Spontaneous Secondary Spiking in Excitable Cells

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Kepler & Marder (1993, Biol. Cybern. 68, 209–214) proposed a model describing the electrical activity of a crab neuron in which a train of directly induced action potentials is sometimes followed by one or more spontaneous action potentials, referred to as spontaneous secondary spikes. We reduce their five-dimensional model to three dimensions in two different ways in order to gain insight into the mechanism underlying the spontaneous spikes. We then treat a slowly varying current as a parameter in order to give a qualitative explanation of the phenomenon using phase-plane and bifurcation analysis. We demonstrate that a three-dimensional model, consisting of a two-dimensional excitable system plus a slow inward current, is sufficient to produce the behaviour observed in the original model. The exact dynamics of the excitable system are not important, but the relative time constant and amplitude of the slow inward current are crucial. Using the numerical bifurcation analysis package AUTO (Doedel & Kernevez, 1986, AUTO: Software for Continuation and Bifurcation Problems in Ordinary Differential Equations. California Institute of Technology), we compute bifurcation diagrams using the maximum amplitude of the slow inward current as the bifurcation parameter. The full and reduced models have a stable resting potential for all values of the bifurcation parameter. At a critical value of the bifurcation parameter, a stable tonic firing mode arises via a saddle-node of periodic bifurcation. Whether or not the models can exhibit transient or continuous spontaneous spiking depends on their position in parameter space relative to this saddle-node of periodicities.

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1. Introduction

In the space-clamped (spatially uniform) Hodgkin–Huxley (1952) equations, a sufficiently large brief depolarizing current pulse results in a single action potential followed directly by a return to the resting potential. A series of these depolarizing pulses results in a train of directly induced action potentials again followed by a return to rest. The addition of a single inward current activated by depolarization with slow first-order kinetics can substantially enrich this behaviour. A model incorporating such a current was proposed by Kepler & Marder (1993) to describe the spontaneous initiation of action potentials in a crab neuron. They showed that their model could exhibit “extra” or “spontaneous” action potentials following a train of directly induced action potentials. The number of spontaneous action potentials depended both on the number of action potentials in the initial spike train and on the frequency of stimulation.

The Kepler and Marder model was motivated by some experimental work by Meyrand et al. (1992) on the lateral gastric (LG) neuron of the stomatogastric nervous system of the crab Cancer borealis. Meyrand et al. found that under certain conditions, action potentials traveling along the axon of an LG neuron can spontaneously initiate additional action potentials.
at peripheral sites up to 2 cm away from the stomatogastric ganglion. The number of peripherally initiated action potentials was strongly influenced by the presence of the neurotransmitter, serotonin, as well as an imposed depolarization of the soma. Since the duration of the train of peripherally initiated action potentials could be controlled by current injection into the soma, they suggested that a slow voltage-dependent conductance might be responsible for initiation of the additional spikes.

The crab neuron is not the only place where seemingly spontaneous action potentials arise following trains of directly induced action potentials. Indeed, apparently spontaneous action potentials known as delayed afterdepolarization-induced triggered activity in cardiac cells bear a remarkable resemblance to the Kepler and Marder spontaneous secondary spiking. This kind of triggered activity has been known to occur in the presence of various drugs, such as catecholamines and cardiac glycosides, and under other unusual conditions in the simian mitral valve (Wit & Crane, 1976), the canine coronary sinus (Wit & Crane, 1977), and canine Purkinje fibers (Valenzuela & Vassalle, 1983; Ferrier & Moe, 1973; Ferrier et al., 1973). It is suspected to play a role in the genesis of a number of cardiac arrhythmias (Antzelevitch & Sicouri, 1994). The clinical importance of triggered activity provides us with ample motivation for studying the simpler, yet seemingly related, phenomenon of spontaneous secondary spiking.

In this paper, we examine the space-clamped version of the Kepler and Marder model to see how spontaneous secondary spikes are initiated and how the parameters of the model affect their initiation. We begin by introducing the Kepler and Marder model. To gain a better understanding of how this five-dimensional model produces spontaneous action potentials, we reduce it to two distinct three-dimensional models by different methods. We then treat the slow inward current in these reduced models as a parameter, further reducing them to two dimensions. Using the resulting two-dimensional models, we use a combination of phase-plane and bifurcation analysis to explain the phenomenon qualitatively.

We then return to the full three-dimensional and five-dimensional models to explain how certain critical parameters, which affect the amplitude and time constant of the slow inward current, determine the occurrence of spontaneous spikes. Using a combination of analytical and numerical bifurcation analysis, we predict when the models are likely to respond with spontaneous spikes. We demonstrate that both of the three-dimensional models yield the same qualitative behaviours as the original five-dimensional model. Furthermore, we show that one of the three-dimensional models collapses to two dimensions if the slow inward current is too fast and, hence, no longer exhibits spontaneous spikes. The other two models also lose their ability to generate spontaneous spikes as the time constant of the slow inward current is decreased, thus highlighting the importance of the relative time constants in these models. Lastly, we predict numerically the circumstances under which spontaneous spiking can occur when the time constant of the slow inward current is large, thus double checking the results from our earlier bifurcation analysis.

2. The Mathematical Model

The Kepler and Marder (KM) model is given by the following system of equations:

\[
\frac{dv}{dt} = -I_{HH}(v,m,h,n) + zI_s + I_{app}(t),
\]

\[
\frac{dm}{dt} = \frac{m_x(v) - m}{\tau_m(v)},
\]

\[
\frac{dh}{dt} = \frac{h_x(v) - h}{\tau_h(v)},
\]

\[
\frac{dn}{dt} = \frac{n_x(v) - n}{\tau_n(v)},
\]

\[
\frac{dz}{dt} = k_s [\theta(v - V_T) - z]
\]

where

\[
I_{HH}(v,m,h,n) = \tilde{g}_N m^3 h(v - v_N) + \tilde{g}_K n^4 (v - v_K) + \tilde{g}_L (v - v_L).
\]
Equation (1) relates the transmembrane potential $v$ to the membrane currents according to Kirchoff’s current law. The left-hand side of this equation describes the capacitive effect of the membrane, and the successive terms on the right-hand side represent the Hodgkin–Huxley-type dynamics for the Na$^+$, K$^+$, and leakage currents, the slow inward current $(zI_s)$, and an applied (injected) current $(I_{app})$. The maximum conductances of the Na$^+$, K$^+$, and leakage currents are denoted by $g_{Na}$, $g_K$, and $g_L$, respectively, while $v_{Na}$, $v_K$, and $v_L$ are the reversal potentials. These currents are modulated by the gating variables $m, h, n$, which are assumed to obey the relaxation eqns (2)–(4). The voltage dependencies of the activation curves $(m_x, h_x, n_x)$ and the time constants $(\tau_m, \tau_h, \tau_n)$, as well as the parameters of the model, are listed in the appendix.

