Analysis of Neural Excitability and Oscillations

1 Introduction

Qualitative features of the dynamics of excitable/oscillatory processes are shared by broad classes of neuronal models. These features are expressed in models for single cell behavior as well as for ensemble activity, and they include excitability and threshold behavior, beating and bursting oscillations and phase-locking, bistability and hysteresis, etc. Our goal here is to illustrate, by exploiting a specific model of excitable membrane, some of the concepts and techniques which can be used to understand, predict, and interpret biophysically these dynamic phenomena. The mathematical methods include numerical integration of the model equations, graphical/geometric representation of the dynamics (phase plane analysis), and analytic formulae for characterizing thresholds and stability conditions. The concepts are from the qualitative theory of nonlinear differential equations and nonlinear oscillations, and from perturbation and bifurcation theory. In this brief chapter, we will not consider the spatio-temporal aspects of distributed systems so the methods apply directly only to a membrane patch, to a spatially uniform, equipotential cell, or to a network with each cell type perfectly synchronized.

One may be familiar with models which exhibit one or two of the different dynamic behaviors, e.g. generation of individual or repetitive action potentials. However, one should realize that a given model, even a seemingly simple one, may display a great variety of response characteristics when a broad range of parameters is considered. This means that a given cell or ensemble may behave in many different modes, e.g. as a generator of single pulses, as a bursting pacemaker, as a bistable "plateauing" cell, or as a beating oscillator, depending upon the physiological conditions (neuromodulator or ionic concentrations) or stimulus presentations (applied currents or synaptic inputs). The nonlinear nature of the models provides the substrate for this broad repertoire; in contrast, linear models may be characterized by exponential and/or oscillatory time courses over their entire parameter ranges. It is important when studying a nonlinear model that stimulus-response properties be considered over ranges of the biophysical parameters.

Here, we show that a simple, but biophysically reasonable, two-current excitable membrane model is sufficiently robust to exhibit such behavioral richness, as parameters are systematically varied. By adjusting channel densities, activation dynamics, and stimulus intensities, we find that the cell can exhibit quite different threshold characteristics for spike generation (finite or infinite latency, with or without intermediate amplitude responses) and for onset of repetitive firing (finite or zero minimum frequency). The cell shows various types of bistable behavior: two different rest states in one case, and, in another case, a rest state with a coexistent oscillatory response around a depolarized level. The latter situation can provide a mechanism for rhythmic bursting when additional slower processes (e.g., slow channel kinetics, or a channel affected by slow ion accumulation) respond differently at the two potential levels. The spike-generating dynamics significantly influence the burst's waveform so there can be several different types of bursting depending on the nature of the fast dynamics; e.g., parabolic bursting does not depend on bistability in the spike-generating processes. Finally, by considering the phase-resetting behavior for a self-oscillatory cell, we show that the response to a single brief, arbitrarily-timed, perturbing stimulus can often be used to predict phase-locking responses to periodic stimulation, and to predict the synchronization properties of weakly coupled cells.

The underlying qualitative structure for these behaviors will be revealed here with graphical phase plane analysis, complemented by a few analytic formulae. The concepts we will cover include steady states, trajectories, limit cycles, stability, domains of attraction, and bifurcation of solutions. Phase plane characteristics and system dynamics will be interpreted biophysically in terms of activation curves, current-voltage relations, etc. A user-friendly program `XPP` (developed by G.B.Ermentrout) for X-windows computers allows one to interactively generate, explore, and visualize most of the behaviors described here in the same spirit as an experimental "setup". Its numerical procedures are summarized in Appendix B. The concepts apply to higher order systems, and in many cases appropriate projections of phase space, motivated by differences in time scales for certain variables, can lead to similar insights.

2 Models for excitable cells and networks

Most models for excitable membrane retain the general Hodgkin-Huxley (HH) format (Hodgkin and Huxley 1952), and can be written in the form:

$$C\,\frac{dV}{dt} + I_{ion}(V, W_1, ..., W_n) = I(t) \tag{1}$$

$$\frac{dW_i}{dt} = \phi\frac{[W_{i,\infty}(V) - W_i]}{\tau_i(V)} \tag{2}$$

where V denotes membrane potential (say, deviation from a reference, or "rest" level), C is membrane capacity, and I_{ion} is the sum of V- and t-dependent currents through the various ionic channel types; $I(t)$ is the applied current. The variables $W_i(t)$ are used to describe the fraction of channels of a given type which are in various conducting states (e.g., open or closed or ...) at time t. The first-order kinetics for W_i typically involve V-dependence in the time constant τ_i; ϕ is a temperature-like, time scale factor which may depend on i. If the current, I_j, for channel type j may be suitably modelled as ohmic, then it might be expressed as

$$I_j = \overline{g}_j\,\sigma_j(V, W_1, ..., W_n)\,(V - V_j) \tag{3}$$

where $\overline{g}_j$ is the total conductance with all j-type channels open (product of single channel conductance with the total number of j-channels), σ_j is the fraction of j-channels that are open (It may depend on several of the variables W_i), and V_j is the reversal potential (usually Nernstian) for this ion species. For some channel types the current-voltage relation may be more appropriately represented by the Goldman-Hodgkin-Katz expression, or by a barrier-kinetics scheme (Hille 1992), and the gating kinetics might involve a multi-state Markov description. In the classical HH model (Hodgkin and Huxley 1952) for squid giant axon, there are three variables W_i, denoted as m, h, and n, to describe the fractions, m^3h and n^4, of open Na^+-channels and K^+-channels, respectively.

For some purposes, it is important that the current balance equation (1) contain terms to account for ionic pump currents. These currents, as well as some channel conductances, may depend upon time-varying second messengers or ionic concentrations , e.g. in diffusionally-restricted intracellular and/or extracellular volumes. For such considerations, additional variables and transport/kinetic balance equations would be included in the model, and these will carry along their own time scales. Indeed, some models that include the dynamics of intracellular free calcium handling have assumed time constants which are orders of magnitude longer than channel kinetics and thereby set the time scale for phenomena like bursting oscillations (e.g., as in Chay and Keizer 1983). We also note that the form of (2) is not unique; in a phenomenological model of Rall (see Goldstein and Rall 1974), the corresponding equations are nonlinear in the W_i.

Some models for excitability contain many variables and represent numerous channel types, especially if one seeks to account for rather detailed aspects of spike shape and dependence upon many different pharmacological agents. On the other hand, if qualitative or semi-quantitative characteristics of spike generation and input-output relations are adequate, say in network simulations, then a reduced model having just a few variables may suffice. Such reductions can sometimes be obtained when time scale differences allow certain approximations such as relatively fast variables being instantaneously relaxed to pseudo-steady-state values, e.g. if τ_j is small relative to other time constants, then one might set $W_j = W_{j,\infty}(V)$ in (2). Likewise, functionally related variables with similar time scales might be lumped together. In this spirit, FitzHugh (1960) considered reductions of the HH model (also see Rinzel 1985 and Kepler, Abbott, and Marder 1992) and then introduced (FitzHugh 1961) an idealized, analytically tractable, two-variable model (also see Nagumo, Arimoto, and Yoshizawa 1962) which is widely studied as a qualitative prototype for excitable systems in many biological/chemical contexts. A FitzHugh-Nagumo/Hodgkin-Huxley hybrid was formulated and studied by Morris and Lecar (1981), in the context of electrical activity of the barnacle muscle fiber. The model incorporates a V-gated Ca^{2+}-channel and a V-gated, delayed-rectifier, K^+-channel; neither current inactivates. A simple version of this model is represented by the equations:

$$C\frac{dV}{dt} = -I_{ion}(V, w) + I \tag{4}$$

$$\frac{dw}{dt} = \phi \, \frac{[w_\infty(V) - w]}{\tau_w(V)} \tag{5}$$

where

$$I_{ion}(V, w) = \bar{g}_{Ca} \, m_\infty(V) \, (V - V_{Ca}) + \overline{g}_K \, w \, (V - V_K) + \overline{g}_L \, (V - V_L). \tag{6}$$

In equations (4)-(6), w is the fraction of K^+-channels open, and the Ca^{2+}-channels respond to V so rapidly that we assume instantaneous activation. One might introduce dimensionless variables, as in (FitzHugh 1969) or (Rinzel and Ermentrout 1989), in order to (i) reduce the number of free parameters and identify equivalent groups of parameters, and (ii) identify and group "fast" and "slow" processes together. However, in the interest of clarity, we will keep all equations in their original form. In (5), τ_w has been scaled so its maximum is now one, and ϕ equals the temperature factor divided by the pre-scaled maximum ($= 1/\overline{\lambda_w}$ in (Morris and Lecar 1981). The V-dependent functions, m_∞, w_∞, and τ_w, and the reference parameter sets are given in Appendix A. All the computations and figures in this chapter are based on equations (4)-(6), and extensions of them for generating bursting behaviors.

