

Criterion for stable reentry in a ring of cardiac tissue

John W. Cain

Received: 11 September 2006 / Revised: 29 March 2007
© Springer-Verlag 2007

Abstract We model electrical wave propagation in a ring of cardiac tissue using an m th-order difference equation, where m denotes the number of cells in the ring. Under physiologically reasonable assumptions, the difference equation has a unique equilibrium solution. Applying Jury's stability test, we prove a theorem concerning the local asymptotic stability of this equilibrium solution. Our results yield conditions for sustained reentrant tachycardia, a type of cardiac arrhythmia.

Keywords Jury stability test · Local asymptotic stability · Cardiac restitution · Reentrant tachycardia

Mathematics Subject Classification (2000) 39A11 · 37N25 · 92C99

1 Introduction

The primary purpose of the heart is to pump blood throughout the body. Cardiac arrhythmias can degrade pumping performance, in some cases completely blocking the heart's ability to deliver blood to vital organs such as the brain and kidneys. Because these organs fail unless they receive the oxygen and nutrients contained in blood, abnormal heart rhythms often have fatal consequences.

Mechanical contraction of the heart is driven by electrical activity. The right atrium of the heart contains a cluster of specialized cells called the sinoatrial (SA) node, which serves as the heart's natural pacemaker. When the SA node provides a stimulus, the surrounding atrial tissue becomes electrically excited. An electrical wave of excitation

J. W. Cain (✉)
Department of Mathematics, Virginia Commonwealth University,
1001 West Main Street, Richmond, VA 23284-2014, USA
e-mail: jwcain@vcu.edu

known as an *action potential* propagates through the atrium and is then transmitted to the ventricles. These propagating action potentials are responsible for cardiac muscle contraction.

Most mathematical models of the cardiac action potential involve partial differential equations that govern, among other things, the voltage across each cell membrane in a sample of tissue [20,21,24,27]. However, when studying cardiac arrhythmias, one typically follows the progress of propagating action potentials without tracking the transmembrane voltage of each cell [21,28]. Indeed, several recent studies [3,11,15,31,33] have used difference equations and coupled map lattices to model action potential propagation in cardiac tissue.

As noted in [12,15,31], under certain circumstances, closed loops of tissue can form in the heart allowing unidirectional recirculation of action potentials. When these reentrant paths of excitation form, the period of circulation can be substantially faster than the period of the SA nodal cells. Reentry has been linked to various faster-than-normal rhythms (*tachycardias*) such as atrial flutter and ventricular tachycardia [15]. In an even more troubling scenario, it is believed that breakups of action potential wave fronts emanating from a stable reentrant source can initiate and maintain lethal ventricular fibrillation [26,38].

From a physiological standpoint, it is desirable to determine conditions under which abnormal reentrant tachycardias can persist. Ito and Glass [15] considered the following natural question regarding reentrant excitation in a ring of cardiac tissue:

Question: When reentrant circulation is initiated in a ring-shaped piece of cardiac tissue, under what conditions does the reentry persist? In particular, what are the criteria for stable, reentrant excitation with a fixed period?

To address this question, Ito and Glass exploited the restitution properties (see Sect. 2) of cardiac tissue to propose a kinematic model of action potential propagation, presented as a system of coupled maps. Their subsequent computations suggest a rather simple stability criterion, which they support both analytically and numerically. In a later study by Sedaghat et al. [31], the authors expand upon the work of Ito and Glass, using a nonlinear difference equation (see Eq. 10) to analyze the convergence, oscillation and bistability of pulse circulation. In particular, they provide (1) sufficient conditions for existence of a unique equilibrium state in which the pulse circulates with constant speed and (2) sufficient conditions for local asymptotic stability of this equilibrium state.

In this paper, we prove that the stability criterion proposed by Ito and Glass [15] is not only sufficient but also *necessary*¹ for local asymptotic stability of the aforementioned equilibrium. To do so, we linearize the equations appearing in [15,31] about the unique equilibrium state. Letting m denote the number of cells in the ring, the $m \times m$ Jacobian matrix associated with the linearized system has a convenient block structure and leads to an m th degree characteristic polynomial for which many of the coefficients are repeated. Applying the Jury stability test [1,16], we obtain a necessary and sufficient condition for all roots of the characteristic polynomial to lie in the open unit disc in the complex plane. As we shall see, the resulting stability criterion

¹ In proving necessity, we resolve the open problem stated in Sect. 3.4, Remark 4 of Sedaghat et al. [31].

(Theorem 2) agrees with the one conjectured by Ito and Glass. After proving this theorem, we compare and contrast our findings with previously reported results [4, 7].

We emphasize that, although the present study is motivated by a problem concerning cardiac dynamics, the techniques used in the proof of the main theorem are of independent pedagogical interest. Indeed, although the Jury test is commonly used to determine stability of equilibria of low-dimensional ($n = 2, 3$) discrete dynamical systems, the Jury algorithm can be used to determine whether roots of certain classes of polynomials of *arbitrary* degree lie within the open unit disc in the complex plane.

2 Background on cardiac electrophysiology

2.1 Ionic models

Like the famous Hodgkin–Huxley model of the nerve action potential, models of the cardiac action potential are typically presented as systems of differential equations that govern (1) the transmembrane voltage v of the cells and (2) the conductances of various ion channels in the cell membrane. The *cable equation*

$$\frac{\partial v}{\partial t} = \kappa \frac{\partial^2 v}{\partial x^2} - \frac{I_{\text{total}}}{C_m}, \quad (1)$$

is commonly used to model propagation of action potentials in a one-dimensional excitable medium. Here, C_m denotes the cell membrane capacitance and I_{total} is a sum of all transmembrane ionic currents. The diffusion coefficient κ incorporates, among other things, the cell's longitudinal electrical resistivity. For details about the cable equation including its derivation, see the texts of Keener and Sneyd [21] and Plonsey and Barr [27].