The slow inward current, which we will refer to as $I_s$, consists of an amplitude parameter $I_s$ and a gating conductance $z$, which increases and decreases slowly when $v$ is above and below $V_T$, respectively, according to the relaxation eqn (5). Since spiking in the soma seemed to be required for peripheral spike initiation, Kepler and Marder assumed that the slow inward current would activate only above the spike threshold of $-45$ mV for the soma. Thus, they chose $V_T > -45$ mV. Rather than using the Kepler and Marder step function

$$\theta(v - V_T) = \begin{cases} 1, & v - V_T \geq 0, \\ 0, & v - V_T < 0, \end{cases}$$

(7)

to describe the activation curve, we used the smoother sigmoidal function

$$\theta(v - V_T) = 0.5(1 + \tanh [c(v - V_T)])$$

(8)

with $c = 55$ mV$^{-1}$ to smooth out the discontinuity at $V_T$. The rate constant $k_s$ was assumed to be small because several depolarizations were required before any peripheral spiking occurred. In order to account for the dependence of the peripheral spiking on serotonin, the amplitude parameter $I_s$ was assumed to be a graded function of the serotonin concentration. Thus, high and low values of $I_s$ correspond to high and low values of serotonin concentration, respectively.

Kepler and Marder demonstrated that if two current pulses are applied to their model axon, then three qualitatively different outcomes can be observed, as shown in Fig. 1. [The simulations for the systems of ordinary differential equations were performed using the numerical package LSODE (Hindmarsh, 1983).] For sufficiently low $I_s$ (low serotonin concentration) and low applied current frequency, only the two directly initiated action potentials are observed [Fig. 1(a)]. This type of behaviour is typical of a Hodgkin–Huxley-type model lacking the slow inward current. For a higher applied current frequency, several extra action potentials, which Kepler and Marder refer to as spontaneous secondary spikes, can occur [Fig. 1(b)]. If $I_s$ is sufficiently high [Fig. 1(c)], the two directly initiated action potentials may be followed by continuous spontaneous secondary spiking which will go on indefinitely.

3. Simplified Models

Since the ionic currents involved in spontaneous secondary spike initiation in the LG neuron have neither been identified nor characterized, the Kepler and Marder model is a qualitative, not a quantitative, model. They demonstrated that a slow inward current interacting with a standard excitable system [the Hodgkin-Huxley (HH) equations] can result in the initiation of secondary spikes. To determine which components of the KM model are required for the initiation of secondary spikes, we consider two simplified models which approximate the four-dimensional excitable subsystem by two-dimensional subsystems, preserving the one-dimensional inward current. We show that the two simplified models maintain the important qualitative behaviour of the system.

3.1. FITZHUGH–NAGUMO APPROXIMATION

The FitzHugh–Nagumo (FHN) equations exhibit many of the properties of the HH equations and yet lend themselves to analytical techniques and phase-plane analysis. Although they represent a caricature of the HH equations, we find that
FIG. 1. The response of the Kepler and Marder space-clamped model axon when two rectangular current pulses ($I_{app}$) of amplitude 100 $\mu$A and duration 1.25 ms are applied. The qualitative response depends on the amplitude $I_s$ of the z-current and the frequency $f$ of the applied current pulses. When $f = 65$ Hz, the lag between the beginning of the first and second current pulses is 15.4 ms, and when $f = 100$ Hz, the lag is 10.0 ms. (Based on Fig. 1 in Kepler & Marder, 1993.)

FIG. 2. The responses of $V$ (solid line), $W$ (lower dashed line), and $z$ (upper dashed line) in the ZFN model when four current pulses ($I_{app}$) of amplitude 0.1 and duration 0.5 are applied for different values of $I_s$ and applied current frequency $f$. (Note: If the unit of time in these dimensionless equations is considered to be ms, then the unit of frequency shown here would be Hz.)

replacing the HH variables in the KM model by the FHN variables preserves the qualitative behaviour (see Fig. 2). The resulting model, which we call the ZFN model, is given by

\[
\frac{dV}{dt} = - V(V-a)(V-1) - W + zI_s + I_{app}(t), \tag{9}
\]

\[
\frac{dW}{dt} = \varepsilon(V - rW), \tag{10}
\]

\[
\frac{dz}{dt} = k_s[\theta(V - V_T) - z] \tag{11}
\]

where $\theta(V - V_T)$ is given by eqn (8), and we have chosen $a = 0.1, \quad r = 2.5, \quad \varepsilon = 0.01, \quad k_s = 0.005, \quad V_T = 0.3, \quad$ and $c = 55$. These parameters were chosen to ensure that (a) the FHN equations are excitable (not bistable), (b) the time constant of the slow inward current is larger than the time constants of the excitable subsystem, (c) the smooth activation curve $\theta(V - V_T)$ approximates a step function, and (d) $V_T$ is above the threshold for initiation of an action potential.

Finally, note that we speed up the time scale by a factor of ten in these dimensionless equations so that all results, including simulations and periods in bifurcation diagrams, shown in this paper appear to be on roughly the same time-scale as the original KM model. For the sake of comparison, we will consider time in the ZFN equations to be
measured in ms. The time scaling is achieved by multiplying the right-hand sides of the ZFN equations (9)–(11) by a factor of ten.

3.2. APPROXIMATION OF THE KM MODEL

The ZFN model derived above is little more than a caricature of the KM model. While still exhibiting the same spontaneous spiking behaviour, it differs qualitatively from the KM model in a number of ways. (Compare the shapes of the action potentials in the simulations in Figs 1 and 2, for instance.) In order to obtain a simple three-dimensional model which more accurately reflects the qualitative features of the original KM model, we reduced the Hodgkin–Huxley equations using a technique motivated by the method of equivalent potentials (Kepler et al., 1992). The key idea that we have borrowed from the method of equivalent potentials is to transform all of the gating variables into dimensionally equivalent forms and then utilize the exposed degeneracies in the system of equations to reduce the order of the system.

