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Asymptotic approximation of an ionic model for cardiac restitution

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Abstract

Cardiac restitution has been described both in terms of ionic models—systems of ODE’s—and in terms of mapping models. While the former provide a more fundamental description, the latter are more flexible in trying to fit experimental data. Recently we proposed a two-dimensional mapping that accurately reproduces restitution behavior of a paced cardiac patch, including rate dependence and accommodation. By contrast, with previous models only a qualitative, not a quantitative, fit had been possible. In this paper, a theoretical foundation for the new mapping is established by deriving it as an asymptotic limit of an idealized ionic model.

1 Introduction

1.1 Background information

When a small piece of cardiac muscle is subjected to a sequence of brief electrical stimuli whose strength exceeds a critical threshold, the myocytes respond by producing *action potentials*, see Figure 1. The *duration of action potential* refers to the period when the voltage is elevated above its resting value. The interval between the time when the voltage returns to its resting value and the next stimulus is called the *diastolic interval*. We use the acronyms APD for action potential duration; DI for diastolic interval; and, assuming periodic pacing, BCL for the interval between stimuli, also known as basic cycle length.

There is great interest in cardiac restitution: i.e., determining how, under repeated stimulations, each APD depends on previous history. This is a key step in a program to understand how arrhythmias arise and sometimes progress to sudden cardiac death [1,2,12,22]. Restitution information from experiments is often presented in a restitution curve: i.e., a graph of APD vs. DI under one of various protocols [11]. Figure 2 shows one of these, the so-called *dynamic restitution curve*. In this protocol, for each of many periods B , the tissue is paced periodically with this period until it reaches a steady-state 1:1 phase-locked response, and then the steady-state action potential duration A_{ss} and diastolic interval D_{ss} are recorded. The pairs of points (D_{ss}, A_{ss}) resulting from various values of B form the dynamic restitution curve.

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¹To be precise, one needs to specify a level of accuracy for the phrase “resting value”. In experiments, this is often interpreted to mean 90% repolarization: i.e., in symbols, $v - v_{rest} = 0.1(v_{max} - v_{rest})$.

Each APD depends most strongly on the previous DI. In their seminal paper [15], Nolasco and Dahlen abstracted this behavior in a phenomenological model

$$A_{n+1}=G(D_n), \quad (1)$$

where A_n denotes the duration of the n^{th} action potential, D_n denotes the duration of the n^{th} diastolic interval, and $G(D)$ is a monotone increasing function of the diastolic interval. If B denotes the BCL with which the stimuli are applied, then $D_n = B - A_n$, see Figure 1. Substituting into (1), we see that in this model the sequence A_n is determined recursively by iteration of a 1D mapping. If the data in Figure 2 were described by a model of the form (1), then the thin curve in the figure would be the graph of G .

Despite its successes, the Nolasco-Dahlen model misses many important phenomena. In particular, it does not capture any memory effects [6,10,14]. To illustrate this, consider tissue that, after repeated pacing with period B_0 , has achieved a steady-state response. Then suppose the BCL is abruptly decreased to a new value and held there. According to (1), all pairs of points (D_n, A_{n+1}) in the transient to the new steady state would lie on the graph of the function $G(D)$ in the D, A -plane. However, in experiments (see for example Kalb et al. [11]), the approach to steady state occurs along a completely different curve, as illustrated in Figure 2. Moreover, evolution towards the steady state is very slow, much slower than other time scales in the data. See Schaeffer et al. [17] and the references in that paper for a more thorough discussion of memory issues.

1.2 The goal of this paper

In Schaeffer et al. [17], we introduced a 2D mapping and chose parameters that gave a quantitatively accurate description of the full restitution behavior, including memory, measured from a bullfrog ventricle. The present paper is concerned with this model, but we study its theoretical foundations rather than apply it to fitting experimental data.

