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STABILITY OF IMPULSIVELY FORCED EXCITABLE FIBERS TO PERTURBATIONS OF THE FORCING PERIOD

JOHN W. CAIN†

Abstract. Fibers of electrically coupled nerve or cardiac cells are among the best-known examples of excitable media. Such fibers are often forced periodically at one end by an impulsive electrical stimulus current, eliciting sequences of traveling pulses. If the excitable medium happens to be cardiac tissue, it is natural to ask whether a sudden change in the period of the forcing (e.g., the heart rate) might induce an abnormal pattern of electrical wave propagation. In this manuscript, we analyze the transient response of an excitable medium following a change in the period of impulsive forcing. There are two specific questions that we shall address: First, under what conditions is a periodic train of identical traveling pulses stable to small perturbations in the period of forcing? Second, in the stable regime, what can be said analytically regarding the transient behavior in response to a perturbation in the period of forcing? Instead of using the traditional reaction-diffusion model for wave propagation in excitable fibers, we analyze a kinematic model which describes the progress of each propagating wave front and wave back. The linearization of the kinematic model, presented as a recursive sequence of ordinary differential equations, can be solved exactly in terms of generalized Laguerre polynomials integrated against an exponential kernel. The solution gives the desired approximation to the transient behavior following a change in the forcing period and, with the aid of some basic functional analytic formalism, a criterion for linear stability of a periodic pulse train. In the appendix, we illustrate how this framework applies to a specific model of an excitable cardiac fiber.

Key words. excitable medium, periodic forcing, kinematic model, cardiac, action potential

AMS subject classifications. 92C50, 33C90, 34A37

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1. Introduction. Fields of dry grass, cardiac cells, and toilets are among the many examples of excitable systems in nature [19]. An excitable system is one with the following property: if the system is sufficiently well rested, then a sufficiently strong stimulus elicits a dramatic response followed by an eventual return to the resting state. It is instructive to interpret the various terms in this definition in the context of each of the examples listed above. If a sufficiently large fire (stimulus) forms in a field of dry grass, the fire may elicit a propagating wave of flames (dramatic response) spreading across the field. The field cannot respond to further stimuli (fires) until enough time has passed for the grass to start growing back. Similarly, if we apply a sufficiently strong force (stimulus) to the handle of a quiescent toilet, the toilet will flush (dramatic response). During the flush, pressing on the handle again cannot elicit another response until some threshold amount of time (the refractory time) has passed. Finally, in the cardiac cell example, a sufficiently strong electrical current (stimulus) may cause the voltage across the cell membrane to experience a prolonged elevation (dramatic response) before eventual repolarization to the resting potential (see Figure 1). Physiologists would refer to that dramatic response as an action potential. Henceforth, cardiac tissue is the excitable medium that we shall consider.
For the benefit of readers unfamiliar with electrophysiology jargon, we shall keep such terminology to a minimum.

In spatially extended tissue, superthreshold stimuli can elicit propagating action potentials because neighboring cells are electrically coupled via gap junctions (see [24], Chapter 9). To be specific, let \( v = v(x, t) \) denote transmembrane voltage measured at time \( t \) in a cell at position \( x \) within a tissue sample. When the tissue is quiescent, \( v(x, t) \) remains at some constant resting potential. Applying a single superthreshold stimulus elicits an outward-propagating wave of elevated \( v \) (an action potential). For “one-dimensional” fibers of cells joined end-to-end, the response is a pair of traveling pulses moving in opposite directions; for “two-dimensional” sheets of tissue, the response is an expanding “ring.”

Periodic stimulation, or pacing, generates a train of propagating action potentials. If the pacing period \( B \) is large (slow pacing), the generic steady-state response is a periodic wave train. Gradually varying \( B \) affects both action potential duration (APD) and propagation speed, a property known as restitution, and the dependence of steady-state APD upon \( B \) is quantified by the restitution function. Importantly, if \( B \) becomes critically small, the periodic wave train may suffer a loss of stability (see, for example, [6]). This bifurcation can induce discordant alternans, abnormal spatial heterogeneity of APD in which adjacent regions of tissue exhibit out-of-phase beat-to-beat alternation of APD [9, 25, 33]. Alternans is believed to create a substrate for potentially fatal arrhythmias [23, 25, 27]. See Pastore et al. [23] for an explanation of the cascade from discordant alternans to unidirectional block of an action potential, subsequent formation of a reentrant spiral wave, and eventual degradation to an often deadly rhythm known as ventricular fibrillation. Regarding the latter transition, [10] contains a compendium of mechanisms describing how spiral wave breakup leads to turbulent patterns reminiscent of fibrillation. Consequently, considerable effort has been devoted towards understanding the bifurcation to alternans mathematically; see, for example, [7, 11, 16, 22, 31] or most of the other studies referenced in this paragraph. The earliest of those articles [22] advanced what is now referred to as the restitution hypothesis, which states that the stability threshold occurs at \( B \) for which the slope of the restitution function has magnitude 1.

In this article, we use a novel technique to show that the restitution hypothesis correctly predicts whether periodically paced excitable fibers are stable to perturbations of the pacing period, provided that repolarization occurs via a phase wave.\(^1\)

\(^1\)For an explanation of this term, see the key assumption in section 2 and related discussion in section 5.
This result is stated abstractly as Proposition 4.2, and subsequently interpreted as a restatement of the restitution hypothesis. Readers familiar with kinematic analyses of waves in excitable media will recognize that Proposition 4.2 agrees with its counterpart in Courtemanche, Keener, and Glass [6] where, under the same assumption that repolarization occurs via a phase wave, it is shown that the restitution hypothesis is the correct stability criterion for a reentrant action potential circulating in a one-dimensional ring. Indeed, the more novel contributions of the present article lie in the mathematical techniques (see next paragraph) introduced to prove Proposition 4.2, and our methods offer several advantages over prior analyses of kinematic models. First, a natural side effect of our calculations is a detailed approximation of the transient response to perturbed pacing (see (3.8)). Second, our sole simplifying assumption is not supplemented by ad hoc additional assumptions of the sort appearing in [9], namely, the rather artificial introduction of advection and diffusion terms in an amplitude equation describing spatial APD variation. Finally, by analyzing a paced fiber as opposed to a reentrant action potential in a ring (as in [6, 15, 29]), we are free to simulate pacing however we wish rather than having the cycle length determined by a reentrant pulse.

