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(February 23, 2000)

A general method is presented for the analysis of the asynchronous state in networks of identical, all-to-all coupled, limit-cycle oscillators of arbitrary dimension and with arbitrarily strong coupling. It is shown that, with strong coupling, this state can be destabilized in directions orthogonal to the limit-cycle, which may change the units' behavior qualitatively. An example, involving integrate and fire neurons with spike adaptation, exhibits a bifurcation to a synchronized bursting state for strong feedback coupling. The analysis can account for transitions that cannot be studied in the commonly used phase-coupled approximation.

PACS number(s): 87.10.+e, 87.18.Sn, 05.45.Xt

The study of temporal organization of populations of coupled nonlinear oscillators has a long history [1,2]. Such systems are of interest, since they describe a wide array of phenomena in physics, chemistry and, particularly, biology. Examples are synchronized activity in pacemaker cells of the heart and in circadian rhythms as well as in insulin secreting cell in the pancreas [2,3]. In other systems synchrony is detrimental: Both Parkinson disease and Epileptic seizure are accompanied by synchronous activity in different brain areas [4]. A thorough understanding of the synchronizing properties of networks of non-linear oscillators is therefore of more than academic interest.

Considering the wide variety of behaviors that interacting non-linear units can display, it is unlikely that a single theory can adequately account for all possible phenomena. It is more fruitful to study such networks in special cases. A special case in which much theoretical progress has been made is in the case of oscillators with weak interaction. These systems can be studied using perturbation theory: One first characterizes the units by analyzing how they react to small transient perturbing input in the absence of interactions, and then closes the system by relating these perturbations to the activity of the other cells [5,6]. Because the interactions are weak, perturbations in directions orthogonal to the limit-cycle trajectory can be neglected. This results in a system in which the units are described by a phase variable, that denote their position on the limit-cycle, and the interactions depend only on their phase differences.

However this reduction is only valid if the sum of all interactions is small compared to the intrinsic 'driving force' of the oscillators. As a result it does only describes networks in which the feedback only marginally affects the oscillator frequency, the equilibrium state is approached extremely slowly, and even moderately weak noise swamps the feedback. Most systems of interest have

stronger interactions between the units. This can in result in qualitatively different behavior of the network. In particular perturbation orthogonal to the limit-cycle can no longer be neglected. Strong interaction may destabilize modes in these directions. Because such a destabilization drives the oscillators away from their limit-cycle they may qualitatively change the units' activity.

To study these effects, I consider simple networks of identical oscillators with strong all-to-all coupling. Previously [8] the analysis of the asynchronous state has been developed for such networks with units described by 1 dimensional oscillators. Here this analysis is generalized to limit-cycle oscillators of arbitrary dimension. Close to the asynchronous state, the activity of the units can still be reduced to a single phase variable, taking into account the transverse modes. An example shows the effect of destabilization of these modes.

Consider a network of  $N$  identical limit-cycle oscillators. The state of unit  $i$  is described by a  $K$  dimensional vector  $\mathbf{x}_i$ . The evolution of  $\mathbf{x}_i$  satisfies

$$\frac{d\mathbf{x}_i}{dt} = \mathbf{F}(\mathbf{x}_i) + g_s E_i(t) \mathbf{G}(\mathbf{x}_i). \quad (1)$$

Here the first term,  $\mathbf{F}$ , describes the dynamics of the oscillator when it receives no input and the second term accounts for the the effect of the input the unit receives from the other cells in the network. The second term describes the interaction, the variable  $E_i$  characterizes the level of activity of this input,  $\mathbf{G}$  describes its (normalized) effect when the oscillator is in state  $\mathbf{x}_i$ , and  $g - s$  its strength.

