Wave propagation in an excitable medium with a negatively sloped restitution curve

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Recent experimental studies show that the restitution curve of cardiac tissue can have a negative slope. We study how the negative slope of the restitution curve can influence basic processes in excitable media, such as periodic forcing of an excitable cell, circulation of a pulse in a ring, and spiral wave rotation in two dimensions. We show that negatively sloped restitution curve can result in instabilities if the slope of the restitution curve is steeper than -1 and report different manifestations of this instability.
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Rotating spiral waves occur in a variety of nonlinear excitable media. The appearance and multiplication of spiral waves disturb the spatial organization of the medium and may result in turbulent or chaotic behavior. If such a regime occurs in cardiac tissue it causes cardiac fibrillation. One of the most studied instabilities which can result in breakup of spiral waves occurs if the restitution curve of cardiac tissue, which relates the duration of cardiac pulses to the recovery time between the pulses, has a slope of more than one. This instability has been studied only in the case of a restitution curve with a positive slope. Recent experimental studies showed the existence of restitution curves with a negative slope. It occurs in cardiac tissue prone to atrial fibrillation. In this article, we study the effects of a negatively sloped restitution curve and the possible associated instabilities which can occur in three different contexts: a periodically forced excitable cell, circulation of a pulse in a ring of excitable tissue, and a spiral wave rotating in two dimensions.

I. INTRODUCTION

Complicated spatiotemporal patterns play an important role in excitable media of various types. If such patterns occur in cardiac tissue they cause cardiac fibrillation, which is one of the main causes of death in the industrialized world.[1] In many cases, complex spatiotemporal patterns arise as a result of some type of instability. The type of instability most studied today is the so-called alternans instability. This instability may occur if one forces an excitable medium with a sufficiently short period. In this case, instead of a periodic response with the same period as the stimulus, the durations of successive action potentials begin to alternate (e.g., short–long–short–long, etc.). There is a simple criterion governing the onset of alternans, based on the restitution curve of the tissue, which relates the action potential duration (APD) to the diastolic interval. The diastolic interval (DI) is the time that has elapsed between the end of the preceding action potential and the start of the next one. An alternans instability can occur if the slope of the restitution curve is more than one.[2,3] In two-dimensional excitable media, an alternans instability can cause spiral breakup: fragmentation of one spiral wave into a spatiotemporally chaotic pattern comprising many wavelets of various sizes.[4–8] Spiral breakup is now one of the most actively pursued candidates for the mechanism underlying onset of ventricular fibrillation.

The theory of restitution instability was developed assuming that the slope of the restitution curve is always positive. This assumption is reasonable as it means that longer recovery times lead to longer action potential durations as has been confirmed in numerous experimental studies. However, it was shown recently that in some cases, the slope of the restitution curve can become negative as well. For example, it was shown that the restitution curve has a region with negative slope in remodeled atrial tissue, i.e., in tissue which sustains chronic atrial fibrillation.[9] It was also shown that there is a small region with negative slope in the restitution curve of normal human ventricular tissue.[10,11] In spite of the existence of negatively sloped restitution curves this phenomenon has hardly been studied. In the only published paper in that area known to us,[12] it was found that the addition of a nonmonotonic region to the restitution curve can result in increased instability of the pulse rotating in a ring of the cardiac tissue. However, mechanisms underlying this effect as well as the precise role of the nonmonotonicity in the loss of stability were not clear.

In this article, we study the effects of negatively sloped restitution in several contexts whose study lead to a good understanding of the alternans instability: a periodically forced excitable cell, circulation of a pulse in a ring, and spiral wave rotation in two dimensions. Our main conclusion is that negative restitution can induce instabilities if the slope of the restitution curve is steeper than -1.

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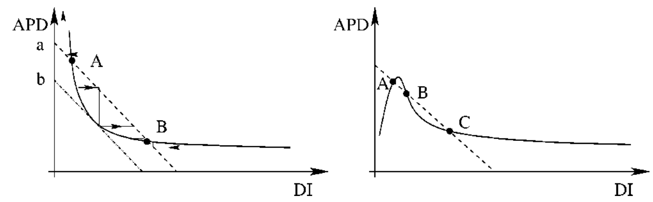

FIG. 1. Qualitative dynamics in an excitable medium with negatively sloped APD restitution. Points of intersection of the restitution curve (the solid line) and the dashed and dotted lines a and b, defined by the relationship $\mathrm{APD} = T_{a,b} - \mathrm{DI}$ give the equilibria of map (1).

