Instabilities of a Propagating Pulse in a Ring of Excitable Media

Marc Courtemanche,[(1),(2)] Leon Glass,[(1)] and James P. Keener[(3)]
[(1)] *Department of Physiology, McGill University, 3655 Drummond Street, Montreal, Quebec, Canada H3G 1Y6*
[(2)] *Applied Mathematics, University of Arizona, Tucson, Arizona 85717*
[(3)] *Department of Mathematics, University of Utah, Salt Lake City, Utah 84112*
(Received 23 December 1992)

Instabilities in the circulation of a pulse in a ring of excitable cardiac tissue are analyzed using two different formulations: (1) a reaction-diffusion partial differential equation (PDE) model for cardiac electrical activity using the Beeler-Reuter equations to represent ionic currents in the cardiac cells; (2) a neutral delay-differential equation that we propose as a model for the PDE. Stability analysis and numerical simulation of the delay equation agree with results from simulations of the PDE model.

PACS numbers: 87.10.+e, 05.45.+b, 87.22.As

At the turn of the century, Mines demonstrated that a ring of cardiac tissue could sustain a continually circulating wave of contraction [1]. This landmark achievement has formed the cornerstone for both experimental and theoretical studies of wave propagation in excitable media [2–10]. Understanding the dynamics of these systems has not only provided a significant theoretical challenge, but it is fundamental to our understanding of life-threatening cardiac arrhythmias in which the rhythm of the heart is set not by the normal pacemaker, but by reentrant excitation of the sort envisioned by Mines.

Although there has been extensive theoretical analysis of the propagation of reentrant spirals in two-dimensional excitable media [6–10], there are fewer results about wave propagation in a ring of excitable media [3, 9]. Recent experiments in rings of cardiac tissue have shown that steady circulation of a depolarization pulse can be destabilized by reducing the circulation time around the ring [2]. This loss of stability is associated with oscillations in pulse duration and recovery time, where the recovery time is the time interval between the end of an excitation pulse and the onset of the following one. Similar instabilities have been observed in partial differential equation (PDE) models [4] upon decreasing the ring circumference, and studied theoretically in a discrete model [3].

In the following we present a theory for instabilities of pulse circulation in a continuous one-dimensional ring of excitable media. We present results from simulations of a nonlinear PDE model for pulse propagation in cardiac tissue, using the Beeler-Reuter equations [11] to represent the electrical properties of the cardiac cells. The dynamics of the PDE can be understood in the context of a neutral delay-differential equation whose derivation is based on the physical mechanisms controlling pulse propagation.

We simulate electrical pulse propagation in a one-dimensional ring of cardiac tissue, using a simple forward Euler method [12] to integrate the equation

$$\frac{\partial V}{\partial t} = -\frac{I_{\rm BR}}{C_m} + \frac{1}{C_m S_v \rho}\frac{\partial^2 V}{\partial x^2}, \tag{1}$$

where V is the membrane voltage (mV), $I_{\rm BR}$ is the membrane current obtained from the Beeler-Reuter equations (μA cm^{-2}), $C_m = 1.0$ μF cm^{-2} is the membrane capacitance, $S_v = 5000$ cm^{-1} is the surface-to-volume ratio, and $\rho = 0.2$ kΩ cm is the tissue resistivity. The Beeler-Reuter equations [11] describe eight variables used to calculate the total membrane current $I_{\rm BR}$. The equations are frequently used as a model in cardiac electrophysiology [4, 5, 8].

A circulating pulse is obtained by first stimulating the proximal end of a long cable to obtain a propagating pulse. As the excitation approaches the distal end of the cable, its two ends are joined numerically into a ring. After the circulating pulse stabilizes, the ring circumference is decreased in successive steps until steady circulation becomes unstable and oscillations in the pulse dynamics arise. We use -60 mV as our threshold between the recovered state ($V < -60$ mV) and the excited state ($V > -60$ mV). The recovery time is defined as the interval between the onset of an excitation pulse and the end of the previous pulse. We consider the evolution of the recovery time t_r, the pulse duration A, the pulse speed C, and the circulation time T as a function of the location x along the ring.

