Spiral Breakup in an Array of Coupled Cells: The Role of the Intercellular Conductance

A. V. Panfilov

Department of Theoretical Biology, Utrecht University, Padualaan 8, Utrecht, 3584 CH, The Netherlands

We study numerically how the intercellular conductance affects the process of spiral breakup in an array of coupled excitable cells. The cell dynamics are described by the Aliev-Panfilov model, and the intercellular connection is made via Ohmic elements. We find that decreasing intercellular conductance can prevent the breaking up of a spiral wave into a complex spatiotemporal pattern. We study the mechanism of this effect and show that the breakup disappears because of increasing the diastolic interval of an initial spiral wave.

Many cardiac arrhythmias are characterized by rotating waves of excitation [1,2] which are similar to spiral waves of excitation found in a wide variety of nonlinear excitable media [3]. The appearance and multiplication of spiral waves in excitable medium disorders the spatial pattern of excitation and may result in turbulent or chaotic behavior. One of the most important examples is electrical turbulence in the heart muscle (or ventricular fibrillation) which is the main cause of sudden cardiac death in the world [4].

There are several types of spiral wave dynamics in excitable media: stationary rotation [5], which can be destabilized into meandering or drift of spiral waves via the Hopf instability [6]; turbulent behavior, which can be a result of many different types of instabilities: the lateral instability [7], the absolute or convective Eckhaus instability [8,9], the so-called alternans instability [10,11], and some others. Alternans instability occurs 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 pulses of excitation (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 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. Alternans instability can occur if the slope of the restitution curve is more than one [10,11]. This criterion was found from analytical studies of one-dimensional maps and was later extended in analytical study of an integral-delay equation for pulse propagation on a one-dimensional ring of excitable tissue [12]. Studies of alternans instability in two dimensions were carried out mainly numerically. They showed that alternans instability due to a steep restitution curve can cause spiral breakup: fragmentation of one spiral wave into a spatiotemporally chaotic pattern comprising many wavelets of various sizes [13–16]. Spiral breakup due to a steep restitution curve is now one of the most actively pursued hypotheses of ventricular fibrillation [13–17]. Recent experimental measurements have confirmed the existence of steep restitution curves in canine myocardium [18]. The

measured values of the maximal slopes of the restitution curves were remarkably close to the magic value of one, implying that small interventions could be potentially crucial for promoting or for preventing breakup in the heart. In this Letter, we study how basic properties of cardiac propagation can effect the process of spiral breakup. One of the important characteristics of cardiac tissue which affects wave propagation in the heart is the conductance of gap junctions, which are specialized membrane structures connecting adjacent cardiac cells [19]. It is well established that the number of gap junctions substantially changes during cardiovascular disease [19]. In this Letter, we study numerically how changing the conduction properties of cardiac tissue can affect the phenomenon of spiral breakup in an array of coupled excitable cells.

Model and results.—Each excitable cell is described by the Aliev-Panfilov model [20]:

$$de/dt = -ke(e - a)(e - 1) - er + I_{ex}, \quad (1)$$

$$dr/dt = [\epsilon + \mu_1 r/(\mu_2 + e)][-r - ke(e - b - 1)]. \quad (2)$$

Here the variable e stands for the transmembrane potential, I_{ex} stands for the external current from the neighboring cells, and variable r stands for the conductance of the slow inward current. The function $-ke(e - a)(e - 1)$ in Eq. (1) determines the fast processes, such as the initiation of the upstroke of the action potential. The dynamics of the recovery phase of the action potential are determined by the time course of the variable r, mainly by the function $\epsilon + \mu_1 r/(\mu_2 + e)$. The particular parameters in this model do not have a clear physiological meaning but are adjusted to reproduce key characteristics of cardiac tissue, such as shape of action potential, refractoriness, and restitution of action potential duration. The values of the parameters used in this investigation are $\mu_2 = 0.3$, $k = 8$, $\epsilon = 0.01$, and $b = 0.1$, while parameters μ_1 and a were varied in different runs.