Numerous authors have proposed ionic membrane models that aim to track the various transmembrane currents. Among the simplest models are those of Mitchell and Schaeffer [23] and Fenton and Karma [10], which express I_{total} as a sum of two and three ionic currents, respectively. The more detailed model of Luo and Rudy [22] incorporates 14 different ionic currents, pumps, and exchangers. As we shall explain in the upcoming subsections, several authors have derived restitution mappings as asymptotic limits of ionic models, thereby providing a connection between the more traditional PDE model approach and the discrete model that we use in the present study.

2.2 Pacing

When a cardiac cell is repeatedly stimulated, or *paced*, each stimulus typically² elicits an action potential. The recovery period between two successive action potentials is called a *diastolic interval* (DI). By specifying a threshold voltage v_{thr} , one may define

² Rapid pacing can lead to more complicated phase-locked responses [13, 25, 37]. However, such rhythms will not be considered in what follows.

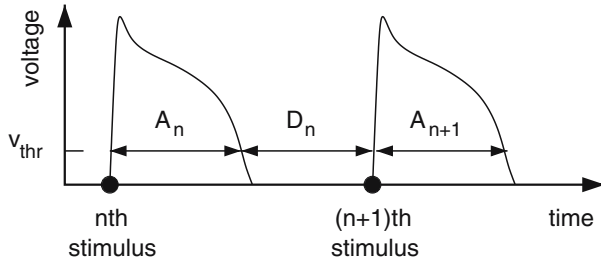


Fig. 1 Voltage trace of two consecutive action potentials in a paced cardiac cell

the *action potential duration (APD)* as the amount of time during which $v > v_{thr}$ between successive stimuli. The *DI* is the amount of time during which $v < v_{thr}$ between successive action potentials. When considering a paced cardiac cell, we will let A_n denote the duration of the n th action potential and D_n the duration of the subsequent DI. This notation is illustrated in Fig. 1, which shows a voltage trace of two successive action potentials in a cardiac cell.

2.3 APD restitution

One of the most significant features of paced cardiac cells is the shortening of APD values as the interstimulus interval decreases, a property known as *APD restitution*. Based upon their experimental results, Nolasco and Dahlen [25] proposed a phenomenological mapping model of APD restitution:

$$A_{n+1} = f(D_n). \tag{2}$$

The graph of f , known as an *APD restitution curve* (Fig. 2a), is monotone increasing, reflecting the fact that increased recovery time leads to larger APD values. More specifically, APD restitution curves often have the same qualitative shape as the graph of

$$f(DI) = APD_{max} - \beta e^{-DI/\tau}, \quad \text{if } DI \geq \theta, \tag{3}$$

where APD_{max} , β , τ and θ are positive constants. Here, θ denotes the *refractory time*, the minimum DI that a cell requires in order to recover excitability [15]. Because we are primarily concerned with sustained propagation, in what follows we will assume that DI values are larger than θ so that reentrant action potentials are not blocked.

If a cell is paced with period B , the mapping (2) can be written in the form $A_{n+1} = f(B - A_n)$. As the parameter B is decreased, this mapping may experience a period-doubling bifurcation leading to alternation of APD (and DI) values. The resulting period-2 response, known as *alternans*, is viewed as a precursor to fatal arrhythmias [19,29].

Several studies [2,23] have shown that one-dimensional return mappings of the form (2) can be derived from a two-current ionic model [18,23] using asymptotic

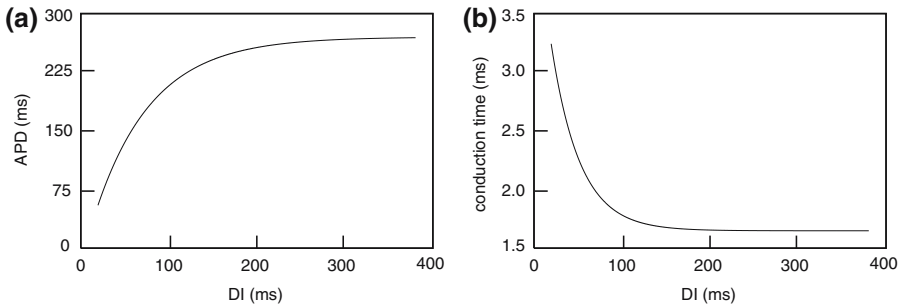


Fig. 2 Sample restitution curves: **a** an APD restitution curve, **b** a CT restitution curve showing time required to traverse a distance of $\Delta L = 1.0$ mm

methods. In other words, it is possible to extract a restitution function f from the differential equations of an ionic model. As we shall explain in the Sect. 5, more sophisticated ionic models actually give rise to higher-dimensional mappings [35].

2.4 CT restitution

Cardiac cells are electrically coupled via gap junctions, allowing action potentials to propagate spatially through tissue [21,27]. Like APD, the propagation speed, or *conduction velocity*, of action potentials depends upon the preceding (local) DI. The analogue of the APD restitution curve, known as the *dispersion curve*, displays the dependence of conduction velocity upon the local DI. Dispersion curves are qualitatively similar to restitution curves (see Eq. 3)—specifically, they are monotone increasing in DI so that increased recovery time leads to faster propagation speeds. We will let $v(\text{DI})$ denote the functional form of the dispersion curve.

