

FOCUS ISSUE: Fibrillation in Normal Ventricular Myocardium

Evolving perspectives during 12 years of electrical turbulence

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This Focus issue describes a problem in electrical dynamics which has fascinated generations of physiologists. There are today so many views of fibrillation that only the rarest generalization can embrace all of them. Fifty-two prominent investigators collaborate here to present aspects of the problem in these eighteen articles (including this introduction) tailored for readers whose principal expertise lies elsewhere. In “The High One’s Lay” (Norse Runes, ca. 800) Odin remarks, “Much too early I came to many places: the beer was not yet ready, or was already drunk...” but to this one we come at very nearly the right time in 1998. This introduction attempts to guide newcomers by noting the changed or multiple meanings of novel technical terms while sorting the key facts and ideas into an order that facilitates comparison and contrast with those of a dozen years ago. This Focus issue is authored by some of the foremost innovators of both theory and experiment in this area. By assimilating their presentations the readers of *Chaos* can become well poised to appreciate and evaluate the definitive evidence expected in the next few years. © 1998 American Institute of Physics. [S1054-1500(98)02701-3]

The introductory paragraph of many recent papers on this topic reminds us (see American Heart Association web site www.amhrt.org/1997/stats) that fibrillation is the dominant immediate cause of death in the industrialized world. In the USA sudden cardiac death, usually involving fibrillation, ends at least 1000 lives daily (1 out of 6 deaths). Probably these hearts were not all as normal as the victims had believed, but probably 1/4 of them were, so far as prior symptoms or subsequent autopsy could detect. For the sake of simplicity, reproducibility, and hope of quantifiability, in this collection of studies we try to focus on fibrillation in healthy, normal ventricular myocardium. Because fibrillation is immediately fatal in the ventricles, its longest history of successful investigation concerns not the ventricles but the atria. And the practical motivation of this problem, of course, derives from the misbehavior of diversely abnormal tissues. So we include several contributions to connect this attempted focus to those larger contexts. All but these bridging exceptions address electrophysiological preparations as close to “normal ventricles” as could be arranged, considering that most are *in vitro*, thus denervated, and in many cases sliced thin and imperfectly perfused, lacking the natural blood supply. But there are no infarcts or deliberately imposed random inhomogeneities, and few simulated or real pharmaceutical modifications of normal electrophysiology. These may be practically important features of myocardium in the clinical context, but our aim is to understand the nominally normal case first, if only because it can be clearly described.

These papers were refereed mostly within the same group of authors. Referees did not accept every paper and did not agree with everything here printed. There remain differences of experimental outcome in ostensibly similar laboratory protocols, differences of preference for theoretical frameworks of interpretation, differences of emphasis in the maze of seemingly contradictory “experimental facts” and of numerical metaphors alluded to in the prior literature, and differences of outcome after analytical or numerical reasoning. As always, where topics overlap the critical reader has an opportunity to learn by comparison and contrast. We made a special effort to enhance this opportunity by adopting a tutorial style, avoiding or defining technical terms, and cross-referencing each other. I contribute (I hope) by embedding all contributions in my own context. As in any other area of long investigation, special vocabulary accumulates over the decades. In genetic evolution analogous processes result in speciation and barriers to interbreeding; efforts like this introduction aim to promote cross-fertilization by removing some of the barriers. In hopes that it helps for orientation, I try below to provide a perspective on the questions addressed in this issue by salting their recent history with notes hopefully clarifying terminology.

This production required a major effort from every author, from several outside referees, and from our editorial assistant, Janis Bennett. On behalf of Chaos readers I convey earnest thanks to all for your diligence and patience.

THE LAYOUT OF THIS ISSUE

First we have contributions focused most closely on ventricular fibrillation in normal myocardium: 2- and 3-dimensional simulations (**Biktashev, Fenton, Gray, Pan-**

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filov) and 2-dimensional observation of 3-dimensional experiments (**Jalife, Witkowski, Bayly**). These are followed by strictly 2-dimensional experiments (**Cabo, Chen, Kim**). Complementing these, several contributions touch applications to abnormal myocardium: experiments *in vitro* (**Chen, Kim**), *in vivo* with (**Janse**) and without (**Bayly**) total cardiopulmonary bypass, and *in numero* (**Xu**), deliberately involving ischemia and pharmaceutical alterations. From an experimentalist's point of view most of the numerical experiments presented (**Biktashev, Fenton, Gray, Panfilov, Trayanova, Xu**) might be considered to represent abnormal myocardium in the sense that there are no Purkinje fibers (whose importance is stressed by **Janse**), no innervation, and/or no rotational anisotropy, that the presumed ionic channel mechanisms are still undergoing major revisions from year to year (for example, **Xu** makes an order-of-magnitude alteration of the Luo–Rudy model), and/or that intercellular coupling coefficients are accentuated by 1–2 orders of magnitude (**Gray, Panfilov**). Then the converse, with an eye to the practical motivation behind this puzzle: calculations attempting to understand and optimize electrical *defibrillation*, necessarily in at least 2 dimensions (**Keener, Krinsky, Roth, Trayanova**.) Finally, a methods paper points to the necessary future of simulation in this area with a practical algorithm for calculating bidomain electrophysiology (**Keener and Bogar**).

All laboratory reports here are 2-dimensional, though some may favor or even require 3-dimensional interpretations such as given in modeling papers (**Biktashev, Fenton, Gray, Panfilov**.) **Bayly** seeks a general-purpose algorithm to characterize the complexity of high-dimensional fibrillation, which **Chen** seeks in the bifurcation sequences known to lead to low-dimensional chaos. **Cabo** focuses on propagation failure where activation fronts have such short periods that they cannot adopt the short radius of curvature needed to get around a sharp corner (with attention to what “curvature” means in an anisotropic medium). **Jalife** reviews evidence of the scroll waves expected in thick heart walls, and of unexpected rotors and fibrillation in even the smallest hearts. **Janse** reminds us that fibrillation may have quite different characters depending on wall thickness and on the presence or absence of an endocardial lining of Purkinje fibers seldom included in models. **Chen** shows that fibrillation can start and continue without them in otherwise normal ventricles. **Kim** makes the first determined attempt to characterize meander in myocardial rotors, but finds their motion so unsteady that they seem subject to annihilation and creation events at intervals of only a few rotations, corroborated by Gray *et al.* (1998). **Witkowski** presents a new standard of resolution in epicardial mapping of fibrillation.

For tutorial introductions, readers who want to test the completeness of their background information before proceeding might first want to browse sections in **Cabo, Fenton, Gray, Jalife, Janse, Roth, and Trayanova**. While most of these papers review background, they also present novel research findings for the first time. How can the reader new to this area recognize interesting novelty? Partly by noting divergences of opinion between these overlapping presentations, but maybe more economically by finding in a review

article of modest vintage some old snapshots for contrast against present-day advances. Workers in the field carry such snapshots in memory, but cross-disciplinary readers might not. Thirteen years ago I wrote such a review (Winfree, 1987), stressing fibrillation as a 3-dimensional dynamical mode of normal myocardium alternative to its usual mode, i.e., as a spatial pattern of normal response to encroaching activations, a pattern masked by rather than based on random parametric inhomogeneities. This review remains both familiar to me and sufficiently out of date to provide the wanted contrast, so I use it here as a benchmark standard of what was then understood or thought to be understood or at least queried, to highlight the clearer views provided in today's Focus issue.

THE GROWTH OF A RESEARCH AREA

The 420 citations in this “benchmark” fall off by half for every 5 years of age (starting to 1–2 years prior, reflecting a lag in assimilating new publications.) The 595 distinct papers cited in this Focus issue include some of those plus 450 newer. Sorted by time since publication, their normalized histogram is not distinguishable from the older one, nor from the 1000-item reference list of an earlier book on related topics (Winfree, 1980, graphed on page 459.) This shape probably combines the growth of research publication generally [doubling in every 8 years in my *cumulative* bibliography of citably valuable contributions maintained since 1980 (<http://cochise.biosci.arizona.edu/~art/4559> and 4560 .more)] with a tapering of interest by half for every 12 years of vintage. Accordingly, the week “benchmark” was sent to the printer (Nov. 1985) I noted on a long-term calendar that I'd like to find an opportunity to organize another review by 1997, after interest in those papers fades by half more, being superceded by as many reports then unforeseen. This is it. Electrical stimulation, fibrillation, and defibrillation are still not quantitatively understood, and the case in which that may first be achieved (normal, healthy myocardium) still attracts less attention of experiment and simulation than do illuminating aberrations. The analyses in this Focus issue compensate by converging on normalcy from all sides. Some of the themes that stand out in this review are the following.

- A. The influence of parameters for prevention or reversal of fibrillation
 1. Pharmaceuticals
 2. Current density
- B. The dynamics of rotors in 2D and in 3D, both models and real myocardium
 1. Ballpark figures for orientation
 2. Jargon
 3. Rotors in 2D
 4. Rotors in 3D
 5. More jargon
- C. Technological advances for observation of hearts and of equations
- D. Where does this problem stand today?

In the next few pages I outline these topics, referring in

boldface by first author to the papers in this Focus Issue, and by (author, year) to a hundred others, half of them not mentioned elsewhere in this issue.

A. The influence of parameters, for prevention or reversal of fibrillation

Prevention and control of cardiac arrhythmias are currently exercised through chronic systemic pharmaceuticals and through acute electrification. Understanding, predicting, and optimizing their effects is necessarily a major growth area for theory. The aim of both classes of treatment is to so modify the electrical dynamics of cardiac tissue that it becomes less vulnerable to short-period rhythms and to their instabilities that end in fibrillation. At present both classes of treatment are approached in a completely and frankly empirical way, and not entirely successfully. The present trend is toward electrical devices, away from drugs.

It is not yet known that rotors are prominently involved in developed ventricular fibrillation; my impression 8 years ago (Winfree, 1991a p. 511) that “nothing like the putative vortices are visible in this first high-resolution movie of a fibrillating epicardium,” seems still valid. But they do seem prominent during the transition to fibrillation, so it is important to relate pharmaceutical concentrations and electric current densities to their dynamics.

A.1. Molecular interventions

“Antiarrhythmic” pharmaceuticals of four classes are licensed by the Food and Drug Administration on grounds of what seems in retrospect rather indirect inference that they should prove beneficial. Class II (beta blockers like isoproterenol, based on the inhomogeneity theory discussed in **Cabo**, in **Janse** and in **Xu**) have clearly worked quite well by insulating the myocardium from sympathetic neural stimulation. But several belated large-scale controlled clinical trials of several widely prescribed class I and class III drugs had to be terminated since the late 1980s because users were dying three times as fast as matched patients taking placebos. Moore (1995) estimates 40 000 excess deaths/year in the USA (100/day) due to these prescriptions. Empirical selection of new molecules by animal experiments calibrated by “surrogate endpoints” is not working well in the absence of quantitative theory.

Electrophysiologists do not know how to introduce drug concentrations as parameters into the reaction-diffusion equations used to simulate the electrical vortices. There have been hopeful beginnings (e.g., Krinsky, 1978; Zykov, 1984; Winfree, 1991b; Starobin *et al.*, 1994; Starmer *et al.*, 1995) but their outcomes have not commanded widespread attention. Though the subject is definitely regarded with the keenest interest, I was unable to obtain for this issue a theoretical analysis of the problem that proved understandable to a series of referees. Something new is needed and it is not entirely clear where to begin. Readers viewing our problems from unusual perspectives may find something unique to contribute.

