

## Chemical waves and fibrillating hearts: discovery by computation

A T WINFREE

Regents Professor, Department of Ecology and Evolutionary Biology, University of Arizona, Tucson, AZ 85721, USA

(Fax, 1-520-6219190; Email, winfree@email.arizona.edu)

### 1. Introduction

The distinct dynamics, on the one hand of chemical kinetics, and on the other of electrophysiology in cell membranes, seldom seem closely related. Nor do they often appear in the same journal report. But this has been changing in recent years, for example, since calcium waves have been found in brain tissues. Mathematicians are accordingly becoming involved with laboratory physiologists in these studies. It is a curious feature of such studies that so many of their phenomena were first discovered and explored by computation and only then confirmed *in vivo* or in the laboratory.

Consider the effects that would arise from spatially coupling such local dynamics through either molecular diffusion or through the mathematically equivalent spread of electric potential. This would be a set of first-order rate equations, one telling the rate of change of each chemical or physical quantity as a continuous function of all those affecting it. Were we talking well-stirred chemistry, this would be a set of ordinary differential equations like:

$$\partial \text{state} / \partial t = f(\text{state})$$

where “state” is just a list of the quantities. Since we are instead talking about a spatially-distributed system, things are a bit different from place to place, and so the local dynamics and concentrations differ between neighbours and the dynamics of each is supplemented by diffusion to and from each immediate neighbour:

$$\partial \text{state} / \partial t = f(\text{state}) + D \nabla^2 \text{state}$$

i.e., some rate equations are supplemented by a Laplacian operator, so the package is actually not just an ordinary differential equation, but rather a parabolic partial differential equation.

Here again “state” means the list of all concentrations and potentials that mutually affect one another’s rates of change on the time scale of interest, “*f*” is a different rate

law for each, and *D* is a matrix of all their diffusion coefficients. Supposing a parametrically uniform continuous medium, only the spatial and temporal scales of solutions would be affected by multiplying all reaction rates or diffusion coefficients by any fixed real factor, so qualitative behaviour depends only on ratios among the several diffusion coefficients, and on the sort of dynamics exhibited at each point of the ordinary differential equation part, *f*, of this partial differential equation. A first guess might be that from spatially uniform initial conditions, only the local dynamics would be displayed (of course also in a spatially uniform way) and that any slight imperfection of the intended uniformity would be gradually levelled by diffusion. This guess is correct in many cases, but two fascinating exceptions appeared in otherwise unrelated biology papers coincidentally published in 1952:

(i) Alan Turing (1952) analytically showed an instability toward growing periodic spatial pattern, given reactions that cross-excite and cross-inhibit, if the inhibitor diffuses faster. Origins of this insight in Rashevsky (1940) had been forgotten. Theoretical biologists took this up as a possible mechanism of pattern formation in developing organisms. There are still no clear biological examples. The first indisputable chemical example was presented by Castets *et al* (1990), Ouyang and Swinney (1991), Lengyel *et al* (1993), and Boissonade *et al* (1995).

(ii) Alan Hodgkin and Andrew Huxley (1952) experimentally filled in the specific quantitative details of an ordinary differential equation representing local “excitability” for nerve membrane and then added diffusion of electrical potential to make it a partial differential equation. Electrical potential is the “activator” variable; the “inhibitor” is a membrane-bound protein that diffuses not at all, opposite to the Turing case. Hodgkin and Huxley computed from this quantitative model a remarkably close approximation to the propagating action potential in the squid’s big escape reflex nerve. Such an “excitable” reaction has a self-exciting part that takes off only

beyond a threshold offset from the locally attracting steady state. There is no instability. Though the two sets of equations are similar except for the ratio of diffusion coefficients, this behaviour is not analogous to Turing's. Such partial differential equation models were then already standard in neurophysiology, but because specific values of reaction and diffusion coefficients were unknown and the mechanisms remained unclear, they had been considered speculative. Two decades later these computations of one-dimensional propagation were extended to two dimensions, then to three dimensions after yet another decade, in each case with amazing results that seem pertinent to clinical reality.

This Perspectives commentary reviews the evolution of contribution (2). It evolved to conquer the chemistry laboratory as (1) was expected to. And there it illuminated a mechanism of two- and three-dimensional pattern formation unlike Turing's. 16 years later the first Turing patterns were tardily discovered in the laboratory, too, as told in § 2 below. And in § 3 you will see that biologically these understandings progressed from one-dimensional application in nerve fibers to two- and three-dimensional application in heart muscle. In all these developments computation led the way, from a stiffly nonlinear ordinary differential equation iterated through  $10^4$ – $10^6$  steps (iterations) to the same implemented in  $10^2$  consecutively coupled cells propagating an impulse along a line, to  $10^2 \times 10^2$  sheets supporting vortex-like sources and the activation fronts they radiate, to  $10^2 \times 10^2 \times 10^2$  volumes supporting tangles of vortex rings emitting curved sheets of activation front. Meanwhile the nature of the substrate evolved to embrace not just one continuum of whatever dimension (the classical "monodomain" model for cellular tissues) but two finely intermingled, one inside cells and one between cells: the "bidomain" model.