The remainder of this manuscript is organized as follows. In section 2.1 we recall a kinematic model [19, 26] for wave propagation in a one-dimensional excitable medium with impulsive, periodic forcing applied at one of the boundaries. In that model, a recursively-defined sequence of ordinary differential equations (ODEs) governs the progress of the wave fronts and wave backs in a train of propagating pulses. Although the use of kinematic models is quite common in the study of waves in excitable media [3, 6, 9, 12, 15, 29, 33], for the benefit of readers familiar with the more standard partial differential equation (PDE) models, we briefly recall how the kinematic model equations can be derived from a PDE model. Section 2.2 sets the framework for proving the two main results: (3.8) and Proposition 4.2. Namely, we establish the initial and boundary conditions that simulate a sudden change in the forcing period, working under the assumption that the system had exhibited a stable, periodic wave train prior to the perturbation. Anticipating the derivation of the stability criterion later in the manuscript, we linearize the kinematic model equations to obtain an infinite, recursive sequence of linear ODEs. We solve those ODEs in section 3 and, while the process is slightly tedious, it involves a technique that may be applicable in the study of other infinite-dimensional systems of differential equations. The exact solution of the linearized kinematic model equations (3.8) allows us to approximate the transient response to the perturbation in the pacing period. In section 4, some basic formalism from functional analysis offers a convenient framework for deriving the stability criterion. In section 5, we conclude with (i) a discussion of our key assumption regarding phase waves, (ii) an example showing how the ideas in this manuscript apply to a specific model of the action potential appearing in the appendix, and (iii) examples of problems for future study.

2. Derivation of the governing equations.

2.1. Reaction-diffusion and kinematic models. Let us briefly describe two types of models for action potential propagation in a one-dimensional fiber: reaction-diffusion models (the most common type) and kinematic models (the type analyzed in this manuscript).

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The unphysical discontinuities that those authors aimed to prevent using such terms are a nonissue in this study, as we shall not analyze the discordant alternans regime.
Reaction-diffusion models describe the dynamics of $v(x,t)$ as well as other variables, such as transmembrane currents associated with individual ions. In the simplest case, $v(x,t)$ is coupled to just one\(^3\) other variable $h(x,t)$, an inactivation gate variable which prevents $v$ from becoming too large during an action potential; see the model in the appendix for an example. Often, the model equations are scaled into the form

$$
\epsilon \frac{\partial v}{\partial t} = \epsilon^2 \frac{\partial^2 v}{\partial x^2} + F(v,h), \quad \frac{\partial h}{\partial t} = G(v,h),
$$

where $\epsilon > 0$ is a small parameter. The functions $F$ and $G$ are chosen to model the salient features of excitability, and are generally rooted in Hodgkin–Huxley formalism [14]. For derivations of (2.1) using standard cable theory, see the texts of Keener and Sneyd [19] or Plonsey and Barr [24]. There is a vast literature devoted towards understanding the dynamical behavior of (2.1) including, for example, mathematical analyses of (i) how and whether propagating waves evolve from initial data [17, 21], (ii) whether propagating pulses are stable to perturbations [32], and (iii) how self-sustaining structures such as spiral waves form in $\geq 2$ dimensions [18]. Not surprisingly, singular perturbation reductions are commonly used in such analyses.

Kinematic models [26], by contrast, track only the progress of each propagating wave as opposed to the complete spatiotemporal dynamics of $v(x,t)$ and $h(x,t)$. That kinematic models lack the detail of reaction-diffusion models is not necessarily a liability. Tracking the locations of wave fronts and wave backs is sufficient for many purposes (including our present goal of analyzing stability of a periodic traveling wave train),\(^4\) and the reduced complexity of kinematic models facilitates computation and mathematical analysis.

To establish the connection between these two types of models, consider a one-dimensional fiber of cells, identified with the interval $0 \leq x \leq L$. Suppose that impulsive forcing is applied at $x = 0$, with each stimulus eliciting a propagating action potential. The left panel of Figure 2 illustrates a typical space-time portrait of the resulting train of pulses. At each $x \in [0, L]$, the system is alternately excitable or refractory over time according to whether the variable $v$ exceeds some threshold

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\(^3\)Most models of the action potential incorporate multiple inactivation gates, not to mention ion-specific currents, ion pumps and exchangers, and so on, in which case $h(x,t)$ is actually vector valued. For a repository of cardiac action potential models, see www.cellml.org.

\(^4\)When attempting to contain a wildfire, locating the leading and trailing edges of the flames is more essential than a detailed spacetime rendering of flame temperature.
For our purpose of analyzing stability of propagating trains of pulses, we need not solve (2.1) to obtain \( v(x, t) \)—rather, we need only track the progress of each wave front and wave back. A two-dimensional space-time rendering of these fronts and backs can be generated by (i) taking the intersection of the plane \( v = v_{\text{thr}} \) with the surface plot of \( v(x, t) \) versus \( x \) and \( t \), and (ii) projecting the resulting family of curves onto the \( x-t \) plane (right panel of Figure 2). Let \( n \) index the number of impulsive stimuli that have been applied at the \( x = 0 \) boundary. At each position \( x \), let \( A_n(x) \) denote the total amount of time over which the medium is in the refractory state \( (v \geq v_{\text{thr}}) \) following the arrival of the \( n \)th wave front. Let \( D_n(x) \) denote the amount of time in which \( v < v_{\text{thr}} \) following the \( n \)th excitation and preceding the arrival of the \((n+1)\)st wave front. These definitions are illustrated in the right panel of Figure 2.

If the \( x = 0 \) boundary is paced periodically with period \( B \), it must be the case that \( A_n(0) + D_n(0) = B \).

The derivation of the kinematic model equations is based upon the following.