A.2. Current density

In contrast, we **do** know where to begin in the case of current density as a parameter modulating dynamics. And here the need is comparably great. Defibrillation by massive electroshock may be the best currently available expedient, but it is crude by any standard. Theoretical inquiry into the cellular biophysics of electrical defibrillation is almost entirely a post-benchmark production. A basic problem is that the heart is inhomogeneously shocked: even with the best practical electrode geometry, power density is 2 orders of magnitude greater in the few percent of volume most electrified than in the least (Ideker *et al.*, 1991, Winfree, 1991a, Min and Mehra, 1998, Fig. 4). The power range between minimum effectiveness [conductivity times $(5 \text{ V/cm})^2$] and membrane damage [conductivity times $(50 \text{ V/cm})^2$] is no wider. Providing adequate electrification everywhere can therefore entail harmful overdose in some regions, besides running down the batteries of implanted devices. **Biktashev** reviews some novel low-power alternatives based on isotropic monodomain theory of rotors (see also Winfree, 1990e, Section 7 and A.3. below).

What is a stimulus? This question sounds so simple that anyone could be forgiven for imagining it must have been answered long ago. But it remains a hot area for both experiment and theory (Roth, 1994), and so far as normal myocardial tissue is concerned, theory and experiment still differ tenfold. The difficulty derives from the facts that myocardium is cellular (a conducting volume segregated by insulating membranes on the scale of hundredths of a mm into inside and outside connected pathways), that the cells are resistively connected by gap junctions, that they are oriented fibers (anisotropic), that their orientation rotates plane by plane through the heart wall (i.e., the anisotropy is nonuniform on the scale of several mm), and most crucially, that current is deliverable only through the extracellular space. Moreover both cell-scale and tissue-scale electrical discontinuities create voltage inhomogeneities even where bulk current density is uniform. The effective stimuli thus might occur only as “hot-spots,” extremes in the spectrum of inhomogeneities, about which we learn little from mean field approximations.

A related problem is that in the experimental literature thresholds for pacing, for instigation of fibrillation, and for defibrillation are characterized in ways that remain hard to interconvert: local transmembrane current density or potential shift (**Biktashev**, **Trayanova**), total energy or current or voltage from an electrode (of whatever shape, seldom exactly specified except in theoretical papers), or local extracellular current density or voltage gradient as used here. For example, when Knisley *et al.* (1992) rechecked the benchmark vision of rotor creation by spatially patterned reset of myocardial cells along their excitation-recovery cycle (Winfree, 1987 Figs. 4.9a and A2-3) and the corresponding roles of a critical 5 V/cm field (Winfree, 1989a, 1991a), they had to calibrate laboratory stimuli in terms of extracellular potential gradients (V/cm on their Fig. 6) whereas the first theoretical diagrams (lower left Fig. 4.9a) were necessarily calibrated in transmembrane $\mu\text{A/cm}^2$. These diagrams are operationally comparable because both span about 1 to 20

times diastolic threshold, but the biophysical mechanisms of conversion remain uncertain.

Along fibers, about 0.6 V/cm of voltage gradient applied extracellularly (Frazier *et al.*, 1988) suffices to stimulate well-recovered excitable tissue, considered in bulk. The cellularly driven extracellular voltage gradient that excites tissue ahead of a moving activation front is no more than twice this size. Such fields induce the 20 mV displacement of transmembrane potential needed to cross the cell's firing threshold. A field about five times as strong is needed to initiate a vortex in experiments quantifying the ventricular fibrillation threshold, or to erase one in attempts to determine a defibrillation threshold. To interpret these facts in cellular terms will require bidomain continuum theory and perhaps other devices which are only beginning to appear. At benchmark the qualitative idea had developed as follows. On the crude analogy of myocardium to a conducting gel, one could estimate the voltage gradient a few cm from the extracellular source, then suppose that randomly oriented cells respond (on average in bulk) to that field. In more orderly models, based on the analogy of straight conducting cylinders embedded in such a gel, the intervening membrane responds only to currents crossing between these intracellular and interstitial domains not far from extracellular source (Weidmann, 1970): the response is to the divergence of the gradient, the Laplacian, rather than to the gradient of voltage (Roth, 1994). A third view was that because fibers in fact irregularly twist, turn, branch, and connect through resistive junctions, current does not *get to* stay on one side of the membrane, but is continually repartitioned, depolarizing membranes as it crosses even several cm from the extracellular source. At any distance from source then, curving fibers are skewered by about the same small fraction of local current density (empirically, around 1/1000), resulting in microscopic adjacent patches of hyperpolarization and depolarization, some of them apparently sufficient to balloon into large depolarizations.

Today **Keener, Krinsky, Roth, and Trayanova** view from different quantitative perspectives the bulk stimulation of myocardium by electric fields or current. There remains doubt about the mechanisms by which an electric field between remote electrodes elicits or prolongs action potentials (Dillon, 1992; Knisley *et al.*, 1992; Roth, 1994, Section 6; **Roth**). The roles of anisotropy, fiber or field curvature, and electrical discontinuities particularly still need clarification. At benchmark, it was clear that fields must drive current through cylindrical cells in proportion to the external bulk current density or voltage gradient, and that the consequence would depend on the angle between field and fiber, but it was supposed that fiber wiggleness would largely average out such distinctions within volumes exceeding several mm³. Macroscopic results accordingly might depend on averaged anisotropy (direction) but should not depend on polarity. Frazier *et al.* (1988) reported that stimulation in 3-dimensional anisotropic myocardium occurs wherever 0.6 V/cm is exceeded longitudinally or 1.8 V/cm transversely, and inferred that this corresponds to roughly 4 mA/cm² of extracellular current density independent of direction (which is incompatible with monodomain continuum models, but might agree

with estimates possible in the bidomain model with acceptable choices for its unknown resistivity ratios). Polarity did not matter. At benchmark, attempts to understand Frazier's result in terms of a "sawtooth" model fell short of observation by an order of magnitude, and a comparable gap remains today despite deployment of immensely sophisticated analyses. Maybe some physical principle is missing. An anatomical basis for the "hot-spots" of Winfree and Guilford (1988) arose in the mm-scale "unit bundles" of Krassowska *et al.* (1990), but while these would repair the order-of-magnitude discrepancy, their physiological reality remains to be proven (Gillis *et al.*, 1996). **Roth** suggests that an additive combination of physically distinct mechanisms will be needed to explain the observed low thresholds for field stimulation.

A.3. Defibrillation by a single brief electrical shock

The mechanism of electrical defibrillation by the classical rough treatment with a single large direct-current shock, applied from extracellular sources at least several cm apart, remains still unknown. Issues supplementary to those involved in mere stimulation are that the defibrillating stimulus is bigger, perhaps going outside the domain of validity of membrane models, and that the tissue so stimulated was heterogeneously active, not uniformly quiescent. In 3 dimensions the Laplacian argument still says that part of the large current should cross membranes to enter or exit cells within a mm or so from the extracellular source, leaving membranes unstimulated in the larger bulk where current flows separately within the interstitial medium and within the connected volume of cells. But the fact is (e.g., Frazier *et al.*, 1988; Zhou *et al.*, 1995) that centimeters from electrodes there **are** fields sufficient to stimulate, and they do arrest fibrillation. During preparation of the benchmark review my own attempted analyses in terms of changing orientations of fibers and fields in 3 dimensions ground to an inconclusive halt at least because of unfamiliarity with bidomain theory and because there were no quantitatively reliable figures for the pertinent resistivities and fiber curvature rates, nor measurements of thresholds in relation to anisotropy. Things are much better today though still imperfectly quantitative (Roth, 1994, Section 6). **Keener, Krinsky, Roth, and Trayanova** work through the pertinent electrophysics in different ways, still obtaining high estimates of stimulus threshold from each physical mechanism separately, but estimates of defibrillation threshold seem closer to reality. Monodomain ionic membrane models such as **Biktashev's** still define stimuli in transmembrane terms ($\mu\text{A}/\text{cm}^2$ or mV displacement), necessarily content with loose estimates of the imposed extracellular fields that would induce such consequences. Bidomain models like **Trayanova's** are necessary to provide a quantitative "exchange rate" formula between external V/cm defibrillating fields and biophysically meaningful transmembrane currents or potential displacements.

At benchmark the microscopic heterogeneity of potential in a current-skewed cell was thought to subvert a traditional conceptual framework in which tissue is seen as convoluted membrane projected to a state space where every patch executing normal action potentials traverses a closed loop (narrower, the shorter the period) and every rotor maps

to the area inside the loop executed at that period. Fibrillating tissue may thus map to a multilayered image. There are many ways a single stimulus can so distort this state-space image that it loses stability and shrinks to uniform equilibrium, ending reentrant propagation. This may be *defibrillation*. One of the simplest ways is modest displacement along the voltage axis (e.g., Winfree, 1978, Fig. 23; Keener, Section 3.2). This would make immediate sense if we were dealing with *intracellular* electrification (e.g., by a micropipette uniformly hyperpolarizing or depolarizing each cell) but if that current comes from outside, skewering membranes in all directions, then this coherent image is shredded to opposite voltage extremes on a microscopic scale. Like many theorists, I can only think in state-space images, but when in print usually with an apologetic note that the postulated displacement of the cell's image has to somehow compromise opposite displacements of its minute parts, and a wistful hope that someone will figure out how this is effected (e.g., Winfree, 1987, 1989a, 1990e Section 7, and 1991a p. 511). Tung and Borderies (1992) then Krassowska and Neu (1994) achieved this. Membrane potential displacements directly caused by the transfixing current of course integrate to zero over the closed membrane, but their variance does the job. Hyperpolarized patches let current in to discharge the membrane, which enhances depolarization on the other side of the cell until those patches cross threshold for regeneratively active depolarization, letting in even more current. Taken as an integral over the closed membrane, these active potential displacements initiated by the extracellular field constitute a uniform *intracellular* potential that plays the wanted role analogous to space-clamped transmembrane potential in models lacking geometry. This vision makes possible an understanding of the dynamics during extracellular stimulation of each cell as a single point in an abstract state space such as here deployed to good effect in **Biktashev, Keener, Krinsky** or in the pre-benchmark defibrillation model of 1978.

The latter may also interpret the remarkable observation of Dillon (1992) that within msec every patch of tissue in heterogeneously fibrillating tissue exposed to a defibrillating field, regardless of its initial phase in the 100-ms cycle of fibrillation, resets to the beginning of that cycle and synchronously executes a 100-ms action potential. [Knisley *et al.* (1992) made a similar observation in non-fibrillating tissue.] Described in the simpler concepts of the later benchmark review (Fig. 4.9a) or of Gray *et al.* (1998), this resembles the "type 0 phase resetting" that plays such a central role in creation and destruction of phase singularities. Suppose that during fibrillation membrane is found only in the rotor's special area of state space and along its bounding loop traversed by fronts propagating away from rotors at that short period. Then to erase all such "reentrant" (uninterruptedly circulatory) patterns, uniform electrification by little more than about a loop diameter should suffice. During field stimulation the cell membrane's image in state space is shredded in opposite directions by transfixing currents, but an integral over the membrane defines an intracellular potential which behaves as though the cell were uniformly charged (Krasowska and Neu 1994). During this time it still has a representation as a single point in state space alongside those of

neighboring cells, and they all move in a dynamical flow similar to that of a current-biased uniform patch.

