PHYSICAL REVIEW E **70**, 041903 (2004)

Stimulation of unidirectional pulses in excitable systems

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(Received 19 April 2004; published 21 October 2004)

Using a judicious spatial shape of input current pulses (and electrodes), responses of an excitable system (FitzHugh-Nagumo) appear as unidirectional pulses (UDP's) instead of bidirectional ones (in one dimension) or circular ones (in two dimensions). The importance of the UDP's for a possible mechanism for pinpointing the reentry cycle position and for a possible use in tachycardia suppression is discussed.

DOI: 10.1103/PhysRevE.70.041903 PACS number(s): 87.19.Hh, 87.10.+e

I. INTRODUCTION

The normal heart tissue is an excitable medium in which electrical signals emitted by the sinus node propagate and induce muscle contractions and blood pumping [1–5]. Excitable media are ubiquitous in other systems as well [6,7]: axons, the respiratory system, etc., in animal biology; chemical reactions such as the Bellousov-Zhabotinsky one; fluid flow; electrical systems, etc. A particular definition of an excitable medium [8] is its ability to sustain a propagating pulse once the latter is initiated. Model calculations for such media are abundant for one-dimensional (1D) cases [9] as well as for two and three dimensions [10]. The one-dimensional calculations are applied, e.g., for pulses propagating in axons [11] and for reentry paths [12] in the heart. The latter example is very important and is repeatedly referred to here. Input pulses usually take the form of short duration current spikes, concentrated spatially at or around a specific position. Such inputs originate either in the system itself (e.g., in the sinus node of the heart) or at implanted electrodes (e.g., implanted pacemakers). Responses to such inputs depend on their magnitude. For small inputs (below threshold) no propagating pulses develop, while for large enough inputs (above threshold) action potential pulses are developed and propagate through the medium. Propagation takes place symmetrically around the application point. Thus, in one dimension, two pulses are generated (e.g., [9]), one of which propagates to the right and one to the left. In two dimensions, a circular pulse is created [13] and propagates outward from its initiation point. A "ringlike" medium [5] (such as a reentry path in the myocardium) behaves in an in between manner, depending on its boundary conditions. For boundary conditions that enforce zero value for the electrical voltage, two arclike pulses appear in response to the triggering input, and, like the parts of a circle which they are, propagate to the left and to the right with an ever increasing radius.

In this paper we demonstrate for a specific, albeit very versatile, model of an excitable medium that by stimulating it with a specific spatially *asymmetric* current, a unidirectional pulse (UDP) is produced. Such UDP's are shown for 1D, 2D, and ringlike media in the next section. Unidirectional wave propagation in reaction-diffusion systems has been previously achieved by the creation of a unidirectional block for waves in the medium. These waves were constructed either for the purpose of potential use in logic operations [14] of computing devices or for the purpose of explaining the reentry mechanism. Thus a "diode" for the transfer of chemical pulses was developed [15–18] based on asymmetrical arrangement of two adjacent regions of the medium and the use of a gap or a pseudogap between them. The asymmetry was achieved either geometrically or by special illumination methods [19]. Here we employ asymmetric driving of *uniform* media. Note that since an excitable medium (say a 1D one) is capable of sustaining a UDP, for example, each of the two pulses discussed above propagating only to the right (or only to the left), it is clear that such a pulse can always be created by using as a stimulating pulse the exact UDP which is sustained by the medium. This procedure would imply, however, using additional changes of variables (of the inhibitory type) besides that of the input current. It is explicitly such changes, which are hardly possible, that we wanted to avoid.

II. THE MODEL

We consider the FitzHugh-Nagumo system [9,20]

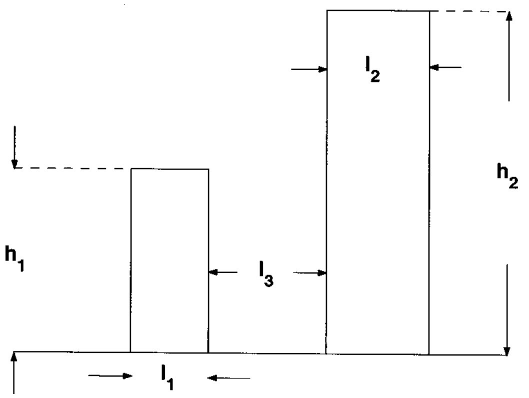

FIG. 1. An asymmetric input: Dual electrode. Note: All variables in figures are in nondimensionless units.

