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THE SIMPLIFIED FITZHUGH-NAGUMO MODEL WITH SLOW RECOVERY PROPERTIES AND 2-D WAVE PROPAGATION

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Abstract

A modification of the simplified FitzHugh-Nagumo equations is proposed by incorporating the recovery (restitution) properties of excitable media. The three step-wise approximation of $\epsilon(E)$ which is widely used in current publications is replaced in a new model by a four step approximation. This change is used for studying the effects of restitution properties independently of the action potential duration and refractory period on 2-D wave propagation in an isotropic matrix (made by 128x128 nodes). The transition to the new step (ϵ_4) occurs when the outward current reaches a chosen level (I_{min}). The method for fitting the model to the given experimental restitution data (obtained from isolated superfused myocardial cells) is presented. It is based on a well known exponential approximation of the restitution curve of action potential duration. Using a computer simulation on a massively parallel computer (Connection Machine), the existence of a window of vulnuerability in two dimensional excitable media is shown. These windows are characterized by the appearance of single and double spiral waves in response to premature stimulation applied inside the window. It is shown that restitution properties affect the size and location of this window. In particular, it is shown for heart muscle that under the influence of the drug Quinidine (which slows the restitution properties) the location of the window of vulnerability is shifted. The application of premature beats in this case causes the appearance of nonstationary spiral waves. Restitution properties of APD may have pronounced effect on the formation of reentrant rhythms.

Keywords: excitable media simulation, FitzHugh-Nagumo simplified model, 2-D wave propagation, heart muscle simulation, recovery properties

1 Introduction

Restitution can be defined as a property of excitable media to fully recover in time after excitation. For example, a cardiac muscle cell requires a time equal to several APD's to recover fully. If stimulation is at shorter cycle lengths, then the recovery process will result in action potentials of shorter duration.

McAllister, Noble and Tsien [1] showed that restitution in cardiac Purkinje fibers is due to the time dependent component of potassium current which decays very slowly after the completion of the repolarization phase of the action potential.

It is evident that the time course of restitution of APD directly affects the degree of dispersion of repolarization, when stimulation is applied during the process of restitution. It is known that the greater the dispersion of repolarization, the easier will be the induction of circus movement reentry [2].

Over the last 10 years, many valuable contributions have been made in wave propagation studies using the simplified FitzHugh-Nagumo (F-N) equations (see [3, 4, 5, 6]). However, the parameters of these equations, particularly, the function $\varepsilon(E)$, provide limited, if at all, time dependent changes in restitution properties. Here we present the results of a computer simulation of wave propagation in a 2-D piece of an isotropic homogeneous excitable media (128x128 nodes) with physiologic restitution properties [2]. To reproduce the restitution curves obtained in physiological experiments using the simplified FitzHugh-Nagumo equations, we use $\varepsilon(E, dI/dt, I)$ instead of $\varepsilon(E)$. All computer simulation studies were carried out using a massively parallel computer system, the Connection Machine (CM) [7] .

2 The FitzHugh-Nagumo Simplified Equations And Their Properties

The basic F-N simplified equations when reduced to dimensionless form [9] are:

$$\frac{\partial E}{\partial t} = \Delta E + F(E) - I + I_{stim} \quad (1)$$

$$\frac{\partial I}{\partial t} = \varepsilon(E)[f(E) - I] \quad (2)$$

E – membrane potential displacement between the interior and exterior of the cell

$\Delta = \partial^2/\partial x^2 + \partial^2/\partial y^2$ – two dimensional Laplacian operator

$F(E)$ – current-voltage characteristic of the fast inward current

$f(E)$ – current-voltage characteristic of slow outward current

$\varepsilon(E)$ – small parameter inversely proportional to the time constant of the slow outward current

The initial and boundary conditions used in the simulation are:

$E(x,y,0) = I(x,y,0) = 0$; $\frac{\partial E}{\partial x}\,|_B = \frac{\partial E}{\partial y}\,|_B = 0$

The piece-wise linear approximation of the functions $F(E)$, $f(E)$, and $\varepsilon(E)$ is shown on Fig. 1.

The commonly used standard set of parameters is:

$G_s = 1$; $G_f = 1$; $G_r = 30$; $E_{th} = 0.16$

$$\varepsilon = \begin{cases} \varepsilon_1 = 0.5 & \text{if } 0.00 < E < 0.01 \\ \varepsilon_2 = 0.01 & \text{if } 0.01 \leq E \leq 0.95 \\ \varepsilon_3 = 0.5 & \text{if } E > 0.95 \end{cases} \tag{3}$$

The relationships between the action potential duration (APD), refractory period (R), and the model parameters G_s , G_f, and ε are presented in [3] for the model without diffusion (point model). These dependencies reflect qualitatively the essential properties of heart muscle cells, but do not correctly express the restitution properties.

The normalized restitution curve for the F-N simplified model with standard parameters is compared to data obtained in physiological experiments in Fig. 2. The comparison shows the marked disagreement of the model and experimental data. We introduced the normalized form of the restitution curve to facilitate the comparison of computer simulation data obtained in dimensionless form and data from physiological experiments. Usually, the restitution curve is presented as a function: $APD = f(DI)$, where APD designates the duration of the action potential caused by the second stimulus applied after the specified diastolic interval (DI). The normalized representation of the restitution curve (RC) has the form:

$$APD_2/APD_1 = h(DI/APD_1)$$

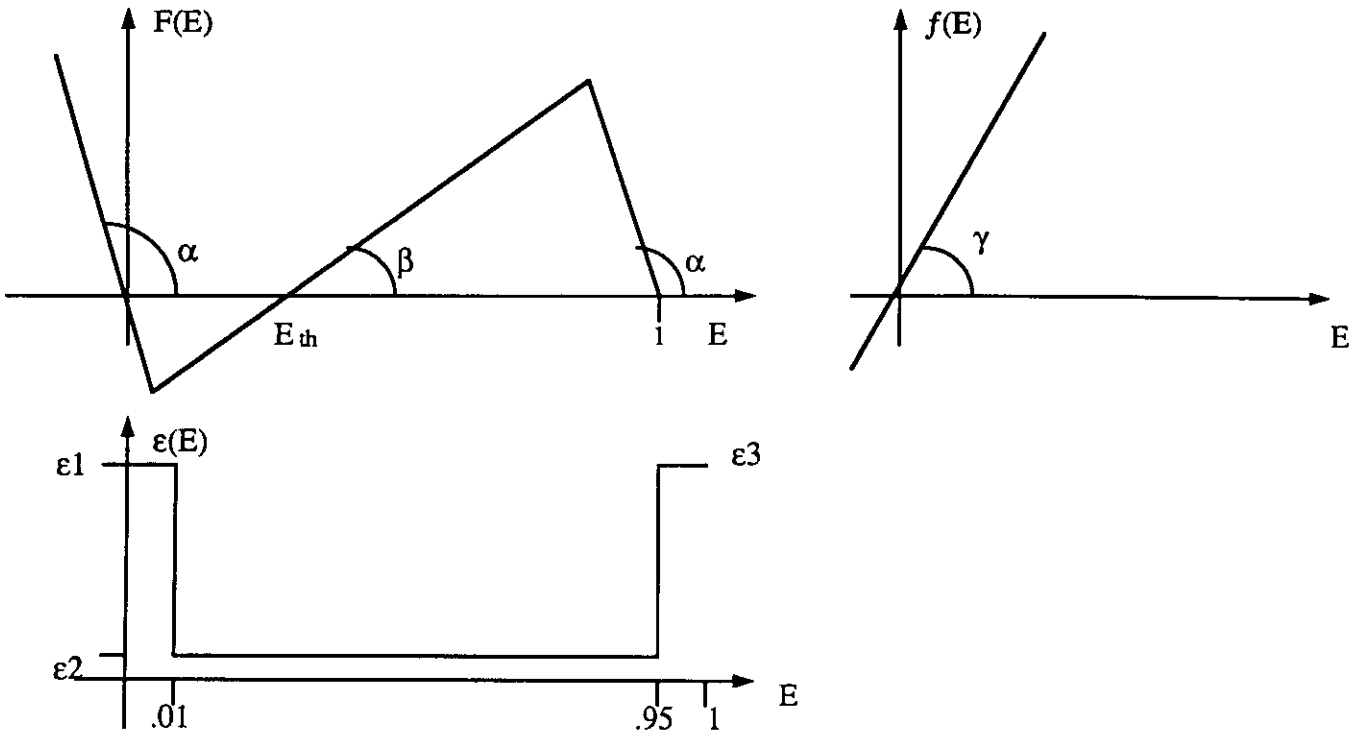


Figure 1: The piece-wise linear approximation of functions $F(E)$, $f(E)$, and $\varepsilon(E)$. $\tan\alpha = G_r$; $\tan\beta = G_f$; $\tan\gamma = G_s$; E_{th} – the threshold potential.