My focus here is discovery by computation; I am not telling the laboratory side of these exploratory adventures.

## 2. Chemical pattern formation in excitable media

Excitable media differ from those capable of Turing instability in that one reaction is directly self-exciting (rather than exciting an inhibitor), and the inhibitory substance need not diffuse faster than the excitatory substance (or electrical potential), if it diffuses at all.

In one-dimensional media, with parameters in the right range, such media respond to strong enough stimulation by propagating a soliton-like pulse at steady speed, with steady profile, which however extinguishes (rather than reflecting) at a no-flux boundary or in collision with another going the other way (rather than passing through.) Otherwise nothing like pattern-formation occurs, nor is

there any linear instability of the spatially uniform state. This was well known at the time of Hodgkin and Huxley's beautiful papers of 1952. The best chemical example is the Belousov-Zhabotinsky medium (Zaikin and Zhabotinsky 1970), coincidentally discovered and first written up, but not published, while Turing and Hodgkin and Huxley were independently writing their own manuscripts for less hostile referees.

Twenty years later a quasi-mathematical argument described something qualitatively different in two-dimensional context: such media should support a region where excitor and inhibitor concentration gradients cross transversely in a way that induces both to rotate together. This region should have a characteristic size, independent of initial conditions, and should radiate a spiral wave like the magnetic spiral around a pulsar, but with a unique period and pitch (Winfree 1972). The initializing stimulus has to be big: this "rotor", as it came to be called, cannot grow spontaneously from a linear instability of the uniform state. This scheme was implemented computationally in the USSR in 1973 and in the USA (Winfree 1974a,b; 1977) and the hoped-for rotor was computationally found to be stably persistent for at least hundreds of cycles. Meanwhile almost the same thing (but observed during just a couple initial rotations heavily affected by transients of startup from peculiar initial conditions) appeared in the USSR (Gul'ko and Petrov 1972 without comment on the rotor itself but only on the waves radiating from it; and Shcherbunov *et al* 1973 without stability). This initiated a 20-year effort by applied mathematicians worldwide to produce an analytical model of such pattern formation. Much has been achieved (e.g. peruse Kapral and Showalter 1995; Panfilov and Holden 1997; Winfree 2001) but much remains still challenging.

The rotor is commonly referred to as a "vortex". Little about it resembles fluid vortices and the term "vorticity" referring to the presence of such spinning structures has no relation to the divergence-free vorticity defined in fluid mechanics. Nothing moves but a pattern of activations repeated at the source's unique period of rigid rotation in each point of the motionless medium.

After the early 1970s it was universally supposed that the rotor's period is uniquely selected by the system's parameters, but there was never a mathematical proof. Would an intuition-guided computational search for counter-examples help? I tried it and discovered parameter ranges of simple generic media in which two (or maybe more) distinct alternative periods for stable rotors evolve from sufficiently different initial conditions (Winfree 1990; Winfree 1991b). This has been confirmed by similar computations in two other labs (Karma 1990; Lee *et al* 1996) but has not yet been reported in the Belousov-Zhabotinsky chemically excitable medium (probably because the parameter domain is small), nor is

heart muscle (probably because heart muscle is not sufficiently uniform).

One of the most intriguing phenomena unexpectedly discovered in the lab was “meander” of the rotor, a drift of its center along a curved path with periodically modulated curvature . . . this in a uniform isotropic medium with time-independent parameters. The path thus resembles a flower-like “spirograph” drawing. This modulation period is comparable to the rotation period but in general not a rational multiple. This had been seen experimentally (the name was coined in Winfree 1973) but was not then understood to arise from two-dimensional reaction and diffusion alone, unaided by parametric inhomogeneities. We now know that it does, and is generic, but due to bad luck in choice of parameters, no computational model showed meander before 1979 (Rössler and Kahlert 1979; Zykov 1986). It was first discovered computationally that this second periodic mode arises by Hopf bifurcation as the parameters of excitability are varied (conjectured in Nandapurkar and Winfree 1989; Jahnke *et al* 1989 and Lugosi 1989, all from the same lab, then demonstrated through more refined computation by Barkley *et al* 1990 and independently by Karma 1990). This new mode has strictly no interaction with the first mode (the basic rotation), even at high amplitude (Barkley *et al* 1990; Barkley 1992, 1994, 1995). Though rotors in heart muscle show no such simple regularities to date, meander in the Belousov-Zhabotinsky medium became the subject of abundant studies. Computationally, further modes bifurcate at other loci in parameter space, making the “flowers” more complex and inducing the -meander” (Winfree 1991a,b). Despite several efforts (Plesser and Muller 1994; Zhang and Holden 1995; Diks *et al* 1995; Diks 1996; Biktashev and Holden 1998) computational hyper-meander has not yet been convincingly distinguished from multiple quasi-periodicity nor from spatio-temporal chaos. Hyper-meander has been found in well-regarded computational models of the Belousov-Zhabotinsky chemically excitable medium (Jahnke and Winfree 1991) and of heart muscle (Beaumont *et al* 1998) but only two-period meander been reported in chemical rotors, and rotors in heart muscle seem far less predictable than even hyper-meander.