A mapping provides a flexible way to fit restitution data from experiments, but it suffers from the limitations of a phenomenological model. For example, a more complete description of propagation of action potentials in extended tissue is provided by a more fundamental type of model, an ionic model. For a single cell or a small piece of tissue, an ionic model consists of a system of ODEs that specifies how the voltage across the cell membrane changes in response to currents of ions that flow through the cell walls. Both idealized ionic models [14,18]—low-dimensional systems aimed at qualitative understanding—and realistic models [8,13]—complicated systems intended to describe all currents in the cell—have been proposed. As in the Hodgkin-Huxley equations, given these ODEs, one may introduce an appropriate diffusive term in the voltage equation (or equations, if the bidomain model is used) to obtain PDEs that describe propagation in extended tissue.

In this paper we complement the modeling of Schaeffer et al. [17] by showing that the mapping of that paper arises as an asymptotic limit of an idealized ionic model. We begin in Section 2 by recalling from Schaeffer et al. [17] both the ionic model and the mapping. In Section 3 we derive the mapping from the ionic model as the leading term in an asymptotic expansion. A concluding discussion is presented in Section 4.

2 The ionic and mapping models

2.1 The idealized ionic model

The present model builds on the two-current ionic model of Karma [12] and of Mitchell and Schaeffer [14]. The two-current model contains two functions of time, the transmembrane potential $v(t)$ and a gating variable $h(t)$, both of which are dimensionless and scaled to lie in the interval $(0, 1)$. We augment the two-current model by adding a third variable, a (dimensionless) generalized concentration c , and modifying the equations as given in equations (2, 4, 6) below. These equations involve ten positive parameters, values of which can be obtained by fitting the model with experimental data. For example, the values listed in Table 1 were obtained in Schaeffer et al. [17] from experiments with a bullfrog ventricle.

(i) The equation for the transmembrane potential reads

$$\frac{dv}{dt} + J_{\text{in}}(v, h, c) + J_{\text{out}}(v) = 0, \quad (2)$$

where the outward current in (2) is linear in the voltage, $J_{\text{out}}(v) = v/\tau_{\text{out}}$, and the nonlinear inward current is the sum of *concentration-independent* and *concentration-dependent* parts

$$J_{\text{in}}(v, h, c) = -\frac{hv}{\tau_{\text{in}}} \{ \varphi_{\text{ci}}(v) + \beta e^{-c} \varphi_{\text{cd}}(v) \}, \quad (3)$$

where $\beta > 0$ is a constant. It may be seen from (3) that the build-up of charge in the cell weakens the inward current, thereby shortening action potentials. The behavior of the model is not very sensitive to the exact form of the functions $\varphi_{\text{ci}}(v)$ and $\varphi_{\text{cd}}(v)$. In the present work, to facilitate the calculations, we set these functions equal to piecewise linear functions of v , as follows:

$$\varphi_{\text{ci}}(v) = \begin{cases} v/v_{\text{crit}} & \text{if } v \leq v_{\text{crit}}, \\ 1 & \text{if } v_{\text{crit}} < v \leq 1 - v_{\text{crit}}, \\ (1-v)/v_{\text{crit}} & \text{if } 1 - v_{\text{crit}} < v. \end{cases}$$

and

$$\varphi_{\text{cd}}(v) = \begin{cases} 0 & \text{if } v \leq v_{\text{crit}}, \\ 1 - \frac{|1-2v|}{1-2v_{\text{crit}}} & \text{if } v_{\text{crit}} < v \leq 1 - v_{\text{crit}}, \\ 0 & \text{if } 1 - v_{\text{crit}} < v. \end{cases}$$

(ii) Depending on the voltage, the gating variable h opens or closes according to the equation

$$\frac{dh}{dt} = \begin{cases} (1-h)/\tau_{\text{open}} & \text{if } v \leq v_{\text{crit}}, \\ -h/T_{\text{close}}(v) & \text{if } v > v_{\text{crit}}. \end{cases} \quad (4)$$

