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ORGANIZING CENTERS IN A CELLULAR EXCITABLE MEDIUM†

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Excitable media provide much of the subject-matter of physiology, especially of electrophysiology. We simulate excitability in a cubical three-dimensional grid of discrete cells. Topologically distinct organizing centers for self-sustaining rhythmic activity (at period 4) arise from suitable initial conditions. Two are shown: the scroll ring and the linked pair of twisted scroll rings. The first has already been observed in a chemically excitable reagent and possibly in heart muscle; the second, and others of a predicted "periodic table of organizing centers", remain to be observed outside computers.

1. Introduction

The essence of excitability is responsiveness to a threshold-transgressing stimulus from an adjacent excited cell. The response consists of becoming excited in the same way, then, during an interval of exhaustion, recovering the former excitability. In such a medium excitation is contagious and propagates as a pulse. In sheets of excitable medium (cortex of the brain, retina, smooth muscle, atrial muscle, to name only a few) the pulse is a wavefront. In solid blocks of such media (left ventricular muscle, possibly certain parts of the brain) the wavefronts can presumably be two-dimensional surfaces. Is their geometry essentially the same as in wave-propagating media familiar to physicists, viz. concentric sphere-like "bags" without any edge unless only on the boundary of the medium? It would be of interest to conduct simulations of three-dimensional excitable media to learn what geometrically distinctive varieties of wave might inhabit them, given appropriate initial conditions and boundary conditions. The prospect of encountering qualitatively new kinds of wave should entice anyone intrigued by the qualitatively distinctive peculiarities of excitable media, such as their susceptibility to fibrillation and a host of simpler arrhythmias.

Three-dimensional integration of the pertinent stiff partial differential equations remains prohibitively expensive, even after decades of fast exponential decline in the unit cost of computation. However, the first such have already been reported [1–3]. As such undertakings come within reach, it is important to be ready with potentially interesting initial conditions. Toward this end we simulate

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an array of A by B by C cubical cells. Each cell may be in one of three states, Q, E, or T. It is normally "quiescent" (Q) and "excitable": if one of its six neighbors is excited, then in the next moment, it too becomes excited (E). In the moment following it is "tired" (T) and therefore cannot be re-excited. In the next moment it is again quiescent and therefore excitable again. An exception to these rules occurs along the boundaries of the array, in that a cell on a face, edge, or corner has only five, four, or three neighbors. This is equivalent to saying in the language of differential equations that we use Dirichlet boundary conditions: the cell just beyond each face is imagined to be held quiescent. The usual alternative to Dirichlet (fixed-state) boundaries is Neumann (no-flux) boundaries: the array is imagined to abut an appropriately mirror-imaged array along each face. In our discrete-state caricature of excitability either rule has the same effect.

Initial conditions consist of an arrangement of E's and T's in a sea of Q's, emplaced by an automatic algorithm or by keyboard entry via an editor subprogram. Then the array is repeatedly scanned, updating each cell's state according to the foregoing rules. The array settles into a period-four repeat after a number of updates no greater than the longest array dimension. This "repeat" consists only of quiescence in one-dimensional simulations ($A = B = 1$) with these absorbing boundary conditions. In two dimensions ($A = 1$, like quadrille paper or window-screen), uniform quiescence may also result, but another frequent result is some arrangement of period-four rotating spirals with one or more arms. The period, in this case, reflects the perimeter of the smallest closed ring in this discrete medium. In a medium with more states intervening between excitation and restored excitability, the shortest closed path of circulation would have at least that perimeter (and period).

Even without digital assistance one can understand these phenomena immediately by simply following the rules with pencil and eraser on quadrille paper. It proves interesting to start from quiescent initial conditions surrounding a bilayer of active cells, excited on the front side, tired on the rear side, reaching from an edge into the interior of the rectangle array. The dangling endpoint of this plane wave will quickly evolve into the pivot and source of a spiral wave. An even simpler initial condition, which develops a mirror image pair of adjacent spirals, is uniform quiescence (E) punctuated by a single pair of non-quiescent cells: one excited, and one tired neighbor.

Such media and their spiral waves have been thoroughly explored [4–8]. Though obviously quantized in an extreme way, they behave very much like waves in analogous continuous excitable media, such as the Belousov–Zhabotinsky chemical reagent [9–11], various idealizations formulated as partial differential equations [12 and refs. in 13], slime mold [14, 15], thin layers of heart muscle [16–19], cerebral cortex [20, 21], and the retina [22].