Even network models in certain approximations can reduce to a few variables. One example is the Wilson-Cowan model (Wilson and Cowan 1972): (for another, see Chapter 11 in this volume)

$$\mu_e \, \frac{d\mathcal{E}}{dt} = -\mathcal{E} + S(\alpha_{ee} \, \mathcal{E} - \alpha_{ie} \, \mathcal{I} - \theta_e) \tag{7}$$

$$\mu_i \, \frac{d\mathcal{I}}{dt} = -\mathcal{I} + S(\alpha_{ei} \, \mathcal{E} - \alpha_{ii} \, \mathcal{I} - \theta_i). \tag{8}$$

Here, $\mathcal{E}$ and $\mathcal{I}$ represent the respective firing rates of a population of excitatory and inhibitory interneurons. The parameters μ_e, μ_i are the membrane time constants; θ_e, θ_i are the firing thresholds; $\alpha_{ee}, \ldots$ are the "synaptic weights"; and $S(\cdot)$ is a nonlinear saturating function similar in form to $m_\infty(V)$.

3 Understanding Dynamics via Phase Plane Analysis

While an experimenter typically can measure membrane potential, it is usually impossible to monitor other dynamic variables, like ionic currents, during non-clamped activity. For a theoretical model, we must compute explicitly the time courses of all dependent variables. Thus we have more information at hand and so we can obtain additional insight by comparing the time courses and identifying the contributions and temporal relationships of the different dynamic variables. A valuable way to simultaneously view the response of multiple variables and their relationship to physiological functions is by phase-plane profiles, *i.e.* curves of one dependent variable against another. Moreover, such plots allow us also to represent and interpret geometrically aspects of the model (e.g., activation curves) along with the response trajectories. At a glance we can see if the model has one or multiple steady states, and which stimuli might invoke switching between states, and where these steady states lie in relation to activation and I-V characteristics. While the phase plane view provides a full description for two-variable models, judicious two-dimensional projections from phase spaces of higher order systems can yield some of these same insights.

Phase plane analysis was used effectively by FitzHugh (1960, 1961, 1969) to understand various aspects of the HH equations and the two-variable FitzHugh-Nagumo model. His review (FitzHugh 1969) also defines some basic mathematical terminology of nonlinear dynamics and supplements our presentation. For additional mathematical introduction, we recommend the books by Edelstein-Keshet (1988) and Strogatz (1994).

3.1 The geometry of excitabliity

Let's begin by considering the Morris-Lecar model in the case that there is a unique rest state and a threshold-like behavior for action potential generation. Figure 1A shows the V-responses to brief current pulses of different amplitudes. The peak V is graded, but the variation occurs over a very narrow range of stimuli; in this case, as in the standard HH model, the threshold phenomenon is not discrete, but rather, steeply graded. In Figure 1B these same responses are represented in the V-w plane. The solution path in the space of dependent variables is called a trajectory, and direction of motion along a trajectory is often indicated by an arrowhead. In Figure 1B, the flow is generally counterclockwise. All the trajectories shown here ultimately lead to the rest point: $V = \overline{V}, w = \overline{w} = w_\infty\ (\overline{V})$. One says that the rest state is globally attracting. Each trajectory has a unique initial point, a horizontal displacement from the rest point corresponding to instantaneous depolarization by a brief current pulse. A trajectory's slope conveys the relative speed of w to V; e.g., a shallow slope means V is changing faster (see next paragraph). The trajectory of an action potential shows the following features: an upstroke with rapid increase in V (trajectory is moving rightward with litte vertical component) and then the transient depolarized plateau with the delayed major increase in w, corresponding to the slower opening of K^+ channels. When w is large enough, the abrupt downstroke in V occurs - the trajectory moves leftward, nearly horizontal, as V tends toward V_K. Finally, as w decreases (the potassium channels close) the state point returns to rest with a slow recovery from hyperpolarization.

In the phase plane, the slope of a trajectory at a given point is dw/dV which is just the ratio of dw/dt to dV/dt, and these quantities are evaluated from the righthand sides of the differential equations (4)-(5). (The program `XPP` has a command to plot short vectors which indicate the flow pattern generated by the equations. This allows a global view of the flow without having to compute the trajectories. The program also computes nullclines, defined next.) Thus a trajectory must be vertical or horizontal where $dV/dt = 0$ or $dw/dt = 0$, respectively. These conditions:

$$0 = -\overline{g}_{Ca}\, m_\infty(V)\,(V - V_{Ca}) - \overline{g}_K\, w\,(V - V_K) - \overline{g}_L\,(V - V_L) + I \tag{9}$$

$$0 = \phi\, \frac{[w_\infty(V) - w]}{\tau_w(V)} \tag{10}$$

define curves, the V- and w-nullclines, which are shown dashed in Figure 1B. This provides a geometrical realization for where V and w can reach their maximum and minimum values along a trajectory in the V-w plane; notice how the trajectories cross the nullclines either vertically or horizontally in Figure 1B. The w-nullcline is simply the w-activation curve, $w = w_\infty\ (V)$. The V-nullcline, from equation (9), corresponds to V and w values at which the instantaneous ionic current plus applied current is zero; below the V-nullcline, V is increasing and above it, V is decreasing. The cubic-like shape seen here reflects the N-shaped *instantaneous* $I-V$ relation, $I_{ion}(V, w)$ versus V with w fixed (equation (6)), which is typical of excitable membrane models in which the V-gated channels carrying inward current activate rapidly. From another viewpoint, which is motivated by the slower time scale of w, suppose we fix w, say, at a moderate value. Then the three points on the V-nullcline at this w correspond to three pseudo-steady states; at the low-V state, small outward and inward currents cancel while at the high-V state, both currents are larger but are again in balance. These states are transiently visited during the plateau phase and the return-to-rest phase of an action potential. Notice how the trajectory is near the right and left branches of the V-nullcline during these phases.

If ϕ were smaller still, then the phase plane trajectories (except when near the V-nullcline) would be nearly horizontal (since dw/dV would be small). In this case, the action potential trajectory during the plateau and recovery phases would essentially cling to, and move slowly along, either the right or left branch of the V-nullcline. The downstroke would occur at the knee of the V-nullcline. The time course would be more like that of a cardiac action potential. Also, in the case of smaller ϕ, the threshold phenomenon would be extremely steep; the middle branch of the V-nullcline would act as an approximate separatrix between sub- and super-threshold initial conditions. In contrast, for larger ϕ, the response amplitude is more graded. This theoretical conclusion led to an experimental demonstration for squid axon (Cole, Guttman, and Bezanilla 1970) that, at higher temperatures, the action potential does not behave in an "all-or-none" manner.

We remark that phase plane methodology applies to systems which are autonomous, i.e. in which there is no explicit time dependence in the equations. This means that the nullclines and flow field do not change with time. This could not be done if, for example, I were periodic in t; the treatment of periodic stimuli will be covered later. However, the phase plane method extends to cases where a step change in a parameter occurs. At the time a parameter's value jumps, the nullclines would change instantaneously, but not the present location of V and w. FitzHugh (1961) uses this trick to interpret anodal break excitation and Somers and Kopell (1993) have used this to analyze the behavior of coupled Morris-Lecar oscillators when ϕ is very small.

