



## A Simple Two-variable Model of Cardiac Excitation\*

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**Abstract**—We modified the FitzHugh–Nagumo model of an excitable medium so that it describes adequately the dynamics of pulse propagation in the canine myocardium. The modified model is simple enough to be used for intensive 3-dimensional (3D) computations of the whole heart. It simulates the pulse shape and the restitution property of the canine myocardium with good precision.

In 1952, Hodgkin and Huxley proposed the first quantitative mathematical model of wave propagation in squid nerve [1]. This work has had a great impact on modeling of various nonlinear phenomena in biology. On the basis of this model Noble in 1962 developed the first physiological model of cardiac tissue [2]. Further studies in this field resulted in the development of several realistic ionic models of cardiac tissue which were derived from voltage clamp and patch clamp experiments [3–6].

Ionic models accurately reproduce most of the basic properties of cardiac tissue. These include the depolarization and repolarization phases of the action potential, restitution properties, dynamical changes in ionic concentration, etc. Such models are suitable for modeling solitary myocytes, myocardial fibers and even synthytium, which may consist of up to tens of thousands of myocardial cells [7].

However, ionic models are not very suitable for modeling many important problems, such as the problem of re-entrant cardiac arrhythmias. The main difficulty is that small space and time steps are required to integrate ionic models, whereas re-entry occurs only in quite large spatial regions of cardiac tissue. For example, the usual value for the spatial integration step for the Beeler–Reuter model is about 0.1 mm [8]; this means that at least one million cells are needed to represent each cubic centimeter of cardiac tissue.

To avoid computational difficulties researchers often use other models of cardiac tissue, especially the two-variable FitzHugh–Nagumo (FHN) models [9, 10]. These models permit analytical estimations and are numerically effective for studying 2D and 3D pulse dynamics in the heart [11–14]. Although successfully describing qualitative aspects of excitation propagation, they fail to simulate several quantitative parameters of cardiac tissue such as the shape of the action potential and restitution properties of the tissue.

Restitution of cardiac tissue shows how duration of action potential, *APD*, depends on cycle length, *CL* [15]. In myocardium there is quite a strong dependence: for example, ventricular *APD* in canine myocardium changes from 330 ms at *CL* = 5000 ms to 150 ms at *CL* = 350 ms [15]. Such a shortening of action potential is very important, especially at the initial moment of formation of cardiac arrhythmia when the heart rate suddenly increases. The restitution should also be taken into account for those processes which involve changes in the period of heart excitation. This occurs, for example, during a drift of a vortex, which

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results in a Doppler shift [16]; in the process of overdriving anti-arrhythmic stimulation, when there is an interference of external high frequency sources with the inherent frequency of arrhythmia [17]. Recent theoretical investigations show that restitution property is important for the appearance of instabilities of wave propagation in quasi 1D loops [18], and in generation of fibrillation-like 2D patterns due to the spiral break-up [19].

Several attempts have been made to improve FHN models so that they would describe quantitative parameters of cardiac tissue such as the shape of action potential [20] and the restitution property of cardiac tissue [21–23]. These modifications did in fact improve the models. However, in our opinion, the modified models involve unnecessarily complicated mathematical representation of the equations which makes them difficult to use for qualitative analysis. Some of these models use step-wise functions, which may reduce the stability of numerical computations.

In this paper we propose a simple model which simulates the restitution property of cardiac tissue, adequately represents the shape of action potential and can be used effectively in computer simulations, particularly, in whole heart modeling. The proposed model is as simple as the original FHN model [9]. Note that in our approach we do not try to simulate internal cell dynamics, i.e., to mimic adequately all the membrane currents which occur in a cardiomyocyte. We have tried to design simple equations which describe properly the integral characteristics of the propagation pulse in canine myocardium. In other words our approach is to solve ‘the inverse problem’.

Our model consists of two equations describing fast and slow processes:

$$\begin{aligned}\partial u/\partial t &= \partial/\partial x_i d_{ij} \partial u/\partial x_j - ku(u-a)(u-1) - uv \\ \partial v/\partial t &= \varepsilon(u, v)(-v - ku(u-a-1))\end{aligned}\quad (1)$$

where  $\varepsilon(u, v) = \varepsilon_0 + \mu_1 v/(u + \mu_2)$ ,  $k = 8$ ,  $a = 0.15$ ,  $\varepsilon_0 = 0.002$ ,  $\mu_1$  and  $\mu_2$  are the parameters to be fixed later and  $d_{ij}$  is the conductivity tensor accounting for the heart tissue anisotropy.