Rather than considering the velocity of propagating action potentials, it will be convenient to measure the time required for the wavefront of an action potential to traverse a small distance ΔL . We define

$$c(\text{DI}) = \frac{\Delta L}{v(\text{DI})}, \quad \text{if } \text{DI} \geq \theta \tag{4}$$

and refer to the graph of $c(\text{DI})$ as the *conduction time (CT) restitution curve*. Because $v(\text{DI})$ is monotone increasing, note that $c(\text{DI})$ is monotone decreasing (Fig. 2b).

As with APD restitution functions, one may use asymptotic methods to derive an approximation of the CT restitution function $c(\text{DI})$ from Eq. (1). For example, in [3], the authors derive a leading-order asymptotic approximation of the CT restitution curve directly from the cable equation, using the two-current ionic model [23] to determine I_{total} .

3 The model

We now recall the equations used by Ito and Glass [15] and later by Sedaghat et al. [31] to model reentry of action potentials in a ring-shaped piece of tissue.

3.1 The main equation

Consider a ring-shaped piece of cardiac tissue composed of m cells, each of length ΔL . We adopt the following assumptions for the remainder of this paper:

- (A1): The ring is homogeneous in the sense that the APD and CT restitution functions are the same for each cell.
- (A2): The APD and CT restitution functions can be applied locally at each cell in the ring.
- (A3): The APD restitution function $f(DI)$ is monotone increasing and the CT restitution function $c(DI)$ is monotone decreasing.

We index the cells in the ring using subscripts $i = 1, 2, \dots, m$, and will let $A_{i,n}$ and $D_{i,n}$ denote the n th APD and DI of the i th cell. By assumptions (A1) and (A2) above, we may write

$$A_{i,n} = f(D_{i,n-1}), \quad 1 \leq i \leq m, \tag{5}$$

and

$$CT_{i,n} = c(D_{i,n-1}), \quad 1 \leq i \leq m, \tag{6}$$

where $CT_{i,n}$ denotes the conduction time required for the n th action potential wavefront to traverse the i th cell in the ring.

Each cycle of the action potential can be divided into two distinct phases, the APD followed by the DI. At a given cell in the ring, we may express the cycle length in two different ways (see Fig. 3):

$$A_{i,n} + D_{i,n} = \sum_{j=1}^{i-1} CT_{j,n+1} + \sum_{j=i}^m CT_{j,n}, \quad 1 \leq i \leq m. \tag{7}$$

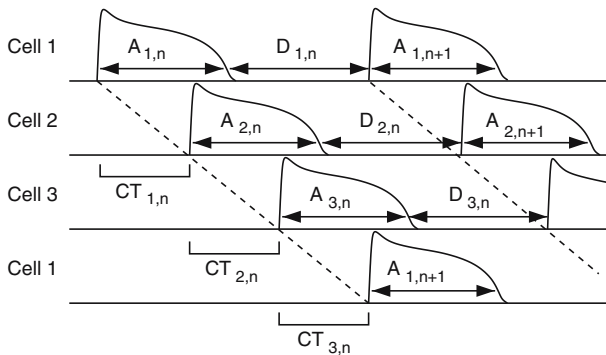


Fig. 3 Schematic diagram of an action potential propagating with constant speed in a ring composed of $m = 3$ cells. Note that $A_{1,n} + D_{1,n}$ is equal to the sum of the conduction times to traverse the three cells

By Eqs. (5) and (6), we may write Eq. (7) as

$$D_{i,n} = \sum_{j=1}^{i-1} c(D_{j,n}) + \sum_{j=i}^m c(D_{j,n-1}) - f(D_{i,n-1}), \quad 1 \leq i \leq m. \quad (8)$$

Following [31], we convert Eq. (8) into an autonomous m th-order difference equation by introducing the variable

$$x_{mn+i} = D_{i,n}. \quad (9)$$

Combining Eqs. (8) and (9), we obtain the *main equation*

$$x_k = \sum_{j=k-m}^{k-1} c(x_j) - f(x_{k-m}). \quad (10)$$

Given an initial state vector $(x_{-m+1}, x_{-m+2}, \dots, x_0)$, Eq. (10) generates a sequence $\{x_k\}_{k=1}^\infty$ of DI values.

3.2 Dynamics of the main equation

Equation (10) can exhibit a wide variety of dynamical behavior. Here, we single out four particularly interesting responses and discuss the corresponding physiological implications. For a more complete review of the dynamics of Eq. (10), we refer the reader to Sects. 3 and 4 of Ito and Glass [15] and Sect. 3.5 of Sedaghat et al. [31]. In particular, because not all steady-states of (10) are of physiological interest, it is useful to generate an admissible region for the APD and CT restitution curve parameters (c.f., Fig. 4 in [15]).

Figure 4 illustrates several types of responses that one may observe when solving Eq. (10) numerically for particular choices of restitution curves. Each panel shows a time series of x_k values over the course of several cycles of reentry. These behaviors are described as follows:

- *Sustained reentry with fixed period.* In Fig. 4a, the ring exhibits sustained reentry in which the sequence of DI values has converged to a fixed point of Eq. (10). Physiologically, this corresponds to a situation in which the pulse recirculates with constant speed. Such a steady-state is typically observed for rings that are appropriately long (i.e., large m).
- *Quasi-periodic variation of DI.* For shorter ring lengths, the ring may tend to a phase-locked quasiperiodic response as illustrated in Fig. 4b. The oscillations in DI occur over a spatial scale of wavelength slightly shorter than twice the length of the ring. Similar results have been reported previously by Courtemanche et al. [6]. Observe that some cells in the ring exhibit long-short alternation of DI, while others exhibit short-long alternation. This phenomenon, known as *discordant alternans*, is viewed as a precursor to lethal arrhythmias [36].