Our objective was to determine how far this discrete-state, discrete-space simulation mimicks the anticipated behavior of continuous excitable media in three dimensions, as a preliminary to undertaking calculations from continuous differential equations. Anticipations for the three-dimensional case include a great variety of topologically distinct sources, all of the same period except in the regions of extreme curvature. All are generalizations of the two-dimensional spiral. The simplest one (see below) has been observed in vitro [23, 24], in vivo [25], and in numero [1]. The next simplest source has only been described mathematically and animated by computer graphics on videotape.

In this report we demonstrate it dynamically in three dimensions for the first time.

First, as a "control experiment", we demonstrate the simplest scroll ring. In a continuum this is a surface of revolution which can be visualized as a spiral swung about an axle. The source of the spiral in each plane radial to the axle is a point; in the surface of revolution that point becomes a ring, the edge of a wave rolled up around it. This

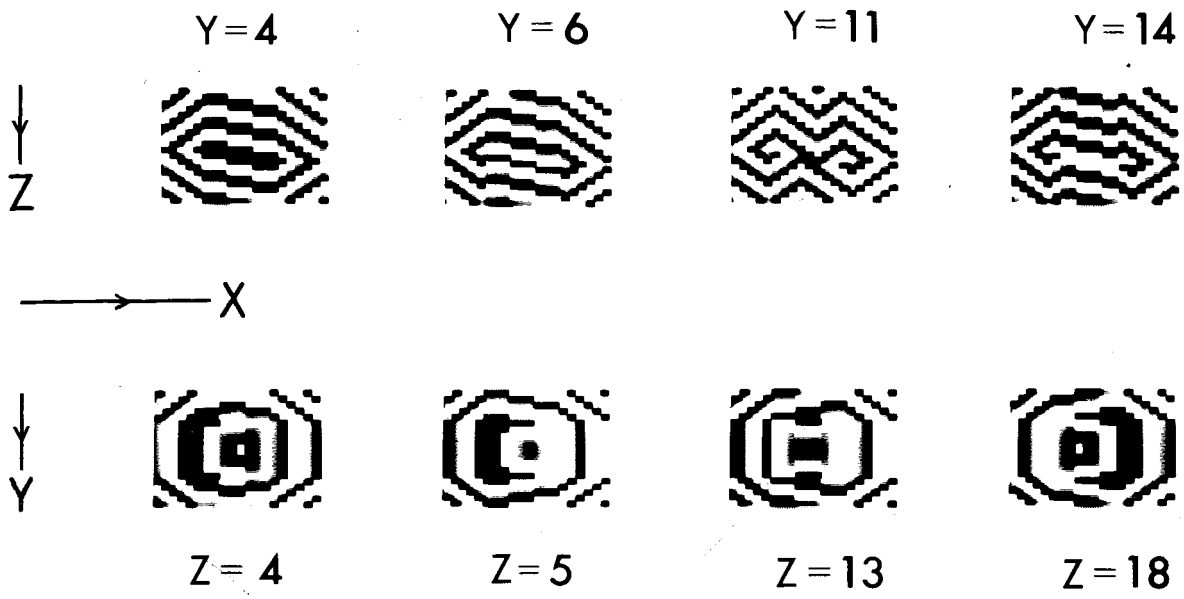

Fig. 1. A $20 \times 20 \times 20$ cube of idealized excitable medium harbors a scroll ring, shown here in 4 planar cross-sections at successive values of Y, and four perpendicular cross-sections at successive values of Z as indicated. The scroll's singularity is a 10×9 rectangular ring slightly tilted out of the XY plane at $Z = 12 + -1$. Excited (E) cells are black, tired (T) cells are grey, and quiescent cells (Q) are blank. Notice in cross-section $Y = 11$ the pair of mirror-image spirals radiating outward to left and right, and inward to center; in perpendicular section $Z = 13$ these waves are seen as concentric rings propagating outward and inward. The repeat period is 4.

source ring (or, in more elaborate cases, an arrangement of mutually linked knotted rings) is called the organizing center for the spatially and temporally periodic activity that radiates from it.