**Key assumption.** For each \( x \), both the duration and the (local) propagation speed of each action potential depend upon the amount of recovery time that the system was allowed following the previous action potential. In particular, recovery of excitability following an action potential occurs via a system was allowed following the previous action potential. In particular, recovery of excitability following an action potential occurs via a

That is, \( A_n(x) = f(D_{n-1}(x)) \) for each \( x \in [0, L] \), for some appropriately chosen restitution function \( f \), and the propagation speed has a similar functional dependence on \( D_{n-1}(x) \) which we shall denote by \( c(D_{n-1}(x)) \). Furthermore, it is natural to assume that both \( f \) and \( c \) are smooth, monotone increasing functions which eventually plateau (i.e., qualitatively similar to a constant minus a decaying exponential function). To understand why, we draw intuition from the toilet flushing example from the introduction. If a toilet is flushed for the \( n \)th time almost immediately after the \((n-1)\)st refractory period ends (i.e., very small \( D_{n-1} \)), then the flush will be “weaker” than if the tank had been allowed to completely refill. Allowing for a longer \( D_{n-1} \) elicits a more dramatic flush and, for all values of \( D_{n-1} \) above some threshold corresponding to complete refilling of the tank, all flushes are identical.

With the preceding paragraph and Figure 2 in mind, the kinematic model equations are straightforward to write down. Referring to the figure, let \( \phi_n(x) \) denote the arrival time of the wave front of the \( n \)th traveling pulse at position \( x \), and let \( \beta_n(x) \) denote the arrival time of the \( n \)th wave back (which marks the end of the \( n \)th refractory period). The difference between the arrival times of the \( n \)th and \((n+1)\)st wave fronts is

\[
\phi_{n+1}(x) - \phi_n(x) = A_n(x) + D_n(x) = f(D_{n-1}(x)) + D_n(x). \tag{2.2}
\]

Next, observe that the slope of \( \phi_n(x) \) is the multiplicative inverse of the propagation speed, keeping in mind that Figure 2 shows a plot of \( t \) versus \( x \), not vice versa. That is, \( \phi'_n(x) = 1/c(D_{n-1}(x)) \). Defining \( q(D_n) = 1/c(D_n) \) to simplify future notation, we differentiate both sides of (2.2) and rearrange terms to obtain

\[
\frac{d}{dx} [D_n(x) + f(D_{n-1}(x))] = q(D_n(x)) - q(D_{n-1}(x)). \tag{2.3}
\]

Combined with the previously stated boundary condition \( D_n(0) = B - f(D_{n-1}(0)) \) and an initial function \( D_0(x) \), the kinematic model equation (2.3) and the relationship

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The validity of this assumption is discussed in section 5.
2.2. Linearized kinematic model. Now we turn our attention toward simulating the effects of a perturbation to the period of impulsive forcing at the \( x = 0 \) boundary. Suppose that the interval between the \( n \)th and \((n + 1)\)st stimuli is \( B_{\text{old}} \) if \( n \leq 0 \) and \( B_{\text{new}} \) if \( n > 0 \). This imposes the boundary condition

\[
D_n(0) = \begin{cases} 
B_{\text{old}} - f(D_{n-1}(0)), & n \leq 0, \\
B_{\text{new}} - f(D_{n-1}(0)), & n > 0. 
\end{cases}
\]

Assume that prior to the perturbation (i.e., \( n \leq 0 \)), the medium achieved a steady response consisting of a periodic train of identical traveling pulses marching along with constant speed. In particular,

\[
D_0(x) = D^*_{\text{old}},
\]

where \( D^*_\text{old} \) is the unique\(^6\) solution of \( D^*_\text{old} + f(D^*_\text{old}) = B_{\text{old}} \). Combining (2.3), (2.4), and (2.5), we obtain a sequence of equations that can be solved iteratively to determine \( D_n(x) \) for \( n > 0 \) and \( 0 \leq x \leq L \). Figure 3 illustrates the sort of spatial variation in \( D_n(x) \) that one might observe by solving (2.3) subject to the boundary condition (2.4) and initial condition (2.5).

To analyze the transient behavior following the change in the pacing period, we linearize (2.3), (2.4) for \( n \geq 0 \). The resulting sequence of initial value problems (see (2.7), (2.8)) leads to our main sequence of equations (see (2.12)), which we solve exactly in the next section to obtain approximations of the functions \( D_n(x) \) for \( n \geq 0 \).

To linearize (2.3), (2.4) for \( n \geq 0 \), let \( D^*_\text{new} \) denote the unique steady-state associated with long-term forcing with period \( B_{\text{new}} \) and let \( y_n(x) \) denote our approximation of \( D_n(x) - D^*_\text{new} \). By (2.5), we have

\[
y_0(x) = D^*_\text{old} - D^*_\text{new},
\]

a constant. For \( n > 0 \), the linearization of (2.3), (2.4) about \( D^*_\text{new} \) is given by

\[
\frac{d}{dx} [y_n(x) + \alpha y_{n-1}(x)] = -\lambda [y_n(x) - y_{n-1}(x)],
\]

\[
y_n(0) = -\alpha y_{n-1}(0) \quad (n > 0),
\]

\(^6\)Uniqueness follows from the fact that \( f \) is monotone increasing.
where

\[ \alpha = f'(D_{\text{new}}^*) \]

is the magnitude of the Floquet multiplier of the one-dimensional mapping \( A_{n+1} = f(D_n) = f(B_{\text{new}} - A_n) \) and

\[ -\lambda = q'(D_{\text{new}}^*). \]

The negative sign in (2.10) emphasizes that \( q(D) = 1/c(D) \) is a monotone decreasing function since \( c \) is monotone increasing (see previous subsection). Note that \( \alpha \) is dimensionless and \( \lambda \) has units of \((\text{length})^{-1}\).