The model involves dimensionless variables  $u$ ,  $v$  and  $t$ . The actual transmembrane potential  $E$ , and time  $t$  can be obtained with the formulae:

$$E[\text{mV}] = 100u - 80 \quad t[\text{ms}] = 12.9t[t.u.].\quad (2)$$

In this case the rest potential  $E_{\text{rest}}$  is  $-80$  mV and the amplitude of the pulse is 100 mV. Time was scaled assuming  $APD$  measured at the level of 90% of repolarization,  $APD_0 = 330$  ms [15].

The nullclines of our model are shown in Fig. 1. The right-hand side of equation (1) is similar to that of the original FHN model [9]. The nonlinear function for the fast variable  $u$  has a cubic shape as in Ref. [9]. In contrast to the FitzHugh paper, we used the term  $uv$  instead of  $v$ . This improves the description of the shape of action potential (Fig. 2) [24, 25]. Particularly, in the model (1) the left branch of the nullcline  $\{u_t = 0\}$  does not enter the region where  $u < 0$ . This prevents the system from becoming super-repolarized, which occurs typically in the original FHN model, but does not exist in real myocardium. In contrast to the linear nullcline of the slow variable,  $\{v_t = 0\}$  [9], we used a quadratic term in our model. Because of this,  $\{v_t = 0\}$  in a large region is parallel to the nullcline of the fast variable,  $\{u_t = 0\}$ . Such nullcline geometry is more appropriate for the heart tissue, than the linear nullcline  $\{v_t = 0\}$  which is normally used (compare with experimentally observed nullclines [24]). The dependence of  $\varepsilon$  on  $u$  and  $v$ , which is absent in the original FHN model, allows us to tune the restitution curve to that experimentally observed by adjusting the parameters  $\mu_1$  and  $\mu_2$ .

Elharrar and Surawicz [15] show that the shape of the restitution curve in the canine

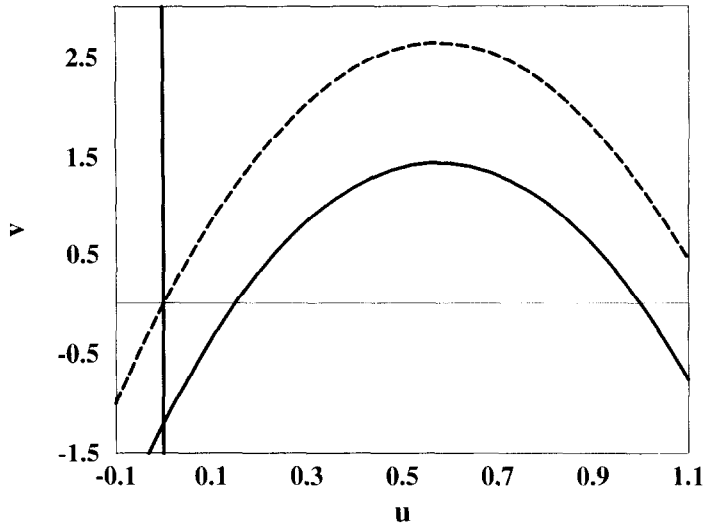


Fig. 1. Nullclines for equation (1):  $\{u_t = 0\}$  is depicted with a thick solid line;  $\{v_t = 0\}$  – with a thick dashed line.

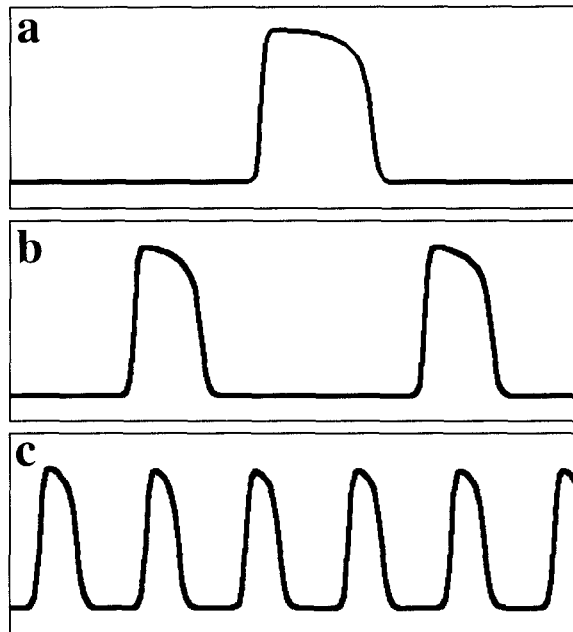


Fig. 2. Pulse profile depending on the period of stimulation,  $T$ : (a) free pulse ( $T = \infty$ ,  $APD = APD_0$ ); (b)  $T = 2.5APD_0$ ; (c)  $T = APD_0$ .