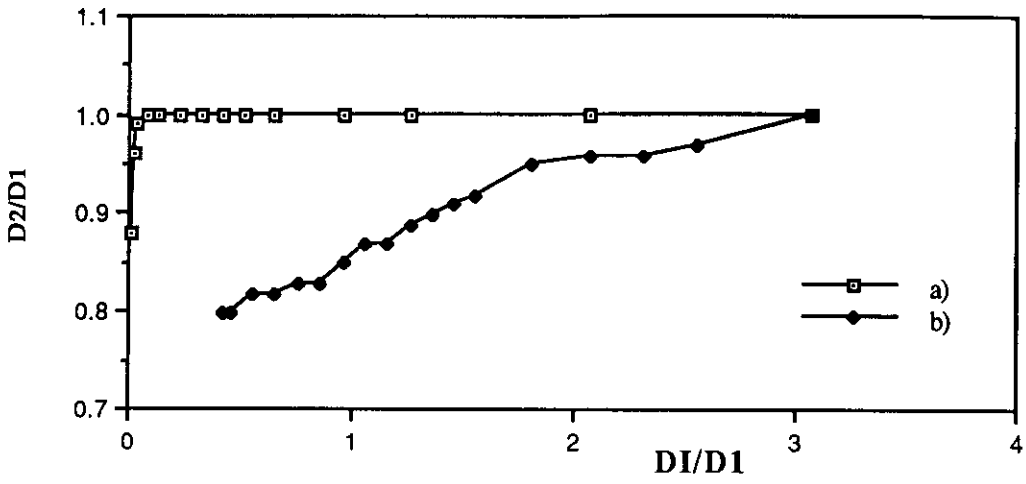


Figure 2: The normalized restitution curve for a) the FitzHugh-Nagumo simplified model with standard set of parameters [3], and b) canine heart muscle tissue in normal conditions(control), obtained from experimental data [2].

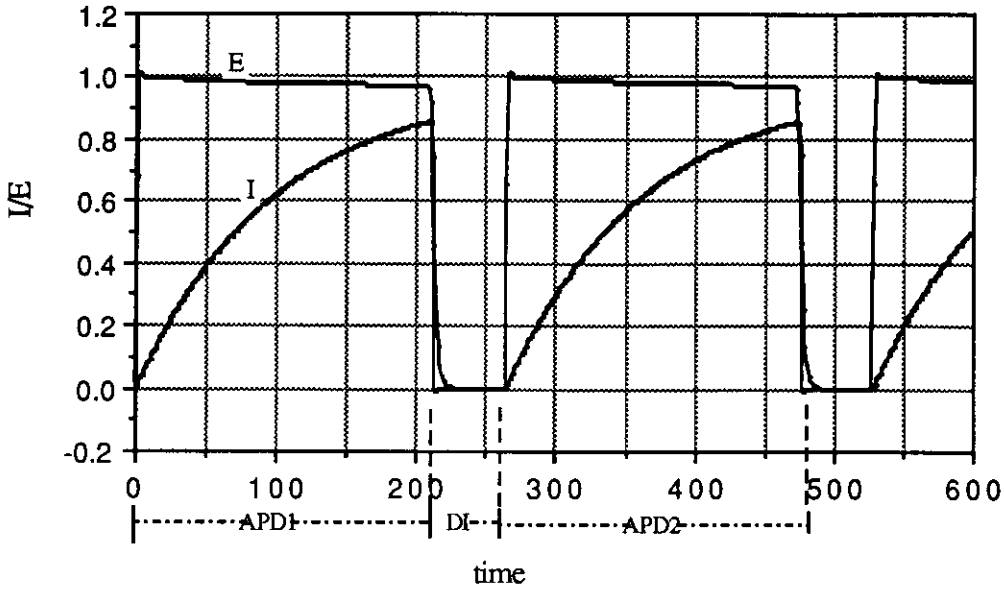


Figure 3: The $E(t)$, and $I(t)$ for short diastolic interval. $DI/APD_1 = 0.234$; $APD_2/APD_1 = 1$ (in Pertsov model [3]).

where APD_1 is the duration of the AP obtained after the full completion of the recovery processes. Hereafter $APD_1 = D_1$ and $APD_2 = D_2$.

The transients of E and I in a cardiac cycle with a small DI are shown on Fig. 3 for the standard parameters of the F-N simplified model. One can see that the outward current I reaches zero just after the AP returns to the resting potential. Thus, a stimulus applied after a short DI produces a subsequent AP approximately of the same duration as the previous one, because the time course of the restitution is very fast (almost instantaneous). We therefore modified the characteristics of the transient outward current $I(t)$, by slowing its time course of recovery, i.e. by causing recovery of this current to occur over a much extended period of time.

3 Some Approaches To Restitution Curve Fitting

One method of modifying the transient outward current $I(t)$ is to use two values of ϵ dependent on the sign of dI/dt:

$$\varepsilon(dI/dt) = \begin{cases} \varepsilon_1 & \text{if } dI/dt > 0 \\ k\varepsilon_1 & \text{if } dI/dt \leq 0 \end{cases} \tag{4}$$

This approach was proposed by Zykov [8] to change the refractory period independently of the AP duration in eq.(1,2) with the standard set of parameters. The increase in the the refractory period to longer than the duration of the AP contradicts the normal properties of heart muscle tissue. Changing the parameter k also changes the restitution properties simultaneously with the refractory period. The use of only one parameter (k) does not permit the required shaping of $I(t)$ to fit restitution properties, nor does it permit the separate investigation of the effect of refractory and restitution properties on impulse propagation.

Our approach is to use a more complicated logical function to control the changes of the small parameter ε . Namely :

$$\varepsilon = \begin{cases} \varepsilon_1 & \text{if } E < 0.01 \text{ and } dI/dt > 0 \\ \varepsilon_2 & \text{if } E \geq 0.01 \text{ and } dI/dt > 0 \\ \varepsilon_3 & \text{if } I > I_{min} \text{ and } dI/dt \leq 0 \\ \varepsilon_4 = k\varepsilon_2 & \text{otherwise} \end{cases} \tag{5}$$

This leads to a piece-wise exponential approximation of the current function $I(t)$.

The values for ε_1, ε_2, and ε_3 are chosen to satisfy the requirements of the given action potential duration and its refractory period. ε_4 is chosen to meet the required restitution properties. The proper value of ε_4 and I_{min} can be matched to the experimental restitution curve by computer simulation trial and error or by a direct analytical approach. The normal restitution curve is commonly approximated by the formula [9]:

$$D = D_\infty(1 - e^{-\beta T}) \tag{6}$$

Here $D = APD_2$ and D_∞ = the plateau APD after an infinitely long DI; β is a constant; and $T = APD_1 + DI$.

From (6) follows:

$$-ln(1 - D/D_\infty) = \beta T \tag{7}$$

Thus the relationship between $-ln(1 - D/D_\infty)$ and T is linear, and the experimental data can be represented by a straight line, which can be obtained by the least-squares method of approximation. The results of this approximation are shown in Fig. 4 for two sets of experimental data [2] from normal tissue and tissue intoxicated by Quinidine.

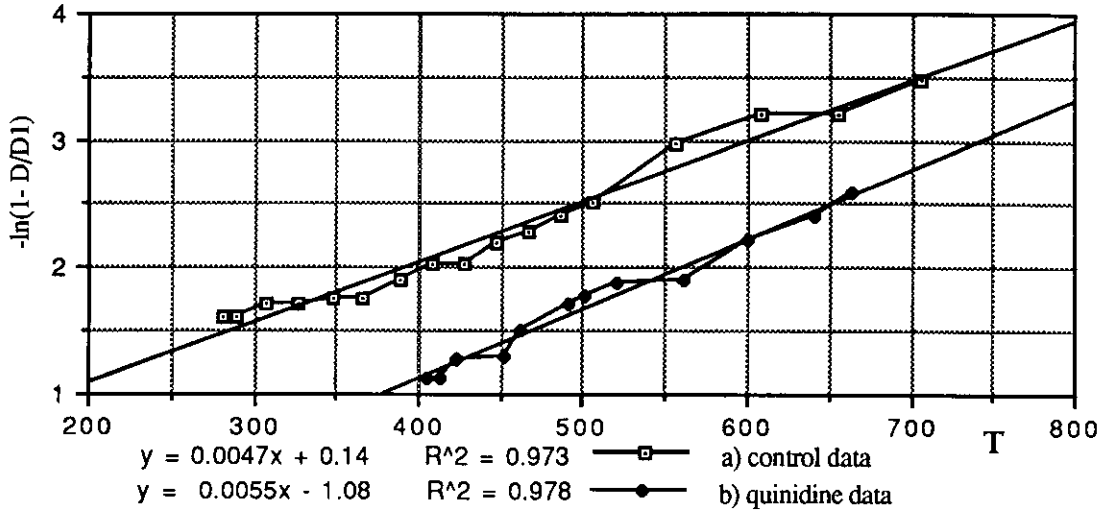


Figure 4: Determination of ε_4 from experimental data a) control data $(D_\infty)_{exp} = 198[ms]$; $(D_\infty)_{sim} = 50[units]$; $(\varepsilon_4)_c = 0.018$, b) Quinidine data $(D_\infty)_{exp} = 242[ms]$; $(D_\infty)_{sim} = 50[units]$; $(\varepsilon_4)_q = 0.024$.

