Mechanisms of Phase-Locking and Frequency Control in Pairs of coupled Neural Oscillators

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July 17, 2000
(Revised)

Acknowledgments:

Work partially supported by NIH grant RO1-MH47150 to NK and GBE, NSF grant 9706694 to NK and a NSF grant to GBE. We thank J. Ritt and S. Epstein for careful readings and helpful comments.

To appear in *Handbook of Dynamical Systems, vol 3: Toward Applications*, eds: B. Fiedler, G. Iooss and N. Kopell, Elsevier.

INTRODUCTION

Oscillations occur in many networks of neurons, and are associated with motor behavior, sensory processing, learning, arousal, attention and pathology (Parkinson's tremor, epilepsy). Such oscillations can be generated in many ways. This chapter discusses some mathematical issues associated with creation of coherent rhythmic activity in networks of neurons. We focus on pairs of cells, since many of the issues for larger networks are most clearly displayed in that context. As we will show, there are many mechanisms for interactions among the network components, and these can have different mathematical properties. A description of behavior of larger networks using some of the mechanisms described in this chapter can be found in the related chapter by Rubin and Terman. For reviews of papers about oscillatory behavior in specific networks in the nervous system, see Gray (1994), Marder and Calabrese (1996), Singer (1993), and Traub et al (1999).

The chapter is organized by mathematical structure, focusing on some of the techniques that have been found to be useful to understand the behavior of networks of neurons. The behavioral repertoire of two-component networks includes synchronized oscillations, antiphase oscillations, phase-locked oscillations with phase difference other than zero or π, as well as non-phase-locked solutions and steady states. We concentrate on the oscillatory phase-locked solutions, including some that occur when neither of the cells is itself an oscillator. One aim of the chapter is to provide methods for understanding what aspects of the cells and their interaction determine which of these behaviors are found, especially in complicated contexts. We pay particular attention to how changes in various time scales associated with the cells and their connections affect the behavior of the network. Though the focus is on pairs of components, we discuss implications for larger networks throughout the chapter.

The component cells we have in mind are modeled by voltage-gated conductance equations, which have the form

$$C\frac{dv}{dt} = -\sum I_{ion} + I_A. \tag{1.1}$$

(Rinzel and Ermentrout 1998). Here I_{ion} represents an ionic current; it is the product of a driving force of the form $v - v_R$ and a conductance (inverse of resistance). Here v_R denotes the "reversal potential" of the current, which depends on the ion carried by the current. The value of v_R determines whether the current is depolarizing (inward, moving the voltage toward the threshold and making it easier for the cell to fire an action potential) or hyperpolarizing (outward, moving the voltage away from threshold for firing an action potential).

The conductance depends in a dynamic way on the voltage, adding further differential equations; there are voltage-dependent "gates" that open or close with kinetics that also depend on the particular current. For example, for a sodium current, the conductance is usually written in the form $\overline{g}m^3h$, where

$\overline{g}$ is the maximal conductance, and m and h satisfy the equations

$$\frac{dx}{dt} = [x_\infty(v) - x]/\tau(v),$$

where $x = m$ or h. $m_\infty(v)$ is a monotone-increasing sigmoidal function (saturating for large and small v), while $h_\infty(v)$ is a monotone-decreasing sigmoidal function). The kinetic functions $\tau(v)$ are different for h and m, and also differ between currents in the same cell; in general, the gating equations have slower kinetics than the voltage equation. Thus, the full equations are highly nonlinear, and have a range of time scales. The term I_A is the applied current, sometimes referred to as the drive to the cell. It can model current injection by an experimenter, or a modulatable (time-independent) quantity representing processes slow enough to be treated as constant, and affecting the overall excitability of the cell.

None of the techniques we present deals directly with the full Hodgkin-Huxley equations, though the last deals with some equations of this type. Rather, in each of the succeeding sections, we first present reduction techniques that allow us to deal with a class of simpler equations. We then present methods of analysis for that class, and some contexts in which the analysis gives answers about phase and frequency of the networks. In some cases, such as electrical coupling between cells or parts of cells, we visit the subject in several different sections, producing complementary insights with complementary methods.

Section 2 concerns weakly coupled oscillators. If the oscillators have robust limit cycles, the full equations reduce (to lowest order) to ones whose interactions are through the differences of their phases. Though much has been written about such equations, e.g., (Hoppensteadt and Izhikevich 1997, Kopell 1987, Ermentrout and Kopell 1990), we focus here on some novel uses of these equations, including analysis of interactions with conduction delays. Another regime we discuss concerns oscillators near a Hopf bifurcation. In this case, the equations can be analyzed using normal forms that take into account amplitudes as well as phases. Using analysis and geometry, we apply these ideas to showing how interactions via diffusion can lead to non-synchrony between oscillators.

Section 3 describes the interaction of spiking neurons, for which other approximations can be made that enable analysis. In this section, we treat the cells as "integrate-and-fire" (I&F) neurons. We describe the "spike-response method", a formalism that describes the time-dependent response of the voltage of the cell to the history of the pulsatile inputs that it has received. Though this method can in principle be used quite generally, it is most useful when the dynamics are fairly simple in the interval between spikes (as in I&F neurons). We use this method to see how the dynamics of the synapses affects the network behavior, including synchronization and emergent frequency; we focus mainly on inhibitory networks. We also apply the method to electrically coupled neurons to show how the shapes of the spikes can affect whether or not the electrical (diffusive) coupling is synchronizing, and how, in turn, that depends on the frequency of the network.

The spike-response method can sometimes be applied to networks of excitatory and inhibitory neurons. But when there are small numbers of cells, different kinds of cells in the network, and complicated dynamical patterns, another kind of reduction, considered in Section 4, can be more effective for analysis. This reduction looks at Poincaré maps in a neighborhood of a particular periodic solution. Though the full equations (and the Poincaré map) can be high-dimensional, the spread of time scales in the system can allow it to be well approximated by low-dimensional maps. We use these ideas to discuss precise synchronization in the presence of conduction delays.

Section 5 deals with bursting oscillators. A bursting neuron is one that emits a fast sequence of spikes, interspersed with a well-defined inter-burst interval. Such a neuron has at least three time scales even without coupling: the time scale of the voltage change within a spike, the scale of the recovery variable within a spike, and some slower process that starts and/or ends the bursts. There has been much work on mechanisms that produce such bursting. (See Izhikevitch (2000A) for many references, and the chapter by Rubin and Terman (2000A) of this volume.) In this section, we shall simplify the bursting neurons by working with the envelope of the spikes, ignoring the fast currents that produce the individual spikes. The work in this section is complementary to related work in Rubin and Terman (2000A); we focus on network behavior when there are fast excitatory or inhibitory synapses, with no extra time scales associated with the coupling. We introduce geometrical ideas associated with "fast threshold modulation" and time metrics for computing synchronizing effects, and show how synaptic thresholds can affect the frequency of the coupled system. We also discuss how strong electrical coupling of "compartments" of a single cell can have some unexpected mathematical properties.

2. PHASE OSCILLATORS AND AVERAGING

It is not possible to analyze the general behavior of a pair of coupled nonlinear oscillators. However, if the coupling is sufficiently weak, then it is possible to reduce the behavior of a general coupled system to something much simpler. In most of this section, we work with an identical pair of oscillators that have stable limit cycles. In that case, the full system can be reduced to a single equation for the difference in the phases of the oscillators. The special structure of neural equations and the kinds of coupling between them translates into constraints on the reduced equations that can be used to understand the circumstances under which the oscillators synchronize or stabilize at other phase differences. In this section, we derive the equation, and show how to make use of the special structure. We then apply the ideas to oscillators with delays in the signals.

If the limit cycle of the oscillators is only weakly stable, i.e., comparable in strength to the coupling, then the reduced equations must take into account not only the phases, but how the deviation of the trajectories from the limit cycle affects the phases. Such a situation occurs near a Hopf bifurcation. In that case, there is another reduction procedure, using a normal form, that encodes the behavior of the system. We discuss that derivation and apply it to show why coupling via discrete diffusion need not lead to stable synchrony. The analytical computations have a geometric counterpart, as we show.

2.1 Derivation of phase-difference equations

Consider a system of two similar coupled nonlinear oscillators:

$$\frac{dX_i}{dt} = F_i(X_i) + \epsilon G_i(X_i, X_j), \quad X_i \in \mathbf{R}^m, \; i = 1, 2, \; i \neq j \tag{2.1}$$

with $0 < \epsilon << 1$. Suppose

$$\frac{dX_i}{dt} = F_i(X_i)$$

has an orbitally asymptotically-stable limit cycle, $X_0^i(t)$, with period $T_i = T + 0_i(\epsilon)$. (For this we assume that $|F_2 - F_1| = 0(\epsilon)$.) Then for sufficiently small ϵ the solutions to (2.1) have the form $X_i(t) = X_0(\theta_i) + O_i(\epsilon)$ and, up to lowest order in ϵ,

$$\begin{aligned} \frac{d\theta_1}{dt} &= 1 + \epsilon H_1(\theta_2 - \theta_1) \\ \frac{d\theta_2}{dt} &= \omega_2 + \epsilon H_2(\theta_1 - \theta_2) \end{aligned} \tag{2.2}$$

where θ_1, θ_2 are coordinates on a torus and represent the phases of the two oscillators. 1 and ω_2 are the frequencies of the uncoupled oscillators, with $|1 - \omega_2| = 0(\epsilon)$. A rigorous derivation (Ermentrout and Kopell 1984) uses center manifold ideas to get equations on a torus; the use of averaging then shows that the interactions are (to lowest order) through the difference of the phases. A formal method producing equation (2.2) in a computationally simpler way is given in Ermentrout and Kopell (1991).

The functions H_i are $T-$periodic in each of their arguments and can be explicitly computed from the original equations. Let $\phi = \theta_2 - \theta_1$. Then

$$H_1(\phi) = \frac{1}{T}\int_0^T X^*(t) \cdot G_1(X_0(t), X_0(t+\phi)) \; dt. \tag{2.3}$$

A similar formula holds for H_2 with the ϕ replaced by $-\phi$. The function $X^*(t)$ is the normalized $T-$periodic solution to the adjoint equation:

$$\frac{dX^*}{dt} = -DF(X_0(t))^T X^*, \quad X^*(t) \cdot X_0'(t) = 1.$$

The average in (2.3) is easy to calculate; the only difficulty lies in the computation of $X^*(t)$. Williams and Bowtell (1997) devised a simple way to compute $X^*(t)$ for a stable limit cycle: Start with random initial conditions and integrate

$$dy/dt = -DF(X_0(t))^T y$$

backwards. Since all Floquet multipliers of the periodic solution are outside the unit circle (except for a multiplier of 1), backward integration will converge to the periodic solution. Thus, one can calculate the adjoint and the interaction function (2.3) for any given differential equation with a stable limit cycle.

So far, the form of the coupling between oscillators has been very general. Coupling between neurons is typically very special and is usually through only one component in the equations, the membrane potential, V_i . The coupling is generally additive and has one of two different forms depending on whether the synapse is chemical or electric. In the first case the coupling from cell j to cell i has the form:

$$I_{coupling} = g_{ij} s_j(t)(V_i(t) - V_{ij,syn}).$$

The variable $s_j(t)$ is related (perhaps in a very complicated fashion) to the potential $V_j(t)$ and g_{ij}, $V_{ij,syn}$ are constants. For example, $s_j(t)$ may satisfy an auxiliary equation, such as

$$ds_j/dt = k(V_j)(1 - s_j) - s_j/\tau.$$

Let $V^*(t)$ be the voltage component of the adjoint and $V_0(t)$ the voltage component of the periodic trajectory of the uncoupled system. We let $s_0(t)$ be the periodic solution to the equation for s when V is set equal to $V_0(t)$. Then, from (2.3), the coupling function of cell 2 to cell 1 becomes

$$H_1(\phi) = \frac{g_{12}}{T} \int_0^T V^*(t) s_0(t+\phi)(V_{12,syn} - V_0(t))dt.$$

A similar formula holds for H_2, which is a function of $-\phi$, by replacing ϕ by $-\phi$ and interchanging the indices.

There is a nice intuitive interpretation of the voltage component of the adjoint: it is an infinitesimal phase response curve (see Section 4.5 for more details). That is, it gives the effect on the phase of the oscillator when the latter is perturbed with a brief positive current pulse, i.e. a delta function. Thus, the function $H_1(\phi)$ is obtained as the convolution of the infinitesimal phase response curve with the current $s_0(t+\phi)(V_{12,syn} - V_0(t))$ that carries the coupling signal. The latter can be experimentally measured so that, even in the absence of an explicit membrane model, it is possible to derive a phase equation description for weakly coupled neurons.

The other kind of coupling considered here, through electrical synapses or "gap junctions," is much simpler in form. The coupling is directly dependent on the difference of the potentials, i.e. the coupling from cell j to cell i is a discretized form of the Laplacian:

$$I_{coupling} = g_{ij}(V_j - V_i).$$

In this case, (2.3) implies that the associated coupling function is

$$H_1(\phi) = \frac{g_{ij}}{T}\int_0^T V^*(t)(V_0(t+\phi) - V_0(t))dt.$$

One important distinction between gap junctions and general synapses is that for gap junctions, $H_1(0) = 0$ whereas for synapses, $H_i(0)$ will not generally vanish. As we will see, the size and sign of $H_i(0)$ is relevant to the frequency of the coupled system, which need not be the same as that of the uncoupled oscillators. Furthermore, if $H_i(0) \neq 0$, for at least one of the coupling terms, then larger arrays of oscillators need not synchronize (Kopell and Ermentrout 1986, 1990).

2.2 Computing frequency, phase lags and stability for pairs of coupled oscillators.

The main reason for the development of the present theory is to study the synchronization properties of coupled neural oscillators. We start by considering a pair of mutually coupled identical oscillators with symmetric coupling. Then equations (2.2) hold with $H_1 = H_2$ and $\omega_1 = 1$. Let $\phi = \theta_2 - \theta_1$ as above. We can rewrite this system as

$$\frac{d\phi}{dt} = -2\epsilon H_{odd}(\phi) \tag{2.4}$$

$$\frac{d\theta_1}{dt} = 1 + \epsilon H(\phi),$$

where H_{odd} is the odd component of H. Phase-locked solutions are solutions for which the phase difference ϕ is constant at a root of $H_{odd}(\phi)$. Since H_{odd} is an odd periodic function, there are always at least two roots, synchronous ($\phi = 0$) and antiphase ($\phi = T/2$). The frequency of these solutions is $\Omega = \frac{1+\epsilon H(\phi)}{T}$. Note that, for the synchronous solution, synaptic coupling changes the frequency by $\epsilon H(0)/T$, but electrical coupling keeps the frequency the same.

