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Heart Tissue Simulations by Means of Chemical Excitable Media

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Abstract—A set of dimensionless parameters describing pulse propagation in the heart, BZ reaction and FHN model is estimated for comparison of the systems. The ranges of the parameters measured allow the BZ reaction to be considered as a rough experimental model of excitable heart tissue. Vulnerability in the BZ reaction is used as an analogue for vulnerability in cardiac tissue.

1. INTRODUCTION

Excitation propagation in the heart muscle has been studied since the last century. There is a wide spectrum of models describing this phenomenon: cellular automaton models proposed by Wiener and Rosenblueth [1, 2]; a family of simple two variable models, the FitzHugh–Nagumo (FHN) models [3–10]; biophysical models such as the Beeler–Reuter (BR) and Noble (N) models [11, 12]. The more complicated the model, the closer computations simulate experimental observations, but the larger the computer resources required. In fact, extensive two- and three-dimensional simulations using the BR or N models can be carried out only on supercomputers like CRAY. This is one of the reasons why the relatively simple FHN models are widely used in computer simulations [3–10].

On the other hand, propagation of excitation in the heart muscle has similar properties to that observed in a chemical excitable medium, the Belousov–Zhabotinsky (BZ) reaction [13–16]. The BZ reaction is convenient for experiments and is the best-studied excitable medium. Similarity of the wave patterns in the BZ reaction and in the heart has not gone unnoticed, and some parallels were drawn in refs [17–19]. The present paper presents several dimensionless parameters which can be measured in experiments and serve to compare wave characteristics in cardiac muscle, the BZ reaction and in the FHN model. The parameters illustrate the similarity of wave processes in the different systems and promote the main idea of the paper—the use of the BZ reaction as an experimental model for heart tissue.

The second part of the work is devoted to studying vulnerability, i.e. unusual responses which occur after stimulation of the wake of a propagating wave. Potentially life-threating heart arrhythmias can be initiated in such a way [19–24]. Vulnerability is studied using a chemical excitable medium as an analogue for cardiac tissue.

2. DIMENSIONLESS PARAMETERS OF PROPAGATING PULSES

The study of wave processes occurring in different excitable media has revealed an extremely wide range of values of quantitative characteristics—the velocity, space and time periods vary by several orders of magnitude between heart tissue, amoebae populations, and the BZ reaction [25]. However, all these excitable media show qualitatively similar wave patterns.

Table 1 presents a set of characteristics observed in the heart, BZ reaction, and in the FHN model. Here T_{front} is the duration of the front of a propagating pulse. In the heart this value is determined by the time of activation and inactivation of fast sodium channels, in the BZ reaction—the duration of $HBrO_2$ pulse, and in the FHN model—the time of fast variable changes from its lowest to its largest value. T, λ and v with the subscript 'vortex' denote the temporal and spatial periods, and the wave velocity exhibited by vortices (spirals, or functional reentries) in the media. d_{core} is the size of the core around which a vortex rotates. Regardless of the shape of the vortex-tip trajectory (under different conditions the trajectory may have a circular, linear, or flower-like shape) d_{core} may be determined as the minimum diameter of a circle embracing the vortex-tip path during one turn. v_{pulse} is the velocity of a solitary pulse or plane wave. In the heart this is taken as the velocity of a pulse at the resting heart rate, and in the BZ reaction it is the velocity of pulses in a train with period several times greater than T_{vortex}. D is the diffusion coefficient, for the heart the meaning and the value of D has been discussed in ref. [26].

There are two reasons used for selection of these parameters: first, the parameters must be measurable in experiments in all these media; second, any parameter must have a constant value under fixed conditions (for example, the period of focal sources which occur in the heart and the BZ reaction vary depending on the source-type and location [27, 28], and so the characteristics of focal sources are not used here). Obviously, the table does not cover all the appropriate parameters describing excitable media, but only a set of the most frequently-used characteristics of an excitable system.

To compare wave processes in different media it is natural to introduce dimensionless characteristics evaluated from those measured in the laboratory. A set of such parameters, calculated on the basis of Table 1 data, is presented in the Table 2.† Here $p1$ is the stiffness (the value inverse to the small parameter) of the system, which characterizes propagating pulses; $p2$, the ratio of the vortex wavelength to the core size is a parameter of vortex rotation and must be close to π for ordinary autowave processes; $p3$ reflects the dispersion characteristics of the medium: v_{vortex} is normally close to the minimal possible velocity of stationary propagating pulses in the medium, while v_{pulse} is close to the maximal velocity of a pulse, their ratio shows the range of velocities which occur in the medium;‡ $p4$ reflects the influence of the diffusion term on vortex rotation.