myocardium can be well approximated by the formula:

$$APD = CL / (aCL + b)$$

where  $APD$  denotes the duration of the action potential, and  $CL$  is the cycle length. This formula can be rewritten in a dimensionless form convenient for mathematical analysis:

$$1/apd = 1 + b/cl$$

where  $apd = APD/APD_0$ ,  $cl = CL/APD_0$ , and  $APD_0$  denotes  $APD$  of a free propagating pulse.

We computed several restitution curves for different values of parameters  $\mu_1$ ,  $\mu_2$  and found that the best fit was at  $\mu_1 = 0.2$ ,  $\mu_2 = 0.3$ . In Fig. 3 we plot the various experimental curves obtained by [15] and the restitution curve obtained in our model. It can be seen that the shape of the restitution curve in our model is the same as in the experiments: it is well approximated by a straight line  $1/apd = k_1 + k_2/cl$ . The values of coefficients  $k_1$  and  $k_2$  in our model are  $k_1 = 1.016 \pm 0.0043$  and  $k_2 = 1.059 \pm 0.011$ . The parameter  $k_2$ , the slope of the line, is responsible for the restitution properties at small  $CL$ .  $k_1$  reflects the restitution properties at large  $CL$ . These values are very close to those measured experimentally [15]. The small error in parameters  $k_1$  and  $k_2$  in our model (estimated by the method of least squares) shows that the dependence of  $1/apd$  on  $1/cl$  is linear with good accuracy, as it is in the experiments. We believe that the restitution curve obtained in our model can be considered as acceptable in simulations of restitution properties of cardiac tissue.

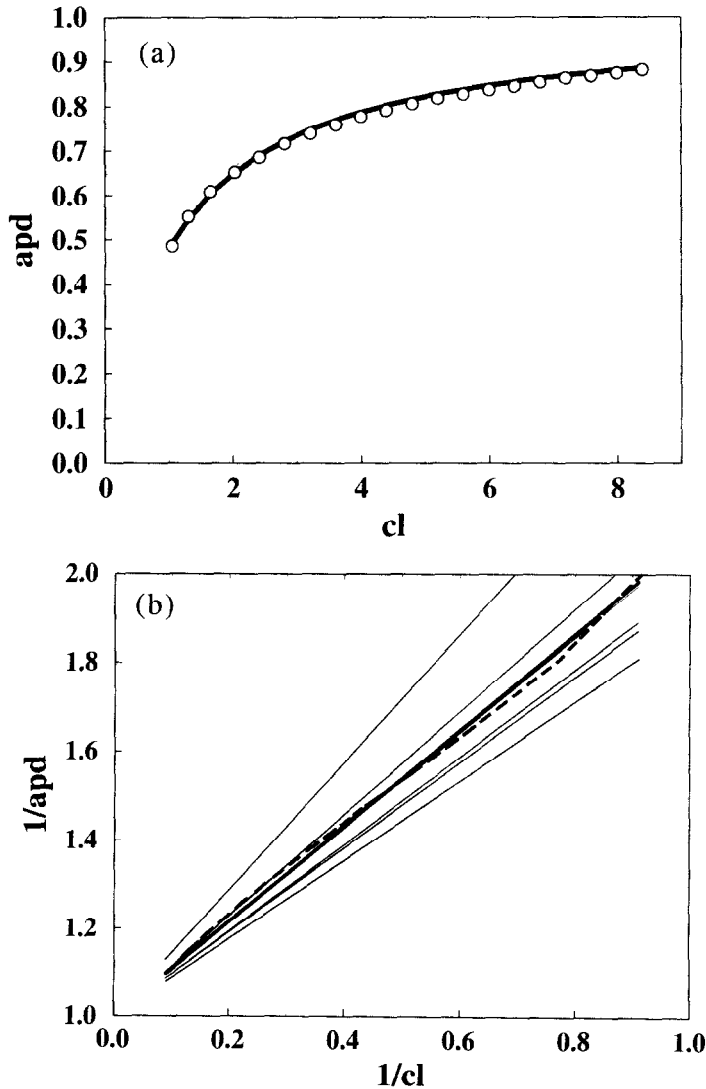


Fig. 3. Restitution property of the medium: (a)  $apd$  vs  $cl$ . Solid line—averaged restitution property for the canine myocardium plotted on the basis of data in [15]; circles— $apd$  simulated in equation (1); (b) restitution property  $1/apd$  vs  $1/cl$ . Thin solid lines represent the experimental data from [15]. Thick solid line is the best fit of experimental data; dashed line— $apd$  simulated in equation (1).