3.2 Oscillations emerging with non-zero frequency

In the phase plane treatment, the rest state of the model is realized as the intersection of the two nullclines; such steady state solutions are also referred to as singular or equilbrium points. From the geometrical viewpoint, one sees how different parameter values could easily lead to multiple singular points - by changing the shapes and positions of the nullclines. In Figure 1, the unique singular point is attracting. Technically, we say it is asympotically stable, i.e. for any nearby initial point the solution tends to the singular point as $t \to \infty$. In general, the local stability of a singular point can be determined by a simple algebraic criterion (Edelstein-Keshet 1988; Strogatz 1994). The procedure is to linearize the differential equations and evaluate the partial derivatives at the singular point (this matrix of partial derivatives is called the Jacobian). Then one asks whether the exponential solutions to this constant coefficient system have any growing modes. If so, then the singular point is unstable; if all modes decay, then it is stable. For equations (4)-(6), the linearized equations which describe the behavior of small disturbances, $V \approx \overline{V} + x, w \approx \overline{w} + y$, from the singular point are

$$\frac{dx}{dt} = a\ x + b\ y \tag{11}$$

$$\frac{dy}{dt} = c\ x + d\ y \tag{12}$$

where,

$$a = -\frac{\partial I_{ion}(V, w)}{\partial V} \tag{13}$$

$$b = -\frac{\partial I_{ion}(V, w)}{\partial w} \tag{14}$$

$$c = \frac{\phi}{\tau_w}\frac{dw_\infty}{dV} \tag{15}$$

$$d = -\frac{\phi}{\tau_w}\ . \tag{16}$$

Solutions are of the form $\exp(\lambda_1 t)$, $\exp(\lambda_2 t)$ where $\lambda_{1,2}$ are the eigenvalues of the Jacobian matrix in equations (11)-(12); they are roots of the quadratic:

$$\lambda^2 - (a + d)\lambda + (ad - bc) = 0\ . \tag{17}$$

For the parameters of Figure 1, the two eigenvalues are both real and negative.

As parameters are varied, the singular point may lose stability. In our example, the rest state could then no longer be maintained and the behavior of the system would change - it may fire repetitively or tend to a different steady state (if a stable one exists). Let us consider the effect of a steady applied current, and ask how repetitive firing arises in this model. We will apply linear stability theory to find values of I for which the steady state is unstable. First, we note that for equations (4)-(6), and for nerve membrane models of the general form (1)-(2), a steady state solution $\overline{V}$ for a given I must satisfy $I = I_{ss}(\overline{V})$, where $I_{ss}(V)$ is the steady state $I - V$ relation of the model which is given by:

$$I_{ss}(V) = I_{ion}(V, w_\infty(V)). \tag{18}$$

If I_{ss} is N-shaped, there will be three steady states for some range of I. However if I_{ss} is monotonic increasing with V, as for the case of Figure 1, then there is a unique $\overline{V}$ for each I, and moreover, $(\overline{V}, \overline{w})$ cannot lose stability by having a single real eigenvalue pass through zero. Destabilization can only occur by a complex conjugate pair of eigenvalues crossing the axis $Re\ \lambda = 0$ as I is varied through a critical value I_1. At such a transition, a periodic solution to equations (4)-(6) is born - and we have the onset of repetitive activity. This solution, for I close to I_1, is of small amplitude and frequency proportional to $Im\ \lambda$. Emergence of a periodic solution in this way is called a Hopf bifurcation (Edelstein-Keshet 1988; Strogatz 1994).

From equations (11)-(12), or (17), we know that $\lambda_1 + \lambda_2 = a + d$. Thus, loss of stability occurs for the I whose corresponding $\overline{V}$ satisfies

$$\frac{\partial I_{ion}(V, w)}{\partial v} + \frac{\phi}{\tau_w} = 0\ . \tag{19}$$

The first term here is the slope of the instantaneous $I-V$ relation and the second is the rate of the recovery process; this condition also applies approximately to the HH model (Rinzel 1978). From (19) we conclude that loss of stability occurs: (1) only if the *instantaneous* $I-V$ relation has negative slope at $\overline{V}$; (2) when the destabilizing growth rate of V from this negative resistance just balances the recovery rate; and (3) only if recovery is sufficiently slow, i.e. if ϕ is small (low "temperature"). In Figure 2A, $\overline{V}$ is plotted versus I (this is the *steady state* $I-V$ relation, but shown as V against I) and the region of instability is shown dashed.

Figure 2A also shows the maximum and minimum values of V for the oscillatory response. Just as a singular point can be unstable, so too can a periodic solution (Strogatz 1994); unstable periodics are indicated by open circles. Here we see that the small amplitude periodic solution born at $I = I_1 = 93.85\ \mu\text{A/cm}^2$ from the loss in stability of $\overline{V}$ is itself unstable; it would not be directly observable. (In the phase plane, but not generally for higher order systems, an unstable periodic orbit can be determined by integrating backwards in time.) Note, that solutions along this branch depend continuously upon parameters and they gain stability at the turning point or knee at $I = I_\nu = 88.3\ \mu\text{A/cm}^2$. A stable periodic solution is called a *limit cycle*. The upper branch (solid) corresponds to the limit cycle of observed repetitive firing. The frequency increases with I over most of this branch (Figure 2B). At sufficiently large I repetitive firing ceases as $\overline{V}$ regains stability at $I = I_2 = 212\ \mu\text{A/cm}^2$. This figure is referred to as a bifurcation diagram; it depicts steady state and periodic solutions, and their stability, as functions of a parameter and it shows where one branch *bifurcates* (from the Greek word for branch) from another. Bifurcation theory allows one to characterize solution behavior analytically in the neighborhood of bifurcation points, e.g., the frequency of the emergent oscillation at the Hopf point is proportional to $\mid Im\ \lambda_{1,2} \mid$. When the Hopf bifurcation is to unstable periodic solutions, back into the parameter region where the steady state is stable, then it is called *subcritical* (i.e., a hard oscillation); if the opposite occurs, the bifurcation is *supercritical.*

For a range of I values (between the knee, I_ν and the Hopf bifurcation, I_1) this model exhibits *bistability*: a stable steady state and a stable oscillation coexist. Figure 3A illustrates the phase plane profile in such a case; a periodic response here appears as a closed orbit. There is a stable fixed point shown as the intersection of the two nullclines and a stable periodic orbit (labeled SPO). The two attractors are separated by an unstable periodic orbit (UPO). Initial values inside the unstable orbit tend to the attracting steady state and initial conditions outside of it will lead to the limit cycle of repetitive firing. A brief current pulse, whose phase and amplitude are in an appropriate range, can switch the system out of the oscillatory response back to the rest state. Such behavior has been seen for many models and observed, for example, in squid axon membrane (Guttman, Lewis, and Rinzel 1980). In Figure 3B, two $30\ \mu\text{A/cm}^2$ current pulses 5 msec in duration are given at $t = 100$ msec and then at $t = 470$ msec. The first switches the membrane from rest to repetitive firing while the second pushes the membrane back to rest. This bistable behavior is critical for the occurence of bursting oscillations when a very slow conductance is added to the model.

3.3 Oscillations emerging with zero frequency

The Hopf bifurcation is one of a few generic mechanisms for the onset of oscillations in nonlinear differential equation models. In that case, the frequency at onset of repetitive activity has a well-defined, non-zero minimum. In contrast, some membranes and models (see, e.g. Connor, Walter, and McKown 1977) exhibit zero (i.e., arbitrarily low) frequency as they enter the oscillatory regime of behavior; Rall's model (Goldstein and Rall 1974) also behaves this way. A basic feature in such systems is that I_{ss} versus V is N-shaped rather than monotonic as in the previous section. For equations (4)-(6) this occurs if the V-dependence of K^+-activation is translated rightward (see Appendix A, and note value of V_3) so that the inward component of I_{ss} dominates over an intermediate V-range. Thus, for some values of I, below the repetitive firing range, there are three singular points in the phase plane. We discuss this case, when the system is excitable, first. In Figure 4B we see the nullclines intersecting three times. As determined by linear stability theory, the singular points are the stable rest state (**R**), an unstable saddle-point threshold (**T**), and an unstable spiral (**U**). The system is excitable with the lower state being a globally attracting rest state: initial conditions near **R** lead to a prompt decay to rest, while larger stimuli lead to an action potential - a long trajectory about the phase plane. The phase plane portrait moreover reveals that this case of excitability indeed has a distinct threshold which is due to the presence of the saddle point, **T**. To understand this we note that associated with the saddle are a unique pair of incoming trajectories (bold dashed lines) corresponding to the negative eigenvalue of the

Jacobian matrix; together these represent the *stable manifold.* Corresponding to the positive eigenvalue are a pair of trajectories (bold lines) that enter the saddle as $t \to -\infty$; these are the *unstable manifold.* `XPP` has a command which generates these manifolds. The stable manifold defines a separatrix curve in the phase plane which sharply distinguishes sub- from super-threshold initial conditions. For initial conditions near the threshold separatrix there is a long latency before firing or decaying as a subthreshold response (see Figure 4A). This is because the trajectory starts close to (but not exactly on) the stable manifold and so the solution comes very near the saddle singular point (where it moves very slowly) before taking off. If w is started at rest, w_R, then there is a unique value of $V = V_T$ (between -22.1 and -22.2 mV in the present example) where the stable manifold intersects the line $w = w_R$. This is the voltage threshold.