We may solve (2.7), (2.8) for \( y_n(x) \) in terms of \( y_{n-1}(x) \), resulting in a recursive sequence of equations. After rewriting (2.7) as

\[ \frac{d}{dx} [y_n(x) + \alpha y_{n-1}(x)] = -\lambda [y_n(x) + \alpha y_{n-1}(x)] + (\alpha + 1)\lambda y_{n-1}(x), \]

use \( e^{\lambda x} \) as an integrating factor, apply the boundary condition (2.8), and rearrange terms to obtain

\[ y_n(x) = -\alpha y_{n-1}(x) + (\alpha + 1)\lambda \int_0^x e^{-\lambda(x-s)} y_{n-1}(s) \, ds \quad (n \geq 1). \]

\[ \text{3. Solution of the linearized equations.} \]

The recurrence (2.12) can be solved exactly, yielding a closed formula for \( y_n(x) \). While some of the technical details make for some rather dry reading, we find it encouraging that this procedure may be applicable in the analysis of other sequences of ODEs. Assume without loss of generality that the function \( y_0(x) \), a constant, is identically 1. By inserting \( y_0(x) \equiv 1 \) into the recursion (2.12), we compute that the first two iterates are

\[ y_1(x) = -\alpha + (\alpha + 1)(1 - e^{-\lambda x}), \]
\[ y_2(x) = 1 + (\alpha^2 - 1)e^{-\lambda x} - (\alpha + 1)^2\lambda xe^{-\lambda x}. \]

Seeking a pattern in the recursion process is the most challenging step, and is facilitated by two observations. First, it is evident that the \(-\alpha y_{n-1}(x)\) term in (2.12) will cause powers of \(-\alpha\) to accumulate during the iterative process of generating \( y_n(x) \) from \( y_0(x) \). Second (and less transparently), rescaling the integrand in (2.12) so that the upper limit of integration is \( \lambda(\alpha + 1)x/\alpha \) aids in factoring out those powers of \(-\alpha\). It is natural to conjecture that \( y_n(x) \) can be written in terms of an integral of a polynomial \( P_{n-1} \) of degree \((n-1)\) integrated against an exponential kernel and, with the preceding observations in mind, we make the following proposition.

\[ \text{Proposition 3.1.} \]

\[ y_n(x) = (-\alpha)^n \left[ 1 - \int_0^{\lambda(\alpha + 1)/\alpha} e^{-\alpha s} P_{n-1}(s) \, ds \right] \quad (n \geq 1), \]

where \( P_{n-1} \) is a polynomial of degree \((n-1)\) and \( P_{n-1}(0) = n \).

\[ \text{Proof.} \] We prove Proposition 3.1 by induction on \( n \) and, in the course of doing so, we shall derive a recurrence that the polynomials \( P_n \) must obey. Regarding the
"base" case for the induction, factor \(-\alpha\) from the expression for \(y_1(x)\) in (3.1) above:

\[
y_1(x) = -\alpha \left[1 - \frac{(\alpha + 1)}{\alpha} (1 - e^{-\lambda x})\right] = -\alpha \left[1 - \int_0^{\frac{\lambda(x+1)}{\alpha}} e^{-\frac{\alpha}{\alpha+1}} ds\right].
\]

It follows that \(P_0(x) \equiv 1\).

Now for the inductive step, suppose that the claim holds for \(y_n(x)\) for some \(n \geq 1\), and insert the expression (3.2) into the recurrence (2.12) to generate \(y_{n+1}(x)\). The result is

\[
y_{n+1}(x) = -\alpha y_n(x) + (\alpha + 1) \lambda e^{-\lambda x} \int_0^x e^{\lambda s} y_n(s) ds
\]

\[
= (-\alpha)^{n+1} \left[1 - \int_0^{\frac{\lambda(x+1)}{\alpha}} e^{-\frac{\alpha}{\alpha+1}} P_{n-1}(s) ds\right]
\]

\[
+ (\alpha + 1) \lambda e^{-\lambda x} \int_0^x e^{\lambda s} (-\alpha)^n \left[1 - \int_0^{\frac{\lambda(x+1)}{\alpha}} e^{-\frac{\alpha}{\alpha+1}} P_{n-1}(\xi) d\xi\right] ds.
\]

Factoring out \((-\alpha)^{n+1}\) and evaluating \(\int_0^x e^{\lambda s} ds\), we find that

\[
y_{n+1}(x) = (-\alpha)^{n+1} \left[1 - \int_0^{\frac{\lambda(x+1)}{\alpha}} e^{-\frac{\alpha}{\alpha+1}} P_{n-1}(s) ds - \left(\frac{\alpha + 1}{\alpha}\right) (1 - e^{-\lambda x})\right]
\]

\[
+ \frac{\lambda(\alpha + 1)}{\alpha} e^{-\lambda x} \int_0^x \int_0^{\frac{\lambda(x+1)}{\alpha}} e^{\lambda s} e^{-\frac{\alpha}{\alpha+1}} P_{n-1}(\xi) d\xi ds.
\]

Focus temporarily on the iterated integral alone, and reverse the order of integration:

\[
\int_0^x \int_0^{\frac{\lambda(x+1)}{\alpha}} e^{\lambda s} e^{-\frac{\alpha}{\alpha+1}} P_{n-1}(\xi) d\xi ds = \int_0^{\frac{\lambda(x+1)}{\alpha}} \int_0^x e^{\lambda s} e^{-\frac{\alpha}{\alpha+1}} P_{n-1}(\xi) d\xi ds
\]

\[
= \frac{1}{\lambda} \int_0^{\frac{\lambda(x+1)}{\alpha}} \left[e^{\lambda x} - e^{-\frac{\alpha}{\alpha+1}}\right] e^{-\frac{\alpha}{\alpha+1}} P_{n-1}(\xi) d\xi.
\]

Returning to our most recent expression for \(y_{n+1}(x)\), we replace the iterated integral with this single integral and revert from \(\xi\) to \(s\) as our dummy variable of integration:

\[
y_{n+1}(x) = (-\alpha)^{n+1} \left[1 - \int_0^{\frac{\lambda(x+1)}{\alpha}} e^{-\frac{\alpha}{\alpha+1}} P_{n-1}(s) ds - \left(\frac{\alpha + 1}{\alpha}\right) (1 - e^{-\lambda x})\right]
\]

\[
+ \left(\frac{\alpha + 1}{\alpha}\right) \int_0^{\frac{\lambda(x+1)}{\alpha}} [1 - e^{-\lambda x} e^{-\frac{\alpha}{\alpha+1}}] e^{-\frac{\alpha}{\alpha+1}} P_{n-1}(s) ds\right].
\]

