



SUPEREXCITABILITY INDUCED SPIRAL BREAKUP IN EXCITABLE SYSTEMS

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Received August 1, 1995; Revised September 23, 1995

We introduce a 2D coupled map lattice model which, besides simulating the two variable FitzHugh–Nagumo reaction diffusion mechanism, accounts also for a superexcitable period. Superexcitability in the threshold dynamics of excitable media has been recently observed in experiments on cardiac tissues. By this model, we can reproduce the transition from normal cardiac behavior toward fibrillating processes in a 2D assembly of cardiac cells. The role of superexcitability results in producing two states of wave propagation and a spiral breakup mechanism in qualitative agreement with the experimental evidence of coarse and fine fibrillation in human hearts.

Excitable media (EM) have been extensively studied in various fields, as chemical reactions (e.g. Belousov–Zhabotinsky reaction), competition of biological species and propagation of infection in biological populations (for a review see [Murray, 1989; Meron, 1992]).

In particular, EM has been analyzed and simulated in order to reproduce the cardiac behavior [Khramov & Krinsky, 1977; Tyson & Keener, 1987; Winfree, 1991a] in 2D assemblies of cardiac cells.

EM dynamics is ruled by two coupled nonlinear reaction diffusion equations, for the concentrations u and v of the reacting species. Calling τ_u and τ_v the corresponding damping times and ℓ_u , ℓ_v their diffusion lengths, Kerner and Osipov [1990] have provided a complete classification of the different EM behaviors, in which the temporal and spatial scales play a fundamental role in producing stationary spatial or Turing instabilities (K -systems) [Turing, 1952], uniform temporal or Hopf instabilities (Ω -systems) or spatio-temporal or Turing–Hopf instabilities (K - Ω -systems). Such instabilities can

occur when the system shows either reaction times (Ω -systems) or diffusion lengths (K -systems) or both ($K\Omega$ -systems) very different from one another.

Furthermore, in the last decade, an extensive simulation of EM has been provided using cellular automata models (CA) [Markus & Hess, 1990], or coupled map lattices models (CML) [Barkley, 1991], or by direct numerical simulations of the partial differential equations (PDE).

With reference to the cardiac case, 2D spiral formation and spiral meandering has been observed and characterized in the FitzHugh–Nagumo (FHN) model (see e.g. [Winfree, 1991a]), while recently Karma [1993] has obtained spiral breakup in the simulation of a different two variable model.

The aim of the present paper is to study how modifications on the threshold of excitation drastically change the behavior of the medium, allowing transitions from regular dynamics to spatio-temporal chaotic regimes. According to what is observed in cardiac cells [Chialvo *et al.*, 1990a,b], we introduce a short time interval during which the

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threshold of excitation is smaller than the normal one. We call this time interval *Supernormal Period* (SNP) and we will show that its presence is of great importance in determining spiral breakups and a transition toward “fibrillating” states. Although superexcitability experimentally has been observed on a single cell in particular conditions, it seems that it can be induced *also through a purely dynamical process involving only stimulation parameters* [Vinet et al., 1990]. Here we assume that each cell of the medium under study always displays superexcitability and hence the results here presented are to be viewed as alternative possibilities of explanation of physiological phenomena as the primer of fibrillation in the heart.

We deal with the particular situation in which the considered reaction-diffusion system shows two very different time scales, so that $\varepsilon \equiv \tau_u/\tau_v$ is close to zero. The limit $\varepsilon \rightarrow 0$ of the proposed model has been already treated in [Giaquinta et al., 1994] where the evolution of the two reacting species was described by a single global variable accounting for all the relevant dynamical properties of the system. Simulation of the dynamics of such a variable was performed by a CA model.

In fact, experiments on cardiac cells suggest that ε ranges from 0.01 to 0.001 [Winfree, 1991b]. Hence, in order to account for the finite value of ε , in the following we will focus on a new CML model exploiting the effects of superexcitability on spiral stability.

Particularly, we will show how to obtain a transition between normal behavior and spatiotemporal decorrelation by slightly modifying the unstable branch of the FHN model in order to introduce the SNP in the temporal evolution of their excitability threshold.