Spatially coupled cells were placed in a rectangular array, with each cell connected to four neighbors via Ohmic elements with a conductance g. For a cell at the location

i, j on a uniform grid, the total external current I_{ex} is the sum for the following four currents:

$$I_{ex} = g(e_{i+1,j} - e_{i,j}) + g(e_{i,j+1} - e_{i,j}) \qquad (3)$$

$$+ g(e_{i-1,j} - e_{i,j}) + g(e_{i,j-1} - e_{i,j}). \qquad (4)$$

The propagation of the wave is substantially affected by the value of the intercellular conductance g. In our model, if g was less than $g_{min} = 0.033$ the wave propagation was blocked. We used this value to measure the intercellular conductance in dimensionless units.

Computations were performed using an explicit time integration scheme on an $N \times N$ array, with $N = 333$. The time integration step was $dt = 0.02$. No-flux boundary conditions were imposed. To initiate the first spiral wave we used initial data corresponding to a broken wave front, the break being located at the middle of the excitable tissue. If spiral persisted for 80 cycles without fragmentation we considered that at these parameter values breakup was absent.

We studied the effect of intercellular conductance g on the possibility of spiral breakup. Since the model given by (1) and (2) describes action potential generation using two basic currents (fast and slow), we have studied how modification of each of these currents affects the phenomenon of spiral breakup. In particular, we modified the slow outward current by changing the parameter μ_1 in (2): decreasing μ_1 increases the duration and the refractory period of the action potential. We also modified the fast inward current by changing its threshold of activation through the parameter a in (1). Decreasing a increases the excitability of the cell and prolongs the duration and the refractory period of the action potential. The results of these computations are presented in Fig. 1. For both parameters, breakup occurred if the parameter value was below some critical value. We see that for both parameters decreasing conductivity decreases the window in parametric space in which breakup occurs.

We have studied the changes which occur in the spatial pattern under the change of intercellular conductivity g. For that, we fixed the value of parameters $\mu_1 = 0.11$ and $a = 0.1$ and varied parameter g only (as shown by the dashed line in Fig. 1a).

Figure 2 shows the patterns of excitation after 80 cycles of spiral for two values of g marked by the diamonds in
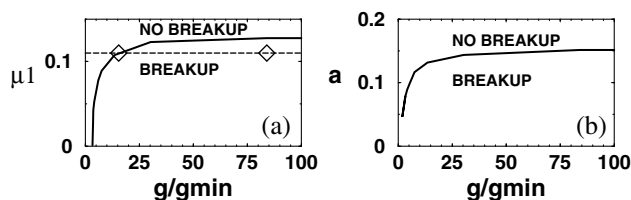
Fig. 1a. For $\frac{g}{g_{min}} = 84$ we see the normal breakup pattern which comprises many wave breaks of various sizes. Development of this pattern started as fragmentation of the wave close to the core of the initial spiral. For $\frac{g}{g_{min}} = 15.5$ the situation is quite different. The fragmentation in this case occurs far from the core and does not spread to the whole medium. The initial spiral persists until the end of this computation. These processes can be summarized in the following way: Decreasing the value of g shifts the fragmentation area farther and farther from the core of the initial spiral; finally, the region of the first fragmentation reaches the boundaries of the excitable medium and breakup does not occur.

To find out why breakup disappears if g decreases, we studied how main characteristics of spiral waves, such as its period, diastolic interval, and restitution properties of the tissue were affected by g (Fig. 3).