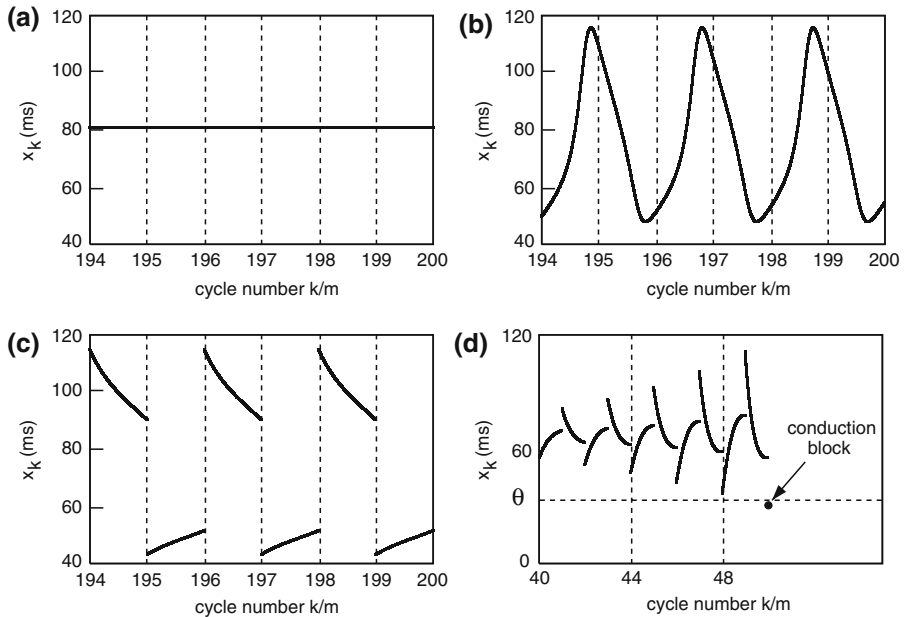


Fig. 4 Time series of DI values. Each panel shows x_k versus k/m obtained by numerical simulation of Eq. (10) for particular choices of the restitution curves. **a** Sustained reentry with no variation in DI. **b** Sustained reentry with quasi-periodic variation of DI. **c** Sustained reentry with beat-to-beat alternation of DI in each cell. **d** Growing oscillations of DI leading to conduction block. The first computed DI in the 50th beat is smaller than the refractory time $\theta = 35$ ms, thereby preventing further propagation

- *Concordant alternans*. Figure 4c shows a periodic response in which each cell in the ring experiences alternans. Note that the alternans is not spatially discordant as in the previous panel.
- *Conduction block*. Finally, Fig. 4d illustrates the last ten beats of reentry prior to conduction block. The ring exhibits concordant alternans of growing amplitude until, at the start of the 50th cycle, Eq. (10) returns a value smaller than the refractory time θ (chosen to be 35 ms in this case). The reentrant pulse is blocked from propagating any further. Physiologically, the wave front of the reentrant pulse catches up with its own tail, reaching a region of refractory tissue that is not ready for subsequent excitation. The cascade from stable reentry to conduction block can lead to disorganized excitation patterns reminiscent of fibrillation (see, for example, Fig. 6b in Karma [19]).

In the following section, we derive a condition under which the steady-state response illustrated in Fig. 4a is stable to a small perturbation. For mathematical results concerning the other responses in which DI values exhibit persistent oscillations, see [31]. The mathematical analysis of spontaneous initiation and termination of reentry is the subject of an ongoing study, although some preliminary results have been reported [32].

4 Main result

Equilibrium solutions of Eq. (10) satisfy the equation

$$x^* = \sum_{j=k-m}^{k-1} c(x^*) - f(x^*) = mc(x^*) - f(x^*). \tag{11}$$

Under certain reasonable assumptions [31], the main equation (10) has a unique equilibrium solution in which $x_k = x^*$ for all k :

Lemma 1 *Suppose that the following conditions hold:*

- *The function $f(DI)$ is defined, positive, continuous and monotone increasing for $DI \geq \theta$ where θ denotes the refractory time,*
- *The function $c(DI)$ is defined, positive, continuous and monotone decreasing for $DI \geq \theta$, and*
- *There exists $\tilde{D} \geq \theta$ such that $mc(\tilde{D}) > f(\tilde{D}) + \tilde{D}$.*

Then Eq. (10) has a unique equilibrium solution x^ .*

The first two assumptions in Lemma 1 express the fact that more rest (i.e., larger DI) results in longer action potentials that propagate faster. The last assumption expresses the fact that reentry cannot be sustained if the propagation around the ring is too fast [31].

Assuming the hypotheses of Lemma 1, linearizing Eq. (10) about x^* leads to the characteristic polynomial (see Sect. 4.6 of [8], and [31])

$$p(\lambda) = \lambda^m + \beta \sum_{j=1}^{m-1} \lambda^j + \beta + \alpha, \tag{12}$$

where

$$\alpha = f'(x^*) \quad \text{and} \quad -\beta = c'(x^*). \tag{13}$$

By Assumption (A3) above, note that $\alpha, \beta > 0$.

