computed using equation 2.28 are plotted in Figures 2A through 2C. The first example, displayed in Figure 2A, is for a high firing rate, 80 Hz, and a small \(V_s = 0.4\) mV. In this case, \(C(0)\) and \(C(\pm T/2)\) are local minima, and \(C\) is maximum at time shifts \(\pm \tau\), with \(\tau \approx T/6\). Figures 2B and 2C for different values of \(V_s\), \(V_s = 11.2\) mV and \(V_s = 8\) mV and the same firing, \(f = 20\) Hz. In both cases, \(C(\tau)\) has a local maximum at \(\tau = 0\), but for \(V_s = 11.2\) mV, the amplitude of this maximum is extremely small. It is much more pronounced for \(V_s = 8\) mV. For \(V_s = 11.2\) mV, \(C\) is also maximum at \(\tau = \pm T/2\). Therefore, the pattern of firing of the neuronal pair is different in the two cases. For \(V_s = 8\) mV, the neurons fire most of the time in synchrony, whereas for \(V_s = 11.2\) mV, the neurons fire most of the time in antisynchrony. The three shapes of the CCs described in Figure 2 are typical. A phase diagram showing the domain of parameters corresponding to each shape can be computed. It is plotted in Figure 2D. In the dark gray region, the CC has only one maximum, located at \(\tau = 0\). For large \(V_s\) and sufficiently small frequency (gray-and-white striped region), the CC displays another peak at \(\tau = \pm T/2\). However, \(C(0)\) decreases sharply below the boundary of the gray and white striped region. In most of this region, \(C(\pm T/2)\) is much larger than \(C(0)\), that is, the neurons are more likely to fire in antisynchrony than in synchrony. In contrast, for a small \(V_s\) and a large frequency (light gray region), the CC has two maxima, symmetrical around 0, at \(\pm \tau\) with \(0 < \tau < T/2\). Figure 2E displays the CC against \(V_s\) and \(\tau\) for a fixed frequency, \(f = 20\) Hz. It shows that at this frequency, the CC is maximum around \(\tau = 0\) but broad at small \(V_s\). The peak becomes more pronounced when \(V_s\) increases. However, when \(V_s\) is too large, the amplitude of this peak decreases, whereas a peak around \(\tau = \pm T/2\) appears.
Figure 2: Cross-correlations of a pair of QIF neurons interacting via inhibitory synapses. (A–C) CCs for three values of $V_s$ and $f$ for $g_{inh}/\sigma^2 = 20$. The synaptic time constants are $\tau_1 = 1$ msec, $\tau_2 = 6$ msec. (A): $V_s = 0.4$ mV, $f = 80$ Hz. The CC is peaked at $\pm T/6$. (B) $V_s = 8$ mV, $f = 20$ Hz. The CC has only one peak located at $\tau = 0$. (C) $V_s = 11.2$ mV, $f = 20$ Hz. The CC is peaked at $\tau = \pm T/2$ (antiphase). It also exhibits a small peak at $\tau = 0$ (see inset). (D) The phase diagram. Regions in which the CCs have different shapes have different gray codes. Dark gray: CCs with a peak at $\tau = 0$. White: CCs with a peak at $\tau = \pm T/2$. Light gray: CCs with peaks at $\pm \tau$ with $0 < \tau < T/2$. Dark gray and white: CCs with a peak at $\tau = 0$ and at $\tau = \pm T/2$. (E) The CCs as a function of $V_s$ for $f = 20$ Hz.

The phase diagram in Figure 2 was computed for $\tau_1 = 1$ msec, $\tau_2 = 6$ msec. Similar phase diagrams are found for other values of $\tau_1$ and $\tau_2$, but the positions of the transition lines are different. The slower the inhibition, the smaller the region where CC displays a peak around $\tau = \pm T/2$ (gray-and-white striped region) and the larger the region where CC has a maxima at $\pm \tau$ with $0 < \tau < T/2$ (red).

3.1.3 Electrical Couplings Mediate Synchrony or Antisynchrony Depending on $V_s$ and the Firing Frequency. A detailed study of $C(\tau)$ for a fixed frequency, $f = 50$ Hz, shows that when $V_s$ increases from $V_s = V_r \equiv 0$ to $V_s = V_T \equiv...
12 mV, the shape of the CC undergoes a continuous transformation. This is shown in Figure 2E, where the CC is plotted against $V_s$ and $\tau$ for a fixed frequency, $f = 50$ Hz. For a sufficiently small $V_s$, the CC is peaked around $\tau = \pm T/2$ and has a trough at $\tau = 0$. When $V_s$ increases, the trough persists, but when $V_s$ becomes sufficiently large, the CC is no longer maximum at $\tau = \pm T/2$. The two maxima, symmetrical around 0, are then located at some intermediate time delay, the distance of which decreases when $V_s$ increases. The trough at $\tau = 0$ is also reduced, and the distribution becomes flatter when $V_s$ increases. For some value of $V_s$, the two maxima merge, and the CC becomes monomodal at $\tau = 0$. The CC keeps this shape, becoming sharper and then again flatter, as $V_s$ increases. Therefore, for $f = 50$ Hz, the CC can have three qualitatively different shapes when $V_s$ changes. Examples are plotted in Figures 3A through 3C.

The phase diagram plotted in Figure 3D as a function of $V_s$ and $f$ shows that the three types of CCs described above for $f = 50$ Hz are also found for other values of the firing rate. It also shows that for sufficiently small frequency, a fourth type of CC is found for $V_s$ sufficiently close to $V_T$. It is maximum at $\tau = 0$ but also at $\tau = \pm T/2$. The closer $V_s$ is to $V_T$, the larger the amplitude of the CC near $\tau = \pm T/2$ (not shown).

