

Stability and bifurcation in an integral-delay model of cardiac reentry including spatial coupling in repolarization

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We present the bifurcation analysis of a revised version of the integral-delay model [Courtemanche *et al.*, Siam J. Appl. Math. **56**, 119 (1996)] of reentry in a one-dimensional ring that includes a spatial coupling in the calculation of the action potential duration. This coupling is meant to reproduce the modulation of repolarization by the diffusive current flowing through the intercellular resistance. We show that coupling modifies the criterion for the stability of the period-1 solution, which is no longer uniquely related to the action potential restitution curve, but depends also on the degree of coupling between cells and on the dispersion relation of the velocity. Coupling also changes the scenario from an infinite-dimension Hopf bifurcation to a finite sequence of Hopf bifurcations that take place at different ring lengths.

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Reentry, the name given to the self-sustained propagation of an activation front in an excitable medium, is known to be a major mechanism of cardiac arrhythmia, and has been observed in clinical and experimental preparations [2–4]. It has also been studied in a host of mathematical representations of the cardiac excitable tissue [5–10]. A one-dimensional ring, represented as a continuous cable of model cardiac cells, is among the simplest reaction-diffusion models for reentry [11–15]. The characteristics of reentry as a function of circumference of the ring (L) have been studied by numerical simulation for rings holding different versions of the Beeler-Reuter (BR) ionic model of cardiac myocytes [13]. In all instances, stable period-1 reentry was found to exist down to a critical length L_{crit} . In most cases, solutions below L_{crit} were quasiperiodic, persisting until a minimal L_{min} below which sustained reentry was impossible. Different types of bifurcation from periodic to quasiperiodic motion were observed, each exhibiting a relatively small number of quasiperiodic modes of propagation [1,12–14].

Upon superthreshold stimulation, the space-clamped BR-type models produce long-lasting action potentials (typically 100 ms or more) during which the system remains unexcitable. The duration of the action potential (D_{AP}) depends on the diastolic interval (R), the time between the end of the previous action potential, and the onset of the stimulation. As a consequence, the sequence of R produced by a succession of superthreshold stimuli applied with a constant period of stimulation (T) can be described by the finite-difference equation [16],

$$R_{i+1} = T - D_{\text{AP}}(R_i). \quad (1)$$

The fixed point of Eq. (1), corresponding to period-1 orbit, is stable if $dD_{\text{AP}}/dR < 1$. Equation (1), supplemented with a

rule for subthreshold stimuli and representative $D_{\text{AP}}(R)$ functions, was shown to reproduce the bifurcation structure of the entrainment responses of the space-clamped BR ionic models as a function of T [16]. The system is thus a low-dimensional model complementary to the nonlinear ionic models, suitable for analytical investigation. This finite-difference model was extended by Courtemanche *et al.* to represent reentry around a one-dimensional ring [1]. $T(x)$, the time between two successive activations, is the time needed for the activation front to complete one rotation at any given location x on the ring of length L . $\theta(x)$, the speed of the activation front, is only a function of the local R for most ionic models. Thus, $T(x) = \int_{x-L}^x [\theta(R(u))]^{-1} du$, and Eq. (1) can be rewritten as

$$R(x+L) = \int_x^{x+L} \frac{1}{\theta(R(u))} du - D_{\text{AP}}(R(x)). \quad (2)$$

Propagation proceeds as long as $R(x)$ remains larger than R_{min} , the R value corresponding to the end of the refractory period. Otherwise, reentry stops. Courtemanche *et al.* have analyzed the integral-delay Eq. (2) in the case in which $D_{\text{AP}}(R)$ and $\theta(R)$ were monotonic increasing functions [1]. They have proven that period-1 reentry, corresponding to $R(x) = R^*$, a constant around the ring, is stable if $dD_{\text{AP}}/dR|_{R^*} < 1$. The loss of stability occurs at the value of L where $dD_{\text{AP}}/dR|_{R^*} = 1$ through a Hopf bifurcation in which an infinite number of quasiperiodic modes (numbered $k = 0, 1, 2, \dots$) are created simultaneously. The spatial wavelengths of these modes near the bifurcation are close to $2L/(k+1)$. They did not study the nature of the bifurcation, which is expected to be either subcritical or supercritical, depending on the choice of $D_{\text{AP}}(R)$ and $\theta(R)$ functions [14]. The main weakness of the integral-delay model regarding its capability to reproduce the dynamics of the ionic ring models is its prediction of the existence of an infinite number of quasiperiodic modes of propagation. Spatial oscillations of R