The empirical measure of "loop diameter" for such type-0 phase resetting was "whatever extracellular field suffices to create a rotor, in theory by pushing cells across the loop traversed in state space during normal excitation and recovery." Membrane models said that this critical stimulus, S^* , should be several times the nominally 1-V/cm field needed for diastolic stimulation (e.g., the ratio of 100-mV loop diameter to 20-mV threshold in the Beeler-Reuter model.) This "should" and apparently does suffice for defibrillation with two orders of magnitude less energy than present clinical standards (Winfree, 1990a, 1991a), and requires no such understanding of geographical dynamical patterns as sought in this Focus Issue (Sections B.3, B.4). But it requires more uniform fields than can be arranged by practical electrode designs, and of course such minimization leaves no safety margin.

A shock below S^* of course achieves phase-dependent and therefore place-dependent "type 1" resetting. Its spatial pattern near a rotor amounts to a systematic geographical displacement of that rotor. Repeated periodically at the intervals of detected fibrillation, this might constitute a "kinder, gentler" method of defibrillation (Winfree 1978, 1988b, 1990e, **Biktashev**.) This worked (Kirchhof *et al.*, 1993; Alessie *et al.*, 1994; KenKnight *et al.*, 1995) in the sense that a region of fibrillation can be entrained to freedom from phase singularities (reentry) but whether it worked by the mechanism originally proposed remains uncertain.

This dual import of the singular stimulus (inducing fibrillation if some region gets a steep gradient through S^* , defibrillating if every place gets $>S^*$ or repeatedly $<S^*$) came to be called "the critical point hypothesis" or "the upper limit of vulnerability hypothesis" of defibrillation. It is sometimes contrasted against the earlier "total extinction hypothesis" or "critical mass hypothesis" according to which the only requirement is simultaneous activation of most of the muscle mass (with no specifications regarding area, volume, or shape of the exceptions). But to my mind they are all aspects of the same idea, viz., the benchmark view (pp. 135–138) that intensity $>S^*$ must be realized for a few ms throughout the fibrillating volume, leaving no pockets big enough to hide a rotor and without creating new singular points or vortex filaments better isolated than that where field inhomogeneities steeply fall through S^* . (For a view from Fall 1988 with 3-dimensional implications, see Winfree, 1990e Fig. 26-14). Some statements of this hypothesis include the idea that there is an "isoelectric window" of at least some tens of ms after extinction of fibrillation before new critical points blossom into renewed fibrillation. This remains controversial (Witkowski and Penkoske, 1990a and b; Chen *et al.*, 1991; Ideker, 1991; Walcott *et al.*, 1996; Kwaku and Dillon, 1996; Gray *et al.*, 1997) so its absence should not be used to exclude the central idea.

Roth (Fig. 10) and **Trayanova** explore the role of continuously changing relative orientation of fiber/field in an ionic bidomain model. **Trayanova** provides a model of extracellular defibrillation by analyzing not gap junction discontinuities, but fiber/field orientation quantitatively and ex-

hibiting an instance of rotor exorcism in a bidomain with cell membranes that follow a realistic ionic mechanism. At first glance the result might look like the method illustrated in the laboratories of Mehra (1984), Mehra and Santel (1995), and of Bonometti *et al.* (1995): a pair of rotors (similar to **Trayanova's** single rotor near a no-flux barrier) has its rotation obstructed by an activation propagated from a stimulus electrode into the narrow common pathway between them just in time to collide and annihilate. These experiments required careful placement of electrodes and timing of the stimulus. In contrast, **Trayanova** does it more in the style of erasing multiple rotors in a chemically excitable medium by illumination. A 10 ms pulse at 19 V/cm directly deforms the rotor by a field effect independent of gap junctions and independent of propagated activations. My interpretation is that this shock displaced the rotors' image in state space by more than half the diameter of the excitation-recovery loop, thus kicking the rotor off its stable vortex in the standard excitation-recovery loop, whereupon it vanishes while its image collapses in state space (see Winfree, 1978, Fig. 23.) However, this is not explicitly graphed in the bidomain computation shown here, and should be checked.

This method does not require careful timing or placement of electrodes. It only requires that the local field should exceed (as **Trayanova's** does by at least a factor of 4) roughly S^* within an area linking every rotor to one of opposite handedness or to the boundary. This numerical experiment is noteworthy because the usual demonstration of rotors in an ionic model of myocardium completely neglects the extracellular medium, and so *cannot* represent defibrillation by extracellular shock. Though 19 V/cm \times 10 ms may seem a big shock compared to **Krinsky's** estimate of 14 V/cm longitudinally at 4 ms, or to laboratory experience near 5 V/cm for 3 ms (Ideker *et al.*, 1991; Winfree, 1991a p. 512; Knisley *et al.*, 1992), this is the first time any extracellular shock has been quantitatively shown to do the job in a biophysical model. The target is clear and theory is converging on it.

A.4. Electrical induction of VF

To induce fibrillation deliberately, electrical pacing at a very short or shortening rate suffices (**Janse, Bayly**). The mechanism is not yet quantitatively understood, but has something to do with the instability of very short-period activation fronts.

Electric shock will also induce rotors by the simpler "pinwheel experiment protocol" (Roth, 1998) or "crossed gradients" protocol of benchmark antiquity as done in a chemically excitable medium (Winfree, 1985, Fig. 12.19), calculated from a cardiac ionic model (Winfree 1986, p. 97), and executed in ventricular myocardium (Shibata *et al.*, 1988; Witkowski *et al.*, 1998b). This was designed to test the notion that a phase singularity of predictable handedness must arise where gradients of phase and of effective stimulus intensity (whatever its cellular mechanism may be) cross through a critical pair of values. It was repeated with radial or mirror symmetry in several laboratories under new names "S1-S2 protocol" (**Xu**), "twin-pulse protocol" (**Biktashev, Frazier et al., 1989), "twin stimulus protocol" (**Biktashev,****

or "cross-field stimulation" (**Biktashev, Chen, Jalife, Roth, Trayanova**). This last name, as originated by **Davidenko et al.** (1991) and **Pertsov et al.** (1993) seems to connote at most (perhaps not even) *one* "field": the refractoriness gradient behind an S1 activation front. The name mutated with the protocol (from "crossed gradients") but it is not clear that the stimulus field or S^* play any important role, but extreme curvature of the front probably does, also in contrast to the original version. Just as in **Wiener and Rosenblueth** (1946), this protocol imposes a mere pacing-size localized stimulus (along a bipole-pair of long wires extending down the timing gradient from refractory to excitable regions) to initiate opposite-going activation fronts. Their critically curved endpoints at the refractory zone race apart at the speed of propagation then presumably rotate as the tips drag behind and become rotors. This is more like the 1985 chemical experiment, with barely trans-threshold stimulation along a line, except that front curvature plays a crucial role and the redundant mirror-image part is now not occupied by tissue. In any case, these several names are *not* consistently used or distinguished in recent literature.

At benchmark, the design for such experiments anticipated outcomes systematically ranging in concentric rings from fibrillation to no response, around a "phase singularity" or "singular point" (mutated in citing literature to "critical point" by **Frazier et al.**, 1989) on a plane describing possible stimuli by time and size. The top of the central "black hole" or "bull's eye" of fibrillation has come to be called the "upper limit of vulnerability." Such experiments have since appeared, using diverse methods and preparations, and all show the anticipated target pattern with upper and lower limits of vulnerability (Winfree, 1983; Winfree, 1993b with figures from **Shibata et al.**, 1988; **Frazier et al.**, 1989; and **Davidenko et al.**, 1991; and **Fabritz et al.**, 1996.)

In contrast, **Chen** stresses that the onset of fibrillation is probabilistic: no threshold can be strictly defined. It should also be noted that the vulnerable phase single-shock electrical "ventricular fibrillation threshold" is really a threshold only for creation of rotors and onset of tachycardia. **Jalife** argues that this may be the same thing in 2-dimensional situations: some kinds of fibrillation consist of a single rotor. Geometrical thresholds for transition to 3-dimensional fibrillation are discussed below.

B. The dynamics of rotors in 2D and 3D

B.1. Ballpark figures for orientation

It helps, for orientation, to begin with an awareness of the dimensions and magnitudes of a handful of prominent entities, at least to order of magnitude. One is the dimensionless ratio, $O(10^0)$, of squared propagation speed times activation rise time to the gross macroscopic electrical coupling coefficient, D . Another is the "quality factor" $Q = O(10^2)$, the dimensionless ratio of rotor period times squared propagation speed to the electrical coupling coefficient, D . It then follows that the dimensionless ratios of rotor period to activation rise time, and of rotor wave train spacing

(period times speed) to the critical radius of curvature (D/speed) for a viable nucleus of expanding excitation, are both $O(10^2)$.

A few dimensioned numbers are also helpful for orientation. The “coupling coefficient” alias “electric potential diffusion coefficient,” D , is probably about $1 \text{ cm}^2/\text{s}$ along fibers and $10^{-1} \text{ cm}^2/\text{s}$ transversely (though **Cabo** uses twice this along fibers and **Fenton** uses twice this transversely, and **Gray** and **Panfilov** use much larger values). In normally excitable media propagation speed is accordingly about 70 cm/s along fibers and $1/3$ that transversely. Rotor diameter is about 1 cm along fibers or $1/3$ that transversely or transmurally, which is close to the observed threshold thickness for fibrillation. (**Jalife** suggests these estimates should be adjusted downward for his mouse hearts.) The corresponding area is close to that of the smallest hearts able to sustain rotors. Rotor period is about 10^{-1} s , activation rise time is about 10^{-3} s . The macroscopic singular stimulus intensity, S^* , seems about 5 V/cm of extracellular field (or 20 mA/cm^2 current density) needed to create rotors (thus quantifying the ventricular fibrillation threshold) or to erase them (thus quantifying the local requirement for defibrillation (Winfree, 1990a; 1991a; Knisley *et al.*, 1992).) S^* is the stimulation threshold (about 5 times diastolic threshold) at the stage of recovery called “the vulnerable phase.” Traditional use of gross extracellular field intensities to characterize electrical thresholds independent of fine anatomy is, of course, purely empirical. The assumption is that any block of tissue some mms in diameter presents fibers in all possible orientations to the field and so will respond in the same way as any other block when the gross field intensity is the same. Maybe it would be better to use 3 V/cm transverse to fibers and 9 V/cm along fibers, but at the present stage the mean is used indiscriminately. Big stimuli achieve threshold S^* along a surface of large area far from source. Smaller stimuli may not achieve it at all, but achieve the lower threshold for stimulation in a tiny area close to electrode, which, repeated at critically short intervals as in the experiments of **Janse**, may create rotors by another mechanism which remains to be modeled convincingly, perhaps some such mechanism as reviewed by **Xu**.

