Analysis of excitable cell models

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Abstract

Electrically excitable cells, e.g., neurons, cardiac cells, and pancreatic \( \beta \)-cells, must function properly to maintain health. In this paper, we describe some of the research on excitable cells that we have carried out over the past 15 years. In particular, we describe some electrical phenomena observed in these cells and how we are trying to understand the mechanisms causing them by using modeling techniques, analysis, numerical computations, and computer technology. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction to excitable cells

Electrical activity is ubiquitous in our bodies and is essential to maintain life. This electrical activity is manifest in electroencephalograms and electrocardiograms, but the sources of this activity are at the cellular level, for example, neurons in the brain, cardiac cells in the heart, and \( \beta \)-cells in the pancreas. In particular, this electrical activity is a result of the distribution and movement of electrically charged ions. In the brain, neurons permit signalling of information to other parts of the brain and body via action potential propagation along axons; pacemaker cells insure proper sequential contraction of parts of the heart to pump blood to all regions of the body; and pancreatic \( \beta \)-cells undergo bursting electrical activity to secrete vitally essential insulin to control blood glucose levels.

In this paper, we review some of the research on excitable cells that we have carried out over the past 15 years. In particular, we describe some basic aspects of the modeling and analysis of
models of these excitable cells. All cells have a thin outside envelope consisting of a lipid bilayer membrane that is capable of separating electrical charges. However, these membranes are not simply capacitive elements, but rather they may have holes in them as a result of proteins, called channels or pores, which are inserted into the membrane. Generally, channels are specific and permit only certain types of ions to pass through them.

Furthermore, there may be energy consuming mechanisms which can move ions across the membrane against a concentration gradient and/or an electric potential gradient. Ions then will pass through the membrane resulting in unequal ionic concentrations on the outside (extracellular) and the inside (intracellular) of the cell membrane. For the cells we will consider here, this difference in ionic concentrations results in an electric potential difference across the membrane, called the resting membrane potential, which is steady and stable to small perturbations. This potential difference is negative inside relative to the outside. Deflections of this membrane potential towards less negative values are called “depolarizations” and towards more negative values are called “hyperpolarizations”.

In excitable cells, transient depolarizations and hyperpolarizations of this potential can occur and can correspond to various physiological functions. In the brain, such transient behavior of the membrane potential can be propagated from many neurons to a single neuron, and these signals can collectively cause the target neuron to “fire”. These transient signals have durations on the order of milliseconds and are called “action potentials” or “spikes”. Similar signalling occurs in the heart where the signals lead to muscle contractions that are needed to pump blood to the body. In pancreatic $\beta$-cells, these transient deflections are manifest as periodic bursts of electrical activity of several seconds duration and are separated by periods of relative silence. This bursting electrical activity is correlated to the rate of insulin release by the $\beta$-cells.

2. Excitable cell models

Electrical activity in excitable cells is a consequence of the movement of ions across the cell membrane between the extracellular and intracellular spaces. As noted earlier, these ions move through ion channels due to the electro-chemical gradients acting on them, as well as energy-consuming mechanisms, pumps. Here, for the transient phenomena we will investigate, we will not consider the pumps, but rather focus on the ionic currents which flow through the membrane.

2.1. Hodgkin–Huxley modeling

In 1952, Hodgkin and Huxley [5] published a series of papers describing experiments and a theory for action potential production and propagation in squid giant axon. That theory treated the cell membrane as an analog of an electrical circuit where the membrane is treated as a leaky capacitor with variable conductances for the different ions. In the squid axon case, these ions were the major ions, $\text{Na}^+$, $\text{K}^+$, and $\text{Cl}^−$. Locally, the capacitive current and the ionic currents satisfy Kirchhoff’s law. Furthermore, one could add in spatial effects by accounting for extracellular and intracellular ion movements due to potential gradients. However, for most of our discussion here, we will assume that the cells are spatially “compact”, thereby avoiding the need to incorporate spatial effects into the equations.
Membranes of many different kinds of cells are similar, and therefore, it is accepted that excitable cell membranes can be modelled using ionic current models of Hodgkin and Huxley-type [5]. The model consists of a current balance equation obtained using Kirchoff’s law and relaxation equations for the components in the ionic conductances. This means that the membrane current model consists of a capacitive current term and a variety of ionic current terms appropriate for a specific type of cell. The general form of the spatially-independent model with \( n \) ionic currents is