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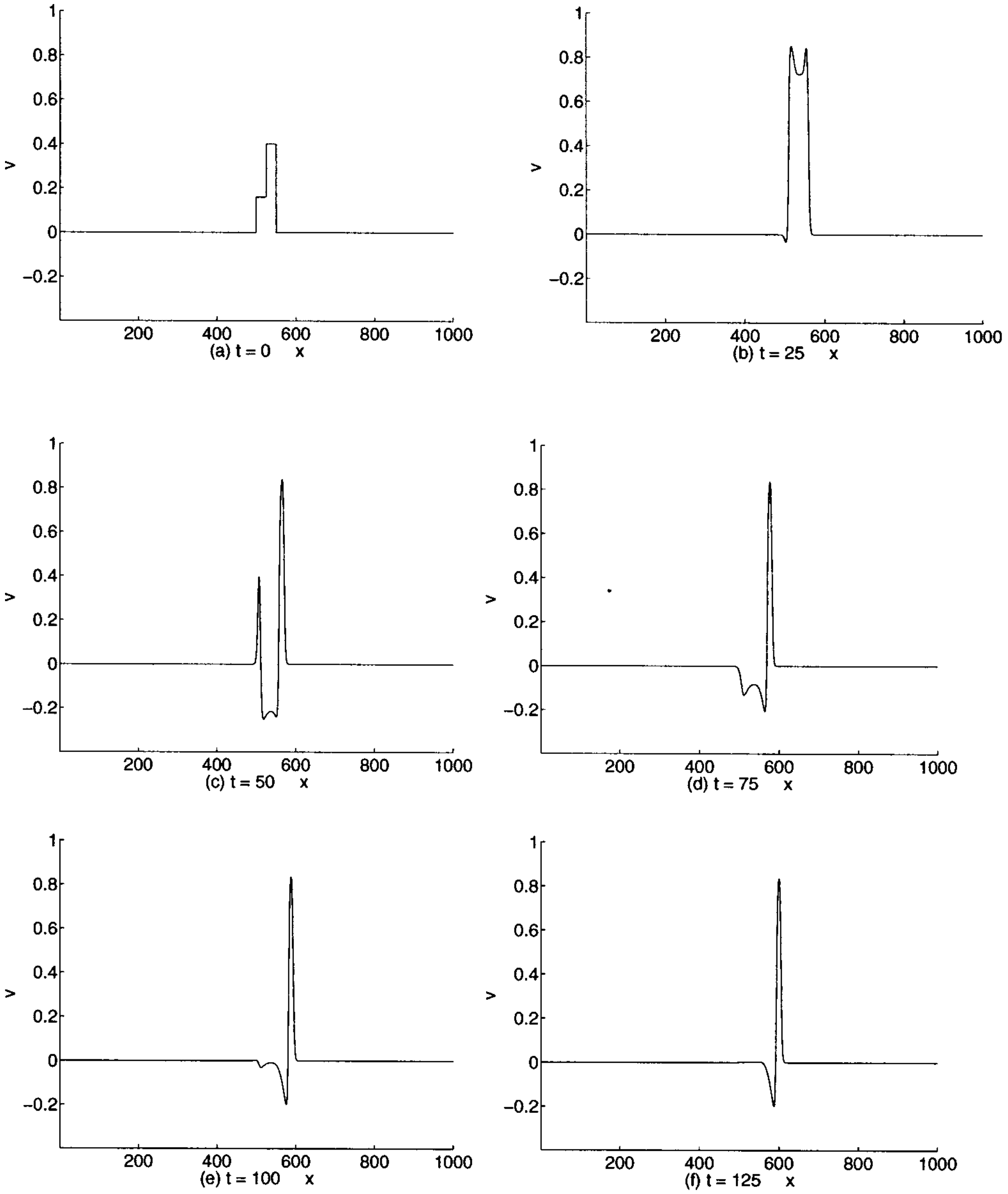

FIG. 2. Initiating a 1D UDP: $a=0.1, c=0.01, d=3, D=1, L=1000, l_1=l_2=25, h_1=0.16, h_2=0.4$.

$$\dot{v} = D\nabla^2 v + f(v,w) + I(t,\vec{r}),$$

$$\dot{w} = g(v,w), \tag{1}$$

where all the variables are in nondimensional units.