Readers looking for quantitative consistency should take warning that numerically specific prediction is new to this area. Discrepancies as small as twofold between observations or about fivefold between experiment and theoretical expectation are still considered encouraging. For example, **Keener**'s model, invoking only the influence of gap junctions, estimates 5 V/cm ($\times 10 \text{ ms}$) needed for longitudinal stimulation of quiescent tissue (c.f. $0.6 \text{ V/cm} \times 3 \text{ ms}$ reported by **Frazier et al.**, 1988) and **Biktashev** takes 10 V/cm as the defibrillation criterion (c.f. 5 V/cm above.) **Panfilov** and **Gray** simulate propagation with 2 to 20 times the longitudinal D value suggested above and 5 to 50 times the transverse value. The importance or unimportance of such choices remains to be clarified. It is usual to take liberties with these parameters, especially in assigning units to dimensionless abstract models, because, modulo a rescaling of time and space, normal parameters are equivalent to abnormally larger D and slower kinetics. If all aspects of local membrane ki-

netics were slowed by factor $\text{slo} > 1$ and all components of D were magnified by $\text{mag}^2 > 1$ then the outcome from simulating such a heart of size H (e.g., using dog anatomical data) would be the same as from computation with normal parameters on a smaller heart of size $H/\text{mag}/\text{slo}$ that beats slo times faster (e.g., rabbit). After such a model's time and space units are chosen to match laboratory propagation speed and rotor period, the reader still needs to ask what these ratios were, whether they were consistently used, and what the consequences are. For example, selectively exaggerating transverse D (as in 3-dimensional models that neglect anisotropy) makes the heart wall disproportionately thinner electrically, so a superficially 3-dimensional model may in fact be functioning 2-dimensionally.

B.2. Jargon

A collection of near-synonyms throughout this Focus issue describe the rotors resulting from such symmetric electrification. Following a related usage in cardiology (for paired vortices on the epicardium, whatever may be the mechanism) the pair is sometimes called “figure-of-eight reentry” (e.g., in **Chen**.) Their pivot points were originally called “phase singularities”, and the diffusion-integrated cm-size areas around them were called “rotors” (Winfree, 1978). At benchmark, naming conventions still distinguished among alternative hypothetical mechanisms with distinctly different characteristic behaviors. For example, the mechanism of Wiener and Rosenblueth (1946) involves an inexcitable obstacle, thus fixing the reentrant source in place with idiosyncratic period longer than the rotor's; Garrey's (1924) mechanism is restricted to a blockable 1-dimensional path; the “leading circle” of **Allessie et al.** (1977) has a shorter period than the rotor, having no excitable gap. Any such mechanism of reentry (uninterrupted circulation of an impulse) radiates a “spiral wave” or “reverberator” into an adequate area of surrounding tissue. Of course, laboratory preparations are seldom that large unless cell-cell coupling is weaker than suggested above (**Delgado et al.**, 1990; **Davidenko et al.**, 1992; **Pertsov et al.**, 1993) so one seldom sees more than a slightly curved segment of activation front spasmodically circulating around an irregularity. These distinctions have become blurred in recent years, so that now “spiral wave” often refers not to such a wave (which is not present) but to the source, the rotor, which presumably *would* develop an observable spiral in a larger tissue. “Rotor” has also come to mean any and all possible rotating source mechanisms (**Jalife**). It may even be true that “spiral waves are usually called rotors” (**Roth**, referring mainly to simulations, since spirals are hard to find in normal myocardium.) **Xu** initially conforms to this broadened meaning but finally recommends that it would have been more useful to retain the original distinctions (rotor=a rotating source with reaction-diffusion mechanism, spiral wave=a wavefront resembling a spiral, from whatever source.) Post-benchmark literature also renamed “phase singularity” to “critical point,” and “vortex” became a common substitute for “ro-

tor” and even for “rotor & surrounding spiral wave;” however, Gray *et al.* (1998) and Witkowski *et al.* (1998b) revert to benchmark terminology.

Readers unfamiliar with convention in this area should also stay alert to the distinction between two common kinds of map of the heart surface. Both are “epicardial maps” but they are intermingled and their contourings are topologically different. One kind presents in each of a series of snapshots an instantaneous contouring of local membrane potential, assayed by an array of monopolar electrodes or at better-resolved pixels recording the fluorescence of a membrane-bound dye (Bayly, Jalife, Roth, Witkowski), or computed from a reaction-diffusion model (Bayly, Biktashev, Fenton, Gray, Panfilov, Trayanova, Xu). In such maps all contour lines must be closed rings unless interrupted by a boundary. There are no internal endpoints. Contours, most congested in the activation front (rapid depolarization), are shown at intervals spanning the full range of the action potential. If activations repeat at intervals longer than 200 ms, the action potential’s flat plateau (“systole”) shows as a wide featureless region followed up by close-spaced contours where repolarization leads to another featureless plain of quiescence (“diastole”). At intervals of 100 ms or shorter, however, there is no plateau, repolarization is more gradual, and there is no region of quiescence at resting potential (Witkowski and Penkose, 1990; Dillon 1992; Salama *et al.*, 1994; Kwaku and Dillon, 1996).

Pictures in the other format (Biktashev, Cabo, Janse, Panfilov) are typically intermingled, displaying only the single half-contour along which the potential changes most rapidly in time. Such an event may be detected as above, or using bipolar electrodes to record the time when an abrupt voltage gradient appeared more or less along their direction. (Note that fronts passing perpendicular to the bipole are invisible.) This is the activation front, where isovoltage contour lines are most congested spatially. It is displayed successively at 10 or 20 ms intervals on a single map spanning the cycle duration of such tachycardia, then the next map carries on though the next cycle. In such maps contour lines need not be closed rings. In a vortex a full cycle of them must terminate in cyclic order at a pivot point (“phase singularity”) or on a closed locus (rim of rotor or arc of conduction block) around which activations circulate. Such “isochronal” contours are made by erasing half of the isopotential contour where $dv/dt < 0$, e.g., in Biktashev Fig. 11 and Fenton Fig. 17a. If only the time of a large deflection is recorded at discrete bipolar electrode sites, electrodes or the space around them are often color-coded for event time in either of two topologically distinct ways. The traditional spectrum runs from red to blue for T_1 to T_2 with a color discontinuity where one cycle joins the next. The color-wheel style introduced in Winfree (1983, 1987) joins T_1 to T_2 through purples because $\text{phase}_1 = \text{phase}_2$. In lieu of colors, isophase contours may be sketched by hand between electrodes. Sometimes this is attempted by software, but never correctly: the algorithm necessarily draws closed rings as though contouring single-valued elevations, then the resulting picture misleads fundamentally. (Since 1985 I have been drawing this problem to the attention of software makers—for ex-

ample, for ocean tide maps—but so far as I know it remains unsolved.) For example, Chen Fig. 3 shows closed-ring color bands and closed-ring contours inside individual rotors. This misrepresents even the topology of the underlying reentrant data (not shown). Pointillist color coding of data as in Chen Fig. 6 and Kim Fig. 1 is more faithful to reality.

This locus where isochronal contours converge to terminate is the “path of the tip” (Biktashev, Kim) or rim of the rotor or vortex or core. Like “electron,” such areas are named for behavior observed outside them while nothing clear is observed inside. There remains some uncertainty whether the tip of the circulating wave front runs around a small disklike area, elongated about 3:1 by local fiber anisotropy (or 2:1 in Fenton, Panfilov), or lashes back and forth along a narrower near-discontinuity (Biktashev, Fenton) that looks extra-long only when it happens to align with the fibers. This is called an “arc of conduction block” or “arc of functional block.” There seem to be two kinds, not distinguished by name: one parallel to contours, as when part of a front fails to continue as naively expected, and one at which contours terminate perpendicularly, circulating around it as around a hole. If the raw data are made isotropic with the help of an image processor (dilating the picture by the observed speed ratio transverse to fibers) it sometimes appears that contours equally faithful to the data might be drawn more symmetrically (i.e., fitting a small disklike area) before restoring the data with contours to their native anisotropy.

It is also possible, in principle, to flag an area as “rotor” without looking outside. In that area a second local variable of state (e.g., potassium channel conductivity, independent of membrane potential) has a characteristic pattern. Though this variable might not lend itself to direct observation outside numerical experiments, it can be deduced during observation by on-line inference from the time course of the one observable’s spatial pattern. I have done this in chemically excitable media (Winfree, 1993b; Winfree *et al.*, 1996) but its implementation in CCD movies of myocardial rotors (Winfree 1994a) would require noise-free resolution somewhat better, even, than Witkowski has recently made feasible.

Measures of rotor or core area are still diversifying: the area inside the envelope of all perpendiculars to the wave front, the area circumscribed by the moving point at which the contour of threshold voltage intersects its recent position, the area in which the magnitude of the cross-product of local state-variable gradients exceeds some threshold, the smallest confined area in which periodic rotation can persist, etc. The small area in which fluctuations of the diffusing variable or of one of the non-diffusing variables are less than 10% or 30% (etc.) of that observed elsewhere is sometimes called “the center of the core.” In confusing contrast, “the core of the core” means a huge area: in abnormally depressed media the inner tip (“rotor”) of the spiral wave traverses at propagation speed an arbitrarily long circular path around an enormous lake of quiescence. In this way also “rotor” and “tip” become interchangeable terms, then we hear of “rotors” moving at a goodly fraction of propagation speed when what is really observed may be the edge of an activation front confined between refractory walls. If the walls then vanish, the dangling tip may then round up to *become* a rotor and

desist from its former travels (**Xu**; Courtemanche, 1966.)

A leading laboratory in experimental observation of cardiac rotors achieves a record minimum by defining the core as the area of anisotropic medium within which the circulating wave tip can be felt more than once (twice) per cycle, which could be no area at all or a disk with diameter no more than a few 1 mm passive space-constants. Their experimental result is 13.5 mm^2 in sheep ventricles (**Jalife**). Their corresponding assay in mouse ventricles was 3.36 mm^2 , indicating that something is indeed electrophysiologically quite different in this preparation. One candidate is the long plateau phase of the cardiac action potential. With essentially no conduction time in such a small heart, nor long distances for muscles to contract in systole, the mouse omits this customary time delay (Witkowski *et al.*, 1997). It can accordingly support reentry at 50–60 ms intervals, far shorter than known in larger mammals (Morley *et al.*, 1997). The dimensionless quality factor $Q = \text{speed}^2 \times \text{period} / D$ of rotors in those larger hearts is two- to threefold larger than common in other excitable media (which also lack the idiosyncratic plateau phase of myocardium), but in the mouse this Q is more typical at $(13 \text{ cm/s})^2 \times 0.055 \text{ s} / (\text{presumed } 1 \text{ cm}^2/\text{s}) = 93$.