\[
C \frac{dV}{dt} = - \sum_{i=1}^{n} \bar{g}_i x_i^p y_i^q (V - V_i) + I_{\text{appl}}(t),
\]

\[
\frac{dx_i}{dt} = \frac{x_{i\infty}(V) - x_i}{\tau_{x_i}(V)}, \quad i = 1, 2, \ldots, n,
\]

\[
\frac{dy_i}{dt} = \frac{y_{i\infty}(V) - y_i}{\tau_{y_i}(V)}, \quad i = 1, 2, \ldots, n,
\]

where \( C \) is the capacitance, \( V \) is the membrane potential, \( \bar{g}_i \) is the maximal conductance of the channel for ion \( i \), \( x_i \) and \( y_i \) are the activation and inactivation variables, respectively, for the conductance and vary between 0 and 1, \( V_i \) is the Nernst potential for the \( i \)th ion, \( I_{\text{appl}} \) is the applied current, \( x_{i\infty}(V) \) and \( y_{i\infty}(V) \) are the steady state activation and inactivation values at potential \( V \), respectively, and \( \tau_{x_i} \) and \( \tau_{y_i} \) are the relaxation time constants at potential \( V \).

3. Spiking and oscillations in neurons

There are many different types and frequencies of oscillations in the electrical activity of neurons in the brain. One manifestation of these oscillations is the frequency distribution in the electroencephalogram during sleep and wake states [17]. In the sleep state, the observed frequencies are in the 3–5 Hz range, whereas in the wake state, there coexist additional frequencies of about 30–40 Hz. One long-term objective of these studies of electrical activity in neurons is to explain the appearance of these disparate frequencies. Here we will describe some techniques which we have developed in order to understand the origin of specific frequencies in neurons.

3.1. Frequency domain analysis

As noted above, neurons are excitable cells and can exhibit spike activity as well as remain in a quiescent resting membrane potential state. The descriptor “excitable” has no clear definition, but we can describe it qualitatively. After small depolarizations of the membrane potential from the resting state, the membrane potential returns monotonically to the resting state. However, for sufficiently large depolarizations, a spike or many spikes may be generated, resulting in large excursions in the membrane potential before returning to the resting state. Thus, there is a “threshold” between these two membrane potential ranges, which are called the “subthreshold” and “suprathreshold” ranges, respectively. In the subthreshold range, away from the threshold, small applied current inputs give proportional voltage responses, i.e., effectively operating in a linear range. We take advantage of the linearity to investigate the origin of observed spike frequencies in neurons.
It is well known that constant amplitude current inputs at different frequencies can evoke variable amplitude voltage responses. We believe that the amplification of voltage responses in some frequency range (resonance) can lead to enhanced spike activity in that range. The reason is that the membrane potential is pushed closer to the threshold in this range, and the presence of inherent membrane noise increases the probability that the potential will exceed threshold, thus giving a spike.

Electrophysiological studies of neurons involve the penetration of neuronal membranes with glass microelectrodes that are used to inject current and measure voltage responses. Common protocols include the use of a current clamp, e.g., the injection of step current pulses into the cell, and a voltage clamp, e.g., using an electronic feedback system to control the current input to maintain the voltage at some fixed value. Early studies used sinusoidal current inputs to determine the voltage response of the membrane to input signals at specific frequencies over a range of frequencies. Such studies correspond to frequency domain analysis of the neuronal membrane.