In the interest of coaxing this expression into the form that would complete our inductive step, it is helpful to rewrite

\[
\left(\frac{\alpha + 1}{\alpha}\right) (1 - e^{-\lambda x}) = \int_0^{\frac{\lambda(x+1)}{\alpha}} e^{-\frac{\alpha}{\alpha+1}} ds
\]
so that

\[ y_{n+1}(x) = (-\alpha)^{n+1} \left[ 1 - \int_0^\lambda \frac{\lambda^{(n+1)x}}{\alpha} e^{\frac{-\alpha x}{\lambda}} (1 + P_{n-1}(s)) \, ds \right. \]

\[ \left. + \left( \frac{\alpha + 1}{\alpha} \right) \int_0^\lambda \frac{\lambda^{(n+1)x}}{\alpha} e^{\frac{-\alpha x}{\lambda}} P_{n-1}(s) \, ds \right] . \]  

(3.3)

Our proof will be complete once we argue that

\[ \left( \frac{\alpha + 1}{\alpha} \right) \int_0^\lambda \frac{\lambda^{(n+1)x}}{\alpha} e^{\frac{-\alpha x}{\lambda}} P_{n-1}(s) \, ds = \int_0^\lambda \frac{\lambda^{(n+1)x}}{\alpha} e^{\frac{-\alpha x}{\lambda}} Q_n(s) \, ds, \]

where \( Q_n \) is a polynomial of degree \( n \). We claim that this is, in fact, the case with \( Q_n(x) = \int_0^x P_{n-1}(s) \, ds \). To see why, first observe that the left-hand side of (3.4) can be expanded as

\[ \left( \frac{\alpha + 1}{\alpha} \right) \int_0^\lambda \frac{\lambda^{(n+1)x}}{\alpha} e^{\frac{-\alpha x}{\lambda}} P_{n-1}(s) \, ds - \left( \frac{\alpha + 1}{\alpha} \right) e^{-\lambda x} \int_0^\lambda \frac{\lambda^{(n+1)x}}{\alpha} P_{n-1}(s) \, ds \]

\[ = \left( \frac{\alpha + 1}{\alpha} \right) \int_0^\lambda \frac{\lambda^{(n+1)x}}{\alpha} e^{\frac{-\alpha x}{\lambda}} P_{n-1}(s) \, ds - \left( \frac{\alpha + 1}{\alpha} \right) e^{-\lambda x} Q_n \left( \frac{\lambda(\alpha + 1)x}{\alpha} \right). \]

(3.5)

This is precisely the same expression one obtains by integrating the right-hand side of (3.4) by parts. Define \( P_n(x) = 1 + P_{n-1}(x) - Q_n(x) \) (a polynomial of degree \( n \)). Then \( P_n(0) = 1 + P_{n-1}(0) = n + 1 \), and

\[ y_{n+1}(x) = (-\alpha)^{n+1} \left[ 1 - \int_0^\lambda \frac{\lambda^{(n+1)x}}{\alpha} e^{\frac{-\alpha x}{\lambda}} P_n(s) \, ds \right], \]

completing the proof. \( \square \)

A pleasant side effect of the preceding proof is the generation of a recurrence relation for the polynomials \( P_n \):

\[ P_0(x) \equiv 1 \quad \text{and} \quad P_n(x) = 1 + P_{n-1}(x) - \int_0^x P_{n-1}(s) \, ds \quad (n \geq 1). \]

(3.6)

In other words, we have passed from a recurrence (2.12) for \( y_n(x) \) to a recurrence for the polynomials that appear in the integrand of the closed formula for \( y_n(x) \). This is a clear advantage over the original recurrence in that recurrence relations involving polynomials have been well studied in the context of special functions. Equation (3.6) is no exception, and has a closed form solution which can be expressed in terms of generalized Laguerre\(^7\) polynomials. We quote the following definition from Szegő [30].

**Definition 3.2.** Let \( \beta > -1 \) and \( n \geq 0 \). Then the generalized Laguerre polynomial \( L_n^{(\beta)}(x) \) is defined as

\[ L_n^{(\beta)}(x) = \sum_{m=0}^n \binom{n + \beta}{n - m} \frac{(-x)^m}{m!}. \]

---

\(^7\)As is frequently the case in the study of special functions, determining which class of polynomials satisfies a recurrence such as (3.6) requires a combination of both luck and time.
With Definition (3.7) in mind, we make the following proposition.

**Proposition 3.3.** The solution of (3.6) is given by $P_n(x) = L^{(1)}_{n+1}(x)$.

**Proof.** Again, we induct on $n$. Clearly the proposition holds for $n = 0$, so suppose inductively that

$$P_n(x) = \sum_{m=0}^{n} \binom{n+1}{n-m} \frac{(-x)^m}{m!}$$

for some $n \geq 1$. Applying (3.6) with the index $n$ incremented by 1,

$$P_{n+1}(x) = 1 + \sum_{m=0}^{n} \binom{n+1}{n-m} \frac{(-x)^m}{m!} - \int_0^x \sum_{m=0}^{n} \binom{n+1}{n-m} \frac{(-s)^m}{m!} ds$$

$$= 1 + \sum_{m=0}^{n} \binom{n+1}{n-m} \frac{(-x)^m}{m!} - \sum_{m=0}^{n} \binom{n+1}{n-m} \frac{(-x)^{m+1}}{(m+1)!}$$

$$= 1 + \sum_{m=0}^{n} \binom{n+1}{n-m} \frac{(-x)^m}{m!} - \sum_{m=1}^{n+1} \binom{n+1}{n+1-m} \frac{(-x)^m}{m!}$$

The terms indexed $m = 1$ through $m = n$ can be combined into a single summation,

$$P_{n+1}(x) = 1 + \binom{n+1}{n} + \sum_{m=1}^{n} \left[ \frac{n+1}{n-m} + \frac{n+1}{n+1-m} \right] \frac{(-x)^m}{m!}$$

$$+ \binom{n+1}{0} \frac{(-x)^{n+1}}{(n+1)!}$$

$$= (n+2) + \sum_{m=0}^{n} \frac{n+2}{n+1-m} \frac{(-x)^m}{m!} + \binom{n+1}{0} \frac{(-x)^{n+1}}{(n+1)!}$$

$$= \sum_{m=0}^{n+1} \frac{n+2}{n+1-m} \frac{(-x)^m}{m!} = L^{(1)}_{n+1}(x),$$

where we have used a combinatorial identity $\binom{n+1}{n-m} + \binom{n+1}{n+1-m} = \binom{n+2}{n+1-m}$ and the fact that $\binom{n+1}{0} = \binom{n+2}{0} = 1$.