One of the goals of the analysis is to determine the stability of the synchronous and antiphase solutions and how it depends on the parameters in the models. It follows from (2.4) that a phaselocked solution $\bar{\phi}$ is stable if and only if $H'_{odd}(\bar{\phi}) > 0$. In particular, the synchronous solution is stable if and only if $H'(0) > 0$.

For synaptically coupled neurons, stability of synchrony can be investigated by looking at the sign of the integral

$$H'(0) = \frac{1}{T}\int_0^T V^*(t)s_0'(t)(V_{syn} - V_0(t))\ dt. \tag{2.5}$$

For neurons coupled with gap junctions,

$$H'(0) = \frac{1}{T}\int_0^T V^*(t)V_0'(t)\ dt.$$

The key to understanding situations that lead to synchrony for weakly coupled neuronal oscillators is found in the evaluation of these integrals. In Figure 2.1 we illustrate these integrals for excitatory synaptic coupling, in which the driving term $(V_{syn} - V_0(t))$ is positive. (For inhibitory coupling, the driving term is negative, changing the sign of $H'(0)$). In Figure 2.1A, the adjoint is non-negative, as is the case in many simple cortical neural models. For an excitatory synapse that persists for a few milliseconds, the function $s_0(t)$ rises quickly and then decays more slowly; thus the derivative, $s_0'(t)$ is positive only very briefly during the rise time and is then negative after that. This implies that the product, $V^*(t)s_0'(t)$, is negative for most of the time (bottom of Figure 2.1A) and so the integral (2.5) is negative and synchrony is unstable. On the other hand, in cortical models that have spike-frequency adaptation (an additional outward ionic current that tends to slow the firing down), the PRC/adjoint can be negative for some time after the spike. The intuition behind this is that, when there is such a current, stimulation after the spike creates more outward current, and thus delays the onset of the next spike. In Figure 2.1B, we depict this situation. The result is that the product $V^*(t)s_0'(t)$ is now primarily positive and thus the integral (2.5) is positive and the synchronous solution stabilizes.

A similar analysis can be used to show that gap junction coupling is stable for systems with a PRC shaped like V^* in Figure 2.1A. PRC's of this shape occur when the spike is very narrow; $V_0'(t)$ is positive for most of the cycle corresponding to a slow depolarization (increase in voltage) leading to the next spike. Thus the product of $V_0'(t)V^*(t)$ is mainly positive resulting in a positive integral and a stable synchronous state. Adaptation does not change this picture. The key observation is that, for very narrow spikes, the time-window in which the potential is decreasing is small and occurs at a time when the PRC is small in magnitude. Thus, even though this derivative is quite large and negative, its effect is strongly diminished by the neuron's inability to respond to stimuli at that point in time. In Section 3.3. we use other methods to show that changing the shape of the spike can change this conclusion, especially at high frequencies. In Section 2.5 we also consider oscillations that are more gradual (less spikelike), and show why gap junctions can destabilize synchrony.

If the oscillators are not identical, but are close in frequency, a phaselocked solution can be found from (2.2). We may also relax the assumption that the coupling is symmetric. If the oscillators are to be phaselocked, we must have $d\theta_1/dt = d\theta_2/dt$, so the analogue of (2.4) is

$$d\phi/dt = \epsilon(\Delta + H_2(-\phi) - H_1(\phi))$$

where $\epsilon\Delta = 1 - \omega_2$. It can be seen from this equation that the result of unequal frequencies and/or differences in the coupling is that a phase-locked solution does not necessarily lock at synchrony, but with a phase-lag that compensates for the difference in frequency and/or coupling. In Section 4, we will contrast this behavior with that of relaxation oscillators, which can synchronize even when the oscillators are different and the coupling is asymmetric.

2.3 Delays.

As we mentioned above, the function $s_j(t)$ can be quite complicated in its relationship to the potential, V_j. For example, suppose that the synapse occurs on a dendrite some distance from the cell soma where the oscillations are generated. Then the effect of this distant synapse must be filtered through the dynamics of the dendrite. In the case of passive dendrites, the filtering is linear and

$$s_R(t) = \int_0^\infty R(t')s_0(t - t')\ dt', \tag{2.6}$$

where $s_0(t)$ is directly related to the potential of the presynaptic neuron and $R(t)$ is the filter function. In the simplest case, the filter can be a simple delay, $R(t) = \delta(t - \tau)$ so that $s_R(t) = s_0(t - \tau)$. Because the delays are linear, it is very simple to compute the effect of these on the averaged coupling functions. Let

$$H_0(\phi) = \frac{1}{T}\int_0^T V^*(t)s_0(t + \phi)(V_0(t) - V_{syn})\ dt$$

be the interaction function in absence of the filter R, as in (2.3). Then, using (2.6) and changing the order of integration, we get that the full interaction function is just

$$H_R(\phi) = \int_0^\infty R(t')H_0(\phi - t')\ dt'. \tag{2.7}$$

That is, the true interaction function is obtained just by averaging the restricted interaction function against the functional R. In particular, delays lead to a phase translation of the interaction function:

$$H_\tau(\phi) = H_0(\phi - \tau).$$

In many neural systems, there exists the possibility of delays at many levels. There are delays due to axonal propagation and synaptic transmitter diffusion, and delays encountered when synaptic input occurs far from the source of the oscillation and must be communicated through dendrites. A delay, whether explicit or via a functional relationship like (2.6) can cause the rising phase of the synapse to occur during the maximal sensitivity of the phase-response curve, and thus the integral will be positive (negative) for excitatory (inhibitory) synapses and synchrony will be stable (unstable). This is the principle that underlies the results of van Vreeswijk et al. (1994), Crook et al. (1997, 1998a), and many others. This is illustrated in Figure 2.2 for the case of a pure delay in the synapse.

As we mentioned above, one source of the delay can be the propagation time down the axon. In this case, $\tau = d/v$ where d is the distance between the two neurons and v is the axonal conduction velocity. Thus, neurons that are connected at different distances can have different synchronization properties solely due to this conduction delay. These ideas were exploited in Crook et al. (1997) in a one-dimensional spatial network of cells. In this model, the excitatory synapses were synchronizing with short delays but desynchronizing with long delays. Thus, if most of the connections are local, synchronized activity is stable. If connections between cells have a longer range, then the delay destabilizes the synchronous solution and waves result. Similar models involving inhibitory synapses show that delays can change synchronization properties.

Another source of delay occurs due to the passive propagation of potential down the dendrite of a neuron. Crook et al. (1998a) show that the position of a synapse on a dendrite (Figure 2.3) can alter the stability of the synchronous solution. For simplicity, we assume that the dendrite can be modeled as an infinite cable satisfying:

$$\tau_m \frac{\partial V}{\partial t} = -V + \lambda^2 \frac{\partial^2 V}{\partial x^2}$$

where τ_m is the membrane time constant and λ is the space constant of the membrane. To compute the effect of a synapse that is a distance d away from the actively oscillating soma, we use the Green's function for passive cables:

$$G(x,t) = \frac{1}{\sqrt{4\pi\lambda^2 t/\tau_m}} e^{-\frac{t}{\tau_m} - \frac{(x/\lambda)^2}{2t/\tau_m}}.$$

In this case, our filter is simply $R(t) = G(d,t)$. Figure 2.4 illustrates $R(t)$ for three different distances from the soma and the corresponding function $H(\phi)$. From (2.7), we have

$$H_R'(0) = \int_0^\infty R(t') H_0'(-t')\, dt'.$$

Thus, the effect of the dendrite is similar to the delay. For example, suppose that $H_0'(0) < 0$ so that synchrony of a directly coupled synapse is unstable. Then, by putting the synapse farther out on the dendrite, we can weight the above integral to a point where H_0' is positive and thus stabilize the synchronized state. By adding additional structure to our simple point neurons (such as passive dendrites or axonal delay) we are able to alter the synchronization properties of a pair of mutually coupled cells. Any linear manipulation of the timing directly translates into a weighted average of the original interaction function through (2.7). Bressloff and Coombes (1997b) offer a complete analysis of coupled integrate-and-fire neurons with dendritic delays. We discuss the general ideas later in the chapter.

2.4 Frequency effects and the rise/fall time of synapses.

In the arguments above, we have altered either the phase-response curve (through adding an adaptation current) or the timing of the synapse. If we hold the timing of the synapses fixed and vary instead the frequency of the underlying oscillations, we see that the effect is almost as if the synaptic timing is varied. This is illustrated in Figure 2.5 for a biophysically-based cortical neuron model with a fast *excitatory* synapse (rise time is 0.05 msec and decay is 2 msec.). The odd part of the interaction function is illustrated. Zeros are phase-locked solutions and those with a positive slope are stable and those with a negative slope are unstable. As the frequency decreases the antiphase state loses stability through the appearance of an intermediate locked state. This stably persists until the frequency is quite low and the synchronous state becomes stable. One can summarize this behavior via the bifurcation diagram shown in Figure 2.6. The analogous behavior is seen for *inhibitory* coupling but the stability is reversed. Van Vreeswijk et al. (1994) obtained a similar result with I&F neurons but the frequency was held fixed and the timing of the synapse was varied. As we show in Section 3, similar results can be obtained using the spike-response methods, even when the coupling is strong. In that case, however, the frequency of the coupled system is determined only implictly.

2.5 Interaction near a Hopf bifurcation or a homoclinic orbit

Near a Hopf bifurcation, the resulting periodic orbits are only weakly stable. Thus, trajectories that have initial conditions off the limit cycle may take a significant amount of time to return to the latter; during this time, the dynamics can act on the system to stabilize or destabilize a configuration.

For most kinds of neural coupling, the assumption that the system is near a Hopf bifurcation is not very useful. The reason is that supercritical (i.e. stable) Hopf bifurcations are of low amplitude, and these are not large enough to trigger chemical synaptic interactions, which are via all-or-nothing spikes. (But low-amplitude oscillations *can* contribute to interactions of spikes. See section 4.5.) For coupling involving electrical synapses (gap junctions), small amplitude oscillations can be sufficient to carry coupling signals. In the rest of this subsection, we discuss the normal form associated with coupled oscillators, each near a Hopf bifurcation. We then use these and some geometric ideas to show why the discrete version of diffusion need not be stabilizing.

Near a Hopf bifurcation, the equations for a single oscillator can be expressed compactly using complex notation z (instead of a 2-dimensional real system), and neglecting terms higher than the third power. With appropriate change of coordinates, and linear coupling between the oscillators with variables z_1 and z_2, the truncated coupled equations take the form (Aronson et al, 1990):

$$\frac{dz_1}{dt} = \mu_1(a+bi)z_1 - (p+qi)z_1^2\bar{z}_1 + \nu(d_1+id_2)(z_2-z_1)$$
$$\frac{dz_2}{dt} = \mu_2(a+bi)z_2 - (p+iq)z_2^2\bar{z}_2 + \nu(d_1+id_2)(z_1-z_2).$$

The parameters here are real, and we will consider only the case $\mu_1 = \mu_2 = \mu$, a small parameter measuring the distance to the Hopf bifurcation. There are two conceptually important parameters to consider here. One is $\eta = q/p$, which measures the "twist" in the system for an individual oscillator. This parameter describes how much the local angular velocity at any point off the limit cycle deviates from that *on* the limit cycle. The second important parameter is $\alpha = d_2/d_1$, which measures how much the coupling deviates from being scalar (a real number times the difference between the positions of the two oscillators).

To understand why these parameters matter, we consider a simple case motivated by an example of Sherman and Rinzel (1992), who showed numerically that weak gap-junction coupling (in cells of the pancreas) could lead to antiphase solutions. The equations have limit cycles that are relatively sinusoidal in shape, without spikes or well-defined plateaus as in the relaxation regime of the van der Pol equation. For illustration, we use the Morris-Lecar equations (Morris and Lecar 1981), in the non-relaxation regime. These equations (uncoupled) have the form

$$C\frac{dv}{dt} = -\left[\bar{g}_{Ca}m_\infty(v)(v-V_{Ca}) + \bar{g}_K w(v-V_K) + \bar{g}_L(v-V_L)\right] \tag{2.8a}$$
$$\frac{dw}{dt} = [w_\infty(v) - w]/\tau. \tag{2.8b}$$

The following idea shows why the twist and the deviation from scalar coupling can conspire to desynchronize the synchronous state. Consider a limit cycle with two pairs of initial conditions, and the direction those trajectories are pushed by the coupling (Figure 2.7). Recall that neural oscillators interacting through gap junctions have a coupling term only for the v-component; hence the coupling pulls each trajectory horizontally. Consider the bottom pair of initial conditions, where the limit cycle has increasing v and increasing w. The leading trajectory is pulled inward and the lagging one is pulled outward. Here is where the twist is relevant: the cells are pulled somewhat off the limit cycle, and in the new position moves faster or slower compared to the limit cycle. The change in speed cannot be seen from the phase-plane diagram, but can be seen from the second equation, which says that the rate of change of w is proportional to the vertical distance to the w-nullcline. The leading oscillator is pulled inward, and hence closer to the nullcline, while the lagging oscillator is pulled outward and hence farther from the nullcline. Thus, in that portion of the trajectory, the leading oscillator slows down and the lagging one speeds up, creating a synchronizing effect. A similar analysis shows that the opposite is true for the pair of conditions in the region in which v is decreasing while w continues to increase. Thus, there are synchronizing and desynchronizing effects along different portions of the trajectory, and whether the synchronous state is stable depends on a balance of those effects.