If, at time  $t_i$  the first variable of unit  $i$ ,  $x_{i,1}$  passes through a threshold value  $x_{th}$  from below, the cell fires, the activation variable  $E_j$  is augmented by a single pulse response,  $E_s(t - t_i)$ , weighted by a coupling strength  $J_{ij}$ .  $E_s(t) = 0$  for  $t < 0$  and  $\int dt E_s(t) = 1$ . It is assumed that the coupling to all unit is of the same strength,  $J_{ij} = (1 - \delta_{i,j}) / (N - 1)$ . In the large  $N$  limit one can develop a mean-field theory by approximating  $E_i$  by  $E_i(t) = E(t)$ , where  $E$  is given by

$$E(t) = \frac{1}{N} \sum_{i,k} E_s(t - t_i^{(k)}) \equiv \int_0^\infty dt' R(t - t') E_s(t'). \quad (2)$$

Here  $t_i^{(k)}$  is the  $k$ th time that unit  $i$  fires,  $R(t)$  is the network averaged firing rate,  $R(t) = N^{-1} \sum_{i,k} \delta(t - t_i^{(k)})$ .

Consider a network that is in an asynchronous state, in which the rate  $R$  is constant. In this case the states of the oscillators will satisfy  $\mathbf{x}_i(t) = \mathbf{x}_A(t - t_i)$ , where  $\mathbf{x}_A$  is

a periodic solution of Eqn. (1) in which  $E_i(t)$  is set to  $R$ . Assuming that  $x_{A,1}$  passes through  $x_{th}$  from below only once per period, consistency requires that this period be  $1/R$ . In what follows it is convenient to define  $\mathbf{x}_A$  so that  $x_{A,1}(0) = x_{th}$ .

Since, by assumption, the uncoupled units oscillate, there is an asynchronous solution for  $g_s = 0$ . The asynchronous state will persist for finite but sufficiently small  $g_s$ . For larger  $g_s$  the consistent periodic solution may not exist [9]. The network behavior beyond this point will depend on the type of bifurcation through which this solution disappears. From here on I will assume that  $g_s$  is such that an asynchronous solution exists with rate  $R = R_0$ . Then  $\mathbf{x}_i$  can be written as  $\mathbf{x}_i = \mathbf{x}_A(\phi_i/\omega_0)$ , where  $\omega_0 = 2\pi R_0$  and the  $2\pi$  periodic phases  $\phi_i$  are uniformly distributed between 0 and  $2\pi$  and satisfy  $d\phi_i/dt = \omega_0$ . Is this solution stable? To determine this, we first investigate how an single oscillator that receives a constant input  $R_0$  reacts to a small perturbing input.

Consider an isolated oscillator  $i$  whose state vector  $\mathbf{x}$  obeys Eqn. (1) with  $E_i(t) = R_0 + \epsilon\delta(t - t_0)$ , where  $0 < t_0 \leq T_0 \equiv 1/R_0$ , and, for  $t < t_0$ ,  $\mathbf{x}_i(t) = \mathbf{x}_A(t)$ . When  $|\epsilon| \ll 1$ , it is straightforward to show that if we write  $\mathbf{x}(t) = \mathbf{x}_A(t) + \epsilon\xi(t)\Theta(t - t_0)$ , the perturbation  $\xi$  of the state variable  $\mathbf{x}$  satisfies to leading order in  $\epsilon$

$$d\xi(t)/dt = M(t)\xi(t), \quad (3)$$

and  $\xi(t_0) = g_s \mathbf{G}(\mathbf{x}(t_0))$ . Here the  $M$  is the Jacobian of  $\mathbf{F} + g_s R_0 \mathbf{G}$ ,  $M_{ij}(t) = \partial[F_i(\mathbf{x}_A(t)) + g_s R_0 G_i(\mathbf{x}_A(t))]/\partial x_j$ .