Comparing the dimensionless characteristics from Table 2, it is seen that the three

Table 1. Typical wave characteristics observed in the heart, BZ reaction, and in the FHN model

	Heart tissue	FHN model	BZ reaction
T_{front}	0.002 s [34]	0.1 t.u. [10]	20 s [35]
T_{vortex}	0.13 s [32]	13 t.u. [10]	240 s [35]
λ_{vortex}	7/3 cm* [33]	20 s.u. [10]	0.5 cm [35]
d_{core}	2 cm [33]	5 s.u. [10]	0.12 cm [35]
v_{pulse}	63/22 cm/s* [33]	2 s.u./t.u. [10]	3.10^{-3} cm/s [35]
v_{vortex}	53/23 cm/s* [33]	1.5 s.u./t.u. [10]	2.10^{-3} cm/s [35]
D	1 cm^2/s [26]	1 $s.u.^2/t.u.$ [10]	2.10^{-5} cm^2/s [35]
ϵ		0.1 [10]	

The reference numbers indicate where the value was obtained or evaluated using the presented data.

*Because of the heart tissue anisotropy, the values measured depend on the direction of pulse propagation.

†For anisotropic media (i.e. for the heart tissue) the parameters were averaged over direction.

‡In the heart there are also slow waves with velocity significantly lower than that shown in Table 1, but these have other origins (calcium-activated waves [30]).

Table 2. Dimensionless parameters of wave propagation in the heart tissue, FHN model, and BZ reaction

	Heart tissue	FHN model	BZ reaction
$p1$	65	130	12
$p2$	2.5	4	4
$p3$	1.2	1.3	1.5
$p4$	190	30	50

$p1 = T_{vortex}/T_{front}$; $p2 = \lambda_{vortex}/d_{core}$; $p3 = v_{pulse}/v_{vortex}$; $p4 = (v_{vortex}\lambda_{vortex})/D$.

systems studied have relatively close $p2$ and $p3$ parameters, and more scattered $p1$ and $p4$. The BZ reaction and FHN model show comparable deviations of parameters from those estimated for the heart tissue. This enables one to consider the BZ reaction as a model of heart tissue at least under the circumstances when the use of FHN model is acceptable.

3. VULNERABILITY IN THE BZ REACTION

Cardiac vulnerability, the initiation of self-maintained high-frequency wave sources after an extra stimulus is applied in the wake of a propagating pulse, has long been regarded as a precursor to dangerous arrhythmias [1–2, 19–24, 28–29]. The mechanisms responsible for the appearance and development of these wave sources have not been studied in detail. Here this problem is examined by studying vulnerability in the BZ reaction.

Standard techniques were used for experiments with the BZ reaction: a solution of sodium bromate (0.25 M), malonic acid (0.25 M), sulphuric acid (0.25 M), and Ferroin (6.25 mM) was carefully stirred and poured into a Petri dish forming a layer 0.8 mm thick. After several minutes delay (to allow bromomalonic acid synthesis and equilibration) the medium was ready for the experiments.

To study the effect of vulnerability, the wakes of plane waves, serving as reference waves, were stimulated by a 0.2 mm diameter silver wire. Dependent on the distance from the wave front of the reference wave, stimulation resulted in one of three possible wave patterns: (i) stimuli close to the wave front (Fig. 1(a), left) produced damped responses, because these were in the absolute refractory zone, (ii) distant stimuli (Fig. 1(a), right) were applied to resting medium and initiated circular waves, (iii) stimuli in the intermediate zone initiated couples of rotating vortices that emit high-frequency waves (Fig. 1(a), middle). This intermediate zone in the heart is the vulnerable window (VW) [20, 23–24]. Figure 2 illustrates the time evolution of responses to stimulation at different distances from the reference wave. The figure shows 1D sections of the evolution of 2D wave patterns similar to those of Fig. 1. The (a), (b) and (c) sections show propagation of the reference waves, and a damped pulse (c), unidirectional propagation (b) (corresponding to a vortex pair formation in 2D medium) and bidirectional propagation (a), which in the 2D medium is a circular wave.