The voltage-dependent closing rate is taken as piecewise linear in v ,

$$\frac{1}{T_{\text{close}}(v)} = \begin{cases} \frac{1}{\tau_{\text{fclose}}} - \left(\frac{1}{\tau_{\text{fclose}}} - \frac{1}{\tau_{\text{sclose}}} \right) \frac{1-v}{1-v_{\text{sldn}}} & \text{if } v > v_{\text{sldn}}, \\ \frac{1}{\tau_{\text{sclose}}} & \text{if } v \leq v_{\text{sldn}}. \end{cases} \quad (5)$$

Note that two different time-scale parameters, τ_{fclose} and τ_{sclose} , derive from the closing of the gate. (Remark: The subscripts *fclose* and *sclose* are mnemonic for “fast close” and “slow close”, respectively; *sldn*, for “slow down”.)

(iii) The concentration is determined by a balance between $I(t)$, the current which leads to the build-up of charge in the cell, and constant linear pumping, which removes charge from the cell:

$$\frac{dc}{dt} = -I(t) - \frac{c}{\tau_{\text{pump}}}. \quad (6)$$

The current $I(t)$ should satisfy two key properties:

- $I(t)$ is nonzero only during the upstroke of an action potential, and
- A fixed charge ε enters the cell during each action potential; in symbols

$$\int_{t_{\text{stim}}}^{t_{\text{stim}}+B} I(t) dt = -\varepsilon. \quad (7)$$

The precise form of $I(t)$ is not important; to achieve the properties above we choose²

$$I(t) = \begin{cases} \frac{\varepsilon}{1-v_{\text{crit}}}(J_{\text{in}} + J_{\text{out}}) & \text{if } v > v_{\text{crit}} \text{ and } \frac{dv}{dt} > 0, \\ 0 & \text{otherwise.} \end{cases} \quad (8)$$

Note that the time constants in Table 1 satisfy the following property:

$$\tau_{\text{in}} \ll \tau_{\text{out}} \ll \tau_{\text{open}}, \tau_{\text{fclose}}, \tau_{\text{sclose}} \ll \tau_{\text{pump}}. \quad (9)$$

Below in deriving a mapping to describe the behavior of (2), (4) and (6), we shall assume that (9) holds, as well as

$$\varepsilon \ll 1. \quad (10)$$

Although it is not critical, we shall also assume that $1 - v_{\text{sldn}} \leq v_{\text{crit}} \ll 1$.

The ionic model (2), (4) and (6) can be used to model action potentials produced by a cardiac patch under repeated stimulation. For example, Figure 3 shows two time traces of solutions at a basic cycle length $B = 650\text{ms}$, with model parameters chosen as in Table 1. The solid curve represents the steady-state response following many stimuli at this basic cycle length, while the dashed curve represents the response to the *first* stimulus with $B = 650\text{ms}$, following many stimuli at $B = 750\text{ms}$.

²Strictly speaking, this choice does not satisfy (7) exactly, only to leading order in the asymptotics.

2.2 Approximation of the ionic model by a mapping

Complicated evolution of the ionic model, such as in Figure 3, can be described approximately, with far less computation, in terms of the 2D mapping introduced in [17]. The variables in the mapping are A_n and C_n . Here A_n denotes the duration of the n^{th} action potential as illustrated in Figure 1, and C_n specifies the ion concentration c at the start of the $(n+1)^{st}$ action potential. Intuitively, one may think of C_n as a memory variable³: i.e., a slowly evolving, auxiliary quantity that modifies the electrical properties of the cell. Provided the diastolic interval D_n is not too short, the mapping is given by the formula

$$A_{n+1} = G(D_n) + \Phi(C_n) \quad (11)$$

$$C_{n+1} = (C_n + \varepsilon) e^{-B/\tau_{\text{pump}}}, \quad (12)$$

Where

$$G(D) = A_{\text{max}} + \tau_{\text{fclose}} \ln \left\{ 1 - \alpha e^{-D/\tau_{\text{open}}} \right\} \quad (13)$$

and

$$\Phi(C) = \tau_{\text{sclose}} \ln \left\{ \frac{1 + \beta e^{-C}}{1 + \beta} \right\}. \quad (14)$$

The new constants A_{max} and α are expressed in terms of the parameters of Table 1 in equations (28) and (29) below, respectively. As we shall see, A_{max} is the longest possible APD.