The interactions induced by electrical synapses are diffusive. In contrast to chemical synapses, the synaptic currents they induced do not have intrinsic kinetics but depend on the membrane potential time course of the pre- and postsynaptic neurons. Subsequently, for electrical synapses, the current depends on the size and the shape of the action potential. In our model, this means that the amplitude of the spike, $\theta$, may affect the synchronization properties of the neurons. In fact, we found that the phase diagram is affected quantitatively only when $\theta$ is changed. When $\theta$ increases, the gray-and-white striped region shrinks and the white region expands. However, it can be shown that the white region always remains confined to the left half-part of the phase diagram, where $V_s < 6$ mV.

### 3.1.4 Three Modes of Interplay Between Electrical and Inhibitory Synapses.

The results of the previous sections demonstrate that the CCs of a pair of QIF neurons coupled via inhibition or electrical synapses depend crucially on the parameter $V_s$. Moreover, comparing the phase diagram in Figure 3 with the one in Figure 2 reveals that these two types of synapses may have similar or opposing effects on synchrony, depending on $V_s$ and $f$. Therefore, it is likely that when combined, the two types of synapses can either cooperate in promoting synchrony or be antagonistic, depending on the parameters.

Using equations 2.28, 2.27, and 2.23, one can see that the number of maxima and minima of $C(\tau)$ and their location depend on the coupling constants via their relative value, $g_{gap}/g_{syn}$ alone. However, other properties of $C$, for example, the amplitude of the extrema and their widths, depend on the absolute values of $g_{gap}$ and $g_{syn}$.
We first investigate how the combination of these two types of synapses affects the extrema of $C$ and the corresponding phase diagram as a function of $f$ and $V_s$. As the ratio $g_{gap}/g_{inh}$ varies from 0 to $\infty$, the phase diagram gradually modifies from the one in Figure 3D to the one in Figure 2D. For example, Figure 4A plots the phase diagram for $g_{gap}/g_{inh} = 1/2$. The codes have the same meaning as in Figures 2D and 3D. Comparing Figures 4A and 3D shows that adding inhibitory synapses to electrical synapses reduces the size of the region of antisynchronous firing (white region), and increases the domain of intermediate phaseshift (light gray region) as well as the domain of bistability (gray-and-white striped region). Comparing Figure 4A with Figure 2D, one sees that adding electrical synapses to inhibitory synapses reduces the size of the domain of synchronous firing (dark grey region). This
Figure 4: A pair of QIF neurons interacting via dual coupling. The coupling ratio $g_{gap}/g_{inh} = 1/2$. (A) Phase diagram. The parameters and the codes are the same as in Figures 2D and 3D. Note the small region at large $V_s$ and small frequency in which the CCs have a peak at $\tau = 0$ and at $\tau = \pm T/2$. (B) The CC as a function of $V_s$ for $f = 50$ Hz.

also decreases the size of the bistability domain (gray-and-white striped region). Figure 4B displays the CC as a function of $V_s$ and $\tau$ for a fixed frequency, $f = 50$ Hz.

The CCs for electrical synapses, alone, dual synapses, or inhibition alone are compared (from left to right) in Figure 5 for different values of the parameters $V_s$ and $f$. In the top row ($V_s = 2$ mV and $f = 50$ Hz), electrical synapses alone promote antisynchronous firing, whereas inhibition promotes synchronous firing. When combined together, the CC is maximum for some intermediate time delay (neither 0 nor $\pm T/2$). Note also that the CC is less modulated for dual coupling than for electrical or inhibitory couplings alone. Therefore, for these values of $V_s$ and $f$, starting from dual coupling and blocking inhibition increases dramatically the probability of antisynchronous firing while suppressing almost completely the probability of synchronous firing. Blocking electrical synapses improves synchronous firing.

In the middle row ($V_s = 8$ mV, $f = 50$ Hz), both electrical synapses and inhibitory synapses promote synchronous firing. When together, the synapses cooperate to increase further the probability of synchronous firing and to sharpen the CC around $\tau = 0$. Therefore, in this case, blocking electrical synapses or inhibition reduces the probability of the neurons of firing in synchrony.

In the bottom row ($V_s = 11.2$ mV and $f = 20$ Hz), electrical synapses alone promote synchrony, but with inhibition alone, the maxima of $C$ are at $\tau = 0, \pm T/2, C(\pm T/2)$, being much larger than $C(0)$ (in fact, the maximum at $\tau = 0$ cannot be seen in the figure because of its scale). For dual
Inhibitory and Electrical Synapses in Synchrony

Figure 5: Different regimes of interplay of electrical and inhibitory couplings for QIF neurons. (Left column) Electrical synapses (same parameters as in Figure 2). (Right column) Inhibitory synapses (same parameters as in Figure 3). (Middle column) Dual coupling. (Top row), $V_s = 2 \text{ mV, } f = 50 \text{ Hz}$. Antagonistic effects of electrical and inhibitory synapses on synchrony: electrical synapses impede synchrony, but inhibitory synapses promote it. (Middle row), $V_s = 8 \text{ mV, } f = 50 \text{ Hz}$: Electrical and inhibitory synapses cooperate. Bottom row, $V_s = 11.2 \text{ mV, } f = 20 \text{ Hz}$. Antagonistic effect of electrical and inhibitory synapses on synchrony: electrical synapses promote synchrony, but inhibitory synapses impede it.

coupling, the CC is maximum for $\tau = 0, \pm T/2$, with a larger correlation at $\tau = 0$ than at $\tau = \pm T/2$. However, $C(0)$ is substantially smaller in comparison to the case of electrical coupling alone. Hence, in this case, starting with neurons interacting via dual coupling and blocking inhibition would increase the probability of synchronous firing, whereas blocking electrical synapses would reduce it substantially and increase the probability of anti-synchronous firing.
In summary, the weak coupling theory yields three parameter regimes for the interplay of electrical and inhibitory synapses in synchrony. In one regime, the synapses exhibit cooperative interplay, both of them promoting synchrony. In the other regimes the synapses act antagonistically. This may happen in two ways: because electrical synapses oppose synchrony but inhibitory synapses promote it or because electrical synapses promote synchrony but the net effect of the inhibitory interactions opposes it.