The normal form contains the essential information about this balance. For the equations of Sherman and Rinzel, deVries et al. (1998) carried out the normal form analysis. As in Aronson et al. (1990), they do a change of coordinates to polar form, with

$$z_j = \sqrt{\frac{\mu_j a}{p}} r_j e^{i\theta_j}.$$

If $\mu_2 = \mu_1 = \mu$ the equations for the polar variables are given by

$$\begin{aligned}
\dot{r}_1 &= r_1(1 - r_1^2) + \gamma(\cos\phi - \alpha\sin\phi)r_2 - \gamma r_1 \\
\dot{r}_2 &= r_2(1 - r_2^2) + \gamma(\cos\phi + \alpha\sin\phi)r_1 - \gamma r_2 \\
\dot{\phi} &= +\eta(r_1^2 - \Delta r_2^2) - \gamma(\sin\phi + \alpha\cos\phi)\frac{r_2}{r_1} - \gamma(\sin\phi - \alpha\cos\phi)\frac{r_1}{r_2}
\end{aligned}$$

where $\phi = \theta_2 - \theta_1$ and $\gamma = \nu d_1/\mu a$. Note that γ may be interpreted as the strength of the coupling compared with the attraction of the limit cycle.

It was shown in Aronson et al. (1990) that the synchronous solution is stable if and only if

$$\gamma(1+\alpha^2) + (1+\alpha\eta) > 0.$$

This implies that if $\alpha\eta > 0$, the synchronous solution is always stable; if this product is sufficiently negative, then γ must be large enough to produce stability.

The condition for stability of the antiphase solution is

$$\begin{aligned}
&\gamma < 1/4 \\
&0 < \gamma(1+\alpha^2) + (1+\alpha\eta)(2\gamma - 1).
\end{aligned}$$

This implies that, if $(1+\alpha\eta) < 0$, then for small enough coupling, the antiphase solution is always stable. DeVries et al. (1998) computed the values of the parameters in the normal form, and showed that the antiphase solution is stable, and the synchronous one is unstable.

We note that the parameters α and η also turn out to be important in creating spatio-temporal chaos in the complex Ginzberg-Landau equations (Kuromoto, 1984)

$$z_t = \lambda z - (1 + i\eta) z^2 \overline{z} + \gamma(1 + i\alpha) z_{xx}.$$

A situation in which the desynchronization can be seen immediately from the geometry, without a normal form analysis, is given in Han et al. (1995). In this situation, the limit cycle is near a homoclinic orbit and thus spends a great amount of time near the saddle point. Suppose that the trajectory of each oscillator comes close to the stable manifold of the saddle point (Figure 2.8). Consider initial conditions in which both trajectories are approaching the saddle point. The trailing oscillator will be pulled outside of the limit cycle while the leading oscillator will be pulled inside the limit cycle. Thus, the trailing oscillator will be pulled closer to the stable manifold of the saddle while the leading oscillator is pulled further away. The oscillator on the trajectory nearer to the stable manifold moves slower, and hence the phase-difference widens. A similar analysis holds for initial conditions in which the trajectories are moving away from the saddle point.

A final remark is that the destabilization of the synchronous state by twist and non-scalar coupling happens in a range well described by a normal form near a Hopf bifurcation; it fails when the oscillations are in a relaxation regime. The reason is that the trajectories are held so closely to the nullclines that the twist has too minor an effect to change stability.

3. INTERACTIONS OF SPIKING CELLS

3.1 Spike response method and periodic solutions

Most neurons fire all-or-nothing action potential (spikes), and the interactions of the neurons are via signals induced by the receipt of the spikes. In some simple cases, this leads to a different kind of reduction than the weak-coupling limit. This subsection of the review is taken from C. Chow (1998).

The simplest version of such a reduction assumes that the nonlinearities of currents in (1.1) are localized in time to the action potential. That is, away from the spike, the voltage equation has the form

$$\frac{dv}{dt} = I - v.$$

As described in Section 2, this is known as an integrate-and-fire model. When the potential reaches threshold, a delta function pulse is subtracted to reset the potential to $v = 0$ and we say that the cell has spiked. Though this may appear too highly abstracted to be useful, it is a reasonable approximation when the behavior between the spikes is essentially linear. A biophysical model that behaves in a very similar way is one reduced from a compartmental model of Traub and Miles (1991). (See appendix of Ermentrout and Kopell, 1998 for the reduction.)

With synaptic current, the equation for the *ith* cell is

$$\frac{dv_i}{dt} = I_i - v_i - \sum_l \delta(t - t_l^i) + J \sum_l S(t - t_l^j);\ i \neq j, \tag{3.1}$$

where t_l^i are the times that cell i reaches threshold, $J > 0$ for excitatory interactions and $J < 0$ for inhibitory interactions. The functions δ (the Dirac delta function) and S above are each defined only when the argument is non-negative. The synaptic current S can be modeled in various ways. One simple and explicit version has the current induced from each spike as a double exponential

$$S(t) = \exp(-\beta t) - \exp(-\alpha t) \tag{3.2}$$

where β is the synaptic decay rate and α is the synaptic rise rate. Note that this describes the synaptic current explicitly as a function of t, rather than obtaining it as a solution to an auxiliary differential equation as in Section 2. With $\alpha > \beta$, there is a rapid rise, followed by a slower decay, as in solutions to auxiliary equations described in Section 2.

A central idea in working with some networks of spiking cells is to consider the *effects* of the spikes, rather than the differential equation (3.1). This leads to a formalism known as the spike-response method (Gerstner 1995, Chow 1998). The dynamics are encoded in two sets of kernels, representing the effects on a cell of its own spikes and those of the other cell. That is

$$v_i(t) = I_i + \sum_l \eta_i(t - t_l^i) + J \sum_l \epsilon_i(t - t_l^j). \tag{3.3}$$

The kernels are zero for $t - t_l^k < 0$. The kernel $\eta_i(t)$ describes the recovery dynamics of neuron i after it fires, while the kernel $\epsilon_i(t)$ represents the response to synaptic inputs (see Figure 3.1). Arguments using the kernels for integrate-and-fire, which can be explicitly computed, generalize to other kernels having similar qualitative properties. But the theory has some constraints. For example, it assumes that the form of the synaptic kernel does not depend on the time of arrival or phase of the synaptic input. Thus the interaction kernel has the form

$$\epsilon(t) = \int_0^t L(s)\, S(t-s)\, ds, \tag{3.4}$$

where $S(t)$ is the synaptic input and $L(t)$ is the linear response function.

With a prescribed synaptic signal, it is possible to address questions about existence and stability of periodic solutions in the network. One such way is to look for self-consistent solutions, taking into account all the history of the previous spikes. Suppose that the cells have been firing with (so far unknown) period T, with neuron 2 lagging neuron 1. We pick the origin in time so that cell 1 has fired at $t_l^1 = -lT$, and cell 2 has fired at $t_l^2 = (\phi - l)T$, $l = 1, 2, ..$, where $0 \leq \phi < 1$. Cell 1 fires again at $T = 0$, and then self-consistency requires that

$$1 = v_1(0) = I_1 + \sum_{l \geq 1} \eta(lT) + \sum_{l \geq 1} J\epsilon(lT - \phi T). \tag{3.5a}$$

Cell 2 fires again at $t = \phi T$, and self-consistency then implies that

$$1 = v_2(\phi T) = I_2 + \sum_{l \geq 1} \eta(lT) + \sum_{l \geq 0} J\epsilon(lT + \phi T). \tag{3.5b}$$

The difference in the index of the second sum in (3.5a) and (3.5b) arises because cell 1 fires before cell 2. Hence, the input to cell 2 (from all negative times) includes the $l = 0$ input from cell 1, which occurs at $t = 0$. However, the $l = 0$ firing of cell 2 is at $t = \phi T > 0$, which is not included as an input to cell 1.

One can derive a relationship for the phase ϕ by subtracting (3.5b) from (3.5a) to get

$$0 = I_1 - I_2 - G_T(\phi) \tag{3.6a}$$

where

$$G_T(\phi) = J \sum_{l \geq 1} (\epsilon(lT - T + \phi T) - \epsilon(lT - \phi T)) \tag{3.6b}$$

Note that, from (3.4), $\epsilon(0) = 0$; this implies that $G_T(0) = 0 = G_T(0.5)$. Hence, if the neurons are the same ($I_1 = I_2$), there is a synchronous solution ($\phi = 0$) and an antiphase solution ($\phi = 0.5$). The difficult part is determining stability. The consistency equations do not give a map that takes a phase difference ϕ between the cells at some time to the phase difference at the next cycle, only a condition to be satisfied at steady state. Hence, other arguments are needed to deal with stability.

We refer the reader to Chow (1998) and Bressloff and Coombes (1997a) for the stability argument. This is subtle because the system is infinite-dimensional; one needs to know information about all past cycles. Chow (1998) looks at small perturbations around a periodic phaselocked solution; assuming that the kernels decay very fast, so that they are negligible after some time, he derives a high dimensional return map. The analysis shows that a necessary, but not sufficient, condition for stability is that $G_T'(\phi) > 0$. In related work, van Vreeswijk et al. (1994) argued heuristically that this condition was associated to stability. Gerstner et al. (1996) did a related analysis with $N \to \infty$ neurons; this allows the population to force a single neuron without itself being affected by that neuron, creating a somewhat easier problem. The methods of Chow (1998) can also be used for larger networks.

We can now see how this model is related to the weak coupling theory. Indeed, if $I_1 = I_2 = I$ (that is, the oscillators are identical), then we must solve a pair of equations for the ensemble period, T and the phase, ϕ:

$$0 = -\; G_T(\phi)$$
$$1 = I + \bar{\eta}(T) + J\,\bar{\epsilon}(T,\phi)$$

where $\bar{\eta}(T)$ and $\bar{\epsilon}(T,\phi)$ are the first and second sums in (3.5). This set of equations should be compared to phase-locked solutions to (2.4):

$$0 = -2\epsilon H_{odd}(\phi)$$
$$\frac{1}{T} = 1 + \epsilon H(\phi).$$

Note that for *weak* coupling, the phase is determined independent of the period. For the spike-response model, $G_T(\phi)$ changes with T, and so the non-synchronous solutions have frequency-dependent phases. ($G_T(0) = 0$ for all T.) In the case of weak coupling for the spike-response model (J small), we can approximate T by the uncoupled period and obtain a function G_T that is essentially (to lowest order) independent of T. Furthermore, since the period does not vary to lowest order, the stability is reduced to that of a 1-dimensional system, as in the first equation of (2.4). The condition $G_T'(\phi) > 0$ is a sufficient condition (and, as above, necessary) for stability for the weak coupling case and, up to a scaling factor, $G_T = H_{odd}$. Bressloff and collaborators have extended the theory of coupled integrate-and-fire models to arrays and networks where they then use the results of Kopell and Ermentrout on large systems of phase models (Bressloff and Coombes 2000). This is possible since the resulting equations are functions of phase-differences only and fixed points correspond to periodic phaselocked solutions. As in the case of two oscillators, the main technical difference is that the ensemble period is implicitly defined while in the weakly coupled case, it is explicit.

Bressloff and Coombes (1997b) have applied the techniques of this section to a pair of integrate-and-fire neurons coupled through passive dendrites in a manner similar to the work of Crook et al. (1998a). In their work they can explicitly compute the stability boundaries for synchrony as a function of the position of the synapse on the dendrite for arbitrary coupling strength since the model is essentially linear. They have also studied the role of synaptic depression and other effects on the phase-locked behavior of coupled integrate-and-fire oscillators. They have developed elegant machinery for analyzing arbitrary networks of integrate-and-fire neurons that goes beyond the special cases considered in this section.

3.2 Networks with inhibitory connections

Many theoretical papers have remarked that inhibition may play a more important role in synchronization of networks than excitation (van Vreeswick et al. 1994, Gerstner et al. 1996, White et al. 1998). Hence we focus on inhibition; similar methods work for excitatory connections and show, as in the case of weak coupling, that such an interaction is not synchronizing. For inhibitory networks, we show below that the inhibition provides both the synchronizing signal and determines the frequency of the coupled network. The work is motivated by experimental work on a slice preparation of the hippocampus, in which the action of the excitatory cells is blocked and the relevant part of the network contains only inhibitory cells (Whittington et al. 1995).

3.2.1 Synchronization by inhibition

For inhibitory connections, we set $J = -1$. (The size of J is taken into account in the definition of ϵ.) Starting from formula (3.6) for the function $G_T(\phi)$ and an explicit form for the synapses, we can compute the necessary conditions for stability of synchrony, namely $G'_T(0) > 0$. We first note that, from (3.6),

$$G'_T(0) = -T\varepsilon'(0) - 2T\sum_{l\geq 1}\varepsilon'(lT).$$

Thus, the synchronous solution is unstable if $\varepsilon'(0) > -2\sum_{l\geq 1}\varepsilon'(lT)$. For a particular form of the synapse, such as the double exponential (3.2), the ε kernel can be explicitly computed, and used to compute $G'_T(0)$. It can be shown that if the rise rate α is infinite, then the necesssary condition is violated; otherwise the necessary condition is always satisfied for integrate-and-fire neurons. It can be shown that some sufficient conditions are also satisfied except possibly for some very small periods. Van Vreeswijk et al. (1994) made the same argument for the special case of the standard integrate-and-fire model with synapses of the form $s(t) = \alpha t\exp(-\alpha t)$. The same conclusion is reached by working with weak coupling methods, as in Section 2.2. Indeed, the function $s(t)(V_{syn} - V)$ in that section plays the same role as the explicit synaptic function $S(t)$ plays in computing $\epsilon(t)$ in (3.2).

The integrate-and-fire formalism captures some essential behavior of what has been called "Type 1" neurons (Rinzel and Ermentrout 1998). These are neurons for which the transition between stable equilibrium and periodic firing (as applied current is increased) is via a saddle node. "Type 2" neurons are associated with Hopf bifurcations near the onset of periodicity with increasing drive. As we will see below, the differences between Type 1 and Type 2 affect synchronization properties. We remark here that Type 2 cells have behavior that is not captured by the integrate-and-fire formalism; in particular, such neurons need not synchronize with inhibition. For a kernel approach to that behavior, see Kistler et al. (1997).

For Type 1 neurons, the stability analysis shows that the synchronous solution for homogeneous cells is stable over a very wide range of periods (changeable by modulating the applied current). However, the stability is fragile when there is heterogeneity, e.g., in the drive I. (Relevant simulations are in Wang and Buzsaki (1996) and White et al. (1998).) For heterogeneous neurons, a similar analysis can be done (Chow 1998). When the heterogeneity is too large, there is no locked solution. For smaller heterogeneity, there is a locked but not synchronous solution.