II. PERIODIC FORCING OF AN EXCITABLE SYSTEM

We start with a simple analysis. Consider stimulating an excitable cell with a constant period T and denote the action potential durations of the successive pulses as APD_n and their diastolic intervals as DI_n. Because the period of stimulation is constant, $\mathrm{APD}_n + \mathrm{DI}_n = T$. The action potential duration of the pulse APD_{n+1} is determined by the previous diastolic interval, or

$$\mathrm{APD}_{n+1} = f(\mathrm{DI}_n) = f(T - \mathrm{APD}_n), \tag{1}$$

where f stands for the restitution properties. The dynamics of this map can be easily studied. An equilibrium point of this map corresponds to a periodic response of the excitable medium. Such an equilibrium becomes unstable, however, as soon as $|df/d\mathrm{DI}|>1$. The case $df/d\mathrm{DI}>1$ corresponds to the alternans instability discussed in Refs. 2 and 3, the case $df/d\mathrm{DI}<-1$ corresponds to a new instability which is induced by negative restitution. Therefore, if the slope of the restitution curve becomes steeper than -1, we can expect instabilities in the excitable medium.

A useful graphical representation of possible dynamics in this case is shown in Fig. 1. The solid lines represent restitution curves. In order to obtain the dynamics of map (1) under periodic forcing one should draw a straight line $\mathrm{APD} = T - \mathrm{DI}$ and perform the well-known "cobwebbing" method with respect to this line (similar to Refs. 2 and 13).

Figure 1(a) shows an example of a restitution curve with everywhere negative slope. The dashed line represents forcing with one possible period. We see that, in this case, the map defined by Eq. (1) has a stable equilibrium B at a long DI and an unstable equilibrium A at a short DI. We see that the solution perturbed from the stable equilibrium B returns to it without oscillations (no alternans) and there is a basin of attraction of this equilibrium: if one perturbs the system to a DI shorter than that given by point A, the series of APDs goes to infinity. If we decrease the period of forcing, the dashed line shifts downward. As a result, the equilibria A and B approach each other and the basin of attraction of equilibrium B shrinks. Further decrease in the period of external forcing results in the disappearance of the equilibria via a saddle-node bifurcation at some period which corresponds to the dot-dashed line in Fig. 1. The condition for the saddle-node bifurcation is given by the following pair of equations:

$$\frac{d\mathrm{APD}(\mathrm{DI}^*)}{d\mathrm{DI}} = -1, \tag{2}$$

$$T = \mathrm{APD}(\mathrm{DI}^*) + \mathrm{DI}^*, \tag{3}$$

where DI^* is the equilibrium value of DI.

If the restitution curve is nonmonotonic and has regions of negative as well as of positive slope [Fig. 1(b)], map (1) can have three equilibria: a stable equilibrium C, an unstable equilibrium B, and an equilibrium A which can be either stable or unstable. If both equilibria A and C are stable, we can obtain two different stable durations of the action potential at *the same forcing period*. Note, however, that three equilibria are possible only if the restitution curve has a region with slope steeper than -1. As in the previous case, changing of the period of forcing results in disappearance of either equilibria A and B or of equilibria B and C via a saddle-node bifurcation.

Therefore, our conclusion is that periodic forcing of an excitable medium with negatively sloped restitution curve can result in instability if the slope of the restitution curve is steeper than -1. In this case, the APD is not alternating but monotonically increasing. Note, that if due to this instability the refractory period of cardiac tissue becomes longer than the period of forcing, Wenckebach blocks[14] can occur and produce quite complex dynamics. These dynamics can potentially be studied using map (1).

In Sec. III we study the effects of negatively sloped restitution curve on propagation of periodic waves: circulation of excitation in a ring of excitable tissue with negatively sloped restitution.

III. CIRCULATION IN A RING

Consider a pulse circulating in a ring of excitable medium with negatively sloped restitution. If circulation is stationary, we can find its characteristics from the solution of the following:

$$\frac{L}{c(\mathrm{DI}^*)} = \mathrm{APD}(\mathrm{DI}^*) + \mathrm{DI}^*, \tag{4}$$

where L is the length of the ring, and $c(\mathrm{DI})$ is the dispersion relation (dependency of the velocity on DI), and APD(DI) is the restitution of curve cardiac tissue.