Because  $M$  is periodic with period  $T_0$ , one can write  $\exp(\int_0^t dt' M(t'))$ , using the Floquet representation [10], as  $U(t)S \exp(Kt)S^{-1}$ , where  $U(t)$  is a  $T_0$  periodic matrix and  $U(0)$  is the identity matrix.  $K$  and  $S$  are given by  $K_{ij} = \kappa_i \delta_{ij}$  and  $S_{ij} = v_i^{(j)}$  respectively. Here  $\kappa_k$  is the  $k$ th eigenvalue of  $\int_0^{T_0} dt M(t)$  and  $\mathbf{v}^{(k)}$  its right eigenvector. Thus  $\xi$  can be written as

$$\xi(t) = g_s U(t) S e^{K(t-t_0)} S^{-1} U^{-1}(t_0) \mathbf{G}(\mathbf{x}_A(t_0)). \quad (4)$$

Due to the perturbation the firing times will, for  $n > 0$ , be shifted from  $t_n = nT_0$  to  $t_n = nT_0 + \delta_n$ , where  $\delta_n$  is of order  $\epsilon$ . This shift can be found by imposing  $x_{i,1}(nT_0 + \delta_n) = x_{th}$ . Thus, to leading order,

$$\delta_n = -\frac{g_s \epsilon}{\omega_0} \sum_{k=1}^K \Gamma_k(\omega_0 t_0) e^{\kappa_k(nT - t_0)}, \quad (5)$$

where the phase response functions  $\Gamma_k$  are given by

$$\Gamma_k(\phi) = \omega_0 S_{1k} \frac{\sum_{i,j=1}^K S_{ki}^{-1} U_{ij}^{-1}(\phi/\omega_0) G_i(\mathbf{x}_A(\phi/\omega_0))}{F_1(\mathbf{x}_A(0)) + R_0 G_1(v_{\mathbf{x}_A}(0))}. \quad (6)$$

Remembering that we want to study a network of interacting oscillators, in which the input from the cell  $i$  is

determined by the firing times  $t_i^{(n)}$  of that unit, we want to describe the activity of the oscillator by a phase like variable  $\phi_i$  for which  $\phi_i(t_i^{(n)}) = 0 \pmod{2\pi}$ . Up to terms of order  $\epsilon^2$ ,  $\phi_i$  can be written as

$$\phi_i(t) = \omega_0 t + g_s \epsilon \sum_{k=1}^K \Gamma_k(\phi_i(t_0)) e^{\kappa_k(t-t_0)} \Theta(t - t_0). \quad (7)$$

This result can readily be generalized to input  $E(t) = g_s(R_0 + \epsilon(t))$ , with  $|\epsilon(t)| \ll 1$ . In which case  $\phi_i$  satisfies

$$\frac{d\phi_i}{dt} = \omega_0 + g_s \sum_{k=1}^K v_k(\phi_i, t), \quad (8)$$

where

$$v_k(\phi, t) = \Gamma_k(\phi) \epsilon(t) + \kappa_k \int_0^\infty dt' \epsilon(t - t') \Gamma_k(\phi - \omega_0 t') e^{\kappa_k t'}. \quad (9)$$

It should be noted that, since  $\mathbf{x}_A(t + \tau)$  is a solution Eqn. (1) with  $E = R_0$  for any value of  $\tau$ , one of the eigenvalues, say  $\kappa_1$ , is equal to zero.

Applying this to the network defined by Eqns. (1) and (2), one sees that, as long as the system stay close to the asynchronous state,  $|E(t) - R_0| \ll 1$ , the activity of the cells can be described by Eqn. (8), where  $\epsilon$  satisfies

$$\epsilon(t) = \int_0^\infty dt' [R(t - t') - R_0] E_s(t') \quad (10)$$

and  $R(t)$  is determined by the phases  $\phi_i$ . Thus, the original system with  $KN + 1$  variables is reduced to one with  $N + 1$  variables. Analysis of the stability of the asynchronous state can be performed along lines similar to those in networks of 1 dimensional oscillators [8].