From our numerical simulations of Eq.(1), we find that the transition between stable and unstable circulation occurs between ring lengths $L = 13.425$ cm and $L = 13.25$ cm. For $L = 13.425$ cm we find stable circulation with $t_r \approx 112$ ms. For $L = 13.25$ cm we find oscillations in the speed, recovery time, pulse duration, and circulation time. The wavelength Λ of the oscillations is slightly less than twice the ring length, $\Lambda \approx 26.0$ cm. Figure 1(a) shows a trace of $t_r(x)$ for $L = 13.25$ cm. Because the wavelength is not exactly twice the ring length, the dynamics of the recovery time at a fixed location

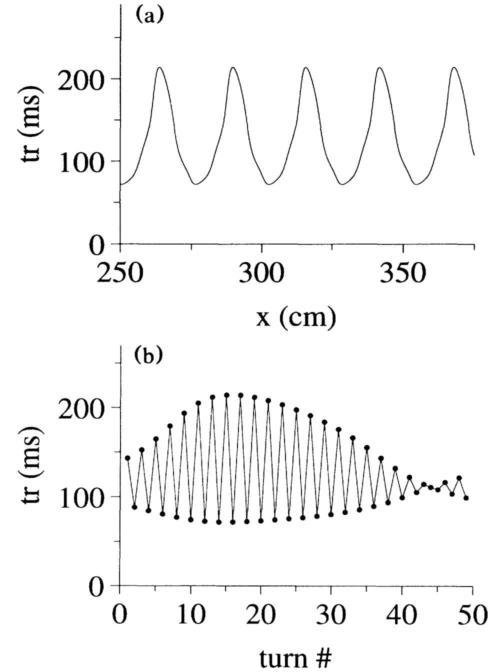

FIG. 1. Dynamics of a circulating pulse in a ring of length $L = 13.25$ cm found from numerical integration of the Beeler-Reuter equations. (a) Recovery time t_r as a function of the location x along the ring. The wavelength is $\Lambda \approx 26.0$ cm. (b) Recovery time t_r as a function of the number of turns around the ring at a fixed location along the ring.

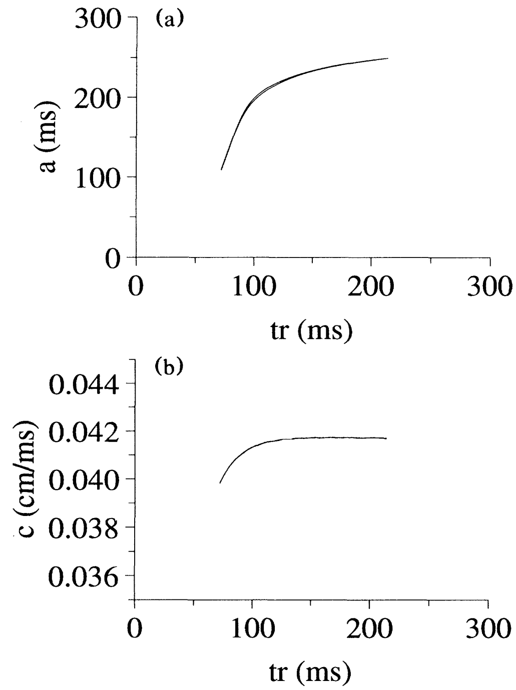

FIG. 2. (a) Restitution curve $a(t_r)$ and (b) dispersion curve $c(t_r)$ derived from the PDE simulation of Fig. 1.

along the ring are quasiperiodic. Figure 1(b) displays a time series for t_r as a function of the number of rotations around the ring. These results agree qualitatively with experimental observations by Frame [2] in living cardiac tissue. Pulse circulation in the PDE model is no longer supported upon decreasing the circumference of the ring from $L = 12$ cm to $L = 11.875$ cm.

Given a pulse circulating around a ring, using the quantities $A(x)$, $t_r(x)$, and $C(x)$, we obtain

$$t_r(x) = \int_{x-L}^{x} \frac{ds}{C(s)} - A(x - L). \tag{2}$$

This "conservation" equation must hold for any x since it is a mathematical statement of the simple relation "recovery time = circulation period−pulse duration." The central assumption of our theory is that both the pulse duration and speed are functions of the recovery time t_r. Although there is no *a priori* justification for this assumption, it is common in the analysis of cardiac propagation [2, 3, 5, 6, 9]. In Fig. 2 we plot pulse duration and speed as functions of t_r, based on data from the simulation in Fig. 1. The oscillations in recovery time shown in Fig. 1(a) are accompanied by oscillations in pulse duration and speed. We can measure all three quantities at each location x along the ring and plot the relations between them. The curve $a(t_r)$ is called the *restitution curve* and $c(t_r)$ is called the *dispersion curve.* In this case, both curves are well-defined functions of t_r. Given the restitution and dispersion curves, we may rewrite Eq.(2) as

$$t_r(x) = \int_{x-L}^{x} \frac{ds}{c(t_r(s))} - a(t_r(x - L)). \tag{3}$$

Equation (3) is an integral-delay equation. It has a steady-state solution $t_r(x) = t_r^*$, where t_r^* satisfies $t_r^* = L/c(t_r^*) - a(t_r^*)$.