The only difference between Eq. (1) and Eq. (4) is that while the left-hand side of Eq. (1) is constant ($T = \mathrm{const}$), that of Eq. (4) is a function of $\mathrm{DI}:(L/[c(\mathrm{DI}^*)])$.

We can easily find spatially uniform equilibria of Eq. (4) using a graphical method similar to that of Fig. 1. For that, as in Fig. 1, we first need to draw the restitution curve. Then, however, instead of drawing the straight lines $\mathrm{APD} = T - \mathrm{DI}$, we need to draw the curves $\mathrm{APD} = L/[c(\mathrm{DI})] - \mathrm{DI}$. Because in normal conditions velocity c is a monotonically increasing function of DI, the dashed lines $\mathrm{APD} = L/[c(\mathrm{DI})] - \mathrm{DI}$ become curves and their slopes become steeper at small DI. Graphically, this means that these lines curve upwards from the straight dashed lines in Fig. 1. The patterns presented in Fig. 1 will, however, remain the same qualitatively: For the monotonically decreasing restitution curve from Fig. 1(a), we can expect two equilibria, for the nonmonotonic restitution curve from Fig. 1(b) we can expect three equilibria, etc. These spatially uniform solutions will also disappear via a bifurcation similar to the saddle-node bifurcation shown in Fig. 1(a). The following condition for this bifurcation is, however, slightly different from Eq. (2):

$$\frac{d\mathrm{APD}(\mathrm{DI}^*)}{d\mathrm{DI}} = -1 - \frac{L}{c^2(\mathrm{DI}^*)}\frac{dc(\mathrm{DI}^*)}{d\mathrm{DI}}. \tag{5}$$

Because $[dc(\mathrm{DI}^*)]/d\mathrm{DI}$ is assumed to be positive, bifurcation in this case occurs for slopes of the restitution curve steeper than -1.

Let us study the stability of these spatially uniform solutions. Our analysis of this problem uses the method developed in Ref. 15 with some modifications to account for the negative slope of the restitution curve. Assume that we have an excitatory pulse revolving in a ring of the length (L) and that the velocity of the wave (c) and duration of the pulse (APD) depend on DI only. Such a pulse can be described by the following delayed integral equation:

$$\int_{x-L}^{x}\frac{ds}{c(\mathrm{DI}(s))} = \mathrm{DI}(x) + \mathrm{APD}(\mathrm{DI}(x-L)), \tag{6}$$

where x is the space coordinate along the ring. Equation (6) basically equates the time of wave rotation around the ring at point x: $\int_{x-L}^{x}(ds/[c(\mathrm{DI}(s))])$ to the sum of the diastolic interval and APD at this point: $\mathrm{DI}(x)+\mathrm{APD}(\mathrm{DI}(x-L))$.

Assume that this equation has a spatially uniform solution, Eq. (4), corresponding to a steady traveling pulse of excitation. The stability of this solution can be found by computing the growth factor, Q, of the perturbation

$$\mathrm{DI} = \mathrm{DI}^* + be^{Qx/L}, \tag{7}$$

which, after substitution of Eq. (7) into Eq. (6), yields the following eigenvalue problem:[15]

$$e^{Q} = \frac{A+QB}{A+Q}, \tag{8}$$

where

$$A = \frac{L}{c(\mathrm{DI}^*)^2}\frac{dc}{d\mathrm{DI}}(\mathrm{DI}^*), \quad B = -\frac{d\mathrm{APD}}{d\mathrm{DI}}(\mathrm{DI}^*).$$

We study this equation in the case of a negatively sloped restitution curve $(B>0)$ and a normal dispersion curve $(A>0)$.

First, following Ref. 15, let us prove that if $0<B<1$, the real part of Q cannot be positive and therefore the circulation is stable. In fact, if we assume that $\mathrm{Re}(Q)>0$, then, on the one hand, the modulus of the left-hand side of Eq. (8) is greater than one $(|e^{Q}|>1)$. On the other hand, $|A+QB|<|A+Q|$ and the right-hand side of Eq. (8) is less than 1. Therefore, we have a contradiction which proves that for $0<B<1$ the circulation of the pulse in the ring is stable.