The drawback in using single frequency inputs is that measurements over a discrete set of frequencies then require long time intervals to complete. Over such time intervals, the state of the neuron, e.g., intracellular ion concentrations could change or a well-sealed penetration of the neuron by the microelectrode could be lost. Therefore, we devised a measurement protocol in which a fixed (small) amplitude, variable frequency, current input is injected into the neuron and repeated periodically [14,15]. One example of this “ZAP” (impedance amplitude profile) current is

$$I(t) = a \sin(bt^3)$$  \hspace{1cm} (4)

where $t$ is time and $a$ and $b$ are constants. This has a constant amplitude with increasing frequency. A schematic of this is shown in the upper part of Fig. 1 where $V(t)$ is the voltage response to the current input $I(t)$. As evident in the figure, the amplitudes of the voltage response are larger over a certain range of frequencies, the resonance phenomenon. This is seen more clearly in the frequency domain by taking the ratio of the Fourier transform of the voltage response to the Fourier transform of the current input. The resulting impedance, $Z$, is a complex-valued function of frequency given by

$$Z(\omega) = \frac{\text{FFT} V(t)}{\text{FFT} I(t)}$$  \hspace{1cm} (5)
where $\omega$ is the frequency. The impedance magnitude $|Z|$ in the lower part of Fig. 1 clearly shows the resonant hump and the intrinsic frequency preference [6–9].

To analyze this resonance mathematically, we can take the membrane model consisting of the capacitive current and several active membrane currents, i.e., with voltage dependent conductances, and linearize them about the rest state, cf. [14], appendix. For only one active current, the resulting linearized equations are identical mathematically to the equations for an electrical circuit consisting of passive capacitor, resistor, and inductor in parallel. It then is straightforward to derive the impedance magnitude as a function of frequency by putting in sinusoidal inputs of different frequencies, and to determine the resonant frequency.

The manifestation of this subthreshold resonance phenomenon occurs in the suprathreshold regime (see Fig. 2). A constant amplitude sinusoidal current input is injected into a real neuron so that near the resonant frequency, the amplification in the voltage response exceeds the threshold membrane potential. In the case shown in Fig. 2, this occurs at approximately 1 Hz, and we see that action potentials are produced on top of the voltage amplifications. However, at a lower frequency of 0.2 Hz and at a higher frequency of 20 Hz, the voltage response is not amplified above threshold, so no action potentials are generated. Since the threshold region is in the nonlinear range, we conjecture that if the input had a frequency content which included components with sufficient amplitude at about 1 Hz, then an output train of action potentials would occur at about 1 Hz.

### 3.2. Electronic pharmacology

The determination of membrane electrical properties, i.e., the identification of the different ion channels in the membranes, is usually achieved using various drugs to block specific channels. However, some drugs are more selective than others in the channels that they block. We have studied membrane electrical properties of real neurons using a combination of mathematical modelling and computer technology, the “reactive current clamp” [7]. We call this “electronic pharmacology”.

We describe the results using Figs. 3 and 4. In the left panel of Fig. 3 is the experimental frequency–impedance magnitude diagram for a neocortical neuron with a membrane that exhibits resonant behavior, cf. the peak at about 2 Hz. In the right panel, we show the same diagram (note the scale changes along the both axes) with the lower trace corresponding to the control curve in the left panel, and the upper trace is the impedance magnitude trace after the neuron has been treated extracellularly with $\text{Cs}^+$ at a concentration of 3 mM. The effect of the drug application is to block the $I_h$ channels (these are hyperpolarization-activated channels, i.e., they open at hyperpolarized
Fig. 3. Pharmacological blockade of $I_h$. Left panel: Frequency–impedance magnitude diagram for a resonant neocortical neuron. Right panel: Lower trace is the same control as in the left panel. The upper nonresonant trace is obtained after blockade of $I_h$ by extracellular application of 3 mM Cs$^+$. potentials). These $I_h$ currents are responsible for the resonant behavior, as seen by the monotone decrease in the impedance magnitude indicating a purely passive membrane with constant capacitance and resistance.

In the left panel of Fig. 4, the experimental frequency–impedance magnitude diagram is shown for a nonresonant neocortical neuron. The reactive current clamp used in this example stores a mathematical model of the $I_h$ current in a computer. As the membrane voltages are measured, these voltages are fed into the computer, and the corresponding $I_h$ current at that voltage is computed and injected into the neuron. This is done simultaneously with the injection of a ZAP current from which the impedance trace is obtained. In the right panel, the upper trace corresponds to the control curve given in the left panel, and the resulting impedance magnitude curve with the electronically added $I_h$ current is the lower trace. We easily see the characteristic resonant peak.

