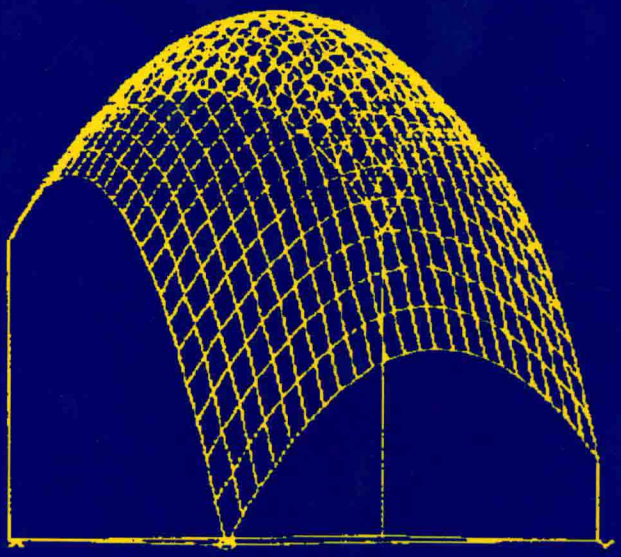
Proceedings of the International Conference on Mathematical Biology

Advanced Topics in Biomathematics



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Advanced Topics in Biomathematics

PREFACE

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The Twentieth Century has seen the dawning of mathematical biology, and witnessed its maturation. It has been an international enterprise, emerging from the work of the great mathematician Volterra in Italy; from Lotka in the United States and Kostitzyn in the Soviet Union; and from a succession of monumental contributions in population genetics from Fisher and Haldane in the United Kingdom, Wright in the Unites States, and Kimura in Japan. The development was so rapid and wide that it would be impossible to do justice to the scope and extent of the multiple lines that developed, but it is unlikely that any nation has been left untouched. China, in particular, has seen a rapid development of the subject through the contributions of numerous scholars, many represented in this volume, in recognition of the fact that many of the problems that mathematics can best help to address-population growth and its environmental consequences, pollution and the loss of healthy ecosystems, the spread of infectious diseases and the need for assuring a sustainable future-have a particular relevance to that great nation. It is noteworthy and timely that an international congress on mathematical biology be held in China, in conjunction with the publication of the first issue of a new Chinese journal on the subject (*Bulletin of Biomathematics*), attesting to the entry of China as a major international center for research in mathematical biology. Similar conferences have been held recently in Europe, Japan, India, Israel, Africa and the Americas, showing the international growth of the subject.

The diversification of mathematical biology in terms of its participants has been matched by a diversification and maturation of the subject matter. Research in mathematical biology, restricted in its early states to a few areas of biology, has advanced at the same blinding speed as has biological and medical research. Fundamental contributions are being made not only in population biology, but also in neurobiology, immunology, epidemiology, physiology, development, protein folding and sequence analysis, among other areas. The mathematical methods used include sophisticated statistical analyses, deterministic and stochastic dynamical models, topological methods and high speed computation, among others. Most notably, even as the biological and mathematical methods have grown in sophistication, the connections between mathematics and biology have become stronger, and the participants on all sides have broadened their understanding of the complementary fields.

The result has been that mathematical biologists spend less time than they once did in meetings such as that which gave rise to this volume, and more at meetings that address their specific disciplinary interests. In this, they are indistinguishable from their more biological colleagues, a positive sign of the degree to which mathematical methods and mathematicians themselves have become integrated into biological research. This is, in all regards, an impressive development.

Yet meetings like the one that stimulated this volume serve an essential role. They allow scientists in different disciplines to educate one another about problems in other areas of biology, and they help in the cross-fertilization that comes from the exploration of common themes, such as pattern formation, self-organization and collective dynamics, not to mention the now standard bodies of research in statistics and dynamical systems theory. Thus, on behalf of all of the participants, I thank the Chinese organizers who made this meeting possible, and hope that it will be the beginning of a tradition.