The slope of the line obtained in this manner directly shows the values of β . To reproduce the restitution properties of the experimental data in the computer model, it is necessary to choose ε_4 such that:

$$\varepsilon_4 = \beta \frac{(D_\infty)_{exp}}{(D_\infty)_{sim}} \tag{8}$$

Where $(D_\infty)_{exp}/(D_\infty)_{sim} = m$ is a scale factor.

The results of restitution curve(RC) fitting for heart muscle tissues under normal conditions (control) and with the tissue exposed to Quinidine are presented in Fig. 5a and Fig. 5b, respectively. In both cases the close agreement with experimental data was obtained by making $\varepsilon_4 = \beta m$ and choosing an appropriate value for I_{min}. The maximum and RMS error in the region $0.5 < DI/APD_1 < 3.0$ for the control data are respectively: 0.03 and 0.0066, and for the Quinidine are: 0.038 and 0.010. It was found that a small decrease of the parameter G_f improved the fitting of the Quinidine experimental data. This approach also gives a slight increase in the refractory period in comparison with AP duration.

The temporal changes of $E(t)$ and $I(t)$ in Fig. 6 correspond to the point in Fig. 5a with $DI/D1 = 0.2$. Here the restitution properties are shown distinctly.

4 The Influence of Restitution Properties on Wave Propagation in 2-D Tissue

The study of the influence of heart muscle cell restitution properties on excitation wave propagation was carried out using the modified FitzHugh-Nagumo equation of the form of (1),(2), and (5). The equations were implemented in a 128x128 grid of nodes on the Connection Machine (CM-2) [7]. It is worthwhile to begin with two simple cases: propagation of waves with rectilinear and circular fronts. These two idealized cases facilitate the separation of the effect of curvature from the effect of the recovery processes. For both cases we will consider the propagation of two waves generated successively with a specified time interval and the propagation of repeated waves with a specified period.

For rectilinear and circular waves, the initial excitation of the tissue produces a wave which propagates with a velocity and a wavelength strictly corresponding to the cell's parameters, its coupling coefficients and the characteristics of the front curvature. If the next wave is generated after a time

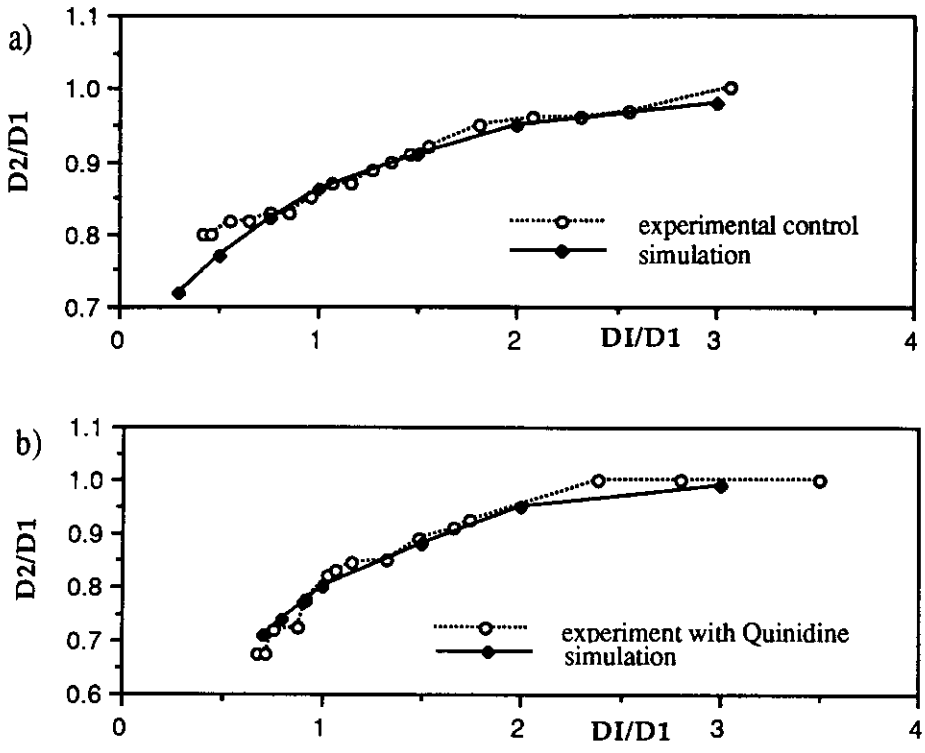


Figure 5: Comparison of restitution curve experimental data [2] to simulation results a) normal tissue (control) b) tissue under Quinidine influence. The model parameters that provide the best coincidence with experimental data are: For control RC: $G_r = 30, G_f = 0.7, G_s = 1.0, \varepsilon_1 = 0.5, \varepsilon_2 = 0.02, \varepsilon_3 = 0.5, \varepsilon_4 = k\varepsilon_2 = 0.018, I_{min} = 0.35$ For RC with Quinidine: $G_r = 30, G_f = 0.7, G_s = 1.0, \varepsilon_1 = 0.5, \varepsilon_2 = 0.02, \varepsilon_3 = 0.5, \varepsilon_4 = k\varepsilon_2 = 0.024, I_{min} = 0.90$. Note that beyond the left portion of the graph is the refractory period.

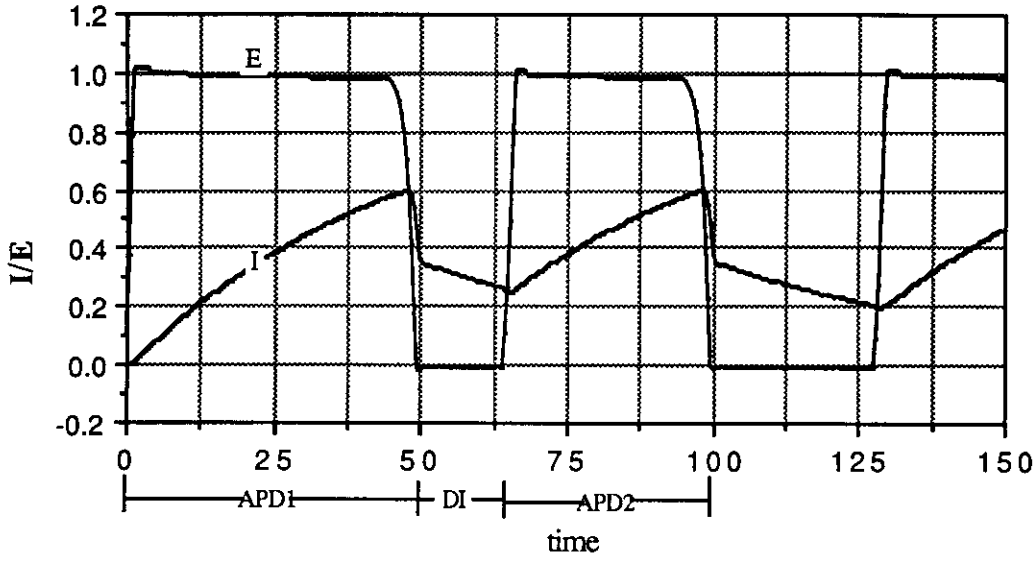


Figure 6: The transients of $I(t)$ and $E(t)$ in the 4 ϵ model. Model parameters are the same as for the control model in Fig. 5a. $DI/APD_1 = 0.27$; $APD_2/APD_1 = 0.71$

interval when all recovery processes are complete, no changes are observed in the propagation of the second wave .

However, when the next wave is generated after a time interval when the recovery process is not yet complete, the wave will propagate through recovering areas of slow outward current (I) left by the first wave. Thus, each cell will be excited with nonzero initial conditions with variable (I) values which grow with decreasing diastolic interval. This decreases the duration of the generated AP as well as the speed (θ) and wavelength (λ) of the propagated waves. The corresponding relationships obtained in the course of computer simulations of rectilinear wave propagation are shown in Fig. 7a and 7b . They cover the situations with slightly, normally and increasingly pronounced restitution properties, corresponding to the standard F-N model, the ε_4 F-N model fitted to experimental control data, and the ε_4 F-N model fitted to Quinidine data [2]. In the case of circular wave propagation, the θ and λ values change with wave radius. Therefore, θ and λ are averaged over the range from the first appearance of a wave to its disappearance (Fig. 8a and 8b).

In the case of periodic excitation with a cycle shorter than the full recovery period, it is possible to observe the phenomena of wavelength and speed alternation which resembles the well-known rhythm alternation in cell activity [10] . The corresponding computer simulation results are presented in Fig. 9 and 10 for rectilinear propagation.

It is easy to observe that the wavelength and speed of propagation are decreased by a decrease of stimulation period T. There exists some critical value of $T = T_{min}$ when only odd waves can propagate (Fig. 9b). Under the influence of Quinidine, this phenomenon is more distinctly pronounced (Fig. 10b). In the case of circular wave propagation, similar relationships were obtained as a function of average values of wavelength and speed of propagation. In Fig. 11 an example of wavelength alternation is shown.