Note that these three modes of interplay stem from the dependence of the CCs on $V_s$ for electrical or inhibitory synapses alone combined with the fact that the function $G(\Delta)$ that determines the CCs for dual coupling, equation 2.28, depends linearly on the two interactions.

3.2 Beyond Weak Coupling and Weak Noise: The Nonlinear Interplay Between Electrical and Inhibitory Synapses. The analytical formula for the CCs used above in the derivation of the phase diagrams was established assuming weakly coupled neurons and weakly noisy inputs. Do the effects of $V_s$ on the CCs found in this limit for inhibitory or electrical synapses alone still persist when the coupling and the noise are not weak? In the weak coupling limit, electrical and inhibitory synapses interact in a linear manner when they are combined. What are the nonlinear effects that occur at strong couplings? To answer these questions, we performed numerical simulations.

Figure 6 displays the CCs obtained in numerical simulations (circles) for two values of $V_s$, $V_s = 2$ mV and $V_s = 8$ mV, with various coupling strengths and three combinations of the interactions (electrical, inhibitory, and dual). The noise was also varied to keep the ratios $g_{\text{inh}}/\sigma^2$, $g_{\text{gap}}/\sigma^2$ fixed to 10 and 20, respectively. This is because the weak coupling theory predicts that the CCs depend on $\sigma^2$ and on $g_{\text{inh}}$ and $g_{\text{gap}}$, via these ratios, as can be seen from equations 2.21 and 2.28. The solid lines in Figure 6 correspond to the CCs computed from the latter equations for the same values of these ratios.

In the left column of Figure 6, which corresponds to relatively weak electrical and inhibitory couplings corresponding to postsynaptic potential of an amplitude of 0.2 mV, the simulations agree perfectly with the results from the weak coupling analysis. The middle column corresponds to coupling strengths, which are four times larger than in the left column. The agreement remains excellent except for dual coupling at $V_s = 2$ mV. Indeed, in this case, the weak coupling theory predicts that the CC should display a trough at zero time shift and that the firing probability should be maximum close to $T/8$. In contrast, in the simulations, the CC is maximum at zero time shift.

Results for further increase of coupling strength by a factor of 3 are displayed in the right column in Figure 6. This corresponds to postsynaptic potentials of a typical size of 2 mV.

For $V_s = 8$ mV, weak coupling theory predicts synchronous firing for electrical synapses alone. Synchrony is also found in the simulations, but
Figure 6: CCs of a pair of QIF neurons for different coupling strengths. Circles and dash lines: Results from simulations (averaging over 100 sec of activity). Solid lines: Predictions from weak coupling theory. The strength of the electrical synapses is from left to right: $g_{\text{gap}} = 0.0025, 0.01$ and $0.03$ corresponding, respectively, to coupling coefficients of 0.02 mS/cm$^2$, 0.06 mS/cm$^2$, and 0.16 mS/cm$^2$. The strength of inhibitory synapses is from left to right: $g_{\text{inh}} = 0.005$ mS/cm$^2$, 0.02 mS/cm$^2$, and 0.06 mS/cm$^2$. The noise and the external current were adjusted to keep constant $g_{\text{gap}}/\sigma^2 = 10$ and $g_{\text{inh}}/\sigma^2 = 20$. The firing frequency is fixed (50 Hz). (A) $V_s = 2$ mV. (B) $V_s = 8$ mV.

the CC is much more peaked than predicted. This is due to direct threshold crossing, which is rare when the coupling is weak but contributes a great deal to the firing of the postsynaptic neuron for strong electrical coupling. For inhibitory coupling, the agreement between the theory and the simulations remains reasonable. Combining the two interactions sharpens the
CC, as predicted by the weak coupling theory, but quantitative agreement is poor.

For $V_s = 2 \text{ mV}$, the agreement is excellent for inhibitory coupling. For electrical coupling, the theory predicts antisynchronous firing. However, in the simulations, the CC is flat—the probability of firing is almost homogeneous, as it would be without coupling. Remarkably, in spite of the fact that electrical synapses are not able to induce synchrony, they strongly amplify synchrony and sharpen the CC when they are added to the inhibitory synapses (compare the CC in the middle line, right column). This nonlinear interplay between the two types of synapses requires strong couplings.

### 3.3 Predicting the Shape of the CCs from the Shape of the Phase Response Function.

Our study of the QIF model in the weak coupling limit relies on the analytical formula, equation 2.28, which relates the CC to the synaptic couplings and the neuronal PRFs. The main effect on the PRF of changing $V_s$ is to shift the location of its maximum. It varies continuously from 0 to 1, as $V_s$ increases from $V_r$ to $V_T$ (see Figure 1). Since equation 2.28 holds for any neuronal dynamics, our analysis of the QIF model suggests that more generally, synchrony may be predicted from the shape of the PRF independent of the details of the neuronal dynamics. These predictions can be summarized as follows. For electrical synapses, a pair of neurons with PRF skewed to the right tends to fire synchronously when interacting via electrical synapses. In contrast, neurons with PRF sufficiently skewed to the left tend to fire antisynchronously. For inhibitory synapses, CCs always have a peak at $\tau = 0$ unless the PRF is too skewed to the left and the firing rate, $f$, of the neurons is too large. When the PRF is strongly skewed to the right and $f$ is sufficiently small, the CC is also peaked around $\tau = \pm T/2$. The latter peaks may be much higher than the peak at $\tau = 0$, indicating that the net effect of inhibition opposes synchrony. The faster the synapses, the larger the domain of parameters in which this happens. Our simulations of the QIF model indicate that these predictions from the weak coupling theory remain relevant, at least qualitatively, within a broad range of coupling strengths.