Here, v is the potential (an excitatory variable) and w is the refractivity (an inhibitory variable). The functions $f(v,w)$ and $g(v,w)$ are given by

$$f = v(v-a)(1-v) - w, \quad g = c(v - dw), \tag{2}$$

and $I(t,\vec{r})$ is the input current. The constants D, a, and c are, respectively, the diffusion constant, the excitability parameter, and the ratio (temperature dependent) between the fast and the slow time constants. The constant d depends on the application of the model (for example, in the axon case it is related to the specific membrane fluid resistivity). In our treatment we use $D=1, d=3$, and vary the remaining parameters. Note that a spatial dependence occurs only in the diffusion term, which has the appropriate form for the 1D, 2D, or 3D case, and (for a short period) in the input current term. It is the latter that we address. Usually $I(t,\vec{r})$ is given by

$$I(t,\vec{r}) = I_1(t) I_2(\vec{r}) \tag{3}$$

where $I_1(t)$ is a short time dependent function and $I_2(\vec{r})$ is usually obtained by the shape of the contacting electrode. The "best" form of $I_1(t)$ has been thoroughly investigated (e.g., [21,22]) for problems of external pacing and defibrillating of the heart. Here we consider the spatial part $I_2(\vec{r})$. A symmetric form of I_2 (say, a Gaussian or a square) evidently induces a symmetric response which appears as two (left and right) propagating pulses in 1D, a circularly propagating pulse in 2D, etc. We, however, consider an asymmetric I_2. For the 1D case the form we use is shown in Fig. 1. Practi-

