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Two-Term Asymptotic Approximation of a Cardiac Restitution Curve*

John W. Cain†
David G. Schaeffer‡

Abstract. If spatial extent is neglected, ionic models of cardiac cells consist of systems of ordinary differential equations (ODEs) which have the property of excitability, i.e., a brief stimulus produces a prolonged evolution (called an action potential in the cardiac context) before the eventual return to equilibrium. Under repeated stimulation, or pacing, cardiac tissue exhibits electrical restitution: the steady-state action potential duration (APD) at a given pacing period B shortens as B is decreased. Independent of ionic models, restitution is often modeled phenomenologically by a one-dimensional mapping of the form \( \text{APD}_{\text{next}} = f(B - \text{APD}_{\text{previous}}) \). Under some circumstances, a restitution function \( f \) can be derived as an asymptotic approximation to the behavior of an ionic model.

In this paper, extending previous work, we derive the next term in such an asymptotic approximation for a particular ionic model consisting of two ODEs. The two-term approximation exhibits excellent quantitative agreement with the actual restitution curve, whereas the leading-order approximation significantly underestimates actual APD values.

Key words. asymptotic expansion, cardiac restitution curve, mapping model, ionic model, alternans

AMS subject classifications. 92C50, 34E05, 34C60

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1. Introduction. Cardiac tissue is an example of an excitable medium. Applying a sufficiently strong stimulus to a cardiac cell leads to a prolonged elevation of transmembrane voltage \( v \) known as an action potential. When spatial extent is negligible, the cardiac action potential can be modeled by systems of nonlinear ODEs [1, 19]. Such models are referred to as ionic models because they describe the transport of various ions across the cell membrane.

Modeling the flow of transmembrane ionic currents represents one of the biggest challenges in cardiac electrophysiology [16], and many authors have proposed ionic models [1, 5, 8, 12, 18, 19, 20, 21, 23, 25]. An excellent database of the most well known models appears at http://www.cellml.org/examples/repository/index.html, and a listing of selected ionic models appears in Table 1. We remark that ionic models come in a variety of flavors—some are specific to certain types of cardiac cells, some are specific to certain animals, and some are especially concerned with accurate handling...
Table I  Selected ionic models of the cardiac action potential.

<table>
<thead>
<tr>
<th>Model</th>
<th>Year</th>
<th>Tissue type</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noble</td>
<td>1962</td>
<td>Purkinje fiber</td>
<td>one of the first adaptations of the Hodgkin–Huxley model to cardiac tissue</td>
</tr>
<tr>
<td>Beeler–Reuter</td>
<td>1977</td>
<td>mammalian, ventricular</td>
<td>uses four ionic currents; among the first models of the ventricular action potential</td>
</tr>
<tr>
<td>Luo–Rudy</td>
<td>1994</td>
<td>guinea pig, ventricular</td>
<td>a pioneering study for the handling of calcium dynamics</td>
</tr>
<tr>
<td>Jafri–Rice–Winslow</td>
<td>1998</td>
<td>ventricular</td>
<td>incorporates more sophisticated calcium handling</td>
</tr>
<tr>
<td>Courtemanche et al.</td>
<td>1998</td>
<td>human, atrial</td>
<td>uses human experimental data to formulate the various ionic currents</td>
</tr>
</tbody>
</table>

![voltage](image)

Fig. 1  Schematic action potentials.

of particular ions. For example, the Luo–Rudy dynamic model [19], developed in part from guinea pig ventricular data, was among the first models to treat calcium cycling between the intracellular space and the sarcoplasmic reticulum. Although ionic models have been developed for many types of cells, most models are similar in spirit to the well-known Hodgkin–Huxley model [10] of the nerve action potential.

Not surprisingly, ionic models that are “more physiological” tend to be more complex mathematically. Among the simplest ionic models is the Fenton–Karma model [8], which expresses the total transmembrane current as the sum of three ionic currents. The Fenton–Karma model mimics the dynamics of the Beeler–Reuter model [1], which uses four ionic currents and a total of eight state variables. The Luo–Rudy dynamic model [19] incorporates a total of fourteen ionic currents and pumps.