We see that when breakup occurs (approximately $g/g_{min} > 20$), the changes in the average period of spiral wave and diastolic interval Di are not apparent because of large deviations in average values due to the complexity of spatial patterns. However, if we increase g in absence of the breakup (in interval $g/g_{min} < 20$), we clearly see the decrease in the period and Di of a spiral wave. This fact can explain the observed phenomena: The mechanism of spiral breakup in models (1) and (2) is due to a steep restitution curve [21]. Figure 4 shows three restitution curves obtained for different values of intercellular coupling. We see that increasing g shifts the location of a spiral wave on the restitution curve to regions of higher slope facilitating the spiral breakup.

We have also studied how random breaking of electrical connections between cells affects the spiral breakup. At $g/g_{min} = 84$, we randomly removed a certain percentage of intercellular connections. Note that at these parameter values with homogeneous connections we have a pronounced breakup shown in Fig. 2a. We find that removal of a small percentage (16%) of connections suppresses spiral breakup, resulting in a stable spiral shown in Fig. 5a. Increasing the percentage of removed connections considerably affected the wave propagation, creating nonround wave shapes and wave breaks. However, it did
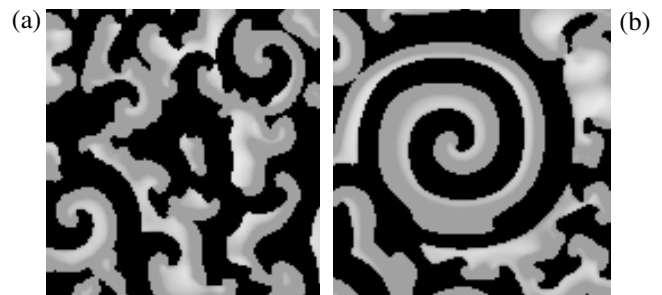

FIG. 1. (a) The dependence of critical value of μ_1 at fixed $a = 0.1$ below which breakup is possible on the intercellular conductivity. (b) The same for parameter a at a fixed value of $\mu_1 = 0.07$.

FIG. 2. Wave pattern at time $t = 2600$ for (a) $g/g_{min} = 84$ and (b) $g/g_{min} = 15.5$. The black area represents the excited state of the tissue ($e > 0.6$) and intermediate shading from gray to white shows different levels of recovery.
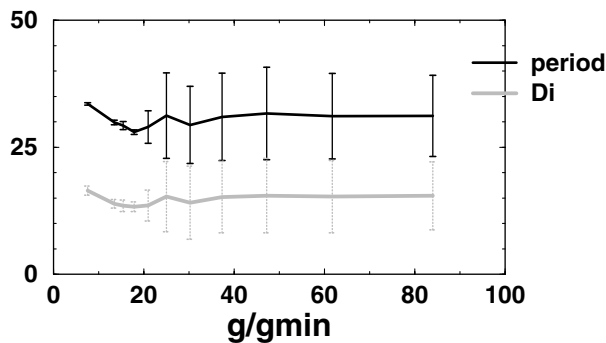
FIG. 3. The average period and the average Di of a spiral wave as a function of g/g_{min}. Error bars show the standard deviations from different cells in the same medium.

not induce spiral breakup (Fig. 5b). The mechanism of this effect is similar to that discussed earlier, namely increasing the period and Di of the spiral wave. The period of spiral in Fig. 5a was $T_s = 32.01 \pm 4.15$ and $Di = 14.85 \pm 3.16$, while in Fig. 5b $T_s = 37.38 \pm 0.07$ and $Di = 18.57 \pm 0.92$. Hence, it is shown that heterogeneity in coupling suppresses the onset of complex spatiotemporal patterns. Figure 6 shows the region of existence of spiral breakup as a function of the percentage of the removed connections. We see that this region shrinks when the percentage is increased, and when it approaches 40%, spiral breakup disappears. The dependence in Fig. 6 is similar to that in Fig. 1: In both cases, decreasing the conductivity decreases the region of existence of spiral breakup.