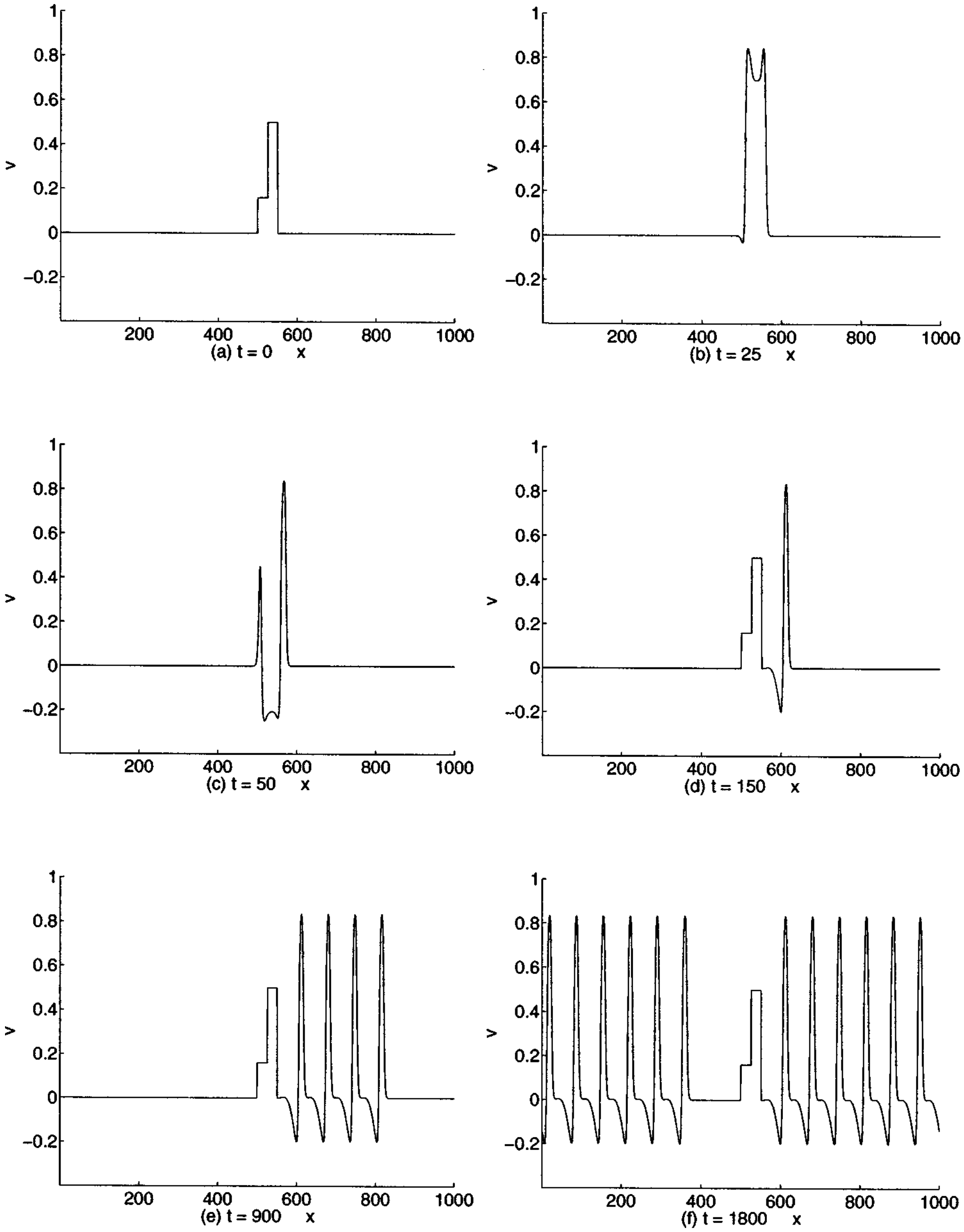

FIG. 3. Initiating a 1D train of UDP's: $a=0.1, c=0.01, d=3, D=1, L=1000, l_1=l_2=25, h_1=0.16, h_2=0.5$.

cally, this shape can be achieved by a dual electrode, where each subelectrode renders a different current. For $I_1(t)$ we use a square short pulse or a δ function. Responses to such an input pulse (IP) depend on its height and on the ratios of its two parts. For small IP's no propagating pulses appear at all. Above some threshold, either a bidirectional or a UDP response is obtained depending on these ratios. As is well known [11], for a small symmetric IP of height h and width l, it is the product $A=hl$ that defines the threshold, for small enough l's. For $A>A_{\mathrm{th}}$ two (left and right) propagating pulses appear. As l increases, however, h_{th} does not decrease as $1/l$ but approaches a constant h_0. For example, if $D=1, a=0.125, c=0.01, d=3$ we get $h_0=0.22$. Consider now an IP of the form depicted in Fig. 1. It consists of two square pulses that are l_3 apart. Unless otherwise stated we assume $l_3=0$. Suppose that l_1, l_2, and h_1 are given ($h_1 l_1$ is below threshold) and h_2 is varied. The responses are as follows. There exist two constants α and β, such that for $0<h_2<\alpha$ no propagating pulse is obtained, for $\alpha<h_2<\beta$ a UDP appears, and for $h_2>\beta$ the usual bidirectional pulse is produced. For example, taking $l_1=12$, $l_2=4$, and $h_1=0.16$ we obtain $\alpha=0.353$ and $\beta=0.403$; while for $l_1=l_2=8$ and $h_1=0.16$ we get $\alpha=0.252$ and $\beta=0.262$. Thus the *range* of h_2 for a UDP is much larger for a larger l_1/l_2 ratio. Note that A_1 values ($=h_1 l_1$) for UDP production are smaller for the 12:4 case than for the 8:8 one, implying that it is easier to obtain a UDP in an asymmetric case, namely, for $l_1>l_2$.

The explanation for obtaining a UDP using the electrode of Fig. 1 can be given as follows. The squares (l_1, h_1) and (l_2, h_2) initiate bidirectional pulses P_1 and P_2, respectively. While the left part of P_1 (denoted by P_1^l) decays for small h_1, the right part of P_1 (denoted by P_1^r) and the left part of P_2