Because cardiac arrhythmias are often characterized by temporal phenomena (i.e., timing of excitation and recovery), one frequently considers the duration of action potentials, not the complete voltage trace. To establish notation, refer to Figure 1, which shows a voltage trace of several consecutive action potentials in a repeatedly stimulated, or paced, cardiac cell. By specifying a threshold voltage \(v_{\text{thr}}\), one may define the action potential duration (APD) as the amount of time in which \(v > v_{\text{thr}}\) during an excitation. The subsequent recovery time during which \(v < v_{\text{thr}}\) is called the diastolic interval (DI). We will denote the APD following the \(n^{th}\) stimulus by \(A_n\) and the subsequent DI by \(D_n\) (see Figure 1).
Based on their experimental work, Nolasco and Dahlen [22] proposed a phenomenological mapping model to describe the dynamics of a paced cell, i.e.,

$$A_{n+1} = f(D_n) = f(B - A_n),$$

where $B$ denotes the pacing period. The graph of $f$, known as the restitution curve (RC), is qualitatively similar to the graph of

$$f(D) = \text{APD}_{\text{max}} - C e^{-D/\tau}, \quad \text{APD}_{\text{max}}, C, \tau > 0.$$  

Although the approximation (1) is unrealistically simple,\textsuperscript{1} it nonetheless adequately models some important phenomena. In particular, (i) for slow pacing rates (large $B$), the cell exhibits a phase-locked 1:1 response in which every stimulus yields an identical action potential, that is, the mapping (1) has a unique, stable fixed point [26]; and (ii) as shown by Guevara et al. [9], alternans, an abnormal beat-to-beat alternation of APD values, can result from a period-doubling bifurcation of (1) as the parameter $B$ is gradually decreased. The fact that alternans has been linked to the onset of ventricular fibrillation and sudden cardiac death [15, 24, 27] alludes to the potential clinical use of RCs. Namely, it is believed that slopes of RCs can be used to predict the transition from normal 1:1 rhythms to alternans [9, 13].

In this paper, rather than introducing an ad hoc RC based on fitting experimental data, we derive an approximation of an RC as the asymptotic limit of a particular idealized ionic model. The first term of this asymptotic expansion, which was derived in [20], can significantly underestimate the actual APD values from the ionic model. Here, we derive the second term of the expansion, and this approximation exhibits excellent quantitative agreement with the actual RC.

Independent of the cardiac application, the derivation has pedagogical interest because it involves a common phenomenon in asymptotics, i.e., “falling off a nullcline” that turns back on itself. Other examples of this phenomenon arise in the context of the van der Pol relaxation oscillator [3, 17] and the singular Fitzhugh–Nagumo equation [6]. In a different context, a similar phenomenon is analyzed in [2]. This situation leads to a singular expansion with fractional powers and logarithms of the small parameter [17]. We believe that our straightforward exposition enhances the pedagogical potential of this problem.

1.1. A Two-Current Ionic Model. We recall the two-current model [14, 20] consisting of two ODEs. The notation is summarized in Table 2.

The \textit{voltage equation} has the form

$$\frac{dv}{dt} = J_{\text{in}}(v, h) + J_{\text{out}}(v) + J_{\text{stim}}(t),$$

where $J_{\text{in}}$, $J_{\text{out}}$, and $J_{\text{stim}}$ denote inward, outward, and stimulus currents, respectively. The stimulus current is discussed below. The inward and outward currents are given by