For weak enough synapses, the interplay of electrical and inhibitory interactions is essentially linear. This property stems from the general formula, equation 2.28, and therefore it is not restricted to the QIF model. Hence, we expect that for general neuronal dynamics, the shapes of the CC for dual coupling can be predicted from the effect of each synapse taken separately, provided the interactions are not too strong. When the interactions are strong, nonlinear effects start to be significant. Nevertheless, knowing the PRF of the neurons can serve to qualitatively predict the interplay of the two types of interactions. For instance, from the analysis of the QIF model, we predict that for neurons with a PRF skewed to the left, adding strong electrical synapses to inhibitory synapses amplifies synchronous firing, although singly electrical synapses would not lead to synchrony. This effect
is a consequence of the rapid direct threshold crossing induced by strong electrical synapses when they act at a time when the postsynaptic neuron is not far from threshold. Therefore, one may expect that such synergetic interplay of electrical and inhibitory interactions is a general effect that occurs in conductance-based models and in real neurons.

4 Cross-Correlations in a Conductance-Based Model

The results of the previous section suggest that the shape of the CC of a pair of neurons can be related to their intrinsic properties, provided one knows how ionic channels and neuronal morphology shape their PRF. In this section, we verify that this indeed holds in the framework of a two-compartment conductance-based model neuron. The somatic compartment incorporates one fast and one persistent sodium current and a delayed rectifier potassium current. The dendritic compartment is passive. Details of the model are given in section 2. To be specific, we focus on the effects of the persistent sodium current and the dendritic compartment on the synchrony of the neurons. The results presented in this section lead to experimentally testable predictions, as explained in section 5.

4.1 Increasing $g_{NaP}$ in the Conductance-Based Model and Decreasing $V_s$ in the QIF Model Have Similar Effects on the PRF. The effect of $I_{NaP}$ on the voltage trace and the PRF of the neuron is shown in Figures 7A and 7B. For all the considered values of $g_{NaP}$, $Z(\phi)$ is positive for all $\phi$. It is also nonmonotonic and monomodal. The PRF is small just before, during, and just after the action potential. The position of the maximum depends on $g_{NaP}$. For $g_{NaP} = 0$, it is in the second half of the period at $\phi \approx 2/3$. As a result, the global shape of the PRF is skewed toward the second half of the period of the neuron. The response of the neuron increases with $g_{NaP}$, especially in the first half of the period. This shifts the maximum of $Z(\phi)$ toward smaller $\phi$. For large enough $g_{NaP}$, the PRF is skewed toward the left. The PRF also depends on the firing rate, $f$. For a given parameter set, the maximum of $Z$ moves closer to $1/2$ when $f$ goes to 0; in that limit, the function $Z$ becomes proportional to $1 - \cos 4\pi \phi$ (Ermentrout, 1996), as in the QIF model. Therefore, increasing $g_{NaP}$ in our conductance-based model or decreasing $V_s$ in the QIF model affects the PRF of the neurons in a similar way. Hence, we may expect that this should also affect the CCs similarly. We show that this is indeed the case.

4.2 The Effect of the Persistent Sodium Current on the Cross-Correlations. In this section, we assume that $g_c = 0$ (in this case, the model has a single compartment). Figure 8 plots the CCs for three values of $g_{NaP}$—when the neurons are coupled solely via electrical synapses (left column), chemical synapses (right column), or both synapses (middle column). The synaptic conductances were $g_{gap} = 0.005$ mS/cm$^2$ and $g_{inh} = 0.02$ mS/cm$^2$. 
Figure 7: Voltage traces and phase-response functions of the conductance-based model neuron are shaped by the persistent sodium current. The soma and the dendrite are decoupled ($g_c = 0$). (A) Voltage traces. (B) PRF. The PRFs were obtained by computing the delay on the spike times induced by small perturbations (see Hansel et al., 1993). The external current was adjusted to keep the firing constant, $f = 50$ Hz: The external currents are $1.1 \mu A/cm^2$, $-0.3 \mu A/cm^2$, and $-1.04 \mu A/cm^2$, respectively, for $g_{NaP} = 0, 0.2 mS/cm^2$, and $0.7 mS/cm^2$.

The corresponding spikelets and IPSPs are also shown in Figure 8A. Their peak amplitudes are about $0.3 mV$ and $0.4 mV$, respectively.

The results obtained for $g_{NaP} = 0.7 mS/cm^2$, $f = 50$ Hz are similar to those obtained for the QIF model with $V_s = 2 mV$ and the same firing frequency (see Figure 5 left line). In both cases, electrical synapses promote antisynchrony, whereas inhibition alone promotes synchrony. For dual coupling, the two trends compete, and the peak of the CC around $\tau = 0$ is very flat. Reducing $g_{NaP}$ to $g_{NaP} = 0.2 mS/cm^2$ but keeping the frequency constant, $f = 50$ Hz, electrical synapses or inhibitory synapses alone promote synchronous firing. For dual coupling, the two types of synapses cooperate, leading to more synchronous activity than when each of them is considered alone. This is similar to what was obtained in the QIF model for $V_s = 2$, $f = 20$ Hz (see Figure 5, middle row). For even smaller $g_{NaP}$ and also reducing the frequency ($f = 20$ Hz) (see Figure 8B, bottom row) leads to CCs that are similar to those for $V_s = 11.2 mV$ and $f = 20$ Hz in the QIF (bottom row in Figure 5). In both cases, electrical synapses alone favor synchronous firing. Adding inhibitory interactions substantially reduces the probability of the neurons’ firing simultaneously. This is because for $g_{NaP} = 0$, electrical and inhibitory synapses act antagonistically, since the latter promote antisynchrony (see Figure 8B, bottom row, right column).