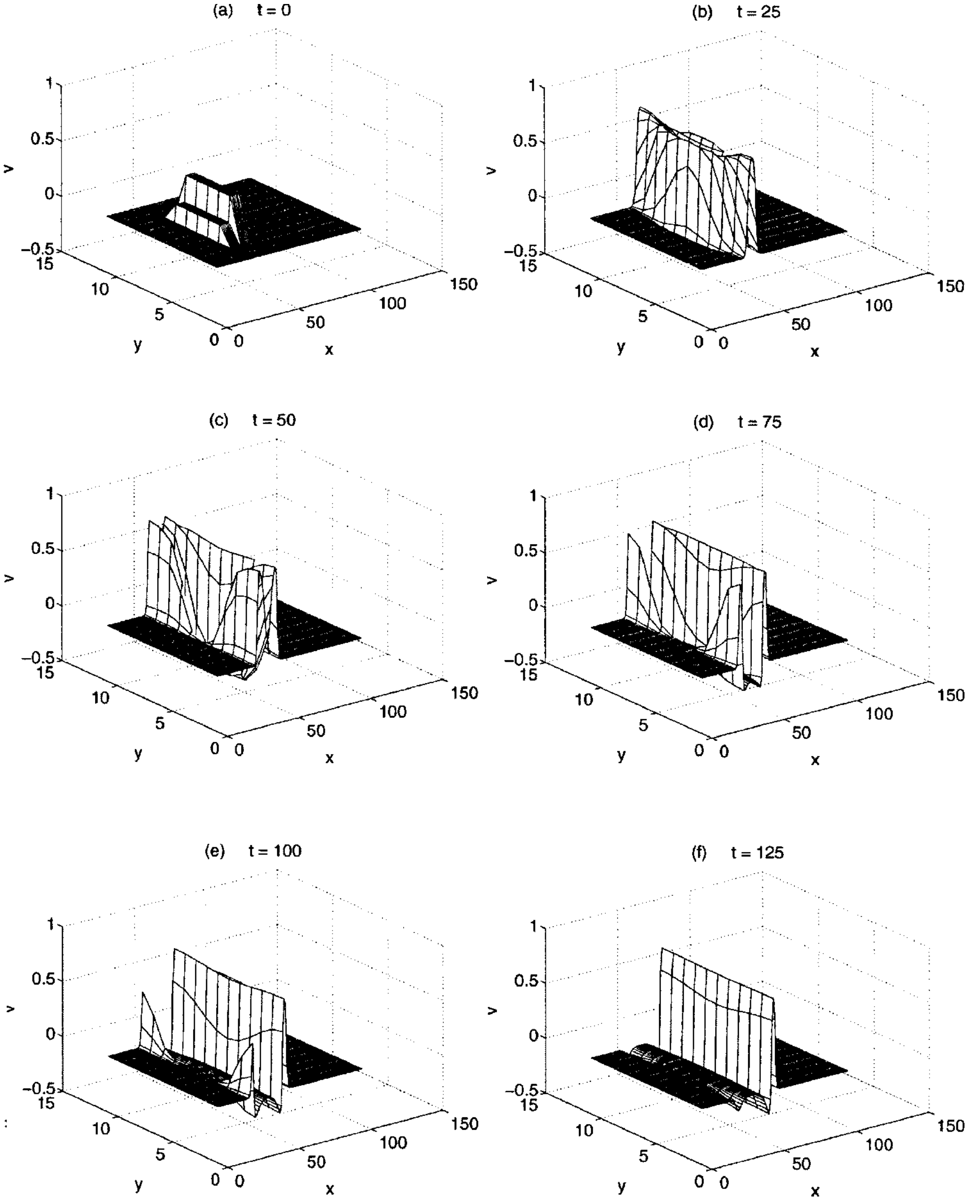

FIG. 4. Initiating a 1D UDP in a ringlike medium: $a=0.1$, $c=0.01$, $d=3$, $D=1$, $L=1000$, $Y=20$, $W=10$, $l_1=l_2=25$, $h_1=0.16$, $h_2=0.4$.

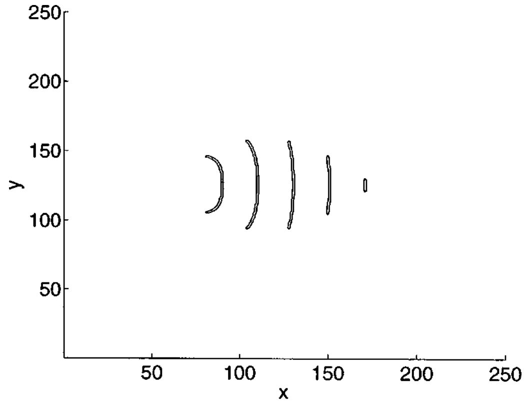

FIG. 5. A disappearing 2D UDP: $a=0.06$, $c=0.138$, $d=3$, $D=1$, $L=2000$, $Y=2000$, $W=40$, $l_1=l_2=30$, $h_1=0.14$, $h_2=0.4$, $0\leqslant t\leqslant 2200$.

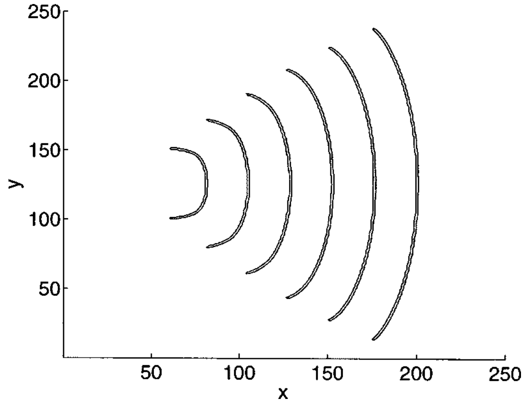

FIG. 6. A sustained 2D UDP: $a=0.06$, $c=0.135$, $d=3$, $D=1$, $L=2000$, $Y=2000$, $W=40$, $l_1=l_2=30$, $h_1=0.14$, $h_2=0.4$, $0\leqslant t\leqslant 2000$.