Now, assume $B=1$. In that case we have infinitely many roots of Eq. (8) with $\mathrm{Re}(Q)=0$, which are

$$Q_k = i2\pi k; \quad k=0,1,2,\text{etc.} \tag{9}$$

and a real root $Q=-A$, which for a normal dispersion curve $(A>0)$ is negative and cannot contribute to the instability.

Now let us show that if $B>1$, the pulse becomes unstable. To do this, we find the dependency of Q_k on B close to the point $B=1$. In this case, we can assume that $Q_k(B)\equiv\alpha_k(A,B)+i\beta_k(A,B)$ is a differentiable function of A,B and find its derivatives at $B=1$:

$$\frac{\partial\alpha_k}{\partial B} = \frac{4\pi^2k^2}{A^2+4\pi^2k^2}, \quad \frac{\partial\beta_k}{\partial B} = \frac{2\pi Ak}{A^2+4\pi^2k^2}, \tag{10}$$

$$\frac{\partial\alpha_k}{\partial A} = \frac{\partial\beta_k}{\partial A} = 0. \tag{11}$$

This yields the following linear approximations close to $B=1$ for the wavelengths of the perturbations $\Lambda_k = 2\pi L/\beta_k$ and their increments α_k:

$$\alpha_k \approx \frac{4\pi^2k^2(B-1)}{A^2+4\pi^2k^2}, \quad \Lambda_k \approx \frac{L}{k}\left(1-\frac{A(B-1)}{A^2+4\pi^2k^2}\right). \tag{12}$$

We see that $\alpha_k>0$ if $B>1$, hence the pulse becomes unstable if the slope of restitution curve becomes steeper than -1 and the growth rate of perturbations near the bifurcation is fastest for the perturbations with the shortest wavelengths.

To validate the results of these analytical computations, we performed computations using Eq. (6) with

$$\mathrm{APD}(\mathrm{DI}) = a + \frac{h}{\mathrm{DI}}, \quad c(\mathrm{DI}) = j\mathrm{DI} \tag{13}$$

and parameter values $a=10$, $h=50$, $j=1$. DI was assumed to be non-negative. For such choice of functions, Eq. (6) has just one positive spatially uniform equilibrium point for $L>50$ (solving $L=\mathrm{DI}^{*2}+10\mathrm{DI}^*+50$), which becomes unstable for $L<170.71$. We set DI to this fixed point of Eq. (6) everywhere in the ring and then imposed perturbations of the form $\mathrm{DI}=\mathrm{DI}^*(1+A\sin(kx))$. Figure 2 compares the growth factors of perturbations of different wave numbers k. Numerical and analytical results match almost exactly.

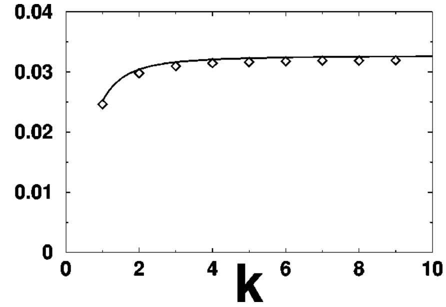

FIG. 2. Growth factors of perturbations with initial amplitude $A=10^{-4}$ in a ring of the length $L=168$. Computations were done using Eq. (6) with functions given in Eq. (13), and $a=10$, $h=50$, $j=1$. Further explanations are in the text.

What type of bifurcation do we have at $B=1$ and what is the direction of this bifurcation? Unfortunately, it was not possible to perform a nonlinear analysis similar to Ref. 15. This is because, for roots (7) of the characteristic equation (8), nonlinear amplitude terms in asymptotic expansions of Eq. (6) disappear, which makes the problem highly degenerate. Therefore, we studied the behavior of our system around the bifurcation point numerically using Eq. (6) with parameters as in Fig. 2. We have determined the basin of attraction of the spatially uniform equilibrium point of this equation