Let us consider a reaction diffusion system described by

$$\begin{aligned}\tau_u \frac{\partial u}{\partial t} &= \ell_u^2 \nabla^2 u + f(u, v), \\ \tau_v \frac{\partial v}{\partial t} &= \ell_v^2 \nabla^2 v + g(u, v),\end{aligned}\quad (1)$$

where u and v represent, respectively the action potential and the membrane permeability of a single cardiac cell and τ_u , τ_v , ℓ_u and ℓ_v have been specified above.

Calling $\varepsilon = \tau_u/\tau_v$, $\delta = D_v/D_u$ (D_v and D_u being the associated diffusion constants defined by $\ell_s^2 = D_s \tau_s$, $s = u, v$), rescaling space and time

coordinates as

$$\begin{aligned}t &\rightarrow t/\tau_v, \\ (x, y) &\rightarrow \sqrt{\varepsilon}(x, y)/\ell_u,\end{aligned}\quad (2)$$

and assuming to have a non-diffusive v variable ($\delta = 0$), the system (1) can be rewritten as

$$\begin{aligned}\varepsilon \partial_t u &= \varepsilon \nabla^2 u + f(u, v), \\ \partial_t v &= g(u, v),\end{aligned}\quad (3)$$

where ∂_t stays for the temporal derivative.

We need to specify the analytical form of the two coupling nonlinear functions. In the piecewise-linear FHN model [Barkley, 1991], which is a reduction from the original Hodgkin and Huxley model [Hodgkin & Huxley, 1952], f and g are taken to be

$$\begin{aligned}f(u, v) &= -u(u-1)(u-u_{\text{th}}), \\ g(u, v) &= u-v,\end{aligned}\quad (4)$$

where the excitability threshold u_{th} is given by

$$u_{\text{th}} = \frac{v+b}{a},$$

a , b being suitable real parameters.

If one looks at the nullclines $f = 0$ and $g = 0$ in the (u, v) phase-space, while $g = 0$ is a straight line, $f = 0$ is composed of two stable branches ($u = 0$ and $u = 1$) plus an unstable branch ($u = u_{\text{th}}$). Since at a given time t the excitability threshold is represented by the distance between the point ($u = 0$, $v = v(t)$) lying on the unexcited branch and the point ($u = u_{\text{th}}(v(t))$, $v = v(t)$) lying on the unstable branch, this threshold monotonically decreases in the course of time during the relative refractory period (RRP) (period in which the cell is unexcited and v is relaxing toward the stable state).

In order to account for superexcitability, we modify the unstable branch as follows

$$u_{\text{th}} = \frac{v+b}{a} + C_1 \exp\left[-\left(\frac{v-v_{\text{se}}}{C_2}\right)^2\right], \quad (5)$$

where C_1 , C_2 , v_{se} are real parameters with the following meaning: v_{se} gives the location of SNP within RRP, C_2 states its duration in time and $C_1 < 0$ fixes the superexcitable threshold determining a smaller value with respect to that calculated at $v = 0$.

The shape of the nullclines $f(u, v) = 0$ and $g(u, v) = 0$ in the phase-space is shown in Fig. 1.