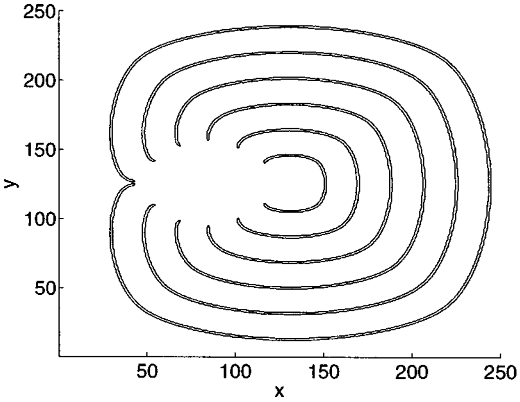

FIG. 7. A developing 2D bidirectional pulse: $a=0.06$, $c=0.125$, $d=3$, $D=1$, $L=2000$, $Y=2000$, $W=40$, $l_1=l_2=30$, $h_1=0.14$, $h_2=0.4$, $0\leqslant t\leqslant 2200$.

(denoted by P_2^l) advance in opposite directions and therefore collide and annihilate each other (at some range of the parameters). This leaves only the right part of P_1^l (denoted by P_2^r) as a single pulse (the UDP) moving to the right. From an engineering point of view, it is essential that the two electrodes are separated by some distance $l_3>0$. This constraint is actually an advantage, since it enables P_1^r to increase a little and ensure the destruction of P_2^l. Thus, if $l_3>0$ a UDP is more likely to be initiated than if $l_3=0$. One should note however that l_3 cannot be too large since then P_1^r will completely vanish before its collision with P_2^l and the net outcome will be a bidirectional pulse initiated by (l_2,h_2).

Figure 2 shows the early part of the temporal development $v(x,t)$ of a UDP. It is seen that at first two pulses are created, but due to the different w values generated for them, the left-going pulse shrinks and disappears while the right-going one remains and continues to propagate.

Figure 3 demonstrates that even a train of UDP's can be obtained by applying a train of stimulating IP's each of the form of Fig. 1. For a 1D ring case (periodic boundary conditions), as shown in Fig. 3, the whole circle can be filled up by such a train.

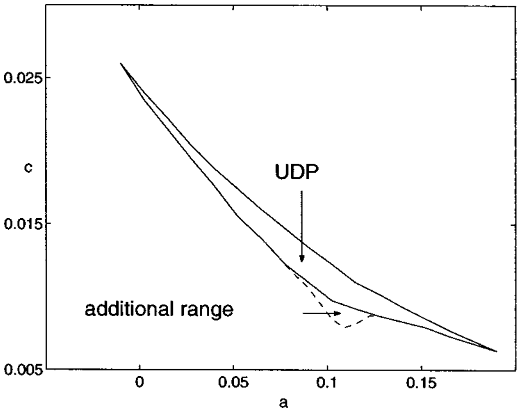

FIG. 8. A typical UDP's range for a ring-shaped case: $D=1$, $L=1000$, $Y=20$, $W=10$, $h_1=0.16$, $h_2=0.4$, $l_1=l_2=25$ (solid line) $l_1=15$, $l_2=35$ (dashed line).

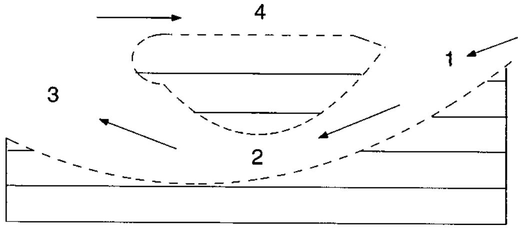

FIG. 9. Schematic reentry circuit.

Periodic boundary conditions were also used to check annihilation of an existing pulse (no graph is shown). A 1D medium in which a single pulse oscillates is a simulation of a reentry circuit. In the usual situation [9], a triggering pulse to such a circuit causes the following effect. The trigger stimulates two propagating pulses. The one going in the direction opposite to that of the existing pulse annihilates it when they meet, while the one going in the direction of the existing pulse remains and "resets" it at a different phase along the circle. Only when the trigger is applied at the refractory period of the existing pulse can there be a different result. Application at the absolute refractory period causes no effect, while application at the "vulnerable window" [23,24], which is a small period in the trailing edge of the existing pulse, results in a single retrograde (backward) going UDP which annihilates the existing pulse. The usual result, therefore, is that the existing pulse is rarely annihilated (the latter happens only when the trigger occurs exactly at the vulnerable window). On the other hand, a UDP created by our asymmetric trigger, if directed opposite to the existing pulse, almost always annihilates it at the encounter point. When applied at the refractory period of the existing pulse, it has a similar effect to the usual or symmetric trigger, except that the vulnerable window is wider and includes all of the lower part of the tail of the existing pulse.