The advantage of electronic pharmacology is that we can modify a very specific current in a cell, adding or subtracting variable amounts of that current, even adding in a current which is not present...
in a neuron, as shown in Fig. 4. Note, however, that this is purely an electrical effect, and we are unable to mimic the chemical effects of the corresponding ion.

4. Triggered activity and spontaneous secondary spiking

In cardiac cells, there is an electrical phenomenon called “triggered activity”. This is illustrated in Fig. 5 for a cardiac Purkinje fiber. Each of the four diagrams shows the membrane potential trace as a function of time. Below each of the four traces is a set of six dots which indicate the times at which a stimulus is given to the fiber. The excursions in the voltage then reflect the responses to these stimuli. The stimuli are given with different basic cycle lengths (BCL). In the upper left diagram with a BCL = 800, we see that each stimulus elicits a single spike, and at the end there is a delayed afterdepolarization (DAD). For a BCL = 700, an extra spike is generated where previously the DAD was located. Each of the successive figures shows an increase of one additional spike over the previous figure. Reducing the BCL even further would continue to increase the number of spontaneously generated spikes, and this phenomenon is called “triggered activity”. The appearance of these additional unstimulated spikes could lead to serious clinical consequences such as heart arrhythmias. For a detailed analysis of cardiac triggered activity using the DiFrancesco–Noble model, see Enns [3].

There is a related phenomenon called “spontaneous secondary spiking”, which was observed by Meyrand et al. [11] in the lateral gastric axon in the stomatogastric nervous system of the crab. They observed that stimulated action potentials propagated down the axons, but the number of spikes that arrived at the other end exceeded the number of spikes generated by the stimuli. Furthermore, action potentials were propagated back towards the location of the stimuli, indicating a spontaneous generation of spikes in the interior of the axon length.
4.1. Kepler and Marder’s Model

Kepler and Marder [10] proposed a minimal model to explain spontaneous secondary spiking. Their model, which includes the Hodgkin–Huxley model with parameter values for crustacean axons and a hypothesized slow inward current, is given by the five-dimensional system

\[
\begin{align*}
C \frac{\partial V}{\partial t} &= -I_{HH}(V, m, h, n) + zI_s + I_{\text{app}}(t) + \gamma \frac{\partial^2 V}{\partial x^2}, \\
\frac{\partial m}{\partial t} &= \frac{m_\infty(V) - m}{\tau_m(V)}, \\
\frac{\partial h}{\partial t} &= \frac{h_\infty(V) - h}{\tau_h(V)}, \\
\frac{\partial n}{\partial t} &= \frac{n_\infty(V) - n}{\tau_n(V)}, \\
\frac{\partial z}{\partial t} &= k_s[\theta(V - V_T) - z],
\end{align*}
\]

where \( z \) is the slow variable, \( I_s, \gamma, \) and \( k_s \) are constants, and the second-order derivative term in (6) accounts for the spatial dependence. The quantities \( m_\infty, h_\infty, n_\infty, \tau_m, \tau_h, \) and \( \tau_n \) are empirically determined functions of \( V \), and the additional functions, \( I_{HH} \) and \( \theta \), are given by

\[
I_{HH} = g_{Na} m^3 h(V - V_{Na}) + g_K n^4(V - V_K) + g_L(V - V_L),
\]

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

where \( V_T \) is the threshold for the half-activation point for the slow variable. The phenomenon of spontaneous secondary spiking can be seen in Fig. 6, which shows a space–time portrait of spike propagation and spontaneous spike generation obtained from numerical solution of the Kepler–Marder model.

In Fig. 7, three different types of spike train solutions for the Kepler–Marder model are shown, namely, one-to-one spikes, i.e., one spike per stimulus (black circle), in the upper panel, three extra spikes in the middle panel, and tonic or continuous spiking in the lower panel. The value of \( I_s \) and the frequency, \( f \), of the stimulus are given to the right of each panel.