The evolution of APD and the concentration in the simulation behind Figure 3 is illustrated in Figures 4 (a,c), which graph A_n and C_n as functions of the beat number n . If, as in Figure 1, all BCL's are equal to some constant B and if the first stimulus occurs at $t = 0$, then $C_n = c(nB)$. The first fifty beats in Figure 4 show the steady values for these variables following many stimuli at $BCL = 750\text{ms}$ (assuming parameters as given in Table 1). At $n = 51$, the BCL is abruptly decreased to 650ms . This results in an immediate decrease in A_n , followed by a slow evolution over 250 beats during which C_n increases and A_n decreases. Figures 4 (b,d) show blow-ups of the evolution during the first few beats after the change in BCL ; note that C_n changes only slightly over this short time.

Regarding short DI's, the above formulas hold provided

$$D_n \geq D_{\text{sldn}} = \tau_{\text{open}} \ln \left[1 - \frac{\tau_{\text{in}} v_{\text{crit}}}{\tau_{\text{out}} (1 - v_{\text{sldn}})} \right]^{-1}. \quad (15)$$

For the parameters in Table 1, we have $D_{\text{sldn}} = 46\text{ms}$. See Section 3.2(b) for treatment of DI's shorter than this.

³Ad hoc mapping models with a memory variable were introduced by Chalivo et al. [4] and Fox et al. [9].

3 Leading order approximation of the ionic model

3.1 Overview of the derivation

As sketched in Figure 5, an action potential has four distinct phases. In each phase there are different balances between the equations (2, 4, 6) and their associated time scales. Note from (9) that the fastest time scales are associated with the voltage equation (2). Thus, the nullcline of this equation,

$$-\frac{hv}{\tau_{\text{in}}} \{\varphi_{\text{ci}}(v) + \beta e^{-c} \varphi_{\text{cd}}(v)\} + \frac{v}{\tau_{\text{out}}} = 0, \quad (16)$$

plays a central role in the asymptotics. By contrast, equation (6) for the concentration contains only an extremely slow time scale, so c is nearly constant over one action potential; thus, in (16), c is regarded as a constant. Apart from the trivial case $v = 0$, equation (16) expresses the condition that the inward and outward currents are exactly balanced. Solving this equation for h as a function of v yields

$$h = \frac{\tau_{\text{in}}}{\tau_{\text{out}}} \frac{1}{\varphi_{\text{ci}}(v) + \beta e^{-c} \varphi_{\text{cd}}(v)}. \quad (17)$$

The nullcline is the dashed curve graphed in Figure 5(b). Let $h_{\min}(c)$ be the minimum value for h on this curve. Since $\beta > 0$, it is easy to find from (17) that

$$h_{\min}(c) = \frac{\tau_{\text{in}}}{\tau_{\text{out}}} \frac{1}{1 + \beta e^{-c}}. \quad (18)$$

Equation (16) may also be solved for v as a function of h , but one encounters multivaluedness: i.e., as may be seen in Figure 5(b), for a given value of h , besides $v = 0$ there typically are two nonzero solutions of (16).

The dominant behavior in each phase of an action potential may be described as follows and as summarized in Table 2. The fact that c is approximately constant over each phase is not repeated in the description. (See Mitchell and Schaeffer [14] for a more detailed discussion of the asymptotics.)

(1) Upstroke phase—Following a successful stimulus⁴, the inward current J_{in} dominates the outward current J_{out} . In a time on the order of τ_{in} , during which the change in the gating variable h is negligible, the voltage rises quickly to the right branch of the nullcline (16).

(2) Plateau phase—As the gate closes according to equation (4), the voltage follows the nullcline, keeping the inward and outward currents balanced. In the present model, the plateau phase may be subdivided into a fast-closing subphase ($v > v_{\text{sldn}}$) and a slow-closing subphase ($v < v_{\text{sldn}}$), which have time scales τ_{fclose} and τ_{sclose} , respectively.