The population dynamics is analyzed using the density  $\rho(\phi, t)$ , defined by  $\rho(\phi, t) = N^{-1} \sum_i \delta(\phi_i(t) - \phi)$ , and flux  $J(\phi, t) = [\omega_0 + \sum_k v_k(\phi, t)] \rho(\phi, t)$ . These satisfy the continuity equation

$$\frac{\partial}{\partial t} \rho(\phi, t) = -\frac{\partial}{\partial \phi} J(\phi, t) \quad (11)$$

and boundary condition  $J(0, t) = J(2\pi, t)$ . The rate  $R(t)$  is just the flux through  $\phi = 0$ ,  $R(t) = J(0, t)$ . The asynchronous state is characterized by the solution  $\epsilon = 0$ ,  $\rho(\phi, t) = \rho_{eq} = (2\pi)^{-1}$ , and  $J(\phi, t) = J_{eq} = R_0$ .

The stability of this state is analyzed by setting  $J(\phi, t) = J_{eq} + j(\phi, t)$  and  $\rho(\phi, t) = [J_{eq} + j(\phi, t)]/[\omega_0 + \sum_k v_k(\phi, t)]$  and linearizing the latter in  $j(\phi, t)$  and  $\epsilon(t)$ . This is inserted in the continuity Eqn. (11) and solved for  $j(\phi, t) = j_\lambda(\phi) \exp(\lambda t)$  and  $\epsilon(t) = \epsilon_\lambda \exp(\lambda t)$ , taking the boundary condition into account. Combining this with Eqn. (10) one obtains the eigenvalue equation

$$\frac{1}{\tilde{E}_s(\lambda)} = \frac{g_s \lambda}{\omega_0} \sum_{k=1}^K \frac{\int_0^{2\pi} d\phi \Gamma_k(\phi) e^{(\lambda - \kappa_k)\phi/\omega_0}}{e^{(\lambda - \kappa_k)/R_0} - 1}, \quad (12)$$

where  $\tilde{E}_s(\lambda) = \int_0^\infty dt E_s(t) e^{-\lambda t}$ .

If the coupling is weak,  $g_s$  small, the eigenvalues will be given by  $\lambda = \lambda_{k,n} \approx \Lambda_{k,n}$ , where

$$\Lambda_{k,n} = \kappa_k + in\omega_0, \quad (13)$$

and  $\lambda = \lambda_i^s \approx \Lambda_i^s$ . Here  $\Lambda_i^s$  for  $i = 1, \dots, i_s$  are the  $i_s$  solutions of  $1/\tilde{E}_s(\lambda) = 0$ . For reasonable choices of  $E_s(t)$ ,  $\Lambda_i^s$  will have negative real parts. If furthermore the units are stable limit-cycle oscillators, so that  $\text{Re}(\kappa_k) < 0$  for  $k = 2, \dots, K$ , the only eigenvalues that could have a positive real part are  $\lambda_{1,n}$ . These are just the eigenvalues associated with modes of perturbation along the limit-cycle. Thus in the weak coupling limit the phase coupled model is recovered.

The solutions of the eigenvalue Eqn. (12), and their associated eigen-modes, vary continuously with the coupling strengths  $g_s$ . Therefore even for stronger coupling one can continue to identify the eigenvalues with  $\lambda_i^s$  or  $\lambda_{k,n}$ . However if the coupling is strong,  $|\lambda_{k,n} - \Lambda_{k,n}|$  need not be small, so that  $\text{Re}(\lambda_{k,n})$  could be positive for some  $n$  and some  $k \neq 1$ . Thus a mode that can be ignored in the weak coupling limit may become unstable.