4.2. ZFN model

The mathematical mechanisms responsible for spontaneous secondary spiking also occur in the FitzHugh–Nagumo (FHN) equations when a slow inward current is added. The spatially independent FHN equations consist of two first-order ODEs with polynomial right-hand sides. They are a caricature of the HH equations and possess many similar properties, e.g., spikes. Addition of the same
Fig. 6. Spontaneous secondary spiking. The two filled circles along the vertical axis correspond to stimuli at $x = 0$ that generate two propagating action potentials as seen in the space–time picture. Two spontaneously generated action potentials in the interior are clearly seen and propagate both orthodromically and antidromically.

Fig. 7. Spike train solutions of the Kepler–Marder model. Two stimuli at frequency $f$ are given with fixed values of $I_s$. The upper panel shows that only a DAD occurs, whereas the middle and lower panels show three extra spikes and tonic firing, respectively.

Slow inward current as in (6) results in a system of three first-order ordinary differential equations (ODEs), which we call the “3-D ZFN model” [4], namely,

$$\frac{dV}{dt} = -V(V - a)(V - 1) - w + zI_s + I_{\text{appl}}(t),$$

(13)

$$\frac{dw}{dt} = \alpha(V - rw),$$

(14)
The bifurcation diagram shows the transition from a stable steady state to a large amplitude oscillatory solution, then back to a stable steady state as the bifurcation parameter $I_z$ is increased.

\[
\frac{\partial z}{\partial t} = k_s[\theta(V - V_T) - z].
\] (15)

The voltage solutions to the ZFN model are very similar to those for the Kepler–Marder model in that they exhibit one-to-one spiking, extra spikes, and tonic firing.

A better understanding of the dynamical structure of the solutions comes from the bifurcation diagrams. For the FHN equations with a constant forcing term, $I_z$, we have the equations

\[
\frac{dV}{dt} = -V(V - a)(V - 1) - w + I_z,
\] (16)

\[
\frac{dw}{dt} = \varepsilon(V - rw),
\] (17)

and the bifurcation diagram with bifurcation parameter $I_z$ is shown in Fig. 8. As $I_z$ is increased, the stable steady state undergoes a bifurcation into a large amplitude oscillatory solution. This oscillatory solution continues until a larger value of $I_z$ is reached where the oscillations cease. On the other hand, the bifurcation diagram in Fig. 9 for the ZFN model with bifurcation parameter $I_s$ is much more complicated. However, the basic dynamical mechanisms are the same for these two different models. As $I_s$ is increased, there is a bifurcation from a stable steady state to a large amplitude oscillatory solution at the saddle-node of periodics (SNP).
5. Pancreatic $\beta$-cells

Pancreatic $\beta$-cells are responsible for the secretion of insulin, which is needed to maintain blood glucose levels within a normal physiological range. Insufficient secretion of insulin or insensitivity of cells to utilize insulin can result in hyperglycemia (or diabetes), i.e., abnormally high levels of blood glucose. The opposite condition is hypoglycemia. Bursting electrical activity (BEA) is the hallmark of activity in pancreatic $\beta$-cells, see the upper traces in Fig. 10 where the membrane potential is plotted as a function of time. Note the periodic behavior of the bursts with active phases separated by silent phases. One measure of the level of BEA is the “plateau fraction”, which is defined as the ratio of the time the membrane potential spends in the active phase to the period of the BEA. There is a strong correlation between the rate of release of insulin from the pancreatic $\beta$-cells and the plateau fraction, see the lower graph in Fig. 10.

5.1. Models for BEA

Our objective here will be to describe a method for computing the plateau fraction to leading order in a small parameter. The first mathematical model for BEA in pancreatic $\beta$-cells was proposed in 1983 by Chay and Keizer [1]. In the 1980s, many other models were proposed depending on the specific ionic currents which were included [2]. All of these models had two common features: (1) they consisted of three first-order ODEs, and (2) two of the variables were “fast” variables and one was a “slow” variable. The latter feature means that for some part of the period of the BEA, one of the variables evolved slowly in time relative to the other two. We can take advantage of this slow variable, i.e., of the small parameter in the equations, from the point of view of dynamical systems theory and perturbation theory.