The relaxation equations for \( m, h, \) and \( n \) all have the form

\[
d\frac{dx}{dt} = \frac{x_\infty(v) - x}{\tau_x(v)}. \tag{12}
\]

Since \( x_\infty(v) \) is a monotonic function of \( v \), we can make the transformation \( x = x_\infty(\bar{v}_x) \) where \( \bar{v}_x \) is the new equivalent potential. Using the chain rule, eqn (12) can be written as

\[
d\frac{d\bar{v}_x}{dt} = \frac{x_\infty(v) - x_\infty(\bar{v}_x)}{\tau_x(v)x'_\infty(\bar{v}_x)}. \tag{13}
\]

Therefore, the Hodgkin–Huxley equations (1)–(4) can be rewritten in terms of the variables \( v, \bar{v}_m, \bar{v}_h, \) and \( \bar{v}_n \), so that all of the variables now are dimensionally equivalent. This change of variables reveals that this fourth-order system does not fully utilize all four degrees of freedom. In fact, the time evolution of the new variable \( \bar{v}_m \) is nearly indistinguishable from that of the variable \( v \). Similarly, the time evolution of \( \bar{v}_n \) is quite similar to that of \( v_n \). Since our objective is to obtain a system that is simpler than the original KM model, we replace \( \bar{v}_m \) by \( v \) and \( \bar{v}_n \) by \( v_h \). Renaming these new equivalent potentials \( V \) and \( U \), respectively, we obtain a new three-dimensional model, which we refer to as the method of equivalent potentials (MEP) model:

\[
C \frac{dV}{dt} = -I_{\text{MEP}}(V, U) + zI_s + I_{\text{app}}(t), \tag{14}
\]

\[
\frac{dU}{dt} = \frac{h(V) - h(U)}{\tau_h(V)h'(U)}, \tag{15}
\]

\[
\frac{dz}{dt} = k_s[\theta(V - V_f) - z] \tag{16}
\]

where

\[
I_{\text{MEP}}(V, U) = \tilde{g}_{Na}m^3(V)h(V)(V - v_{Na}) + \tilde{g}_K^n(V)h'(V) + \tilde{g}_L(V) - v_L. \tag{17}
\]

Despite our ad hoc reduction, the action potentials produced by the MEP model strongly resemble those produced by the KM model. (Compare Figs 1 and 3.) Of course, there are some quantitative differences.

4. The Slow Inward Current as a Parameter

In this section, we will give a graphical demonstration of the mechanism of spontaneous secondary spiking. To do this, we will compare the behaviour of the three-dimensional ZFN and MEP models with the dynamics of their excitable subsystems for given fixed values of the slow inward current \( I_z = zI_s \). (Recall that \( I_s \) is a parameter describing the maximum possible amplitude of the current \( I_z \). The actual amplitude of \( I_z \) reflects the state of the gating variable \( z \).) This technique is particularly useful for explaining the behaviour of the model when \( k_s \) is very small, or, equivalently, when the inward current is very slow.

Viewing \( I_z \) as a constant has two advantages: (1) the two-dimensional excitable subsystems can be analysed geometrically using the phase plane, and (2) \( I_z \) can be used as a bifurcation parameter for the excitable subsystems. One-parameter bifurcation diagrams are computed using XPPAUT (Ermentrout, 1994), which contains
both the numerical bifurcation package AUTO (Doedel & Kernevez, 1986) that finds the stationary solutions (fixed points and periodic orbits) and their stability for systems of ordinary differential equations and the phase-plane analysis package XPP. The Gear’s algorithm in XPP is used to obtain the steady state, which then is used in AUTO as a starting point for its continuation calculations.

4.1. ZFN MODEL

If the slow inward current in the ZFN equations is so slow that we can treat it as a constant, then the ZFN equations reduce to the FHN equations,

\[
\frac{dV}{dt} = -V(V-a)(V-1) - W + I_z, \tag{18}
\]

where \( I_z \) is a constant applied current. The \( V \)-nullcline (the line where \( \dot{V} = 0 \)) is the cubic curve, \( W = -V(V-a)(V-1) + I_z \), which is raised or lowered by \( I_z \) as shown in Fig. 4(a). The \( W \)-nullcline (\( \dot{W} = 0 \)) is a straight line, \( W = V/r \), independent of \( I_z \). These nullclines separate regions of increasing and decreasing \( V \) and \( W \), respectively, and define the fixed point of the system where they intersect.

The fixed point may be stable or unstable, depending on where the nullclines intersect. When \( I_z \) is low (e.g., \( I_z = 0 \)), the fixed point occurs on the left branch of the \( V \)-nullcline, and we can
show analytically that it is stable, corresponding to a low resting potential. Similarly, for high $I_z$ (e.g., $I_z = 0.2$), the fixed point occurs on the right branch and is also stable, corresponding to a high resting potential. However, if the fixed point is on the middle branch, then it may be stable or unstable depending on how close it is to the local maximum or minimum of the cubic, located at

$$V = \tilde{v}^\pm = (1/3) [(a + 1) \pm \sqrt{a^2 - a + 1}],$$

respectively. Hopf bifurcation occur at

$$V = v_{HB} = (1/3) [(a + 1) \pm \sqrt{a^2 - a + 1 - 3er}]$$

when $I_z = V/r + V(V - a)(V - 1)$. For the parameters used here, the Hopf bifurcation (HB) points occur at $I_z = 0.02704$ and $0.1424$, as shown in Fig. 4(a). In between the HB points, the fixed points are unstable. Thus, if $er$ is small, then most of the fixed points occurring on the middle branch of the $V$-nullcline are unstable. The Hopf bifurcations give rise to limit cycles (oscillations). In between the Hopf bifurcations, we see [Fig. 4(b)] that the limit cycle manifests itself as a stable counterclockwise oscillation, representing tonic firing, around the unstable fixed point.

Figure 5 shows the bifurcations diagram for the FHN equations calculated by AUTO using $I_z$ as the bifurcation parameter. Note that the limit cycles rise abruptly out of the Hopf bifurcations. The initially unstable limit cycles grow rapidly until they become stable, large-amplitude limit cycles, corresponding with full action potentials. Thus, for medium $I_z$ (e.g., $I_z = 0.08$) in between the two HB points, we get the stable tonic firing of Fig. 4(b). For small $I_z$, we see a stable resting potential which corresponds to a fixed point on the left branch of the $V$-nullcline. When $I_z$ is relatively large, we get a stable resting potential, which corresponds to a fixed point on the right branch.