Rotor area is commonly estimated from isotropic theory as roughly the square of its nominal 1 cm diameter in mammals larger than the mouse (being 0.1 s period $\times 60 \text{ cm/s}$ speed / π), or $\pi/4$ as much to round the square to a disk with perimeter equal to the spacing (= period \times speed) between turns of the spiral radiating from the rotor. This speed being implicitly the fast, longitudinal speed, area is threefold less in anisotropic media with transverse speeds (and therefore rotor proportions) compressed threefold transversely. This anatomical area, (geometric mean spacing) $^2 / 4\pi$, would be 25 mm^2 . Lee *et al.* (1996) measure it as 25–29 mm^2 , and **Kim** shows similar results during meander. These measurements seem compatible with the report by **Jalife** that the 100 mm^2 area of their mouse ventricle can be induced to support one or two rotors, and almost compatible with their report (Morley *et al.*, 1997) that in a mouse left ventricle of area 20–30 mm^2 two rotors persistently sustain fibrillation. As they report, if this perfused heart is normal then their observation ends 80 years adherence to the fiction that such small hearts do not sustain fibrillation. For example, Salama *et al.* (1994) report guinea pig hearts must exceed 2.5 grams (cf. mouse 0.1 gram) to support reentry. This would be about 320 mm^2 (cf. mouse 100 mm^2 .)

These observations focus attention on an unanswered question of physics. Suppose an isotropic medium supports 10 mm rotors, therefore $10 \times 3 \text{ mm}$ rotors in the 3:1 anisotropic case. What would the corresponding dimensions be in a coupled stack of such layers, with the fiber direction rotating 90° in little more than $1/2 \text{ mm}$ of depth, as in the mouse heart wall if it conforms to the architectural standards of larger mammals? $10 \times 10?$ $3 \times 3?$ This might be answered in a computation like **Biktashev**'s Fig. 12, **Fenton**'s Figs. 12 or 16, or in one like **Panfilov**'s Fig. 8, where the right wall's thickness seems compressed by raising D to about 50 times nominally normal $0.1 \text{ cm}^2/\text{s}$.

Some authors say the "core" is the area staying at fully

recovered and fully excitable steady-state, others say the core remains depolarized or not activated (**Xu**), others say it is irregularly invaded (hyper-meander?) or invaded regularly more than once per cycle during biperiodic meander. This term "meander" was coined in 1973 to mean ostensibly random wandering of the (chemical) spiral's center, and was still so used in Courtemanche and Winfree (1991), Courtemanche (1996), and in **Biktashev**. But it has also evolved to mean the quasiperiodic special case observed in parametrically depressed membrane models (Winfree, 1991b; Efimov, *et al.* 1995; **Fenton**). It should also be remembered that all exploration of meander is confined to 2-dimensional contexts. The only study of meander in 3 dimensions prior to **Fenton** (Winfree, 1994c, 1995) concluded that the 2-dimensional case is probably ungeneric, being equivalent to a meandering 3-dimensional filament constrained to retain perfect synchrony along its length, which is unphysical because the filament's local curvature and twist alter the style of local meander. **Kim** tries to observe in the laboratory such meander as seen in idealized 2-dimensional models, but finds that the rotor in thin myocardium is slapped by an activation front as often as every 2–3 rotations, whereupon it at least jumps aside (**Cabo**, Section IIIC) or, according to **Chen**, **Kim**, and Lee *et al.* (1996), is somehow destroyed. Only a couple loops of the anticipated meander flower can be traced between these discontinuities.

I used the word "spacing" above where the theoretical literature of spiral waves often uses "wavelength" (e.g., **Panfilov**) because in cardiology "wavelength" means propagation speed times the duration, not of the whole cycle, but only of the fully depolarized phase of the action potential (e.g., **Gray**, **Janse**.) These terms were seldom distinguished at benchmark, because many still believed that spiral waves in myocardium have no "excitable gap." The action potential duration was thought to be the whole cycle. This belief stemmed from thinking of 2-dimensional reentry in terms of a pulse circulating on a shrinking 1-dimensional ring or in terms of the Wiener and Rosenblueth 2-dimensional model of 1946 (which omitted diffusion of electric potential), or in terms of reaction-diffusion mechanisms selecting rotor period at the tangent to the dispersion curve of speed vs spacing (thus at minimum period.) At least until Winfree (1978), many thought rotors adopt the shortest possible period at which their medium could respond. This impression may have affected perception of myocardial vortices, which at benchmark were still considered to have no excitable gap, even though **Allessie et al.** (1973) showed about 30 ms = $1/3$ cycle of excitable gap in 100 ms atrial rotors. When a substantial gap was noticed in ventricular vortices, it was imputed (Frame and Hoffman, 1984) to the peculiar electrical anisotropy of that preparation, despite the facts that even in the absence of anisotropy such a gap occurs around rotors (i.e., in solutions of the electrophysiologist's reaction-diffusion equation) and that (in monodomain continuum theory) uniform anisotropy of arbitrary magnitude has no influence on temporal behavior, thus on gap duration. In other words, such interpretations rejected the electrophysiologist's standard models. However, it now appears that models were more reliable in this respect than originally

thought: Except in cases of marginal excitability, reaction-diffusion models seem to select rotor period near the tangent to the speed vs period curve (Winfree, 1991b) rather than to the speed vs spacing curve. This means the rotor does not have the minimum stable period. While this empirical generalization about period selection in reaction-diffusion models has been confirmed neither analytically nor in any experimental system (in fact, almost all experimental publications show the dispersion curve ending at spiral period, I think simply because shorter periods were not tried), it does guarantee an excitable gap, and in fact myocardium observably does have “spacing” well in excess of “wavelength” at the period of rotors. This may be related to a phenomenon that seemed inconceivable in our benchmark time capsule: the entrainment of a small area of fibrillation to periodic stimuli (**Bayly**; KenKnight *et al.*, 1993). The connection may be capable of further clarification: during fibrillation in myocardium as opposed to models, the very concepts of action potential duration and of excitable gap become surprisingly elusive.

B.3. Rotors in 2 dimensions

At benchmark, it was not known whether a detailed ionic model of myocardial membrane would support rotors of plausible size and period. This was first tested using isotropic monodomain continua with Beeler–Reuter membrane (Winfree, 1989a; Courtemanche and Winfree, 1991). The main results were that the period is twofold too long, that fronts break up even in fully excitable parametrically uniform 2-dimensional continua (a phenomenon never before been seen in such computations nor in chemical media), that rotors are rare in comparison to activation front edges cruising near Mach 1 along “slow repolarization fronts”, and that rotors seldom last long enough to exhibit familiar meander. Even a decade later it is still unclear which of these surprises represent new insight into real myocardium, and which represent the defects of pre-benchmark ionic models. Here **Biktashev** and **Xu** extend and improve such calculations and **Roth** and **Trayanova** extend them to anisotropic bidomain continua.

The first models showed that something like rotors do in fact arise, with roughly the size and period expected from back-of-envelope physics and from prior *in vivo* experiments, but their most instructive result may have been the unexpected irregular lashing about of the tip of the activation front. Not all tips formed rotors: More commonly they cruised at almost normal propagation speed along the edges of “slow repolarization fronts,” so that the activation map often contained several disjoint segments of front bounded by such cruising ends (Courtemanche, 1996). These may be artifacts of the unrealistically steep restitution curve of the Beeler–Reuter ionic membrane model, unlike the reproducible subset of the seventy-some such laboratory curves I have collected over the years. Such rapid motion of rotors, or of wavefront tips that might have been expected to form rotors, was surprising, but comparably abrupt displacements have since been observed in real myocardium (**Jalife**) and some such “wavebreaks” are seen in **Witkowski** Fig. 10.

When the computed front tips did form rotors, they turned typically no more than a couple of rotations before

some other front intruded, resulting in another rapid displacement. During such irregular reentry, the spacing between successive fronts fluctuated dramatically: there was usually an excitable gap, but its width was unpredictable. There was seldom for long any such definite periodicity as commonly expected from less complicated membrane models, nor any extended or persistent “spiral waves.” There were commonly multiple segments of wave front dragging their endpoints along refractory walls, sometimes to a quiet death such as **Bayly** Fig. 4. These features can be seen, for example, in Courtemanche (1996), and are high-lighted in color in Winfree (1993a, pages 671 and A20). They seem to resemble the key features observed by Gray *et al.* (1998), by **Kim** and by **Chen** in epicardial slices, as also reported from their laboratory by Lee *et al.* (1996).

Something was overlooked in those 1987–8 ionic model movies because they did not employ pacing faster than rotor period nor introduce obstacles, nor attenuate excitability far below normal. That was the failure of sustained activation where a barely propagating front diverges around a microscopically sharp corner, reported about the same time in an FHN-like model (Pertsov *et al.*, 1990; Winfree, 1990d; Panfilov and Keener, 1993) then in myocardial thin layers (Cabo *et al.*, 1994 and 1996.) This provides another way rotors can be born into a continuum formerly dominated by short-period activation from some remote source. If the period becomes enough shorter than the rotor period in the same medium then the incompletely-recovered medium just ahead of each front is barely excitable, and if excitation must spread around a sharp enough corner, so that a critical front curvature is exceeded, then propagation fails and the activation front is left with a tip dangling so far from the boundary that it has space and time to develop into a rotor (**Cabo, Xu**).

Cabo reviews experiments in thin slices of sheep epicardium, modeled on prior analogous experiments in chemically excitable media, aimed at checking such consequences of sharp activation front curvature. Fronts in critically inexcitable tissue do actually “tear loose” from tissue edges where the boundary sharply turns away from the advancing front. A rotor is thus created at the dangling end of this activation front, where its curvature exceeds critical. This concept of “critical curvature,” introduced by Zykov (1980) with myocardium in mind, intrigued only theorists for 15 years before it found its way into the electrophysiological laboratory. In the setting of anisotropic epicardium it becomes troublesome in ways that have occasioned complicated discussion in the recent literature. The idea is that excitation from a sufficiently convex wave front diverges so much that it thins below threshold and fails to excite the surrounding medium. So a tiny disk of depolarized tissue simply executes its action potential in place without expanding. How tiny? In the case of marginally excitable media, even slight curvature spoils the reliability of propagation: the critical radius can be immense. But in fully excitable isotropic media it is comparable to the thickness of the propagating activation front, which is less than 1 ms times perhaps half a meter per second, thus less than 1/2 mm. It makes no difference that epicardium is 3:1 anisotropic, except that due to a peculiarity in the definition of “curvature” one way of measuring this “ra-

dus'' can produce smaller or very much larger numbers. The circle of critical radius becomes a 3:1 ellipse with radius of curvature at the pointy longitudinal end shortened threefold, thus becoming threefold shorter than the unchanged longitudinal activation front thickness. Meanwhile on the flat transverse sides it has lengthened 9-fold, becoming 27-fold longer than the shortened transverse front thickness (Winfree, 1997a). These peculiarities of the geometric definition are obviated by rescaling the pictures to isotropy before measuring. **Cabo** describes some of the first experiments attempting to check such phenomena as the monodomain reaction-diffusion metaphor anticipates for epicardium. **Xu** further plays out this theme in context of a realistic model of ischemia.

Various 2-dimensional continuum breakup mechanisms have since been considered as models of fibrillation, thus implicating rotors at least in the transition from tachycardia, and possibly in fibrillation itself (perhaps in a 3-dimensional way after the first 10–20 cycles). But one sees very little of anything like a rotor in 3-dimensional myocardium, and then only fleetingly and only in the very beginning of fibrillation that started with a pair of rotors induced by the “pinwheel protocol” (Gray *et al.*, 1998; Witkowski *et al.*, 1998b). Even artificially thinned 2-dimensional myocardium, when somehow induced to “fibrillate”, exhibits reentry in forms not readily described in terms of the familiar behavior of isolated 2-dimensional rotors (Lee *et al.* 1996; **Chen, Kim**).