Simon Levin
Co-Chair
June 10, 1997

CONTENTS

BURSTING OSCILLATIONS IN AN IDEALIZED MODEL FOR AN ACTIVITY-DEPENDENT SPINE

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Dendritic spines are the major target for excitatory synaptic inputs in the vertebrate brain. In recent years they have become the focus of many biochemical, biophysical, and modeling studies, and are considered to be important loci for plastic changes underlying memory and learning processes. We formulate and analyze an ordinary differential equation model for an activity-dependent spine with active membrane channels in the head. In the model the spine stem conductance depends (slowly) on the local electrical interactions between the spine head and the dendritic cable; parameter regimes are found for bursting, steady-states, continuous spiking, and more complex oscillatory behavior. We show that solutions to this system approximate the dynamics of a full (partial differential equation) cable description of the model when the spine head membrane potential exhibits relaxation oscillations.

1 Introduction

Dendritic spines, which are small evaginations of the dendritic surface of several functionally important classes of nerve cells, are a major target for excitatory synaptic inputs in the vertebrate brain. Recent studies estimate that over 90% of central nervous system synapses occur on spines and that they are considered to be an important locus for plastic changes underlying memory and learning processes (see the excellent review articles by Harris and Kater [1], and Shepherd [2]).

Spines have a general knoblike appearance of a bulbous head and a tenuous stem. Typical dimensions include stem lengths of order $1.0\mu m$ with diameters of order $0.1\mu m$ and head surface areas of order $1.0\mu m^2$. Spines have different sizes, shapes and configurations. The stems can be long or short, fat or thin, branched or unbranched. The heads can be small or large but are usually globular in shape. There can be two-headed spines and a spine head can have multiple transmission zones. Evidence that synaptic morphology may be activity-dependent [3] and that spine head membrane may be endowed with voltage-dependent (excitable) channels [4] is the motivation for this present study.

Recently, Wu and Baer [5] formulated a cable equation with a single spine boundary condition located at $X = 0$ and a sealed end boundary condition at $X = L$, to explore the threshold and dynamical properties of an excitable spine

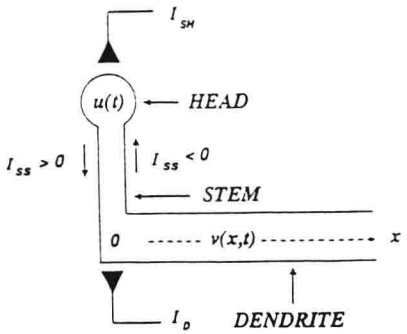


Figure 1: A schematic of a dendritic spine attached to a passive cable.

when a synaptic input (I_{SH}) and a dendritic input at the spine base (I_D) are modeled as steady current sources (see Fig. 1). They examined the possibility that the spine stem resistance (R_{ss}) is activity-dependent. Their idealized hypothesis was that a spine with passive membrane bombarded by synaptic activity tends to strengthen its electrical connection to the dendrite over time, but if this activity decreases to the extent that the dendritic current source dominates, then a passive spine tends to become more isolated (electrically) over time. To explore this hypothesis they assumed that the time rate of change of the spine stem conductance ($G_{ss} = 1/R_{ss}$) is proportional to the current through the stem (I_{ss}); i.e., $dG_{ss}/dt = \epsilon I_{ss}$, where $\epsilon \ll 1$. Activity that drives I_{ss} from the spine head to the dendrite ($I_{ss} > 0$) slowly increases G_{ss}, and dendritic input that drives the current from the dendrite to the head ($I_{ss} < 0$) slowly decreases G_{ss}. When excitable channels were then added to the membrane properties of the spine head, the cable model generated different patterns of electrical activity. This activity ranged from continuous spiking to irregular and regular bursting oscillations to constant steady-states; and the electrical length of the dendrite controlled transitions between these modes of electrical activity (see Fig. 3a).

Wu and Baer proposed a simplified model to replace the cable equation when the spine head membrane exhibits relaxation oscillations. In this paper we give a heuristic formulation of this simple model, investigate its dynamical properties analytically and numerically, and show that its solutions approximate the dynamics of the full cable description. In Section 2 we formulate the model. In Section 3 we investigate analytically the static spine case; i.e., when G_{ss} is fixed. Finally, in Section 4, we investigate the dynamics of the model when the spine is activity-dependent.