Just as the well-known Routh–Hurwitz test [14] can be used to determine whether all roots of a polynomial have negative real parts, the Jury stability test [16] can be used to determine whether all roots of a polynomial have modulus less than one. We state the Jury stability test as it appears in [1]:

Theorem 1 *(Jury stability test) All roots of the polynomial*

$$q(x) = a_m x^m + a_{m-1} x^{m-1} + \dots + a_1 x + a_0 \tag{14}$$

lie in the open unit disc in the complex plane if and only if

- (J1): $a_m q(1) > 0$,

- (J2): $(-1)^m a_m q(-1) > 0$, and
- (J3): $|r_j| < 1$ for $j = 1, 2, \dots, m$, where r_j are given by the following iterative procedure. First, set $b_j = a_{m-j}$ for $j = 0, 1, \dots, m$ and define $r_m = b_m/a_m$. Then, define $a_{j-1}^{\text{new}} = a_j - r_m b_j$ for $j = 1, 2, \dots, m$. This gives the coefficients $a_{m-1}, a_{m-2}, \dots, a_0$ for the next iteration.

We now apply Theorem 1 to the characteristic polynomial (12) to establish our main result, Theorem 2. Physiologically, Theorem 2 provides a criterion for stable reentry with a fixed period—namely, the sum of the slopes of the two restitution curves must not exceed one. This agrees with the criterion that is proposed in the paper of Ito and Glass [15]. We shall prove Theorem 2 by demonstrating that the only non-trivial restriction that the Jury test imposes on α and β is the requirement that $\alpha + \beta < 1$.

Theorem 2 *The fixed point x^* of Eq. (10) is locally asymptotically stable if and only if $\alpha + \beta < 1$.*

Proof Applying Theorem 1 to the characteristic polynomial in Eq. (12), condition (J1) requires that $1 + \beta(m - 1) + \beta + \alpha > 0$, which is trivially satisfied since, by Assumption (A3), both α and β are positive. If m is even, condition (J2) requires that $(1 + \alpha) > 0$, which is trivially satisfied since $\alpha > 0$. If m is odd, condition (J2) yields $\alpha + \beta < 1$. We remark that this condition on $\alpha + \beta$ will be duplicated below, regardless of the parity of m .

For the first iteration of (J3), we arrange the coefficients of the characteristic polynomial in a table:

j	0	1	2	\dots	$m - 2$	$m - 1$	m
a_j	$\beta + \alpha$	β	β	\dots	β	β	1
b_j	1	β	β	\dots	β	β	$\beta + \alpha$

Here, a_j is the coefficient of λ^j in Eq. (12), and $b_j = a_{m-j}$. We compute

$$r_m = \frac{b_m}{a_m} = \beta + \alpha, \tag{15}$$

which, by (J3), yields the requirement $\alpha + \beta < 1$. Setting

$$a_{j-1}^{\text{new}} = a_j - r_m b_j = \begin{cases} \beta[1 - (\beta + \alpha)], & j = 1, 2, \dots, m - 1, \\ 1 - (\beta + \alpha)^2, & j = m, \end{cases} \tag{16}$$

we obtain the updated coefficients for the second iteration of the procedure. The updated table reads

j	0	1	\dots	$m - 2$	$m - 1$
a_j	$\beta[1 - (\beta + \alpha)]$	$\beta[1 - (\beta + \alpha)]$	\dots	$\beta[1 - (\beta + \alpha)]$	$1 - (\beta + \alpha)^2$
b_j	$1 - (\beta + \alpha)^2$	$\beta[1 - (\beta + \alpha)]$	\dots	$\beta[1 - (\beta + \alpha)]$	$\beta[1 - (\beta + \alpha)]$

Observe that (1) this new table has one fewer column than the first one and (2) the coefficients a_0, a_1, \dots, a_{m-2} are identical, but a_{m-1} is different. Moreover, from the

above table we find that

$$r_{m-1} = \frac{\beta[1 - (\beta + \alpha)]}{1 - (\beta + \alpha)^2} = \frac{\beta}{1 + \beta + \alpha}. \tag{17}$$

Note that the condition $|r_{m-1}| < 1$ is automatically satisfied since both α and β are positive.

The repetition of coefficients in these tables allows for straightforward computation of the values r_j referred to in (J3). More specifically, we need only track the values in the first (or, by symmetry, last) column of these tables. Let y_k and z_k denote the values of a_0 and b_0 , respectively, obtained during the k th iteration of the Jury test. For example, from the two tables above we have

$$y_1 = \beta + \alpha, \quad z_1 = 1, \quad y_2 = \beta[1 - (\beta + \alpha)], \quad z_2 = 1 - (\beta + \alpha)^2. \tag{18}$$

Then condition (J3) of the Jury criterion requires that

$$\left| \frac{y_k}{z_k} \right| < 1, \quad k = 1, 2, \dots \tag{19}$$

Due to the symmetry in the table formed during the second iteration, an inspection of how (J3) updates the table between successive iterations reveals a system of recurrence relations:

$$y_{k+1} = y_k - \frac{y_k^2}{z_k}, \tag{20}$$

$k = 2, 3, \dots$

$$z_{k+1} = z_k - \frac{y_k^2}{z_k}. \tag{21}$$

By computing several iterates, one is led to conjecture that

$$\frac{y_k}{z_k} = \frac{\beta}{1 + \alpha + (k - 1)\beta}, \quad k = 2, 3, \dots, \tag{22}$$

Indeed, for $k = 2$, we have by Eq. (18)

$$\frac{y_2}{z_2} = \frac{\beta}{1 + \alpha + \beta}. \tag{23}$$

Assume that (22) holds for $k = n$. From Eqs. (20) and (21), we compute that

$$\frac{y_{n+1}}{z_{n+1}} = \frac{y_n - y_n^2/z_n}{z_n - y_n^2/z_n} = \frac{y_n}{z_n} \left(\frac{1 - y_n/z_n}{1 - y_n^2/z_n^2} \right) = \frac{y_n}{z_n} \left(\frac{1}{1 + y_n/z_n} \right). \tag{24}$$