We also investigated the effect of $g_{NaP}$ on the CCs when the synapses are strong. Results are shown in Figure 9 for synaptic conductances six times
Figure 8: Effects of the persistent sodium current and the firing frequency on the CCs in the conductance-based model. (A) Postsynaptic potentials due to one presynaptic spike are shown (for $g_{NaP} = 0$). The soma and the dendrite are decoupled ($g_c = 0$). (Left) Electrical coupling, $g_{gap} = 0.005 \text{mS/cm}^2$. (Right) Inhibitory coupling, $g_{inh} = 0.02 \text{mS/cm}^2$. (Middle) Dual coupling. (B) CCs are computed over 100 sec of activity for three values of $g_{NaP}$. The SD of the noise is $\sigma = 0.15 \text{mV/ms}^{1/2}$. (Top row) $g_{NaP} = 0.7 \text{mS/cm}^2$, $f = 50 \text{Hz}$, ($I_{ext} = -1.04 \mu\text{A/cm}^2$). Electrical and inhibitory synapses have antagonistic effects on synchrony. Electrical synapses suppress synchrony and inhibition-induced synchrony. (Middle row) $g_{NaP} = 0.2 \text{mS/cm}^2$, $f = 50 \text{Hz}$, ($I_{ext} = -0.30 \mu\text{A/cm}^2$). Electrical and chemical synapses cooperate. (Bottom row) $g_{NaP} = 0$, $f = 20 \text{Hz}$, ($I_{ext} = 0.56 \mu\text{A/cm}^2$). Electrical and inhibitory synapses have antagonistic effects on synchrony. Inhibitory synapses suppress synchrony, but electrical synapses promote it.
larger than in the results depicted in Figure 8, namely, for $g_{gap} = 0.03 \text{ mS/cm}^2$ and $g_{inh} = 0.12 \text{ mS/cm}^2$. The amplitude of the corresponding spikelets and inhibitory postsynaptic potentials is about 2.5 mV (see Figure 9A). The coupling coefficient for electrical synapses is 20%. This corresponds to synapses with strengths in the upper physiological range. Our numerical simulations confirmed that the crucial influence of the constant sodium current on the CCs also occurs for such strong synapses. Indeed, for $g_{NaP} = 0.2 \text{ mS/cm}^2$, the neurons fire in synchrony, and the CC has a peak at $\tau = 0$ (see Figure 9C, left panel). In contrast, for $g_{NaP} = 0.7 \text{ mS/cm}^2$ (see Figure 9B, left panel), the central peak of the CC is suppressed. Note, however, that the peak is sharper and larger in Figure 9C than in Figure 5B, and the peaks of the CC in Figure 9A are around $\tau = \pm 3T/8$ and not at $\tau = \pm T/2$, as in the corresponding case for weaker coupling (see Figure 5).

The right panels in Figures 9A and on B show the CCs for strong inhibition. Reducing $g_{NaP}$ has a minor effect on the CC peak value, as in the corresponding case in Figure 5. However, in contrast to weak coupling, this also decreases the firing probability around $\tau = T/4$ and increases it at $\tau = T/2$. This did not happen at weaker coupling (see Figure 5).

The most significant difference between the CCs at weak and strong couplings occurs when electrical and inhibitory interactions are combined and $g_{NaP}$ is sufficiently large. Indeed, in this case, the two types of synapses show synergy. As in the QIF model, for small $V_s$, synchronous firing is completely suppressed for electrical synapses alone. But when added to inhibition, the peak of the CC at $\tau = 0$ is amplified.

### 4.3 Synchrony of Neurons Coupled via Electrical Synapses Decreases When the Somato-Dendritic Coupling Increases.

We now assume $g_{NaP} = 0$ and discuss the effect of the dendrite on synchrony. Therefore, we assume $g_c \neq 0$. In this case, perturbations acting on the somatic or the dendritic compartment affect the firing of the neuron differently. Therefore, two PRFs can be defined, one, $Z_{\text{soma}}$, for perturbations on the soma and the other, $Z_{\text{dendrite}}$, for perturbations on the dendrite. These two functions are plotted in Figure 10A for our two-compartment model assuming $g_{NaP} = 0$, a somato-dendritic coupling conductance $g_c = 0.3 \text{ mS/cm}^2$ and for a firing frequency, $f = 50 \text{ Hz}$. The somatic PRF for $g_c = 0$ and $f = 50 \text{ Hz}$ is also plotted on the same figure (dashed line).

The coupling with the dendritic compartment affects the shape of the somatic PRF by skewing it toward the first half of the period (compare the somatic PRFs for $g_c = 0.3 \text{ mS/cm}^2$ and $g_c = 0$). This is because the voltage perturbation at the soma backpropagates to the dendrite, and from there reverberates back to the soma. Therefore, the overall response to a perturbation at the soma is the sum of two contributions. The first one is the same as though the dendrite was absent. The second one, which is due to the dendrite, is a delayed and broadened version of the first one. Together, these
Figure 9: Nonlinear interplay between strong electrical and inhibitory synapses for conductance-based neurons. Synaptic conductances are $g_{\text{gap}} = 0.03 \text{ mS/cm}^2$ and $g_{\text{inh}} = 0.12 \text{ mS/cm}^2$. The SD of the noise is adjusted to obtain $g_{\text{gap}}/\sigma^2$ and $g_{\text{inh}}/\sigma^2$ to $\approx 1.1$ and $\approx 4.4$. The external current is such that $f = 50 \text{ Hz}$. (A) Postsynaptic potential induced by a presynaptic action potential for (left to right) electrical coupling alone, dual coupling, and inhibitory coupling alone. (B) $g_{\text{NaP}} = 0.7 \text{ mS/cm}^2$ ($I_{\text{ext}} = -1.04 \mu\text{A/cm}^2$). Electrical synapses alone reduce probability to fire in-phase (top), but combined with inhibitory synapses they amplify synchronous firing, (see right panels). (C) $g_{\text{NaP}} = 0.2 \text{ mS/cm}^2$ ($I_{\text{ext}} = -0.30 \mu\text{A/cm}^2$). Electrical synapses strongly amplify the peak in-phase with or without inhibitory synapses.