$$J_{\text{in}}(v, h) = \frac{h}{\tau_{\text{in}}} v^2(1-v),$$

$$J_{\text{out}}(v) = -\frac{v}{\tau_{\text{out}}},$$

\textsuperscript{1}For example, the model (1) does not exhibit any rate dependence or memory [4, 13]. See [25] for a two-dimensional mapping model with memory that may be derived as the asymptotic limit of an idealized ionic model.
Table 2  Summary of notation associated with the two-current model.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Meaning</th>
<th>Units</th>
<th>Typical value(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$v$</td>
<td>scaled voltage</td>
<td>dimensionless</td>
<td>[0,1]</td>
</tr>
<tr>
<td>$h$</td>
<td>gate variable</td>
<td>dimensionless</td>
<td>[0,1]</td>
</tr>
<tr>
<td>$\tau_{in}$</td>
<td>time constant</td>
<td>milliseconds</td>
<td>0.1</td>
</tr>
<tr>
<td>$\tau_{out}$</td>
<td>time constant</td>
<td>milliseconds</td>
<td>2.4</td>
</tr>
<tr>
<td>$\tau_{open}$</td>
<td>time constant</td>
<td>milliseconds</td>
<td>130</td>
</tr>
<tr>
<td>$\tau_{close}$</td>
<td>time constant</td>
<td>milliseconds</td>
<td>150</td>
</tr>
<tr>
<td>$v_{crit}$</td>
<td>critical voltage</td>
<td>dimensionless</td>
<td>0.13</td>
</tr>
<tr>
<td>$h_{min}$</td>
<td>$4\tau_{in}/\tau_{out}$</td>
<td>dimensionless</td>
<td>0.17</td>
</tr>
</tbody>
</table>

where $\tau_{in}$ and $\tau_{out}$ are time constants. The gate variable $h$, which ranges from 0 to 1, represents a nondimensionalized conductance and regulates the flow of inward current. We assume that $h$ obeys the gate equation

$$ \frac{dh}{dt} = \begin{cases} \frac{1-h}{\tau_{open}}, & v \leq v_{crit}, \\ \frac{-h}{\tau_{close}}, & v > v_{crit}. \end{cases} $$

where $\tau_{open}$ and $\tau_{close}$ are time constants and $v_{crit}$ represents a critical voltage. For voltages $v < v_{crit}$, the gate “opens,” allowing the flow of inward current. For voltages $v > v_{crit}$, the gate “closes” and shuts off the flow of inward current. For convenience, we set $v_{thr} = v_{crit}$ so that the APD is the amount of time in which $v > v_{crit}$ during an action potential. We shall not specify a functional form for the stimulus current $J_{stim}$, requiring only that it satisfy two conditions:

- $J_{stim}(t)$ is periodic with period $B$, and
- each stimulus consists of a brief (duration $\ll \tau_{in}$) pulse of current of sufficient strength to elicit an action potential.

We shall assume that the time constants satisfy

$$ (7) \quad \tau_{in} \ll \tau_{out} \ll \tau_{open}, \tau_{close}. $$

Thus, in the absence of a stimulus current, the voltage changes more rapidly than the gate variable unless $(v, h)$ is close to a nullcline of (3). Note that (3) has two nullclines: the trivial nullcline $v = 0$ and the nullcline given by

$$ (8) \quad h = \frac{\tau_{in}}{\tau_{out} v(1-v)} \quad (0 < v < 1). $$

Equivalently, we may solve (8) for $v$:

$$ (9) \quad v = v_{\pm}(h) = \frac{1}{2} \pm \frac{1}{2} \sqrt{1 - \frac{h_{min}}{h}}, $$

where

$$ (10) \quad h_{min} = \frac{4\tau_{in}}{\tau_{out}} $$

denotes the minimum value of $h$ on the nullcline. We refer to $v_{+}(h)$ as the excited branch of the nullcline.
1.2. Leading-Order and Two-Term Approximations of the RC. Mitchell and Schaeffer [20], assuming that the time constants satisfy (7) above, derive the leading-order approximation for the RC associated with the two-current model. Letting $f(DI)$ denote the actual RC obtained numerically from the ODEs (3) and (6), they demonstrate that

\begin{equation}
 f(DI) \sim f_0(DI) = \tau_{\text{close}} \ln \left[ \frac{1 - (1 - h_{\text{min}}) e^{-\frac{DI}{\tau_{\text{open}}}}}{h_{\text{min}}} \right]
\end{equation}

as the parameter

\begin{equation}
 \epsilon = \frac{\tau_{\text{out}}}{\tau_{\text{close}}}
\end{equation}

tends to 0. Figure 2(a) shows a comparison of $f_0(DI)$ with actual RCs (obtained numerically) for several choices of $\epsilon$. In each case, $h_{\text{min}} = 1/6$, $\tau_{\text{open}} = 130$ ms, and $\tau_{\text{close}} = 150$ ms. Note that $f_0$ underestimates the true APD values, although the error does tend to 0 as $\epsilon \searrow 0$.