(3) Repolarization phase—When the gating variable reaches $h_{\min}(c)$ on the nullcline, the solution trajectory “falls off the nullcline”: i.e., the outward current J_{out} dominates the inward current J_{in} and the voltage drops toward $v = 0$ (see the solid line in Figure 5(b)). This occurs on a time scale of order τ_{out} .

⁴The stimulation process is analyzed in Section 3.3 below.

(4) Resting phase, or diastolic interval—The voltage stays small and the gate reopens with a time constant τ_{open} . This continues until the next stimulus is applied.

An APD consists of all of phase 2 plus parts of phases 1 and 3. According to (9), phases 1 and 3 are much shorter, so to a first approximation⁵, the APD is the duration of phase 2.

3.2 Derivation of the mapping

(a) Preliminaries—Assuming that (2, 4, 6) is stimulated repeatedly, we wish to estimate A_{n+1} —the duration of the action potential produced by the $(n+1)^{\text{st}}$ stimulus (assumed successful)—and C_{n+1} —the concentration when the $(n+2)^{\text{nd}}$ stimulus arrives. In our approximation, these quantities depend only on D_n , the diastolic interval preceding the $(n+1)^{\text{st}}$ stimulus; C_n , the concentration when the $(n+1)^{\text{st}}$ stimulus arrives; and B , the interval between the $(n+1)^{\text{st}}$ and the $(n+2)^{\text{nd}}$ stimuli. In our principal application, periodic stimulation, every two consecutive stimuli are separated by the same interval, so in our notation we do not include a subscript on B .

The estimate for C_{n+1} is easily obtained. Given (9) and the assumptions on $I(t)$ in the ODE (6), we see that following phase 1 of the $(n+1)^{\text{st}}$ action potential, the concentration evolves by

$$c(t) = \{C_n + \varepsilon\} e^{-t/\tau_{\text{pump}}}$$

where $t = 0$ corresponds to the arrival time of the $(n+1)^{\text{st}}$ stimulus. Thus (12) follows for stimuli separated by period B .

In phase 2, v is determined to leading order as a function of h and c by (16). On substitution of the resulting formula for v into (4), we obtain an ODE for h . In this equation, c , which may be approximated as constant over one APD, appears as a parameter. We will solve this ODE subject to the initial value for h given in the following lemma.

Lemma 3.1: *At the start of phase 2 of the $(n+1)^{\text{st}}$ action potential*

$$h_{\text{init}} \approx 1 - e^{-D_n/\tau_{\text{open}}}, \quad (19)$$

and at the end of this phase

$$h_{\text{term}} \approx h_{\text{min}}(C_n). \quad (20)$$

Proof: As noted above, $h_{\text{term}} \approx h_{\text{min}}(C_n)$ defines the end of phase 2: i.e., the point at which h has decayed so much that the inward current can no longer balance the outward current. This verifies (20).

Equation (19) may be verified by analyzing the preceding DI. The initial condition for the gate h at the start of this DI, say $h(0)$ where we have redefined the time origin, is approximately $h_{\text{min}}(C_n)$, which is the value of h at the end of phase 2 of the previous action

⁵In this approximation, APD does not depend on the percentage of repolarization used to define APD.

potential. More accurately, because h continues to decay during phase 3 of the previous action potential, we have

$$0 < h(0) < h_{\min}(C_n).$$

However, $h_{\min}(C_n) \leq \tau_{\text{in}}/\tau_{\text{out}}$, which by (9) is a small quantity. Thus we may take $h(0) \approx 0$. By solving the initial-value problem for $dh/dt = (1 - h)/\tau_{\text{open}}$ with $h(0) = 0$ over the interval $0 < t < D_n$, we see that the value of h at the end of the n^{th} DI is given by (19). Since h does not change appreciably during phase 1 of the $(n + 1)^{\text{st}}$ action potential, the lemma is proved. ■