Recall that $I_z$ is not actually fixed but is slowly varying in proportion to $z$; then continuous spontaneous secondary spiking can be explained qualitatively in terms of the ZFN model. Initially, $I_z = 0$. The first applied inward current pulse generates an action potential, which causes $I_z$ to slowly increase as long as the membrane potential remains above the threshold $V_T$. [Note the initial increase in $z$ in Figs 2(a)–(c).] When the voltage drops below the voltage threshold $V_T$, $I_z$ slowly decreases back towards zero. If a second current pulse is applied, the resulting action potential will cause $I_z$ to increase again. If the two action potentials are sufficiently close together, then $I_z$ does not have time to decrease back to zero before the second action potential occurs and will rise even further the second time. If the $I_z$ current builds up enough, the $V$-nullcline may rise high enough to place the fixed point in the unstable region. As a result, the trajectory would begin to oscillate about the unstable fixed point. If $I_z$ is moving quickly, then $I_z$ will decay
sufficiently fast to move the fixed point out of the unstable region, allowing only a few secondary spikes or none at all, before the voltage decays to zero. On the other hand, if $I_z$ is moving slowly enough, the fixed point may stay in the unstable region and continuous spontaneous secondary spiking may occur.

A fine balance is required for continuous spontaneous secondary spiking [Fig. 2(c)]. The natural frequency of the fast subsystem must be sufficiently high that $I_z$ does not decay enough in between action potentials to move the fixed point out of the unstable regime. On the other hand, if the frequency is too high, $I_z$ may continue to increase, until it reaches its maximum $I_s$. In this case, the system can reach a stable elevated resting potential (not shown), depending on the magnitude of $I_s$. This balance which involves the time constants of the fast subsystem, the rate constant $k_s$, and the magnitude $I_s$ will be explored in Sections 5 and 6 for the full system.

4.2. MEP MODEL

As we did with the ZFN model, we can examine the dynamics of the excitable subsystem of the MEP model using $I_z$ as a bifurcation parameter. As before, we can examine the $U$- and $V$-nullclines of the resulting two-dimensional model. The $U$-nullcline is defined by the straight line $V = U$. The $V$-nullcline is defined implicitly by the equation

\[
\tilde{g}_{Na} m_a^3(V) h_a(U)(V - v_{Na}) + \tilde{g}_K n_a^4(U)(V - v_k) + \tilde{g}_L(V - v_L) = I_z. \tag{22}
\]

These nullclines, shown in Fig. 6, share certain similarities with the nullclines of the FHN equations in Fig. 4. In particular, there is always a single fixed point which shifts as $I_z$ changes. However, in the case of the MEP equations, an increase in $I_z$ deforms the left-hand branch upward rather than uniformly raising the entire nullcline. In addition, the shapes of the nullclines at $I_z = 0$ differ substantially. For this reason, a hyperpolarizing pulse would tend to invoke an action potential in the FHN equations (post-inhibitory rebound) while the voltage in the MEP equations would merely hyperpolarize and then return to rest.

The bifurcation diagram with $I_z$ as the bifurcation parameter was calculated using AUTO for both the MEP model and the original KM model. The bifurcation diagrams for these two models, shown in Fig. 7, are qualitatively similar, although they differ quantitatively due to the approximations made in the reduction process. Since spontaneous secondary spiking involves a transition from a low resting potential to tonic firing, the behaviour of the models near the left HB point is very important. The MEP and KM models have a subcritical (abrupt) HB at the left. This means that the spontaneous secondary spikes will have an all or none response. The FHN equations can have either two subcritical bifurcations or two supercritical bifurcations depending on the choice of $\varepsilon$. We have chosen $\varepsilon$ sufficiently small to ensure subcritical bifurcations. This means that the FHN equations will exhibit the same all or none response as the MEP and KM equations in the important region near the left HB point.

Due to the similarities between the ZFN and MEP models, the qualitative explanation of spontaneous secondary spiking given for the ZFN model also applies to the MEP model. We have gained a qualitative understanding of spontaneous secondary spiking by assuming that $I_z$ was sufficiently slow, so we could treat it as a parameter. Intuitively, we see that continuous spontaneous secondary spiking occurs when the frequency of firing is high enough that $z$ grows as
FIG. 7. Bifurcation diagrams for $V$ and the period calculated by AUTO using the bifurcation parameter $I_s$ for (a) the MEP model and (b) the KM model.

much as it decays during every cycle. However, it is not clear from the previous analysis how large $I_s$ must be for this to occur, nor is it clear how small the rate constant $k_s$ must be. In the following two sections, we discuss how these two very important parameters for the slow inward current determine when spontaneous secondary spiking may occur.

5. The Role of $I_s$

Kepler & Marder (1993) demonstrated numerically why continuous spontaneous secondary spiking can occur for sufficiently large $I_s$. They plotted the firing frequency of the HH equations as a function of the amplitude of an applied inward current. They superimposed this on a plot of the slow inward current $zI_s$ generated by the KM model as a function of stimulus frequency at various values of $I_s$. Whether or not the two curves intersected depended on the value of $I_s$.

The intersection of the two curves at a high frequency corresponded with continuous spontaneous secondary spiking (Fig. 2, Kepler & Marder, 1993). This plot clearly pointed out the importance of the parameter $I_s$ and indicated that a bifurcation analysis treating $I_s$ as the bifurcation parameter would be useful.

As mentioned before, $I_s$ is the maximum amplitude of the slow inward current $I_z$, corresponding to the case $z = 1$. Since $0 \leq z \leq 1$, it is difficult to predict from the value of $I_s$ whether spontaneous secondary spiking will occur. To understand the effect of the amplitude parameter $I_s$, we examine the stability of the full 3D and 5D models. We first determine the position and stability of the steady states for the 3D ZFN model. Then we use AUTO to obtain a global picture of each of the models, including the steady states and limit cycles corresponding to different values of the
bifurcation parameter $I_s$. The bifurcation diagrams obtained using $I_s$ as the bifurcation parameter in the ZFN, MEP, and KM models are qualitatively similar. These diagrams allow us to predict when spontaneous secondary spiking is likely to occur based on the value of $I_s$.

5.1. STEADY STATES AND BIFURCATION ANALYSIS OF THE ZFN MODEL

The fixed points of the ZFN model occur at the intersections of the $V$, $W$, and $z$-nullclines, namely where $\dot{V} = 0$, $\dot{W} = 0$, and $\dot{z} = 0$. To see how the fixed points depend on $I_s$, we look for intersections in the $V$–$W$ plane of the two curves obtained from the $V$, $W$, and $z$-nullclines described by

$$
\dot{V} = \dot{z} = 0: \ W = -f(V; a) + I_s \theta(V - V_T), \quad (23)
$$

$$
\dot{W} = 0: \ W = \frac{V}{r} \quad (24)
$$

where $f(V; a) = V(V - a)(V - 1)$, as illustrated in Fig. 8(a)–(d). We assume that $\theta(V - V_T)$ is approximated by the step function (7) to find the fixed points $(v_{ss}, w_{ss}, z_{ss})$. The stability of each fixed point is determined from

$$
|J(v_{ss}) - \lambda I| = 0 \quad (25)
$$

where the Jacobian of the ZFN equations is given by

$$
J(v_{ss}) = \begin{pmatrix}
-f_s(v_{ss}; a) & -1 & I_s \\
\varepsilon & -\varepsilon r & 0 \\
k_s \theta_r(v_{ss} - V_T) & 0 & -k_s
\end{pmatrix} \quad (26)
$$