In the next section, we compute the next-order correction to $f_0$. As we shall see,

\begin{equation}
 f(DI) \sim f_0(DI) + \epsilon^3 f_1(DI) \quad (\epsilon \searrow 0),
\end{equation}

where

\begin{equation}
 f_1(DI) = 2.33811 \tau_{\text{close}} \left( \frac{1 - e^{-\frac{DI}{\tau_{\text{open}}}}}{1 - (1 - h_{\text{min}}) e^{-\frac{DI}{\tau_{\text{open}}}}} \right).
\end{equation}

We remark that the DI dependence in (14) is quite weak. Indeed, if $h_{\text{min}} \approx 0$, then the correction term in (13) is approximately equal to the constant $2.33811 \tau_{\text{close}} \epsilon^{2/3}$. Figure 2(b) shows a plot of the leading-order approximation (11), the two-term approximation (13), and the actual RC (obtained numerically) using the parameters in Table 2. Observe that the leading-order approximation considerably underestimates the true APD values, whereas the two-term approximation exhibits excellent quantitative agreement with the actual RC.
2. Derivation of the Two-Term Asymptotic Approximation. The computations used to derive the two-term asymptotic approximation of \( f(DI) \) are similar to those originally performed by Dorodnicyn [7] to estimate the period of the van der Pol oscillator. In preparation for our derivation of (14), we recall the derivation of (11); for details, see Mitchell and Schaeffer [20].

2.1. The Leading-Order Asymptotic Approximation. To leading order, the response of (3), (6) during one pacing period may conveniently be divided into four phases, as labeled in Figure 3:

- Phase I, or upstroke, immediately following a successful stimulus. In a time on the order of \( \tau_{in} \), \( v \) rises to approximately 1 and \( h \) hardly changes.
- Phase II, or plateau. In a time on the order of \( \tau_{close} \), \( h \) decays from its initial value to \( h_{min} \) given by (10), while \( v \) follows passively to the value 1/2. This phase ends when the trajectory “falls off” the nullcline (8).
- Phase III, or repolarization. In a time on the order of \( \tau_{out} \), \( v \) decays toward 0 while \( h \) changes only slightly.
- Phase IV, or DI. For the time remaining until the next stimulus, the gate recovers toward the open state \( h = 1 \) with a time constant \( \tau_{open} \), while \( v \) remains close to 0.

The APD consists of all of Phase II and parts of Phases I and III. However, because of (7), to leading order only Phase II contributes to APD. To estimate \( A_{n+1} \), we first examine the recovery of \( h \) during the preceding DI. If \( t = 0 \) corresponds to the beginning of the \( n \)th DI, \( h \) satisfies the following initial value problem until the \((n + 1)\)th stimulus is applied:

\[
\frac{dh}{dt} = \frac{1 - h}{\tau_{open}},
\]

\[
h(0) = h_{min}.
\]

The value of \( h \) at the end of the \( n \)th DI is

\[
h(D_n) = 1 - (1 - h_{min})e^{-D_n/\tau_{open}}.
\]
To leading order, $h$ does not change during stimulation or Phase I of the $(n + 1)$th action potential. Thus $A_{n+1}$ is estimated by the time required for $h$ to decay from $h(D_n)$ to $h_{\text{min}}$. This yields the approximation

\begin{equation}
A_{n+1} = \tau_{\text{close}} \ln \left[ \frac{h(D_n)}{h_{\text{min}}} \right],
\end{equation}

from which (11) follows.