Discussion.—The main result of our study is that decreasing gap junction conductivity suppresses spiral breakup. However, it is well established that arrhythmias do occur under reduced gap junction conductivity [19]. Thus, our study suggests that the mechanism of ventricular fibrillation which occurs in conditions of lower gap junction conductivity can be different from the mechanism of spiral breakup. The following facts also argue in favor of this hypothesis: Spiral breakup occurs due to a steep restitution curve, and flattening of
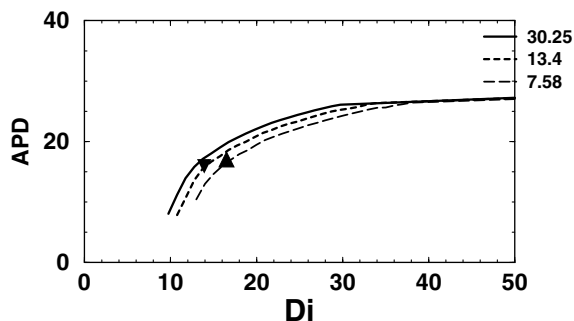

FIG. 4. Action potential duration (APD) as a function of diastolic interval (Di) (restitution curves) for three values of g (shown at the right upper corner). The down and the up triangles show the position of a spiral wave on the restitution curve for $g = 7.6$ and 13.4, respectively. The restitution curve was computed for a pulse rotating in a ring of excitable tissue, by varying the length of the ring.

the restitution curve is proved to prevent spiral breakup both in numerical computations and in experiments [17]. Several experimental studies suggest that the restitution curve is flattened in conditions of decreased gap junction conductivity, which is the case studied in our paper. For example, the gap junction conductance is reduced during ischemia [19], and the restitution curve in ischemic hearts becomes flatter [22]. Similar data exist for atrial tissue: In atrial tissue, prone to chronic atrial fibrillation, the gap junction coupling between cells is reduced [23], and the slope of the restitution curve is small and can even become negative [24].

Although results of our paper imply that drugs slowing the conduction of the cardiac pulse can be effective against ventricular fibrillation, we think that making such a conclusion for clinical cardiology would be an oversimplification. There are many different types of cardiac arrhythmias and probably many different types of ventricular fibrillation [25]. Spiral breakup due to a steep restitution curve is just one of the possible hypotheses. Slowing the cardiac conduction can provoke other types of arrhythmias and, in some cases, can even increase the mortality of cardiac patients [26].

Another conclusion of this paper is that removal of a small percentage of connections between cells can prevent spiral breakup. An open question is whether this approach can be applied practically for fighting cardiac arrhythmias. In this paper, we did not study in detail how this effect might depend on different random configurations of intercellular coupling. The work presented here was mainly focused on uniform cell connections rather than on random configurations.

We have also found that the fragmentation of a spiral wave in our model can occur either close to the core or far from the core of the initial spiral depending on the proximity in parameter space to the boundary of the spiral breakup (Fig. 2b). Breakup far from the core of the initial spiral is similar to that which occurs due to the convective instability in oscillatory excitable media [8]. In our case, however, it occurs in the medium which has a stable steady state. Note that different types of fragmentation of spiral waves in ionic models of cardiac tissue have also been observed in [27].

FIG. 5. Wave pattern at time $t = 2600$ for $g/g_{min} = 84$ if 16% (a) and 40% (b) of intercellular connections are removed. The other notations are as in Fig. 2.
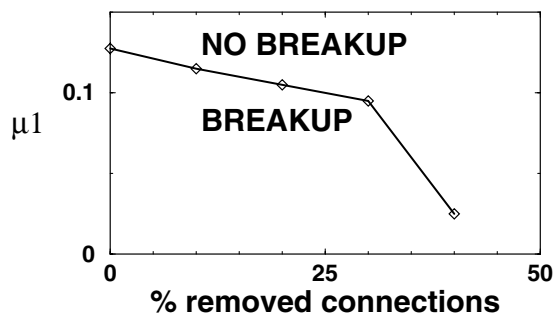
FIG. 6. Dependence of critical value of μ_1 below which breakup is possible on percentage of removed intercellular connections for $g/g_{min} = 84$ and $a = 0.1$.