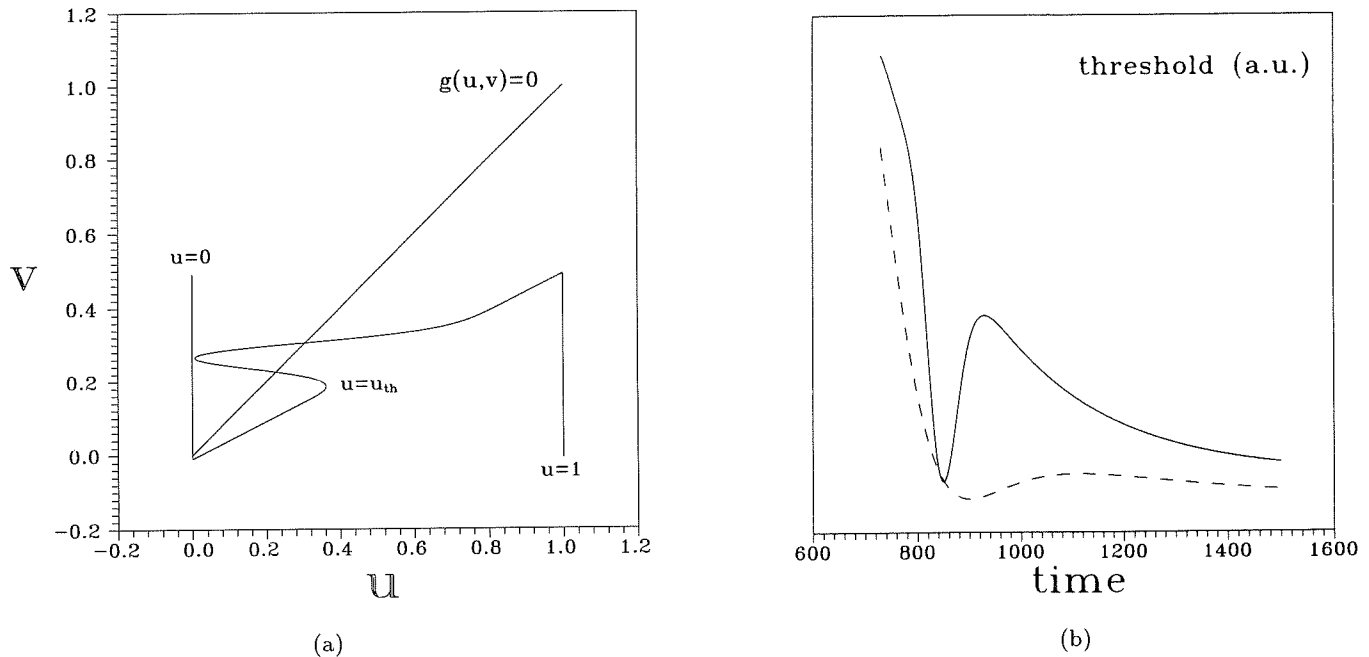


Fig. 1. (a) Nullclines $f(u, v) = 0$ and $g(u, v) = 0$ as in Eqs. (4) with excitability threshold as in Eq. (5) plotted in the phase space (u, v) . $g = 0$ is a straight line. $f = 0$ is composed by two stable branches ($u = 1$ and $u = 0$) and one unstable branch ($u = u_{th}$). $a = 0.5$, $b = 0.01$, $C_1 = -1.1$, $C_2 = 0.05$, $v_{se} = 0.55$. The two further fixed points arising from the intersection of $g = 0$ and the unstable branch $u = u_{th}$ of $f = 0$ are unstable. (b) Plots of the excitability threshold (in arbitrary units) during RRP for $\eta = 0.67$ (solid line) and $\eta = 4.67$ (dashed line). Other parameters as in (a). x axis is in units of Δt .

Here we are interested in exploring the role of SNP in determining the spiral breakup, thus we have performed a 2D simulation of the model presented above. For simulating Eqs. (3) with f and g as in (4) and (5) we used a square grid of $N \times N$ points updated with a time step Δt . We call L the physical length of the grid edge, hence $h = L/(N - 1)$ is the grid spacing, $r = \Delta t/h^2$ is the mesh ratio. Space and time are discretized so that the grid points (x, y, t) are given by $(ih, jh, n\Delta t)$, with i, j, n integers. The fields u and v at the grid point (x, y, t) will be denoted by $u_{i,j}(n)$ and $v_{i,j}(n)$.

For the Laplacian term, we have used a 5 point approximation. Defining

$$\mathcal{L}u_{i,j} = (u_{i+1,j} + u_{i,j+1} + u_{i-1,j} + u_{i,j-1} - 4u_{i,j})/h^2,$$

we can write a pair of CML approximating (3) with coupling functions as in (4) and (5) in the grid point i, j as follows

$$\begin{aligned} u_{i,j}(n+1) &= \Delta t \mathcal{L}u_{i,j}(n) \\ &\quad + \frac{\Delta t}{\varepsilon} f(u_{i,j}(n), v_{i,j}(n)) + u_{i,j}(n), \\ v_{i,j}(n+1) &= \Delta t g(u_{i,j}(n), v_{i,j}(n)) + v_{i,j}(n), \end{aligned} \quad (6)$$

where we choose $r < 0.25$ in order to assure stability for the Laplacian operator.

Furthermore, as suggested by Barkley [1991], we have used a semi-implicit formula, where the two jumps of the u variable (from unexcited to excited and from excited to unexcited state) are considered. When u is moving from the unexcited to the excited branch, or from the excited to the unexcited branch, we put in Eqs. (6)

$$f = -u_{i,j}(n)(u_{i,j}(n+1) - 1)(u_{i,j}(n) - u_{i,j,th}(n)),$$

or

$$f = -u_{i,j}(n+1)(u_{i,j}(n) - 1)(u_{i,j}(n) - u_{i,j,th}(n)).$$

With this simulation scheme, we have explored the range of parameters C_2 , v_{se} , while C_1 has been set in order to obtain always a superexcitable threshold equal to 0.6 times the rest state threshold.