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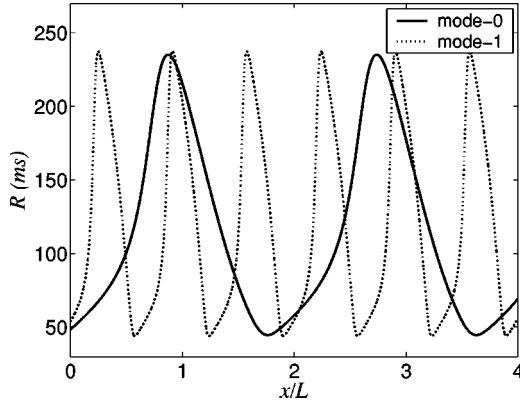


FIG. 1. Spatial profiles of R in mode 0 (continuous curve) and mode 1 (dotted curve) as a function of the position of the activation front for successive turns. The modes were calculated with Eq. (3) and the functions $D_{AP}(R)$ and $\theta(R)$ derived from the modified BR (MBR) ionic model [Fig. 2(c)] as described in [14].

correspond to neighboring sites producing action potentials of different durations. In ionic models, these are associated with spatial differences in voltage, which produce currents through the coupling resistances that smooth the spatial D_{AP} profile and limit its gradient. This explains why only the two lowest modes ($k=0$ and 1, Fig. 1) of quasiperiodic propagation have been observed in the ionic models. In some versions of the BR model, it has also been reported that the appearance of modes 0 and 1 was not simultaneous, but rather occurred at different values of L [13].

In a previous paper, we have proposed a modified version of Eq. (2) that includes an empirical representation of the effect of the resistive coupling on the spatial profile of D_{AP} [14]. In this formulation, $D_{AP}(R(x))$ in Eq. (2) is replaced by a weighted spatial average over a neighborhood α [chosen such that $w(\alpha) \rightarrow 0$],

$$R(x+L) = \int_x^{x+L} \frac{1}{\theta(R(u))} du - \int_{-\alpha}^{\alpha} w(u) D_{AP}(R(x+u)) du \quad (3)$$

with $w(x) = \chi^{-1} \exp[-(\beta u)^2]$, in which χ^{-1} is a normalization coefficient and β^{-2} is the variance of the weighting function.

$R(x+L)$ and $R(x)$ are the state of recovery of a point at the time of the current and previous excitation, respectively. $R(x+L)$ is the time interval between the current excitation and the end of the previous action potential. It thus corresponds to the time elapsed since the previous excitation, represented by the first term on the right-hand side of Eq. (3), minus the duration of the action potential produced by that previous excitation. Coupling allows the propagation, and in the new formulation it modulates the local repolarization. The first term on the right-hand side embeds the influence of the points activated before $x+L$ in the current rotation. It is the only way in which the distribution of R during one rotation has an influence on the local excitability during the same rotation. The second term describes the effect of the distribution of R in the previous rotation on the calculation of R

during the current rotation. Since this previous excitation has occurred with a diastolic interval $R(x)$, it would have produced an action potential of duration $D_{AP}(R(x))$ if the point has been disconnected from its neighbors. However, because of the effect of coupling represented by the integral over a neighborhood of width 2α , the duration of the local action potential is rather a weighted average of the duration of the action potentials that would have been produced at each point of the neighborhood if it had been isolated. It could be argued that the coupling term handles the point and his neighbors as if their action potentials have been produced simultaneously, neglecting the delay introduced by the propagation. For the BR model, this has a minimal influence near the bifurcation since it occurs in a range of R where the speed is still constant and maximal. However, we have introduced elsewhere a formulation including the delay of propagation to be used in a more general context [17].

Numerical simulations of Eq. (3) (with $\beta = \sqrt{800}$ cm and $\alpha = 0.5$ cm) were found to reproduce all the details of the bifurcation, as well as the properties of the different quasiperiodic modes of propagation in the regime of fully developed alternans far from the bifurcation, predicting accurately the number of quasiperiodic modes, the evolution of their spatiotemporal profile as a function of the loop length, and the specific limiting loop length at which each mode was disappearing. These numerical results thus suggest that our integral delay embeds the minimal properties needed to capture the dynamics of the ionic loop model both close to and far from the bifurcation. Moreover, the integral-delay model was also used to investigate the effect of external stimulations on reentry. It has uncovered new scenarios of reentry annihilation that have not been described before. These were found afterwards to exist in the ionic loop model and to be related to observations made on a canine experimental model of atrial flutter [13,14,17,18]. It has also been used to investigate the dynamics of discordant alternans in paced cable [19,20]. The purpose of this paper is to present an analytical investigation of the bifurcation properties of Eq. (3).