Fig. 1 shows planar sections of the simplest organizing center, a solitary ring in a 20 by 20 by 20 cube. This scroll ring was initiated with a slight tilt relative to the grain of the array in order to expose its cross-sections in a more generic way. This is particularly important for the serial sections at fixed Y. These sections expose concentric inward and outward ring-shaped waves. They are separated by expanding crescents where the section plane grazes one edge of the scroll, i.e. a vertically-travelling broadside has just penetrated the section plane. In fig. 2 a line-drawing outlines waves photographed [24] on fixed and stained serial sections of Belousov–Zhabotinsky reagent. Fig. 3 similarly outlines (as a time sequence rather than serial sections at fixed time) the activation front emerging through the surface in a piece of heart muscle, recorded by an array of microelectrodes [25]. All six pictures are about 1 cm in diameter.

In all three cases the initial conditions were similar: a wavefront abruptly terminating along a circular edge. In the discrete simulation it was a five by six disk of E cells backed up by a layer of T cells; its perimeter became the organizing center. In the chemical reagent, stimulation at a point produced a hemispherical wave whose circular edge was then abutted against another block of quiescent medium to create the ring source. In the heart muscle, the hemisphere was ruptured by encountering a block of heart muscle artificially made inexcitable; when excitability returned, activity began to issue from the block at a period comparable with that of two-dimensional rotating waves in heart muscle.

Several years ago it was predicted that scroll rings might exist in greater variety, distinguishable by topological indices [26]. In particular, it was

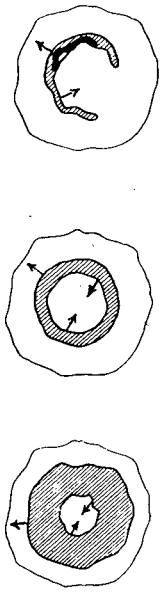

Fig. 2. A piece of rabbit heart muscle appears to harbor a slightly tilted scroll ring, in the interpretation of Medvinsky et al. [25]: waves radiate as concentric inward and outward rings from a circular locus beneath the surface of the muscle. The outer circular wave is about 1 cm diameter. As the inner wave erupts as a broadside into the exposed surface, it is caught at 103, 113, and 143 ms after first stimulation. Their repeat period (106 ms) is close to that of spiral waves in this medium (82 ms).

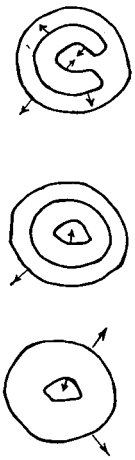

Fig. 3. Waves from a slightly tilted scroll ring are caught in serial sections across a "pancake" of the Belousov–Zhabotinsky excitable medium. They radiate inward and outward as in figs. 1 and 2. The outer ring is 0.8 mm diameter (from ref. 24).