A pair of vortices initiated after stimulation inside the VW forms a stable high-frequency source of waves. From cardiac experiments it is known that sometimes an extra stimulus evokes a finite train of pulses from a temporary source [29]. A possible mechanism is that stimulation near the VW boundary results in the initiation of two vortices placed close to each other. Such a pair of vortices collapses after several rotations because of interaction of the vortices [31]. Figure 3 illustrates this behaviour. In successive snapshots two vortex

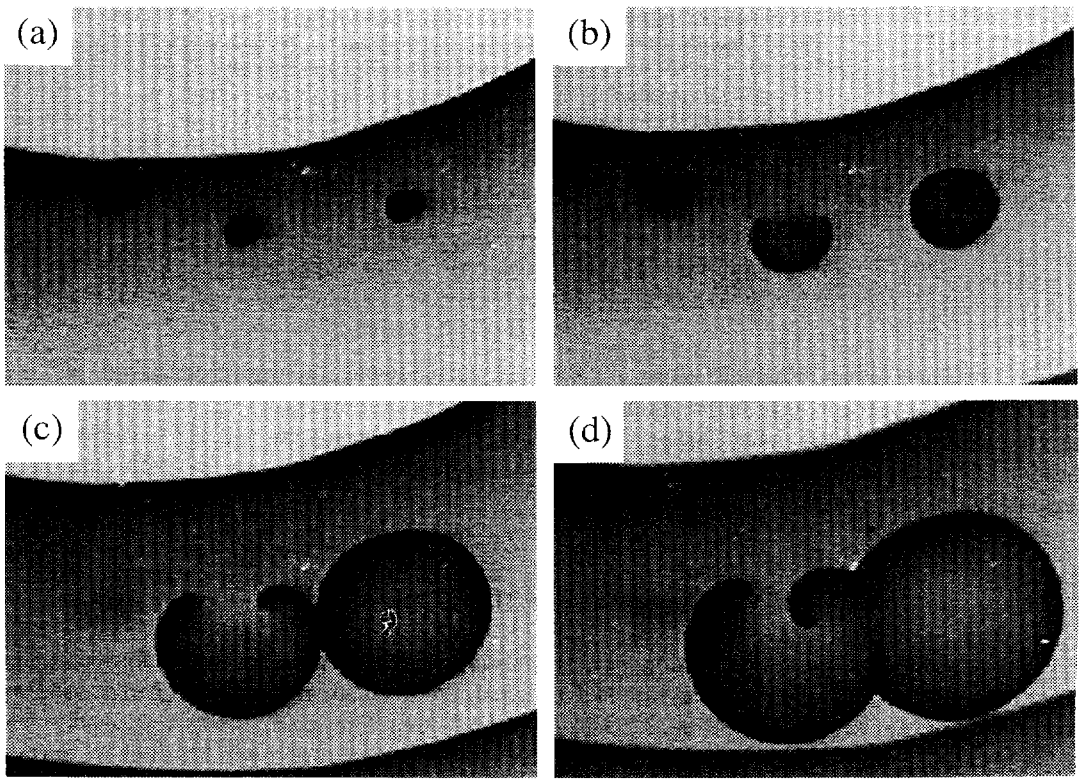

Fig. 1. Vulnerability in the BZ reaction. Stimulation at increasing distances from the propagating wave front results in the different wave patterns. The middle stimulus (see section (a)) is inside the VW and results in the formation a vortex pair. Snapshots (a)–(d) were taken at times 0, 30, 85, and 111 s, respectively.