We studied pulse propagation in periodically stimulated 1D cable of 400 elements. We found no pulse instability when the period of stimulation was decreased up to the minimal possible value. The period of propagating waves was constant and equal to the period of stimulation.

We have measured the velocity–curvature relation for periodic wave trains in two dimensions and found that for small curvature,  $k$ , the dependence is described by the formula  $c = c_0 + kD$  with good accuracy; here  $c_0$  is the velocity of the plane waves,  $D$  is the effective diffusion coefficient. We have found that the period of waves has no effect on the value of  $D$  which is equal to 1 in dimensionless equations (1) provided that  $d_{ij} = 1$ .

The restitution property discussed above has a significant effect on the vortex dynamics. Figure 4 illustrates the initiation of the vortex by a stimulation inside the vulnerable window [26]. We applied an extra stimulus in the wake of the passing wave (Fig. 4(b)) that resulted in the development of the wavebreak (Fig. 4(c)) which then evolved into the rotating vortex (Fig. 4(d)). We found that due to restitution, the duration of the pulse in Fig. 1(a) is approximately two times longer than the duration of pulses in the rotating vortex (Fig. 4(d)).

Figure 5 illustrates the changes in the *APD* after initiation of a vortex. The vortex was

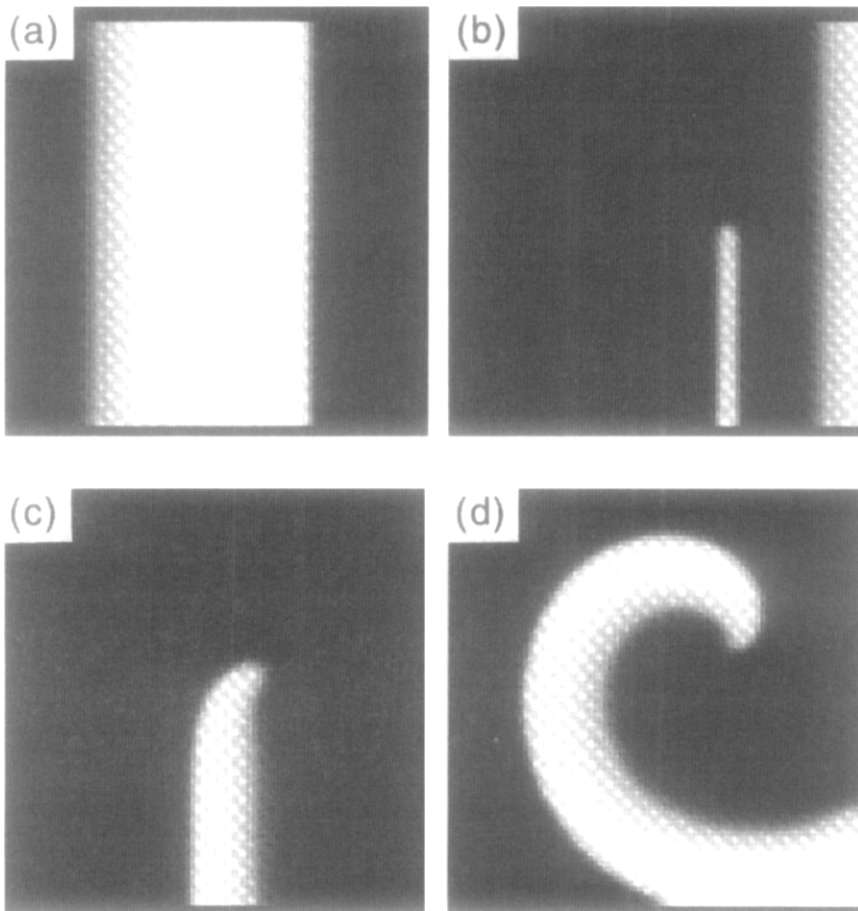


Fig. 4. Initiation of a vortex by a premature stimulation. (a) Freely propagating pulse; (b) premature stimulation (seen as a narrow white stripe) in the wake of a propagating pulse (white region near the right wall); (c) wavebreak developed from a premature stimulation is curled into a vortex (d). Note the difference action potential width in (a) and (d). The snapshots were taken at moments 0, 38.8, 51.8 and 245.9 ms.