I. LINEARIZATION OF THE MODEL

In period-1 reentry, $R(x) = R^*$ fulfills the relation $R^* = [L/\theta(R^*)] - D_{AP}(R^*)$. If both $dD_{AP}/dR > 0$ and $d\theta/dR > 0$, as it is assumed in this paper, a unique R^* exists for each $L > [D_{AP}(R_{min}) + R_{min}]\theta(R_{min})$ and $dR^*/dL > 0$. Since for all the cases related to BR ionic models, $L \gg 2\alpha$ and $\exp[-(\beta\alpha)^2]$ is close to zero, we extend the limits of the averaging integral from $(-\infty, \infty)$ and obtain the linearized version of Eq. (3) for a perturbation $z(x)$ around R^* as

$$z(x+L) = \left(\frac{1}{\theta(R^*)} \right)' \int_x^{x+L} z(s) ds - D'_{AP}(R^*) \times \int_{-\infty}^{\infty} w(z) z(x+s) ds.$$

Assuming that $z(x) = e^{\lambda x}$, the characteristic equation becomes

$$e^{\lambda L} \left[\left(\frac{1}{\lambda \theta(R^*)} \right)' - 1 \right] = \left(\frac{1}{\lambda \theta(R^*)} \right)' + D'_{AP}(R^*) e^{(\lambda/2\beta)^2}.$$

Defining $\lambda L = Q$, $v' = [L/\theta(R^*)]'$, $a' = D'_{AP}(R^*)$, and $\eta = (2\beta L)^{-2}$, this yields

$$e^Q (v' - Q) = v' + a' Q e^{\eta Q^2}. \quad (4)$$

Q corresponds to the eigenvalue of the linearized system expressed in the spatial nondimensional coordinate x/L , as in [1]. We look for solutions that fulfill the conditions $\text{Re}(Q)=0$ and $Q=iq$, corresponding to the loss of stability of R^* . The norm of Eq. (4) provides the first condition,

$$a' = e^{\eta q^2}, \quad (5)$$

in which the square root is removed because $a' > 0$. This condition shows that a' is always greater than 1 unless $\eta=0$, which corresponds to the original model of Courtemanche *et al.* without spatial averaging. The value of a' also increases with q , which is specified by the second condition

$$\tan\left(\frac{q}{2}\right) = \frac{q}{v'} \quad (6)$$

obtained by solving Eq. (4) after substitution of a' by Eq. (5). The condition (6) does not depend explicitly on coupling and it is also a condition for the characteristic equation of Eq. (2). It has an infinite number of solutions, symmetric with respect to zero (zero is also a solution, indicating the rotational invariance of z around the ring). Since $v' < 0$, the successive positive solutions $q^{(k)}$ are located between $(2k+1)\pi$ and $2(k+1)\pi$, where $k=[0,\infty]$ are the mode numbers. If $|v'| \ll 1$, as is the case over a large R^* interval for the BR ionic models, the positive roots can be approximated by

$$q^{(k)} \approx (2k+1)\pi + \frac{2|v'|}{(2k+1)\pi} + O(v'^2). \quad (7)$$

Inserting this approximation in Eq. (5) shows that (i) a' is always greater than 1 and $a' \rightarrow 1$ as $\beta L \rightarrow \infty$, corresponding to the case without coupling; (ii) a' increases with k , meaning that higher modes appear at shorter values of L ; (iii) the number of modes is limited since a' , which is defined only for $R > R_{\min}$, spans a limited range of values; and (iv) the value a' at the bifurcation also depends on v' , this effect being more important for lower modes.

Since we assume that $dD_{AP}/dR > 0$ and $d\theta/dR > 0$, R^* (or L in the dimensional model) can be used as a bifurcation parameter. A specific $q^{(k)}$ is associated with a Hopf bifurcation if $d \text{Re}(Q)/dR^* = r' \neq 0$ at the bifurcation. The sign of r' at the bifurcation, where $r=0$ and conditions (5) and (6) are satisfied, is determined by

$$r' \propto \ln a' [2v''(1 - \cos q^{(k)})] - [q^{(k)} \sin q^{(k)} - (q^{(k)})^2] \times \left(\frac{a''}{a'} - \frac{\eta'}{\eta} \ln a' \right). \quad (8)$$