By our inductive assumption we have

$$\frac{y_n}{z_n} = \frac{\beta}{1 + \alpha + (n - 1)\beta}. \quad (25)$$

Combining Eqs. (24) and (25), one easily verifies that

$$\frac{y_{n+1}}{z_{n+1}} = \frac{\beta}{1 + \alpha + n\beta}, \quad (26)$$

and the claim (22) is proved. Since α and β are positive, Eq. (22) shows that the requirement (19) is automatically satisfied for $k \geq 2$. Hence, the only non-trivial condition imposed on α and β by the Jury stability test is that $\alpha + \beta < 1$. \square

5 Discussion and conclusions

Anatomical obstacles such as regions of dead tissue can lead to reentrant paths of excitation, allowing abnormal, unidirectional recirculation of action potentials. Using a kinematic model of electrical wave propagation in a ring of cardiac tissue, we have derived a criterion under which reentry is stable to small perturbations. The model is presented as an m th-order nonlinear difference equation which, under reasonable assumptions, has a unique fixed point. By the Jury stability test, the fixed point is stable if and only if the sum of the slopes of the APD and CT restitution curves at the fixed point is less than one.

We remark that, although the methods used in the present study are of independent pedagogical interest, our main result is based upon an *idealized* model of reentry. We now discuss several limitations of the present study and contrast our results with previously reported findings [4, 7].

Memory. Because the heart is such a complex dynamical system, it is far too optimistic to believe that a restitution mapping of the form (2) could model all relevant features of a paced cardiac cell. Indeed, it is known that the APD restitution curve depends upon the pacing protocol that is used in its measurement [9, 17]. Specifically, consider two different experimental protocols for measuring APD restitution curves:

- *Dynamic pacing protocol.* Suppose a cell is paced (repeatedly stimulated) with a fixed period B . Assume that B is large enough to lead to a phase-locked 1:1 stimulus-response pattern, and record the steady-state (DI, APD). Repeating this procedure for various choices of B and plotting the collection of steady-state (DI, APD) pairs yields the *dynamic restitution curve* [4, 17].
- *Standard or S1–S2 pacing protocol.* Again the cell is paced with a fixed period B until an approximate steady-state is reached. Then, following a *prescribed DI*, one additional stimulus is applied and the resulting APD value is recorded. This (DI, APD) pair is plotted and the entire procedure is repeated using different prescribed DI values. The resulting curve is known as an *S1–S2 restitution curve* [4, 17].

Experiments [9, 17] have shown that dynamic and $S1$ – $S2$ restitution curves are *not* identical. It follows that the mapping (2), which asserts that A_{n+1} is completely determined by D_n without regard to the past pacing history, is too simplistic to model APD restitution. Several authors [5, 30, 34] have proposed *memory models* in which A_{n+1} depends not only upon D_n but also upon previous APD and DI values. For example, Schaeffer et al. [30] derive a mapping of the form $A_{n+1} = f(D_n, A_n, D_{n-1})$ as an asymptotic limit of a three-current ionic model of the cardiac action potential.

It is important to note that memory effects have an impact on the stability criterion for reentrant pulses. Cherry and Fenton [4] argue that memory can actually prevent alternans from occurring even if the slope of the dynamic restitution curve exceeds 1, whereas the mapping (2) predicts that alternans would always occur in such cases. The model [10] used by Cherry and Fenton is known to exhibit memory [35], which partly explains why their results differ from those of the present study.

Phase waves versus triggered waves. In deriving the main equation (10), Assumption (A2) allowed us to apply the restitution functions locally at each cell in the ring (see Eq. 5). In effect, this means that a cell’s repolarization is not triggered by its repolarized neighbors, but rather by its own internal “clock”. Cytrynbaum and Keener [7] distinguish between these two possibilities for waves in excitable media as follows. A *phase wave* is defined as a wave for which repolarization, at least in leading-order dynamics, is driven by intrinsic factors as opposed to intercellular coupling. A *triggered wave* is one in which intercellular coupling influences the wave propagation and, in particular, diffusion affects the wave backs of propagating action potentials. In adopting Assumption (A2), we restrict ourselves to the case of a reentrant pulse with a *phase wave* back. In contrast, Cytrynbaum and Keener [7] are concerned with linear stability of a pulse with a *triggered wave* back. Consequently, it is not surprising that their stability criterion differs from the one given by Eq. (2). More exactly, it is known [4, 7] that in parameter regimes for which diffusion influences the wave back dynamics (i.e., the wave back is a triggered wave), diffusion can have a stabilizing effect that prevents alternans even if $\alpha > 1$.

The distinction between stability of traveling pulses with phase wave backs or triggered wave backs may also explain some notable differences between the results of Cherry and Fenton [4] and those reported above. Recalling that $-\beta = c'(x^*)$ and $c(x) = \Delta L/v(x)$, we may express β in terms of conduction velocity $v(x)$:

$$\beta = \Delta L \frac{v'(x^*)}{v(x^*)^2}. \tag{27}$$

Equation (27) suggests that as v'/v^2 increases, the stability criterion given by Theorem 2 is harder to satisfy. However, this is inconsistent with the results of Cherry and Fenton, who argue that larger v'/v^2 may actually *promote* stability of a traveling pulse in a ring.