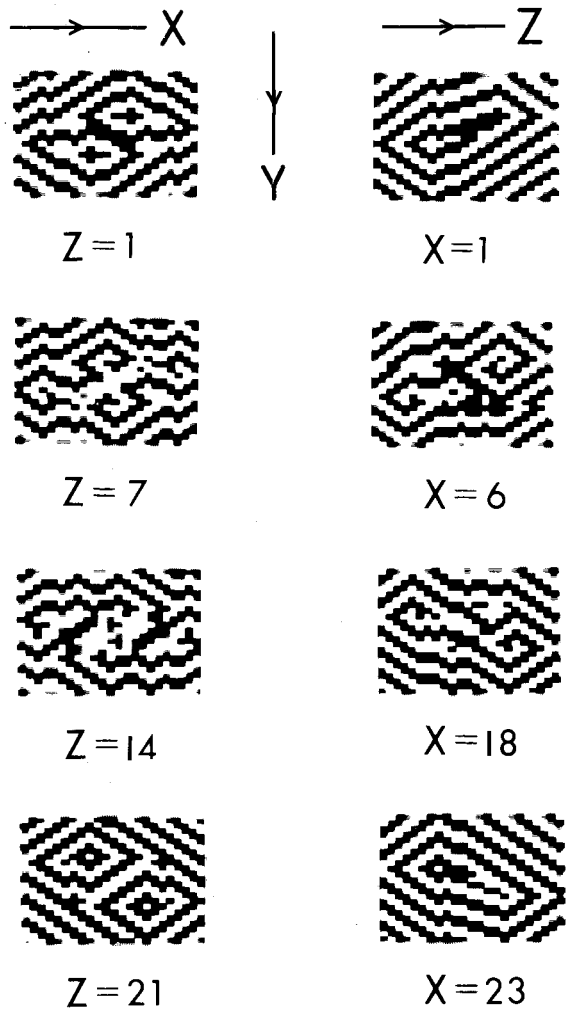

Fig. 4. Comparable to fig. 1, but this time the singularity is a pair of linked rings, each radiating a twisted scroll ring at period 4. At large X or Z the section planes miss the rings altogether. Sections $Z=7$ and $Z=14$ cut both rings (each twice) to expose mirror-image spirals. Section $X=6$ cuts only one ring; $X=18$ cuts the other.

argued that the least complicated of these more elaborate organizing centers in excitable media would be a linked pair of scroll rings. These conjectures were given more substance in a sequence of papers proceeding from geometry and laboratory arrangements for chemical implementation [13] to topology [27–30] and to computer graphics (but not dynamical simulations) [31, 32]. It was discovered that scroll rings could link if they were also twisted in a topological sense. But no one had

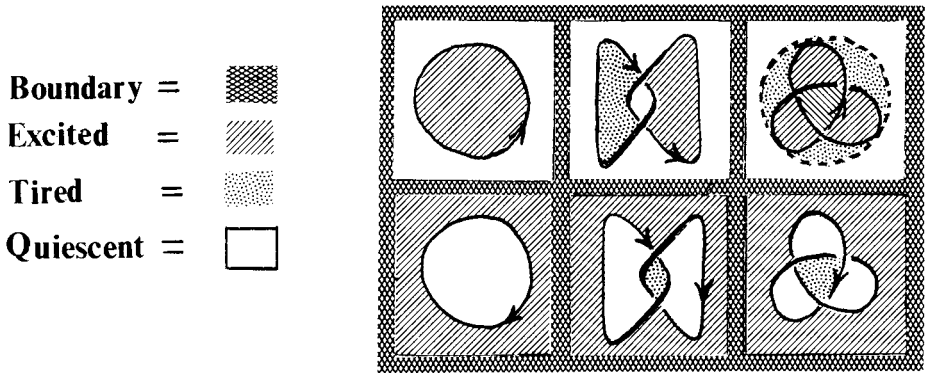

Fig. 5. Top left: initial conditions for a scroll ring consist of a disk of excited (E) cells overlaying (not visible here) a disk of tired (T) cells. This is a piece of wavefront, moving toward the observer where E is exposed, or away where T is exposed. Top Middle: a pair of twisted scroll rings is started from a similar bilayer, but shaped as a twisted band so it has two edges, mutually linked. Top right: initial conditions for a knotted scroll ring are fashioned from two disks of bilayer, joined together by three half-twisted bands. These initial conditions each consist a single surface bounded only by the singular ring(s). Bottom: as in top, but the single bilayer surface is bounded by the singular ring(s) and by the boundary surface of the three-dimensional medium. Arrows orient the wave edges: walking along the edge in the indicated direction you see the wavefront rotating clockwise.

yet computed linked scroll rings to compare with anticipations by topology and computer graphics.

Fig. 4 presents such a simulation in the format of fig. 1, shown at a moment long after initial conditions in a 23 by 23 by 23 cube. Initial conditions consisted, again, of a sheet of wavefront with edges exposed to the surrounding quiescence; those edges became the rotation axes of scroll rings. In this case there were two circular edges and they were linked: the sheet of wavefront was a cylindrical band containing one full twist as shown in fig. 5 (middle column). These edges curled up into counter-rotating scrolls. If a section plane cuts a source ring, it cuts twice, showing spirals of opposite hand as in fig. 1. Some sections in fig. 4 cut no source rings and therefore intercept sheets of wavefront along closed rings; others cut one ring, and so include a pair of opposite spirals; and still others cut both rings, and so show four spirals. This congestion could be alleviated by spacing the initial wavefront edges further apart in a bigger array, ideally of cells packed hexagonally like stacked cannon-balls. But they are far enough apart here to function as independent spiral sources with period four. The integer (unit) twist imposed on the initial band of wavefront persists as the unit twist of each scroll ring and links them together. This was verified by reconstructing the three dimensional wave from transparencies of its three orthogonal sets of serial sections.