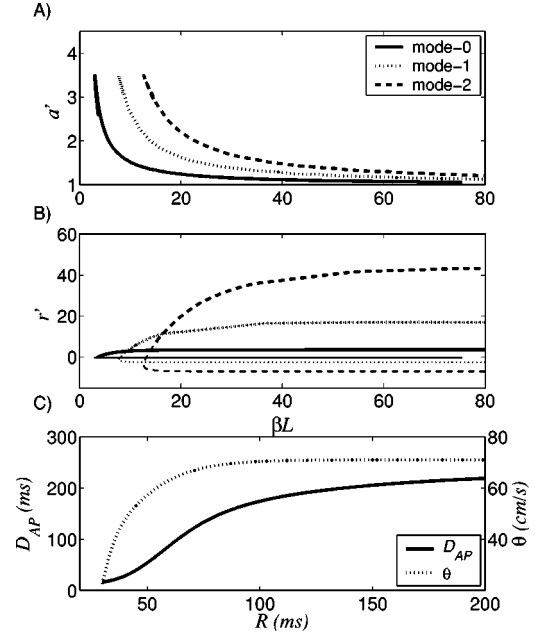


FIG. 2. (a) a' and (b) r' at the bifurcation for the modes $k = \{0,1,2\}$ as a function of βL , using $D_{AP}(R)$ and $\theta(R)$ shown in (c). For each mode, two bifurcation points exist for a given βL [superimposed in (a)] corresponding, respectively, to the loss of stability of the period-1 solution at large L (thin lower curves) and period 1 regaining stability at smaller L (thick higher curves).

The case with $r' < 0$ corresponds to a bifurcation where the period-1 solution loses stability with respect to perturbations proportional to the mode associated with $q^{(k)}$ when R^* or L are reduced. The dominant terms in Eq. (8) are those that are proportional to $(q^{(k)})^2$. Since $q^{(k)}$ lies between $(2k+1)\pi$ and $2(k+1)\pi$, the sign of Eq. (8) depends on $a''/a' - \eta'/\eta \ln a'$. Typically, $D_{AP}(R)$ can be approximated as $a_\infty - \gamma_a \exp(-R/\tau_a)$ in the range where the bifurcations occur, such that $a''/a' = -\tau_a^{-1} < 0$ and is independent of coupling. On the other hand, $-\eta'/\eta = 2/L dL/dR^* > 0$ and this second term is positive ($a' \geq 1$ with $a'=1$ when $\beta \rightarrow \infty$). Decreasing β , which broadens the spatial extent of the coupling, enlarges a' , diminishes the value of L where the bifurcation occurs, and thus enlarges the positive term in r' . As expected, the growth rate of the amplitude of the modes becomes more gradual as coupling is extended.

We have studied the influence of β on the characteristics of the first three solutions $k = \{0,1,2\}$ of Eqs. (5) and (6) using the $D_{AP}(R)$ and $\theta(R)$ curves obtained from the numerical simulations of a version of the BR model (MBR) that has been investigated in details elsewhere [14]. As seen in Fig. 2(c), $D_{AP}(R)' > 0$ everywhere, but includes a portion with slope < 1 at low R values. Figure 2(a) shows $a'(\beta L)$ for each k . To calculate these results, the close interval of R^* in which $a' \geq 1$ is found. Each R^* in this set corresponds to a value of $L = ([R^* + D_{AP}(R^*)]/\theta(R^*))$, a' , and v' . With these values, we solve Eq. (6) to obtain $q^{(k)}$ and Eq. (5) to get β . The following points can be seen when looking at Fig. 2(a): (i) the modes are ranked in increasing order with respect to a' , meaning that their bifurcations occur at decreasing values of R^* ; (ii) the differences between the modes

with respect to the value of a' where the bifurcations occur increase as βL is diminished and spatial coupling is extended; (iii) a' is everywhere greater than 1, and, as $\beta L \rightarrow \infty$, $a' \rightarrow 1$ and the curves corresponding to the different modes come together; and (iv) each mode has a limiting value of βL below which it ceases to exist, the highest modes disappearing first when hitting the maximum a' .