We conclude that restitution properties lead to the appearance of nonuniformities in the excitable characteristics (in time and space) of the otherwise uniform tissue when periodic stimulation occurs during the recovery process of the outward current. This fact gives a new insight into formation and propagation of waves with more complicated forms, in particular, spiral wave reentry.

Gulko and Petrov [11] and independently Winfree [12] were the first to show by computer simulation that spiral waves can arise and propagate in originally homogeneous excitable media (for heart muscle and chemical reactions). The results in [11] were obtained with the physiologically based

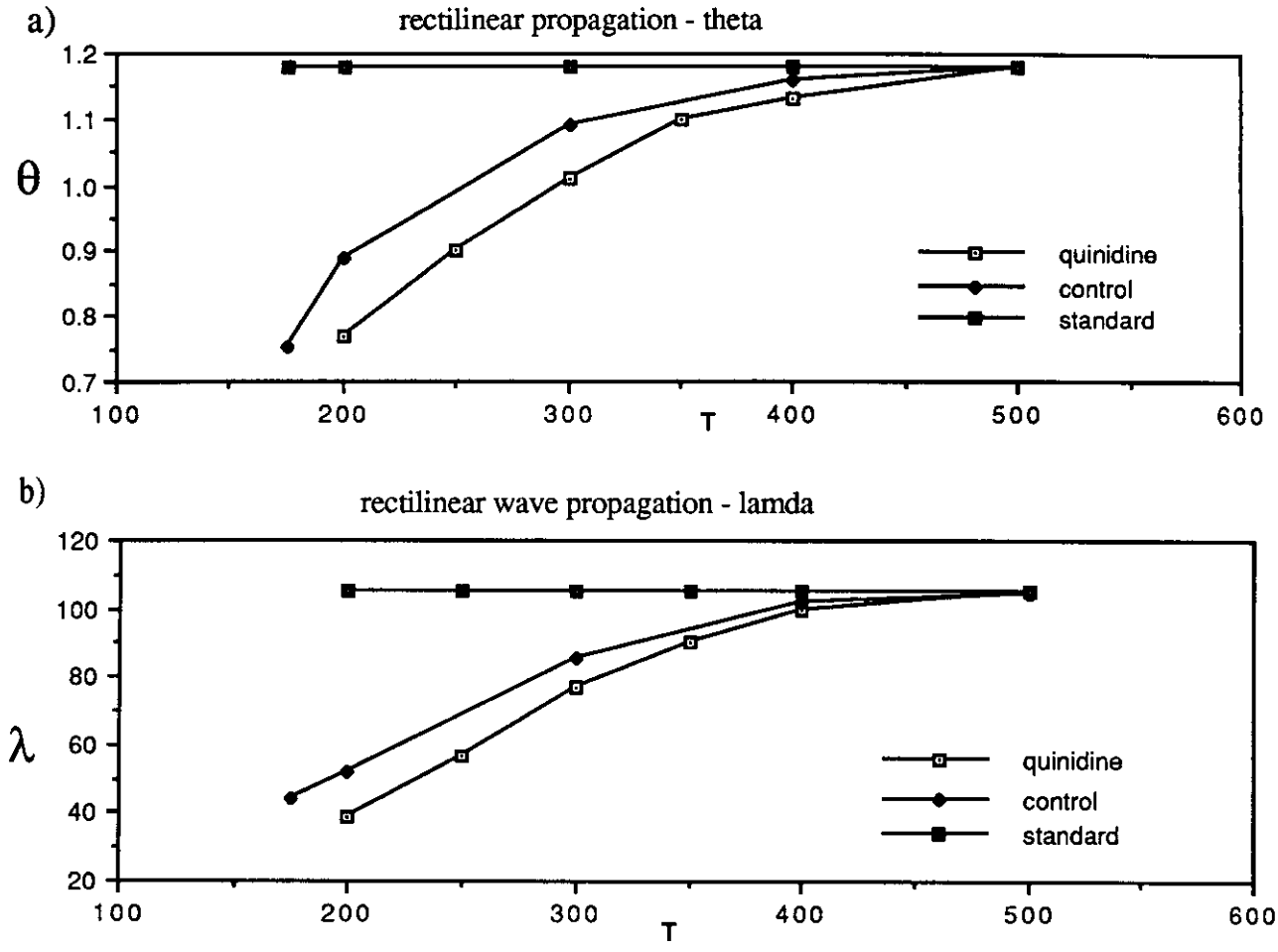


Figure 7: The relationships of speed θ and wavelength λ to period T between two successive excitations of rectilinear waves. a) $\theta(T)$ b) $\lambda(T)$.

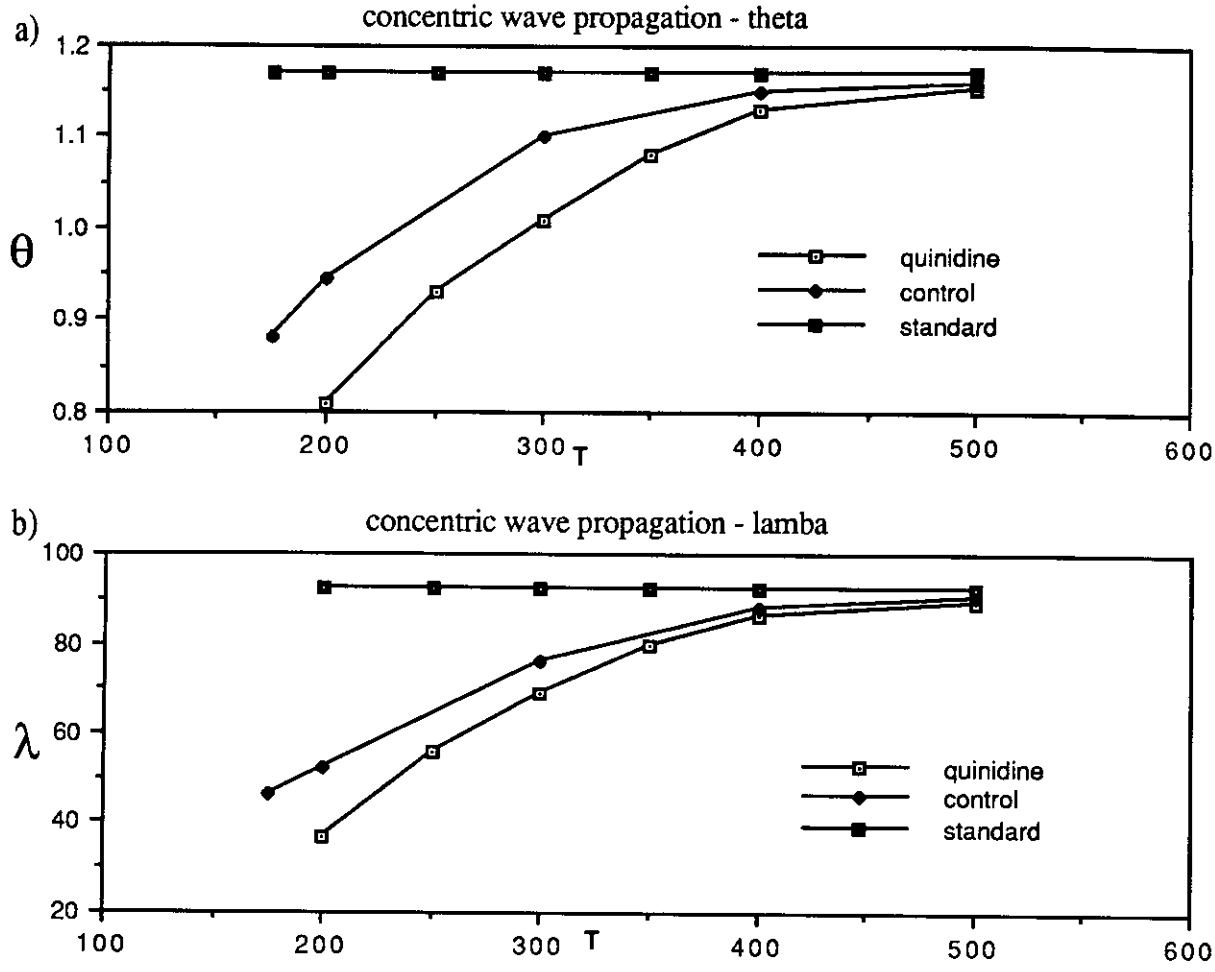


Figure 8: The relationships of speed θ and wavelength λ to period T between two successive excitations of concentric waves. a) $\theta(T)$ b) $\lambda(T)$.