The stability of the latter turns out to depend partly on the emergent frequency of the network, which in turn depends on applied current as well as the synapses (White et al. 1998, Chow et al. 1998, Chow 1998). The close-to-synchronous solutions are stable only in a parameter regime in which the network frequency is governed by the decay time of the inhibition (see section 3.2.2 below). The system can be driven so that individual cells fire at much higher frequencies, but in that case the effect of the heterogeneities is to produce phase drift between the oscillators. In this regime, the synaptic current does not have enough time to change significantly within a cycle, and hence acts effectively as a DC current. This regime has been called the "tonic" regime, for the tonic (i.e., constant) behavior of the coupling current (Chow et al., 1998). If the cells are driven at much lower levels, the effect of the heterogeneity is to cause the faster cell to suppress all firing in the slower one. The highest degree of synchrony occurs when the drive is such that the frequency of the coupled system is closely related to the decay time of the inhibition, a parameter regime that has been called the "phasic" regime. As described in Section 3.2.2, the dependence of the network frequency on the decay time of the synapse is different in the tonic and phasic regimes.

We can get more insight into the way inhibition synchronizes if we consider the case in which only the previous spike from a pre-synaptic neuron is significant in affecting the timing of the post-synaptic neuron. This is a reasonable assumption in the phasic regime. Let t_1 and t_2 be the times of spiking of a pair of coupled cells on some cycle. Assume $t_2 > t_1$, but sufficiently close that the firing of cell 1 does not prevent the firing of cell 2 in that cycle. We start with the analogue of (3.3), namely

$$v_i(t) = I_i + \eta(t - t_i) - \epsilon(t - t_j), \;\; j \neq i.$$

(This ignores the effect of cell 1 on cell 2 in the current cycle , which is permissible if the cells are close together, since $\varepsilon(0) = 0$.) Cell i fires again when $v_i(t) = 1$, at $t = \bar{t}_i$. We wish to compute $\bar{t}_2 - \bar{t}_1 \equiv \overline{\Delta}$ and compare this to $t_2 - t_1 \equiv \Delta$ to check for stability of the synchronous solution. For simplicity, we again assume that the driving currents I_i are equal.

The definitions of t_i imply that

$$\eta(\bar{t}_1 - t_1) - \varepsilon(\bar{t}_1 - t_2) = 1 - I_i$$

To linearize the equation around the values associated with one cycle later, we let T_P be the period of the coupled synchronous solution, and define ρ_i via $\bar{t}_i - t_i = T_P + \rho_i$. Using the relations $\bar{t}_1 - t_2 = T_P + \rho_1 - \Delta$ and $\bar{t}_2 - t_1 = T_P + \rho_2 + \Delta$, we get

$$\eta'(T_P)(\rho_2 - \rho_1) = \varepsilon'(T_P)[(\rho_2 - \rho_1) + 2\Delta].$$

Using $\rho_2 - \rho_1 = \overline{\Delta} - \Delta$, we have

$$\overline{\Delta} = \frac{\varepsilon'(T_P) + \eta'(T_P)}{\varepsilon'(T_P) - \eta'(T_P)}\,\Delta.$$

Note that $\eta'(T_P) > 0$ and we are assuming that T_P is such that $\varepsilon'(T_P) < 0$, i.e., the period is high enough that the synapse is decaying when the next spike appears. (See Gerstner et al. 1996.) Hence the coefficient of Δ is less than 1 in absolute value. Thus, if the rise of the synapse is not infinitely fast, we recover the result from the above theory that the condition $\varepsilon'(T_P) < 0$ is a necessary condition for inhibition to be synchronizing. But the calculation also shows that the condition $\varepsilon'(T_P) < 0$ is sufficient for synchrony, and that the size of $\eta'(T_P)$ helps determine the rate of synchronization near the synchronous state; if $\eta(T_P)$ is small, as it would be if the period is too long relative to the recovery period of the neuron, the rate of synchronization would be low.

A related treatment is done in Chow (1998), assuming that the neuron that fires second is influenced both by the last recent firing of the leading cell and the spike on the previous cycle.

3.2.2 Frequency regulation in inhibitory networks

In the full Hodgkin-Huxley equations, there can be many different time scales associated with the synapses and the intrinsic dynamics. In order to understand how some of these may affect the *period* of the network solution, we use a slightly more complicated version of the integrate-and-fire neurons, one that is not pre-scaled. It is

$$C\frac{dV}{dt} = I - g_m(V - V_r) - gS(t), \tag{3.7}$$

where g_m is an effective membrane recovery conductance and V_r is an effective membrane reversal potential. $V(t)$ is reset to V_0 whenever it reaches the threshold potential V_T. Note that we are assuming identical cells ($I_1 = I_2$) and a synchronous solution, so we may drop subscripts. This section is taken mainly from Chow et al. (1998).

In these equations, there are three natural time scales . The first is the effective membrane time constant $g_m/C = \tau_m$ associated with the passive return to the rest potential after a spike. The second is the decay time τ of the synapse. (Though the rise time is very important for synchronization, it does not play an important role in frequency determination.) The third is the period T when two identical cells are coupled. This time scale is an emergent property of the system, and can be altered by changing the driving current I. Note that, in the absence of coupling, the frequency of an individual neuron can be very high - hundreds of Hz - and the reduced spiking models in White et al. (1998) and Ermentrout and Kopell (1998) also behave this way. When coupled, however, the frequency is affected by time scales in the coupling. The aim of the analysis is to understand the circumstances under which different time scales in the equations dominate the determination of the network frequency.

As in section 3.2, we consider different parameter regimes, which we define asymptotically by relationships between T, τ and τ_m. (As usual with asymptotic analysis, the conclusions hold in some regime larger than the strict definition of the regimes.). The tonic and phasic regimes have been introduced less precisely in the previous section.

Tonic regime:	$T << \tau_m,$	$T << \tau$
Phasic regime:	$\tau_m << T,$	$\tau_m << \tau$
Fast regime:	$\tau << T,$	$\tau << \tau_m$ or $\tau \approx \tau_m$

The phasic and tonic regimes are applicable for slowly decaying inhibition from the synapses, where "slow" here denotes the second inequality defining each of these regimes. The differences in the two are seen in the first inequality; in the tonic regime, the network period is small compared to the membrane time constant, while in the phasic regime it is large. Thus, in the tonic regime, there is significant filtering of the synaptic signals from the cell dynamics; in the phasic regime, the cell time constants are too fast to accomplish significant filtering. The fast regime denotes the parameter ranges for which the network period is long compared to the synaptic decay time. In this regime, the intrinsic membrane time constant may be large or comparable to the synaptic decay constant; the coupling is close to pulsatile. The names "tonic", "phasic" and "fast" refer to the effects of the synaptic currents on the voltage of the post-synaptic cell. Thus, in the tonic regime, the synaptic current varies slowly compared with the other time constants, and hence acts effectively like a constant current. In the phasic regime, the current leads to significant changes in voltage within a network period, and so the signal has a significant phasic component. In the fast regime, the signal decays quickly relative to the period and the filtering properties of the network.

The dependence of T on τ and τ_m can be determined in a way similar to that used to compute the phase relationship between the coupled cells: one assumes a period T and then shows that T is determined uniquely in a self-consistent way. For the simple equations of the form (3.7), one can deduce a general but implicit formula for T. The computations are most transparent for fast synaptic rise times, in which $S(t) = \exp(-t/\tau)$, where $\tau = 1/\beta$ is the decay time of the inhibition. (See Chow et al. 1998 for generalizations.) One finds that for the phasic regime one gets $T = \tau \ln A$, where A is a function of all the parameters, including τ. Thus, the period is essentially proportional to the synaptic decay time, and weakly (logarithmically) dependent on other parameters. For the tonic regime, the dependence is quite different: the period is independent of τ (or weakly dependent for other kinds of synapses). In the fast regime, T depends logarithmically on τ and other parameters, and is proportional to the membrane time τ_m.

One of the significant differences between the phasic and tonic regimes is the network behavior in the presence of inhomogeneities; it is only in the phasic regime that the network can remain coherent in the presence of even mild heterogeneities (see Section 3.2.1). Hence, when there are inhomogeneities and coherence is observed, the theory implies that the frequency should be proportional to the decay time of the inhibition. This appears true for inhibitory networks in the hippocampus (Whittington et al. 1995). The main inhibitory transmitter associated with this (and many other inhibitory networks) is $GABA_A$, whose decay time leads to a frequency that is in the range of 30-80 Hz, depending on excitatory drive. Rhythms outside this frequency range require a different mechanism for the creation of coherence.

3.3 Spike response method and electrical coupling

In the section on phase-difference coupling, the analysis was applied to spiking neurons with very thin spikes, and a heuristic explanation was given to show that electrical coupling need not be synchronizing. We now show that, with the techniques of this section, we can examine the properties of electrical coupling in more detail. The main results (Chow and Kopell 2000) are that the ability to synchronize depends on the shape of the spike, and is highly influenced by the period of the coupled network (which is in turn influenced by the drive to the cells). The reason that the spike shape matters is that the coupling current is a scaled difference of voltages, and therefore depends on the voltage during the spike as well as between spikes.

In order to investigate the role of the shape of the spikes, it is necessary to include the spike shape in the equations; the standard I&F equations just reset the voltage as soon as the threshold for spiking has been reached. Here, the spike is "pasted on" via an extra term in the voltage equation that changes the voltage in ways that depend on the rise rate of the spike, the width of the spike and a constant to calibrate the maximal voltage that the spike creates. All these parameters (or rather some combination of them) affect the voltage of the cell during a spike, which in turn affects the coupling current between the cells. The scaled equation for an uncoupled cell is

$$\frac{dv}{dt} = I - v + A(t - t_l)$$

where

$$\begin{aligned} A(t) &= v_A e^{\xi t} \text{for } \ 0 < t < \Delta \\ &= -(1 + v_m)\delta(t - \Delta) \text{ for } \Delta \leq t. \end{aligned}$$

Here the dimensionless parameters are the applied current I, the spike rise rate ξ, the spike width Δ, and the spike potential scale v_A. The threshold is set at $v = 1$. The term v_m is computed from the parameters in $A(t)$ in order that, just after $t = \Delta$, $v(t)$ is reset to $v = 0$. For a fast rising and narrow spike, v_m can be computed to be approximately $v_A e^{\xi\Delta}/(1+\xi)$ (Chow and Kopell 2000).

The coupled equations have the form

$$\frac{dv_i}{dt} = I_i - v_i + A(t - t_l) + g(v_j - v_i) \tag{3.8}$$

where g is the scaled strength of the electrical coupling (gap junction synapse). As in the case of chemical synapses, it is possible to construct an integrated version of these equations written in terms of kernels that encode the effects of the spikes on the neuron that produced that spike and on the other neuron. This is facilitated by working with the sum and difference of the two equations of (3.8). The analogue of (3.3) is then

$$v_i(t) = \widehat{I}_i + \sum_l \gamma_s(t - t_l^i) + \sum_l \gamma_c(t - t_l^j).$$

Here the kernel γ_s refers to the effect of a spike on the cell that produced it, and is analogous to the kernel η in (3.3); the kernel γ_c encodes the effects of the coupling, and is analogous to $J\varepsilon$. (See Figure 3.2.) Both of these are dependent on the shape of the spikes, as given in the formula for $A(t)$.

The analysis is similar to that for inhibitory coupling described in earlier sections. In particular, the formula for the voltage at the next spike is given by (3.5) with η and $J\varepsilon$ replaced by γ_s and γ_c. The formula for determining the phase difference ϕ is again (3.6), with the same substitution. Thus, the outcome depends critically on the shape of the coupling kernel γ_c.

The necessary condition for a solution with a phase lag ϕ to be stable is that $G_T'(\phi) > 0$. For a fixed T, this can be computed directly from the analogue of (3.6). As for the inhibitory coupling, $\gamma_c'(0) = 0$, reflecting the fact that the cells do not immediately affect one another on firing. Thus, the necessary condition for stability of synchrony is $\sum \gamma_c'(lT) > 0$. Now γ_c is monotone-increasing in a tiny range near t $= 0$, then decreasing for t in some range , and then increasing back up to zero. So if T is sufficiently large, all the terms in the sum are positive; if it is small enough (high frequency), the sum can be negative. This suggests that for high enough frequency, the synchronous solution can be unstable. (It always exists.) This is verified numerically in Chow and Kopell (1999) for a biophysically-based model (White et al. 1998).

A nonsynchronous solution, such as antiphase, may not exist if the coupling is too strong; with strong enough coupling, a spike of one cell quickly produces a spike in the other one, preventing an antiphase solution. How large "strong-enough" is depends on the frequency; for low frequency (high period), the cell receiving the coupling current is close to fully recovered when the spike arrives, and hence a small coupling strength may induce the spike. For fixed coupling strength, antiphase is not possible for low enough frequencies.

Figure 3.3 summarizes the existence and stability of the synchronous and out-of-phase solutions as the drive is decreased, which, in turn increases the network period. The diagram was computed from analysis of the necessary condition for stability for the integrate-and-fire models, and matches the behavior found for a biophysical model (White et al. 1998). At very low periods (high drive), only antiphase is stable (or neither is stable). At a higher period, the antiphase solution loses stability (to a third mode we have not discussed). At still higher periods, the synchronous state becomes stable. With drive decreasing more, antiphase becomes stable again and there is bistability of synchrony and antiphase. At the lowest drives, only synchrony is stable.

We note that antiphase solutions doubles the *network* frequency. The frequencies that can be produced by coherent activity mediated with electrical coupling are much higher (even in the synchronous mode) than can be supported by inhibition, which is tied to the rates of the synapses. With antiphase solutions, the electrical coupling can support frequencies over 200 Hz for biologically reasonable parameters.

We can summarize a role of the spike shape and the strength of the gap junctions on the network behavior by discussing how these parameters change the endpoints of the frequency regimes in which there is synchronous and antiphase behavior. Computation of $G_T(\phi)$ shows that this function depends on a combination δ_c of parameters including ξ and v_A; for fast rising spikes and weak coupling , it can be shown that δ_c is approximately $1 + 2gv_m/(1+\xi)$, where $v_m = v_A \exp(\xi\Delta)/(1+\xi)$. From this, it is possible to compute how the endpoints of the stability regions change with parameters. Increasing δ_c, which can be accomplished by increasing the spike amplitude or increasing the spike width Δ, has several effects. First, it raises the period necessary to have stable synchrony, i.e., makes it harder to have synchrony in high frequency regimes. Second, in the lower frequency regimes, increasing δ_c or Δ increases the lower bound on period for stable anti-synchrony; this diminishes the frequency regime over which the antiphase solution is stable, thus enhancing synchrony. Thus, changing the spike shape can have different effects over different frequency regimes.