Figure 8 shows that the fixed point $V = W = z = 0$ persists for all $I_s$. Since the eigenvalues for this fixed point are all negative, it is stable. A pair of fixed points arises via a saddle-node (SN) bifurcation when $I_s = I_{s(SN)} = V_T/r + f(V_T; a)$. The intersection of the straight line for the $W$-nullcline with the vertical branch in Fig. 8 yields an unstable fixed point described by $V = V_T$, $W = V_T/r$, and $z = I_{s(SN)}/I_s$. Finally, the intersection of the straight line with the right branch of $V = z = 0$ yields a fixed point which is defined by $z = 1$ and $W = V/r$ where $V$ is defined implicitly by $V/r = -f(V; a) + I_s$. A Hopf bifurcation [see Fig 8(e)] occurs on this branch when $I_s(HB) = v_{HB}/r + f(v_{HB}; a)$ where $v_{HB} = (1/3) [(a + 1) + \sqrt{a^2 - a + 1 - 3\varepsilon r}]$. To the left of this Hopf bifurcation, the fixed points are unstable, while they are stable to the right.

In addition to finding the stable resting potentials for the ZFN equations, we need to find any
stable tonic firing modes. To do this, we calculate the bifurcation diagram for the ZFN equations using the numerical bifurcation analysis package AUTO (Doedel & Kernevez, 1986). The results are shown in Fig. 9(a). The position and stability of the steady states calculated by AUTO look quite similar to those calculated analytically for the step-function approximation. Because we have used the smooth function (8) rather than the step function (7) to describe \( \theta(V - V_T) \), the corner at the saddle-node (SN) point in Fig. 9(a) is rounded instead of sharp. As expected from bifurcation theory, a limit cycle arises at the HB point. What is not obvious from our previous analysis is that the limit cycle grows in amplitude, eventually giving rise to stable large-amplitude oscillations.

FIG. 9. Bifurcation diagrams for the (a) ZFN, (b) KM, and (c) MEP models using \( I_s \) as the bifurcation parameter. The projections of the steady states and limit cycles onto \( V \) and \( z \) are shown. Note that \( v \) and \( I_s \) have been scaled by a factor of 55 to make them order one in (b) and (c). The saddle-nodes of periodics, marked SNP, occur at \( I_s = I_{s\text{SNP}} = 0.116 \) in the ZFN model, \( I_s = 2.383 \times 55 = 131 \, \mu\text{A} \) in the KM model, and \( I_s = 3.859 \times 55 = 212 \, \mu\text{A} \) in the MEP model.
5.2. COMPARISON OF THE ZFN, MEP, AND KM MODELS

Figure 9(b) and (c) compares the bifurcation diagram of the original 5D KM model with that of the 3D MEP model calculated by AUTO for the bifurcation parameter $I_z$. The branches of fixed points are qualitatively similar and resemble those in the ZFN model. Careful inspection reveals that the stable branches of limit cycles for the KM and MEP models also are similar qualitatively. The only major difference between the two sets of bifurcation diagrams is in the shape of the branches of unstable limit cycles. Numerical simulation suggests that this difference is relatively unimportant when studying spontaneous secondary spiking. The shape of the branches of limit cycles in the ZFN equations differs slightly from the corresponding branches in the KM and MEP models because of the different dynamics of the excitable subsystem discussed earlier.

The bifurcation diagrams (Fig. 9) for the ZFN, KM, and MEP models share certain qualitative features which are important for spontaneous secondary spiking. Firstly, they all have a stable branch corresponding with $z = 0$ which represents quiescence. Secondly, each has a stable branch of large-amplitude oscillations which correspond to tonic firing with oscillations in $z$. Spontaneous secondary spiking occurs near the saddle-node of periodics, marked SNP, where this branch of stable tonic firing first arises.

Immediately to the right of the SNP, the system has two stable modes: quiescence or tonic firing. The normally quiescent system may be stimulated so that it will respond transiently with a few spontaneous secondary spikes followed by a return to quiescence or switch to the tonic firing mode. An example of the latter was seen for the KM model in Fig. 1(c) in which $I_z$ was set at 150 $\mu$A, well above the SNP at $I_z = 131$ $\mu$A.

For very small $I_z$, the slow inward current $I_z$ is negligible so the system behaves like a normal excitable system in which each induced action potential is followed by quiescence. However, for $I_z$ just to the left of the SNP, the system can exhibit transient behaviour consisting of a few spontaneous secondary spikes followed by quiescence. As the system is driven, $z$ builds up, as discussed earlier. If $I_z$ is sufficiently large, then $I_z$ becomes large enough to place the excitable subsystem in the tonic firing regime. However, the intrinsic firing frequency of the excitable subsystem is insufficient to maintain $z$ at its elevated level, so $I_z$ decays until the system returns to rest. The number of spontaneous secondary spikes depends on how much $I_z$ builds up. When $I_z = 125$ $\mu$A in the KM model, which is below the SNP at $I_z = 131$ $\mu$A, we have seen in Fig. 1(a) that inadequate stimulation fails to lead to any spontaneous secondary spikes. However, increasing the number or frequency of stimuli can lead to an enhanced buildup of $I_z$ and, hence, more spontaneous secondary spikes, as shown in Fig. 1(b). Similar results were seen in Figs 2 and 3 for the ZFN and MEP models.

Based on the results of the original model and its two different reductions, we can conclude that the phenomenon of spontaneous secondary spiking is generic. The key ingredients are a slow inward current and an excitable system that can have either a stable steady state or a stable oscillation. The exact shape of the action potential is unimportant, but the relative time constants of the system are crucial. In the next section, we explore the importance of the relative magnitude of the rate constant $k_s$, which governs the buildup of $I_z$.

6. The Role of $k_s$

In our preliminary attempt to understand spontaneous secondary spiking, we assumed that the slow inward current was much slower than the dynamics of the excitable subsystem. While spontaneous secondary spiking does occur when this is true, a small rate constant $k_s$ is not a necessary condition. In the following sections, we will study the effects of the magnitude of $k_s$ on the behaviour of the models. We will demonstrate that the bifurcation structure and hence the behaviour of the models changes when $k_s$ exceeds a particular value. We will also show that when $k_s$ is too small, spontaneous secondary spiking is unlikely to occur.