(b) Short DI's—Except for very fast pacing, the diastolic interval D_n is larger than D_{sldn} , where

$$D_{\text{sldn}} = \tau_{\text{open}} \ln \frac{1}{1 - h_{\text{sldn}}} \quad \text{with} \quad h_{\text{sldn}} = \frac{\tau_{\text{in}}}{\tau_{\text{out}}} \frac{v_{\text{crit}}}{1 - v_{\text{sldn}}}. \quad (21)$$

If $D_n < D_{\text{sldn}}$, then at the start of the $(n + 1)^{\text{st}}$ action potential, $h_{\text{init}} < h_{\text{sldn}}$ as can be seen from (19) and (21). According to (16), at this time $v < v_{\text{sldn}}$; thus, in solving (4) only the simpler alternative occurs: i.e., $dh/dt = -h/\tau_{\text{sclose}}$. Note that v does not appear in this equation. Thus, regardless of the behavior of v , the gate h has simple exponential decay. Hence, if $D_n < D_{\text{sldn}}$, then A_{n+1} , the time required for h to decay from h_{init} to $h_{\min}(C_n)$, is given by

$$A_{n+1} = \tau_{\text{sclose}} \ln \left(\frac{1 - e^{-D_n/\tau_{\text{open}}}}{h_{\min}(C_n)} \right). \quad (22)$$

(c) General DI's—If $D_n > D_{\text{sldn}}$, then both fast-closing and slow-closing subphases are present in phase 2. The slow-closing phase begins at $h = h_{\text{sldn}}$ and ends at $h = h_{\min}(C_n)$, so it has duration

$$A_{\text{sclose}} = \tau_{\text{sclose}} \ln \left\{ \frac{h_{\text{sldn}}}{h_{\min}(C_n)} \right\}. \quad (23)$$

To determine the duration of the fast-closing subphase, we note from (16) that if $v > v_{\text{sldn}}$, then

$$1 - v = \frac{\tau_{\text{in}}}{\tau_{\text{out}}} \frac{v_{\text{crit}}}{h}.$$

Substituting into (4), we obtain the linear ordinary differential equation for $h(t)$

$$\tau_{\text{fclose}} \frac{dh(t)}{dt} = -h(t) + \left(1 - \frac{\tau_{\text{fclose}}}{\tau_{\text{sclose}}}\right) h_{\text{sldn}}. \quad (24)$$

Resetting (without loss of generality) $t = 0$ in the initial condition for (24), we find the formula for the gating variable in the fast closing sub-phase

$$h(t) = \left(1 - \frac{\tau_{\text{fclose}}}{\tau_{\text{sclose}}}\right) h_{\text{sldn}} + \left\{ h_{\text{init}} - \left(1 - \frac{\tau_{\text{fclose}}}{\tau_{\text{sclose}}}\right) h_{\text{sldn}} \right\} e^{-t/\tau_{\text{fclose}}}. \quad (25)$$

The duration of this subphase, A_{fclose} , is determined by solving for the time when $h(t) = h_{\text{sldn}}$:

$$A_{\text{fclose}} = \tau_{\text{fclose}} \ln \left\{ \frac{[1 - e^{-D_n/\tau_{\text{open}}}] - (1 - \tau_{\text{fclose}}/\tau_{\text{sclose}}) h_{\text{sldn}}}{h_{\text{sldn}} (\tau_{\text{fclose}}/\tau_{\text{sclose}})} \right\}. \quad (26)$$

where we have substituted (17) for (19).