The action potential trajectory follows along the unstable manifold (bold lines) which passes around the unstable spiral and eventually tends to the rest point. Such a trajectory which joins two singular points is called a heteroclinic orbit. The other branch of the unstable manifold is also a heteroclinic orbit from the saddle to the rest point. This heteroclinic pair forces any trajectory which begins outside it to remain outside it - thus preserving the amplitude of the action potential. In this case we do not find graded responses for any brief current pulses from the rest state.

This case also provides a counterexample to a common misconception in which it is believed that if there are three steady states then the “outer” two are stable while the “middle” one is unstable. In fact, in some parameter regimes this model has three singular points, none of which is stable.

Next we tune up I and ask when repetitive firing occurs. Because I_{ss} is N-shaped we know that the lower and middle $\overline{V}\,'s$ move toward each other as I increases, and there is a critical value I_1 where they meet. In the phase plane, this means that the rest point and the saddle coalesce and then disappear; this is called a *saddle-node bifurcation.* Moreover, the heteroclinic pair become a single closed loop, a limit cycle, which for I just above I_1 has very long period (Figure 5). Thus, in this parameter regime, the transition to repetitive firing is marked by arbitrarily low frequency (Figure 6B). For I near the critical current, the frequency is proportional to $\sqrt{I - I_1}$ (Strogatz 1994). When $I = I_1$ the limit cycle has infinite period; it is called a *saddle-node loop* or *SNIC* (saddle-node on an invariant circle). Generally, an infinite period limit cycle is called a homoclinic orbit, one that begins and ends at a singular point. The saddle-node loop is one type of homoclinic orbit; we will encounter another type in the next section. This type of zero-frequency onset is generic and occurs over a range of parameters. Changing another parameter will typically lead to a smooth change in I_1. We emphasize that this mechanism allows arbitrarily low firing rates without relying on channel gating kinetics which are necessarily slow. Such low rates have been associated with the inactivating potassium A-type current (Connor, Walter, and McKown 1977) although the underlying mathematical structure of the saddle-node loop does not, of course, require an A-current (Rush and Rinzel 1995). The fast spike dynamics in several recent models (e.g.,Traub, Wong, Miles, and Michelson 1991) for cortical pyramidal cells have this same zero-frequency onset of repetitive firing (unpublished observations by the authors). The value I_1 is determined by evaluating I_{ss} at the value of V for which $\partial I_{ss}/\partial v = 0$, and this latter condition is equivalent to having the determinant $ad - bc$ of the Jacobian matrix equal zero.

The global picture of repetitive firing is shown in the bifurcation diagram of Figure 6A, with frequency versus I in Figure 6B. The branch of steady states (unstable shown dashed) form the S-shaped curve, and the oscillatory solutions are represented by the forked curve whose open end begins at $I = I_1$. As I increases beyond I_1 the peak-to-peak amplitude on the stable (repetitive firing) branch decreases and the frequency increases. The family of periodic solutions terminates at $I = I_2$ via a subcritical Hopf bifurcation. Except for I in a small interval of this upper range, this system is monostable. Annihilation of repetitive firing as in Figure 3 cannot be carried out for I near I_1 in this case. (However, at the high-current end where there is bistability, annihilition can occur.)

3.4 More Bistability

It is important to realize that the solution behavior (bifurcation diagrams) we have described depend on other parameters in the model. The temperature parameter ϕ is particularly convenient, with useful interpretative value, for additional parametric tuning. This parameter, since it plays no role in I_{ss}, does not affect the values along the S-shaped curve of steady states in Figure 6, or the corresponding curve in Figure 2. The *stability* of a steady state does however depend on ϕ. As is seen from equation (19), when ϕ is large, oscillatory destablization is precluded; Hopf bifurcation from a steady state only occurs when the time scale of w is slow compared to that of V. Thus for large ϕ both the upper and lower branches of the S-curve are stable; the middle branch is of course unstable. This system is bistable. In this large-ϕ limit, the kinetics of the K^+-system are so fast (essentially instantaneous with $w = w_\infty(V)$) that the model reduces to one dynamic variable, V. Then stability is determined only by the slope of I_{ss} so the two "outer" states are stable and the "middle" is unstable. This simple example also shows that sometimes a model can be conveniently reduced to a lower dimension when there are significant time scale differences between variables.

For intermediate values of ϕ, the dynamics of both V and w influence stability and the upper branch is unstable for a certain range of I. Figure 7 shows a bifurcation diagram analogous to that in Figure 6A. As in Figure 6A, the branch of steady states is S-shaped and the stable rest state disappears at a turning point (point **A**). The high voltage equilibrium is stable for large currents but as the current is reduced loses stability at a subcritical Hopf bifurcation (point **B**). An unstable branch of periodic solutions emanates from the Hopf bifurcation point and then becomes stable at a turning point (label **C**). Unlike Figure 6A, however, this branch of stable periodic orbits (solid circles) does not terminate on the knee (**A**) but instead on the unstable middle branch (point **D** on the diagram) as the current decreases to a critical value, I_D. Again the frequency of the limit cycle tends to zero for this branch, but not as the square root. Rather, the frequency is proportional to $1/|\log(I - I_D)|$ (Strogatz 1994). At the critical value of current, I_D, the closed orbit has infinite period; it is called a *saddle-loop* homoclinic orbit. Recall that the middle branch of solutions is a saddle point. One branch of the unstable manifold of this saddle-point exits the singular point and returns via a branch of the stable manifold (cf Figure 8a.) (Contrast this with the saddle-node loop homoclinic in Figures 4-6.) For certain values of the current, this system is *tristable.* That is, there are three stable ststes. If I is chosen to lie between the I-values for points **B** and **C** then, the lower branch still exists and is stable, the upper branch of equilibria is stable, and there is a stable periodic orbit. Figure 8A shows the phaseplane for this case. The stable manifold for the saddle point (bold dashed trajectory) acts to separate the stable periodic orbit (SPO) from the lower rest state. The small unstable periodic orbit (UPO) separates the upper rest state from the stable periodic solution. As in Figure 3B, we can use brief current pulses to switch between states. Figure 8B shows the effect of three 5 msec current pulses switching from the periodic orbit to the lower rest state, back to the periodic orbit, and then to the upper rest state. (Note that perturbations from the upper rest state decay very slowly.) The HH model, adjusted for higher than normal external potassium, exhibits similar multistable behavior (Rinzel 1985).

This example of coexistence between a depolarized limit cycle and a lower resting state is important as it also forms the basis for a general class of bursting phenomena.

4 Bursting and Adaptation: Spiking Dynamics with Slow Modulation.

Many neurons exhibit much more complicated firing patterns than the simple repetitive firing we have described here. *Bursting*, clustering of spikes followed by relative quiescence, is a common mode of firing in neurons and other excitable cells (see Wang and Rinzel 1995 for a brief review). Bursting cannot happen in two-variable models. The slow modulation of spiking during a burst requires additional biophysical mechanisms and dynamic variables. Moreover, just from mathematical considerations, a slowly drifting spike trajectory that recurs would violate the rule that trajectories in the phase plane cannot cross. However, we can build on our idealized two-variable model by adding a slow process and then use it to understand bursting from a simple geometric point of view. In this treatment a slow variable is first viewed as a parameter so that one describes the behavioral regimes of the fast spike-generating kinetics. Then the slow dynamics is overlaid as the full system sweeps through regimes of spiking and quiescence. Unless we state otherwise, bursting for us will imply repetitive bursting.