Computation using a fairly complicated (8-variable) reaction diffusion model in two dimensions (for heart muscle: see §3) first overthrew the former belief that rotors could not arise spontaneously in a parametrically uniform excitable (as opposed to oscillatory) medium. True enough, they never do arise out of nearly uniform initial conditions, but once a rotor is started, the short-period waves it radiates can suffer patchy spontaneous block. This leaves two free ends of wavefront to become mirror-image rotors at the usual characteristic period

(Winfree 1989). Only a few years passed before the same was achieved in simpler 2-variable models (Bar and Eiswirth 1993; Panfilov and Hogeweg 1993). Such turbulence in the plane has been much anticipated and much reported in Belousov-Zhabotinsky excitable media, but in every case I know of, careful attention to laboratory Materials and Methods suggests that the effect crucially depends on fluid convection or inhomogeneities or some gradient in the third dimension. This absence of reaction-diffusion turbulence in chemically excitable media remains a bit of a mystery. [In contrast, when chemical parameters are adjusted to eliminate excitability and evoke quasi-harmonic oscillation, the wave train from the rotor is subject to a slow instability as the waves travel over long distances (Ouyang and Flesselles 1996), as foreseen by Kuramoto (1984).]

By the middle 1980's it had become feasible outside government bomb laboratories to solve reaction-diffusion partial differential equation in three dimensions. It was expected that rotors would become vortex lines in space and that those lines would generically close in rings, possibly linked and knotted, and that some such solutions (“stable organizing centers”) might prove stable (Winfree 1980; Winfree and Strogatz 1984). The first such computation was reported in 1985 (Panfilov and Winfree 1985) but it was unstable. A trefoil-knotted vortex ring was the first to be found stable (Nandapurkar 1988; Henze and Winfree 1991) then a dozen topologically distinct stable configurations turned up (Henze 1993; Winfree 2002).

These computations excluded the “local geometry hypothesis” first articulated (somewhat skeptically) in Winfree and Guilford (1988), on which all mathematical analysis of such structures is still based. According to that conjecture, each segment of vortex filament in a three-dimensional reaction-diffusion excitable medium moves only as determined by certain aspects of its local shape, as in the “local induction approximation” for vortex lines in fluids. No such rules have been found to account for the shapes and sizes of the observed stable organizing centers, nor even to qualitatively affirm their existence.

To me it now seems instead that a non-local factor accounts for their resistance to shrinkage and collapse. The prime suspects at the moment are shock waves from afar. Because waves from one part of the ring collide with those from another part at a collision interface inside the ring, and the periods are unequal, this interface moves ever nearer to the longer-period source until waves slap that segment of filament directly, forcing it outward. This difference of periods arises from an effect of local geometry on local rotation rate: wherever the scroll filament is more twisted, the spirals rotate a little faster. Twist is topologically inevitable when rings are linked or knotted (Winfree and Strogatz 1984).

The computation referred to in §2 used an excitable medium in which rotors never meander, so rotation stayed synchronous along the filament, all rings stayed identical and smooth, and wavefronts erupted through the box walls in a symmetric and perfectly periodic way. The local geometry hypothesis proved inadequate to describe its anatomy, but it becomes more blatantly unworkable in media supporting meander: the filament then moves even when it starts as a perfect straight line and the iso-concentration surfaces around it are initially perfect right cylinders. And what happens to stable organizing centers when parameters are changed to provoke spontaneous meander? For this computational experiment we change to a different excitable medium.