Of course A_{n+1} is the sum of (26) and (23),

$$A_{n+1} = \tau_{\text{fclose}} \ln \left\{ \frac{[1 - e^{-D_n/\tau_{\text{open}}}] - (1 - \tau_{\text{fclose}}/\tau_{\text{sclose}}) h_{\text{sldn}}}{h_{\text{sldn}} (\tau_{\text{fclose}}/\tau_{\text{sclose}})} \right\} + \tau_{\text{sclose}} \ln \left\{ \frac{h_{\text{sldn}}}{h_{\text{min}}(C_n)} \right\}. \quad (27)$$

(d) A convenient rewriting—At slow pacing D_n is large, and under repeated slow pacing C_n converges to approximately zero. Thus, recalling (18) and (21), we see that under repeated slow pacing

$$A_{n+1} \approx A_{\text{max}} = \tau_{\text{fclose}} \ln \frac{\tau_{\text{sclose}}}{\tau_{\text{fclose}}} \frac{\tau_{\text{out}}}{\tau_{\text{in}}} \frac{1 - v_{\text{sldn}}}{\alpha v_{\text{crit}}} + \tau_{\text{sclose}} \ln \left\{ (1 + \beta) \frac{v_{\text{crit}}}{1 - v_{\text{sldn}}} \right\} \quad (28)$$

where

$$\alpha = \left\{ 1 - \frac{\tau_{\text{in}}}{\tau_{\text{out}}} \left(1 - \frac{\tau_{\text{fclose}}}{\tau_{\text{sclose}}} \right) \frac{v_{\text{crit}}}{1 - v_{\text{sldn}}} \right\}^{-1}. \quad (29)$$

Adding and subtracting A_{max} to (27) and rearranging, we obtain equations (11, 13, 14). Incidentally, for the parameter values in Table 1, we have $A_{\text{max}} = 840\text{ms}$ and $\alpha = 1.1$.

3.3 Threshold for stimulation

Up to now we have been assuming that each stimulus was successful in producing an action potential. Let us examine the stimulation process more carefully. When a stimulus current is applied, an extra term must be added to (2),

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

Assume that J_{stim} is nonzero only for an interval of length τ_{stim} that is short compared to all other time scales in the equations. Then at the end of the stimulus, $v \approx v_{\text{stim}}$, where

$$v_{\text{stim}} = \int_0^{\tau_{\text{stim}}} J_{\text{stim}}(t) dt.$$

Let $h_{\text{stim}}(C_n)$ be the corresponding value of h on the nullcline (17): i.e.,

$$h_{\text{stim}}(C_n) = \frac{\tau_{\text{in}}}{\tau_{\text{out}}} \frac{1}{\varphi_{\text{ci}}(v_{\text{stim}}) + \beta e^{-C_n} \varphi_{\text{cd}}(v_{\text{stim}})}.$$

Lemma 3.2—The $(n + 1)^{\text{st}}$ stimulus will produce an action potential if and only if

$$D_n > \tau_{\text{open}} \ln \left(\frac{1}{1 - h_{\text{stim}}(C_n)} \right). \quad (30)$$

Proof—Immediately following the $(n + 1)^{\text{st}}$ stimulus,

$$(v, h) \approx (v_{\text{stim}}, h_{\text{init}}(C_n)) \quad (31)$$

where h_{init} is given by (19). If (30) holds, then the point (31) lies inside the nullcline (16) where J_{in} dominates J_{out} , and the system will begin a normal action potential. If (30) does not hold, then J_{out} dominates J_{in} , and the voltage will quickly decay back to zero with no lasting change in the evolution. ■

3.4 Comparison of the mapping and the ionic model

Figure 6 shows the dynamic restitution curves produced by both the mapping (11–12) and the ionic model (2, 4, 6). As the figure shows, the errors are larger than one would like, especially for faster pacing rates. Cain and Schaeffer [3] have shown that the asymptotic mapping of the two-current model in [14] can be greatly improved by including higher-order corrections. Following a similar line of approach, one can obtain an improved mapping for the ionic model (2, 4, 6). A preliminary version of the improved mapping significantly reduces the errors. This will be discussed elsewhere.

4 Summary and Discussion

Based on asymptotic approximation of a system of nonlinear ODEs, we have derived a two-dimensional mapping, which is able to accurately describe restitution in paced cardiac tissue. Unlike *ad hoc* mappings, the mapping developed here clearly relates to physiological variables through the underlying ODEs, also known as an ionic model. The developed mapping provides a tool to understand cardiac instabilities that may lead to fatal arrhythmias.