Two contributions lead to a response that is stronger and extends earlier in the limit cycle. When the perturbation is on the dendrite, the PRF is skewed to the left, as shown in Figure 10A (solid line) compared to the somatic PRF (dash-dot line). This is because the dendritic compartment delays and filters the perturbation before it can affect the firing of action potentials in the somatic compartment.
Therefore, adding a dendritic compartment to the soma shapes the PRF similarly to reducing $V_s$ in the QIF model or increasing $g_{NaP}$ in the single compartment model. Hence, we expect that for electrical synapses located on the soma, synchrony decreases with $g_c$. We also expect that neurons are less synchronized if the electrical synapses are on the dendrites than if they are on the soma. This is confirmed by the results displayed in Figure 10B, where the CCs of two neurons firing at 50 Hz are compared for somatic electrical synapses for $g_c = 0.3 \text{ mS/cm}^2$ (dash-dot line) and $g_c = 0$ (dashed line) and dendritic synapses (solid line). In the first two cases, the CC is peaked around $\tau = 0$. However, it is much broader and smaller, $g_c = 0.3 \text{ mS/cm}^2$, than for $g_c = 0$. Moving the synapses to the dendrites reduces the synchrony further. In the example shown in Figure 10B (solid line), it even leads to antisynchronous firing. The transition to antisynchrony induced by electrical
synapses when the dendritic compartment is added is basically similar to the transition to antisynchrony in the QIF model when $V_s$ is reduced. As in the QIF, this effect is firing rate dependent. This is shown in Figure 10C, where the CC is plotted for $f = 50$ Hz and $f = 10$ Hz. In the latter case, the CC, although broad, is maximum at $\tau = 0$ in contrast with $f = 50$ Hz, where antisynchrony occurs.

5 Discussion

5.1 Relating CCs to Cellular and Synaptic Properties. We have shown that the CCs of the activity of a pair of tonically spiking neurons interacting via electrical and/or inhibitory synapses can be predicted if one knows the shape of their PRF. Subsequently, one can predict how cellular properties affect the CCs if one knows how the former shape the PRF. Strictly speaking, the PRF is defined only when neurons are weakly interacting. However, in our model, weak coupling predictions remain valid at least qualitatively for spikelet amplitudes and IPSPs as large as 2 to 2.5 mV. These values are similar to those observed in vitro (Galarreta & Hestrin, 2001, 2002).

In the case of the QIF model, we focused on the effect of the parameter $V_s$. The effects of $V_r$ and $V_T$ can be studied in a similar way. In conductance-based models as in real neurons ionic channels determine the PRF (Crook et al., 1998a; Ermentrout et al., 2001; Oprisan & Canavier, 2002; Acker et al., 2003; Pfeuty et al., 2003). We have focused here on the effect of $I_{NaP}$ or of a passive dendrite (modeled as a single compartment), which shifts the maximum of the PRF toward the left. Other inward currents, such as calcium currents, have the same effects on the PRF and must affect synchrony in a similar way. Potassium currents, in contrast, skew the PRF to the right (Ermentrout et al., 2001; Pfeuty et al., 2003). Therefore, we predict that potassium and sodium currents have mirror effects on synchrony (Pfeuty et al., 2003). We have verified these predictions in simulations of conductance-based models (results not shown).

We have found that electrical synapses located on the dendritic compartment of the conductance-based neuron are less synchronizing than if they are located on the soma. One contribution to this effect is the additional delay induced by the dendritic compartment, which is like shifting the PRF to the left. One can similarly predict the effect of conduction or the synaptic delays in the inhibitory interactions. Although we did not include these delays in our model, our approach can be straightforwardly extended to take them into account (Izhikevich, 1998). For given cellular properties, this would amount to shifting the PRF of the neurons to the left, as would be the effect of increasing $g_{NaP}$ without delays.

5.2 Linear and Nonlinear Interplays Between Electrical and Inhibitory Synapses. When the interactions are not too strong, the CCs of the activity of two neurons are very well approximated by our analytical result, equa-
tions 2.21 and 2.28, which relates the CC to the effective phase interaction, $\Gamma$. For dual coupling, $\Gamma$ is the sum of two contributions due to each of the interactions. In this sense, the interactions combine their effect linearly. This implies that the CC for dual coupling is the normalized product of the CCs for each interaction alone. When the interactions are sufficiently strong, substantial deviations from equations 2.21 and 2.28 occurs due, for instance, to nonlinear interaction between electrical and inhibitory synapses. This is what we have found when electrical synapses amplify synchronous firing of a pair of neurons when combined with inhibition, although the CC would display a trough at zero time delay with electrical synapses alone due to the intrinsic properties of the neurons. A counterpart of this synergetic effect in a large network of such neurons is enhancement of synchrony by electrical synapses when combined with inhibition, although alone the latter would promote asynchronous firing (results not shown). This effect should not be confused with the more trivial fact that combining electrical and inhibitory synapses enhances synchrony when the neuronal properties are such that both interactions alone promote synchronous firing.