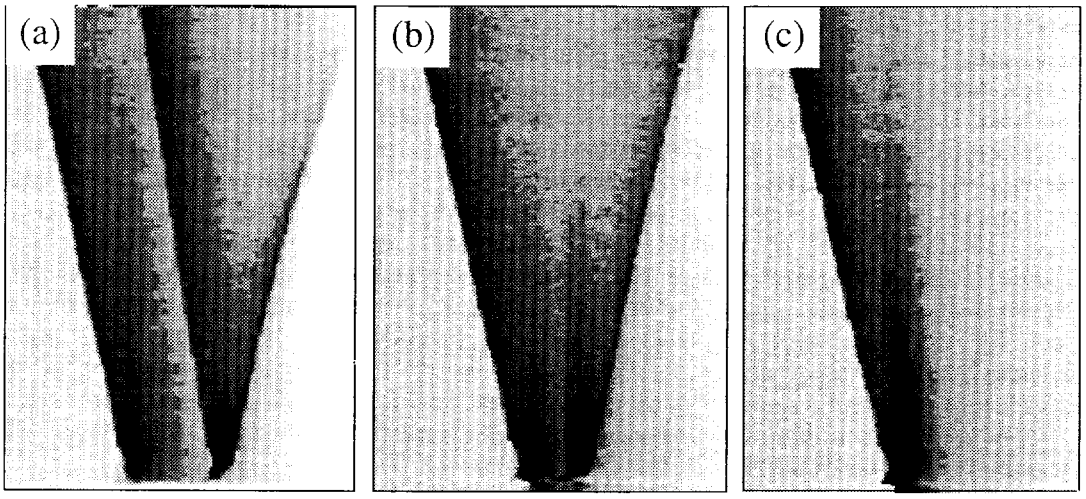

Fig. 2. Space–time presentation of the vulnerability in the BZ reaction. Each row in the figure presents an 1D cut of 2D frames. A stack of such cuts taken at $t = 0$ s (the lowest row) through $t = 77$ s (the uppermost row) forms a space–time chart showing evolution of the response. In all the three sections the reference wave propagating toward the left wall is seen. Applying the stimulus at different distances to the reference wave ((a) 1.9, (b) 1.3 and (c) 5 mm) the three types of response are observed: (a) bidirectional (b) unidirectional propagation, and (c) damped pulse.

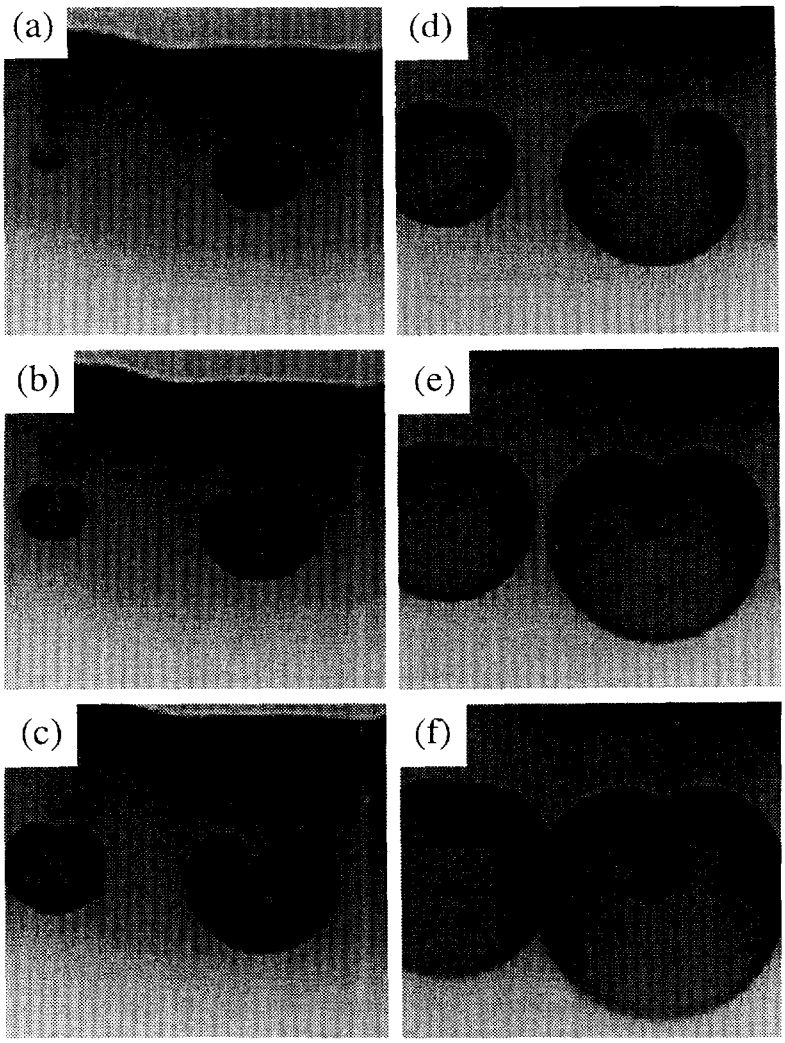

Fig. 3. Stable and unstable vortex pair evolution: after stimulation near the VW boundary a pair of vortices (the left one in (a)–(c)) occur so that the vortex tips are placed close to each other (a). Such a vortex pair is unstable and collapses ((c) and (d)). The other vortex pair initiated in the middle of VW becomes a stable wave source ((e) and (f)). Snapshots were taken through 20 s time interval.

pairs are seen. The right one forms a stable wave source, while the left one collapses, sending a single wave (Fig. 3(a)–(f)). This single wave would be seen as a temporary wave source initiated after stimulation in the wake of a wave.