2.2. The Next-Order Correction. The primary source of error in the leading-order approximation arises from the transition between Phase II and Phase III, which we have called “falling off the nullcline.” Following Mitchell and Schaeffer [20], let us demonstrate that this transition contributes an $O(\epsilon^{2/3})$ correction. Let $t^*$ denote the time in an action potential at which $h$ has decayed to $h_{\text{min}}$. Then, according to (6),

\begin{equation}
h(t) = h_{\text{min}} e^{-\frac{t-t^*}{\tau_{\text{close}}}},
\end{equation}

in a neighborhood of $t = t^*$. Inserting (19) into (3), we obtain the nonautonomous equation

\begin{equation}
\frac{dv}{dt} = \frac{v}{\tau_{\text{out}}} \left( \frac{t_{\text{out}}}{\tau_{\text{in}}} h_{\text{min}} e^{-\frac{t-t^*}{\tau_{\text{close}}} v(1-v) - 1} \right),
\end{equation}

which is valid for $t$ in a neighborhood of $t^*$. Because $h(t^*) = h_{\text{min}}$, we expect that $v(t^*) \approx \frac{1}{2}$ provided that $\epsilon$ is small. Motivated by this observation, we scale time and voltage by introducing “inner” variables

\begin{equation}
\bar{t} = \frac{t - t^*}{\epsilon^{1/3} \tau_{\text{close}}}, \quad \bar{v} = \frac{v - \frac{1}{2}}{\epsilon^{2/3}},
\end{equation}

Rewriting (20) in terms of the scaled variables, we have

\begin{equation}
\epsilon^{1+p-q} \frac{d\bar{v}}{d\bar{t}} = -\frac{1}{2} \epsilon^{1/3} \bar{t} - 2 \epsilon^{2/3} \bar{v}^2,
\end{equation}

where we have retained only the lowest-order terms. Applying the principle of dominant balance, we require that $1 + p - q = q = 2p$ and hence $p = \frac{1}{3}$ and $q = \frac{2}{3}$. Equation (22) becomes a Riccati equation:

\begin{equation}
\frac{d\bar{v}}{d\bar{t}} + 2 \bar{v}^2 + \frac{1}{2} \bar{t} = 0.
\end{equation}

Observe that solutions of (23) blow up in finite time for $\bar{t} > 0$. We use a common trick [11] to convert (23) into a linear equation. Substituting

\begin{equation}
\bar{v} = \frac{1}{2} \frac{W'}{W}
\end{equation}

into (23), we find that

\begin{equation}
\frac{1}{2} \left( \frac{W''W - (W')^2}{W^2} \right) + \frac{1}{2} \frac{(W')^2}{W^2} + \frac{1}{2} \bar{t} = 0.
\end{equation}

Simplification reveals that $W$ satisfies the Airy equation

\begin{equation}
W'' + iW = 0.
\end{equation}
The general solution of (26) has the form
\begin{equation}
W(t) = a_0 Ai(-t) + a_1 Bi(-t),
\end{equation}
where \(a_0\) and \(a_1\) are arbitrary constants\(^2\) and \(Ai\) and \(Bi\) are the standard Airy functions. We shall not need their power series representations, which may be found in [11].

From (24) and (27) we find that
\begin{equation}
\dot{v}(\tilde{t}) = \frac{1}{2} \cdot \frac{a_0 Ai'(-\tilde{t}) + a_1 Bi'(-\tilde{t})}{a_0 Ai(-\tilde{t}) + a_1 Bi(-\tilde{t})}.
\end{equation}

To determine the constants \(a_0\) and \(a_1\), we match to the Phase II outer solution, i.e., let \(\tilde{t} \to -\infty\). The asymptotic behavior of the Airy functions and their derivatives as the argument \(x \to +\infty\) is described by the formulas [11]
\begin{align}
Ai(x) &\sim \frac{1}{2\sqrt{\pi} x^{\frac{3}{2}}} e^{-x}, \quad Ai'(x) \sim \frac{-1}{2\sqrt{\pi}} x^{\frac{1}{2}} e^{-x}, \\
Bi(x) &\sim \frac{1}{\sqrt{\pi} x^{\frac{3}{2}}} e^{x}, \quad Bi'(x) \sim \frac{1}{\sqrt{\pi}} x^{\frac{1}{2}} e^{x},
\end{align}
where
\begin{equation}
\zeta = \frac{2}{3} x^{\frac{3}{2}}.
\end{equation}