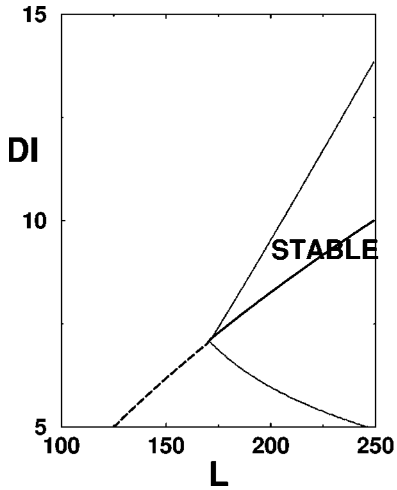

FIG. 3. Bifurcation diagram of spatially uniform solution for a pulse circulating in a ring of excitable tissue. L is the ring length, DI is the diastolic interval, thin lines show the basin of attraction of the equilibrium (thick line, solid for stable, dashed for unstable) with respect to spatially uniform perturbations. See the text for further explanation.

close to the bifurcation point at $L=170.71$. For this, we added spatially uniform perturbations to the exact solution, and checked whether the system returns to equilibrium (Fig. 3). We see that the basin of attraction of the stable solution decreases and becomes zero when we approach the bifurcation point. In all cases the solution becomes unstable without alternans: we observe the successive elongation of APD until the pulse fails to propagate.

Thus, our conclusion is that if the slope of the restitution curve is steeper than -1, a revolving pulse on a ring of excitable tissue is unstable. By "the slope of the restitution curve," we mean the slope evaluated at the DI* corresponding to this pulse. Note that the conditions for this instability coincide with the conditions for instability of a pulse under periodic external forcing considered in Sec. II.

IV. SPIRAL WAVES IN A TWO-DIMENSIONAL EXCITABLE MEDIUM WITH NEGATIVELY SLOPED RESTITUTION CURVE

In this section, we study how a negatively sloped restitution curve affects spiral waves dynamics in a two-dimensional (2D) excitable medium. In Ref. 16 this problem was studied for two models of the excitable medium: a cellular automaton and a reaction diffusion model. Here we review with several modifications a part of this study regarding the reaction-diffusion model, in order to present a comprehensive description of the effects of negative restitution in an excitable medium.

A. Model and method of computation

We used a reaction-diffusion model of FitzHugh–Nagumo type piecewise linear "Pushchino kinetics:"[17]

$$\frac{\partial e}{\partial t}=\frac{\partial^2 e}{\partial x^2}+\frac{\partial^2 e}{\partial y^2}-f(e)-g,$$
$$\frac{\partial g}{\partial t}=\varepsilon(e-g), \tag{14}$$

where e is the transmembrane potential, g is the gate variable, and ε is a function which depends on other variables and will be specified later. In order to make the shape of the action potential as simple as possible, we used the following nonlinear function $f(e)$:[18] $f(e)=\lim_{C\to\infty} Ce$ when $e<0$, $f(e)=-(e-0.1)$ if $0\leqslant e\leqslant 1$, and $f(e)=\lim_{C\to\infty} C(e-1)$ when $e>1$. For this shape of $f(e)$, the excitation pulse has a plateau region at $e=1$, the rest state at $e=0$, and the shape of the pulse is close to rectangular. To model the regions of infinite slope of function $f(e)$ numerically, we use the *if* operators stating that if the variable e is above 1 it is set to 1, and if $e<0$, it is set to 0. It was shown that this procedure gives a sufficiently precise solution of Eq. (14) with f as given previously.[19] In our basic model ε depended on the variable e as follows: $\varepsilon=0.067$ if $0.1<e<0.99$ and $\varepsilon=0.1$ for other values of e. In order to describe a medium with negatively sloped restitution curve, we made the function ε dependent on DI. We put $1/\varepsilon=T(\mathrm{DI})$ (if $0.45\leqslant g\leqslant 0.55$ and $e<0.1$), where $T(\mathrm{DI})$ is the function which influences the slope of the restitution curve and will be chosen later. In fact, if $0.45\leqslant g\leqslant 0.55, e<0.1$, the excitable medium is in the refractory state and the time interval during which the variable g decreases from $g=0.55$ to $g=0.45$ is given by

$$\Delta T=T(\mathrm{DI})\ln\frac{0.55}{0.45}. \tag{15}$$

Therefore, a change of DI results in a change of the refractory period which is proportional to $T(\mathrm{DI})$ and by choosing the function $T(\mathrm{DI})$ appropriately, we can construct an excitable medium with any desired dependency of the refractory period on DI.