5.3 Relation to Previous Studies.

5.3.1 Modeling Works. Previous work has addressed the role of cellular properties in inhibition-mediated synchrony focusing on the interplay between postinhibitory rebound (PIR) and inhibition. They have shown that PIR stabilizes in-phase synchrony (Wang & Rinzel, 1992; Golomb, Wang & Rinzel, 1994) for sufficiently slow and strong inhibition. The synchronizing role of inhibition studied here is essentially different; it occurs for QIF neurons that do not display PIR, and it does not require strong coupling. Rather, it is similar to the mechanism considered by van Vreeswijk et al. (1994) and Hansel et al. (1995). Our study helps clarify how intrinsic neuronal properties affect synchrony in this mechanism.

Previous studies of conductance-based models have shown that a pair of electrically coupled neurons may fire in synchrony or in antisynchrony depending on the model or the firing rate (Sherman & Rinzel, 1992; Han, Kurrer, & Kuramoto, 1995; Chow & Kopell, 2000). For the compartmental model studied by Alvarez, Chow, van Bockstaele, and Williams (2002), electrical synapses located on the soma synchronize the spikes of the neurons in the whole range of frequency investigated. In contrast, for synapses on the dendrites, synchrony occurs only for sufficiently small firing rates. Our work provides a general framework to understand this diversity of behaviors.

Synchrony of a pair of LIF neurons interacting via electrical and/or inhibitory synapses has been studied by Lewis and Rinzel (2003). The PRF of the LIF increases monotonically with the phase, regardless of the cellular parameters (Kuramoto, 1991; Hansel et al., 1995). Such a shape is found in the QIF model for $V_s \rightarrow V_T$. Therefore, in this limit, the properties of
the QIF model resemble those of the LIF. For instance, in the regions in the bottom-right of the QIF phase diagrams for electrical synapses (see Figure 3) and for inhibitory synapses (see Figure 2), the CCs have a peak at $\tau = 0$ and at $\tau = \pm T/2$. Changing the size of the spike $\theta$ and the inhibitory time constants modifies the extent of these regions and their overlap. As a consequence, for large $V_s$ and small $f$, the interplay of the two types of synapses depends on these parameters. For sufficiently large $\theta$ and fast inhibition (the case considered in Figure 4) $C(T/2)$ decreases and $C(0)$ increases when electrical coupling is added to inhibitory coupling, compared to the case of inhibition alone. The opposite effect occurs for slow inhibition and small $\theta$ (result not shown). This is similar to what Lewis and Rinzel (2003) found for the LIF, but it occurs only in a restricted domain of the phase diagrams of the QIF.

The dynamics of networks consisting of a large number of inhibitory interneurons coupled also via electrical synapses have been investigated recently (Traub et al., 2001; Bartos et al., 2002). Bartos et al. found that in a network of Wang-Buszaki (WB) neurons, electrical synapses enhanced synchrony even in the absence of inhibition. This agrees with our work, since one can check that the PRF of WB neurons is qualitatively similar to the one of our model in the absence of $I_{NaP}$. Traub et al. found that in a network of multicompartamental neurons coupled with inhibition, electrical synapses located on the dendrites improve synchrony. The mechanism underlying this effect is not clear since Traub et al. did not study their model when inhibition is suppressed.

5.3.2 Experimental Work. Recent experimental work suggests that electrically coupled pairs of LTS and pairs of FS cells have different synchronization properties (Mancilla, Lewis, Pinto, Rinzel, & Connors, 2002). Alvarez et al. (2002) have shown that synchrony of neurons in locus coeruleus (LC) interacting via electrical synapses is affected differentially by the firing rate of the neurons in adult and neonatal slices. It would be interesting to investigate experimentally whether these differences in synchronization properties can be explained by differences in the neuronal PRF, as our work suggests.

The synchronizing effect of electrical synapses has been also assessed in neocortex and hippocampus by showing a reduction in synchronous oscillations in the gamma frequency range after suppressing Cx36-based electrical synapses (Deans et al., 2001; Hormuzdi et al., 2001). In the work of Tamas et al. (2000), both inhibitory and electrical synapses were found to be required to obtain tight synchrony in a neocortical slice. Although all of these studies support the role of electrical synapses in synchrony, the underlying mechanism remains to be defined in the light of our work, which shows that synchrony occurs in different ways depending on the intrinsic properties of the neurons and on the strength of the interactions.
Figure 11: Predictions for the dependence of the shape of CCs on cellular and synaptic properties. (A) Qualitative predictions for the effect of changing $g_{NaP}$ and the firing frequency for the CCs of a pair of neurons interacting solely via electrical synapses. The coupling strength is fixed. (B) Qualitative predictions for a pair of neurons interacting solely via inhibitory synapses. The synaptic coupling conductance is fixed. (C) Qualitative predictions for the effects of the inhibitory and electrical coupling strength on the shapes of the CCs for dual coupling. The persistent-sodium conductance and the firing rates of the neurons are fixed and sufficiently large.

5.4 Predictions for Experiments. The dynamic clamp technique (Sharp et al., 1993; Prinz et al., 2004; Brizzi et al., 2004) can be used to modify artificially the cellular properties of neurons as well as the couplings between neurons. Therefore, it can serve to study how the dynamics of neurons depend on their intrinsic properties or the nature of their interactions (Prinz et al., 2004; Perez-Velazquez, Carlen, & Skinner, 2001). This approach can be used to test experimentally the predictions of this work, for instance, in pairs of cortical interneurons activated by injection of external noisy currents.