Accuracy of the stability criterion. The stability criterion provided by Theorem 2 is most accurate for a reentrant pulse with a phase wave back propagating in a memoryless excitable medium. Despite the narrow context, there are certain regimes under which

Theorem 2 is able to successfully predict whether a reentrant pulse will circulate with a fixed period. For example, Mitchell and Schaeffer [23] use asymptotics to derive an APD restitution mapping of the form (2) as an asymptotic limit of a two-current ionic model, and it is also known [3] that their model leads to an equally simple conduction time restitution function. Because this model does not exhibit memory, one might expect that Theorem 2 accurately predicts whether the reentrant pulse is stable, at least in parameter regimes for which the wave back is not greatly affected by diffusion.

To confirm this, we performed numerical simulations of the one-dimensional cable equation (1) with periodic boundary conditions and a diffusion coefficient $\kappa = 10^{-3} \text{ cm}^2/\text{ms}$. The total ionic current I_{total} was determined from the two-current model [23], using the parameter values in [2]. After initiating a reentrant action potential in a 20-cm ring, the pulse was allowed to circulate for 30 s to achieve an approximate steady-state. Following Courtemanche et al. [6], we recorded the steady-state DI, APD, and conduction time and then spliced a 0.1-cm segment out of the ring in the vicinity of the wave front. Repeating this procedure for progressively shorter ring lengths allowed us to construct APD and CT restitution curves. As the ring was shortened from 11.1 to 11.0 cm, a loss of stability caused a transition from reentry with a fixed period to the type of quasiperiodic response illustrated in Fig. 4b. Measuring the slopes of the restitution curves at the onset of the instability yielded $\alpha = 0.906$ and $\beta = 0.140$, so that $\alpha + \beta = 1.046$. In this case, we see that the stability criterion provided by Theorem 2 performs reasonably well. We repeated these simulations for a range of parameter values, obtaining comparable results provided that the diffusion coefficient κ remained small.

Fibers versus rings. Ring-shaped geometries allow reentrant action potentials to circulate without repeated external stimulation, whereas one-dimensional fibers require repeated stimulation. Stubna et al. [33] use perturbation techniques to analyze the dynamics of a partial difference equation analogous to (8). Although they use the exact same type of restitution-based kinematic model, the fiber geometry prevents us from easily extending our techniques to determine the local asymptotic stability of their fixed point solution. The first cell in a fiber requires external stimulation at prescribed times, which imposes a boundary condition. Therefore, a substitution such as (9) will not convert their partial difference equation into an ordinary difference equation that can be analyzed as easily as (10).

Closing remarks. Despite the aforementioned limitations of our study, it is likely that the techniques used in this paper can be extended to a homogeneous ring in which restitution mappings are assumed to have “memory” (dependence on several past APD and DI values). However, if the tissue is heterogeneous in the sense that restitution curves can vary from cell-to-cell, the characteristic polynomial obtained in our analysis would not be nearly so simple. In this case, the Jury test may still provide useful necessary conditions for stable reentry. Finally, the issue of spontaneous initiation and termination of reentry will be the subject of a future study.

Acknowledgments The author is grateful to Professor Hassan Sedaghat for his advice concerning this manuscript.