I will now briefly describe a model where one of these modes becomes unstable [12]: Consider an excitatorily coupled network of integrate and fire neurons with spike adaptation. Cell  $i$  is described by a voltage-like variable  $V_i$  and an adaptation current  $A_i$ . The evolution of these variables is given by

$$\frac{d}{dt} \begin{pmatrix} V_i \\ A_i \end{pmatrix} = \begin{pmatrix} I_0 - V_i - A_i + g_s E(t) \\ -\alpha_A A_i \end{pmatrix}. \quad (14)$$

Here  $I_0$  describes an external input into the cells assumed to be above threshold,  $I_0 > x_{th}$ . The adaptation time constant is  $1/\alpha_A$ . If at time  $t = t_i$  the voltage  $V_i$  reaches the threshold  $x_{th} = 1$ , it is immediately reset to zero,  $A_i$  is increased by an amount  $\alpha_A g_A$  and the coupling variable  $E(t)$  is augmented by an amount  $E_s(t - t_i)/N$ .  $E_s(t)$  is the alpha-function  $E_s(t) = \alpha_s^2 t \exp(-\alpha_s t) \Theta(t)$ , where  $\alpha_s$  is the synaptic rate constant.

In the asynchronous state the cells fire periodically with rate  $T_0$ ,  $E(t) = g_s R_0 = g_s/T_0$ , the state variables  $V_i$  and  $A_i$  satisfy, if the neuron last fired at time  $t_i$ ,

$$A_i(t_i + t) = A_0 e^{-\alpha_A t} \quad (15)$$

and

$$V_i(t_i + t) = (I_0 + g_s R_0)[1 - e^{-t}] - A_0 \frac{e^{-\alpha_A t} - e^{-t}}{\alpha_A - 1} \quad (16)$$

for  $0 < t < T_0$ . Here  $A_0 = \alpha_A g_A / [(1 - e^{-\alpha_A T_0})]$ , and  $T_0$  is determined by the constraint  $V(t_i + T_0) = 1$ .

Analyzing the single unit's response to a small perturbing input shows that the  $\kappa_k$  are given by

$$\kappa_1 = 0, \quad \kappa_2 = -\alpha_A + \frac{1}{T_0} \log [1 - c_1 e^{\alpha_A T_0}], \quad (17)$$

and the phase response functions satisfy

$$\Gamma_1(\phi) = c_2 \left(1 - \frac{c_1}{1 - e^{-\kappa_2 T_0}}\right) e^{\omega_0 \phi}, \quad (18)$$

and

$$\Gamma_2(\phi) = c_2 \frac{c_1}{1 - e^{-\kappa_2 T_0}} e^{\omega_0(1 - \kappa_2)\phi} \quad (19)$$

respectively. Here  $c_1 = \frac{\alpha_A A_0 e^{-\alpha_A T_0} e^{-\alpha_A T_0} - e^{-T_0}}{F_1 (1 - \alpha_A)}$ ,  $c_2 = \omega_0 \frac{e^{-T_0}}{F_1}$  and  $F_1 = I_0 + g_s T_0^{-1} - A_0 e^{-\alpha_A T_0} - 1$ . With  $\tilde{E}_s(\lambda) = \alpha_s^2 / (\lambda + \alpha - s)^2$  this determines the eigenvalue Eqn.

For very slow coupling,  $\alpha_s$  close to 0, this equation has solutions  $\lambda_{1,n} \approx in\omega_0$  and  $\lambda_{2,n} \approx \kappa_2 + in\omega_0$ .

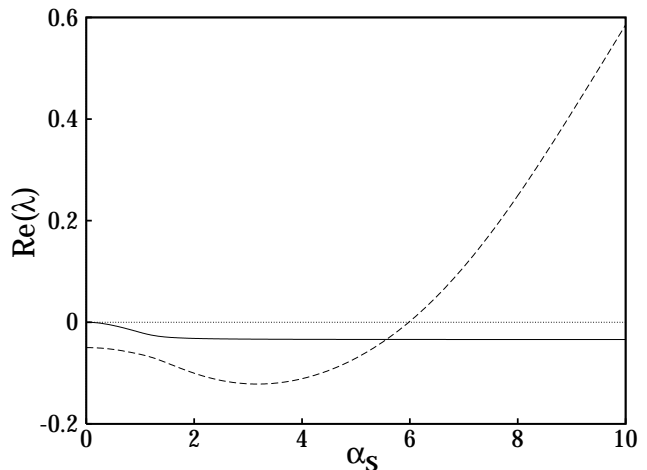


FIG. 1. Real part of the eigenvalues  $\lambda_{1,1}$  (solid line) and  $\lambda_{2,1}$  (dashed line) in a network of integrate and fire neurons with adaptation. Parameters:  $I_0 = 1.1$ ,  $g_s = 0.675$ ,  $\alpha_A = 1/30$  and  $g_A = 0.4$ .