One way to understand why the shape of the spikes might affect the ability to synchronize is to realize that, during the spike of one cell, the coupling current to the other cell increases the voltage, as in excitatory chemical synapses. During the reset portion and return to threshold of one cell, the current experienced by the other cell acts like an inhibition. Thus, there is tension between the effects of the two parts of the cycle. Since the excitation tends to be desynchronizing, one would expect spikes that are larger (in amplitude and duration) to be more destabilizing than smaller ones. The dependence on network period can be understood in a similar way: changing the drive to the cells mainly changes the interspike interval, rather than the spike itself. Thus, higher frequencies are associated with a large relative amount of excitation, and hence are more vulnerable to destabilization of synchrony.

The spike response formalism is the same for both chemical synapses and electrical synapses (gap junctions). Because of the linearity between spikes, the formalism can also be used when there are both chemical and electrical synapses; in that case, the relevant kernels are the sum of the kernels of each kind. Though they do not interact in a nonlinear way (within this class of models), they can produce some nonintuitive effects. For example, if the individual cells are firing at frequencies too high to sustain synchrony even for electrical coupling, addition of inhibition can synchronize the cells. This does not happen by the mechanism described in the section on chemical synapses, which requires that the inhibition be strong enough to dominate the time scale of the emergent rhythm. Even inhibition too weak to do the latter can help, however; at the high frequencies (the tonic regime for inhibitory coupling), the coupling term acts as a constant inhibition, pulling down the frequency enough that the gap junction can perform the synchronization (White, Kopell, Chow, unpublished).

4. OSCILLATORS WITH MULTIPLE SPIKING CELLS

The work in Section 3 concerns a pair of *cells*, interacting via spikes. The spike-response formalism allows one to deal analytically with dependence on many cycles in the past. In this section, we deal with oscillators that are composites of spiking cells, with excitatory and inhibitory interactions within a single unit oscillator. To handle this analytically, we work in frequency regimes in which the response to a cell receiving a signal depends mainly on the timing of the last cycle, not many previous cycles. In this regime, we have another technique, that of low dimensional maps.

There are two different kinds of maps that we will discuss here. One is derived from the classical "phase-response curve (PRC)" theory, which describes how a limit cycle oscillator reacts to a periodic short pulse that perturbs the oscillator (Winfree 1980). The PRC gives the size of a perturbation in phase at the end of a cycle as a function of the time at which the pulse is received. From the PRC, one can read off the possible stable phase lags or leads between the forcing oscillator and the forced one. The theory depends on having the periodic solution of the forced oscillator be sufficiently attracting that the effect of the perturbation is only on the phase, and there is no effect beyond one cycle. This theory can be extended to work with a pair of oscillations whose interactions are via short pulses and is useful in describing interactions via excitatory synapses.

The second kind of map is useful in situations in which the time of firing of a cell depends on decay time of the coordinating current, usually an inhibitory current; we call these "hold-and-fire" systems. For such maps, the firing time of each of the cells involved in the circuits is calculated as a function of previous firing times; since the period of the coupled system is usually significantly different from that of the uncoupled local circuit, the maps are not described in terms of changes of phase, and are calculated directly, not from a PRC. We will refer to these as spike-time maps. Though the spike times of all the cells come into the calculation, the maps can sometimes be approximated by ones that are of very low dimension, even one-dimensional. The essential reason has to do with the multiple time scales in the Hodgkin-Huxley equations: on the time scale of the signals, many intrinsic variables relax to a predictable position, decreasing the number of real degrees of freedom. This collapse is associated with different time scales in different problems, and will be illustrated below. It has not been rigorously proved that the remaining degrees of freedom correspond to a center manifold, but we conjecture that this is true.

4.1 Long-range synchronization of the gamma rhythm

We now give a case study of a spike-time map analysis. We use the gamma rhythm described above in Section 3.2, as seen in a hippocampal slice. In this case, however, the rhythm is induced by stimulation instead of pharmacological agents that block the excitatory cells; hence the network contains both excitatory and inhibitory cells.

At issue is the ability to have precise synchronization of spikes over distances such that the conduction delays are a significant fraction of the period of the rhythm (e.g. 8 ms in a 25 ms period). It was noticed by Traub et al. (1996), in both data from hippocampal slices and large-scale simulations with thousands of neurons (each with many compartments and conductances) that synchronization over distances was found in conjunction with a stereotypic pattern of activity: the inhibitory cells fire doublets on each cycle, the first spike (statistically) at the same time as the firing of the excitatory cells. The goal of the map analysis is to understand the role, if any, of the doublets in the synchronization process, and to use that to predict the parameter ranges in which such a mechanism could work rapidly and robustly in the presence of heterogeneity and/or noise.

A minimal model has two oscillating local circuits, each composed of one excitatory (E) and one inhibitory (I) neuron (Ermentrout and Kopell 1998). Within each local circuit, the E- and I-cells have inputs to one another. Between the local circuits, the most important connection are the long-distance ones from an E-cell to its distant I-cell (Figure 4.1). Generalizations to a network with a more complex set of connections are in Ermentrout and Kopell (1998).

Each of the cells is described by a set of Hodgkin-Huxley equations, with minimal nonlinear currents corresponding to spiking; since there are the usual three gating variables (m,n,h) of the Hodgkin-Huxley equations, each cell is four-dimensional. Furthermore, the synaptic currents have their own dynamics, described as differential equations dependent on the voltage, rather than currents with prescribed time courses. Hence the total number of equations for even a pair of 2-cell circuits is quite large. Nevertheless, under some broad set of hypotheses, it is possible to analyze the stability of the synchronous solution with a one-dimensional map. The hypotheses can be checked numerically and shown to hold for the Hodgkin-Huxley equations in some parameter regimes.

Some of the hypotheses describe properties of each E-I circuit, i.e., give constraints on ranges of parameters for the Hodgkin-Huxley equations. The rhythm is driven by excitation from the E-cells, so the latter must be excitable enough to fire rhythmically; the populations of I-cells can be either excitable (do not fire without input) or oscillatory, but may not fire faster than the E cells. (If they do, they suppress the E-cell activity.) The I cells have the property (shared by some "type 1 cells") that they can have a long latency to firing after being stimulated because of the proximity of a saddle-node point. This provides a form of "relative refractory period", which will be critical to the analysis. We note that this relative refractory period is not encoded in simple integrate-and-fire neurons and is not needed in the contexts discussed in the previous sections; a model that has this property is important only in contexts in which a cell receives excitation shortly after it spikes, as in the case of doublet firing. As discussed below, the second spike of the doublet is provoked by excitation from the distant circuit, arriving before the local I-cell has fully recovered.

The construction of the map follows from the above hypotheses. The E-cells are able to fire when synaptic inhibition has worn off sufficiently. Thus, we treat E cells as linear between spikes, firing when an inhibition-determined threshold has been reached. The I-cells have an extra property, associated with relative refractory period. Suppose a cell fires at $t = 0$, receives excitation at $t = \psi > 0$ and fires again at $t = T_I(\psi)$. The more recovered the cell, the shorter the time to fire. Hence T_I decays with ψ. For ψ very short, the cell may not fire at all. As will be seen below, the behavior of the system follows almost entirely from the properties of the map T_I. This map, and its dependence on network properties, can be found by simulation. It can be shown that T_I is related to the intrinsic refractory period of the I-cells, but is influenced by the rest of the network. For example, increasing the self-inhibition in the local network increases the values of T_I.

We now analyze the dynamics of the network in a neighborhood of the synchronous solution. The following is a simplification of an analysis in Ermentrout and Kopell (1998), using as long connections only excitatory synapses to the I-cells (Figure 4.1). Let t_1 and t_2 be the times of firing of cells E_1 and E_2 on some cycle, with $\Delta = t_2 - t_1$. If the initial conditions are close enough to synchrony ($\Delta = 0$), we can construct a map that gives the times $\bar{t}_1$ and $\bar{t}_2$ of firing in the next cycle, from which we can determine the conditions under which there is a stable solution. The time at which the inhibition for an E-cell wears off enough for it to fire is approximated by the time at which the inhibitory conductance has decayed enough; the latter threshold depends on the drive to the E-cells. We assume that there is saturation of the synapse from the I- to the E-cell, so that it is only the timing of the second spike of the doublet that matters.

Cell I_1 is essentially recovered from firing in the previous cycle when it receives excitation from E_1 at t_1. (We assume no or minimal local conduction delay. We are also implicitly assuming that the membrane time of the inhibitory cells is shorter than the inhibitory decay time, which implies the recovery of an I-cell by the end of a cycle.) Hence it fires a short (history-independent) time t_{ei} later. (This time can be arbitrarily small, depending on the drive to the E-cells, but the latter drive may not be so large that the I-cells fire before the E-cells.) Cell I_1 receives excitation from E_2 at time $t_2+\delta$, where δ is the delay time between the circuits. Cell I_1 then fires the second spike of its doublet at $t_2+\delta+T_I(t_2+\delta-t_1-t_{ei}) \equiv \widehat{T}_I$, inducing an inhibitory current in the E-cell at that time. E_1 fires at $t=\overline{t}_1$ in the next cycle when the inhibitory conductance decays to some threshold level g_*, i.e.,

$$g_{ie}\exp[-(\overline{t}_1-\widehat{T}_I)/\tau] = g_*, \tag{4.1}$$

where τ is the time constant for decay of inhibition and g_{ie} is the maximal conductance of the inhibitory current. g_* is related to the drive to the cell via the intrinsic period p_γ induced by that drive in an uncoupled cell, namely: $g_{ie}\exp[(-p_\gamma+t_{ei})/\tau] = g_*$. From the above, we can compute the time $\overline{t}_1$ in terms of t_1 and t_2 and similarly for $\overline{t}_2$. The ability to do the analyses given below depends on the fact that both $\overline{t}_1$ and $\overline{t}_2$ are closely approximated by functions only of t_2-t_1. This is true for T_I because the I-cells are sufficiently simple that there are no internal degrees of freedom besides the time after firing. Similarly, since the E-cells do not have currents whose gating variables have long time-constants, the time to firing of the E-cell depends only on the times of receipt of inhibition, not other history-dependent variables.

We now show how we can use the above to analyze the range of parameters in which the gamma configuration is stable. It is easy to solve for $\overline{t}_i$ explicitly. Subtracting $\overline{t}_1$ from $\overline{t}_2$ we get

$$\overline{\Delta} \equiv \overline{t}_2-\overline{t}_1 = -\Delta+T_I(-\Delta+\delta-t_{ei})-T_I(\Delta+\delta-t_{ei}) \equiv F_\gamma(\Delta). \tag{4.2}$$

Standard stability analysis implies that the synchronous solution ($\Delta=0$) is stable if $-1<F'_\gamma(0)<1$, i.e., $-1<T'_I(\delta-t_{ei})<0$. T_I is a decaying function, so its derivative is negative for all δ. However, the rate at which the system synchronizes is given by $|F'_\gamma(0)|-1$, and hence becomes small as δ becomes large. Indeed, (4.2) tells us that the conduction delay for which the speed of synchronization (near the synchronous solution) is largest is the one for which $F'_\gamma(0)=0$, i.e., $T'_I(\delta)=-1/2$. The function T_I can be numerically computed for a given biophysical model; for the reduced Traub-Miles model, $T'_I(\delta)$ is close to zero (and so $F'_\gamma(0)$ is close to 1) for δ about 8 ms or larger (Ermentrout and Kopell 1998). This effectively places a limit on the possible conduction delay that can be tolerated and still produce fast synchronization of gamma by this mechanism. We note that when the rate of convergence to the fixed point is small, small differences in the two local circuits can produce significant phase-lags between the circuits; this is another reason why longer conduction delays disrupt synchronization in this mechanism.

Modifications of the parameters in the circuit can change the range of conduction delays in which there is effective synchronization, but not significantly. (See Ermentrout and Kopell (1998) for more details.) The doublet configuration is robustly stable for the minimal circuit involving two sites, each giving excitation to each I-cell. The mathematics describing the minimal network identifies the essential nonlinearity (the relative refractory period) involved in the synchronization, but does not address the question of how this might work in a large, distributed network in which each I-cell gets excitation at many different times from many different E-cells. Such a distributed network was analyzed in Karbowski and Kopell (1999). Using methods of statistical physics, it was shown that the same nonlinearity works to produce synchronization with the doublet configuration, and that the latter is stable in a larger parameter region than the configuration having triplets in the I-cell within each cycle. Furthermore, the analysis showed that a small amount of disorder in the positions of the E-cells (which determine the conduction delays to the I-cells) can increase the parameter range in which the doublet configuration is stable.

4.2 Gamma to beta transition

Traub et al. (1999) noticed that with more stimulation given to cells in a hippocampal slice, the network first produced a gamma rhythm, and then spontaneously switched into a lower frequency rhythm (12-30 Hz) called beta. (See Kopell et al. (1999) for references to papers that discuss the potential significance of such a switch in living animals.) In the hippocampal slice, it is possible to look at the detailed timing of the spikes in the cells, and it was discovered that the lower frequency rhythm has a different structure from that of the gamma rhythm: the inhibitory cells continue to fire at a gamma frequency, while the excitatory cells miss cycles. Furthermore, the excitatory cell population is essentially synchronous, with almost all E-cells missing the same cycles.

Experimental work reveals at least two kinds of changes in the components and coupling of the network in going between the two rhythms. When the network is displaying beta, the E-cells have an extra ionic conductance, a so-called after-hyperpolarization (AHP) current that slows down the E-cells. Furthermore, the effective coupling of the network changes during the transition: the coupling between E-cells, which is sparse in the network before the large stimulation, grows stronger (Figure 4.2). The mathematical question is whether those changes are enough to account for the changes in the network behavior.