4.1 Square-wave Bursters

Consider in Figure 7 the I-interval between A and D. There is a stable rest state around -35 mV and a stable (more depolarized) limit cycle. Suppose the current I slowly varies back and forth across this interval. Then because of the bistability, it is easy to see how a hysteresis loop is formed in which the membrane is alternately at rest and alternately firing repetitively. This provides a simple mechanism, and geometric interpretation, for *square-wave bursting.* However, since the current I is externally imposed, this is forced rather than autonomous bursting. To achieve the latter, one could (as in Rinzel and Ermentrout 1989) redefine I as a dynamic dependent variable in such a way that I decreases when the membrane is depolarized and firing repetitively, and I increases when the membrane is resting. Although artificial, this example demonstrates the basic principle that (very) slow negative feedback together with hysteresis in the fast dynamics underlie square-wave bursting. Many different ionic current mechanisms could likewise produce the slow negative feedback. For further illustration we employ a calcium-dependent potassium current, analogous to that studied by others (see Wang and Rinzel 1995). We assume the current activates instantaneously in response to calcium and that the calcium handling dynamics are slow. Thus, we add to (6) the current I_{K-Ca} given by

$$I_{K-Ca} = g_{K-Ca} z (V - V_K) \tag{20}$$

where g_{K-Ca} is the maximal conductance for this current and z is the gating variable with a Hill-like dependence on Ca (the near-membrane calcium concentration scaled by its dissociation constant for activating the gate, K_D):

$$z = \frac{Ca^p}{Ca^p + 1}. \tag{21}$$

(For simplicity, we set the Hill exponent $p = 1$, although this is not required.) The balance equation for Ca is:

$$\frac{dCa}{dt} = \epsilon(-\mu I_{Ca} - Ca) \tag{22}$$

where the parameter μ is for converting current into a concentration flux and involves the ratio of the cell's surface area to the calcium compartment's volume. The parameter ϵ is a product of the calcium removal rate and the ratio of free to total calcium in the cell. Since calcium is highly buffered, ϵ is small so that the calcium dynamics is slow. This is a greatly simplified model, for example, one could have more complicated calcium handling, including diffusion of calcium in the cytoplasm, nonlinear removal of calcium by pumps/exchangers, perhaps even release of calcium from intracellular pools. If the conductance $g_{K-Ca}z$ of this outward current is large, the membrane is hyperpolarized and if it is small, then the membrane can fire. Thus, when a bifurcation curve is drawn as a function of this conductance, it is reversed from that of Figure 7 which plots the behavior as a function of an *inward* current. When the membrane is firing, intracellular calcium slowly accumulates, turning on this outward conductance and thereby terminating the firing. Figure 9a shows a bursting solution to the three variable model, eqns. 4-6 coupled with the slow calcium dynamics, eqn. 22. Projecting the solution onto the $z - V$ plane, where z is defined in eq. 21, shows (Figure 9B) how the burst's trajectory slowly tracks the attracting branches of the fast subsystem. Rapid transitions occur when the branches terminate at bifurcation points and turning points. We note that any number of alternate mechanisms could provide the slow negative feedback for bursting including a slow gating kinetics for z with fast calcium handling, or slow inactivation of I_{Ca}, driven by V or Ca.

4.2 Chaos and Poincare Maps.

We emphasize that even our minimal three-variable model exhibits the complex dynamics of bursting oscillations. Moreover, because of its simplicity and the geometric viewpoint we offer, the role of each variable is clear; V and w are for fast spike generation with bistability, and Ca provides the slow modulation. Finally, the model is sufficiently robust that in certain parameter ranges, it appears to exhibit chaotic behavior. Increasing the K_D for the calcium dependent potassium conductance, equivalent to decreasing μ, can switch the membrane into a repetitively firing regime. The transition between the bursting and repetitive regimes is very complicated. For example, when $\mu = 1/59$ the burst pattern has period 4, that is every fourth burst is the same. When $\mu = 1/60$, behavior is aperiodic (time course not shown) whose dynamics can be described as follows. Each time that V passes a given value, here when V decreases through 0 mV, we record the concentration of calcium, as well as the value of w. For this particular model, the recorded values of w are all about 0.35. However, the value of calcium varies between 1.56 and 1.73. The solution is approximately represented by the time series of values for the calcium, $Ca_1, Ca_2, \ldots$ Here's how we can generate the one-variable dynamic rule whose solutions approximate these time series. With initial conditions $V = 0$ and $w = 0.35$, we specify a value for calcium, and then integrate the full differential equations until V crosses 0 again getting the next value of calcium. Thus we have a *map* taking a value of calcium, Ca to a new value of calcium, $F(Ca)$. This map is called a *Poincare Map.* The entire dynamics of our burster is captured by this simple map. For $\mu = 1/60$ this map is shown in Figure 9c. From the figure, it is evident that there is an intersection of the line $y = x$ and $y = F(x)$. That means that there is a single concentration of calcium, Ca^* , to which the trajectory returns after one cycle. This corresponds to a periodic solution to the model equations. If $|F'(Ca^*)| > 1$ (as is the case here) the periodic solution is unstable. This type of map is characteristic of dynamics that have *chaotic behavior.* That is, the successive values of calcium appear to be random and aperiodic. By reducing the three-dimensional differential equation to a simple one-dimensional iteration, we can understand the essence of the transition from constant repetitive firing to chaos as we vary a parameter, say μ. More details on one-dimensional maps and chaos can be found in (Glass and Mackey 1988), and for an application to a neuronal bursting system see (Hayashi and Ishizuka 1992).

4.3 Elliptic Bursters.

Bursting that differs from the square-wave pattern above can arise from slow modulation of bistable fast dynamics, since bistability can arise in a number of ways. Consider a parameter regime for eqs 4-6 in which the onset of oscillations is via a subcritical Hopf bifurcation, such as shown in Figures 2 and 3. As for the square-wave burster, there is a regime where the spike-generating dynamics is bistable; a limit cycle and a fixed point coexist. However, unlike the bistability shown in Figure 7, here, the limit cycle "surrounds" the fixed point. Figure 10 shows an example of a so-called *elliptic burst* pattern generated when the fast dynamics of Figures 2 and 3 are coupled with the slow calcium-dependent potassium current used in the previous bursting model (equation 22). Here (Figure 10A) the envelope of the spikes is "elliptical" in shape as the amplitude gradually waxes and wanes. The silent phase is characterized by damping and growing oscillations as the trajectory slowly drifts through the Hopf bifurcation of the fast subsystem. This type of activity pattern has been seen in sleep spindles and a cellular model related to it involves this mathemetical mechanism (Destexhe, McCormick, and Sejnowski 1993) (see also, Wang and Rinzel 1995). As with a square-wave burster, this type of bursting can also have complex dynamics such as quasi-periodic behavior and chaos.

4.4 Parabolic Bursting: Two Slow Processes.

Bursting can arise even without bistability in the spike-generating dynamics. Minimal models for the most widely known endogenous cellular burster, the *Aplysia* R-15 neuron, operate in a regime where the fast dynamics is monostable (Rinzel and Lee 1987). Suppose the spiking dynamics are as in Figures 4-6, where the onset of repetitive firing is through a saddle-node-loop bifurcation and there is no bistability. (Ignore the bistable behavior at high currents. We are interested in the low current regime only, where the rest state is more negative than -30 mV.) The mechanisms for bursting that depend on *one* slow variable cannot produce bursting in this parameter regime since there is no longer a hysteresis loop. A model with a single slow variable interacting with these fast dynamics will, in response to a steady input, slowly approach a maintained state of repetitive firing or rest. The slow transient phase for a depolarizing input could show increasing or decreasing activity depending on whether the slow variable provides positive or negative feedback. Figure 11a illustrates that I_{K-Ca} with slow Ca dynamics provide a mechanism for adaptation in repetitive firing behavior.