We will describe two different transitions toward decorrelated states which correspond to two qualitatively different ways to obtain fibrillating states from normal behaviors. The first one (slow transition) can occur when a spiral wave takes place inside the medium, determining a locally increasing

frequency of excitation. Now, if the distance between the excited front of one arm of the spiral and the excitable front of the previous arm fluctuates in the course of time, as SNP is considered, spirals can break, generating other excitation fronts. The cascade of such a mechanism produces a globally fibrillating state of the medium, occurring quite a long time after the process has started.

The second form of transition (fast transition) leads instantaneously the medium toward fibrillating states, when a short temporal pulse (resembling the extrasystole mechanism) is delivered, without the passage through the above mentioned spiral breakup process.

The two transitions mimic the sequence of processes that cardiologists hypothesize in the primer of

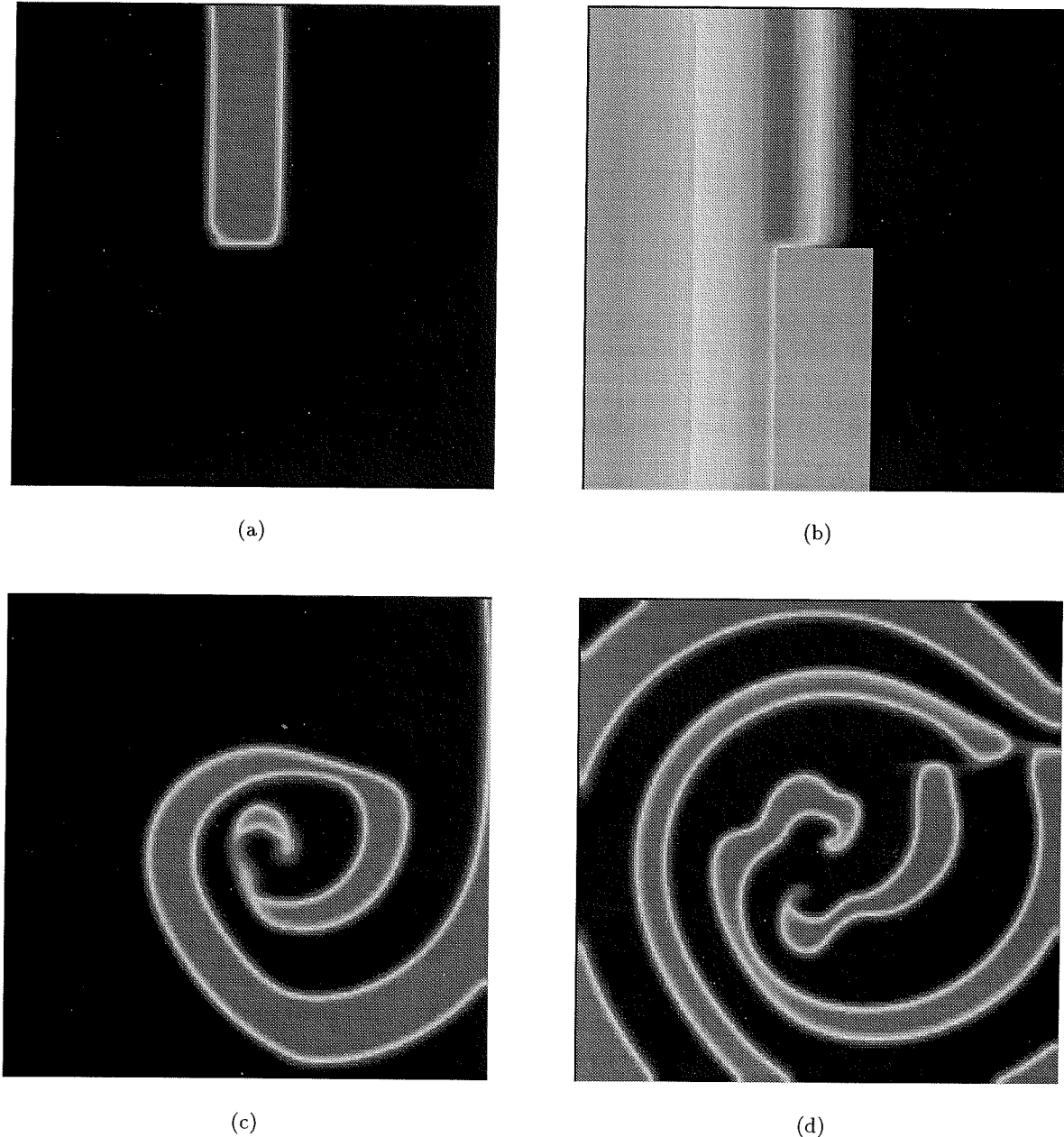