It is clear that slowing down the E-cells can ensure that the latter are unable to keep up with the I-cells, and hence miss cycles. Thus, the balance of excitability of the E- and I-cells is critical to producing the beta rhythm. The question to be investigated, for a local collection of E- and I-cells, is what facilitates the synchronization of the E-cells, so they fire on the same cycles. This is not a straightforward consequence of the E-E coupling, since it is known that E-E coupling can actively prevent synchronization (see Sections 2 and 3). Indeed, in the absence of an I-cell network, typical models of cortical neurons, when coupled with typical synaptic time constants, tend to oscillate in antiphase with one another. However, sometimes slow outward currents can help with synchronization of excitatory cells. This is discussed in Section 4.5, which uses a PRC kind of analysis.

4.3 Long-distance synchronization of the beta rhythm

This section is a variation on Section 4.1, showing here how a different rhythm can be analyzed in a similar way, yielding a different conclusion. The minimal circuit for considering long-distance synchronization of the beta rhythm also uses two networks, each having one E- and one I-cell; since the cells of each type are synchronous in the rhythm whose stability we wish to analyze, we can combine the cells of each type into a single cell. In this formulation, we are assuming that the E-cell represents a synchronous local population, and that this synchrony relies on local E-E connections (see Section 4.5).

For the long-distance synchronization of the two separated circuits, we first consider only E-to-I connections as above for gamma. The map for analysis of the synchronization of two sites, each displaying beta, is a variation of (4.2), with two modifications. The cell I_1 now fires three spikes per beta cycle, two during the gamma cycle in which the E-cells fire, and one during the cycle in which the E-cells are silent. The excitation from the distant cell is, as before, received by an I-cell after it has fired its first spike of the period. The map T_I for the gamma rhythm is replaced by T_β, which is defined to be the interval between the time cell I_1 receives excitation from cell 2 and the time it fires its third (not second, as before) spike; T_β depends on the times t_1, t_2, defined as in Section 4.1. For a graph of T_β, see Figure 4.3. The time at which the third spike of the I-cell fires is $t_2 + \delta + T_\beta(t_2 + \delta - t_1 - t_{ei}) \equiv \widehat{T}_\beta$.

The second modification introduces another, intrinsically-based, source of inhibition, namely the slowly-decaying AHP current of the E-cells, with time constant τ_{ahp}, triggered by a spike of that cell. As in formula (4.1), the time $\bar{t}_1$ of the next E_1 spike is then defined implicitly as the time at which the inhibitory conductance has decayed to some threshold level; in this case the formula takes into account both extrinsic and intrinsic inhibitors:

$$g_{ie} \exp[-(\bar{t}_1 - \widehat{T}_\beta)/\tau] + g_{ahp} \exp[-(\bar{t}_1 - t_1)/\tau_{ahp}] = g_{\beta *}. \tag{4.3}$$

Here g_{ahp} is the maximal *effective* conductance of the slow current, which takes into account the actual maximal conductance $\overline{g}_{ahp}$, but scales it using the maximal value of the gating variable for that current and the ratio of the driving force of the AHP current to that of the synaptic current. A formula for $g_{\beta *}$ analogous to the one for g_* can be found in Kopell et al. (2000).

The analysis of (4.3) is not as straightforward as that of (4.1) since there is no simple explicit formula for $\overline{t}_1$ to obtain a formula analogous to (4.2). However, it is possible to do the stability analysis with the implicit formula (4.3) by linearizing around the solution in which the E-cells are synchronous (while missing beats of the I-cells.). To do this, we define $\rho_i \equiv \overline{t}_i - t_i - p_\beta$, the variation in a given cycle from the periodic rhythm with period p_β. Δ is defined as before. We can rewrite (4.3) as

$$g_{\beta *} = g_{ie} \exp[-(p_\beta + \rho_1 - \Delta - \delta - T_\beta(\Delta + \delta - t_{ei}))/\tau] \tag{4.4}$$

$$+ g_{ahp} \exp[-(p_\beta + \rho_1)/\tau_{ahp}]$$

To lowest order in the small quantities Δ, ρ_1, ρ_2, the above can be expressed as

$$A\rho_1 + B(\rho_1 - \Delta(1 + T'_\beta(\delta - t_{ei})/\tau)) = 0$$

where $A = (g_{ahp}/\tau_{ahp}) \exp(-p_\beta/\tau_{ahp})$ and $B = (g_{ie}/\tau) \exp(-(p_\beta - \delta - T_\beta(\delta - t_{ei}))/\tau)$. A similar formula holds for ρ_2 with Δ replaced by $-\Delta$. Subtracting these two formulae, and noting that $\rho_2 - \rho_1 = \overline{\Delta} - \Delta$, we have that

$$(A + B)(\overline{\Delta} - \Delta) = -2B\Delta(1 + T'_\beta(\delta - t_{ei})/\tau)$$

i.e.,

$$\overline{\Delta} = \frac{A - B - 2BT'_\beta(\delta - t_{ei})/\tau}{A + B}\Delta \equiv D\Delta \tag{4.5}$$

Synchrony is stable if the coefficient D of Δ in (4.5) lies between -1 and $+1$. The fastest synchronization occurs when $D = 0$ and, as above, this is also the range in which there is the most robustness to heterogeneity. As shown in Kopell et al. (2000), the size of D can be analyzed as a function of the conduction delay δ, and for physiological ranges, it turns out to be significantly within the stability range [-1,1] for $\delta = 20\ ms$ or more. Thus, by combining the properties of the new slow current (encoded in the definition of A) and the extra spike of the I-cells in each cycle (affecting both the resulting period and the definition of the key non-linearity T_β), we get that the beta rhythm can allow stable synchronization across much longer conduction delays than can the gamma rhythm in the appropriate physiological parameter regime. This has been confirmed by simulations of the Hodgkin-Huxley equations for the minimal network and for large-scale biophysically accurate representations (Kopell et al. 2000).

So far, the analysis of this subsection concerns only the long-range *synchronous* solution, and makes no use of long-range E-E connections (though local E-E connections are critical to having a local representation using only a single E-cell). We have shown that long E-E connections (see Figure 4.4) are not necessary to the stability of the long-range synchronous solution. Nevertheless, the long E-E connections do play a critical role in the network behavior when the parameters are in the regime to create a beta rhythm. The above analysis does not rule out bistability, and does not address the issue of domain of attraction. As can be seen numerically, without the long-range E-E connections, the solution in which the two E-cells fire in antiphase is stable and has a large domain of attraction. The main function of the long E-E coupling is to insure that the antiphase solution is not a stable alternative to synchrony (Kopell et al. 2000). Adding E-E connections when the parameters are appropriate for the gamma rhythm does not increase the range of conduction delays that are tolerated for synchrony, so it is the difference in the other biophysical factors that creates the advantage for the beta rhythm.

4.4 Changing ionic currents changes synchronization properties

The beta rhythm is significantly slower than the gamma rhythm, partly due to the extra outward current in the E-cells, and partly due to the extra inhibition from the extra I-spike. One might conjecture that the greater robustness of the beta rhythm to conduction delays may depend only on the relative periods, rather than the biophysical details. The following case study shows that the latter interpretation is not correct. Again the analysis uses a spike-timing map, this time to highlight how differences in time constants other than the ones used in Section 4.1 and 4.3 can lead to a 1-dimensional map.

The case study concerns the alpha rhythm (8-12 Hz) in the neocortex, which is slower than gamma or beta. This rhythm is found easily in the neocortex (indeed, much more robustly than is gamma or beta), but its cellular origins are more mysterious. It has been shown that (at least some versions of) this rhythm do not synchronize well over distances, producing variable phase lags instead of synchrony (Roelfsema, et al. 1997, von Stein et al. 2000). To explore how this could come about, Jones, et al. (2000) built a minimal model of a local alpha rhythm using ionic currents known to exist in cells in the layers of the cortex where the alpha rhythm is thought to originate. The key currents are the so-called h- and T-currents, which react differently to inhibition than do most other currents: the h-current is activated by inhibition (its activation current m_∞ is monotone-*decreasing* instead of increasing), while the T-current has a voltage dependence that requires it to be at a low voltage in order to de-inactivate before firing. With these currents, it is possible to create a rhythm in which the inhibition does not determine the frequency. Instead, the time constants of the h- and T-currents of the E-cell are the critical determinants. The I-cells in the network act to provide the essential inhibition needed to turn on those currents in the E-cells. In this rhythm there is no beat skipping, and the I-cells fire almost synchronously with the E-cells.

With only the long E-to-I coupling, the analysis can be done as in the case of the gamma or beta rhythms. Again there are doublets which provide phasing information; the key question is whether the information acts to synchronize. As in the case of Section 4.1, the full equations reduce to analysis of a 1-dimensional map, but the reasons are not the same.

If there is to be only one essential degree of freedom, the general hypotheses of PRC theory should be at least approximately satisfied. That is, the local oscillations, when perturbed, should return approximately to their periodic wave-forms within one cycle; also, the effect of the stereotypic signal from the other local circuit should depend only on the time in the cycle of the recipient oscillator that the perturbation is received. In the case of the circuit-displaying gamma, there is no slow gating variable, and the frequency is determined by the decay of the inhibition; there is no slow variable to hold any memory beyond the end of a cycle. Furthermore, the timing of the I-cell doublet depends essentially only on the time of receipt of the excitation from the circuit and the time of the first spike in the doublet. By contrast, in the case of the alpha rhythm, some of the gating variables of the T- and h-currents are slow (the activation of the h-current, de-inactivation of the T-current). However, special properties of the h- and T-currents allow the hypotheses of the PRC theory to hold. The gating variables of the h- and T-currents are strongly voltage-dependent, and are quickly reset to almost fixed values when the E-cell spikes. Though other gating variables, such as that of the fast-spiking potassium current, do not reset with an E-cell spike, their effects are gone by the end of the long cycle. Thus, for the E-I oscillations in the alpha rhythm, the timing of the E-cell spike paces all of the other variables, and there is no history dependence in the other variables. As above, the time of the doublet spike of the I-cell depends only on time of receipt of the excitation and the time of the previous I-spike, both paced by the spike times of the E-cells. Thus, in spite of the many dimensions in the Hodgkin-Huxley equations, the only essential degree of freedom is the difference in timing of the two E-cells.

The resulting map is an analogue of F_γ of (4.2). In the current case, however, the properties of the analogous function are different: the slopes show that the connection is desynchronizing for some conduction delays, and essentially neutral for small enough delays. The change of sign can be traced to the different processing of inhibition in the network; in the previous rhythms, an inhibitory pulse to an E-cell slows down the rhythm, while for this rhythm an inhibitory pulse speeds up the rhythm by turning up currents that hasten the next spike of an E-cell. Adding long E-E connections does not change this behavior, and can even exacerbate the problem.

It is possible to build networks with flexible synchronization properties by taking advantage of the variation in behavior in different voltage regimes. For example, starting from the simple network model of an alpha rhythm and raising the voltage (by increasing the applied current) brings the network to a range in which the h- and T-currents no longer operate. In that parameter regime, the same network will then display gamma or beta (depending on other parameters). Raising the voltage, which switches the local behavior, then also switches the synchronization behavior: when the local behavior is beta instead of alpha, the two separated networks synchronize rapidly and robustly (Jones et al. 2000).

4.5 Synchronization of excitatory cells

In previous sections, we used spike-timing maps to investigate synchrony. In this section, we use PRC-derived maps to show that some intrinsic properties of cells can lead them to synchronize when they are coupled by excitation, in contrast to integrate-and-fire cells described earlier. The PRC, to be denoted by $P(t)$, describes the advance in time of the next spike of the receiving cell from the time it would otherwise spike next, if the input arrives at time t. Such a PRC may be found experimentally, computed numerically from biophysical equations or sometimes computed analytically from equations.

We can use the function $P(t)$ to create a map for a pair of cells that are mutually coupled. Let t_1 be the time at which cell 1 last fired and let t_2 be the time at which cell 2 last fired. We will assume without loss of generality that $t_2 > t_1$. When t_2 fires, cell 1 is advanced by an amount $P(t_2 - t_1)$ so that

$$\bar{t}_t = t_1 + T - P(t_2 - t_1)$$

where T is the natural period of both cells. (Note that one could have different periods but this complicates the algebra considerably.) By a similar argument, it is clear that

$$\bar{t}_2 = t_2 + T - P(\bar{t}_1 - t_2)$$

is the time that cell 2 fires again. As usual let $\Delta = t_2 - t_1$ and $\overline{\Delta} = \bar{t}_2 - \bar{t}_1$. We then see that

$$\overline{\Delta} = \Delta - P(T - P(\Delta) - \Delta) + P(\Delta) \equiv F(\Delta)$$

and we have again obtained a 1-dimensional map.

We now make use of the condition $P(0) = P(T) = 0$ to note that $\Delta = 0$ is a fixed point of the map F. PRCs derived from real neurons as well as those derived numerically from conductance-based models satisfy this condition, which implies that there is no effect on spike timing if the input comes at the precise time the cell is spiking. (This is not true for the well-known integrate-and-fire model. Thus, the latter requires artificial "absorption" conditions (Mirollo and Strogatz 1990) that are not necessary for more biological PRCs.)

Differentiating F and setting $\Delta = 0$, we find that

$$F(0) = (1 + P'(0))^2$$

so that a necessary and sufficient condition for stability of synchrony is that

$$-2 < P'(0) < 0.$$

Crook et al. (1998b) showed numerically that the presence of adaptation due to a low-threshold, slow-potassium current causes the PRC to have a negative region after spiking, with $P'(0) < 0$. As long as P' is not too negative (for example, if the interaction is not too strong), then the map calculation shows how this alteration of the PRC allows synchrony to be stabilized. In contrast, without adaptation, neurons tend to have strictly positive PRCs when coupled with excitation. The effects of the change on the PRC, and the effect of the latter on stability of synchrony, mirrors changes in the adjoint $V^*(t)$; indeed $V^*(t)$ is a kind of "infinitesimal PRC". (See Figure 2.1 and Section 2.2.)

More recently, Ermentrout, et al. (2000) introduced an analytically solvable model that arises near certain bifurcations. In this model, $P'(0) = 0$. However, by expanding to higher orders, they show that the presence of adaptation leads to a map F that has local behavior $F(\Delta) = \Delta - q\Delta^3$, where $q > 0$ only if there is adaptation and is zero otherwise. Thus, synchrony is weakly stable in this analytical model.