In order to obtain the slow oscillation that underlies parabolic bursting we need yet another slow variable so that there are opposing influences of slow positive (autocatalytic) and slow negative feedback. Thus, suppose that we add a slow *inward* current to the model. This means that there are two slow variables. As the inward current slowly activates, it causes the membrane to fire repetitively. However, this turns on the slow outward current which then shuts the membrane down. If the threshold for the slow inward current is low enough, then it can start up once again and the process repeats. Thus, a combination of a slow outward current and slow inward current can produce slow oscillations that move the fast dynamics into and out of the repetitively firing regime. The generality of this mechanism for parabolic bursting (also realizable with an inward current that slowly activates and then slowly inactivates, as in (Rinzel and Lee 1987) has been described by a number of authors (e.g., Baer, Rinzel, and Carrillo 1995).

To illustrate with the Morris-Lecar model (that includes I_{K-Ca} as above) we need only add a slow autocatalytic process. With considerable freedom of choice, we add an additional slowly activating calcium current:

$$I_{Ca,s} = g_{Ca,s}s(V - V_{Ca})$$

where

$$\tau_s \frac{ds}{dt} = \epsilon(s_\infty(V) - s). \tag{23}$$

For simplicity, we have chosen $\tau_s = 0.05$ as a constant and

$$s_\infty(V) = 0.5[1 + \tanh{(V - 12)/24}].$$

Figure 11b shows the voltage trace of the burst pattern. Note how the interspike interval is relatively longer at the beginning and end of each burst. Figure 11c shows the projection of the two slow gating variables, s and z during a burst. The dashed line represents the boundary between fixed points and oscillation for the fast dynamics when the slow variables are held fixed; it is where the saddle-node-loop bifurcation occurs. Above this line, the fast dynamics are oscillatory and below it, there is a unique stable fixed point.

We have shown how modulating the various types of fast dynamics with one or two slow processes leads to simple mechanisms for generating several different types of bursting oscillations. This geometric viewpoint lets us dissect the mechanisms that underlie some complex neuronal bursting dynamics. Other factors can contribute to burst rhythmogenesis including cable properties and spatially non-uniform channel densities, and nonlinear regenerative factors in the calcium handling system (cf. Wang and Rinzel 1995).

5 Phase-resetting and Phase-locking of Oscillators

We now turn our attention to a brief description of periodically forced and coupled neural oscillators. The behaviors generally involve issues that are very difficult to analyze and we will only touch on them briefly. Before treating a specific example, it is useful to discuss certain important aspects of oscillators. We say that a periodic solution to an autonomous (time does not explicitly appear in the right hand side) differential equation is (*orbitally*) asymptotically stable if perturbations from the oscillation return to the oscillation as $t \to \infty$. The difference between asymptotic stability of an oscillation and that of a steady state solution is that for the oscillation the time course may exhibit a shift. That is, we do not expect the solution of the perturbed oscillation to be the same as the unperturbed, rather there will be a shift (see Figure 12A). This shift is due to the time-translation invariance of the periodic solution. Indeed, in phase-space, the periodic trajectory is unchanged by translation in time. This shift that accompanies the perturbation of the limit cycle can be exploited in order to understand the behavior of the oscillator under external forcing. Suppose that an oscillator has a period, say T. We may let $t = 0$ correspond to the time of peak value of one of the oscillating variables, so that at $t = T$ we are back to the peak. Given that we lie on the periodic solution, if some t is specified then we know precisely the state of each oscillating variable. This allows us to introduce the notion of *phase* of the periodic solution. Let $\theta = t/T$ define the phase of the periodic solution so that $\theta = 0, 1, 2, ...$ all define the same point on the periodic solution. For example, if $\theta = 8.5$ then we are halfway through the oscillator's ninth cycle.

5.1 Phase-response curves

With the notion of phase defined, we now examine how a perturbation shifts the phase of the oscillator. In Figure 12A, we show the voltage time course for the Morris-Lecar system in the oscillating regime. At a fixed time, say t, after the voltage peak, we apply a brief depolarizing current pulse. This shifts the time of the next peak (Figure 12A) and this shift remains for all time (the solid curve is the perturbed oscillation and the dashed is the unperturbed - in this case the time for the next peak is shortened). If the time of the next peak is shortened from the natural time, we say that the stimulus has advanced the phase. If the time of the next peak is lengthened then we have delayed the phase. Let T_1 denote the time of the next peak. The phase shift is $(T - T_1)/T$, and T_1 depends on the time t or the phase $\theta = t/T$ at which the stimulus is applied. Thus, we can define a phase shift $\Delta(\theta) \equiv (T - T_1(\theta))/T$. The graph of this function is called the *phase response curve* (PRC) for the oscillator. If $\Delta(\theta)$ is positive then the perturbation advances the phase and the peak will occur sooner. On the other hand, if $\Delta(\theta)$ is negative then the phase is delayed and the next peak will occur later. We can easily compute this function numerically and the same idea can be used to analyze an experimental system. Moreover, this curve can be used as a rough approximation of how the oscillator will be affected by repeated perturbation (periodic forcing) with the same current pulse. More complete descriptions and numerous examples of phase models and PRC's can be found in (Glass and Mackey 1988; Winfree 1980).

In Figure 12B, we show a typical PRC for the Morris-Lecar model computed for both a depolarizing stimulus (solid line) and a hyperpolarizing stimulus (dashed line). The stimulus consists of a current pulse of magnitude 480 $\mu A/cm^2$ applied for 0.5 msec at different times after the voltage peak. The time of the next spike is determined and this yields the PRC as above. The figure agrees with our intuition; if the depolarizing stimulus comes while $V(t)$ is increasing (i.e. during the upstroke or slow depolarization of recovery), the peak will occur earlier and we will see a phase-advance. If the stimulus occurs while $v(t)$ is decreasing (i.e. during the downstroke), there will be a delay. The opposite occurs for hyperpolarizing stimuli. The curves show that it is difficult to delay the onset of an action potential with a depolarizing stimulus or advance it with a hyperpolarizing one. For different sets of parameters, these curves may change. As we have seen in the previous section, it is sometimes possible to completely stop the oscillation if a stimulus is given at the right time. In this case, the PRC is no longer defined; nearby phases can then have arbitrarily long latencies before firing.

We now show how this function can be used to analyze a periodically forced oscillator. Suppose that every P time units a current pulse is applied to the cell. Let θ_n denote the phase right before the time of the nth stimulus. This stimulus will either advance or delay the onset of the next peak depending on the phase at which the stimulus occurs. In any case, the new phase after time P and just before the next stimulus will be $\theta_n + \Delta(\theta_n) + P/T$. To understand this, first consider the case where there is no stimulus. Then after time P the oscillator will advance P/T in phase. But the stimulus advances or delays the phase by an amount $\Delta(\theta_n)$ so that this amount is just added to the unperturbed phase. This results in an equation for the new phase just before the next stimulus:

$$\theta_{n+1} = \theta_n + \Delta(\theta_n) + P/T \tag{24}$$

This difference equation can be solved numerically. Here we will consider the natural question of whether the periodic stimulus can entrain the voltage oscillation. That is, we ask whether there is a periodic solution to this forced neural oscillation. In general, a periodic solution is one for which there are M voltage spikes for N stimuli where M and N are positive integers. When such a solution exists, we have what is known as *M:N phase-locking.*

Finding $M : 1$ phase-locked solutions is quite easy. We require the oscillator to undergo M oscillations per stimulus period. In terms of (24) this means we seek a solution which satisfies

$$\theta + M = \theta + \Delta(\theta) + P/T \tag{25}$$

for some value of θ. For if such a solution exists and if the solution is stable (to be defined below), then if we start near θ, we can iterate (24) and end up back at θ. This θ is the locking phase just before the next stimulus and since it doesn't change from stimulus to stimulus, the resulting solution must be periodic. Obviously, a necessary condition for a solution to (25) is that $M - P/T$ lie between the maximum and minimum of $\Delta(\theta)$, i.e., we must solve:

$$M - P/T = \Delta\theta \tag{26}$$

Having solved this, we need to determine the stability of the solution. For equations of the form (24) a necessary and sufficient condition for θ to be a stable solution is that $-2 < \Delta'(\theta) < 0$. Since $\Delta(\theta)$ is periodic and continuous there will in general be two solutions to (26) (see Figure 12B), but only one of them will occur where $\Delta(\theta)$ has a negative slope, so that there will be a unique stable solution. We must also worry about whether the negative slope is too steep (i.e., more negative than -2); for small stimuli, this will never be the case - stability is assured. When $\Delta'(\theta) < -2$ (instability), very complex behavior can occur such as chaos (e.g., see Glass and Mackey 1988). The case of $M : N$ phase-locking where $N > 1$ is more difficult to explain so we will not consider it here. It is clear that if the stimulus is weak, the magnitude of $\Delta(\theta)$ will also be small so that $M - P/T$ must be small in order to achieve $M : 1$ locking. On the other hand if the stimulus is too strong, then we must be concerned with the stability of the locked solution. We note that in a sense equation (24) is only valid for stimuli which are weak compared to the strength of attraction of the limit cycle, since for stronger stimuli it will take the solution more than a single oscillation to return to points close to the original cycle. The PRC in Figure 12B shows that, when the stimulus is depolarizing, it is easier to advance the Morris-Lecar oscillator and thus force it at a higher frequency ($0 < P/T < 1$) than it is to force it at a lower frequency ($P/T > 1$). For hyperpolarizing stimuli, we can more easily drive it at frequencies lower than the natural frequency. (The counter results are possible but for small ranges of parameters; also, see Perkel, Schulman, Bullock, Moore, and Segundo, 1964)