We obtain a dynamical equation for $t_r(x)$ by taking derivatives with respect to x in (3). Using $t_r \equiv t_r(x)$ and $t_{r_L} \equiv t_r(x - L)$, we obtain

$$\frac{d}{dx}(t_r + a(t_{r_L})) = \frac{1}{c(t_r)} - \frac{1}{c(t_{r_L})}. \tag{4}$$

This equation describes the evolution of the recovery time t_r as a function of the location x along the ring and completely specifies the dynamics of the circulating pulse once the initial value of t_r is specified on the ring domain. Equation (4) is a *neutral delay-differential equation* [13], whose appearance in this context constitutes a novel aspect of our analysis.

Equation (4) is integrated using a simple forward Euler method, subject to the constraints imposed by the ring geometry. To satisfy these requirements, we use a numerical discretization [14] that makes our finite-difference scheme identical to the discrete model of propagation in

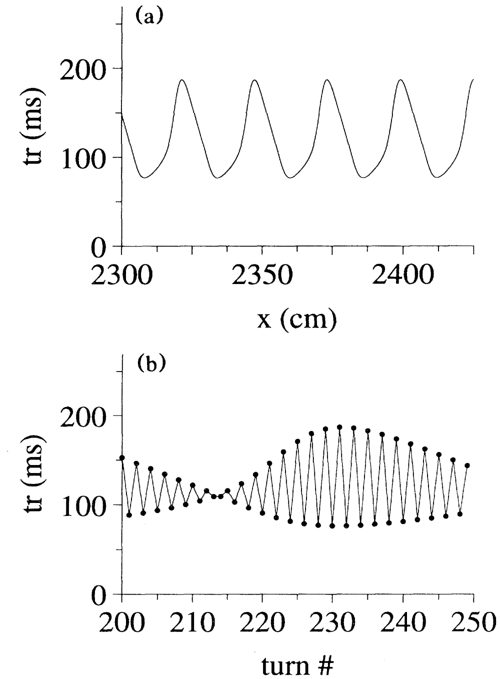

FIG. 3. As in Fig. 1, but from the numerical integration of Eq. (4). (a) t_r as a function of x. The wavelength is $\Lambda \approx 25.9$ cm. (b) t_r at a fixed location along the ring.

a ring developed in [3]. We integrate Eq.(4) using restitution and dispersion curves fitted from the data in Fig. 2 [15]. The steady-state $t_r(x) = t_r^*$ becomes unstable as we decrease the ring circumference from $L = 13.5$ cm to $L = 13.45$ cm. Starting at the steady-state value for $L = 13.25$ cm, there are growing oscillations in the recovery time. Figure 3(a) shows a trace of $t_r(x)$ after stabilization of the oscillations. The wavelength of the oscillation is $\Lambda \approx 25.9$ cm. As in the PDE, the dynamics of t_r at any fixed location along the ring are quasiperiodic, as shown in Fig. 3(b).

The onset of oscillations can be studied in the delay equation using a linear stability analysis of the steady-state solution $t_r(x) = t_r^*$. Using $y(x) = t_r(x) - t_r^*$, the linearized form of Eq.(4) near the steady state is

$$\frac{dy}{dx} + \gamma \frac{dy_L}{dx} = -\alpha(y - y_L)\,, \tag{5}$$

where $\alpha = c'(t_r^*)/c^2(t_r^*)$ and $\gamma = a'(t_r^*)$. We look for solutions of the form $t_r(x) = be^{\lambda x}$ in Eq. (5), solving for all possible eigenvalues λ_k. The steady-state solution is stable if all eigenvalues have negative real parts. This criterion is satisfied whenever

$$|\gamma| = \left| \left. \frac{da}{dt_r} \right|_{t_r = t_r^*} \right| < 1. \tag{6}$$

When $\gamma = 1$, there is an infinite-dimensional Hopf bifurcation with an infinite number of eigenvalues of the form $\lambda_k = i\omega_k$ crossing the imaginary axis. Each of these eigenvalues corresponds to a different mode, with frequency ω_k, becoming linearly unstable at the bifurcation. For $\alpha L \ll 1$, the wavelength $\Lambda_k = 2\pi/\omega_k$ of these modes is approximately

$$\Lambda_k \approx \frac{2L}{2k+1} - \frac{4L^2\alpha}{(2k+1)^3\pi^2}, \quad k = 0, 1, 2, \ldots\,. \tag{7}$$

Using the restitution and dispersion curves fitted to the data in Fig. 2, we compute that the bifurcation occurs when $t_r^* \approx 112.7$ ms, corresponding to a ring of length $L \approx 13.48$ cm. At the bifurcation, the unstable mode corresponding to a wavelength slightly less than twice the ring length is given by Λ_1. Applying Eq. (7) at $L = 13.25$ cm ($\alpha = 0.0076$ cm^{-1}) we find $\Lambda_1 \approx 25.96$ cm, in close agreement with the wavelength of the oscillating solutions in Figs. 1 and 3.