The Ermentrout, et al. (2000) treatment is based on weak interactions, using a convolution with an infinitesimal PRC to create the PRC. For larger interactions, predictions from the infinitesimal PRC can be misleading. This was shown by Ackers, et al. (2000), who constructed the PRC numerically from the Hodgkin-Huxley equations for pairs of cells in the medial entorhinal cortex, a structure that gates the inputs and outputs to and from the hippocampus. The more direct construction reveals global properties of synchronization not apparent in the infinitesimal PRC: for large values of the conductance of the low current, which is associated with prominent subthreshold oscillations for the uncoupled cell, the stable antiphase solution predicted by the infinitesimal PRC approach disappears, and the synchronous solution becomes globally stable instead of bistable with antiphase. These global changes are seen to be associated with the Hopf bifurcation that produces subthreshold oscillations in the uncoupled cells (not found in the equations in (Ermentrout, et al., 2000)). Thus, subthreshold oscillations are seen to be relevant to the domain of stability of the synchronous solution.

We note that the spike-timing maps associated with the PRCs can be globally defined. This is not true of the maps from the "hold-and-fire" systems, which cease to be valid sufficiently far from the synchronous solution. The reason is that a different set of spike times must be considered far from synchrony: in the maps discussed in sections 4.1 and 4.3, the independent variable is $t_2 - t_1$, where the t_i are nearby spike times of the two cells, not dependent on which of the cells is first, provided that the "hold" due to inhibition is larger than $|t_2 - t_1|$. For larger initial differences in spike time, the input most relevant to the receiving oscillator changes, changing the map. The PRCs discussed above keep the order of the relevant spikes the same from cycle to cycle, and the map does not become undefined for large values of the initial difference in spike times.

5 INTERACTIONS OF BURSTING NEURONS

As described in Rubin and Terman (2000A) and Wang and Rinzel (1995), neurons can have complicated firing patterns known as bursts, consisting of a rapid sequence of spikes followed by a quiescent period. Some biophysical models for bursting are given in those references. In studying the interactions of bursting cells, we consider the envelope of the spikes (as do Rubin and Terman); a much-used simple example of such equations are the so-called Morris-Lecar equations (Morris and Lecar 1981), originally designed to describe a calcium spike in muscle (not nerve) tissue. These equations were introduced as (2.8) in an earlier section. In these equations, the activation w of the potassium current is slow (i.e., $1/\tau << 1$). The equations can be understood metaphorically as envelope equations, or as equations for a calcium plateau on which the sodium spikes would ride if the spike currents were included.

The Morris-Lecar equations have phase-plane geometry similar to those of the van der Pol oscillator or its variation, the FitzHugh-Nagumo equations. The nullcline $dv/dt = 0$ is cubic-shaped, and the nullcline $dw/dt = 0$ is monotone-increasing. Depending on the relative positions of the nullclines, the equations can have a stable fixed point on either the left-hand branch or the right-hand branch of the cubic. With the intersection in the middle (and $1/\tau$ sufficiently small), the equations have a stable limit cycle. A variation of these equations uses different currents, but has a similar geometry (Wang and Rinzel 1992).

The Morris-Lecar equations and the FitzHugh-Nagumo equations have a "fast-slow" structure, with the voltage equation significantly faster than the equation for the gating variable. Many results about networks of such cells use only this and other geometric structure, not the details of the biophysical descriptions. In this section, we discuss the interaction of two such neural oscillations, giving results complementary to those in Rubin and Terman (2000), and using the fast-slow structure in a somewhat different way.

5.1 Fast threshold modulation (FTM)

Models of interacting bursting neurons generally use different models of synaptic currents than models using spiking neurons. For the latter, the spikes are very quick or instantaneous, while the currents that result from the spikes have a finite lifetime. Therefore, it is necessary to describe the currents (as above) as explicit functions of time. For bursting neurons, the active state of the cell is a significant fraction of its period. If the time span of the synaptic current from a single spike is short compared to the time of the burst, we can approximate the current by considering it a function of the voltage of the presynaptic cell; the current is on when that voltage (averaged over spikes) is sufficiently high and off when that voltage falls below some threshold. An often-used model of a synaptic current has the same form as an intrinsic current, but the gating of the current is by the voltage of the pre-synaptic cell. Thus, a term of the form

$$-g_{syn}(\widehat{v})(v - v_{syn}) \tag{5.1}$$

is added to the right-hand side of (2.8a), where v is the voltage of the post-synaptic cell and $\widehat{v}$ is the voltage of the pre-synaptic cell. Note that this is the form of the calcium current in the Morris-Lecar equations; that current has one gate (an activation gate) that is instantaneous, so there is no extra differential equation associated with this current. The constant v_{syn} is the reversal potential associated with the synapse. A low value of v_{syn} corresponds to an inhibitory synapse, since the current (5.2) will then be an outward (hyperpolarizing) current; a value of v_{syn} that is above the voltage values produced during activity gives an excitatory synapse, producing inward (depolarizing) current.

The function $g_{syn}(\widehat{v})$ has the same form as the gating in the calcium current of the Morris-Lecar equations: it is a sigmoidal function. If this function saturates for low and high values of its argument, and if the voltages in the active and inactive states correspond to saturated tails of the sigmoid, a further simplification is possible: on the left branch, the synaptic current is zero, while on the right (active) branch, $g_{syn}(\widehat{v})$ is a constant $\overline{g}_{syn}$ independent of $\widehat{v}$. (A limiting version of this is the Heaviside function used in Rubin and Terman (2000A).) Thus, the voltage equation for a coupled cell does not have $\widehat{v}$ explicitly in the equation; one need only keep track of which branch of the $\widehat{v}$-nullcline the partner cell is on. When the partner cell is active, the effect of the synaptic term is to raise or lower the $v' = 0$ nullcline with a change in shape; an excitatory synapse raises the nullcline and an inhibitory one lowers the nullcline (see Figure 5.1). This kind of coupling was called by Kopell and Somers "fast-threshold modulation" (FTM).

The current in (5.1) corresponds to a simple form of synapse described in Rubin and Terman (2000A), ones that are "direct" and rapid compared to intrinsic time scales. That chapter concentrated on the important effects of time scales of the synapses; as shown there, inhibition can be synchronizing if the synapses decay sufficiently slowly compared to some intrinsic processes, and excitation can be desynchronizing if the synapse is fast and if the active portion of the burster is much shorter than the silent portion. The techniques used in that chapter focus on behavior along slow manifolds, and make computations of synchronization or desynchronization using distance metrics within the slow manifold. In our case, the lack of extra time-scales in the synapse brings into relief other aspects of the geometric structure that are better approached using a different kind of metric.

5.1.1 Synchronization via excitatory FTM

Identical cells coupled by excitatory FTM have a synchronous trajectory; this solution is not the same as that of an uncoupled cell. The construction of the synchronous solution uses the fast-slow structure of the equations (2.8). For the coupled system, the slow equation is (2.8b), with $v = v(w)$ determined by setting the right-hand side of (2.8a) to zero. For the unexcited cell, the equation is given by (2.8a), and for a cell receiving excitation there is an extra term $-\ \overline{g}_{syn}(v - v_{syn})$ added to the right-hand side of (2.8a). The trajectory of the synchronous solution is shown in Figure 5.1. (Also see Rubin and Terman, 2000A.) Note that the period of the synchronous solution is in general longer than that of the isolated cell, because the cells have a longer stretch of nullcline to traverse. Though the speed along the raised nullcline can be larger than that of the unexcited nullcline, in most examples (including Morris-Lecar), this effect is not enough to offset the effect of changing the length of the nullcline.

We now show that excitatory coupling through fast threshold modulation leads to synchronization of the cells in the limit $\varepsilon \to 0$. This depends critically on both the fast synapse and the fact that the cells are bursters, with a non-zero active time. (Compare with Rubin and Terman (2000A) and the other sections of this chapter.) We first consider two identical cells, and then discuss the effects of heterogeneity.

The central idea is to use the fast-slow structure of the equations, and the *time* to flow between points on the slow manifold as a distance metric. Suppose that two cells start on the inactive (left) branch at some non-zero distance. When the first jumps to its active state, it changes the nullcline that governs the lagging cell. If the latter is below the knee of the raised nullcline, it will also fire, synchronously in the limit $\varepsilon \to 0$. Right after the jumps, the two cells are on the right-hand branch of the raised nullcline, with the values of w the same as those they had before the jump. (See Figure 5.2.) We denote those values of w by w_0 and w_1.

The crucial hypothesis is that the time it takes a cell to move between w_0 and w_1 is larger on the left-hand branch than on the right-hand one. This can be easily checked for the Morris-Lecar equations, and holds for many classes of equations with similar cubic nullclines. The speed along a branch is determined by (2.8b), and hence is proportional to the distance between w and $w_\infty(v)$. Note that this distance is much greater on the right-hand branch than on the left one for values of w corresponding to points near the knee of the lower cubic. Thus, there is a compression in the time-metric *across* the jump. As the trajectories of the cells move up the right-hand side of the raised cubic, they become closer to one another in the Euclidean metric, but stay the same distance in the time metric. A similar mechanism can work on the jump down from the activated to inactive branch. Each jump further compresses the distance between the cells in the time metric, synchronizing the cells.

A related analysis in Rubin and Terman (2000A) shows synchronization using the Euclidean distance metric. One advantage of focusing on the time metric is that it shows clearly how the rate of synchronization can depend on geometric properties of the oscillations (Somers and Kopell 1993). For example, two coupled Morris-Lecar equations converge to synchrony considerably faster than two FitzHugh-Nagumo equations ($v' = f(v) - w$, $w' = \varepsilon v$; $f(v) = v(1 - v^2)$). The essential reason is that the periodic trajectory of the ML equations is slow near the left knee, since $w_\infty(v) - w$ is small in absolute value in that region; the latter is much larger on the right-hand branch of the cubic slow manifold, leading to a large compression in the time-metric across the jump to the active state. By contrast, the FN equation has a much lower compression across that jump because $|v|$ is not that different along the two slow branches of the cubic nullcline for the same value of w. Again, this analysis is also relevant to the jump down to the inactive state. Other papers that use a time metric to analyze stability of solutions involving bursting neurons are Lofaro and Kopell (1999), Terman and Wang (1995) and Rubin and Terman (2000B).

Suppose now that the cells are not identical; we continue to assume the interaction is via fast threshold modulation. The arguments sketched above show that if the differences are not too large (but still $O(1)$ with respect to ε), there are solutions in which the jumps are synchronous. In order for this to happen, the cell lagging on each of the branches must jump before it reaches the knee of its own (excited or unexcited) nullcline. Thus the coupled pair responds to heterogeneity in the cells by changing the wave-form of at least one of the cells, while preserving the timing of the jumps (Somers and Kopell 1995). Asymmetry in the coupling has similar consequences: if the sizes of the synaptic conductances are different in the two directions, the two cells have different excited nullclines to follow. The mathematics is identical to that in which the coupling is the same but the intrinsic dynamics are different. (See Terman and Wang (1995) for related work about heterogeneity.)

Note that there is a dramatic contrast in the reaction to heterogeneity (intrinsic or coupling) between bursters coupled by FTM and oscillators coupled via phase differences. (Compare to Section 2.3 of this chapter.) There is also another contrast between phase difference and FTM coupling: long chains of oscillators take a large number of cycles to settle into the phase-locked state, while long chains of FTM oscillators can lock within a couple of cycles (Somers and Kopell 1993). Related work about fast synchronization in a network of integrate-and-fire neurons is in Campbell et al. (1999).

Recently, Izhikevitch (2000B) has derived a set of phase models that show some of the properties of relaxation oscillators interacting via FTM. He considers models of the form

$$\mu x' = f(x, y) \quad v' = g(x, y)$$

where μ is a small parameter and the system has a limit cycle with discontinuities analogous to those of relaxation oscillators. For these systems, he is able to compute the singular adjoint trajectory as $\mu \to 0$ and show that there is stable synchronization in the presence of non-uniformities in frequencies. However, the method requires that the coupling strength ϵ satisfy $\epsilon << \mu$, so the coupling must be extremely weak.

5.1.2 Antiphase via excitatory FTM

Suppose now that the time to traverse the right-hand branch in the uncoupled system is less than the time to traverse the left-hand branch. (A precise hypothesis is found in Kopell and Somers 1995.) In the coupled system, there is a set of initial conditions for which one cell stays on the inactive branch during the entire excursion of the other cell on the active branch (see Figure 5.3). With some further conditions, it can be shown that there is a stable antiphase solution with initial conditions in that set.

The mechanism for the antiphase solution is very different and more subtle than that for the synchronous solution. During the active pulse of one cell, the other cell is displaced from the nullcline associated with the uncoupled cell to the (raised) nullcline associated with the active synapse (Figure 5.1). In a large class of equations that includes the Morris-Lecar equations, the movement along the displaced nullcline is slower than along the original one. Thus, the cell that stays in the inactive state experiences a "virtual" delay (the difference between the distance it actually went during the excursion minus the distance it would have gone in that time in the absence of coupling). This is true even though the coupling is excitatory, and leads to advances of the cell for other initial conditions.

The analysis of the behavior is done in terms of the delay as a function of position of one cell when the other begins its active excursion. From this, it is possible to get a Poincaré map, taking the position of cell 1 when cell 2 begins its active phase to the position of cell 2 when cell 1 is at that spot; the fixed point of this is the antiphase solution. Again, time metrics greatly facilitate the analysis of the map.

5.1.3 FTM and Frequency control in "half-center" oscillators

As shown in Rubin and Terman (2000A), bursting cells that are mutually inhibitory, with fast inhibition, do not stably synchronize. In this case, the same mechanism that gives rise to synchronization for fast excitatory synapses leads to antiphase. An oscillating network with the two cells in antiphase is known as a "half-center" oscillator. Such behavior is frequently found as part of networks governing locomotion or other motor patterns, especially if there is antiphase symmetry in the motor outputs

(Marder et al. 1998). In Rubin and Terman (2000A), it was shown that periodic solutions can exist for the coupled pair even if neither is an oscillator. Here we focus on some properties of the antiphase solutions, including the control of their frequency.

When cells are locked but not synchronous, there can be different ways to trigger a switch between active and inactive states of a cell. There are two kinds of distinctions we note: which of the two cells governs the switch (Wang and Rinzel 1992), and whether the mechanism is intrinsic or synaptic (Skinner et al. 1994).