To illustrate these concepts, we have periodically stimulated the Morris-Lecar model (natural period of 95 msec) with the same brief depolarizing current pulse repeated every 76 msec time units. Figure 13 shows that the oscillation is quickly entrained to the new higher frequency. Equation (26) allows us to predict the time after the voltage peak that the stimulus will occur for $1 : 1$ phase-locking. From the PRC we can see that $\Delta(\theta) = 1 - 76/95 = 0.2$ corresponds to two values of θ, one stable (cross in Fig 12B) $\theta = 0.702$ and the other unstable. Thus the locking time after the voltage peak, i.e. when the stimulus occurs, is predicted from the PRC to be $t = T \cdot \theta = 67$ msec. This is exactly the shift observed in Figure 13.

The technique illustrated here is useful for analyzing the behavior of a single oscillator when forced with a short pulsatile stimulus. For more continuous types of forcing, such as an applied sinusoidal current, other techniques must be used. One such technique is the *method of averaging* which is applicable when the forcing is weak. Since periodic forcing is just a special case of coupling, we will only describe the latter.

5.2 Averaging and weak coupling

The general behavior of coupled neural oscillators is very difficult to analyze, however limiting cases can be treated (Kopell 1988). We will describe one method, the method of averaging, that has been used successfully to study the dynamics of two or more neural oscillators that are *weakly coupled* (e.g., Hansel, Mato, and Meunier 1995; Ermentrout and Kopell 1991). In this limit the coupling is sufficiently weak that each oscillator's trajectory remains close to its intrinsic limit cycle. The primary effect of the coupling is to perturb the relative phase between the oscillators much as we described above. However, since the perturbation per cycle is small (with weak coupling) the net effect occurs only over many cycles and the per cycle effect is seen as averaged. For illustration, we summarize the use of averaging to describe the phase-locking properties of two identical Morris-Lecar oscillators when coupled with identical mutually excitatory synapses. Detailed derivations of the equations can be found in the above mentioned papers.

We assume that motion of each oscillator along its limit cycle can be rewritten in terms of a phase variable. Thus an oscillator's membrane potential is periodic with period T and follows the function $V(\theta_j)$ where θ_j is the phase of the j^{th} oscillator, $j = 1, 2$ and V is the voltage component of the limit cycle trajectory. In the absence of coupling the dynamics is given simply as $\theta_j = t + C_j$ where C_j is an arbitrary phase-shift. Now consider the effect of small coupling. A brief, weak synaptic current I_{syn} to cell i from activity in cell j will cause a phase shift in cell i

$$\Delta\theta_i = -V^*(\theta_i(t)) I_{syn}(\theta_i(t), \theta_j(t)) \tag{27}$$

where $V^*(t)$ is the infinitesimal phase-response function, and the minus sign converts excitatory current to positive phase shift. The synaptic current is given by

$$I_{syn}(\theta_i, \theta_j) = g_c \alpha(\theta_j(t))(V(\theta_i(t)) - V_{syn}) \tag{28}$$

where the postsynaptic gating variable $\alpha(t)$ in cell i is activated by the presynaptic voltage $V(\theta_j)$, V_{syn} is the reversal potential for the synapse, and g_c is the strength of the synaptic coupling. The gating variable $\alpha(t)$ could be represented by a so-called (event-triggered) alpha function introduced by Rall (cf. chapter 2 of this volume). Alternatively, it could obey a voltage-gated differential equation.

In the method of averaging we simply "add up" all the phase-shifts due to the synaptic perturbations and average them over one cycle of the oscillation. Thus, after averaging, one finds that the coupled system satisfies:

$$\frac{d\theta_1}{dt} = 1 + g_c H(\theta_2 - \theta_1) + O(g_c^2) \tag{29}$$

$$\frac{d\theta_2}{dt} = 1 + g_c H(\theta_1 - \theta_2) + O(g_c^2) \tag{30}$$

where H is a $T-$periodic "averaged" interaction function, given by

$$H(\phi) = \frac{1}{T}\int_0^T V^*(t)\alpha(t+\phi)(V_{syn} - V(t))\ dt. \tag{31}$$

The key to these models is the computation of H (see Ermentrout and Kopell 1991; Kopell 1988).

In Figure 14A, we show the function $V^*(t)$ along with the synaptic gating variable $\alpha(t)$ over one cycle for exactly the same parameters as in Figure 12B. Here $\alpha(t) = 0.04te^{-t/5}$ is an "alpha" function with a 5 msec time constant. Note the similarity (except for scale) of the excitatory PRC and the infinitesimal PRC, $V^*(t)$. As with the PRC, $V^*(t)$ is mainly positive showing that the predominant effect of depolarizing perturbations is to advance the phase or equivalently speed up the oscillator. In only a very small interval of time can the phase be delayed, and this is a general property of membranes which become oscillatory through a saddle-node bifurcation (Ermentrout 1996).

Figure 14B shows the function $H(t)$ defined in equation (31) for the alpha function shown in Figure 14B and for $V_{syn} = 0$ mV. We can use this function along with equations (29-30) to determine the stable phase-locked patterns for this coupled system. Let $\Theta = \theta_2 - \theta_1$ denote the phase difference between the two oscillators. From equations (29-30) we see that Θ satisfies:

$$\frac{d\Theta}{dt} = g_c(H(-\Theta) - H(\Theta)) + O(g_c^2) \equiv -2g_c G(\Theta) + O(g_c^2). \tag{32}$$

Here $G(\Theta)$ is just the odd part of the function H. Since the coupling is weak, the higher order terms, $O(g_c^2)$ are ignored. Equation 32 is just a first order equation. Phase-locked states are those for which Θ does not change, that is, they are roots of the function $G(\Theta)$ and they are stable fixed points if $G'(\Theta) > 0$. Since any odd periodic function has at least two zeros, $\Theta = 0$ and $\Theta = T/2$ there will always exist phase-locked states. However, these may not be stable, and there may be others. Synchronous solutions ($\Theta = 0$) imply that both membranes fire together. Anti-phase solutions ($\Theta = T/2$) are exactly one half cycle apart. Figure 14b shows the function $G(\Theta)$ and from this we see that there are 4 distinct fixed points: (i) the *synchronous* (precisely in-phase) solution, (ii) the *anti-phase* solution, and (iii) a pair of phase-shifted solutions at $\Theta \approx \pm 15$ msec. Both the synchronous and anti-phase solutions are unstable but the phase-shifted solution is stable. Thus, if two of these oscillators are coupled with weak excitatory coupling and the parameters chosen as above, they will phase-lock with a phase-shift of about 20% of the period. Although the classical view is that mutual excitation leads to perfect synchrony, computations with a variety of neuronal models suggest that this is not generally the case.

This type of analysis is easily extended to systems where the oscillators are not exactly identical, when coupling is not symmetric, and when there are many more oscillators. The behavior of such phase-models and the forms of the interaction functions, H, are the topics of current research.

6 Summary

We have introduced and used some of the basic concepts of the qualititative theory of differential equations to describe the dynamic repertoire of a representative model of excitability. We believe that a geometrical treatment, as in the phase plane, gives one an opportunity to see more clearly and appreciate the underlying qualitative structure of models. One can see which initial conditions, e.g. as the result of a brief perturbing stimulus, will lie in the domain of attraction of any particular stable steady state or limit cycle. This is especially helpful for the design of experiments to switch a multistable system from one mode to another.