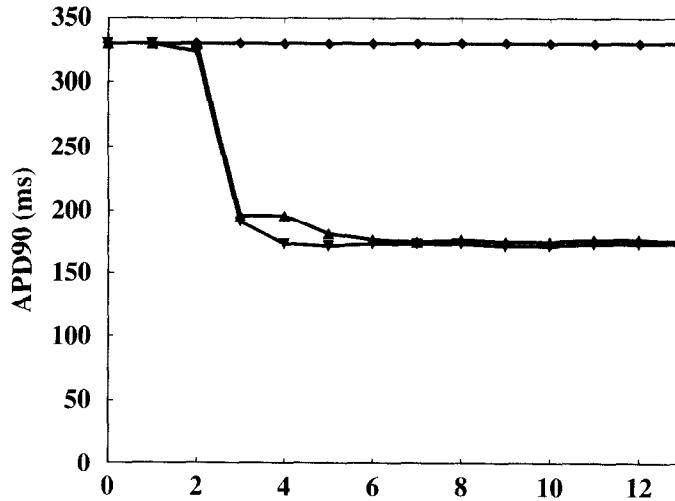


Fig. 5. The  $APD$  dynamics during a vortex formation. A vortex was initiated due to a premature stimulation inside a vulnerable window (upward triangles) and from a wavebreak (downward triangles). The line marked with diamonds is a result of the classic FHN model stimulations.  $APD$  of the vortex is equal to  $APD_0$  in the case of the FHN model.

initiated using two different protocols: stimulation inside vulnerable window (upward triangles) [26] and initiation from a wavebreak (downward triangles) [27]. Both the protocols show similar evolution of the  $APD$ . After several rotations  $APD$  decreased to the value of  $0.53APD_0$ . A different dynamics ( $APD = \text{const}$ , Fig. 5, diamonds) has been observed in the usual FHN model [28].

To estimate the computational effectiveness of the model we performed simulations of 3D re-entry in the whole heart (Fig. 6). We used an electrophysiological computer model of the intact right and left ventricles of a canine heart, which was developed by [28–30]. In this model the heart is located inside a 3D regular grid of size  $127 \times 127 \times 127$  elements. The geometry of the heart and the material properties of cardiac tissue (e.g., conductivity tensor  $d_{ij}$  in equation (1)) are determined on the basis of anatomical data of geometry of the heart and fiber orientation field obtained in experiments by Nielson *et al.* [31] (see Refs [28, 30] for details).

To initiate a 3D re-entry in the right ventricle (Fig. 6) we induced a wavebreak in a partially recovered cardiac tissue. Such initial conditions are similar to those used in the experimental procedure of cross field stimulation [32]. Note, that in our case the tissue cannot be completely recovered. The length of a pulse in the recovered tissue is extremely large and is comparable with the heart size.

In our simulations the wavebreak did several rotations and formed a stationary rotating vortex. This vortex generated waves which propagated around the ventricle cavities and collide near the surface of the left ventricle (Fig. 6). The shape of the waves is a screwed surface close to the wall of the right ventricle; the shape changes to a distorted plane in the left ventricle.

The performed simulations require approximately 35 mins of CPU time of SGI Indy computer per one rotation of a scroll wave, which is similar to the performance in the FHN model [28] and is quite reasonable for such kind of computations.

In this paper we propose a simple model which adequately represents the pulse shape and the restitution property of the canine myocardium. Obviously, however, the proposed equations do not cover as many aspects of the action potential dynamics as do the ionic models. Equation (1) simply mimics properties of cardiac tissue under given conditions.