Chen additionally describes continuous creation of nascent rotors at spontaneous breaks (“arcs of conduction block”) in propagating fronts and at their collisions with other fronts: “In all episodes, reentrant wave fronts were spontaneously initiated by an interaction between two propagating wave fronts roughly perpendicular to each other.” Meanwhile other rotors, after a short lifetime, are destroyed (in contrast to **Cabo**’s observation) by encroaching wave fronts and by encounter with tissue edges. This balance of solitary creations and destructions putatively preserves a fluctuatingly steady abundance. So far as I know, no mechanism has been plausibly modeled in terms of reaction-diffusion vortices that would create or destroy an isolated vortex through wave front collision. Studies of continuous excitable media show the phase singularity, alias vortex, alias rotor, to be merely *displaced*, not erased, by wave front collisions, and show colliding fronts merging without creating new singularities. The benchmark view was that annihilations and creations occur only as mirror-image pairs (except at tissue boundaries), as confirmed in the experiments of Gray *et al.* (1998). Literature contributions are not in harmony here.

Numerical experiments also strengthened the notion that meandering displacement of a rotor could be the mechanism of *torsade de pointes*, a peculiar arrhythmia characterized by waxing and waning periodicity in the electrocardiogram. At benchmark, *torsade* was still thought to represent coincidental onset and offset of a two unrelated ventricular ectopic foci (Bardy *et al.*, 1983; Inoue *et al.*, 1986). An alternative idea is that it might represent a meandering rotor (Winfree, 1988a, 1989a, 1990b, 1993a, 1994b, 1997a, 1997b). Davidenko (1993), Jalife and Davidenko (1993 p. 616–7), and Starmer

and Starobin (1996) ingeniously show how this can be reconciled with the prior notion of focal sources with distinct periods and coincidental onsets and offsets: A moving chemical rotor had been observed to induce Doppler-shifted firing fore and aft (Jahnke *et al.*, 1990; Jahnke and Winfree, 1991); since the electrocardiogram sums local activities over the epicardium, a single drifting rotor could effectively constitute a pair of asynchronous pacemakers with the curious property that when one extinguishes, so necessarily does the other! **Chen** and **Jalife** stress the likelihood that a single meandering rotor could underlie polymorphic tachycardia or even fibrillation.

Bayly decomposes patterns observed on the surface of 3-dimensional ventricle in terms of wave front segments rather than in terms of rotors (see their Fig. 4). Short segments of activation front entering a *cul-de-sac* bounded by temporary refractoriness drag along a pair of nonrotating endpoints that should not be confused with rotors. Like a tidal bore in a fjord, such segments can snuff out for want of a timely exit (as seen, for example, in the old Beeler–Reuter movies cited above). They stress that, at least *in vivo* with progressive ischemia, (spatially extended) fibrillation cannot be usefully regarded as low-dimensional chaos. **Bayly** stresses the importance of imaging a large enough area (ideally the whole surface including internal septum) to reveal the origin and ultimate fate of the front segments that dominate these movies at the characteristic period of rotors.

B.4. Rotors in 3 dimensions

All the above mimic 3-dimensional myocardium with flat 2-dimensional images. The next step toward reality is a curvy, but still effectively 2-dimensional, model. On a curved thick surface resembling the dog’s ventricular epicardium (but scaled to the size of a rabbit heart) **Panfilov**, and **Gray** using Panfilov’s model, illustrate spiral waves in an excitable medium chosen for the inherent instability of its rotors. **Panfilov**’s model of the ventricle has played an important role in recent literature (Panfilov and Holden, 1997). It resembles a famous cellular automaton model of atrial fibrillation (Moe *et al.*, 1964) in that its “cells” are isopotential tissue chunks (1 mm³) and in that its activation fronts easily suffer spontaneous arcs of conduction block. **Gray** reviews some important differences between ventricular and atrial fibrillation (see also **Kim**; Winfree, 1994b p. 1005, or 1997b p. 116). For example, the ventricular wall is thicker and more uniform than the atrial wall, which in most places more resembles a mat of tangled thick roots (the pectinate muscles). **Panfilov**’s model is a major improvement over Moe’s in that its context is a geometrically ventricle-like 3-dimensional volume, including in some instances even a coarse implementation of the directionality of its fibers. As **Panfilov**’s abstract points out, the needed source of ‘inhomogeneity’ is now not patchiness of membrane properties as in the simulated 2-dimensional atrium of 1964, but the inherent patchiness of any coarsely discretized mimic of the fibrous 3-dimensional anatomy of dog ventricles. This parametrically uniform membrane model’s activation fronts are unstable near the short period of rotors, even in 2 dimensions and in the complete absence of any kind of inhomogeneity,

so they easily succumb to patchy conduction block. We do not yet know whether this is also a feature of normal myocardium.

As the authors point out, this is not an attempt to mimic normal myocardium. A simplified and depressed membrane model was necessary for computation on a 1 mm grid. The FHN parameters are chosen so that activation is several-fold slower than normal and as in the mouse “the scaled action potential duration is 3–6 times shorter” (Gray). Activations accordingly propagate several times too slow, and the rotor period is too long. With time and space rescaled to match these numbers to reality, the effective coupling coefficient, D , between cells becomes “an order of magnitude larger than for the normal heart” (Gray). This is evident in the propagation speed’s dependence on curvature, as shown in Fig. 5D: It ends at a critical radius of curvature near 6 mm rather than normal 1/3 mm, with slope D about $-12 \text{ cm}^2/\text{s}$ rather than $-1 \text{ cm}^2/\text{s}$ (contrast with Fig. 1 of Cabo, using $2 \text{ cm}^2/\text{s}$ and normal excitability.) And most of the computations are isotropic, i.e., the transverse coupling coefficient is an additional order of magnitude larger than in real tissue. This makes the heart walls functionally thinner than they look, possibly by an order of magnitude. All figures are isotropic in Gray (so “cardiac fiber orientation did not play a major role in our simulations”), and all but Figs. 6–8 of Panfilov, in which the transverse coupling is enhanced as much as 50-fold, so these walls also may be functionally 2-dimensional. In comparing with Fenton’s anisotropic computation, note that he found it necessary to represent layers of tissue at intervals no greater than 3° of fiber rotation, which would be impossible at 1 mm spacing, so one rightly expects to see different phenomena in these models (see below).

Leon and Horacek (1991) and Colli *et al.* (1991, p. 321) may have been the first to examine numerically the implications of rotating anisotropy for propagation. It twists the activation fronts, leading to the suggestion (Keener and Panfilov, 1994, Panfilov and Keener, 1993) that this may destabilize vortex filaments. Their demonstration in numerical experiments on coarse grids left open the same question for continua. Fenton answers it by describing numerical experiments on meandering electrical vortex filaments in a 3-dimensional reaction-diffusion model of excitability. This is only the second study of 3-dimensional meander, and the first to introduce the rotational anisotropy that characterizes all mammalian heart walls. [Footnote added 2 Jan 98: A third has since appeared: Aranson and Mitkov (1998) find a new instability of 3D meandering filaments, this one again lacking any threshold.] Its parameters are tailored to match the period-dependent idiosyncrasies of real myocardium. This does turn out to induce a novel electrical instability, clearly distinct from those known before, but with about the same threshold of wall thickness for its onset.

One such instability was my proposal (Winfree, 1990a, 1991a) that in the absence of meander but given a transmural gradient of excitability, twist should accumulate along an intramural vortex filament, shortening the period between activation fronts until they are squeezed too close together to admit any excitable gap, and so become liable to patchy

conduction block. Alternatively, when wavefront twist accumulates to almost one rotation along a filament length equal to rotation period times propagation speed, a helical “spring” should erupt which, if the myocardium is also thicker than a transverse rotor diameter (about 4 mm), admits free transmural snaking of the filament. Such a 4 mm threshold of thickness was subsequently observed in living dog hearts, for the transition from rotor-based tachycardia to fibrillation, but its actual mechanism remains still unexamined. Neither of the foregoing were observed in the Fenton simulations because no transmural gradient was imposed and because their new instability arises *first*, on account of meander and the different gradient that *is* included: the rotating anisotropy of intramural fibers. As Fenton Fig. 20 shows, overlaying Winfree (1994b, Fig. 1), this new twist instability of the meandering filament *also* has a thickness threshold close to 4 mm. Its consequence is also much the same: The filament coils up and breaks at the epicardium, multiplying intramural filaments and epicardial rotors. These must then be expected to move rapidly or survive briefly, perhaps as reported in thick myocardium by Bayly, Jalife, Gray *et al.* (1998), and Witkowski *et al.* (1998b). In walls without a transmural gradient of excitability my meander-free instabilities would not arise, maybe those depending on meander would [with no threshold (Winfree, 1994c, 1995)], and Fenton’s “twistons” definitely would (unless the fiber rotation rate is less than found in laboratory mammals.) Anyway, twistons periodically relieve accumulating twist, preserving transmurally graded myocardium against the instabilities that first predicted the 4 mm threshold thickness. Unlike the earlier-nominated instabilities, Fenton’s alternative would greatly broaden the distribution of action potential durations relative to the preceding tachycardia, and shorten their average. In contrast, under the original visions of such filament instability, the histogram of durations would stay about the same. Discrimination awaits useful definition of “action potential duration” during real fibrillation.

[Footnote added 6/27/97: During 1994 while editing galley proofs of a symposium contribution, I pushed the “divide” instead of “multiply” by 9 calculator button to divide by “1/9 cm^2/s ” and so underestimated by 81-fold the relaxation time of twist accumulating along a transmural vortex filament. This made the necessary thickness of myocardium for rapid accumulation of twist seem ninefold greater than correct theory would have it. Alain Karma kindly drew my attention to this arithmetic error in 1997. Its logical consequence was temporary apostasy from my former and I think correct anticipation (Winfree, 1990a p. 405, 1990c p. 203; Henze *et al.*, 1990 p. 701; Winfree, 1991a, p. 516) that twist could substantially accumulate in the thick LV wall. That revisionist paragraph, printed in Winfree (1994a) and unthinkingly copied into a 1994 meeting proceedings (Winfree 1997b) concluded that human or canine LV wall is too thin by an order of magnitude, whereas in the absence of arithmetic error, the proper conclusion is the same as in 1990 and as in subsequent experimental checks: filaments “should” be stable *in walls thinner than* roughly the observed threshold thickness for conversion of monomorphic VT to fibrillation.]

The reader will want to compare discussions of area, thickness, and volume thresholds for fibrillation between **Fenton, Gray, Panfilov**, and Winfree (1994a, 1994b, 1997b). **Gray**, for example, notes an absence of 3-dimensional instabilities. This may be because a combination of depressed kinetics, coarse mesh (1 mm), and large transverse D make their modeled heart wall much thinner than the 4 mm threshold anticipated above. In general the unconfined vortex filament seems to have plenty of instabilities. In 3-dimensional media supporting meander there have been only two studies so far, and both showed new instabilities: Even without dynamical or anatomical twist, the character of 2-period meander (its frequency ratio) depends on filament curvature² (with no threshold) thus meander seems unlikely to remain synchronous along a flexible filament (Winfree, 1994c, 1995), and with more than a threshold amount of anatomical twist, pulses of dynamical twist accumulate and propagate as twistons (**Fenton**).