Since the underlying ionic model is piecewise defined, the resulting mapping also exhibits piecewise smoothness. Piecewise smooth dynamical systems may exhibit various discontinuity-induced bifurcations, such as grazing bifurcations in systems with discontinuous changes in states [7,19,20] and border-collision bifurcations in piecewise continuous maps [5,16,21]. To explore the possibility for discontinuous bifurcations, we first examine the type of discontinuities in the mapping. As established in Section 3, A_{n+1} relates to D_n by (22) when $D_n < D_{\text{sldn}}$ and by (28) when $D_n > D_{\text{sldn}}$. Thus, a discontinuity boundary

of the mapping is associated with $D_n = D_{\text{sldn}}$. It follows from (21) that $h_{\text{sldn}} = 1 - e^{-D_{\text{sldn}}\tau_{\text{open}}}$. Therefore, values of the mapping are continuous at $D_n = D_{\text{sldn}}$, as can be seen from (22) and (28). Moreover, one can verify that first derivatives of the mapping are continuous at the discontinuity boundary, although second derivatives jump. Thus, the mapping satisfies the usual $\mathcal{C}^1$ hypothesis of smooth bifurcations. In any event, in almost the entire range of the experiment of [17], the system is responding in the range $D_n > D_{\text{sldn}}$ above the discontinuity boundary.

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Figure 1. Schematic action potentials, showing action potential duration (A_n) and diastolic interval (D_n). For reference below, measurement times and the concentration C_n in (11, 12) below are also indicated.

Figure 2.

A schematic dynamic restitution curve (thin curve) and a transient to steady state (the sequence of crosses, merging to form the thick curve). The transient occurs when the BCL is abruptly decreased from the steady state conditions indicated by the open circle.

Figure 3.

Voltage, gate and concentration vs. time in the ionic model (2), (4) and (6) with the parameter values in Table 1. *Solid line:* steady state response at $B = 650$ ms. *Dashed line:* First response at $B = 650$ ms, following steady state at $B = 750$ ms.

Figure 4.

(a, c) A_n and C_n vs. n according to the mapping model (11)–(12) following an abrupt decrease in BCL from 750ms to 650ms at $n = 51$ (parameter values as in Table 1). (b, d) The first few beats following the decrease in BCL.

Figure 5.

An action potential consists of four phases: upstroke phase, plateau phase, repolarization phase and resting phase.

Figure 6.
The dynamic restitution curves produced by both the mapping (11–12) (dashed curve) and the ionic model (2, 4, 6) (solid curve).

Table 1

Parameters for the ionic model (2), (4) and (6)

Primary occurrence	Parameter	Value	Units	Meaning
Equation (2)	τ_{in}	0.28	ms	Strength of inward current
	τ_{out}	3.2	ms	Strength of outward current
	β	7.3		Ratio of charge-dep't to charge-indep't current
Equation (4)	v_{crit}	0.13		Change between opening and closing of gate
	v_{sldn}	0.89		Change between fast and slow closing of gate
	τ_{open}	500	ms	Time scale for opening of gate
	τ_{fclose}	22	ms	Time scale for fast closing of gate
	τ_{sclose}	320	ms	Time scale for slow closing of gate
Equation (6)	τ_{pump}	30000	ms	Time scale for pumping ions from the cell
	ε	0.033		Charge entering cell during action potential

Table 2

Summary of asymptotics during the four phases of an action potential

Phase	Name	Duration(order of mag.)	Simplification	Dominant equation
1	Upstroke	τ_{in}	$H \approx \text{Const}$	(2)
2	Plateau	$\tau_{\text{fclose}}, \tau_{\text{sclose}}$	$J_{\text{in}} + J_{\text{out}} \approx 0$	(4)
3	Repolarization	τ_{in}	$h \approx \text{Const}$	(2)
4	Recovery	τ_{open}	$v \approx 0$	(4)