2 A simplified model for an activity-dependent spine

In this section we give a heuristic derivation of a simple model for an activity-dependent spine with relaxation oscillator kinetics. The derivation is based on observations we made integrating the full system [Eqs. (10)-(15) in the paper by Wu and Baer], which consists of a single dendritic spine with FitzHugh-Nagumo (FHN) kinetics attached, at $X = 0$, to a dendritic cable of electrotonic length L. As described in the last section, the cable is sealed at $X = L$; a constant synaptic current input I_{SH} is applied at the spine head; and a constant dendritic input I_D is applied at the spine base. The FHN system exhibits relaxation oscillations for $b \ll 1$.

We observed that when the spine head potential $u(t)$ is a relaxation oscillator, the oscillations penetrate far into the cable with little phase lag and for most of the cycle the dendritic potential tracks the steady-state manifold

$$v(X,t) = v_s(u(t)) \; \frac{\cosh(L-X)}{\cosh L}, \tag{1}$$

where v_s is the membrane potential at the spine base, which depends on $u(t)$. The form of Eq. (1) is easily derived by solving the steady-state passive cable equation, treating v_s as a constant command potential applied at $X = 0$ and imposing a sealed end boundary condition at $X = L$.

We can derive the functional form for $v_s(u)$ directly from the equations (see Wu and Baer), but instead we deduce it from conservation of current at the spine base. First note that the input resistance (see Rall [6]) at the spine base (for the above boundary conditions) is

$$R_{SB} \; = \; R_\infty \; \coth L \tag{2}$$

where the resistance $R_\infty = (2/\pi)(R_m R_i)^{1/2}(d)^{-3/2}$ depends on the cable's membrane resistivity R_m, cytoplasmic resistivity R_i, and diameter d. We next observe that the current at the spine base $v_s(u)/R_{SB}$ has two components: (1) the fraction of head membrane current flowing through the stem and (2) the fraction of dendritic input current that contributes to flow down the dendrite; i.e.,

$$\frac{v_s(u)}{R_{SB}} = G_{ss} \left(\frac{R_{ss}\, u}{R_{ss} + R_{SB}}\right) + \left(\frac{G_{SB}}{G_{SB} + G_{ss}}\right) I_D, \tag{3}$$

where $G_{SB} = 1/R_{SB}$ is the input conductance at the spine base. Multiplying Eq. (3) by R_{SB}, and expressing R_{SB} and G_{SB} in terms of R_∞ and L, v_s can be recast into the following more concise form:

$$v_s(u) \; = \; R_\infty \left(\frac{G_{ss}\, u + \; I_D}{R_\infty\, G_{ss} \; + \; \tanh L}\right). \tag{4}$$

The potential in the head $u(t)$ remains to be determined. Again, from conservation of current, the capacitive current in the spine head must balance with the ionic current, the spine stem current I_{ss}, and the synaptic current I_{SH}. Since we are assuming that the ionic current is governed by FHN kinetics, the simplified model for an activity-dependent spine is

$$\frac{du}{dt} = -f(u) - w - I_{ss} + I_{SH} \tag{5}$$

$$\frac{dw}{dt} = b\,(u - \gamma w) \qquad b \ll 1 \tag{6}$$

$$\frac{dG_{ss}}{dt} = \epsilon\, I_{ss} \qquad \epsilon \ll b, \tag{7}$$

where $f(u)$ is a cubic-shaped function given by

$$f(u) = u(u-1)(u-a) \qquad 0 < a < \frac{1}{2}, \tag{8}$$

and I_{ss} is the stem current defined by

$$I_{ss} = G_{ss}\,[u - v_s(u)]. \tag{9}$$

Equation (5) reflects the current balance relation in the head, and from Eq. (9), if $I_{ss} > 0$ current passes from the head to the dendrite and if $I_{ss} < 0$ current passes from dendrite to head. The parameters b and γ are positive constants and $w(t)$ represents a recovery current which, according to (6), responds slowly, when b is small, to changes in u.

The activity-dependent stem conductance is modeled by Eq. (7). This slow equation provides bi-direction coupling to the fast subsystem through I_{ss}. Note that activity that drives I_{ss} from the spine head to the dendrite ($I_{ss} > 0$) slowly increases G_{ss}, and dendritic input that drives the current from the dendrite to the head ($I_{ss} < 0$) slowly decreases G_{ss}. Our simplified model is related to the FitzHugh-Rinzel model (FHR) formulated in 1976 by FitzHugh and Rinzel (unpublished) and later analyzed by Rinzel[7].