It is not yet known how nearly these computational expedients nevertheless capture something essential about the electrical dynamics of *normal* ventricular myocardium. But they do lead to complicated patterns of reentrant activity ‘‘similar to fibrillation’’ (**Panfilov**), and thereby raise the question **Bayly** addresses: How can we tease apart the essential aspects of such similarities and quantify them so as to distinguish among kinds and models of fibrillation? Witkowski *et al.* (1998b) observe that even during steady perfusion, after 10 min of fibrillation activation patterns on dog epicardium acquire an entirely different, possibly 3-dimensional character, and their characteristic periodicity shortens about 20%. This was not observed by Gray *et al.* (1998) in the sheep heart, similarly prepared but using an inhibitor of muscle contraction. There is a pressing need for quantitative differentiation among ‘‘turbulent-looking’’ patterns.

Jalife observes activations on the curved surface of the fully 3-dimensional heart, fulfilling after a decade the benchmark view that ‘‘in the structurally and electrophysiologically normal heart, cardiac fibrillation is not a totally random phenomenon ... fibrillation in the mammalian ventricles is the result of self-organized electrical rotors giving rise to scroll waves ... such complexity ... may be explained in terms of self-organized 3-dimensional rotors that drift throughout the heart.’’ They illustrate this in a variety of dramatic experiments using the ventricles of mammals ranging in size from sheep to mouse, and go further to show how even a single rotor, if moving much faster and more erratically than ever before thought possible, suffices to impress the electrocardiogram with a fibrillation-like trace. Near the bottom end of the mammalian body-weight scale they present the astonishing apparition of a rotor in presumably normal mouse heart rotating fully within no more than three or four 60 Hz video frames, its period and long diameter hardly more than half what I took to be the all-mammal standard (leftmost datum of Winfree 1994b, Fig. 1).

B.5. More jargon

Efflorescing terminology is usual in times of conceptual change such as our ‘‘post-benchmark’’ dozen years, and de-

mands alertness to multiple meanings. For example, as used in this journal, ‘‘chaos’’ means a kind of deterministic dynamics, usually low-dimensional. But in cardiology the pre-Yorke sense was incorporated into *definitions* of fibrillation, so that the intent of its usage in contemporary discussion of cardiac dynamics is seldom clear. **Chen**, however, describe fibrillation as deterministic chaos, arrived at through a quasiperiodic mode by interaction of ‘‘coupled oscillators’’ (rotors?). **Bayly** shows that if fibrillation *in vivo* without heart-lung support is ‘‘chaos,’’ the dimension is **not** small.

In this journal ‘‘model’’ usually means a construct of ideas, but in cardiology, it means a physiological preparation whose laboratory study is believed to be relevant to a clinical problem. **Chen** uses ‘‘model’’ in this sense, quite different from its import in ‘‘bidomain model’’ (**Keener and Bogar, Trayanova, Roth**) as a set of precise physical relationships represented mathematically, or in ‘‘numerical model’’ (**Bayly, Biktashev, Fenton, Gray, Jalife, Roth, Panfilov**) as a collection of algorithms (seldom allowed space to describe reproducibly in the literature) to mimic some process in the way of a metaphor.

The ‘‘restitution curve’’ depicts the duration of depolarized phase of the action potential as a function of the ‘‘diastolic interval’’ or ‘‘excitable gap’’ (synonyms for the complement of a discrete depolarized phase during periodic excitation) or of the period of repetitious excitation. This curve, in either form (not quite equivalent), is much discussed in connection with pre-fibrillatory tachycardia, and might provide a key to its instability. Such calculations presuppose slope > 1 near the rotor’s period, i.e., require the abbreviated action potential stimulated at such a short interval to lengthen, if the interval be lengthened by Δt , by more than Δt . This is an essential model component in **Panfilov** and in **Chen**, and it appears in **Xu**’s model, but not in **Fenton**’s (‘‘our conclusion is that the most believable curves are not steep enough to produce VF in 2D ... experimental curves also seem insufficiently steep to cause wavebreaks’’). It may be an important mechanism in diseased myocardium. An effort seems called for to establish this curve’s existence and shape during fibrillation: (a) the depolarization of tissue activating at the short intervals typical of fibrillation tapers triangularly (no Ca/K plateau) until the next activation, leaving no diastolic interval (Witkowski and Penkoske, 1990; Dillon, 1992; Salama *et al.*, 1994; Kwaku and Dillon 1996); (b) it has not yet been shown that the duration of depolarization beyond an arbitrary level depends on prior intervals too short for reactivation of Ca channels; and (c) during 2- and 3-dimensional propagation with ever-changing pattern, repolarization time can be forced far from the ‘‘curve’’ that characterized space-clamped restitution (Courtemanche, 1996, Figs. 12–14.)

The dominant paradigm motivating design of experiments and their interpretation since at least 30 years ago stems from the ‘‘dispersion of refractoriness’’ model illustrated numerically in Moe’s cellular automaton (1964) or Krinsky’s continuum (1968). These stress discontinuous patchy irregularity of intrinsic (alias parametric) excitability parameters as the ‘‘*sine qua non*’’ (Moe) of fibrillation. The example computed by **Xu** (prefaced by a succinct tutorial

introduction on inhomogeneities) shows in modern terms how this might work. The experiments described in **Cabo** and in **Janse** (which also contain clear background tutorials) are motivated in this tradition. In contrast, my own peculiar slant on this topic in publications since 1978 has been that such inhomogeneities might be incidental except when exaggerated by disease and might mask a more fundamental mechanism of fibrillation (see paradigms distinguished in Winfree, 1982 or 1989b). The numerical models of **Biktashev, Fenton, Gray, Jalife, Roth, and Panfilov** work in this more recent (benchmark) paradigm in terms of phase singularities of entirely dynamical origin (rotors) that occur even in parametrically uniform media. The advent of this rival outlook in the late 1970's affected word usage. With a time constant of several years, the term "dispersion" became ambiguous. In current literature it is often virtually impossible to figure out whether "dispersion" and "inhomogeneity" mean what they did in the cited literature, or only mean that there are gradients of membrane potential in the tissue (e.g., as in **Roth**), i.e., that it supports propagating activations and electrotonic currents around stimulus electrodes. The grammatical form of explanation is often preserved even while its conceptual import evolves.

Like most polarized "either/or" dilemmas, this one should not be so starkly posed. On the one hand it can be argued that whatever intrinsic inhomogeneities characterize healthy ventricular myocardium play no essential role in the onset of reentrant tachycardia, at least of the kind represented by rotors and vortex filaments, at least when these are initiated by the "pinwheel protocol" (alias cross-field stimulation, twin pulse protocol, etc.). In healthy tissue they might even play little role in the ensuing monomorphic tachycardia, except in a role opposite to traditional expectation: They might "pin" rotors and so *stabilize* tachycardia at a more regular and somewhat longer period than exhibited by the freely meandering rotor. But much depends on the electrophysiological magnitude, and spatial and temporal scales of the putative inhomogeneities; these still need to be sorted out and quantified. And on the other hand, if the period should shorten below about 110 ms, making propagation more precarious, it seems plausible that formerly ignorable parametric inhomogeneities may develop more prominent consequences. At the short period of ventricular fibrillation (80–100 ms: possibly the period of unpinned rotors or of twisted vortex filaments), tissue that could reactivate adequately at longer periods may become a patch of lethargic responsiveness, even of conduction block, until it has recovered by not responding then waiting out an interval until the next activation front encroaches. Then the relatively orderly patterns of activation radiated from a few discrete rotors could become utterly turbulent. Even such slight parametric inhomogeneities could after all turn out to be the "*sine qua non*" of transition from simple vortex reentry to such electrical turbulence.

Note that inhomogeneities of resistivity are quite a different thing and probably *are* essential for electrical defibrillation. It remains to be determined whether the effective ones are intrinsic (gap junctions, collagenous separations, etc.)

and/or the changing angles between gradient fields and curving fibers (**Krinsky, Roth, Trayanova**).

As a synonym for "inhomogeneity", the cardiologist's use of "dispersion" departs from established usage in physics. **Fenton** accordingly renames the dependence of propagation speed on period from "dispersion curve" to "speed restitution curve" for use in this context.

Another conspicuous package of near-synonyms is "arc of conduction block," "wave break," "wavebreak," "break up," "breakup," and "lateral instability" (**Bayly, Gray, Jalife, Panfilov, Witkowski**). The first of these terms stems from antiquity, sometimes to describe the locus of moving endpoints of a front (when not on an obvious physiological discontinuity), sometimes to describe propagation failure along an arc of an activation front. This could represent encounter with a local parametric inhomogeneity, even a rather slight one if the medium is paced near its shortest stable period. When block is suspected to be due to only local dynamics in a parametrically uniform medium, the "break" words are used (e.g., in Winfree, 1994a; Courtemanche, 1996), I think stemming from the discovery of such things in Beeler-Reuter models: "... wave fronts break, nucleating new reentrant vortex pairs ... resembles epicardial maps of the earliest stage of fibrillation." (Winfree, 1989a). This is still the meaning of "breakup" in **Panfilov**, for example. "Wave break" as a noun seems to mean "phase singularity" or "critical point" (e.g., Pertsov *et al.*, 1993, or Witkowski *et al.*, 1998b). "Wavebreak" has evolved to mean a special condition in marginally excitable media, where even slight curvature of the activation front induces conduction block, as in **Jalife**, for example. "Lateral instability" refers to the rapid erosion, in such media of merely marginal excitability (e.g., normal tissue rapidly paced) of fronts bordering such a break, thus widening the arc of conduction block.

The terms "diffusion," "diffusion coefficient," and "reaction-diffusion equation" have caused confusion, even between writers and referees of this Focus issue. The 10^5 V/cm electric potential gradient across the cell membrane is supported by selective barriers to the diffusion of ions. Ions diffuse in cytoplasm at 10^{-5} to 10^{-7} cm²/s. Their diffusion does indeed propagate the *chemical* waves known in neural tissue, such as calcium waves in networks of hippocampal astrocytes and suprachiasmatic nucleus glia, or the ones that make tiny 1-s rotors in single heart cells (Dupont *et al.*, 1996), or those in the Belousov-Zhabotinsky medium. Their mechanisms are well described by reaction-diffusion equations. Because the electrical mechanisms of cardiac membrane are described by similar reaction-diffusion equations, analogous phenomena were anticipated in heart muscle, and some phenomena such as the vulnerable period and the manner of onset of fibrillation were (in cardiological ignorance) "discovered" and understood in a new way during the decade ending with our "benchmark" (e.g., see Winfree, 1982, 1983.) Nonetheless, even though electric current in cells is carried by ions, their diffusion is *not* what is analyzed in that reaction-diffusion equation (the 2- or 3-dimensional version of the classical "cable equation" or

“core conductor model”) of electrophysiology. In this context the emphasis is not on ions but on trans-membrane capacitive electric potential diffusion, with coefficient more like $1 \text{ cm}^2/\text{s}$, a million times larger. The result is that the spatial scale of patterns based on temporally comparable kinetics is a thousand times larger for potential diffusion than for ion diffusion. This diffusion coefficient, D , is often called the “coupling coefficient.” It is the reciprocal product of membrane specific capacitance, cell surface/volume ratio, and a resistivity. In context of monodomain models this D is commonly evoked as a pair of scalars, one along fibers and one an order of magnitude smaller perpendicular to fibers, or a little more elaborately in the bidomain model’s tensor D with twice as many components.