Pairs of interneurons interact frequently via electrical and inhibitory synapses. A first experiment would be to record from pairs coupled only via electrical or inhibitory synapses to study how their CCs vary as a function of the average firing rates. We predict different behaviors, as schematically depicted in Figures 11A and 11B. Which of these behaviors actually occurs depends on the balance between inward and outward currents in the cells and on the location of the synapses on their dendritic trees. A second experiment would be to study the effect of the modifications of the cellular properties. We focus here on the effect of $I_{NaP}$. Depending on the outcomes of the first experiment, the effect would have to be tested by either increasing or decreasing the importance of this current (a decrease can be achieved by simulating a persistent sodium current with a negative conductance). We also predict that the effect of combination between inhibitory and electrical coupling on CCs depends on their strength as depicted in Figure 11C. Of particular interest would be to test the nonlinear interplay of these interactions.
Appendix A: Parameters of the Conductance-Based Model

The dynamics of the membrane potentials of the somatic and dendritic compartments of our conductance-based model are given by

$$\frac{dV}{dt} = I_{\text{ext}} - I_L - I_{Na} - I_K - I_{NaP} - g_c(V - V_d) + I_{\text{noise}} + I_{\text{gap}} + I_{\text{inh}}$$  \hspace{1cm} (A.1)

$$\frac{dV_d}{dt} = -g_l(V_d - V_{id}) - g_s(V_d - V) + I_{\text{gap}},$$  \hspace{1cm} (A.2)

where $I_{\text{inh}} = -g_{inh} s(V_i - V_{inh})$ for the inhibitory current, and $I_{\text{gap}} = -g_{gap}(V_i - V_j)$ or $I_{\text{gap}} = -g_{gap}(V_{di} - V_{dj})$ for current due to an electrical synapse respectively located between somatic or dendritic compartments.

$I_{Na} = g_{Na} m_s^2 h(V - V_{Na})$ and $I_K = g_K n^4 (V - V_K)$ are the spike-generating currents, and $I_{NaP} = g_{NaP} p_{\infty} (V - V_{Na})$ is a noninactivating (persistent) sodium current. The kinetics of the gating variable $h, n, s$ are given by

$$\frac{dx}{dt} = \alpha_x(V)(1 - x) - \beta_x(V)x,$$  \hspace{1cm} (A.3)

where $x = h, n, s$ and $\alpha_h(V) = 0.21 e^{-(V+58)/20}$, $\beta_h(V) = 3/(1 + e^{-(V+28)/10})$, $\alpha_s(V) = 50 (1 + \tanh(V/4))$, $\beta_s(V) = 1/\tau_{inh}$ The activation functions, $m_{\infty}$ and $p_{\infty}$, are given by $m_{\infty}(V) = \alpha_m(V)/(\alpha_m(V) + \beta_m(V))$, where $\alpha_m(V) = 0.1(V + 35)/(1 - e^{-(V+35)/10})$, $\beta_m(V) = 4e^{-(V+60)/18}$, and $p_{\infty}(V) = 1/(1 + e^{-(V+40)/6})$.

Throughout this work, the parameters $g_{Na} = 35$ mS/cm$^2$, $V_{Na} = 55$ mV, $g_K = 10$ mS/cm$^2$, $V_K = -75$ mV, $g_L = 0.15$ mS/cm$^2$, $V_L = -65$ mV, $g_{ld} = 0.15$ mS/cm$^2$, $V_{ld} = -65$ mV, $V_{inh} = -75$ mV, $\tau_{inh} = 6$ msec and $C = 1 \mu$F/cm$^2$ are kept constant. The conductance $g_{NaP}$ varies from 0 to 0.7 mS/cm$^2$, and the conductance between the dendritic and somatic compartment is either $g_c = 0$ (one-compartment model) or 0.3 mS/cm$^2$.

Appendix B: Relationship Between the Phase-Shift Distribution Function and the Cross-Correlation in the Weak Coupling and Weak Noise Limit

The normalized cross-correlation of the spike trains is (see equation 2.14)

$$C(t_2 - t_1) = \frac{< S_1(t_1)S_2(t_2) >}{< S_1(t) > < S_2(t) >},$$  \hspace{1cm} (B.1)

where $S_1(t)$ is defined as 1/δ if there is a spike in a bin with a size δ and 0 otherwise. The average firing rate of the neuron is $< S_1(t) >= P_1(t) = f$. 


We define the joint probability $P_{1,2}(t_1, t_2)$ as the probability that neuron 1 fires between $t_1$ and $t_1 + \delta$ and neuron 2 fires between $t_2$ and $t_2 + \delta$. Then,

$$< S_1(t_1) S_2(t_2) > = P_{1,2}(t_1, t_2) = P_{2|1}(t_2|t_1) P(t_1),$$  \hspace{1cm} (B.2)

where $P_{2|1}$ is the conditional probability that neuron 2 fires between $t_2$ and $t_2 + \delta$ given that neuron 1 fired between $t_1$ and $t_1 + \delta$. Assuming stationarity, this function depends solely on the difference $\tau = t_2 - t_1$: $P_{2|1}(t_2|t_1) = \tilde{P}_{2|1}(\tau)$, and hence

$$< S_1(t_1) S_2(t_1 + \tau) > < S_1(t) > < S_2(t) > = \tilde{P}_{2|1}(\tau) f.$$  \hspace{1cm} (B.3)

Switching from a function of time to a function of phase, we use the equation $\tilde{P}_{2|1}(\tau) d\tau = P_0 \left( \frac{\tau}{T} \right) d \left( \frac{\tau}{T} \right)$, to obtain

$$C(\tau) = \frac{< S_1(t_1) S_2(t_1 + \tau) >}{< S_1(t) > < S_2(t) >} = P_0 \left( \frac{\tau}{T} \right),$$  \hspace{1cm} (B.4)

where $P_0$ is the probability distribution of the phase shift between the two neurons.

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