To illustrate the method for computing the plateau fraction, we will state the results for a specific model due to Sherman et al. [16] given by

$$C \frac{\partial V}{\partial t} = - \tilde{g}_{Ca} m_{\infty}(V) h(V) (V - V_{Ca}) - \tilde{g}_K n(V - V_K) - g_K c_a (C_a)(V - V_K),$$

(18)
Fig. 10. Bursting electrical activity in pancreatic β-cells. Top: Experimental record of BEA in pancreatic β-cells. The two phases of the periodic behavior are the active phase and the silent phase. Bottom: Diagram showing the strong correlation between insulin release rate from β-cells and the plateau fraction.

\[
\frac{dn}{dt} = \frac{n_\infty(V) - n}{\tau_n(V)}, \quad (19)
\]

\[
\frac{dCa_i}{dt} = f[zg_{Na}m_\infty(V)h(V)(V - V_{Ca}) - k_{Ca}Ca_i], \quad (20)
\]

where only the Ca\(^{2+}\), K\(^+\), and Ca\(^{2+}\)-activated K\(^+\) currents are included, the K\(^+\) activation function, \(n\), depends on \(V\) and \(t\) and appears linearly, and the free intracellular Ca\(^{2+}\) concentration evolves according to the last equation.

Nondimensionalization of these equations, elimination of the activation variable, and performing a transformation of variables \([12,13]\) give a system of one second-order ODE and one first-order ODE, namely,

\[
\frac{d^2u}{dt^2} + F(u)\frac{du}{dt} + G(u, c) = \varepsilon H(u, c), \quad (21)
\]

\[
\frac{dc}{dt} = \varepsilon(\beta h(u) - c), \quad (22)
\]

where \(u \equiv \iota n(v + 1)\) with \(v\), the nondimensionalized form of \(V\), is the “fast” variable, \(c\) is the nondimensionalized form of the slow variable, \(\varepsilon \ll 1\) is the small dimensionless parameter, and \(F(u), G(u, c), \text{ and } H(u, c)\) are highly nonlinear functions of \(u\) and \(c\). The solution of these equations are shown in Fig. 11 and illustrate the periodic bursting behavior.
Fig. 11. BEA from the Sherman–Rinzel–Keizer model. The periodic bursting electrical activity is obtained when solving the SRK model. The active and silent phases appear in a very regular pattern.

Fig. 12. Phaseplane portrait for the solution. The $u$-nullcline, given by $G(u, c) = 0$, and the $c$-nullcline, given by $c = \beta h(u)$, are plotted on the $(u, c)$ projection of the $(u, \dot{u}, c)$-phasespace. Superimposed is the BEA trajectory showing the active and silent phases.

To obtain a better understanding of the solution and the method to be developed for computing the plateau fraction, in Fig. 12, we have plotted the nullclines for the $u$-equation and for the $c$-equation, i.e., the curves corresponding to $d^2u/dt^2 = 0 = du/dt$ and to $dc/dt = 0$, respectively. Superimposed on this phase plane is the solution trajectory with labels for the active phase and silent phase. Note that to the left of the $c$-nullcline, given by $c = \beta h(u)$, $c$ is decreasing, and to the right, $c$ is increasing. The middle branch of the $u$-nullcline consists of unstable saddle points, so when the solution oscillations in the active phase hit this branch, the solution is driven towards the silent phase on the left branch.