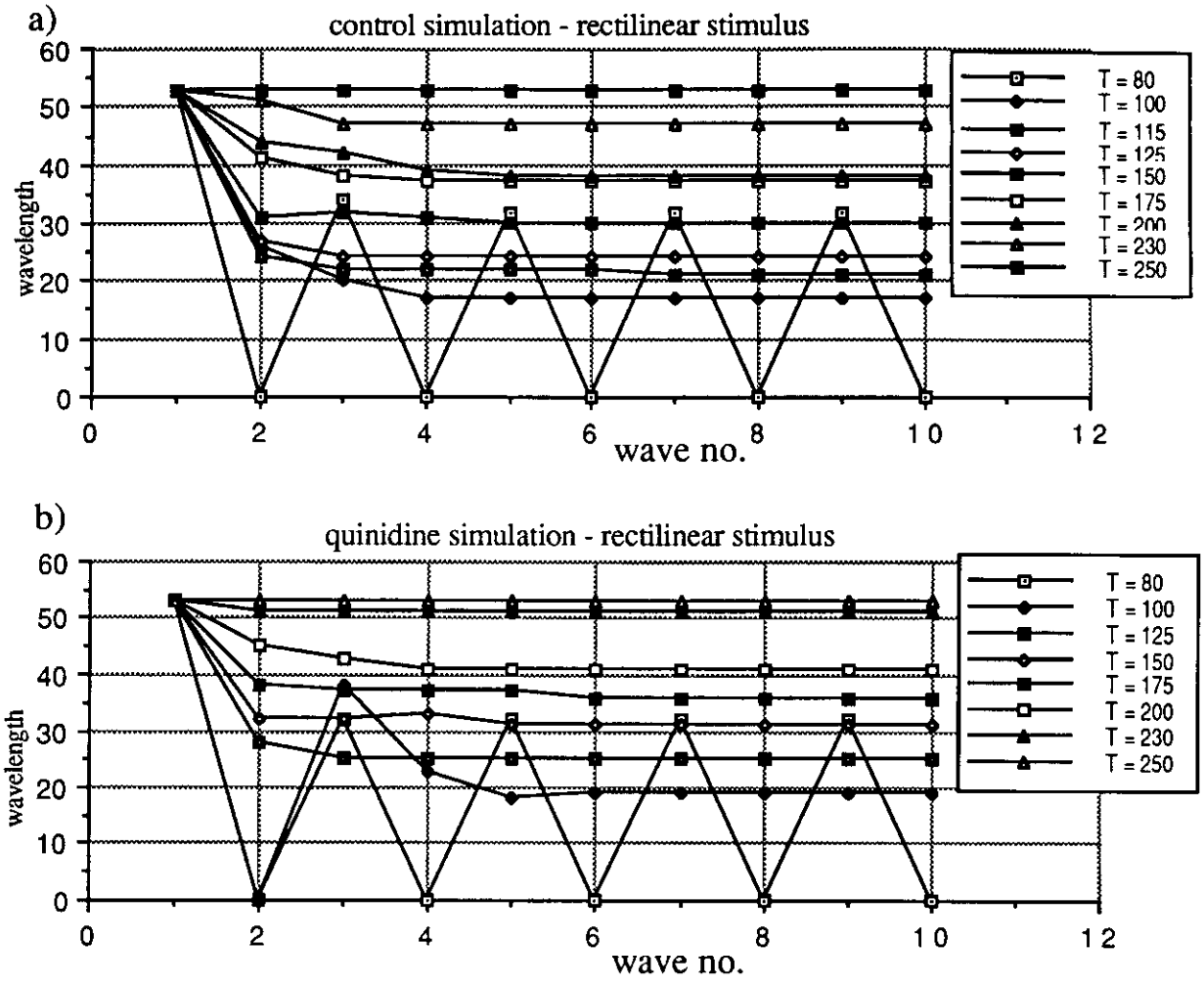


Figure 9: Alternation of wavelength with periodic generation of rectilinear waves. a) with normal (control) restitution b) with Quinidine influenced restitution properties.

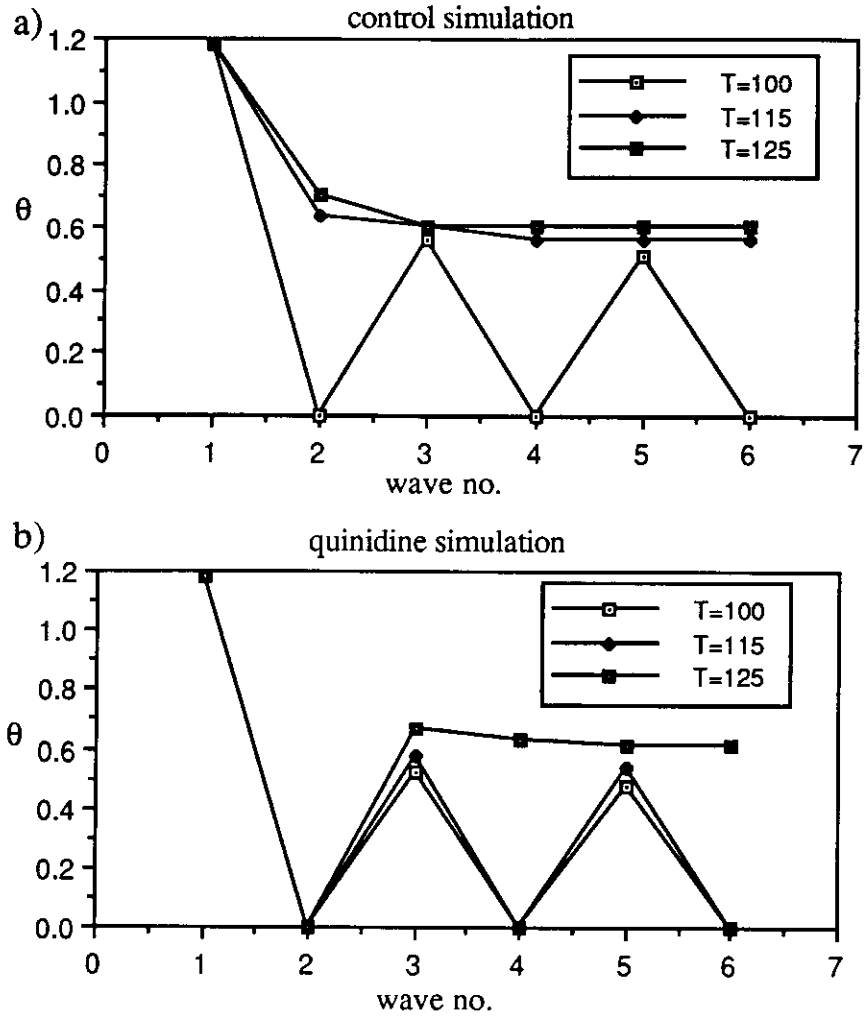


Figure 10: Alternation of propagated wave speed with periodic generation of rectilinear waves. a) Normal (control) restitution properties, b) Quinidine restitution properties.

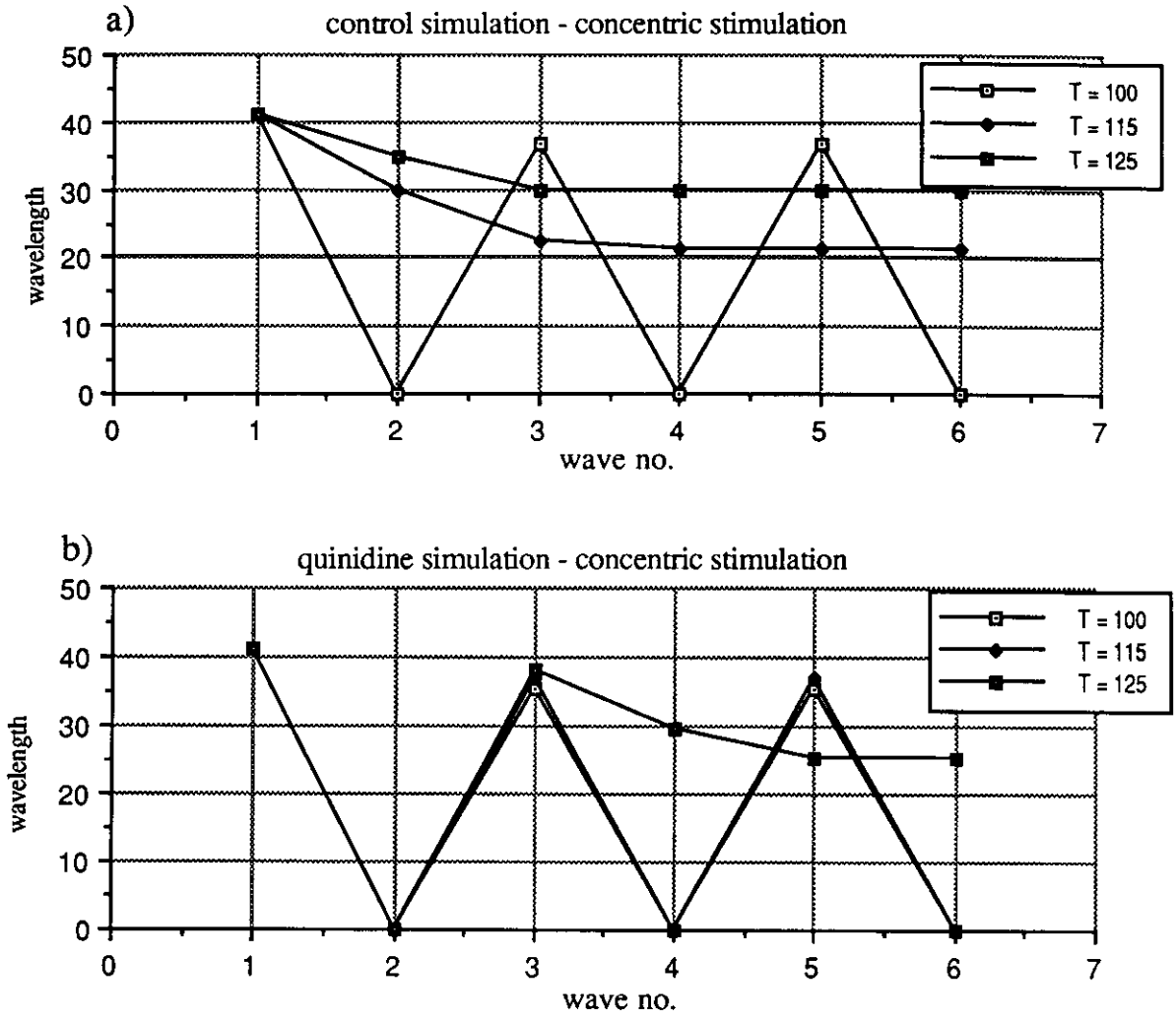


Figure 11: Alternation of wavelength with periodic generation of concentric waves. a) with normal (control) restitution b) with Quinidine influenced restitution properties.

