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NONLINEAR OSCILLATIONS IN NEURONS MODELS

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ABSTRACT

Minimal models of the electro-chemical activity in nerve, muscle and secretory cells often require differential equation systems that have more than two time scales. An example is a phase model for neuronal parabolic bursting, which has three time scales. We review this model and show how the method of averaging is used to analyze this system.

1. INTRODUCTION

Nerve cells have highly nonlinear electrical properties. When a nerve cell is at its electro-chemical equilibrium (rest) there is a steady electrical potential difference across the membrane of the cell. In response to an external current stimulus the cell's membrane potential will (1) return to rest if the stimulus is subthreshold or; (2) generate a large amplitude spike called an *action potential* if the stimulus is above threshold. If a sustained current stimulus is applied that is suprathreshold, a train of repetitive actions potentials, sometimes in the form of relaxation oscillations, are observed. This periodic behavior is called *continuous* or *repetitive spiking*.

The most famous mathematical model of excitability in nerve cells, that is based on experiment, is the Hodgkin-Huxley (1952) system of differential equations. This landmark work won Hodgkin and Huxley the Nobel Prize for Physiology and Medicine in 1963. They measured and modeled the dynamics of ionic current flow across the cellular membrane of the squid axon. Their theory involved a set of four differential equations with functions and parameters fitted to data obtained from voltage-clamp experiments. (see Hille 1992 for elements of the Hodgkin-Huxley work and membrane biophysics.)

In 1976 Neher and Sakmann developed the patch-clamp technique to record current flow through a single ion channel, for which they too won the Nobel prize (see Hille 1992). Since the discovery of the patch-clamp, ionic current flows have been measured in a variety of cells allowing for the development of new mathematical models. Although the methods for collecting data have changed, the Hodgkin-Huxley theoretical framework continues to guide the formulation of new mathematical models.

Hodgkin-Huxley like models have the following general form (Rinzel and Ermentrout 1989):

$$\begin{aligned} C\frac{dv}{dt} &= -I_{ion}(v, w_1, ..., w_n) + I(t) \\ \frac{dw_k}{dt} &= \varphi_k[w_\infty(v) - w_k]/\tau_k \end{aligned} \tag{1}$$

where $v(t)$ is the membrane potential, C is its capacitance, and I_{ion} is the sum of all the ionic currents through the membrane. $I(t)$ is an external current and, for $k = 1, ..., n$, w_k are state variables that model the membrane channel gating processes; φ_k are temperature dependent parameters and τ_k time constants.

Inherent in Hodgkin-Huxley like systems are equations with multiple time scales. A simple example is the well known FitzHugh-Nagumo model (1960, 1962); a simplified two variable lumped caricature of the Hodgkin-Huxley system. The FitzHugh-Nagumo equations can be viewed as a minimal model for studying relaxation oscillations, a phenomena that requires at least two time scales. Most models have more than two time scales and the phenomena can be more complicated. Bursting, which we discuss below, is an example.

In general, minimal or canonical models of Hodgkin-Huxley like systems have a time hierarchical structure of the form

$$\frac{dx_k}{dt} = \epsilon_k f(x_1, ..., x_m)$$

with $x_k \in R^{n_k}, \sum n_k = n$ and $\varepsilon_k \ll \varepsilon_{k+1}$, for $k = 1, \ldots, m$. Systems of this kind, like their more complex counterparts, can be studied using quasi-steady state approximations, multi-scale and averaging methods.

Canonical systems have the added advantage that they are often analytically accessible. In the next section we describe bursting and in Section 3 we examine a minimal phase model, formulated by Baer, Rinzel and Carrillo (1995), which captures many dynamical features of more complex models for autonomous parabolic bursting. We then review how the method of averaging is employed to analyze the phase model.

2. BURSTING OSCILLATIONS

Besides repetitive spiking, some neurons are capable of a more complex pattern of nonlinear oscillations called *bursting*. Bursting is a periodic alternation between a phase of high frequency oscillations (action potentials) and a quiescent phase of slowly changing membrane potential (see Fig. 1). In parabolic bursting the frequency is lower at the beginning and the end of the active phase. In *autonomous* bursting the fast spike generating system is coupled to one or more subsystems which evolve on a slower time scale. There is a two-way interaction between the fast and slow subsystems; the fast variables play a crucial role in the slow dynamics. The most widely studied autonomous parabolic bursting neuron is the R-15 cell of the abdominal ganglion of the mollusk *Aplysia*. Figure 1 shows a typical parabolic bursting oscillations pattern; these were calculated (using $v = sin(\theta)$) with the phase-burster model that it is described in section 3.