The eigenvalue Eqn. was solved numerically for different values of the synaptic rate constant  $\alpha_s$  for a network of oscillators with  $g_A = 0.4$ . Figure 1 shows the real part of the eigenvalues  $\lambda_{1,1}$  and  $\lambda_{2,1}$ . If these are both negative, all other eigenvalues have negative real part too and the asynchronous state, in which the units fire periodically, is stable.  $\text{Re}(\lambda_{1,1})$  decreases from 0 as  $\alpha_s$  is increased and stays negative.  $\text{Re}(\lambda_{2,1})$  initially decreases from  $\kappa_2$  and then increases. It changes sign at  $\alpha_s = \alpha_{cr} \approx 6$ . Numerical simulations show that at this point the asynchronous state is destabilized through a sub-critical Hopf bifurcation. Beyond the critical point the cells fire in bursts. Figure 2 shows voltage traces of two cells in this state. As can be seen, the bursts of the cells are synchronized, but the individual spikes are not.

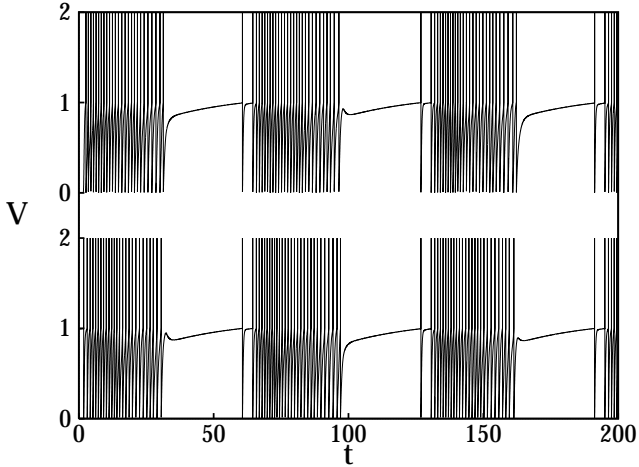


FIG. 2. Voltage trace for two cells in a network past the bifurcation point. the cells fire in bursts, with synchronization on the burst, but not on the spike to spike level. Parameters as in Fig. 1 and  $\alpha_s = 7$

This behavior should be contrasted with that of a network without adaptation. In such networks the asynchronous state is stable for  $\alpha_s$  below a critical value  $\alpha_s = \alpha_{cr}$ . At  $\alpha_{cr}$  these networks undergo a super-critical Hopf bifurcation and just beyond this point the network exhibits weakly synchronized, nearly periodic activity [8,11].

If  $g_A$  is decreased sufficiently  $\text{Re}(\lambda_{1,1})$  rather than  $\text{Re}(\lambda_{2,1})$  becomes positive when  $\alpha_{cr}$  is exceeded, leading to a super-critical Hopf bifurcation similar to that in a network of cells without adaptation. For small  $g_s$  only this second scenario occurs, no matter how large  $g_A$ .

I have presented a general method to analyze the asynchronous state in networks of all to all coupled limit-cycle oscillators. In this method one first determines the asynchronous state self-consistently, and then investigate how a single oscillator, receiving the the appropriate constant input responds to a short perturbing input. While I have discussed an example where the asynchronous solution can be found analytically, the method can also be used for models where asynchronous solution  $\mathbf{x}_A$  and the Jacobian  $M$  have to be determined numerically. An interesting application would be to study networks of more realistic, conductance based, model neurons [13] and compare the results with the phase coupled approximations that are currently, almost exclusively, used to analyze synchronization in such networks.