Finally, we come to “fibrillation.” The idea that fibrillation is utter randomness used to be so firmly entrenched in the medical literature that pre-benchmark publications (and some even today) commonly adopted a revolutionary tone as though espousing heresy when circumstances required recognition of the obvious dominant periodicity or other deterministic aspects of VF. In the clinician’s strict traditional sense fibrillation is whatever is happening in the heart when the electrocardiogram (summing electric dipoles over all surfaces of the muscle) shows an irregular wiggleness on a time scale shorter than about 200 ms. Note that this would seem to include sources with period longer than the freely drifting rotor (whose nominal period seems closer to 100 ms).

Complementing that strictly temporal electrocardiogram-based clinical definition, the term “fibrillation” also has a spatial, mechanistic meaning. In the medical world it originally connoted the presumably independent activity of adjacent fibers of the heart muscle. To many today it still indicates negligible correlation of electrical activity over distances comparable to one passive space constant (about 1 mm) (but see actual measurements in **Bayly**.) There is much discussion in this Focus issue about the transition from ventricular tachycardia (due to the presence of one or a few rotors) to fibrillation in the sense of “a complicated and changing spatial pattern of activation” or “electrical turbulence” (e.g., **Fenton, Panfilov**). Pre-“benchmark,” these temporal and spatial notions were thought probably equivalent, and much of the literature is written as though each cell were performing as irregularly as the summated electrocardiogram trace. But then it was noticed that point recordings during clinical fibrillation can be strikingly periodic, all with nearly the same period (near the period of rotors), and even the collective electrocardiogram is nowhere near so devoid of narrow spectral peaks as some definitions of fibrillation explicitly require. Conversely, the irregular lashing about of one or two ends of a single activation front (a fairly simple geographical picture) creates an electrocardiogram trace resembling “fibrillation” temporally while the epicardial map looks hardly more complicated than during normal sinus activation. (**Jalife**; Gray *et al.*, 1995; **Janse**; Janse *et al.*, 1995).

Crucial inferences take different paths depending on whether “fibrillation” means “the ECG is wiggly” or “cellular activity is irregular and uncorrelated” or “the map looks complicated,” so the critical reader should be alert to those multiple meanings. It is important also to notice

whether the fibrillation is maintained under stable conditions (a heart *in vivo* on heart–lung support, or *in vitro* on Langendorf support, or a piece of ventricle passively perfused in a tissue culture dish) or under progressively deteriorating conditions (a heart *in vivo* developing ischemia after blood pressure falls at the start of fibrillation, or a slice too thick to perfuse passively and perhaps cumulatively affected by an applied drug.)

C. Technological advances for observation of hearts and of equations

Quite a lot of new technology is reviewed here, e.g., **Bayly**’s numerical devices for appraising such patterns as can be detected in 1-mm epicardial maps during fibrillation and **Chen**’s 1.6-mm electrode arrays. Looking to the future, **Keener** and **Bogar** provide the computational means for efficient simulation of bidomain models, and **Witkowski** presents first fruits of his relatively low-intensity fluorescent epicardial mapping system, with emphasis on engineering aspects. Theorists new to this area could be forgiven for imagining that such details do not deserve a prominent place here. I wish to stress the opposite: that much more than may be apparent depends crucially on careful attention to the Materials & Methods section of any experimental paper. My experience is that almost any proposition (and its converse) can be convincingly argued by selective inattention to Materials & Methods sections. The majority of inferences I have rightly or wrongly drawn in this area since 1978, citing published data, differ from those featured in the corresponding Abstracts, Discussions, and Conclusions, but depend heavily on flipping back and forth between Results and Materials & Methods with a question in mind before reading anything else.

As hoped for at benchmark (p. 121) **Witkowski** unveils an optical device for observing fibrillation at much higher resolution and with less invasiveness than possible a few years ago (see also Bove and Dillon, 1998). This optical device records 12-bit 128×128 snapshots of local membrane potential covering most of the front side of a dog’s heart at final effective resolution not much coarser spatially than 1 passive space constant for relatively slow processes like repolarization. This is about the thickness of the normal propagating activation front (thus the finest resolution of possible interest). After much numerical processing to extract signal from noise, the temporal resolution is still only a few 1.2 ms video frames, and events as fast as activation are blurred spatially to no more than a few front thicknesses while propagating about one 1/2-mm pixel per frame. Not all of the heart’s inside and outside surfaces are visible at once, nor can intramural activations be seen. But 13 million voltages are delivered per second, and the spatiotemporal pattern of ventricular fibrillation is plainly revealed without necessary resort to excitation-contraction uncoupling drugs, manual or semiautomatic selection of “activation complexes,” or sketching of interpretive isochronal contours. We have been analyzing these movies from many hearts on a variety of computers, following the *Hobbit*’s recommendation that “There’s nothing like looking, if you want to find some-

thing!” Results are expected shortly (Witkowski *et al.*, 1998b).

D. Where does this problem stand today?

An “outsider” could reasonably surmise that with the advent of reaction-diffusion algorithms to create movies resembling a heart covered with irregularly changing rotors, understanding of fibrillation is basically in the bag. I feel that my job is to draw attention to the possibility that some fundamental surprises still lie in wait. To solve any deep problem it may be admissible to entertain candidate solutions without serious regard for all the facts (which cannot all be correct if some really do, as appears, contradict one another.) But it should at least be explicitly recognized that particular facts don’t seem to fit the prevailing view. For example, any of the following should induce upsets comparable to the Michaelson–Morley outcome of 1881 and 1887, but no one has persuaded all his colleagues that they are all mistaken:

- (1) The observation of Chen *et al.* (1986) that for scores of ms after an electric shock there is an “isoelectric window” during which fibrillation halts and there is no detectable propagation ... then it resumes spontaneously (Ideker, 1991; Walcott *et al.* 1996). Can this represent only a latency of cellular activation plus uncommonly slow conduction to the nearest electrode? Or restriction of activity to a wholly intramural vortex ring until its fronts propagate to the surface electrodes?
- (2) The report of Lee *et al.* (1996) that reentrant vortices arise spontaneously by oblique collision of activation fronts.
- (3) The naggingly persistent absence of a convincingly semiquantitative theory of the ventricular fibrillation threshold in terms of stimulation repeated several times at the shortest possible intervals from a single electrode at strengths only a few times threshold.
- (4) **Chen’s** report that there is no distinct ventricular fibrillation threshold for a single strong shock: rather, induction of fibrillation is as probabilistic as defibrillation. The latter seems understandable in the usual case of tenfold inhomogeneous field intensity, assuming that vortices are moving unpredictably in this field during pre-existing fibrillation. But why should strong stimulation of quiescent tissue produce probabilistic results?
- (5) The observation of Delgado *et al.* (1990) that the electrical threshold for pacing a 4×4 mm square of normal epicardium from a tiny central electrode depends markedly on boundary conditions at least 1.6 mm away. Could this be an early apparition of the “dog-bone” field discovered in bidomain material at much stronger stimulus intensity (**Roth**)?
- (6) Diverse measurements of transverse propagation speed which seem equivalent to assay of D below the minimum compatible with continuum interpretations (see Winfree, 1997a and b).
- (7) Frazier’s (1988) inference that in terms of current density, the stimulation threshold is independent of cardiac fiber orientation.
- (8) The enhanced efficacy of defibrillation when polarity is reversed on a time scale of ms (Feeseer *et al.*, 1990.)
- (9) Universal experience that both biophysical theory of stimulation and laboratory experiments with isolated cells require fields around 10–20 V/cm, an order of magnitude in excess of consistent observation in normal myocardial *tissue* (1–2 V/cm).
- (10) Min and Mehra (1997) used the 5 V/cm isotropic S^* value (guessing that anisotropy will “average out” on the scale of several mm or more due to the rotating of fibers transmurally) to rationalize defibrillation threshold observed using nonuniform fields around internal catheter electrodes. By calculating fields around geometrically complex electrodes in an anatomically detailed model of thoracic conductivities and requiring that S^* (regardless of local field orientation to fibers and to activation fronts) be exceeded in 95% of the heart volume, they come remarkably close to clinically observed defibrillation thresholds of total electrode current and voltage. It is perplexing that their results seem to leave little room for improvement by refinements of bidomain biophysical theory that otherwise seems obviously called for.

Taken at face value such observations seem incompatible with straightforward reaction-diffusion theory in continuous media. Were that whole scheme to prove somehow fatally flawed, it would be remembered that in 1998 the majority of movies of actual ventricular fibrillation only vaguely resembled numerical models, except for the general impression of rapidly changing rough periodicity, presumably originating from rarely observed rotors. I can *imagine*, at least, diverse unexpected apparitions that might emerge from the new high-resolution devices, which would be perfectly consistent with prior looser evidence, yet inconsistent with today’s models unless much backpedaling and redefining is undertaken to salvage appearances. Heraclitus reportedly remarked ca. 500 BC, “If you do not expect the unexpected you will not find it, for it is hard to be sought out, and difficult.” Questions on the agenda should include:

- (1) Does fibrillation in normally excitable tissue really consist mostly of ordinary propagation (all ionic channels active), the same as when paced at comparably short intervals? And what of the exceptional places? Are their electrophysiological states inside the usual excitation-recovery loop (i.e., rotors and other front tips)?
- (2) Are the ultimate sources of this short-period activity just a few rotors, possibly meandering slowly and occasionally displaced abruptly by an activation front slapping the core? Or is developed fibrillation more like computation from undepressed ionic membrane models, dominated not by rotors, but by segments of activation front whose ends only occasionally and briefly round up into rotors but usually glide near propagation speed along ephemeral refractory boundaries (“wandering wavelets”)?
- (3) Does ventricular fibrillation start from a rotor and spread

like an expanding patch of turbulence by arcs of conduction block forming along fronts near pre-existing rotors? Does meander play an essential role in such breakups? Or do fronts emitted by a rotor first break on remote inhomogeneities simultaneously seeding the entire medium with vortices more or less uniformly? Do such 2-dimensional scenarios capture the essence of the tachycardia-to-fibrillation transition, or does it happen through one or another 3-dimensional instability of the vortex filament? How much of the propagation observed during fibrillation is predominantly transmural, erupting onto the visible surfaces? Janse *et al.* (1995, Fig 6) shows about one epicardial eruption per rotor wave spacing² per rotor period, and I think this is typical of other views of fibrillation: Are these from sources in the Purkinje fibers or consequences of rotational anisotropy, i.e., do these fronts reach the surface through intramural access to longitudinal fibers underneath relatively slow propagation on the epicardial surface?

- (4) If, in attempted replicate trials, fibrillation is initiated afresh from one heart at rest, for how long and over what area does its pattern repeat just as before? What are the basic reasons for its presumably negligible repeatability?

The literature abounds with semiquantitative numerical models illustrating most of the notions contemplated here. The questions they pose for us now are, "Which of these potential mechanisms are actually prominent in normal myocardium?" and "Is the answer the same in diseased myocardium?"

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