In this paper we studied the effects of decreasing gap junction conductivity on one of the possible types of dynamics in an excitable medium: spiral breakup. Note that another important type of dynamics is a stably rotating spiral wave. Although we did not study such dynamics specifically, our computations in the region "no breakup" (for $g/g_{min} < 20$ in Figs. 2a and 3) allow us to assume that the decrease in gap junction conductivity should increase the period of stably rotating spiral waves.

Although this work was carried out using a simplified model for cardiac tissue, the mechanism of the effects found here is general and independent of the particular model equations. In fact, it is reasonable to assume that in any model of cardiac tissue decreasing the intercellular coupling will result in increasing the period of spiral wave. Therefore, we expect that the conclusions of this paper will be confirmed in more detailed models of cardiac tissue.

[1] M. A. Allessie, F. I. M. Bonke, and F. J. G. Schopman, Circ. Res. **33**, 54 (1973).
[2] A. M. Pertsov *et al.,* Circ. Res. **72**, 631 (1993).
[3] A. T. Winfree and S. H. Strogatz, Nature (London) **311**, 611 (1984).
[4] R. Pool, Science **247**, 1294 (1990).
[5] A. T. Winfree, Chaos **1**, 303 (1990).
[6] D. Barkley, Phys. Rev. Lett. **72**, 164 (1994).
[7] A. V. Panfilov and A. Marée, Phys. Rev. Lett. **78**, 1819 (1997).
[8] M. Baer and M. Or-Guil, Phys. Rev. Lett. **82**, 1160 (1999).
[9] B. Sandstede and A. Scheel, Phys. Rev. E **62**, 7708 (2000).
[10] J. Nolasco and R. Dahlen, J. Appl. Physiol. **25**, 191 (1968).
[11] M. Guevara, A. Ward, A. Shrier, and L. Glass, IEEE Comp. Cardiol. **562**, 167 (1984).
[12] M. Courtemanche, L. Glass, and J. P. Keener, Phys. Rev. Lett. **70**, 2182 (1993).
[13] A. V. Panfilov and A. V. Holden, Phys. Lett. A **147**, 463 (1990).
[14] M. Courtemanche and A. T. Winfree, Int. J. Bifurcation Chaos Appl. Sci. Eng. **1**, 431 (1991).
[15] H. Ito and L. Glass, Phys. Rev. Lett. **66**, 671 (1991).
[16] A. Karma, Phys. Rev. Lett. **71**, 1103 (1993).
[17] A. Garfinkel *et al.,* Proc. Natl. Acad. Sci. U.S.A. **97**, 6061 (2000).
[18] M. Koller, M. Riccio, and R. Gilmour, Jr., Am. J. Physiol. **275**, H1635 (1998).
[19] H. Jongsma and R. Wilders, Circ. Res. **86**, 1193 (2000).
[20] R. R. Aliev and A. V. Panfilov, Chaos Solitons Fractals **7**, 293 (1996).
[21] A. V. Panfilov, in *Cardiac Electrophysiology. From Cell to Bedside,* edited by D. P. Zipes and J. Jalife (Saunders, Philadelphia, 1999), 3rd ed., pp. 271–277.
[22] P. Taggart *et al.,* Circulation **94**, 2526 (1996).
[23] H. van der Velden *et al.,* Cardiovasc. Res. **46**, 476 (2000).
[24] M. Wijffels, C. Kirchhof, R. Dorland, and M. A. Allessie, Circulation **92**, 1954 (1995).
[25] J. Jalife, Annu. Rev. Physiol. **62**, 25 (2000).
[26] CAST Investigators, N. Engl. J. Med. **327**, 227 (1992).
[27] J. Beaumont, N. Davidenko, J. Davidenko, and J. Jalife, Biophys. J. **75**, 1 (1998).