A ringlike medium is treated next. This medium (Fig. 4) is depicted as a band in the x-y plane. It stretches between $x=0$ and $x=L$ with periodic boundary conditions there, and between $y=0$ and $y=Y$ with Dirichlet boundary conditions there (namely, $v=w=0$). The triggering pulse used is of the following shape: its width W in the y direction is somewhat less than Y, while in the x direction it has the asymmetric form of the 1D case (compare Figs. 2 and 4), although with somewhat different parameters' values. It is seen from Fig. 4 that the ensuing pulse is a plane wave UDP.

By applying a similar triggering current pulse to a 2D medium, interesting responses are obtained (Figs. 5–7). The medium is of length L, width Y, and initial pulse width W. In Fig. 5 a case of a "disappearing" UDP is given. Note that the value of c is high and already in the range where also bidirectional pulses shrink and disappear [25]. The case of a sustained UDP is shown in Fig. 6. It is seen that the envelope of this plane wave is a monotonically (very slowly) increasing function. Figure 7 shows a developing circular front; thus although the initial front is not closed, the two end points approach each other and coalesce.

In order to assess the range of parameters for which a UDP exists we analyzed the ring-shaped case. For fixed d,L,h_1,h_2,Y,W, and $l_1=l_2=25$ Fig. 8 (solid line) provides

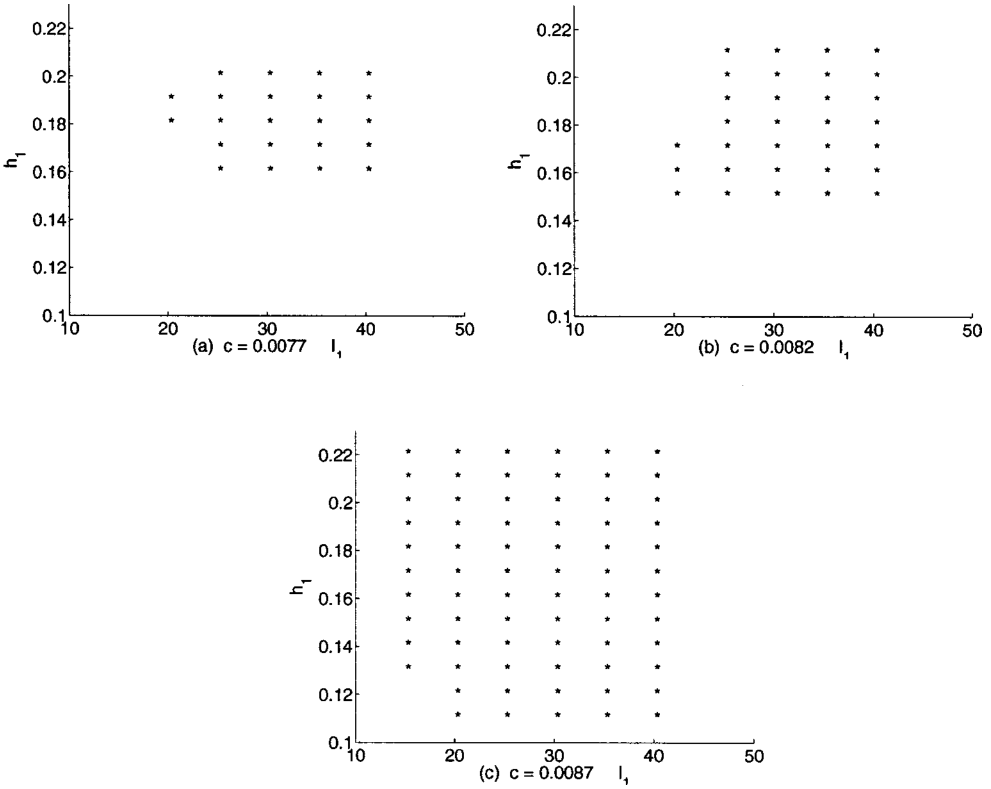

FIG. 10. Dependence of UDP on proximity to ischemia: $a=0.139$, $d=2.54$, $D=1$, $L=1000$, $l_2=25$, $h_2=0.4$.

the range in the *a-c* plane where a UDP is obtained. It should be noted that the upper boundary of this range coincides with part of the boundary of the excitable region (i.e., for larger c values no pulses propagate in the medium whatsoever). Choosing $l_1=15$, $l_2=35$ (leaving the remaining parameters unchanged) causes the range to expand (Fig. 8, dashed line).