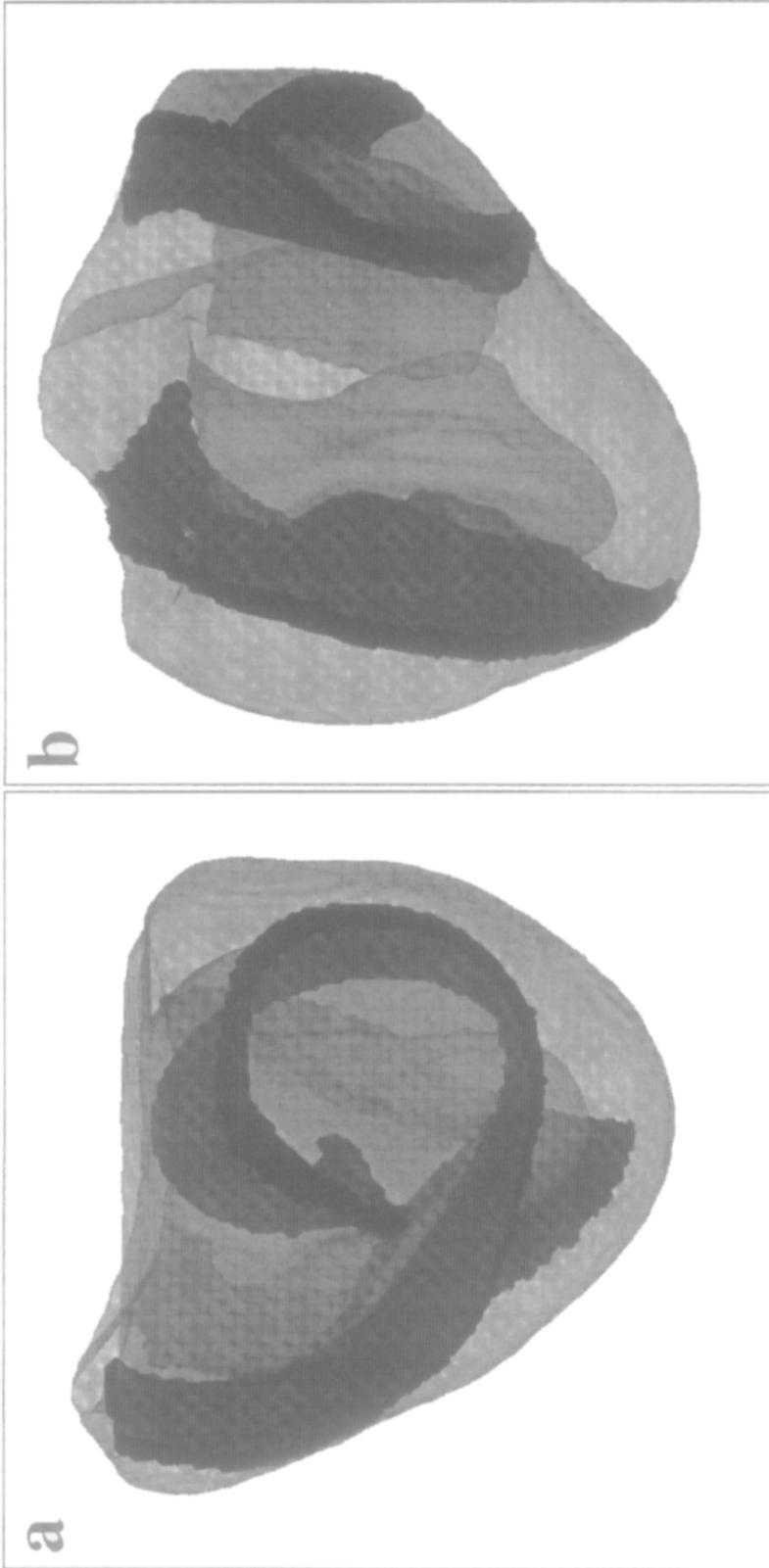


Fig. 6. Re-entry in the whole heart. Note the complicated shape of the re-entry due to the actual geometry of the heart. (a) and (b) sections are the front-view and side-view of the canine heart and the wavefront inside. The pictures are obtained by integrating equation (1) in a cube of size  $127 \times 127 \times 127$  elements.

For example, when the tissue is treated with drugs, and/or if there is a change in extracellular ion concentrations, the coefficients of our model have to be changed. However, our model can still be used if one follows this strategy: (i) measure experimentally the restitution curve and the shape and duration of the action potential under the desired conditions, or compute these properties using a detailed ionic model; (ii) fit the experimental curve using the approach used in our work.

A similar strategy can be applied to account for *APD* changes inside the ventricular wall and from base to apex [33]. In this case the parameters of the model, e.g.,  $\varepsilon_0$  should be described by a 3D field inside the heart. We plan to study the effect of such *APD* dependences on the vortex dynamics in the future works.

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