In this discrete medium, initial conditions for all the foreseen organizing centers can be contrived quite simply as a sheet of wavefront (a bilayer of T and E cells) containing appropriate half-twisted bands. Fig. 5 (top) shows in this format suitable initial conditions for the plain scroll ring, the linked twisted pair of scroll rings (of which there is a mirror-image isomer not shown), and for a trefoil-knotted solitary scroll ring (which also has a mirror-image isomer). Although these wave sources function in complete independence of boundaries, like free particles, it is sometimes convenient to start them from a sheet of wavefront that initially touches the boundaries as in fig. 5 (bottom).

These sheets connected by half-twisted bands correspond in the continuum case to the Seifert surface [27–30, 33] bounded by any set of rings. Any Seifert surface satisfies the "exclusion principle" [27–29, 33] which specifies the unique twist associated with the wavefront near any one of its bounding rings. (We thank Professor Herbert Seifert for confirming our derivation of this fact

and for the tidier proof contained in the appendix.) The sheet of E cells corresponds to a local maximum of excitation (e.g. $HBrO_2$ in the Belousov–Zhabotinsky reagent), and the sheet of T cells behind it corresponds to a local maximum of inexcitability (e.g. Br^- ions in that chemical analog). By implementing such initial conditions for numerical solution of the equations of cardiac electrophysiology or reaction–diffusion equations, it should be possible to determine the stability of diverse organizing centers, or observe their modes of decay into simpler objects. In the case of fig. 1, for example, it appears that in continuous media the ring typically contracts, ultimately to nothing [1, 11, 24, 34]. What becomes of linked or knotted rings? Possible transmutation pathways have been outlined theoretically [29], but up to now the only such transmutation observed is fission of a single ring into two [34]. Much remains to be discovered.

Such discoveries may illuminate modes of arrhythmia in heart muscle that lead to sudden cardiac death [35]. They may provide hints as to the patterns of stimulation which initiate such lethal waves, and suggest means less damaging than high-current electroconvulsion of the ventricle for terminating them.

Acknowledgements

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Appendix A

A property of Seifert surfaces

by Professor Herbert SEIFERT
with comments by A.T. WINFREE

Notation

Given a set of R closed oriented (and possibly knotted) rings $\{K_1, K_2, \ldots, K_R\}$ embedded in three-dimensional Euclidean space E^3, denote by L_{ij} the (integer) mutual linkage of ring K_i through ring K_j' traced arbitrarily near to ring K_j along a compact (nonsingular) oriented surface F whose boundary consists of the R oriented closed rings.† In [27–29, 33] this F was constructed by the Seifert algorithm to span the collection of rings. It is intended to represent a chemical wavefront, half of a closed surface of uniform chemical concentration. By D_i denote a (singular) disk with boundary K_i. This construct has no direct chemical interpretation. So F together with the set of disks $\{D_i\}$ is a closed singular surface, here denoted by G.

We next consider the intersection number of a curve K_i' with F and with G. The intersection number $I(C, S)$ of an oriented curve C with an oriented surface S is the integer number of times the curve penetrates the surface with same orientation, minus the number of penetrations with opposite orientation. Thus the intersection number of any closed curve with any closed surface is 0 in E^3.

Argument

For each i, $I(G, K_i') = 0$. But G is the sum of F and all the D_j, so:

$$0 = I(G, K_i') = I(F, K_i') + \sum_{j=1}^{R} I(D_j, K_i').$$

The first term on the right is 0, since each K' lies on F and can be approximated by a curve that does not meet (non-singular) F at all. The second term (the sum) is the sum of all L_{ij}: $I(D_j, K_i') = I(D_j, K_i)$ is the linkage of K_i with K_j, the boundary of D_j.

In short, $\sum_{j=1}^{R} L_{ij} = 0$ for each i.

† T. Poston suggested this simplification of our usual definition [27–29, 33], which distinguished the case $i = j$.

This is the property remarked on in the text, deduced from physical considerations as an "exclusion principle" delimiting the diversity of chemically realizable "organizing centers" [27–29, 33]. This appendix shows that the exclusion principle, while classifying geometrically consistent organizing centers and assigning quantum numbers L_{ij} to each, has little physical content. Physical principles may further delimit the possibilities by identifying long-term instabilities and modes of decay in some (or all) of these solutions.

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