As is evident from the phaseplane picture in Fig. 12, the solution trajectory in the silent phase follows the left branch of the $u$-nullcline quite closely. A simple perturbation analysis of the system of equations where a new time variable is introduced by $\tilde{t} = \epsilon t$ shows that to leading order, $u$ and $c$ satisfy the algebraic equation, $G(u, c) = 0$. Thus the leading order membrane potential, $U_0$, and the leading order intracellular calcium concentration, $C_0$, are obtained by solving the differential-algebraic
system \[12,13\]

\[ G(U_0, C_0) = 0, \quad \frac{dC_0}{dt} = \beta h(U_0) - C_0. \]  

(23)

One can solve (23) for \(C_0 = \gamma(U_0)\), so that (23) becomes

\[ \frac{dU_0}{d\tilde{t}} = Z(U_0; \beta), \]  

(24)

which can be solved as the quadrature

\[ \tilde{t} = \int_{U_0(0)}^{U_0(\tilde{t})} \frac{d\xi}{Z(\xi; \beta)}. \]  

(25)

For the active phase, we can formally set \(\varepsilon = 0\) to obtain the following leading order problem

\[ \frac{d^2u}{dt^2} + F(u)\frac{du}{dt} + G(u, c) = 0, \quad \frac{dc}{dt} = 0, \]  

(26)

so the leading order solution consists of \(u\) satisfying a Lienard equation and \(c\) held fixed. At this stage, there is no small parameter left in the equation, so we must deal with the full Lienard equation, i.e., with the nonlinearity in the first derivative term, in the active phase. The solution trajectory for values of \(c\) in the range of the active phase corresponds to trajectories approaching a limit cycle, as seen in Fig. 13. As \(c\) increases, the limit cycle gets closer and closer to the homoclinic orbit passing through the saddlepoint that is located on the middle branch of the \(u\)-nullcline. For even larger values of \(c\), the limit cycle disappears, and the solution trajectory moves away to where the equations are no longer valid.

However, a remarkable numerical fact (Pernarowski [13]) allows further progress analytically. In Fig. 14, the solution trajectory is plotted in the \((\dot{u}, \int_0^1 G(u(s), c(s))ds)\)-plane, and one sees that the solution trajectory lies very close to the straight line through the origin with slope \(-1\). This means that the “offending” nonlinear first derivative term is numerically small. In fact, with the parameters
Fig. 14. Approximately a strongly nonlinear oscillator. The solution trajectory in this plane is confined to a narrow band around the straight line through the origin with slope $-1$. Thus the Lienard equation is closely approximated by a strongly nonlinear oscillator.

used, the order of magnitude of this term is $O(\sqrt{\varepsilon})$. Thus, the Lienard equation can be approximated by

$$\frac{d^2u}{dt^2} + G(u, c) = 0,$$

which corresponds to a strongly nonlinear oscillator equation for which some dynamical systems theory exists.

In particular, our main goal is to determine for what critical value of $c$ does the solution trajectory cross the middle branch of the $u$-nullcline from the active phase to the silent phase. For values of $c$ below this critical value, the solution trajectory asymptotes to a limit cycle; therefore, the solution cannot escape to the silent phase, cf. Fig. 12. Only when the limit cycles cease to exist is the solution trajectory free to move to the left branch of the $u$-nullcline. The Melnikov distance, a concept from dynamical systems theory, is a measure for fixed $c$ of the distance between the stable ($\bar{x}^s$) and unstable ($\bar{x}^u$) manifolds emanating from the saddle points on the middle branch, see Fig. 15. An explicit formula for this distance is given by

$$D(c) = \bar{N} \cdot (\bar{x}^s - \bar{x}^u) = 2^{3/2} \int_{a_s}^{b_s} F(u) \sqrt{P(a_s, c) - P(u, c)} \, du$$

where $\bar{N}$ is a normal vector to the separatrix corresponding to (27), $\bar{x}^s$ and $\bar{x}^u$ are points on the stable and unstable manifolds from the saddle point, respectively, and $P(u, c)$ is the potential function for $G(u, c)$. The point $a_s$ corresponds to the zero of $G(a_s, c) = 0$ for given $c$, and $P(a_s, c) = P(b_s, c)$.