Combining Propositions 3.1 and 3.3, we obtain a closed formula for the solution of (2.7), (2.8) in the case that $y_0(x) \equiv 1$, namely,

$$y_n(x) = (-\alpha)^n \left[ 1 - \int_0^{\frac{\Lambda(\alpha+1)x}{\alpha}} e^{-\frac{\alpha s}{x}} L^{(1)}_{n-1}(s) ds \right] \quad (n \geq 1).$$

Given the form of (3.8), our intuition is that a stability criterion of the form $\alpha < 1$ might be required and, as we shall see in the next section, this is the case. With our usual assumption that $y_0(x) \equiv 1$, the condition $\alpha < 1$ is necessary and sufficient for uniform convergence of $y_n(x) \to 0$ over any finite interval $[0, L]$. It is worth interpreting this result in terms of wave propagation in a periodically forced excitable medium. When $\alpha < 1$, the generic behavior following a small perturbation to the period of forcing is for the system to transition from one periodic wave train solution to a new one. The duration of the transient becomes progressively longer as $\alpha \to 1^-$. 
4. The stability criterion and associated formalism. In this section we show that $\alpha = 1$ is the threshold for stability in the sense that the sequence $\{y_n(x)\}$ converges uniformly on each finite interval $[0, L]$ when $\alpha < 1$, and diverges if $\alpha > 1$. To this end, it is helpful to define an operator which captures the recursive process of (2.12). Let $T = -\alpha I + (\alpha + 1)\lambda K$ on the Banach space $(C[0, L], \| \cdot \|_\infty)$, where $I$ denotes the identity operator and

\[(K\psi)(x) = \int_0^x e^{-\lambda(x-s)}\psi(s) \, ds.\]

Then clearly $y_n = Ty_{n-1} = T^n y_0$.

It is worth noting that the operator norm $\| T \|$ can exceed 1 if the length $L$ of the domain is large.

**Proposition 4.1.**

\[\| T \| = \alpha + (\alpha + 1)(1 - e^{-\lambda L}).\]

**Proof.** To see that the expression in (4.2) is a lower bound on $\| T \|$, consider the functions

\[\psi_\delta(x) = \begin{cases} 1, & 0 \leq x \leq (L - \delta), \\ \frac{-1}{\delta}(x - L) - 1, & (L - \delta) \leq x \leq L. \end{cases}\]

Then $\| \psi_\delta \|_\infty = 1$ and it is easily verified that $\| T\psi_\delta \|_\infty \to \alpha + (\alpha + 1)(1 - e^{-\lambda L})$ as $\delta \to 0$. Regarding the upper bound,

\[
\| T \| = \sup_{\| \psi \|_\infty = 1} \| T\psi \|_\infty = \sup_{\| \psi \|_\infty = 1} \sup_{x \in [0, L]} |T\psi(x)| \\
\leq \sup_{\| \psi \|_\infty = 1} \sup_{x \in [0, L]} \left( \alpha \| \psi(x) \|_\infty \right) + (\alpha + 1)\lambda \| \psi \|_\infty \int_0^x e^{-\lambda(x-s)}ds \\
\leq \sup_{\| \psi \|_\infty = 1} \sup_{x \in [0, L]} \left( \alpha \| \psi(x) \|_\infty \right) + (\alpha + 1)\lambda \| \psi \|_\infty \int_0^x e^{-\lambda(x-s)}ds \\
= \alpha + (\alpha + 1)(1 - e^{-\lambda L}). \quad \Box
\]

We remark that it follows that $T$ is a contraction if

\[L < \frac{1}{\lambda} \ln \left( \frac{1 + \alpha}{2\alpha} \right).\]

Although it is useful to know whether $T$ is a contraction, it is still possible that $\| T^n \| \to 0$ as $n \to \infty$ even in cases when $\| T \| > 1$. Recall that $\| T^n \|$ is related to the spectral radius $r(T)$ according to the formula

\[(4.3) \quad r(T) = \lim_{n \to \infty} \| T^n \|^{\frac{1}{n}}.\]

Bearing (4.3) in mind, the stability criterion advertised at the end of the previous section follows from the following proposition.

**Proposition 4.2.** The spectrum of $T$ is given by $\sigma(T) = \{-\alpha\}$. 
Proof. Since $T = -\alpha I + (\alpha + 1)\lambda K$, by the spectral mapping theorem (see, for example, Dunford and Schwartz [8], page 569), it suffices to prove that the spectral radius of $K$ is 0. Computing powers of $K$ is a straightforward process, and for $m \geq 1$ we find that

$$
(4.6) \quad (K^m \varphi)(x) = \int_0^x \int_{s_{m-1}}^{s_{m-2}} \cdots \int_0^{s_1} e^{-\lambda(x-s_m)} \varphi(s_m) ds_m \, ds_{m-1} \cdots ds_1.
$$

Reversing the order of integration, the iterated integral (4.4) simplifies to a single integral

$$
(4.5) \quad (K^m \varphi)(x) = \int_0^x \frac{(x-s_m)^{m-1}}{(m-1)!} e^{-\lambda(x-s_m)} \varphi(s_m) ds_m.
$$

Since factors multiplying $\varphi$ in the integrand of (4.5) are positive, choosing $\varphi \equiv 1$ achieves

$$
\|K^m\| = \sup_{x \in [0,L]} \int_0^x \frac{(x-s_m)^{m-1}}{(m-1)!} e^{-\lambda(x-s_m)} ds_m
\leq \sup_{x \in [0,L]} \int_0^x \frac{(x-s_m)^{m-1}}{(m-1)!} ds_m = \frac{L^m}{m!}.
$$

Taking the $\frac{1}{m}$ power of both sides, invoking Stirling’s large-$m$ asymptotic approximation for $m!$, and letting $m \to \infty$, we infer from (4.3) that $r(K) = 0$. The proposition follows. \[\square\]

Because $\alpha$, by definition, represents the magnitude of the slope of a restitution function, we see immediately that the restitution hypothesis follows from Proposition 4.2. Since the spectral radius of $T$ is $r(T) = \alpha$, (4.3) implies that $\|T^n\| \to 0$ if $\alpha < 1$ and $\|T^n\| \to \infty$ if $\alpha > 1$. Evidently, $\alpha = 1$ is the threshold for stability and, if $\alpha < 1$, we expect (generically) $(T^n y_0)(x)$ to converge uniformly to 0 on each closed interval $[0,L]$. Of course, we must exercise caution in drawing such conclusions if either $\|y_0(x)\|_\infty$ is large or $\alpha$ is close to 1, as the results in this section were derived from linearization of the actual kinematic model equations (2.3).