3 The static spine

It is instructive to first analyze the reduced case when G_{ss} is fixed in Eqs. (5)-(7). When the spine stem conductance is fixed, $\epsilon = 0$ in Eq. (7), the system reduces to a modified FHN equation of the form

$$\frac{du}{dt} = -f(u) - w - G_{ss}\,[u - v_s(u)] + I_{SH} \tag{10}$$

$$\frac{dw}{dt} = b\,(u - \gamma w) \qquad b \ll 1, \tag{11}$$

where G_{ss} is constant.

Multiple steady-states are possible but a condition guaranteeing that there is exactly one is

$$\frac{1}{\gamma} > \frac{1}{3}(1 - a + a^2) - \frac{G_{ss}\tanh L}{R_\infty G_{ss} + \tanh L}. \tag{12}$$

This condition is identical to the one derived by Wu and Baer for the full cable model.

The steady-state solution to Eqs. (10)-(11) is

$$w_s = u_s/\gamma\,, \quad I_{SH} = f(u_s) + u_s/\gamma + G_{ss}[u_s - v_s(u_s)]. \tag{13}$$

To analyze stability, we consider small perturbations of the form $u = u_s + pe^{\mu t}$ and $w = w_s + qe^{\mu t}$ where $|p| \ll 1$ and $|q| \ll 1$. This leads to the following characteristic equation for μ

$$\mu^2 + A\mu + B = 0 \tag{14}$$

where

$$A = f'(u_s(I_{SH})) + b\gamma + \frac{G_{ss}\tanh L}{R_\infty G_{ss} + \tanh L} \tag{15}$$

$$B = b(1 - b\gamma^2) + Ab\gamma. \tag{16}$$

The steady-state is stable (unstable) if $A > 0$, $B > 0$ ($A < 0$ and/or $B < 0$). From the conditions $A = 0$ and $B > 0$ we find two Hopf points, $I_{SH} = I_{SH}^{\pm}$. They satisfy

$$u_s^{\pm} = \frac{1}{3}\left(a + 1 \pm \sqrt{a^2 - a + 1 - 3b\gamma - \frac{3\,G_{ss}\tanh L}{R_\infty G_{ss} + \tanh L}}\right) \tag{17}$$

where $I_{SH}^{\pm}$ are found by back-substituting (17) into the second equation in (13). The frequency at the Hopf point,

$$\omega_0 = \sqrt{b(1 - b\gamma^2)}, \tag{18}$$

is independent of L and G_{ss}. It is important to note that in the full cable model the frequency at the Hopf point **does** depend on L and G_{ss}, however our numerical simulations indicate that variations in the frequency are less than 5% relative error when compared to the above expression.

Figure 2 is a two-parameter (I_{SH} vs. G_{ss}) bifurcation diagram of Hopf points for $I_D = 0$ and five values of L. The stability boundaries are generated

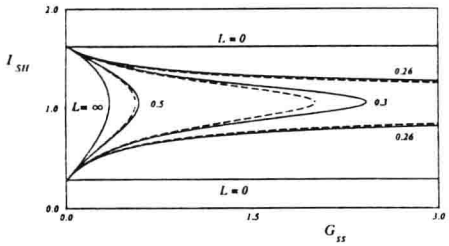


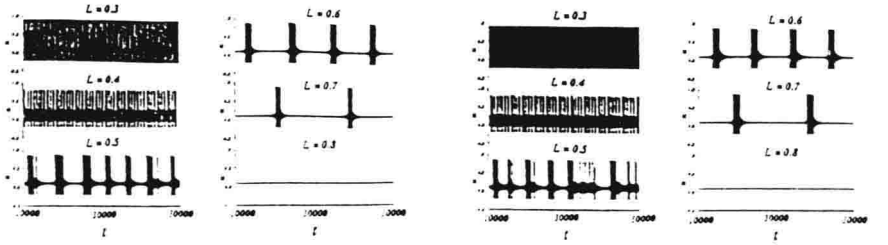
Figure 2: Stability boundaries for five electrotonic lengths.