The neutral delay-differential equation accurately predicts the dynamics of pulse circulation around a ring in the PDE model based on the Beeler-Reuter equations. The theory will be valid for any excitable medium provided the restitution and dispersion functions are adequate to describe the relationship between pulse duration, pulse speed, and the state of the medium. Thus, although the effect we describe here has, to the best of our knowledge, only been observed in cardiac tissue or in models of cardiac tissue, we expect that a similar phenomenon will be observed in nonliving excitable tissues such as in one-dimensional rings that sustain chemical waves or combustion waves. The relevance, if any, of the instability analyzed here to the instabilities observed in the meandering [10] and breakup [6, 8] of spiral waves of excitation remains to be elucidated.

This research has been partially funded by grants from the Heart and Stroke Foundation of Quebec, the Natural Sciences and Engineering Council of Canada, and the National Science Foundation (Grant No. DMS 9000588 to J.P.K.).

[1] G. R. Mines, Trans. R. Soc. Can. **4**, 43 (1914).
[2] L. H. Frame and M. B. Simson, Circulation **78**, 1277 (1988).
[3] H. Ito and L. Glass, Physica (Amsterdam) **56B**, 84 (1991).
[4] W. Quan and Y. Rudy, Circ. Res. **66**, 367 (1990); A. Vinet and J. L. Leon, IEEE Eng. Med. Biol. Soc. **13**, 508 (1991).
[5] T. J. Lewis and M. R. Guevara, J. Theor. Biol. **146**, 407 (1991).
[6] H. Ito and L. Glass, Phys. Rev. Lett. **66**, 671 (1991).
[7] A. T. Winfree, J. Theor. Biol. **138**, 353 (1989).
[8] A. V. Panfilov and A. V. Holden, Int. J. Bif. Chaos **1**, 219 (1991); M. Courtemanche and A. T. Winfree, J. Bif. Chaos **1**, 431 (1991).
[9] V. S. Zykov, *Simulation of Wave Processes in Excitable Media* (Manchester Univ. Press, Manchester, 1987).

[10] D. Barkley, M. Kness, and L. S. Tuckerman, Phys. Rev. A **42**, 2489 (1990); P. Pelce and J. Sun, Physica (Amsterdam) **48D**, 353 (1991); A. Karma, Phys. Rev. Lett. **66**, 2274 (1991); **68**, 397 (1992); D. A. Kessler, H. Levine, and W. N. Reynolds, Phys. Rev. Lett. **68**, 401 (1992); J. P. Keener, SIAM J. Appl. Math. **52**, 1370 (1992); D. Barkley, Phys. Rev. Lett. **68**, 2090 (1992).

[11] G. W. Beeler and H. Reuter, J. Physiol. **268**, 177 (1977).

[12] The partial differential equations are integrated using the finite-difference scheme $V_i^{n+1} = V_i^n + \triangle t I_{\mathrm{BR}}/C_m + D\triangle t(V_{i-1}^n - 2V_i^n + V_{i+1}^n)/\triangle x^2$, where $D = 1/S_v C_m \rho$. The integration is performed with $\triangle x = 0.025$ cm and $\triangle t = 0.025$ ms.

[13] J. K. Hale, *Theory of Functional Differential Equations* (Springer-Verlag, New York, 1977); R. Datko, Quart. Appl. Math. **36**, 279 (1978); J. K. Hale, E. F. Infante, and F. S. P. Tsen, J. Math. Anal. Appl. **105**, 533 (1985); N. MacDonald, *Biological Delay Systems: Linear Stability Theory* (Cambridge Univ. Press, Cambridge, 1989), Appendix 5.

[14] Our discretization scheme for the neutral delay equation is $t_r^{n+1} = t_r^n + \triangle x\{1/c(t_r^n) - 1/c(t_r^{n-N}) - [a(t_r^{n-N+1}) - a(t_r^{n-N})]/\triangle x\}$, where $\triangle x = L/N$. We used $N = 200$.

[15] The data in Fig. 2 are fitted using functions $a(t_r) = 20 + B(t_r)t_r^{5.5}/(72^{5.5} + t_r^{5.5})$, where $B(t_r) = 250 - 90e^{-t_r/145}$ and $c(t_r) = 0.0417 - 0.0135e^{-(t_r-37)/18}$. The units are t_r (ms), a (ms), and c (cm/ms). Propagation is blocked if $t_r < 40$ ms. There is a slight splitting in the restitution curve of Fig. 2(a), not exceeding 2% of the pulse duration, which is not accounted for in the theory.