Analytic methods are also important – for determining and interpreting the stability of solutions (e.g., equation (19) for the Hopf bifurcation) and for approximating aspects of the solution behavior (e.g., equation (25) for phase-locking). Another useful conceptual device is the bifurcation diagram by which we have provided compact descriptions of the system attractors. In several of our illustrations, the bifurcation parameter was I, and in this case the steady-state $I - V$ relation appeared explicitly in the diagram. Any parameter can be used in such considerations such as channel density or synaptic weight as in the Wilson-Cowan network model.

We have shown how a minimal but biophysically reasonable membrane model can be massaged to exhibit robustly a variety of physiologically identifiable firing behaviors. For the simplest two-variable Morris-Lecar model, we illustrated some qualitative differences in threshold behavior when the steady state current-voltage relation is monotonic or N-shaped. In the former case, action potential size may be graded, although generally quite steeply with stimulus strength, and latency for firing is finite. In the latter case, there is a true (saddle point) threshold for action potentials, latency may be arbitrarily long, and intermediate-sized responses are not possible. Correspondingly, for a steady stimulus, the monotonic case leads to onset of oscillations with a well-defined, non-zero frequency (Hopf bifurcation), and with possibly small amplitude (supercritical). In contrast, in the N-shaped case repetitive firing first appears with zero frequency (homoclinic bifurcation). These features are consistent with some of those used by Hodgkin (1948) to distinguish axons with different repetitive firing properties, Class II and Class I, respectively. Additionally, we have provided a geometric interpretation of some common forms of bursting neurons. Many bursters can be dissected into fast dynamics coupled to one or more slow processes that move the fast dynamics between resting and oscillatory states. Coupled and forced oscillators can often be reduced to maps or to continuous low-dimensional systems of phase equations, especially when the interactions are weak.

With regard to implementation of models, there are sophisticated software packages and subroutines available nowadays which help make theoretical experimentation and analysis a real-time endeavor; the "tooling-up" time is greatly reduced. Programs like `XPP` incorporate a mix of numerical integration and analytic formulation (linear stability analysis, bifurcation analysis, averaging - carried out numerically) with graphical representation all in an interactive framework. (The numerical methods employed by `XPP` are described in Appendix B.) To set up and get running the Morris-Lecar model should take less than fifteen minutes. Although we have used `XPP` here for the two-variable model, it can also deal with higher order systems (like the bursting models of Section 4). Stability of steady states can be computed, and time courses plotted interactiviely. The generalization of nullclines to surfaces is not available computationally, but two-variable projections of trajectories from the higher-order phase space can be insightful (e.g., Figure 9). A widely distributed subroutine which we have also found valuable for dissecting nonlinear systems is `AUTO` (Doedel 1981) which automatically generates bifurcation diagrams (as in Figures 2,6,7); see Appendix B. The main components of `AUTO` are included in the package `XPP` thus making `AUTO` an interactive program. We used `XPP-AUTO` for the fast/slow analysis of the bursting models in Section 4. For the evaluation and algebraic manipulation of analytic prescriptions (e.g., lengthy perturbation and bifurcation formulae), many modelers have used symbol manipulation programs like Mathematica and MAPLE with success; see (Rand and Armbruster 1987). In the use of numerical packages we advise that one be generally familiar with the methods being employed, and with their limitations. It is not so uncommon to pose a problem which seems to just miss the criteria for suitablity of a given technique - and one should be careful to recognize the symptoms of breakdown of the particular method being used.

Finally, we emphasize the value of using idealized, but biophysically reasonable, models in order to capture the essence of system behavior. If models are more detailed than necessary then identification of critical elements is often obscured by too many possibilities. On the other hand, if justified by adequate biophysical data, more detailed models are valuable for quantitative comparison with experiments. Thus the modeler should be mindful and appreciative of these two different approaches: which one is chosen depends on the types of questions being asked and how much is known about the underlying physiology.

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7 Appendix A: Morris-Lecar Equations

The differential equations and V-dependent functions are

$$C\frac{dV}{dt} = -\overline{g}_{Ca}\, m_\infty(V)\,(V - V_{Ca}) - \overline{g}_K\, w\,(V - V_K) - \overline{g}_L\,(V - V_L) + I \tag{33}$$

$$\frac{dw}{dt} = \phi\,\frac{[w_\infty(V) - w]}{\tau_w(V)} \tag{34}$$

where

$$m_\infty(V) = 0.5 * [1 + \tanh\{(V - V_1)/V_2\}], \tag{35}$$

$$w_\infty(V) = 0.5 * [1 + \tanh\{(V - V_3)/V_4\}], \tag{36}$$

and

$$\tau_w(V) = 1/\cosh\{(V - V_3)/(2 * V_4)\}. \tag{37}$$

For Figures 1-3, we use the parameters $V_1 = -1.2$, $V_2 = 18$, $V_3 = 2$, $V_4 = 30$, $\overline{g}_{Ca} = 4.4$, $\overline{g}_K = 8.0$, $\overline{g}_L = 2$, $V_K = -84$, $V_L = -60$, $V_{Ca} = 120$, $C = 20\mu\mathrm{F/cm}^2$, and $\phi = 0.04$. All conductances are in $\mathrm{mS/cm}^2$ and voltages in mV. These same parameters are used for Figures 4-6, with the following exceptions: $V_3 = 12$, $V_4 = 17.4$, $\overline{g}_{Ca} = 4.0$, and $\phi = 1/15$. In Figures 7-8, the parameters are as in Figures 4-6 but $\phi = 0.23$. The current, I, (in $\mu A/cm^2$) is generally the only free parameter.

8 Appendix B: Numerical Methods

Most of the figures shown in this chapter were produced by numerically solving the Morris-Lecar equations. We have used a program `XPP` written by G.B.Ermentrout which uses a variety of numerical integration methods to solve the equations on any computer that runs X-windows. It is available via anonymous ftp from `ftp.math.pitt.edu/pub/bardware` and there is an extensive tutorial geared toward neurobiology available on the World Wide Web `http://www.pitt.edu/ ~phase` For the all but the bursting simulations, we have used a fourth order Runge-Kutta algorithm. The bursting simulations employed a variable timestep Gear algorithm (Press, Flannery, Teukolsky, and Vetterling 1986).

For the Morris-Lecar model, the nullclines can be found explicitly by solving each of the equations for w as a function of v. But this is generally not easy, so that numerical techniques are in order. All of the phase-plane pictures were found by numerically computing the nullclines. This is done by breaking the phase-plane into many small boxes, evaluating the functions on each point and then using a linear interpolation to find the zero contours.

Singular points are found using Newton's method with a numerically computed Jacobian. Once a steady state is found, the Jacobian is computed and the QR algorithm is used to find the eigenvalues. These determine the stability of the singular point.

For certain steady states in the Morris-Lecar model, we want to find special trajectories called the unstable and stable manifolds. This is done by computing an eigenvector for a particular eigenvalue (the eigenvectors are tangent to these manifolds) by inverse iteration. Once the eigenvector is known, the equations are integrated (either forward or backward in time) with initial conditions that are on the eigenvector and slightly off of the singular point.

The qualitative behavior of higher dimensional systems as a parameter is varied can be understood and described compactly by determining the bifurcation diagrams. `AUTO` (Doedel 1981) was used in this chapter (through its interface with `XPP`) to trace, essentially automatically, the bifurcation curves as any parameter is varied. This program is able to find all steady states and periodic solutions regardless of their stability. The characteristics of stability, eigenvalues for steady states and Floquet exponents for periodic solutions, are computed along with the frequencies of periodic solutions. Two parameter bifurcation diagrams (similar to Figure 11C) which indicate where steady states and periodic solutions exist and they gain or lose stability can also be computed by `AUTO`.

The computation of the "infinitesimal PRC" is done automatically as part of the `XPP` package. Essentially, it solves an allied linear equation until a particular periodic orbit is found. The integral required for averaging is automatically computed.

A general and practical reference to many of the above numerical methods, which also leads to more literature is (Press, Flannery, Teukolsky, and Vetterling 1986).