We close this section by connecting the operator $T$ to the calculations in the previous section. Since $T = -\alpha I + (\alpha + 1)\lambda K$ is a sum of two operators that clearly commute, we may apply the binomial theorem to obtain

$$
(4.6) \quad (T^n \varphi)(x) = \sum_{m=0}^n \binom{n}{m} (-\alpha)^{n-m} (\alpha + 1)^m \lambda^m (K^m \varphi)(x).
$$

Combining (4.6) and (4.5) yields

$$
(4.7) \quad (T^n \varphi)(x) = (-\alpha)^n \varphi(x) + \int_0^x \Psi_n(x-s) \varphi(s) ds
= (-\alpha)^n \varphi(x) + \int_0^x \Psi_n(s) \varphi(x-s) ds,
$$

where

$$
\Psi_n(s) = e^{-\lambda s} \sum_{m=1}^n \binom{n}{m} (-\alpha)^{n-m} (\alpha + 1)^m \lambda^m \frac{s^{m-1}}{(m-1)!}
= (-\alpha)^{n-1} (\alpha + 1) \lambda e^{-\lambda s} L_{n-1}^{(1)} \left( \frac{\lambda(\alpha + 1)s}{\alpha} \right).
$$
It follows that

\[(T^n 1)(x) = (-\alpha)^n + \int_0^x \Psi_n(s) \, ds \]

\begin{align*}
(4.9) \quad &= (-\alpha)^n + (-\alpha)^{n-1}(\alpha + 1)\lambda \int_0^x e^{-\lambda s} L^{(1)}_{n-1} \left( \frac{\lambda(\alpha + 1)s}{\alpha} \right) \, ds \\
&= (-\alpha)^n \left( 1 - \int_0^{\lambda(n+1)\alpha} e^{-\frac{\alpha s}{\lambda(\alpha + 1)}} L^{(1)}_{n-1}(s) \, ds \right),
\end{align*}

which is merely a restatement of (3.8).

5. Discussion and conclusions. We have analyzed the dynamics of wave propagation in a one-dimensional excitable medium with impulsive, periodic forcing applied at one end of the domain. In particular, we (i) derived a criterion for stability of the periodic train of identical, evenly spaced pulses that one expects to observe in such a system, and (ii) derived a formula (3.8) that approximates the transient behavior following a sudden perturbation to the period of forcing from \(B_{\text{old}}\) to \(B_{\text{new}}\). In doing so, we departed from the traditional reaction-diffusion model (2.1) for waves in excitable media in favor of a kinematic model (2.3). The linearized kinematic model (2.7) with appropriate boundary and initial conditions (2.6), (2.8) is an infinite sequence of ODEs that can be solved exactly. The process of solving those equations began with a motivated ansatz (3.2) regarding the form of the solutions and, during the course of proving that (3.2) was correct, we passed from the recursive sequence of ODEs (2.7) to a much simpler polynomial recursion (3.6). In principle, that maneuver of trading one recurrence for another could be applied to other infinite sequences of linearized ODEs when similar linear stability analyses are required.

The key assumption upon which the kinematic model is based is that repolarization (recovery of excitability) of cells occurs via a phase wave, not a triggered wave [7]. Certainly, the wave front of a propagating action potential is a triggered wave because each cell’s depolarization is triggered by transmission of current (via gap junctions) from a neighboring cell. On the other hand, the wave back of an action potential can be either a phase wave or a triggered wave [7], and both possibilities are equally important in applications [34]. Under the same key assumption, Courtemanche, Keener, and Glass [6] showed that the restitution hypothesis is the correct stability criterion for a reentrant action potential recirculating in a one-dimensional ring. Due to the slight difference in geometry (a ring versus a fiber), their kinematic model is presented as a single integro-differential equation as opposed to a sequence of ODEs. They derive the stability criterion by proving that all roots of a [transcendental] characteristic equation lie in the left half-plane if and only if \(\alpha < 1\). Our analysis has the advantage of providing a more detailed description of the response to perturbed pacing (3.8), along with the potential for generalization as mentioned in the previous paragraph.

Both reaction-diffusion and kinematic models of action potential propagation have their own sets of advantages: the former are grounded in physical principles (e.g., Kirchhoff’s laws, cable theory) and govern the full \(v(x, t)\) profile, while the latter lend themselves to deeper mathematical analysis and high computational efficiency. In our case, the exact solution of the linearized kinematic model equations led to an easily stated criterion for linear stability (a restatement of the restitution hypothesis) and an approximate description of the transient response following a perturbation to the pacing period. The appendix contains a side-by-side comparison of the reaction-diffusion and kinematic models, with specific choices [20] for the functions \(F(v, h)\)
and $G(v, h)$ appearing in (2.1). It is encouraging that the two models exhibit strong quantitative agreement over a wide range of physiologically meaningful parameter choices (see, for example, the plot of relative error shown in Figure 4). Predictably, the discrepancy between the two models becomes significant if either (i) the slope $\alpha$ of the function $f$ approaches 1 or (ii) the magnitude $|B_{\text{old}} - B_{\text{new}}|$ of the perturbation to the period of forcing is too large.