Fig. 2. Slow transition toward fibrillation. A plane wave propagating from the left-hand side of the grid encounters an obstacle in the v variable. (a) and (b) are the u and v fields at $t = 0$. As a consequence a spiral is generated ((c); $t = 500\Delta t$). The system experiences successive spiral breakup ((d) ($t = 1000\Delta t$) and (e) ($t = 1500\Delta t$)) and finally a coarse grain fibrillating process is generated ((f); $t = 5000\Delta t$). $a = 0.5$, $b = 0.01$, $C_1 = -1.1$, $C_2 = 0.035$, $v_{se} = 0.55$, $N = 200$, $L = 30$. Color stipulations for the u variable (a), (c), (d), (e), (f): red: excited state; black: unexcited state. Color stipulations for the v variable (b): black: $v = 0$; red: $v = v_{max}$; turquoise: v is relaxing to $v = 0$ during RRP; yellow: SNP.

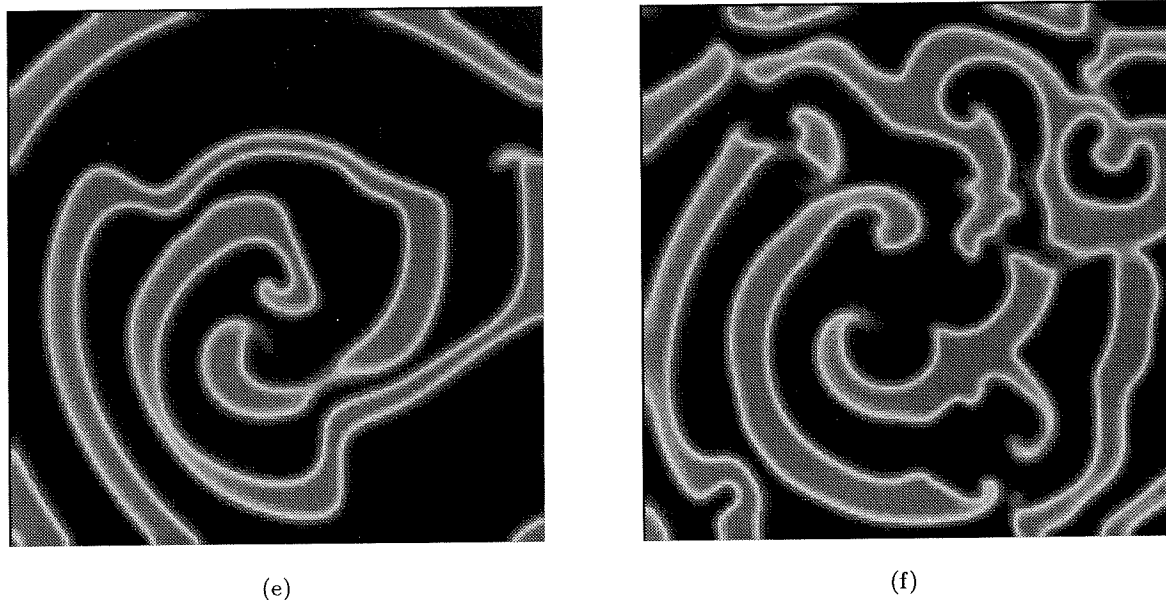


Fig. 2. (Continued)

cardiac fibrillation, and can be explained through the introduction of SNP in the FHN model.

Figure 2 contains a sequence of frames showing an example of the slow transition obtained in our model by fixing the location of SNP and by changing its duration. Namely, fixing the value of v_{se} , we have exploited the C_2 parameter range.