III. DISCUSSION

We have demonstrated that it is feasible to obtain a unidirectional propagating pulse in an excitable medium by a judicious choice of the shape of the input current triggering pulse. This result was obtained numerically for a specific model (FitzHugh-Nagumo) for one-dimensional, ring-shaped (a periodic strip), and two-dimensional media. Although we have not checked other models, we believe that such UDP's can be generated for them as well, since the range of parameters for which UDP's were received was not negligible (Fig. 8).

We now discuss three possible manifestations of the use of a UDP, both as a means of understanding the phenomenon and as a potential practical tool.

A. Reentry mechanism

One of the commonest origins of tachycardia is a reentry phenomenon developed in a reentry path. The latter is a closed path in the myocardium [26], usually developed in a partly scarred tissue produced as a result of a previous myocardial infarction. Such a closed path is a necessary condition for the reentry phenomenon, but usually not a sufficient one. The path has to be excited [27] into activation. Regular heart action potential waves approaching a reentry path will not cause an active reentry phenomenon unless one or more of the following occurs [27–29]. (a) One current direction (say 1-2-3, Fig. 9) has a much larger conductivity than the other (1-4-3), together with a much shorter refractory period. (b) One current direction is either temporarily blocked and opens later when the current from the second direction reaches it from the other side, or unilaterally blocked and opens for the current from the other direction, a so-called unidirectional block. (c) The action potential wave is prematurely originated at an ectopic position and its fluctuations enter the reentry path in a (vulnerable) period when a previous sinus node originated impulse has rendered it susceptible to either (a) or (b). An elegant *in vitro* experimental observation of these processes is described in Ref. [30].

We would like to suggest another mechanism for the activation of a reentry phenomenon when a reentry path already exists. The idea is the following. Assume that the reentry path is connected to the main tissue by a (damaged) dissipative tissue which induces a reduction in potential magnitude. If such a reduction is spatially asymmetric and the form of the wave entering the reentry path is of the form of Fig. 1, a UDP would develop in it [31].

Such a mechanism might be the one responsible for the reentry seen in the simulated ischemia experiments reported in Ref. [31]. This possibility is in line with the following argument. In Ref. [31], the asymmetry and the reentry were enhanced for a higher ischemic situation. To check this point we changed c, l_1, and h_1 but fixed the remaining parameters. In Fig. 10 domains where a UDP is obtained are plotted in the l_1-h_1 plane for various c values. It is seen that, in accordance with Ref. [31], the higher c is (moving in the direction of the excitability limit) the easier it is to obtain a UDP.

B. Catheter mapping

The conventional method of pinpointing the location of a reentry path in the heart is by catheter mapping [28]. A catheter is introduced into the heart and moved around a suspected area. The catheter can perform three tasks. It measures the temporal dependence of the action potentials at different locations in the heart; it delivers pulses to specific points suspected of being in a reentry path, thereby resetting them (or partially annihilating the reentry), to facilitate identifying this path; and, after a reentry path has been identified, it is used to deliver rf waves to ablate it.

By using a dual electrode with a trigger input of the form of Fig. 1, the second task could possibly be made easier. The UDP thus created (instead of the usual bidirectional one) would really annihilate the oscillating circus reentry if the former resides in the principal track (see the discussion of Fig. 1 in Ref. [28]). If the UDP is generated at a subsidiary track, the annihilation would be only temporary, with an eventual resetting.

C. Dual-electrode implant

Tachycardia originating from a specific reentry path is usually treated [33] by drugs, ablation [32] of the suspected area, or a defibrillator, either an internal (implantable) or an external one.

Implanting a dual electrode with a pulse shape of Fig. 1 would stop the reentry phenomenon with a much lower amplitude signal, thus minimizing tissue damage. A dual electrode with a pulse shape given by Fig. 1 could thus hold some possible benefits.

An *in vitro* experiment performed on heart tissue of a mouse [34] actually demonstrated the feasibility of this approach and led to a U.S. patent [35].

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