II. THE CHARACTERISTIC EQUATION NEAR THE BIFURCATION

Setting $a' = e^{-\eta Q^2} + \epsilon$, we carry out an expansion of the roots for a' close to the bifurcation for each $q^{(k)}$ to approximate the growth rates of the different modes. For simplicity, we drop the index k and write Q as

$$Q = iq + \epsilon q_1 + \epsilon^2 q_2 + O(v').$$

Introducing this expression in Eq. (4) and keeping the term of first order in ϵ yields

$$q_1 = \frac{e^{-\eta q^2} [q(q - \sin q) + iq(v' - 1 - \cos q)]}{(v' - 1 - \cos q)^2 + (q - \sin q)^2}.$$

Using Eq. (7) for q , q_1 can be approximated by

$$q_1 \approx e^{-\eta \{(2k+1)\pi - [2v'/(2k+1)\pi]\}^2} \times \left[1 - \frac{2v'}{(2k+1)^2 \pi^2} + i \frac{v'}{(2k+1)\pi} \right].$$

Since the oscillating solution has the form $R(x) = R^* + b \exp(Qx/L)$, the growth rate of the k th mode near the bifurcation is given by

$$\sim \exp \left[\epsilon e^{-\eta \{(2k+1)\pi - [2v'/(2k+1)\pi]\}^2} \left(1 - \frac{2v'}{(2k+1)^2 \pi^2} \right) \frac{x}{L} \right].$$

The coupling in D_{AP} reduces the growth rate of the different modes by a factor

$$\exp \left[-\eta \left((2k+1)\pi - \frac{2v'}{(2k+1)\pi} \right)^2 \right] < 1,$$

such that the reduction of the growth rate is more important for larger k . The instability associated with mode 0 should thus be dominant since it occurs at larger L and its amplitude grows more rapidly. The spatial wavelength associated with each mode can be approximated by

$$\Lambda(k) = \frac{2\pi L}{\text{Im}(Q)} \approx \frac{2L}{2k+1} e^{\eta(2k+1)^2 \pi^2} + \frac{2v' L e^{2\eta(2k+1)^2 \pi^2}}{(2k+1)^3 \pi^2} \times [[2 - 4\eta(2k+1)^2 \pi^2] e^{-\eta(2k+1)^2 \pi^2} - \epsilon] + O(v'^2). \tag{9}$$

When $\eta=0$ (equivalent to $\beta \rightarrow \infty$), the wavelength Λ is reduced to

$$\Lambda(k) = \frac{2L}{2k+1} + \frac{2v' L (2 - \epsilon)}{(2k+1)^3 \pi^2} + O(v'^2)$$

as in [1]. Averaging thus leads to an increase of $\Lambda(k)$ through the exponential term in Eq. (9), which can be related to the smoothing of the voltage profile by diffusion current in the ionic model. The preceding analysis shows that, even in a simple one-dimensional model of reentry, the $D_{AP}(R)$ restitution curve is not the unique criterion governing the stability of the period-1 reentry. Introducing spatial coupling in D_{AP} changes the stability criterion and makes it dependent on the extent of the coupling as well as on the $\theta(R)$ function through condition (6). It is thus not surprising that numerical simulations of ionic models in two-dimensional media have shown that the stability of the periodic solutions could not be explained solely on the basis of the $D_{AP}(R)$ restitution curve. Recently, Cytrynbaum *et al.* [21] have reached a similar conclusion by analyzing a singular Fitzhugh-Nagumo model of reentry in the ring. In their model, D_{AP} and R correspond to the trajectory along the upper and lower branch of the slow manifold, while the transitions between the branches, which are sensitive to coupling, correspond to the activation and repolarization fronts. Considering these two fronts as boundary layers, they have obtained a two-dimensional mapping for the successive returns of these fronts at one location from which they have deduced an analytical expression for the stability of the period-1 solution. It is not clear yet whether a similar approach could be applied to models of cardiac myocytes since, in these, the repolarization phase is a slow process that does not display an abrupt transition that may be treated as a transition layer. Echebarria *et al.* have also developed an alternative approach to analyze discordant alternans in a paced cable [22]. They have derived an amplitude equation from the reaction-diffusion system by using a development in perturbation around the stable periodic solution. This model can probably be extended to study bifurcation from periodic to quasiperiodic reentry in a loop, but it remains to be seen if it can predict the correct bifurcation structure and how far from the bifurcation it can be and still can give an appropriate description of the dynamics. Besides, it is not obvious that this model can be extended to deal with resetting and annihilation of reentry by external stimulations, an area of potential clinical application. The ability of our empirical model to reproduce the details of the bifurcation structure of the ionic model, its behavior far from the bifurcation, as well as in the situation where the reentry is perturbed by multiple stimulations, indicate that it embeds the basic determinants of the dynamics. It will certainly be instructive to compare our model to new alternative low-dimensional formulations that may become available, especially if these were deduced from a formal analysis of ionic reaction-diffusion systems.

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