In cardiac tissue the refractory period is proportional to APD, i.e., the refractory period and APD restitution curves are similar. This is not the case for model (14),(15), as there the change of $T(\mathrm{DI})$ affects the refractory period and does not influence APD. Refractoriness is one of the most important characteristics determining wave propagation in cardiac tissue. Therefore, if we want to study a characteristic of excitable medium described by model (14) which is similar to the APD-refractoriness restitution of cardiac tissue, we need to study the restitution of the refractory period rather than the restitution of APD. We define the refractory period as time from the beginning of excitation until the time where the variable g decreases below the value $g=0.45$, provided $e<0.1$. In order to stress that this refractory period is similar to APD studied in previous sections we denote it throughout this section as APDr.

For numerical modeling of Eq. (14), we used the explicit Euler method with Neumann boundary conditions and a rectangular grid. Numerical integration was performed with a space step $h_s=0.6$ and a time step $h_t=0.03$. The error in these computations, estimated using the difference between the numerically and analytically calculated velocities of plane wave propagation,[18] was about 5%.

To initiate the spiral wave, we used the initial data corresponding to a 2D broken wave front, or alternatively, an S_1S_2 stimulation protocol, which is often used in experimental electrophysiology.[20] To find the average APDr and DI, we first computed them at each point of the domain during sev-

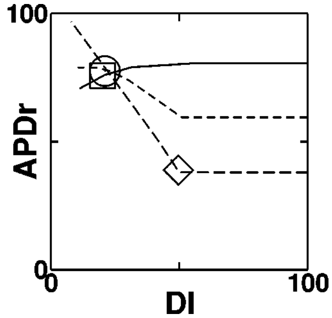

FIG. 4. Restitution curves and corresponding range of average DI. Restitution curves were set up using Eq. (16) with $S=0$ (solid curve), $S=-0.7$ (short-dashed curve), and $S=-1.4$ (long-dashed curve). Spiral locations are indicated by an inverted triangle ($S=0$), a triangle ($S=-0.7$), and a diamond ($S=-1.4$).

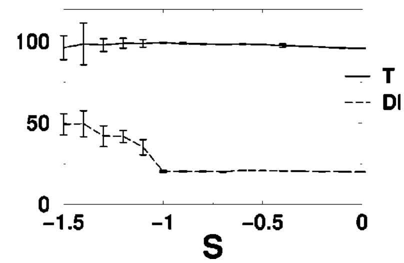

FIG. 5. DI and period of a spiral wave as a function of the slope of the restitution curve S. The average values and standard deviations found for all points of the domain and for 20 rotations of spiral wave.

eral rotations of a spiral wave and then determined their average. We define the diastolic interval to begin when the variable g drops below $g=0.45$ and ends at the moment of excitation.

B. Results

First, we created a medium with a constant restitution curve by setting $T=300$ in Eq. (15) and initiated a spiral wave in this medium. This spiral was rotating stably with APDr$=76$ and DI$=20$. Then, we generated a family of piecewise linear restitution curves which all go through the point (APDr$=76$,DI$=20$), but have slopes at this point ranging between 0 and -1.5. More precisely, we considered the following family of functions (T):

$$T=300+S(\mathrm{DI}-20)\ln^{-1}\frac{0.55}{0.45} \quad \text{for } \mathrm{DI}\leqslant 50, \tag{16}$$

$$T=\mathrm{const}=300+30\,S\,\ln^{-1}\frac{0.55}{0.45} \quad \text{for } \mathrm{DI}>50, \tag{17}$$

where S is the parameter which modifies the slope of the restitution curve for DI$\leqslant 50$. For DI>50, we put $T=$const to mimic the effect of saturation of the restitution curve at long DI. The numerically computed restitution curves for such T are shown in Fig. 4. We found that the numerically computed slope of the restitution curve at the beginning of the negative interval of the curve (close to DI$=50$) was very close to the theoretically predicted value (slope$=S$), however for short DI the slope was generally less negative than predicted, e.g., for $S=0$ the slope of the last part of the restitution curve was slightly positive.