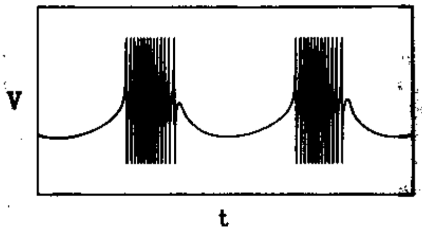

Figure 1. Parabolic bursting

Bursting in biological membranes has been studied experimentally by many authors and various theoretical models have been formulated. (e.g.: Baer, Rinzel and Carrillo 1995; Av-Ron, Parnas and Segel 1993; Smolen and Keizer 1992; Chay and Cook 1988; Plant and Kim 1976 and references there in). Before analyzing bursting models it is important to identify the fast and slow variables. In many biophysical models of bursting there are many equations, so it is often difficult to distinguish the fast from the slow subsystems (see Rinzel and Lee 1987 and more recently Butera, Clark and Byrne 1996). Once the fast/slow dynamics are resolved the system can be dissected using singular perturbation methods and formally classified. Following this approach, in 1987 Rinzel classified a variety of bursting mechanisms. More recently, Bertram, Butte and Sherman (1995) have shown how the various formal classifications of bursting can be extracted from a specific model, and in the process they found some hybrid classifications.

3. PHASE MODEL FOR AUTONOMOUS PARABOLIC BURSTING

Biophysical models of autonomous parabolic bursting require at least four state variables interacting: two variables for the spike generating mechanism and another two for the coupled slow oscillation. However, it is possible to model parabolic bursting with just three state variables if phase modeling is used to simplify the dynamics of the fast subsystem. This approach captures the timing of the burst oscillations but at a cost of losing information about the amplitude and shape of individual actions potentials. A three dimensional autonomous phase model for parabolic bursting, recently developed by Baer, Rinzel and Carrillo (1995) is governed by the following system of differential equations

$$\begin{aligned} \frac{d\theta}{dt} &= f(\theta) + A(x, y, I) \\ \frac{dx}{dt} &= \varepsilon_x[x_\infty(\theta) - x] \\ \frac{dy}{dt} &= \varepsilon_y[y_\infty(\theta) - y] \end{aligned} \qquad (2)$$

In this model the variable θ represents the phase of the fast oscillations (v varies proportional to $\sin\theta(t)$); x and y represent two competing state variables that operate on a slower time scale determined by the time constants $\varepsilon_x, \varepsilon_y \ll 1$. The slow subsystem affects the fast one through the activation function $A(x, y)$. The activation function is monotonically increasing with x and decreasing with y; therefore x and y constitute excitatory and inhibitory variables, respectively. I represents an external stimulus.

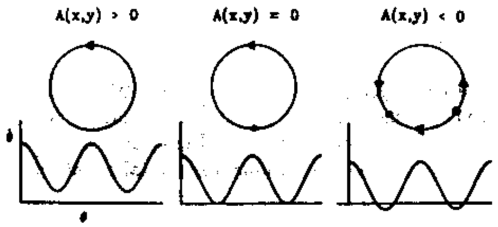

Figure 2. Ring dynamics of the fast subsystem with $f(\theta) = 1 - \cos(\theta)$.

All the functions of θ are 2π-periodic and therefore the fast subsystem dynamics occurs on a ring (Fig. 2). The functions x_∞, y_∞ are assumed to be increasing in the interval $-\pi/2 < \theta < 0$, and the image of the function A contains an interval centered in $f_m = \min\{f(\theta)\}$.

When $A > -f_m$ the angle θ increases through multiples of 2π, causing continuous spiking. At $A = -f_m$, the fast system undergoes a homoclinic bifurcation that coincides with a saddle node bifurcation. This bifurcation destroys the periodic orbit responsible for the continuous spiking behavior and creates an unstable node and a saddle in the fast system that persists for $A < -f_m$ (Fig.2). Correspondingly, as A varies through values less than $-f_m$, the two equilibria of the fast system generate respectively, 2-dimensional stable and unstable quasi-steady state manifolds M^s and M^u, immersed in the 3-dimensional state space of the full system. Manifolds M^s and M^u intersect smoothly forming a 3-dimensional curve that projects onto the plane of the slow variables x, y; the curve is given by equation $A(x, y, I) = -f_m$. This plane curve constitutes a boundary between a "silent" and an "oscillatory region," $\mathcal{S}$ and $\mathcal{O}$. It is called the *homoclinic boundary* (HB), for when the (x, y) trajectory crosses it, the fast system (whose phase variable is θ) undergoes a homoclinic bifurcation; when $(x, y) \in \mathcal{O}$, the potential ($v = \sin\theta$) oscillates rapidly, when $(x, y) \in \mathcal{S}$ the angle θ tracks the slow manifold M^s and hence the potential slowly varies.