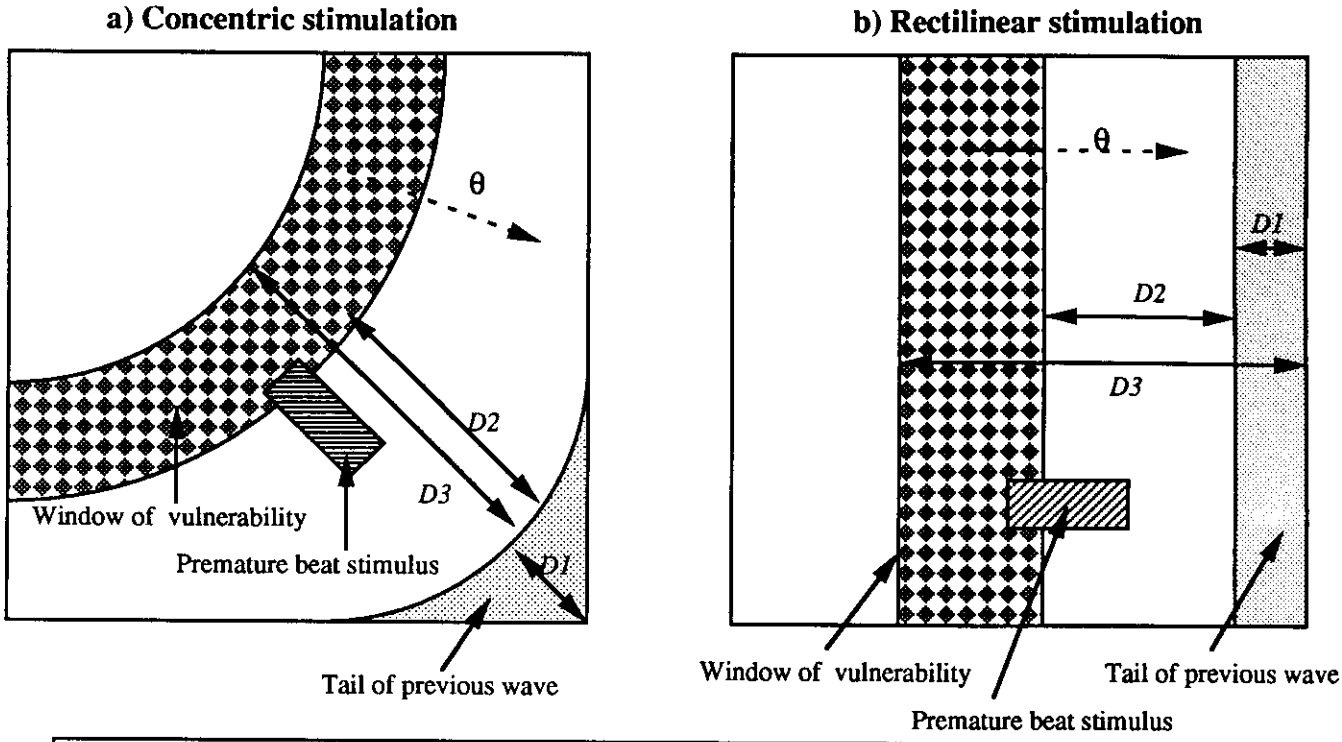
simplified point model which possessed the restitution properties. Much later, Chramov [13] obtained qualitatively similar results with a simplified F-N model which had only negligible restitution properties. Using model [11] it was impossible to separately show the effect of restitution properties on spiral wave propagation.

Our modification of the F-N equations makes it possible to observe the effect of restitution properties on spiral wave generation and propagation. We found that premature beats can generate single and double spiral waves rotating in different directions with either weak or strong restitution properties. The restitution properties determine the size and location in space (the corresponding times and the levels of the outward current) of the area in the wake of the propagated wave where the application of appropriate excitations causes the spiral waves. This area we will term *the window of vulnerability* (WV) by analogy with that defined by Quan and Rudy in [14] where one dimensional AP propagation appeared as a result of unidirectional block in ring-shaped excitation tissue. The major distinctions from [14] of the WV in our case are: WV is two dimensional in space, has a geometry which is similar to that of the previous wave (because there is no diffusion of the current I), and the stimulation inside the WV leads to the appearance of double and single spiral wave circulation (see also Winfree [15, 16]). It is also useful to define the WV in terms of the value of the decreasing outward current .

The WV for rectilinear propagated waves has a rectangular form. The area between the two vertical edges (one which is close and one which is far from the wake of the wave tail) is the space where double spiral waves are generated in response to the proper stimulation. The area of single spiral wave generation is located near the horizontal edges of the WV. The corresponding computer simulation data are presented in Fig. 12b. With the decrease of ε_4 (from $k > 1$ to $k < 1$) the WV displaces in the direction opposite to the previous wave front.

The size and location of the WV for the case of circular wave propagation are presented in Fig. 12a.

The double spiral waves generated as a result of stimuli applied in the vicinity of the near and far WV edges for rectilinear wave propagation are shown in Fig. 13a and 13b. Here we simultaneously display the potential and outward current distributions in space and time (Fig. 14). A single spiral wave generated in normal tissue with rectilinear wave propagation is shown in Fig. 15. Fig. 16 shows single and double spiral waves generated by a premature beat in heart tissue with normal restitution properties. The



Window dimensions	Concentric stimulus	Rectilinear stimulus
Control simulation	D1 - 20	D1 - 5
	D2 - 67	D2 - 67
	D3 - 86	D3 - 89
Quinidine simulation	D1 - 20	D1 - 5
	D2 - 72	D2 - 78
	D3 - 90	D3 - 102

Note: The tail (10x1) section of the premature stimulus must lie completely within the window of vulnerability for a spiral wave to occur. The premature stimulus dimensions are 10x20 units. All dimensions correspond to simulation grid dimentions (128 x 128 grid).

Figure 12: Geometry of the window of vulnerability for rectilinear and concentric stimulation.