I have analyzed the system in the large  $N$  limit using mean-field theory. To assess the validity of this limit for finite networks, one can study the stability of the splay state, in which the units are  $1/N$  out of phase, in finite systems using the techniques developed in [11]. For the above example as few as 10 units are sufficient to yield bifurcation parameters that are, to within numerical accuracy, identical to those in the large  $N$  limit.

The analysis was worked out for a system with a ‘neuron-like’ synaptic coupling. Other types of coupling,

more appropriate other systems, can be studied analogously. For example in a system where the coupling depends directly on the state of both unit

$$\frac{d}{dt}\mathbf{x}_i = \mathbf{F}(\mathbf{x}_i) + N^{-1} \sum_j \mathbf{G}(\mathbf{x}_j, \mathbf{x}_i). \quad (20)$$

Here the asynchronous solution is  $\mathbf{x}_A(\phi)$  is determined by self-consistently solving  $\omega_0 d\mathbf{x}_A/d\phi = \mathbf{F}(\mathbf{x}_A) + \overline{\mathbf{G}}(\mathbf{x}_A)$ , where  $\overline{\mathbf{G}}(\mathbf{x}) = (2\pi)^{-1} \int d\phi' \mathbf{G}(\mathbf{x}_A(\phi'), \mathbf{x})$ . Perturbations of this asynchronous state can be studied using analysis along the lines presented here to derive an eigenvalue equation.

Other generalizations may be less straightforward. It should be possible to account for heterogeneities. One effect of this will be to add a continuous component to the eigenvalue spectrum [6], however this should be easily dealt with. Adding noise to the system is probably more involved. With noise the trajectories of the oscillators in their  $K$  dimensional parameter space are, in the asynchronous state, no longer a 1 dimensional path. As a result it is not clear whether  $KN + 1$  dimensional system with noise can be reduced to a  $N + 1$  dimensional system as has been done above. However some useful approximations of the system with noise have been developed by Sirovich and Everson [14].

I thank D. Hansel for most useful discussions. This work was supported by the Gatsby Foundation.

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- [1] K. Showalter and J.J. Tyson, J. Chem. Ed. **6**, 742 (1987).
  - [2] A.T. Winfree, J. Theo. Biol. **16**, 15 (1964).
  - [3] J. Jalife, J. Physiol. **356**, 221 (1984); A. Sherman, J. Rinzel, and J. Keizer, Biophys. J. **54**, 411 (1988).
  - [4] R.D. Traub, R. Miles, and R.K.S. Wong, Science **243**, 1319 (1989); M. Gentil, P. Polack, and J. Perret, Rev. Neurol. **152**, 105 (1995).
  - [5] Y. Kuramoto, *Chemical Oscillations, Waves, and Turbulence* (Springer, New York, 1984); N. Kopell and G.B. Ermentrout, Math. Biosci. **89**, 14 (1989).
  - [6] S. Strogatz and R.E. Mirollo, J. Stat. Phys. **63**, 613 (1991).
  - [7] L.F. Abbott and C. van Vreeswijk, Phys. Rev. E **48**, 1483 (1993).
  - [8] G.B. Ermentrout and N. Koppell, SIAM J. Appl. Math **50**, 125 (1990).
  - [9] V.I. Arnold, *Ordinary Differential Equations* (MIT Press, Cambridge, MA, 1973).
  - [10] C. van Vreeswijk, Phys. Rev. E **54**, 5522 (1996).
  - [11] C. van Vreeswijk and D. Hansel, Neural Comput. (in press).
  - [12] C. Koch and I. Segev, eds. *Methods in Neural Modeling* (MIT Press, Cambridge, MA, 1989).
  - [13] L. Sirovich and R. Everson, International Journal of Supercomputer Applications **6**, 68 (1992).