If C_2 is very small, the medium behaves as if SNP were not present, since the time spent by a single cell in the superexcitable state is negligible. On the contrary, when C_2 is set to be large, the threshold of excitation becomes a decreasing function of v . As a consequence, setting C_2 larger than or equal to a critical value $C_{2,cr}$, which depends on the choice of v_{se} (for parameter values as in Fig. 2, $C_{2,cr} \simeq 0.03$), the above described mechanism of cascade of spiral breakups leads the system to a final fibrillating state when $\eta \equiv \frac{C_2 - C_{2,cr}}{C_{2,cr}}$ is sufficiently small.

For larger η values, SNP and rest state are not separated by a hill in the threshold shape during RRP as it is evident by comparing the two curves plotted in Fig. 1(b). Thus the propagation is slaved to the minimum threshold which occurs just behind the wave back.

Looking at Fig. 2, it is possible to understand why the proposed mechanism is different from that obtained by Karma [1993]. In the Karma model spiral breakups occur due to a collision of two successive propagating fronts of the spiral arising from a strong variation of the distance between the two

fronts as they are constrained by an excitability threshold which depends very slightly on time during RRP.

On the contrary, here spiral breakup is due to the possibility for a single propagation front to choose between normal and supernormal propagation. Namely, when a single front gets close to SNP, part of it can fall inside and part of it can be pushed out to the rest state. The two propagating states are divided by a sensible hill in the threshold shape, so that, when part of the front is captured inside SNP, the difference in excitability threshold constrains the spiral to break.

This represents the main ingredient for having spontaneous spiral breakups. When, on the contrary, the two possible states of propagation are not divided by any hill in the threshold shape (as it arises for η sufficiently large), the propagating front strictly follows SNP and spontaneous spiral breakup cannot occur.

Notice that such a mechanism leads eventually to fibrillating states which keeps the memory of the generating process, hence it still shows spatial correlation over quite a large domain. The resulting fibrillation process gives rise to a coarse grain fibrillating state of the cardiac muscle.

On the other hand, by setting $C_2 < C_{2,cr}$ and by moving the location of SNP, it is possible to describe the second type of transition. In Fig. 3, a sequence of frames shows the evolution of a normal