analytically from (17) and (13) using supercritical FHN parameter values $a = 0.2$, $b = 0.05$, $\gamma = 0.4$, and cable parameter $R_\infty = 1$. For comparison, the dashed curves shown are the stability boundaries computed from the full cable model. For $L > 0.26$, the upper and lower curves of the stability boundaries coalesce at a limit point. If we denote the critical value at a limit point as G^*_{ss}, then for each value of $G_{ss} < G^*_{ss}$ there are two Hopf points, I^+_{SH} and I^-_{SH} . Within the interval $I^-_{SH} < I_{SH} < I^+_{SH}$ solutions to system (10)-(11) are periodic, outside the interval there are stable steady-state solutions. For $G_{ss} > G^*_{ss}$, only steady-state solutions exist; the voltage sensitive ion channels in the spine head are exposed to too much conductive loading.

Decreasing the length of the cable decreases the conductance loading, and therefore the limit point G^*_{ss} increases. However, there exists a critical length, L_{cr}, below which oscillations exist for all values of G_{ss} (In Fig. 2, $L_{cr} \doteq 0.260$). The biological explanation is simple if one imagines a short cable with an infinite stem conductance ($G_{ss} \to \infty$). The large stem conductance effectively merges (electrically) the spine head membrane into the dendritic membrane, but since the dendrite is short there is not enough dendritic membrane to overload the excitability of the spine head membrane. We can obtain an analytic estimate of L_{cr}. Fixing L small ($\tanh L \sim L$) and letting G_{ss} approach infinity the Hopf points coalesce when the expression under the square root sign in (17) vanishes, i.e., when $L = L_{cr}$ where

$$L_{cr} = \frac{R_\infty}{3} (a^2 - a + 1 - 3\, b\gamma) \,. \tag{19}$$

Thus, for $L \leq L_{cr}$ oscillations exist for all values of G_{ss} , and for $L > L_{cr}$ there exists a finite stem conductance G^*_{ss}; if $G_{ss} > G^*_{ss}$ oscillations are precluded. The expression for L_{cr} is asymptotically equivalent (as $b \to 0$) to the one derived for the full cable model [see Eq. (42) in Wu and Baer].



a The full cable model

b The simplified model

Figure 3: The pattern of electrical activity in the spine head depends on the electrical length.

4 The dynamics of an activity-dependent spine

In this final section we consider the effect of an activity-dependent stem conductance on the excitability properties of a dendritic spine. We show that the simplified model not only captures the dynamics of the full cable system but is also an excellent approximation.

When $\epsilon \ll 1$ in (7), the stem conductance, G_{ss}, is a slow variable rather than a fixed parameter. Figure 3b shows that the simplified model [Eqs. (5)-(7)] reproduces the patterns of oscillations in the full model (Fig. 3a) and over, approximately, the same range of electrotonic lengths. The simulations exhibit steady-state patterns of oscillations after initial transients have decayed for $I_{SH} = 0.04$ and $I_D = 0.2$. The parameters ($a = 0.14, b = 0.008, \gamma = 2.54$) are chosen so that Hopf bifurcations to periodic solutions are subcritical and $R_\infty = \pi^{-1}$. When the cable is electrically short, the spine head potential oscillates with periodic spikes ($L = 0.3$). As the length increases ($0.3 < L < 0.4$) the periodic spiking becomes intermittent spiking and the continuous spike pattern disorganizes. Burst solutions dominate as L increases, but for electrical lengths sufficiently large (e.g., $L = 0.8$) only steady-state solutions exist.

As in the full cable model, the simplified system exhibits autonomous bursting. In Fig. 4, the burst solution of Fig. 3b for $L = 0.6$, is projected onto the G_{ss}-u plane. Superimposed is the bifurcation diagram of the fast subsystem (5)-(6) for fixed values of G_{ss}. Note the characteristic decay and growth of the small oscillations during the silent phase. The point of transition from decaying to growing oscillations is precisely the Hopf bifurcation point of the corresponding static problem; i.e., when $Re[\mu(G_{ss})] = 0$, where μ is an