6.1. LARGER $k_s$

The bifurcation structure of the spontaneous spiking models changes as $k_s$ increases. To
understand the behaviour of the ZFN equations when the slow inward current has approximately the same time constant as the recovery variable of the action potential, we follow the Hindmarsh and Rose method of reducing the order of the system (Hindmarsh & Rose, 1984). In particular, if \( k_s = \epsilon r \), we make the transformation \( I_z = zI_s \) and rewrite the ZFN equations as

\[
\frac{dV}{dt} = -V(V-1)(V-a) - W + I_z, \tag{27}
\]

\[
\frac{dW}{dt} = \epsilon r (V/r - W), \tag{28}
\]

\[
\frac{dI_z}{dt} = \epsilon r [I_0(V-V_T) - I_z]. \tag{29}
\]

This allows us to define a new variable, \( Y = W - I_z \), and combine the last two equations, collapsing the ZFN system to two dimensions:

\[
\frac{dV}{dt} = -V(V-1)(V-a) - Y, \tag{30}
\]

\[
\frac{dY}{dt} = \epsilon r (V/r - I_0(V-V_T) - Y). \tag{31}
\]

Of course, eqn (28) or (29) needs to be solved separately to determine \( W \) or \( z \).

The bifurcation diagram for this degenerate case is given in Fig. 10. A branch of unstable limit cycles arises at the Hopf bifurcation as before [Fig. 10(a)]. Zooming in on this branch in Fig. 10(c), we see that the limit cycle increases in amplitude with increasing \( I_s \) as it circles the stable fixed point to the right of the Hopf bifurcation. At \( I_s(\text{HC}) = 0.1433 \), the limit cycle collides with the saddle point corresponding with \( V = V_T \). The period [Fig. 10(b)] tends towards infinity, suggesting a homoclinic connection. Instead of giving rise to a branch of large-amplitude stable limit cycles, the branch of unstable limit cycles simply terminates.

Clearly, this behaviour is very different from the behaviour exhibited by the Kepler and Marder original model. Thus, we conclude that the rate constant \( k_s \) of the slow inward current must necessarily be smaller than \( \epsilon r \), which is related to the rate of recovery of the action potent-

![Fig. 10. Bifurcation diagram for the degenerate ZFN equations where \( k_s = \epsilon r = 0.025 \) using \( I_s \) as the bifurcation parameter. The projections of the steady states and limit cycles onto \( V \) and the period \( T \) of the limit cycles are shown. [Note that (c) is an expanded view of (a).] A branch of unstable limit cycles arises at the Hopf bifurcation point (HB) and terminates in a homoclinic connection (HC).]
model (or one that is nearly so) is unable to produce spontaneous secondary spiking. Finally, we should note that similar behaviour is observed for the KM model and the MEP model (not shown). Thus, all three models lose their ability to generate spontaneous secondary spikes as \( k \) increases.

6.2. SMALL \( k \)

As \( k \) becomes small, \( z \) moves more slowly and, hence, the oscillations in \( z \) during tonic firing are smaller. [Compare the bifurcation diagrams for the ZFN model with \( k_s = 0.005 \) and \( k_s = 0.001 \) in Figs 9(a) and 11, respectively.] While the steady states are unchanged by a decrease in \( k_s \), the saddle-node of periodics where the tonic firing mode first arises occurs at a lower \( I_s \) value. We can predict where this SNP occurs in the limit as \( k_s \) approaches zero from the dynamics of the excitable subsystem.

We use Kepler and Marder's prediction that \( z \) asymptotically approaches the duty cycle of tonic firing in the limit of small \( k_s \) (Kepler & Marder, 1993) and the fact that \( I_s = zI_s \). If \( t_{\text{on}} \) and \( t_{\text{off}} \) represent the time that \( v > V_T \) and \( v < V_T \), respectively, then the duty cycle is \( DC = t_{\text{on}} / (t_{\text{on}} + t_{\text{off}}) \). We calculate the duty cycle of tonic firing for the FHN equations by measuring the period \( T \), \( t_{\text{on}} \), and \( t_{\text{off}} \) as shown in Fig. 12(a). Notice that the duty cycle \( DC \) in Fig. 12(b) is a monotonically increasing function. Since \( I_s = zI_s \) at any point in time and \( z \) asymptotically approaches the duty cycle, the system will exhibit an oscillation only when the current value of \( I_s \) equals the product of \( I_s \) and the duty cycle. Thus, in Fig. 12(b), we see that oscillations occur for a given value of \( I_s \) if the straight line \( z = I_s/I_s \)

![Fig. 11. Bifurcation diagram for the 3D ZFN equations using \( I_s \) as the bifurcation parameter when \( k_s \) is small \((k_s = 0.001)\). The projections of the steady states and limit cycles onto \( V \) and \( z \) are shown. The saddle-node of periodics (SNP) occurs when \( I_s = I_{s(SNP)} = 0.09712 \).](image1)

![Fig. 12. By measuring the times \( T \), \( t_{\text{on}} \), and \( t_{\text{off}} \) of tonic firing in the ZFN equations for various (fixed) values of \( I_s \) [panel (a)], we can calculate the duty cycle \( DC \) and compare it with the straight lines \( z = I_s/I_s \) for various values of \( I_s \) [panel (b)]. The intersections of these lines give the values of \( z \) as a function of \( I_s \) [panel (c)] found during continuous spontaneous secondary spiking in the ZFN equations in the limit of small \( k_s \).](image2)
intersects the monotonically increasing function $DC$. In Fig. 12(c), we plot the value of $z$ at the intersection(s) in Fig. 12(b) for each value of $I_s$. Thus, Fig. 12(c) shows the value of $z$ seen during tonic firing in the ZFN equations as a function of $I_s$ in the limit as $k_t$ approaches zero.

Figure 12(c) agrees fairly well with the bifurcation diagram of Fig. 11(b) where $k_t$ is small but finite. The saddle-node of periodicities $SNP_1$ predicted in the former bifurcation diagram is at $I = 0.093$, while in the latter, the corresponding SNP is at $I = 0.097$, a slightly larger value. Note that $z(I_s)$ is multivalued near the corners marked SNP and SNP in Fig. 12(c). A careful inspection of Fig. 11(b) shows that the oscillations on the branch of limit cycles between SNP and SNP are stable, while they become unstable as the branch turns at either end. Thus, near SNP and SNP, a stable oscillation coexists with an unstable one.