One more disclaimer should accompany the key assumption underlying our kinematic model, namely, that for each $x \in [0, L]$, the duration of the $n$th action potential is given by $f(D_{n-1}(x))$ and its (local) propagation speed is given by $c(D_{n-1}(x))$. In other words, both the speed and the duration of a propagating pulse depend only upon the amount of “rest” that the medium receives once the immediately preceding pulse has passed. It is known that individual cardiac cells can exhibit short-term memory in the sense that $A_n$ depends not only upon $D_{n-1}$, but also upon $D_{n-2}, D_{n-3}, \ldots, D_{n-m}$. In a future study, we hope to analyze a kinematic model in which this sort of memory is taken into account, including derivation of a stability criterion analogous to the one in this manuscript.

We also remark that, while the reaction-diffusion and kinematic models often exhibit quantitative agreement in the $\alpha < 1$ regime, there are striking differences between the solutions when $\alpha > 1$. When $\alpha > 1$, both models may exhibit discordant alternans: as $n$ increases, $D_n(x)$ alternates short-long for certain $x \in [0, L]$ and long-short at other $x \in [0, L]$. For parameters leading to sustained discordant alternans, numerical simulations of reaction-diffusion models (2.1) suggest that $D_n(x)$ is a smooth function of $x$ for each $n$, even at transition nodes between regions of short-long alternation and regions of long-short alternation. By contrast, similar numerical simulations of the kinematic model suggest that $|\frac{d}{dx}D_n(x)| \to \infty$ at those nodes as $n$ increases. This phenomenon also merits further study.

**Appendix: A specific example.** Here we recall an example of a specific model for waves in excitable media, a two-current model [20] for cardiac action potential propagation in a one-dimensional fiber of electrically coupled cells. The model consists of two dynamic variables: a voltage $v$ and a “gate” variable $h$ which serves to regulate $v$. Both variables are scaled to be dimensionless and between 0 and 1. The two-current model adopts specific forms for the functions $F(v, h)$ and $G(v, h)$ in (2.1), and
can be written as

\[ \frac{\partial v}{\partial t} = \kappa \frac{\partial^2 v}{\partial x^2} + \frac{h}{\tau_{in}} v^2 (1 - v) - \frac{v}{\tau_{out}}, \]

(6.1)

\[ \frac{\partial h}{\partial t} = \left( \frac{1 - h}{\tau_{open}} \right) \Theta(v_{crit} - v) - \left( \frac{h}{\tau_{close}} \right) \Theta(v - v_{crit}), \]

(6.2)

where \( 0 < x < L \). Here, \( \Theta \) is the Heaviside function, \( \kappa \) is a diffusion coefficient, and \( \tau_{in}, \tau_{out}, \tau_{open}, \) and \( \tau_{close} \) are time constants associated with different phases of the action potential. The constant \( v_{crit} \) determines the threshold voltage above which \( h \) decays exponentially (shutting off the “inward current” term in (6.1)) and below which \( (1 - h) \) decays exponentially. At the boundaries, we impose the homogeneous Neumann conditions \( v_x(0, t) = v_x(L, t) = 0 \), and assume that impulsive forcing is applied at \( x = 0 \). Distance \( x \) along the one-dimensional fiber is typically measured in centimeters and time \( t \) in milliseconds.

Under the physiologically justified assumption that the time constants are well separated as

\[ \tau_{in} \ll \tau_{out} \ll \tau_{open}, \tau_{close}, \]

one may derive accurate asymptotic approximations for the functions \( f \) and \( c \) described in section 2 above. Let

\[ \epsilon = \frac{\tau_{out}}{\tau_{close}} \quad \text{and} \quad h_{min} = 4 \frac{\tau_{in}}{\tau_{out}}. \]

In [2], the authors show that

\[ f(D) \sim f_0(D) + \epsilon^2 f_1(D) \]

(6.3)

in the small-\( \epsilon \) limit, where

\[ f_0(D) = \tau_{close} \left[ \frac{1 - (1 - h_{min})e^{-D/\tau_{open}}}{h_{min}} \right] \quad \text{and} \]

\[ f_1(D) = 2.33811 \tau_{close} \left[ \frac{1 - e^{-D/\tau_{open}}}{1 - (1 - h_{min})e^{-D/\tau_{open}}} \right]. \]

Under a similar small-\( \epsilon \) assumption, in [3] it is shown that the propagation speed \( c(D) \) is asymptotic to

\[ \left[ \frac{1}{2} V_+ (D) - V_- (D) \right] \sqrt{\frac{2 \kappa h(D)}{\tau_{in}}}, \]

(6.4)

where

\[ h(D) = 1 - (1 - h_{min}) e^{-D/\tau_{open}} \quad \text{and} \quad V_{\pm} (D) = \frac{1}{2} \left( 1 \pm \sqrt{1 - \frac{h_{min}}{h(D)}} \right). \]

With the previous paragraph’s conventions regarding physical units, \( f(D) \) has units of ms and \( c(D) \) has units of cm/ms.
For this particular model of waves in excitable media, let us compare the results of the reaction-diffusion model (6.1)–(6.2) with those of the linearized kinematic model (2.7)–(2.8) with \( f \) and \( c \) chosen from (6.3) and (6.4). Consider the specific parameter set

\[
\begin{align*}
\tau_{\text{in}} &= 0.1 \text{ ms}, & \tau_{\text{out}} &= 2.4 \text{ ms}, & \tau_{\text{open}} &= 130 \text{ ms}, \\
\tau_{\text{close}} &= 150 \text{ ms}, & v_{\text{crit}} &= 0.13, & \kappa &= 10^{-3} \text{ cm}^2/\text{ms},
\end{align*}
\]

and suppose that the forcing period is suddenly changed from \( B_{\text{old}} = 340 \text{ ms} \) to \( B_{\text{new}} = 320 \text{ ms} \). Figure 4 illustrates the relative error associated with using the linearized kinematic model to approximate the “true” solution of the full reaction-diffusion model. The strong agreement between the two models is encouraging, particularly given that the domain in the figure is huge compared to the physiological scale of a heart. The agreement shown in the figure is typical of parameter sets for which \( \alpha \) is not too close to 1 (i.e., at which the linearization breaks down).

REFERENCES


\(^8\)Showing such a large domain is helpful in visualizing how the relative error worsens at large distances from the forcing site.