We see that all restitution curves closely follow theoretically predicted shapes and small deviations can only be seen at very short DIs. Because all restitution curves go through the point APDr$=76$,DI$=20$, and we found a stationary spiral wave solution for flat restitution curve which shows only small variations of APDr and DI around this point, it is reasonable to assume that a similar spiral wave solution exists for all slopes of the restitution curve and its averaged characteristics are close to APDr$=76$,DI$=20$. We have initiated spiral waves for various values of S with the restitution curves given by Eq. (16) and computed the location of the spiral wave on the restitution curve (Fig. 4). We see that for slopes 0 and -0.7 the spiral is located at approximately the same point, but for slope -1.40, it is considerably shifted to the right.

The complete dependency of average DI on S (slope) is summarized in Fig. 5. We see that for $S>-1$, the DI remains constant and independent of S. However, for $S<-1$ the DI jumps to much higher values close to 50, which is the value at which the oblique segment of the restitution curve ends. We also see that for $S<-1$, DI has a larger standard deviation. This reflects the nonstationarity of spiral wave rotation which we observe in this case. Figure 5 also shows the dependency of the period of spiral waves on S. We see that, although the change of the period is minimal, in the region where $S<-1$, we have a slight decrease of the period if the slope of the restitution curve becomes steeper. Note that this period decrease occurs as the average DI increases. This result is quite unexpected, as prolongation of DI usually results in prolongation of the spiral period. This abnormal behavior can, in our view, be interpreted by assuming a tendency of the spiral wave to minimize its period. In a medium with positively sloped restitution, this results in the selection of the smallest possible DI, which is determined by the excitability of the medium.[21] However, in a medium with negatively sloped restitution curve, the minimal DI does not necessarily mean the minimal period. In fact, for a stationary rotating spiral, the dependency of period on DI can be written as the following function: $P(\mathrm{DI})=\mathrm{APDr}(\mathrm{DI})+\mathrm{DI}$. The minimum of this function can be reached either at the point where

$$\frac{dP}{d\mathrm{DI}}=0, \quad \frac{d^2P}{d\mathrm{DI}^2}>0,$$

or at an end point of the domain of this function. The derivative of this function $dP/d\mathrm{DI}=d\mathrm{APDr}/d\mathrm{DI}+1$, and it is obviously positive if the slope of the restitution curve is less steep than -1. This means that if the slope is less steep than -1, the period P is a monotonically increasing function of DI, and its minimum is at the smallest possible value of DI. However, if the slope is steeper than -1, P becomes a decreasing function of DI and the minimum is at the point where

$$\frac{d\mathrm{APDr}}{d\mathrm{DI}}=-1, \quad \frac{d^2\mathrm{APDr}}{d\mathrm{DI}^2}>0, \tag{18}$$

i.e., at the point where this slope equals -1.

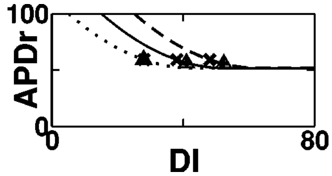

FIG. 6. Spiral in a medium with a parabolic restitution curve (solid line). Computations in a model (14) with T given by Eq. (19), with $R=1/6, T_0=53.2$ (solid line), $T_0=63.2$ (dashed line), and $T_0=33.2$ (dotted line). **X** shows the point where the restitution curve has the slope -1. The time averaged DI of a spiral wave is indicated by a triangle. Medium size was 300×300 elements.

The results shown in Fig. 5 are consistent with this explanation: they show that the spiral wave selects a DI value close to that corresponding to the minimal period for the given restitution curve. However, these computations are insufficient as a test of condition (18) because the slope of the restitution curves given by Eq. (16) jumps discontinuously at DI$=50$ and takes on only two values for each restitution curve. Therefore, we studied a medium whose restitution curve has a continuously varying slope, by choosing the following function T in Eq. (15):

$$T=R*(T_0-\mathrm{DI})^2+150, \quad \mathrm{DI}<T_0, \quad T=150, \quad \mathrm{DI}\geqslant T_0. \tag{19}$$

We initiated a spiral wave in such a medium and found its DI (Fig. 6). We see that the spiral indeed chooses a DI close to the point where the restitution curve has slope -1 (symbol **X**). To obtain additional support for the hypothesis that in a medium with negatively sloped restitution, the spiral wave has a DI at which the slope of the restitution curve is -1, we performed a series of computations with shifted restitution curves. We see (Fig. 6, the dashed and dotted lines) that the average DI is indeed close to the point where the slope equals -1.