From our earlier analysis using $I_z$ as a parameter, we would not expect to see any spontaneous spiking unless $I_z$ reaches the minimum value required for tonic firing in the excitable subsystem. This value can be approximated by the left Hopf bifurcation point in the $V$ versus $I_z$ bifurcation diagram of Fig. 5. Thus, the minimum value for $I_z$ is given approximately by $I_z(V) = V(V - a)(V - 1) + V/r$ where $V = v_{H_{min}} = (1/3) [(a + 1) - \sqrt{a^2 - a + 1 - 3x}]$, or $I_{z_{min}} = 0.027$. If the duty cycle is less than $I_{z_{min}}$, we predict that $z$ will never reach the minimum value necessary for spontaneous secondary spiking. Since neither $z$ nor the duty cycle can exceed one, there is a lower bound on $I_z$, namely $I_z = I_{z_{min}}$, where spontaneous secondary spiking will not occur, regardless of the rate of stimulation. As $I_z$ increases, the minimum $z$, and hence duty cycle, required to achieve spontaneous secondary spiking decreases, so spontaneous secondary spiking is more likely.

Whether or not we see spontaneous spiking depends on the asymptotic value of $z$ and, hence, on the frequency of drive. It also depends on whether $z$ achieves this asymptotic value and, therefore, on the length of the drive. If we set $I_z = 0.090$, which is below $I_z = I_{z_{SNP}} = 0.097$, then $z$ would need to achieve a minimum value of $I_z(\min)/I_z = 0.3$ before spontaneous secondary spiking could occur. This corresponds to a minimum frequency of 88.2 Hz, since the duration of a driven action potential is about 3.4 ms. Simulations in which we paced the system at frequencies above and below 88.2 Hz confirmed that 88.2 Hz is the (approximate) minimum frequency required for spontaneous secondary spiking. Thus, if we drive the ZFN equations with a duty cycle less than 0.3 or equivalently, with a frequency of less than 88.2 Hz, $I_z$ will never reach $I_z(\min)$.

In Fig. 13(a), we show that if the ZFN equations are driven at a frequency of 70 Hz, then the oscillation in $z$ stabilizes so that $I_z$ remains in the region below the limit cycles in the bifurcation diagram for the two-dimensional excitable subsystem. Thus, no spontaneous secondary spikes occur even after very long drives. If we drive the ZFN equations at 100 Hz but only for a short period of time, $I_z$ again fails to reach $I_z(\min)$, so no spontaneous spikes occur [Fig. 13(b)]. However, a longer drive at 100 Hz can result in a few spontaneous spikes followed by a return to quiescence as shown in Fig. 13(c). Lastly, if we make $I_z > I_z(\min)$ then we can get continuous spontaneous spiking as shown in Fig. 13(d).

We performed numerical calculations (not shown) for the KM and MEP equations similar to those done for the ZFN equations in Fig. 12 in order to predict their behaviour in the limit of very small $k_t$. While the period $T$ is monotonically decreasing in the KM and MEP equations, the period in the ZFN equations [Fig. 12(a)] decreases and then increases again with increasing $I_z$. The duration of the action potentials ($t_{on}$) in the KM and MEP equations is roughly constant, while in the ZFN equations it is monotonically increasing with $I_z$. Despite these differences, the net result is that the duty cycle $DC$ in all three systems is monotonically increasing with $I_z$. As a result, the dependence of $z$ on $I_z$ during continuous spontaneous secondary spiking is also qualitatively similar in all three models. Thus, despite the many quantitative and some qualitative differences between the ZFN equations and the KM and MEP equations, the phenomenon of spontaneous secondary spiking is qualitatively the same in all three systems because of the way the duty cycles of the fast sub-systems depend on $I_z$. 
FIG. 13. Simulation of the ZFN equations with small $k_s$ ($k_s = 0.001$) superimposed on the bifurcation diagram for their excitable subsystem. The number of spontaneous secondary spikes depends on $I_s$ and the frequency ($f$) and number ($N$) of applied current pulses. Current pulses of amplitude 0.1 and duration 0.5 ms are applied. Spontaneous secondary spiking fails to occur when (a) the rate of stimulation is inadequate, and (b) the system is not driven for a long enough time. (c) Because $I_s < I_{SNP}$ when the drive ceases, the system only exhibits 4 spontaneous secondary spikes followed by a return to rest. (d) With $I_s > I_{SNP}$, the system exhibits continuous spontaneous secondary spiking when the drive ceases. (□) steady states; (·) limit cycles (o); (—) $V$; (—–) $W$; (—–) $z$. 
7. Discussion

In this paper, we have built upon the Kepler & Marder (1993) analysis of their model of spontaneous secondary spiking in a crab neuron. In order to gain a deeper understanding of the fundamental mechanism underlying spontaneous spiking, we reduced the five-dimensional KM model to two different three-dimensional models. Both reductions relied on the fact that the four-dimensional Hodgkin–Huxley-type excitable subsystem in the KM model does not fully utilize all four degrees of freedom and, hence, can be reasonably well approximated by a two-dimensional system. The resulting three-dimensional approximations, the ZFN and MEP models, both exhibited the same qualitative behaviour as the original KM model, despite quantitative and even some qualitative differences. The relative simplicity of the ZFN model allowed us to make some analytical predictions and to obtain numerous numerical results.

We advanced a qualitative explanation for spontaneous spiking by showing how the slow inward current modulates the behaviour of the two-dimensional excitable subsystem. To predict quantitatively when continuous spontaneous secondary spiking can occur, we performed a bifurcation analysis using the amplitude parameter $I_s$ of the slow inward current as the bifurcation parameter. The bifurcation diagrams of the original 5D model and the reduced 3D models shared certain important features. Firstly, each of the three models had a stable low resting potential for all values of $I_s$. Secondly, a branch of large-amplitude limit cycles, corresponding to a stable tonic firing mode, arose via a saddle-node of periodics bifurcation as $I_s$ increased. The occurrence of spontaneous secondary spiking depends on the location of the parameter $I_s$ relative to this saddle-node of periodics.

Our bifurcation analysis of the models shows that for spontaneous secondary spiking to occur, the dynamics of the slow inward current must be slower than the dynamics of the fast excitable subsystem. In particular, this analysis shows that continuous spontaneous secondary spiking is not possible for the ZFN model for any values of $I_s$ when $k_s$ is too large. As $k_s$ increases towards $\infty$, instead of giving rise to a branch of stable large-amplitude limit cycles, the unstable branch of limit cycles terminates in a homoclinic connection, and at $k_s = \infty$, the three-dimensional ZFN model collapses to two dimensions. The branches of limit cycles in the bifurcation diagrams for the KM and MEP models also terminate in a homoclinic connection rather than giving rise to stable large-amplitude limit cycles when $k_s$ is large.