When the Melnikov distance is equal to zero, the stable and unstable manifolds merge to give the homoclinic orbit. It is (approximately) at this value of $c$ that the solution trajectory crosses the middle branch and goes to the silent phase. For the SRK model, values of the Melnikov distance, $D$, computed from (28), are plotted in Fig. 16, and the critical value of $c$, $c_{cr}$, occurs at $D = 0$. 
Fig. 15. Melnikov distance. The Melnikov distance is a measure of the spread between the stable and unstable manifolds which go through the saddle point. The separatrix is the homoclinic orbit for the reduced equation (27).

Fig. 16. Critical value of $c$. The solution trajectory exits the active phase for $c \approx c_{cr} = 1.301$ where the Melnikov distance is zero. From numerical computations on the full SRK model, we obtain $c_{cr} = 1.295$.

The time that the solution trajectory spends in the active phase is determined by computing the time it takes for $c$ to climb up the right branch of the curve $G(u,c) = 0$ from the minimum value of $c$ (determined from the minimum value of $c$ in the silent phase) up to $c_{cr}$. The difficulty is that in the active phase, the solution undergoes rapid oscillations in $u$ while the slow variable, $c$, increases slowly. Using a multiple scales analysis in the active phase, we introduce both fast and slow time scales, $\tau$ and $\tilde{t}$, respectively, and average over the fast oscillations in $\tau$. Assuming that $c = c(\tilde{t})$ depends only on the slow time, we can integrate over one period of the oscillation in $\tau$, thus obtaining the leading order evolution equation for $c = c_0(\tilde{t})$ (see ([13]) for details)

$$\frac{dc_0}{d\tilde{t}} = \beta \tilde{h}(c_0) - c_0$$

(29)

where

$$\tilde{h}(c_0) = \int_{0}^{1} h(u_0(\tau, \tilde{t}, c_0)) d\tau.$$  

(30)
This is a first order nonlinear ODE which can be solved formally by quadrature. One can approximate $\tilde{h}(c)$ with a quadratic in $c$ by computing $\tilde{h}$ for several values of $c$ and curve fitting the results, i.e., let $\tilde{h}(x) = h_2c^2 + h_1c + h_0$ where $h_0, h_1, h_2$ are fitting parameters. Thus, the leading order active phase duration is given by

$$T_0^a(\beta) = \frac{1}{\varepsilon} \int_{c_s}^{c_a} \frac{dc}{\beta \tilde{h}(c) - c}.$$  \hspace{1cm} (31)

Then the determination of the plateau fraction is computed from

$$\rho_f^0 = \frac{T_0^a}{T_0^a + T_0^s}$$  \hspace{1cm} (32)

where $T_0^a$ is obtained from (31) and $T_0^s$ is obtained from (25) when the lower and upper limits are the most negative and most positive values of $U_0$, respectively, in the silent phase. The approximation results are plotted in Fig. 17 along with the results obtained by computing the plateau fractions for the full SRK model over the given range of $\beta$. The curve for the approximate values of the plateau fraction lies above the more accurate curve because of the reduced denominator in (32) due to omission of the transition times between the silent and active phases. The jumps in the more accurate curve are a result of the gain or loss of an oscillation as $\beta$ changes.

6. Conclusion

In this paper, we have surveyed a variety of electrical phenomena in excitable cells and given the underlying mathematical models which are being developed and analyzed to understand these phenomena. In particular, the model equations still rely on the Hodgkin–Huxley-type [5] currents used almost 50 years ago.

For electrical activity in neurons, we sketched the frequency domain analysis that we have developed to examine resonance phenomena in oscillatory electrical activity in neurons and showed...
how we can use computer technology to mimic pharmacological drug applications to identify ionic membrane currents. We described triggered activity in cardiac cells and showed the similarities with spontaneous secondary spiking observed in axons of the crab. A simple modified FitzHugh–Nagumo model can be shown to exhibit the same phenomena. Electrical activity in pancreatic β-cells occur in bursts, and we showed how one can use a combination of perturbation theory and dynamical systems theory to obtain approximations to the plateau fraction.

The ubiquity of membrane ionic models to understand electrical activity in a variety of cells in the body is surprising. At the same time, it is reassuring to know that it is worth the effort to develop the mathematical methods and theory to try to understand them.

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