Let $\theta_s(x, y)$ be the function that generates the manifold M^s, for $(x, y) \in \mathcal{S}$ close to the homoclinic boundary. The solution $(\theta(t), x(t), y(t))$ of the full system (E), which projects into the silent region ($\mathcal{S}$), rapidly approaches M^s. This is the quiescent phase of the burst oscillation. The solution slowly varies on M^s for as long as the projected trajectory remains in $\mathcal{S}$. Quasi-steady state manifold theory (Hoppensteadt 1966) approximates the slow dynamics, if $\varepsilon_x, \varepsilon_y \ll 1$, by the differential equations

$$\begin{aligned} \frac{dx}{dt} &= \varepsilon_x[x_\infty(\theta_s(x, y)) - x] \qquad (3) \\ \frac{dy}{dt} &= \varepsilon_y[y_\infty(\theta_s(x, y)) - y]. \end{aligned}$$

However, if the behavior of the solution $(\theta(t), x(t), y(t))$ is such that its projection $(x(t), y(t))$ passes through the HB and into the oscillatory region $\mathcal{O}$, then the quasi-steady state approximation breaks down. In this case the averaging method (Carrillo 1984, Verlhust and Sanders 1985) approximates the slow dynamics, if $\varepsilon_x, \varepsilon_y \ll 1$, by the equations

$$\begin{aligned} \frac{dx}{dt} &= \varepsilon_x[\bar{x}_\infty(A(x, y)) - x] \qquad (4) \\ \frac{dy}{dt} &= \varepsilon_y[\bar{y}_\infty(A(x, y)) - y]. \end{aligned}$$

where

$$\begin{aligned} \bar{x}_\infty(A) &= \left(\int_0^{2\pi} \frac{d\theta}{f(\theta)}\right)^{-1} \int_0^{2\pi} \frac{x_\infty(\theta)}{f(\theta)} d\theta, \\ \bar{y}_\infty(A) &= \left(\int_0^{2\pi} \frac{d\theta}{f(\theta)}\right)^{-1} \int_0^{2\pi} \frac{y_\infty(\theta)}{f(\theta)} d\theta. \end{aligned}$$

According to this scheme of analysis, the periodic nonlinear patterns of oscillations (bursting) will occur when the slow (reduced) system given by equations (3) - (4) has a closed orbit that crosses HB.

The singular perturbation approximation, the reduced system (3)–(4), is analytically tractable if the functions in the model are trigonometric. Figure 3 is a bifurcation diagram of the system for the functions: $f(\theta) = 1 - \cos(\theta)$; $x_\infty(\theta) = \sin(\theta - 1.3)$; $y_\infty(\theta) = \sin(\theta - 0.4)$; $A(x, y, I) = \tanh(2x - 5y + I)$ and the parameters values $\varepsilon_x = 0.01, \varepsilon_y = 0.0012$. On the horizontal axis appears the external stimulus I, which is chosen as the bifurcation parameter. On the vertical axis maximum and minimum values of the activation function A (for the reduced system) are plotted for each I.

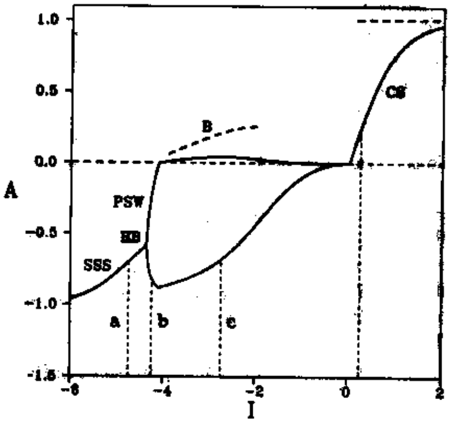

Figure 3. Bifurcations diagram of the reduced system (3) - (4).

For low values of I, the system (3)–(4) converges to a stable steady state (SSS) in the silent region and the full system (2) does the same. Close to $I = -4.42$, there is an Andronov- Hopf bifurcation to periodic solutions; the maximum and minimum values of A are plotted (see b). When the full system tracks this orbit, a slow periodic oscillation in θ is observed. This corresponds to a pure slow wave oscillation of the membrane potential that looks like a bursting pattern without spikes. In this parameter range, since $\varepsilon_y \ll \varepsilon_x$, the pure slow wave is a relaxation oscillation. As I increases, the amplitude of this oscillation grows until it reaches HB, which for this example is the line $A = 0$. For greater values of I (see c), the maximun and minimun values of A have opposite signs, this makes the full system to alternate between periods of high frequency oscillations and periods of quiescence (Fig. 1). The dashed curves in the diagram plot the fraction of the period of the bursting solution that is spent in the active phase (same scale used for A). In the upper range of I the activation function A takes values larger than zero and consequently the full system displays continuous spiking (CS); the reduced system converges to a stable steady state in $\mathcal{O}$.

Although the phase model constitutes a simple mathematical representation of parabolic bursting, the results of our analysis agree qualitatively with the results of simulations that have been carried out for higher dimensional models of Aplysia. The phase model captures the fundamental dynamical structure of parabolic bursting.

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