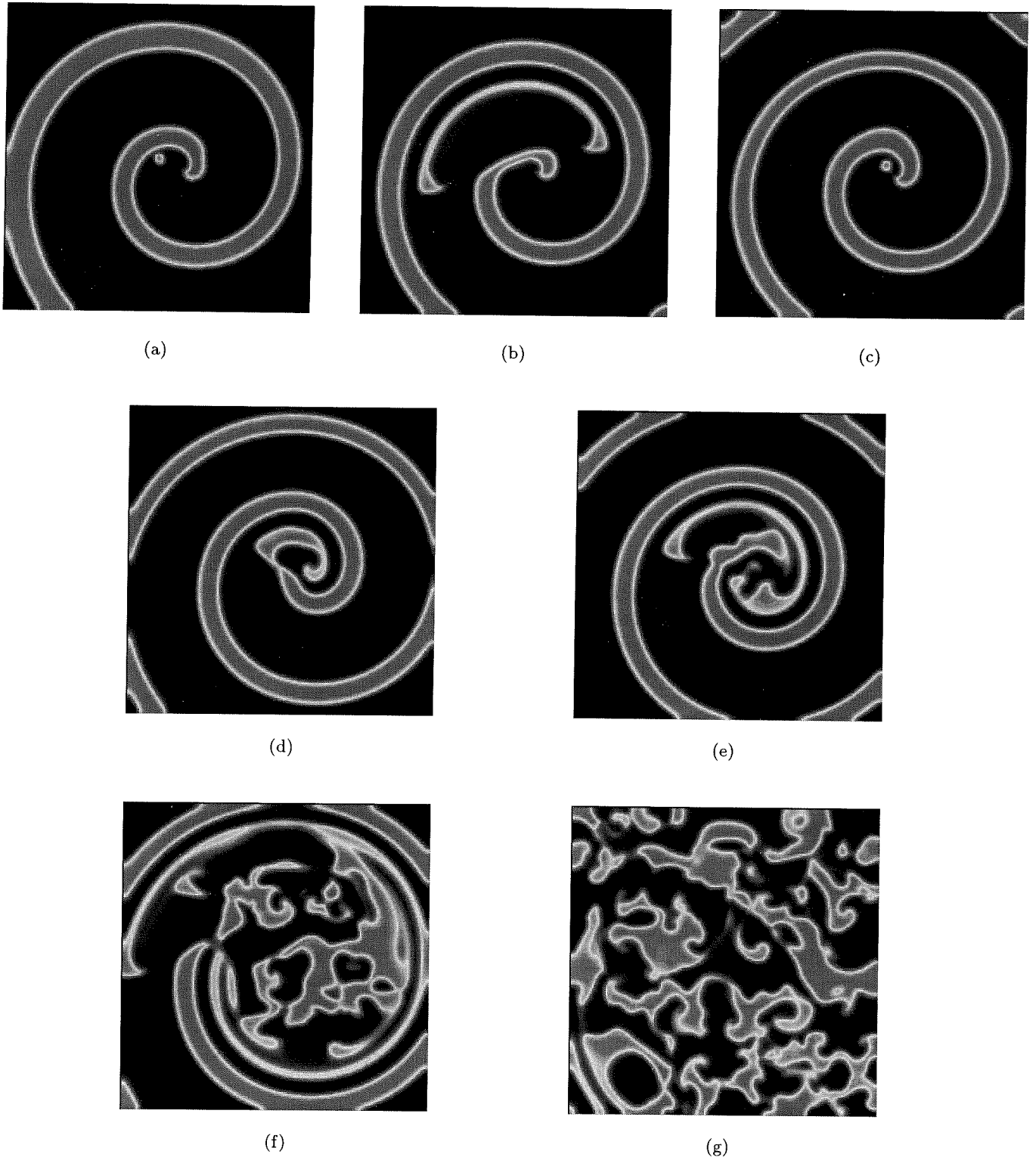


Fig. 3. Fast transition toward fibrillation. A normal spiral is generated (since $C_2 < C_{2,cr}$), then a group of cells lying close to SNP is suddenly excited. When the distance between the perturbing cells and the spiral tip is large ((a); $t = 0$), the perturbation locks to SNP and grows inside the supernormal period ((b); $t = 300\Delta t$). On the contrary, when the distance between perturbation and the spiral tip is sufficiently small ((c); $t = 0$), perturbation acts on the spiral giving rise to an instantaneous mechanism of spiral destruction ((d) ($t = 50\Delta t$), (e) ($t = 100\Delta t$), (f) ($t = 200\Delta t$)), which leads the system to a fine grain fibrillating state ((g); $t = 500\Delta t$). Same color stipulation for the u variable as in the caption of Fig. 2. $a = 0.5$, $b = 0.01$, $C_1 = -1.15$, $C_2 = 0.027$, $v_{se} = 0.575$, $N = 200$, $L = 30$.

spiral when perturbed by a sudden excitation of a group of cells lying close to the SNP. In this case, the front generated by the perturbation can either lock to SNP, hence giving rise to a second excitation front spreading inside SNP (and therefore perpendicularly to the local radius of curvature), or it can strongly perturb the spiral propagation through the mentioned two states propagation mechanism quickly destroying the spiral and the spatial correlation, thus giving rise to a fine grain fibrillating state.

These two different behaviors can occur depending on the distance between the perturbing cells and the spiral tip.

The latter mechanism seems to be in good qualitative agreement with what is experimentally observed in fibrillation induced by extrasystole pulses, where a rapid transition to spatially decorrelated patterns occurs only if the perturbing pulse arises at a suitable time with respect to the period introduced by the reentry mechanism as well as at a suitable distance with respect to the phase singularity represented by the spiral tip.

In conclusion, we have shown how a modification of the FHN model including the presence of SNP in the temporal evolution of the excitability threshold produces drastic changes in the dynamics of a 2D assembly of cardiac cells, leading to the explanation of coarse and fine grain fibrillation emerging from normal behaviors. The obtained results may stimulate further analysis on the nature of SNP, in order to fit the explored parameter ranges with real properties of cardiac cells.

Particularly, experiments on SNP should be carried out in order to exploit the role of superexcitability in producing transitions toward cardiac fibrillation and to find suitable interventions to be carried out for preventing the occurrence of spatially and temporally decorrelated patterns in the cardiac activity.

Acknowledgments

The authors acknowledge L. Tellini for useful discussions on superexcitability in cardiac cells, and G. P. Puccioni for technical assistance.

Work partly supported by EEC Contract no. CI1*CT93-0331.

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