References

1. Åström, K.J., Wittenmark, B.: *Computer Controlled Systems: Theory and Design*. Prentice-Hall, New Jersey (1984)
2. Cain, J.W., Schaeffer, D.G.: Two-term asymptotic approximation of a cardiac restitution curve. *SIAM Rev.* **48**, 37–546 (2006)
3. Cain, J.W., Tolkacheva, E.G., Schaeffer, D.G., Gauthier, D.J.: Rate-dependent propagation of cardiac action potentials in a one-dimensional fiber. *Phys. Rev. E* **70**, 061906 (2004)
4. Cherry, E.M., Fenton, F.H.: Suppression of alternans and conduction blocks despite steep APD restitution: Electrotonic, memory, and conduction velocity restitution effects. *Am. J. Physiol.* **286**, H2332–H2341 (2004)
5. Chialvo, D.R., Michaels, D.C., Jalife, J.: Supernormal excitability as a mechanism of chaotic dynamics of activation in cardiac Purkinje fibers. *Circ. Res.* **66**, 525–545 (1990)
6. Courtemanche, M., Keener, J.P., Glass, L.: A delay equation representation of pulse circulation on a ring in excitable media. *SIAM J. Appl. Math.* **56**, 119–142 (1996)
7. Cytrynbaum, E., Keener, J.P.: Stability conditions for the traveling pulse: Modifying the restitution hypothesis. *Chaos* **12**, 788–799 (2002)
8. Elaydi, S.N.: *An Introduction to Difference Equations*, 2nd edn. Springer, New York (1999)
9. Elharrar, V., Surawicz, B.: Cycle length effect on restitution of action potential duration in dog cardiac fibers. *Am. J. Physiol. Heart Circ. Physiol.* **244**, H782–H792 (1983)
10. Fenton, F., Karma, A.: Vortex dynamics in three-dimensional continuous myocardium with fiber rotation: Filament instability and fibrillation. *Chaos* **8**, 20–47 (1998)
11. Fox, J.J., Gilmour, R.F., Bodenschatz, E.: Conduction block in one dimensional heart fibers. *Phys. Rev. Lett.* **89**, 198101–198104 (2002)
12. Frame, L.H., Simson, M.B.: Oscillations of conduction, action potential duration, and refractoriness: A mechanism for spontaneous termination of reentrant tachycardias. *Circulation* **78**, 1277–1287 (1988)
13. Hall, G.M., Bahar, S., Gauthier, D.J.: Prevalence of rate-dependent behaviors in cardiac muscle. *Phys. Rev. Lett.* **82**, 2995–2998 (1999)
14. Hurwitz, A.: On the Conditions Under Which an Equation has Only Roots with Negative Real Parts. In: Bellman, R., Kalaba, R. (eds.) *Selected Papers on Mathematical Trends in Control Theory*, vol. 65. Dover, New York (1964)
15. Ito, H., Glass, L.: Theory of reentrant excitation in a ring of cardiac tissue. *Physica D* **56**, 84–106 (1992)
16. Jury, E.I., Blanchard, J.: A stability test for linear discrete systems in table form. In: *Proceedings of the IRE*, vol. 49, pp. 1947–1948 (1961)
17. Kalb, S.S., Dobrovolny, H.M., Tolkacheva, E.G., Idriss, S.F., Krassowska, W., Gauthier, D.J.: The restitution portrait: A new method for investigating rate-dependent restitution. *J. Cardiovasc. Electro-physiol.* **15**, 698–709 (2004)
18. Karma, A.: Spiral breakup in model equations of action potential propagation in cardiac tissue. *Phys. Rev. Lett.* **71**, 1103–1107 (1993)
19. Karma, A.: Electrical alternans and spiral wave breakup in cardiac tissue. *Chaos* **4**, 461–472 (1994)
20. Keener, J.P.: Waves in excitable media. *SIAM J. Appl. Math.* **39**, 528–548 (1980)
21. Keener, J.P., Sneyd, J.: *Mathematical Physiology*. Springer, New York (1998)
22. Luo, C., Rudy, Y.: A dynamic model of the cardiac ventricular action potential. *Circ Res* **74**, 1071–1096 (1994)
23. Mitchell, C.C., Schaeffer, D.G.: A two-current model for the dynamics of cardiac membrane. *Bull. Math. Biol.* **65**, 767–793 (2003)
24. Neu, J.C., Preissig, R.S., Krassowska, W.: Initiation of propagation in a one-dimensional excitable medium. *Physica D* **102**, 285–299 (1997)
25. Nolasco, J.B., Dahlen, R.W.: A graphic method for the study of alternation in cardiac action potentials. *J. Appl. Physiol.* **25**, 191–196 (1968)
26. Ohara, T., Ohara, K., Cao, J., Lee, M., Fishbein, M.C., Mandel, W.J., Chen, P., Karagueuzian, H.S.: Increased wave break during ventricular fibrillation in the epicardial border zone of hearts with healed myocardial infarction. *Circulation* **103**, 1465–1472 (2001)
27. Plonsey, R., Barr, R.C.: *Bioelectricity: A Quantitative Approach*. Plenum Press, New York (1988)
28. Rinzel, J., Maginu, K.: Kinematic analysis of wave pattern formation in excitable media. In: Pacault, A., Vidal, C. (eds.) *Non-Equilibrium Dynamics in Chemical Systems*. Springer, Berlin (1984)
29. Rosenbaum, D.S., Jackson, L.E., Smith, J.M., Garan, H., Ruskin, J.N., Cohen, R.J.: Electrical alternans and vulnerability to ventricular arrhythmias. *N. Engl. J. Med.* **330**, 235–241 (1994)

30. Schaeffer, D.G., Cain, J.W., Gauthier, D.J., Kalb, S.S., Krassowska, W., Oliver, R.A., Tolkacheva, E.G., Ying, W.: An ionically based mapping model with memory for cardiac restitution. *Bull. Math. Biol.* (to appear) (2006)
31. Sedaghat, H., Kent, C.M., Wood, M.A.: Criteria for the convergence, oscillation and bistability of pulse circulation in a ring of excitable media. *SIAM J. Appl. Math.* **66**, 573–590 (2005)
32. Sedaghat, H., Baumgarten, C., Cain, J.W., Chan, D.M., Cheng, C.K., Kent, C.M., Wood, M.A.: Modeling spontaneous initiation and termination of reentry in cardiac tissue. In: *Dynamics Days 2007: International Conference on Chaos and Nonlinear Dynamics*, Boston, 3–6 January 2007
33. Stubna, M.D., Rand, R.H., Gilmour, R.F.: Analysis of a nonlinear partial difference equation and its application to cardiac dynamics. *J. Differ. Equ. Appl.* **8**, 1147–1169 (2002)
34. Tolkacheva, E.G., Schaeffer, D.G., Gauthier, D.J., Krassowska, W.: Condition for alternans and stability of the 1:1 response pattern in a “memory” model of paced cardiac dynamics. *Phys. Rev. E* **67**, 031904 (2003)
35. Tolkacheva, E.G., Schaeffer, D.G., Gauthier, D.J., Mitchell, C.C.: Analysis of the Fenton-Karma model through an approximation by a one-dimensional map. *Chaos* **12**, 1034–1042 (2002)
36. Watanabe, M.A., Fenton, F.H., Evans, S.J., Hastings, H.M., Karma, A.: Mechanisms for discordant alternans. *J. Cardiovasc. Electrophysiol.* **12**, 196–206 (2001)
37. Yehia, A.R., Jeandupeux, D., Alonso, F., Guevara, M.R.: Hysteresis and bistability in the direct transition from 1:1 to 2:1 rhythm in periodically driven single ventricular cells. *Chaos* **9**, 916–931 (1999)
38. Zaitsev, A.V., Berenfeld, O., Mironov, S.F., Jalife, J., Pertsov, A.M.: Distribution of excitation frequencies on the epicardial and endocardial surfaces of fibrillating ventricular wall of the sheep heart. *Circ. Res.* **86**, 408–417 (2000)