A graph of typical responses is presented in Fig. 4. Three distinct types of responses are marked by digits 0, 1 and 2 on the y-axis (Fig. 4(a)) designating the regions of damped, unidirectional (vortex pairs formation) and bidirectional (circular) propagation (see Figs 1 and 2). Note that the regions observed in the experiment are overlapped, i.e. a stimulus at a fixed distance near the boundary of a region can evolve in either one of two wave patterns. The reason for such behaviour is the high sensitivity to small perturbations near a region boundary, which results in the formation of nonstationary structures, like a collapsing vortex pair in Fig. 3. Figure 4(b) shows the probability of a unidirectional

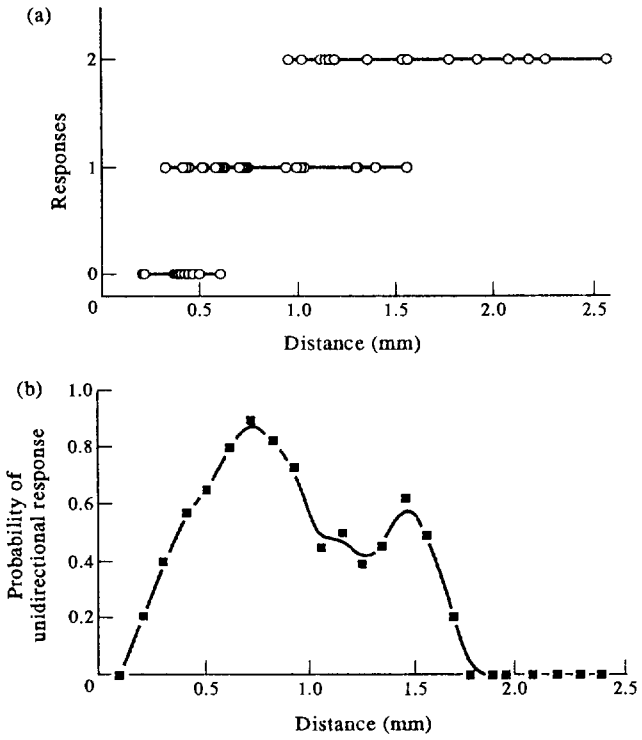

Fig. 4. Graph of typical responses in the BZ reaction. (a) Three distinct types of wave patterns develop as a result of stimulation at different distances to the reference wave front: zero responses (damped pulse), uni or bi directional propagation. (b) The probability of unidirectional response appearance (vulnerable window). The BZ composition is the same as described in the text, except that sulphuric acid was 0.47 M.

propagation observed in response to a stimulus at a given distance to the reference wave front. This curve fences the vulnerable window.

4. DISCUSSION

There are many mathematical models describing excitation propagation in the heart [1–12]. The main idea of the present work is to use a chemical excitable medium (BZ reaction) as an experimental model, or analogue, for heart-tissue simulations. The reason for this is the qualitative similarity of wave patterns in the heart and the BZ reaction. Quantitative characteristics can be evaluated using Table 2 data. The other point is the large computer resources and high costs of supercomputer simulations: the BZ reaction wave patterns in Fig. 2 were developed for 20 min, using only several milligrams of low-cost chemicals. The precision of the simulations is about same as that of FHN models, and can be improved by adjusting the composition of the BZ reaction.

It should be noted that the values presented in the Table 2 are not invariant, but vary slightly while changing the experimental conditions. The coincidence of the four parameters from Table 2 is not a reason to claim the systems are identical. Despite this, the closely related parameters $p1-p4$ must point at closely similar qualitative behaviour that should be expected in the studied systems.

Non-trivial results were obtained while studying vulnerability in the BZ reaction: formation of vortex pairs in response to a single extra stimulus (Figs 1 and 2), initiation of

unstable wave sources (Fig. 3) and the probabilistic character of the wave pattern developed (Fig. 4) as the result of stimulation near VW boundary. These results are believed to occur in the heart tissue as well.

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