Kepler & Marder (1993) stated that, in the limit of small $k_s$, the asymptotic value of the gating variable $z$ is equal to the duty cycle of tonic firing of the excitable subsystem. We employed the Kepler and Marder assertion to predict the range of $I_s$ for which continuous spontaneous spiking would occur, thus finding the critical value of $I_s$ at the saddle-node of periodics bifurcation. Also, we showed how to calculate numerically the minimum frequency of stimulation which can lead to spontaneous spiking when $k_s$ is small and calculated the smallest value of $I_s$ that must be achieved in order to see spontaneous spiking. These results give us a better understanding of why certain types of stimulation lead to spontaneous spiking while others do not.

When the time constant for the slow inward current is much larger than that for the fast subsystem, we can analyse the two systems separately and use the results to predict the behaviour of the full model. Our analysis shows that the slow inward current must reach a sufficient level to induce tonic firing in the excitable subsystem, and thus induce spontaneous secondary spikes in the full system. The number of spontaneous secondary spikes is proportional to the amount of time it takes the inward current to decay below the minimum level for tonic firing. Thus, the number of spontaneous secondary spikes depends on the length of the original drive, the maximum attainable amplitude of the slow inward current, and how fast the slow inward current decays. As a result, very slow inward currents can lead to long trains of spontaneous secondary spikes following lengthy initial drives. A slow inward current with a larger rate constant $k_s$ can lead to a few spontaneous secondary spikes after only a very short initial drive.

Based on our analysis, we conclude that the phenomenon of spontaneous secondary spiking is, in a certain sense, generic. A model must have
a minimum of three dimensions, namely a two-dimensional excitable subsystem plus a one-dimensional slow inward current. The excitable subsystem must be capable of exhibiting either a steady state or tonic firing depending on the amplitude of the applied inward current. The slow inward current builds up during the action potentials and decays in between action potentials. The exact shape of the action potential is not important. The feedback between the slow inward current and the excitable subsystem is bidirectional. On the one hand, the amplitude of the slow inward current dictates the firing mode of the excitable subsystem, including the duty cycle of firing. On the other hand, the duty cycle of the excitable subsystem dictates the asymptotic value of the slow inward current. Because the duty cycle of the excitable subsystem is an increasing function of the slow inward current, a stable oscillation, known as continuous spontaneous secondary spiking, can be achieved for certain $I_s$ values.

Spontaneous secondary spiking is of particular interest from a signal processing point of view in neurophysiology because the system responds differently to incoming signals of different frequencies and to trains of different lengths. In addition, the response of the system can be modulated, e.g., by regulating factors such as hormones, by changing either the maximum amplitude or the rate of change of the slow inward current. In the crab, the spontaneous spikes are important because they influence the duration of contraction of certain muscles in the gastric mill. Furthermore, the number of spontaneous spikes and, hence, the contraction of the muscles, can be regulated by serotonin.

The simplicity of the mechanism of spontaneous secondary spiking suggests that it may occur elsewhere and, therefore, play an important physiological role in many other biological systems. Indeed, a qualitatively similar phenomenon called delayed afterpolarization-induced triggered activity occurs in cardiac cells and may have important physiological implications for pathological functioning of the heart (Antzelevitch & Sicouri, 1994). We have examined a mathematical model of a cardiac Purkinje fibre, called the DiFrancesco-Noble (1985) model, which can exhibit spontaneous action potentials, similar to those studied here, under certain pathological conditions (Enns-Ruttan, 1998). Though the phenomenon of cardiac-triggered activity is somewhat more complex than the spontaneous spiking models studied here, a similar analysis may be applied, revealing, that the basic mechanism is similar. We have found that with an appropriate choice of bifurcation parameter, we can identify a critical saddle-node of periodicities bifurcation similar to the one which gives rise to continuous spontaneous secondary spiking in the KM model. Just to the left of this SNP, the system may exhibit a few transient spontaneous action potentials in response to pacing, but will always return to quiescence. To the right of the SNP, the system is bistable with a quiescent mode and a tonic firing mode. Certain experimental interventions (similar to the application of serotonin here) can either promote or suppress the occurrence of the spontaneous action potentials, referred to as triggered activity, by shifting the bifurcation parameter relative to this SNP.

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REFERENCES


TABLE 1
Parameters of the KM model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$v_{Na}$</td>
<td>55 mV</td>
</tr>
<tr>
<td>$v_{K}$</td>
<td>-72 mV</td>
</tr>
<tr>
<td>$v_{L}$</td>
<td>-67.9 mV</td>
</tr>
<tr>
<td>$g_{Na}$</td>
<td>120 mS cm$^{-2}$</td>
</tr>
<tr>
<td>$g_{K}$</td>
<td>20 mS cm$^{-2}$</td>
</tr>
<tr>
<td>$g_{L}$</td>
<td>0.3 mS cm$^{-2}$</td>
</tr>
<tr>
<td>$C$</td>
<td>1 μF$^{-2}$</td>
</tr>
<tr>
<td>$k_1$</td>
<td>0.1 ms$^{-1}$</td>
</tr>
<tr>
<td>$V_T$</td>
<td>-30 mV</td>
</tr>
</tbody>
</table>

where

$$x_x(v) = \frac{x_{x}(v)}{\tau_{x}(v)} = \frac{\alpha_{x}(v)}{\alpha_{x}(v) + \beta_{x}(v)}$$

and

$$\tau_{x}(v) = \frac{1}{\alpha_{x}(v) + \beta_{x}(v)}$$

The $\alpha$s and $\beta$s in the KM model have the following voltage dependencies:

$$\alpha_{m}(v) = -\frac{0.1(v + 29.7)}{\exp\left(-\frac{v + 29.7}{10}\right) - 1}$$

$$\beta_{m}(v) = 4\exp\left(-\frac{v + 54.7}{18}\right)$$

$$\alpha_{h}(v) = 0.07\exp\left(-\frac{v + 48}{20}\right)$$

$$\beta_{h}(v) = \frac{1}{\exp\left(-\frac{v + 18}{10}\right) + 1}$$

$$\alpha_{n}(v) = -\frac{0.01(v + 45.7)}{\exp\left(-\frac{v + 45.7}{10}\right) - 1}$$

$$\beta_{n}(v) = 0.125\exp\left(-\frac{v + 55.7}{80}\right)$$

APPENDIX

Relaxation equations for $x = m, h, n$:

$$\frac{dx}{dt} = \frac{x_x(v) - x}{\tau_x(v)}$$

can also be written in the form

$$\frac{dx}{dt} = \alpha_x(v)(1 - x) - \beta_x(v)x$$