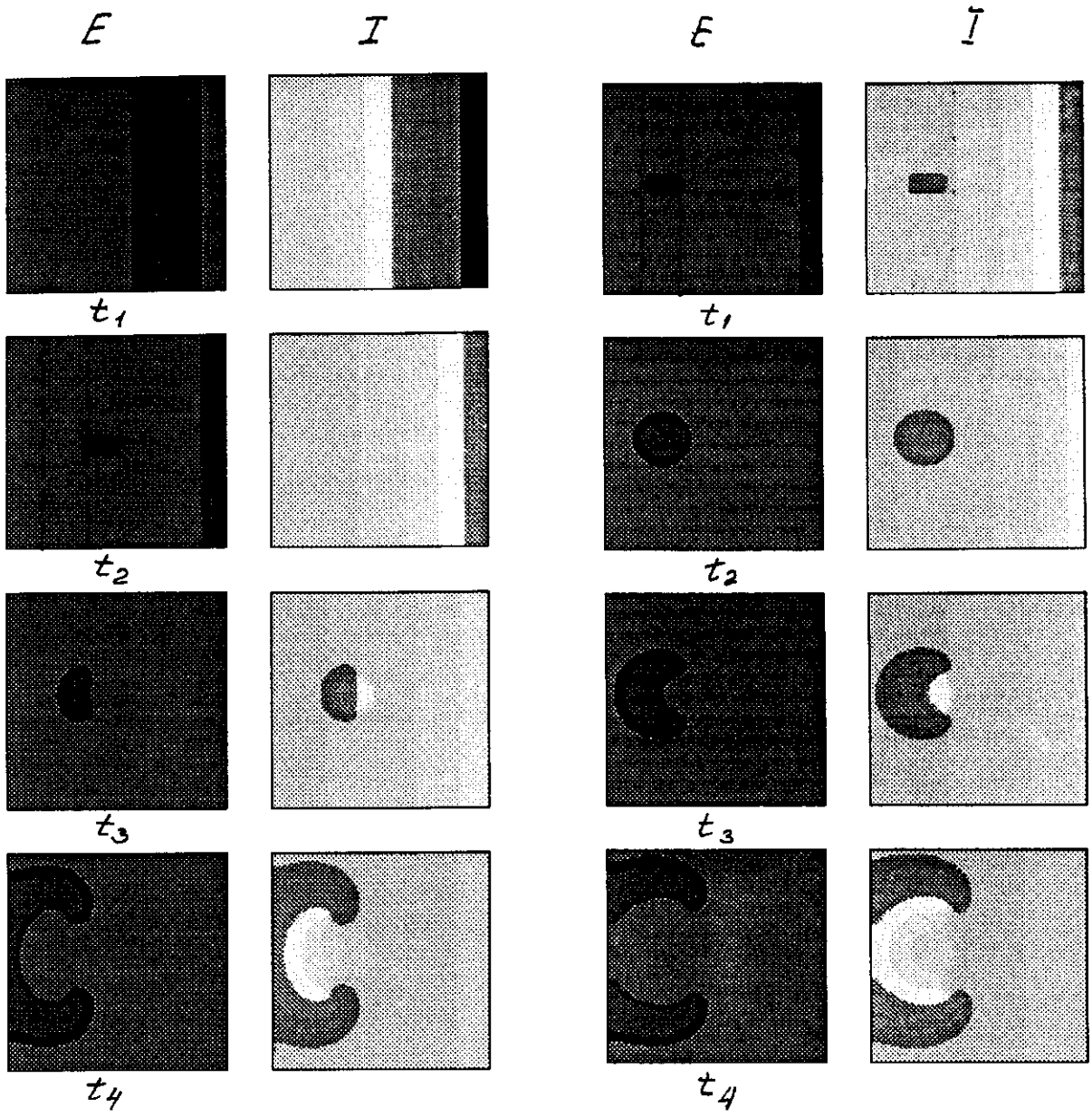
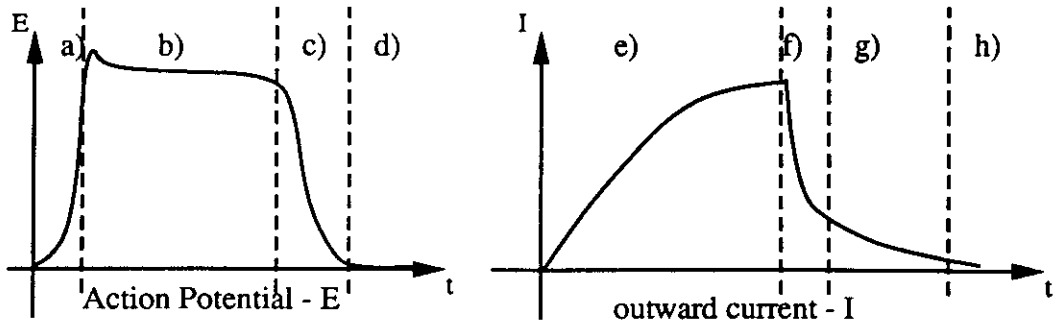


Figure 13: Example of double spiral waves generated by the application of a premature beat in the window of vulnerability of heart muscle tissue with normal restitution properties. The initial wave propagation is rectilinear and to the right of the figure. Note that the left column of pictures in the time series a) and b) is the action potential and the right column is the current distribution. The dashed line indicates the WV edges within which the premature beat is applied. a) The premature beat is applied to the edge of the WV closest to the previous wave's tail. Simulation times are here and in later figures (in dimensionless units): $t_1 = 75$, $t_2 = 104$, $t_3 = 125$, $t4 = 172$. b) The premature beat is applied at the far end of the WV. $t_1 = 106$, $t_2 = 119$, $t_3 = 133$, $t_4 = 161$.



a) black
b) dark grey
c) black
d) grey

e) grey
f) white
g) grey
h) black

Figure 14: Grey level (color) designations for action potential E and current I phases.

computer simulation results for double spiral waves in tissue with restitution properties influence by Quinidine are shown in Fig. 17.

When the stimulation is applied inside the WV, the generated spiral waves have different properties depending on the distance from the right edge of the WV and on the rate of current I decay (value of k). That is, if the restitution properties are weak ($k >> 1$) as in [6], the generated spiral waves quickly become stationary — their tip or tips (in the case of double spiral waves) are rotated along a circle of predetermined radius with a constant angular velocity. In the case of normal restitution properties (control), the stimulation applied close to the right edge of WV causes the appearance of nonstationary spiral wave propagation and when applied near the left edge produces a stationary one. When the tissue of the restricted area is under the influence of Quinidine (which leads to an increase of AP duration and of slope of the RC) only the nonstationary spiral waves propagation could be observed within the restricted area. Depending on the restitution properties of the tissue, the tip of nonstationary spiral waves could meander along curves forming closed or open loop complex curves resembling cycloids. This was shown earlier in [17] using an approximate analytical approach combined with computations and further studied later in [18] by pure computer simulation with a simplified F-N point model where the changes of refractory period were tightly connected with those of restitution properties.

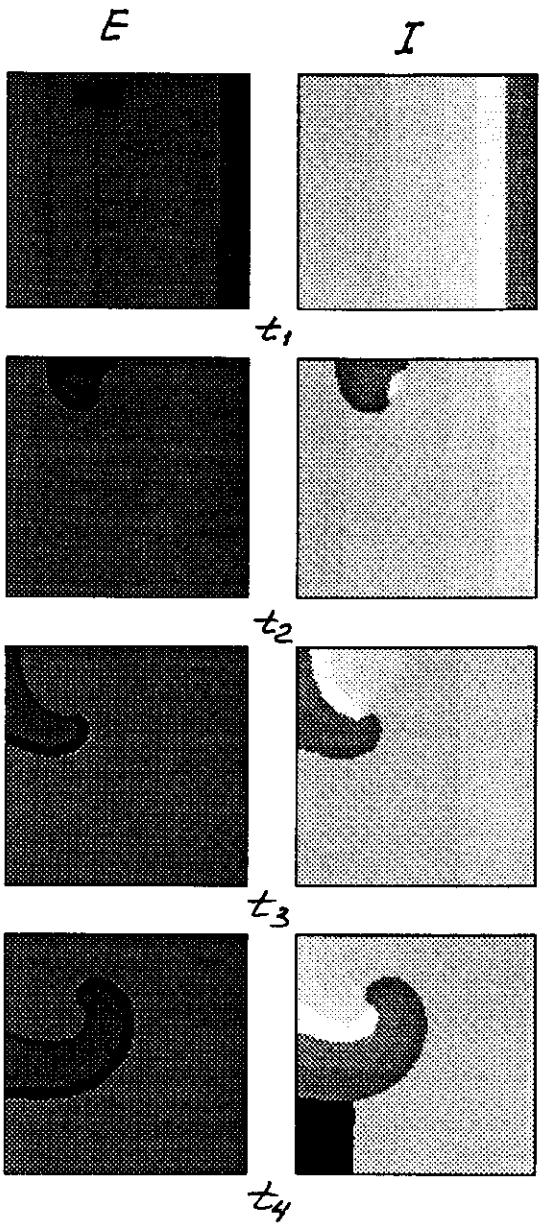


Figure 15: Example of a single spiral wave generated (in normal heart tissue with rectilinear wave propagation) by the application of a premature beat in the center of the WV. $t_1 = 106$, $t_2 = 125$, $t_3 = 161$, $t_4 = 185$.