We start with the instrinsic mechanisms. For these, the synaptic threshold is between the active and inactive branches of both the original and inhibited nullcline. The exact value of the threshold voltage plays no role in the behavior of the coupled network. The first of these intrinsic mechanisms has been called "release" (Wang and Rinzel 1992); it is illustrated in Figure 5.4A. In this setup, the active cell reaches the end of its active plateau and jumps down. Because its jump traverses the synaptic threshold, this changes the governing nullcline for the other cell and releases it from inhibition. As in Figure 5.4A, if the position of the inactive cell is below the new nullcline, it will jump to the active state. The release-induced jump is sometimes called "post-inhibitory rebound". Note that a periodic solution with this mechanism requires that the active state be long enough to allow the inactive cell to traverse enough of the left-hand nullcline to be able to jump up at the same time as the jump down of the active cell.

Figure 5.4B illustrates the mechanism known as "escape": the inactive cell, which is on the left-hand branch of the inhibited nullcline, reaches the lower knee of that nullcline, escaping the inhibition from the other cell and jumping up. This lowers the governing nullcline of the other cell, allowing it to jump down if its trajectory is high enough on this nullcline. Note that a periodic solution of this type requires the *inactive* state to be sufficiently long.

For each of these intrinsic mechanisms, the coupled state is an oscillation with the cells in antiphase and the active and inactive states of each identical in length. Neither mechanism requires that the uncoupled cells be capable of oscillations. There are, however, some constraints on the cells for the half-center oscillator to work. For example, in the release mechanism, there may or may not be a stable critical point for the uninhibited cell and/or the inhibited one; what is critical is that the inhibited cell is able to rebound when it is released.

Further mechanisms of antiphase oscillations are obtained by relaxing the restriction that the synaptic threshold lie between the active and inactive branches. If the synaptic threshold is on one of the branches, then the signal given from one cell to another changes as the former traverses that branch, not during its jump between branches. This has a large effect on the wave-form and frequency of the resulting oscillation. (See Figure 5.5A.) If the threshold is in the low-voltage (inactive) region, the inactive cell escapes when it crosses the threshold, not when it reaches the lower knee; this is "synaptic escape". In this region, increasing the synaptic threshold increases the period of the coupled system. If the threshold is in the high-voltage (active) region, the release also occurs before the releasing cell reaches its own higher knee; this is "synaptic release" (Figure 5.5B). In that region, increasing the synaptic threshold decreases the period. If the threshold is between the branches, changing the former does not affect the period of the coupled system.

It is possible to probe a real network to see what mechanism it is using to switch between states. For the network controlling heartbeat in the leech, this was done using a "dynamic clamp", an apparatus that replaces the real chemical synapses between the cells by ones that are computer-generated to have prescribed characteristics. By varying the synaptic threshold and measuring the frequency of the resulting network, it was found that the period increased with threshold in the low voltage range and decreased with it in a higher voltage range, consistent with the use of synaptic escape mechanisms in the low voltage region and synaptic release in the higher voltage range (Sharp et al. 1996).

5.1.4 Variations: coupling between dissimilar cells.

In this section, we have so far focused on synchronous and anti-synchronous behavior of two bursting neurons coupled by fast excitatory or inhibitory synapses. Here we briefly mention that such synapses between two dissimilar cells can lead to new behavior; these results underscore how flexible even a two-cell network can be.

LoFaro and Kopell (1999), considered a two-cell subnetwork from a well-studied invertebrate network. In this network, the cells are coupled by inhibition and one of the cells has a slow inward current that turns on when the voltage is low. They showed that modulation of the slow current could lead to behavior with one cell bursting N times for each burst of the slower cell, with N adjustable by varying the magnitude or voltage activation curve ($m_\infty(v)$) of the slow current; changes of kinetics of the cell (rate of reset when voltage is high) could allow the same network to produce N:M ratios of bursting instead of just N:1. The mathematical essence is the use of time-metric techniques to reduce the full (5-dimensional) equations to a one-dimensional map, from which the network behavior could be deduced.

Working with other aspects of the same cells, Nadim et al. (1999) showed that, if one of the synapses is more complicated, the network can display switches in control of frequency. The complication is "depression" in the synapses: instead of (5.1), in which there is just one voltage-dependent gate, the synapse is treated as also having an inactivation gate with a monotone-decreasing $h_\infty(v)$, as in the Introduction. In this network, a small increase in the size of the maximal conductance of the depressing synapse can start a regenerative mechanism, leading to a large increase in the synaptic current and a switch from a mechanism in which the intrinsic properties of the cells control the network frequency to one in which the kinetics of the synapse controls the frequency.

Even if the membrane currents are very simple (no voltage-gated membrane currents, only a leak current), a network can produce oscillations using the nonlinearities in the synapses. Manor et al. (1999) modeled another subnetwork of the same invertebrate system, producing a half-center oscillation from two cells, neither of which were modeled with voltage-gated currents. The cells are different in their degree of excitability, leading one to be on and the other off in the absence of synaptic input of a third excitatory cell; the latter, turned on and off by the first two, acts more slowly to change the relative excitability of the two primary cells.

5.2 Electrical coupling of cells or compartments

In Sections 2.5 and 3.4 we used phase equations and the spike response method to show that weak electrical coupling could lead to antiphase solutions; in this section, we shall be concerned with unintuitive behavior of electrical coupling in the strong coupling regime. We shall illustrate this by discussing work concerning a single cell, but one extended in space, and (conceptually) discretized into different "compartments". As in networks of spiking cells, electrical synapses are modeled as discrete diffusion in the voltage equation only. The same mathematical formalism used for coupling between compartments is also used to describe electrical coupling between cells, and we give some examples in which such coupling does not have the effect of synchronizing cells.

5.2.1 Strong coupling within a dendrite

In recent work on dopamine-releasing cells, C. Wilson and J. Callaway (2000) have been investigating the hypothesis that the firing patterns of the cells depend on the differences in dynamics along the dendrites of the cell; they also have evidence for oscillations in the cell, and interpret their data to suggest that each single cell can be thought of as a chain of oscillating compartments, electrically coupled, with a gradient in frequency along the chain. Their first model used a Morris-Lecar-like set of equations for each compartment.

A simpler set of equations that reproduces the numerical behavior of that model uses FitzHugh -Nagumo oscillators coupled electrically (Medvedev and Kopell 2000, Medvedev 1999). For each of two compartments, the equations are

$$\begin{aligned} \varepsilon v' &= f(v) - u + d(\hat{v} - v) \\ u' &= \omega v, \end{aligned} \tag{5.2}$$

where v is voltage of the compartment in question, u is here the concentration of calcium in that compartment, and $\widehat{v}$ is the voltage in the other compartment. The function $f(v)$ is a cubic. ω governs the period in this compartment, as does $\widehat{\omega}$ in the other compartment. ω and $\widehat{\omega}$ need not be even approximately the same. The coupling d is very strong, i.e. $d >> 1$. The strength of the coupling implies that the voltage in the two compartments are almost the same, even though the natural periods of the oscillators are not necessarily close. However, the values of u in the two coupled compartments need not be close.

The system turns out to have an unexpected mathematical structure: in the limit of large coupling, there is an invariant cylinder foliated by periodic orbits, with an integral that is constant on each orbit. For d large but not infinite, this integral becomes a Lyapunov function, with slow drift between orbits that are periodic when $d = \infty$ (See Fig. 5.6). The analysis uses two independent small parameters, ε and $1/d$. The critical idea (backed up by asymptotic expansions, and then proved rigorously) is that $(\widehat{v} - v)$ is $O(1/d)$, so the term $d(\widehat{v} - v)$ is O(1) in $1/d$. Since $\widehat{v} \approx v$, one can think of $d(\widehat{v} - v)$ (to lowest order) as a function of v alone and the branch on which the two trajectories lie; we denote this function $c(v)$.

One works with singular orbits, combinations of solutions to the slow and fast equations with $\varepsilon \to 0$. For definitions of fast and slow equations see Rubin and Terman (2000). The slow equations for (5.2) are

$$
\begin{aligned}
u_1 &= f(v) + c(v) \\
u_2 &= f(v + \delta c(v)) - c(v) \\
u_1' &= \omega_1 v_1 \\
u_2' &= \omega_2 (v + \delta c(v)).
\end{aligned}
\tag{5.3}
$$

Here $\delta = 1/d$ and we are using indices 1 and 2 for the compartments, with $v = v_1$ and $v_2 = v + \delta c(v)$. Note that the coupled equations (5.3) can now be treated as uncoupled within each branch, as in fast threshold modulation. From (5.3) it is possible to get a differential equation for $c(v)$, by differentiating the last two equations and using the first two. To lowest order, one gets

$$
c_0(v) = \frac{\omega_1 - \omega_2}{\omega_1 + \omega_2} f(v) + K \tag{5.4}
$$

where K is an arbitrary constant. This can be used in (5.3) to get u_1 and u_2 as functions of v to lowest order in δ.

It is to next order that one sees the mathematical structure. One can compute this using asymptotic expansions, but it is conceptually clearer to see that there is a Lyapunov function for the singular orbits, which is given explicitly as

$$L(u_1, u_2) = \frac{1}{2}(\frac{u_1}{\omega_1} - \frac{u_2}{\omega_2} + A)^2$$

where

$$A = \frac{1}{T}\frac{\omega_1}{-\omega_2}\omega_1\omega_2 \int f(v(t))dt.$$

Each singular periodic orbit can be associated with a value of K in (5.4) and $L = L(K)$; there is a unique value of K for which $L = 0$, and $L(K) > 0$ otherwise. Furthermore, over one full singular cycle, L decreases by $O(\delta)$, so L is an integral for $\delta = 0$ and a Lyapunov function for $\delta > 0$.

The fact that larger coupling leads to longer-lasting transients is not a property of all relaxation oscillators coupled through the fast system. By changing the nullcline of the slow (u) variable to $v = \gamma u$, where $\gamma = O(1)$ in ε and δ, the rate of synchronization becomes almost independent of δ. There are also slow nullclines for which the coupled system has a 1-parameter family of periodic solutions for every value of d.

5.3 Electric coupling of heterogeneous cells

Strong diffusion-like coupling between identical cells tends to synchronize the cells. If the elements being coupled are very different, the effect of strong coupling is less intuitive. Manor et al. (1997) and Smolen et al. (1993) have shown that oscillations can emerge from the electrical coupling of cells that are not oscillators, provided that some appropriate "average" of the cells can oscillate.

Kopell et al. (1998) considered electrical coupling of a relaxation oscillator and a simple (one-dimensional) bistable cell. They used a new geometrical technique to transform information about the geometry of the fast equation $v' = f(v, w)$ of the oscillator to information about the jumps between high and low voltage when the cells are coupled. The technique shows how the electrical coupling can keep the oscillator pinned at a high or low voltage level longer than the uncoupled oscillator, and that larger coupling may actually be less effective at this pinning than coupling of some intermediate size.

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Figure Captions

2.1. The adjoint, $V^*(t)$ plotted along with the derivative of the synaptic conductance, $s'(t)$, (upper panels) and the resulting product (lower panels). If the sign of the integral of the product is positive (negative) then synchrony is stable (unstable). **A.** A negative product in a neuron without adaptation; clearly the area A1 is larger than A2. **B.** A positive product in a neuron with adaptation; the adjoint has a significant negative region to the right of the origin.

2.2. An appropriate delay τ can shift the positive part of $s'(t)$ toward a region where the adjoint is large and positive, thus stabilizing synchrony since the area of the product will be positive (see Fig. 2.1).

2.3. Diagram of two neurons that make synaptic connections along the dendrite.

2.4. Left: The response function $R(t)$ for synapses on the soma or different compartments of a dendrite of the post-synaptic cell. Right: The odd part, H_0, of the corresponding interaction function. Somatic synapses lead to a small stable phase-lag between identical cells and both the synchronous and anti-phase solutions are unstable. A dendritic synapse near the soma results in bistability of the synchronous and anti-phase states. If the synapse is further away, only synchrony is stable.

2.5. The odd part of the interaction function for a fixed synaptic time at three different frequencies. At high frequencies, only the anti-phase state is stable.

2.6. Schematic bifurcation diagram with frequency as the parameter showing stability of the synchronous state at low frequencies and stability of the anti-phase state at high frequencies.

2.7. Diffusive coupling can be synchronizing or desynchronizing in different portions of the limit cycle. For the lower pair of initial conditions, the coupling pulls nearby trajectories closer together, while the opposite is true for the upper pair. See text for explanation.

2.8. Illustration of why diffusive coupling between voltages near a homoclinic destabilizes synchrony. The stable and unstable manifolds and the limit cycle are illustrated. On the left part of the limit cycle (near the stable manifold) diffusion pulls the slower oscillator closer to the stable manifold and the faster oscillator away from the manifold. Thus the faster cell goes even faster and the slower one goes slower, so that they separate in phase. The same reasoning holds for initial conditions on the right hand side of the rest point.

3.1. Examples of kernels $\eta(t)$ and $\varepsilon(t)$. The two curves for $\varepsilon(t)$ correspond to two choices for the form of the synaptic input S(t).

3.2. Kernels $\gamma_s(t)$ and $\gamma_c(t)$ showing dependence on size of gap junction conductance. The dashed lines correspond to a conductance 10 times as large.

3.3. Bifurcation diagram showing dependence of stable solutions (synchrony and antiphase) on the level of drive to the cells. Higher drive corresponds to lower period.

4.1. Minimal model for synchronization of the gamma rhythm across distances. Each E-I circuit is an oscillator, and there are long E to I connections between the two circuits.

4.2. The change from local gamma rhythms to local beta rhythms requires adding connections between the E-cells.

4.3. The maps T_I and T_β as a function of the delay.

4.4. Long distance synchronization of the beta rhythm requires connections between the distant E-cells to remove solutions competing with the synchronous one.

5.1. Excitation raises the nullcline of the fast variable. For the synchronous solution of the coupled system, this changes the position of the trajectory in phase space.

5.2. The jump from the inactive branch to the active branch leaves the variable w unchanged.

5.3. A. When the active cell reaches the upper knee, it releases the inactive cell from inhibition. **B.** When the inactive cell reaches the lower knee, it escapes from the inhibition imposed by the other cell.

5.4 A. The active cell releases the other cell from inhibition when it crosses the synaptic threshold and stops inhibiting the other cell. **B.** The inactive cell escapes before it reaches the knee: once it crosses the synaptic threshold, it inhibits the active cell, which then jumps down and stops inhibiting the first cell.