The rotation of a spiral wave in media with negatively sloped restitution curve studied in Fig. 6 is nonstationary, but it did not result in break-up. For restitution curves with faster changing slope, however, break-up did occur. Figure 7 shows the evolution of a spiral wave in a medium with parabolic restitution with a twofold increased coefficient R in Eq. (19). We see that the spiral completes many rotations before an instability close to the core appears [Fig. 7(a)] and grows until it causes the fragmentation of the spiral [Fig. 7(b)]. This process then spreads over the entire domain [Figs. 7(c)–7(f)].

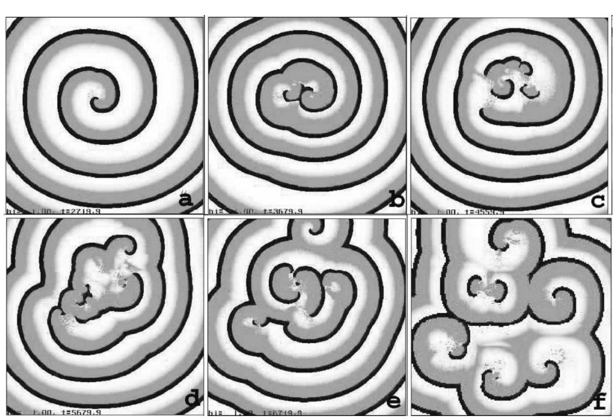

FIG. 7. Spiral breakup for negatively sloped restitution. Computations in the model (14), with the restitution curve given by Eq. (19) with $R=1/3$, $T_0=53.2$, after 25,34,44,53,63, and 204 spiral periods (medium size 800×800).

Thus, we conclude that in excitable media with negatively sloped restitution curve, there is a substantial change in behavior of spiral waves if the slope of the restitution curve becomes steeper than -1. The selection principle for the DI then becomes that the spiral wave chooses a DI at which the slope of the restitution curve is close to -1, independent of other parameters. We have also found spiral breakup if the rate of change of slope is sufficiently high.

V. DISCUSSION

This paper discusses general effects of a negatively sloped restitution curve on stability of wave propagation in excitable media. The main conclusion is that instabilities occur if the slope of the restitution curve is more negative than -1. The manifestation of this instability is different from the alternans instability which occurs if the slope of the restitution curve is positive and steeper than 1. In fact, under periodic forcing, the negative slope restitution instability is associated with a saddle-node bifurcation, and results in a monotonic increase of APD, while the alternans instability is associated with a supercritical flip bifurcation and results in APD oscillations. For a pulse circulating in a ring of excitable medium described by the delayed integral equation (6), negative restitution instability corresponds to an infinite dimensional bifurcation (as infinitely many roots of the characteristic equation cross into the right half-plane). Linear analysis has also shown that the modes with the highest spatial frequency have the largest growth factors. The numerical studies showed the similarity of this bifurcation with a subcritical Hopf bifurcation. In contrast, the alternans instability occurs via a supercritical infinite dimensional Hopf bifurcation.[15] In two-dimensional excitable media with negatively sloped restitution curve the breakup of spiral waves is in some way less pronounced than the breakup known in media with positive restitution. The main difference is that in media with negative restitution, breakup takes quite a long time to develop (tens of rotations), compared to just a few rotations in the case of positive restitution curves.[22] This may be a consequence of the effect found in this paper: shifting of spiral DI to the region where the slope of the restitution curve is -1. In fact, a slope of -1 is the value at which instability first occurs and therefore the growth rate of the instabilities is minimal, which may explain their slow development. Quite differently, in media with positive restitution, the shift of DI is absent and the spiral is usually located in the region with slope much steeper than 1,[23] which results in faster growth of instabilities and faster breakup of spirals.

Still, the effect of DI shifting to the point where the slope equals -1 might in certain situations promote spiral breakup. In fact, this shift should be observed not only for restitution curves with everywhere negative slope, but also for restitution curves whose slope is negative just in a small interval. In such a case, the shift can potentially move the spiral from the region where breakup is absent to the region of slope -1 where breakup is possible.

In conclusion, we have shown that the negatively sloped restitution curve can result in various instabilities for periodically forced systems and for one- and two-dimensional wave propagation in excitable medium. These instabilities can be expected if the slope of the restitution curve is more negative than -1.

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