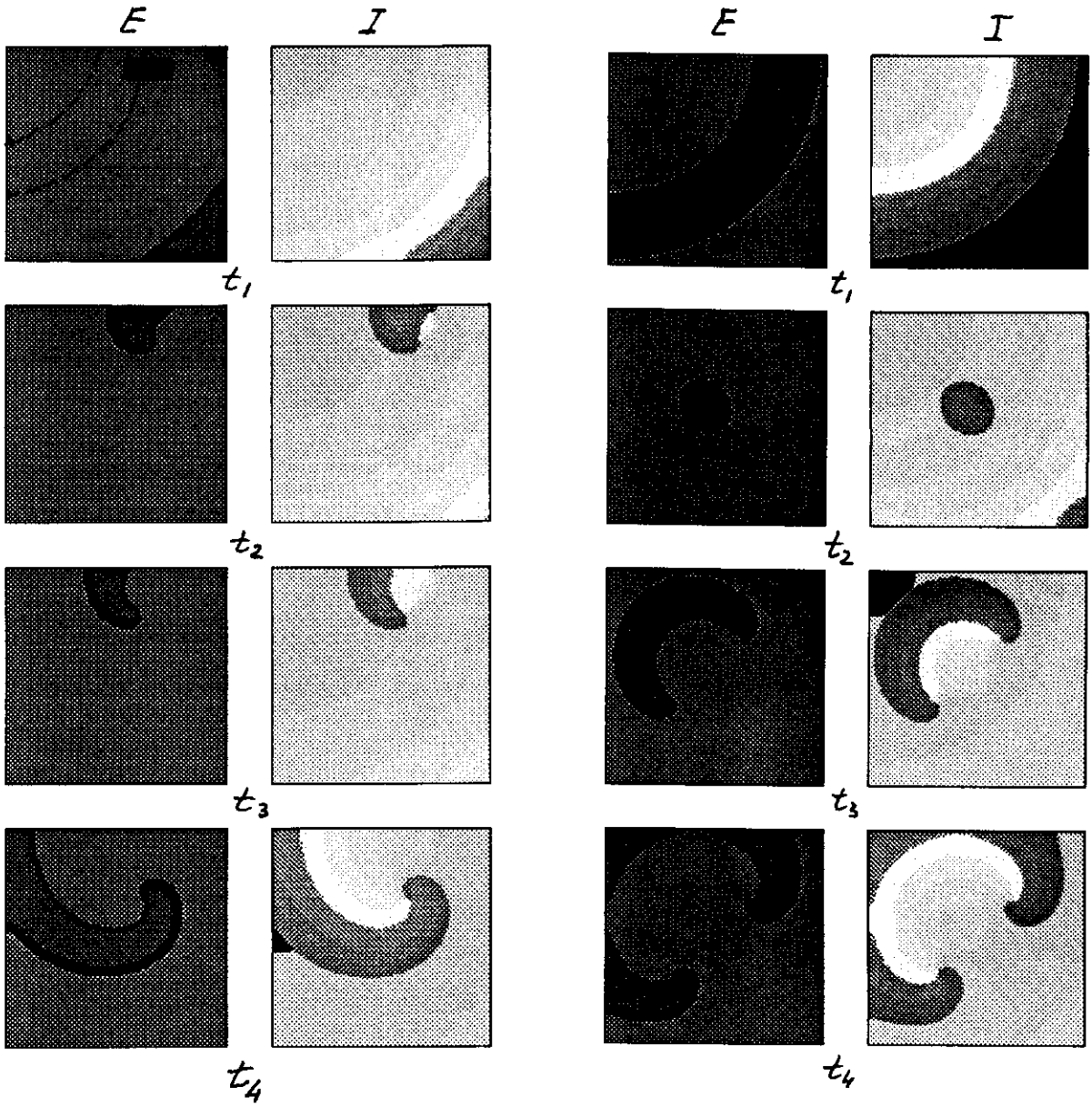


Figure 16: Generation of spiral waves in normal heart tissue with concentric wave propagation. The concentric wave was initiated by an excitation stimulus in the upper left corner. a) Single spiral wave caused by a premature beat applied in the upper center of the WV. $t_1 = 131$, $t_2 = 150$, $t_3 = 162$, $t_4 = 210$. b) Double spiral waves caused by a premature beat at the far edge of the central area of the WV. $t_1 = 86$, $t_2 = 142$, $t_3 = 180$, $t_4 = 206$.

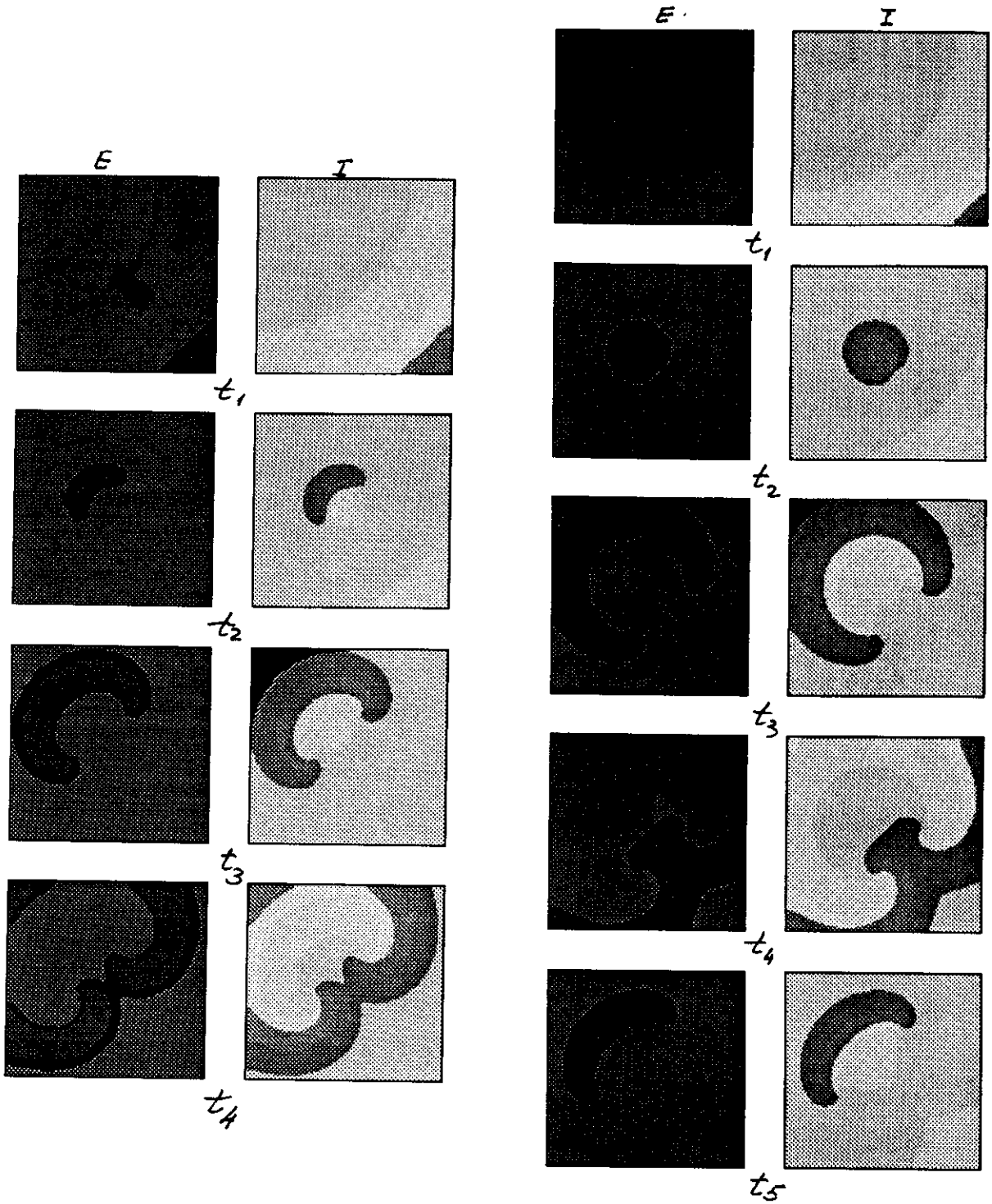


Figure 17: Time series of generation and propagation of double spiral waves in heart muscle influenced by Quinidine. Initial wave propagation is concentric. a) Premature beat is applied at the near edge of the central area of the WV. $t_1 = 133$, $t_2 = 165$, $t_3 = 192$, $t_4 = 220$. b) Premature beat is applied at the far edge of the WV. $t_1 = 140$, $t_2 = 159$, $t_3 = 194$, $t_4 = 233$, $t_5 = 285$.

In [18] the restitution properties were chosen arbitrarily. By contrast, in our computer simulation the restitution properties could be changed without noticeable changes in the refractory period duration and could be adjusted to fit the given experimental data. The display of the residual outward current distribution shows the tendency of spiral waves to propagate in the direction in which the instantaneous minimum of this current is located.

In the light of these observations it is necessary to verify the U- shape dependencies of radius of tip wave circulation on the duration of the AP and the dispersion equation previously obtained in the course of simulation [19] and theoretical studies [17, 20].

5 Conclusion

The restitution properties of excitable media have an important role in the genesis and the properties of wave propagation. In order to investigate the influence of restitution properties independently of the refractory period, we propose to modify the function $\varepsilon(E)$ in the simplified F-N model. A method is developed for fitting the model to given experimental restitution data (from heart muscle). These results provide more realistic simulations without substantial complications of the simplified model. The proposed display of the fast and slow variable (E and I) distributions simultaneously is very useful in understanding wave propagation in the presence of recovery processes.

The results presented in this paper show that the restitution properties affect (while all other characteristics remain unchanged):

1. The development of alternation of speed and wavelength during periodic stimulation at high rates.

2. The existence in excitable media of a window of vulnerability to premature stimulation which can result in the formation of single and double spiral waves.

3. The size and location of the window of vulnerability, and the transition from stationary to non-stationary propagation of induced spiral waves.

In particular, we have shown that Quinidine induced changes in restitution properties cause a shift in the location of the WV, and a transition to non-stationary spiral wave propagation.

These qualitative results for heart muscle require future validation with a point model which reflects physiological properties better than the simplified F–N model (for example Beeler – Reuter's [21]).

The previous theoretical and simulation studies of excitable media focused on its refractory properties. These studies lead to the dispersion equation and the U-shaped relationship between the radius of the tip of spiral wave circulation and the duration of the action potential. In light of the results presented here, these previous findings should be verified in relation to the real restitution properties.

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