Therefore, from (28), (29), and (30) we have
\begin{equation}
\dot{v} \sim \begin{cases} 
\frac{1}{2} \sqrt{-\tilde{t}} & \text{if } a_1 = 0, \\
-\frac{1}{2} \sqrt{-\tilde{t}} & \text{if } a_1 \neq 0,
\end{cases}
\end{equation}
as \(\tilde{t} \to -\infty\). In our case, the voltage should increase as \(\tilde{t} \to -\infty\), so we choose \(a_1 = 0\). By combining (21) and (28) we obtain the following representation for \(v(t)\) with \(t\) close to \(t^*\):
\begin{equation}
v(t^* + \varepsilon \tau_{\text{close}}) \sim \frac{1}{2} - \frac{\varepsilon^{\frac{3}{2}} Ai'(-\tilde{t})}{2 Ai(-\tilde{t})}.
\end{equation}
The approximation (33) is valid as \(\tilde{t}\) increases until \(\tilde{t}\) reaches the first zero of the Airy function \(Ai(-\tilde{t})\), which occurs at
\begin{equation}
\tilde{t}_0 = 2.33811\ldots,
\end{equation}
or, in terms of the original time scale, at
\begin{equation}
t = t^* + \tilde{t}_0 \tau_{\text{close}} \varepsilon^{\frac{3}{2}}.
\end{equation}
At this time the inner solution (33) blows up, indicating the transition to Phase III, which evolves on a faster time scale. Hence, the time spent falling off the slow manifold lengthens each APD by approximately
\begin{equation}
t_{\text{extra}} \approx \tilde{t}_0 \tau_{\text{close}} \varepsilon^{\frac{3}{2}}.
\end{equation}
\(^2\)Observe that (23) is first order whereas (26) is second order. Upon substituting (27) into (24), we can divide both the numerator and the denominator by \(a_0\), leaving only one arbitrary constant, \(a_1/a_0\).
We remark that $t_{\text{extra}}$ can be significant relative to the APD values generated by the leading-order estimate of (11). For example, using the parameters in Table 2, we have $\epsilon = 0.016$ and $t_{\text{extra}} > 22$ ms.

This extra time changes $A_{n+1}$ in two ways: directly by adding $t_{\text{extra}}$ to (18) and indirectly by modifying the recovery of $h$ during the preceding DI. Specifically, during the extra time added to $A_n$, $h$ decays from $h_{\text{min}}$ to $\exp(-\tilde{\tau}_0 \epsilon^{2/3}) h_{\text{min}}$. Therefore, we must replace the initial condition (16) by

$$h(0) = e^{-\tilde{\tau}_0 \epsilon^{2/3}} h_{\text{min}}.$$  

This leads to an improved approximation of $h(D_n)$:

$$h(D_n) = 1 - \left[1 - e^{-\tilde{\tau}_0 \epsilon^{2/3}} h_{\text{min}}\right] e^{-\frac{D_n}{\tau_{\text{open}}}.$$  

Making these two adjustments to (18) and expanding in powers of $\epsilon^{2/3}$, we find that $f(DI) \sim f_0(DI) + \epsilon^{2/3} f_1(DI)$, where $f_0(DI)$ is given by (11) and

$$f_1(DI) = \tilde{\tau}_0 \tau_{\text{close}} \left(\frac{1 - e^{-\frac{DI}{\tau_{\text{open}}}}}{1 - (1 - h_{\text{min}}) e^{-\frac{DI}{\tau_{\text{open}}}}}\right).$$

In conclusion, we note that the $O(\epsilon^{2/3})$-corrections derived above dominate corrections coming from time spent in Phase I or III, since these are $O(\epsilon)$.

REFERENCES


3Recall that $h_{\text{min}}$ represents the smallest $h$ on the nullcline (8), not the smallest $h$ value that can be attained.