The outcome is a triplet of closed rings, each linked through the other two. The three have different and irregular shapes because in generic excitable media (perhaps generically, but at least this one in particular) the two-dimensional vortex center meanders along a looping path, and in three dimensions this becomes asynchronous along the length of the filament. In this figure wavefronts are suppressed and only the vortex line is shown: this is the edge of the wavefront surface, the locus of rotors in three dimensions (analogous to the familiar 2d case: the tip of the spiral wave, the rotor). Were it depicted as a vortex thick enough to encompass the wave-free region whose edge radiates waves, that tube would have perimeter equal to the wavelength and all such tubes would be in contact here and would visually obscure one another. So it is instead drawn as a fine curve, but coloured green-yellow-red across its tiny diameter in the direction of the gradient of the rapidly diffusing excitor variable  $u$  in the defining equation of FitzHugh-Nagumo excitable medium:

$$\begin{aligned}\partial u/\partial t &= 0.2(u - u^3/3 - v) + \nabla^2 u \\ \partial v/\partial t &= 5(u + 0.9 + v/2).\end{aligned}$$

From the rotation of this colour gradient you can see that along each ring the rotor's phase advances through two cycles in linking the two other rings, as foreseen in Winfree and Strogatz (1984). This wiggly imperfectly periodic triplet persisted through about 40 rotor periods without indication of secular change, once established.

The computation was initiated with "0.9" replaced by "0.7", which started the medium outside its meander domain. Segments of filament settled into skew-tangency like meshed gears in an automatic transmission box. After the change to "thermal agitation" by meander (0.9) they were intermittently thrown into contact and might have been expected to pass through one another or cross-connect (Fiedler and Mantel 2000), changing the topology of the ring configuration until only rings without linkage or knotting remain, which promptly shrink and vanish. Expectation was that meander would induce such

transmutations until nothing remains. It didn't. The "heated" organizing centers expanded somewhat and segments of meandering filament stayed clear of one another. Topological integrity persisted. Nothing about this performance could be described as stable or periodic, but we seem to have obtained persistent organizing centers (Winfree 1994a,b, 1995).

Topological persistence may be the one dependable feature. Sutcliffe and Winfree (unpublished) has extended such computations to durations 1–2 orders of magnitude longer (to several hundred rotor periods) and observed that shapes do resume changing on that long time scale . . . but filaments do not encounter one another to reconnect, so topological integrity is preserved for as long as we have thus far calculated several topologically distinct persistent organizing centers.

All of this remains to be checked in the Belousov-Zhabotinsky chemically excitable medium, which might be hard to do because on that time scale (thousands of rotations) it uses up its chemical resources. (Also because no one has yet implemented such initial conditions as suggested in Winfree 1985.)

### 3. Electrical pattern formation in heart muscle

Under a different physical interpretation, the same sort of partial differential equation represents an idealization of heart muscle. The "reactions" are the opening or closing of several kinds of ionic channel in the cell membrane and the charging of membrane capacitance in response to changes of electric potential difference across it. Of the several quantities involved, only one diffuses, the "excitor", viz., that electric potential. Its diffusion coefficient from cell to cell though resistive gap junctions is  $10^5$ -fold larger than typical of chemical diffusion. The reactions are also about  $10^3$ -fold quicker. This is basically the Hodgkin-Huxley story of 1952 and the results are the same: a propagating pulse in one dimension, the action potential. But in two or three dimensions there is something more, the rotating localized pattern called a rotor, the source of an outgoing spiral wave. Its characteristic frequency (found out by computation from the electrophysiologists' latest description of ionic membrane mechanisms) turns out to be indistinguishable from that of the clinical "arrhythmia" that heralds the onset of "fibrillation" and sudden cardiac death.

What is "fibrillation"? When the term was coined a century ago it connoted the presumed independent twitching of adjacent fibrils of diseased heart muscle. Even up to the middle 1980s it was by no means clear that this was a bad description. The implicit assumption was that if it behaves strangely, its parameters must have been altered by disease, as indeed they often are. This

assumption overlooks fibrillation in perfectly normal heart muscle. It was not known (though a minority of one predicted it) that the ionic mechanisms of the heart cell membrane work normally during such fibrillation. The dominant assumption was that the sodium channels or the calcium channels are defunct, seriously altering the rate equations. It was not widely accepted that propagation of action potentials, in the usual sense, occurs at all during fibrillation, nor that there is any conspicuous periodicity to it; in fact the definition in many texts includes “complete irregularity”. Since maybe 1995, however, it seems accepted that during fibrillation, at least in healthy hearts, the cell membrane and its gap junctions are perfectly normal, that normal propagation does occur, and that fibrillation has a characteristic sharp periodicity close to that of rotors. These points were established of course by observation, but the observations were induced by computational demonstration that the normal equations of normal heart muscle, even without inhomogeneities of any sort, have solutions resembling real fibrillation.

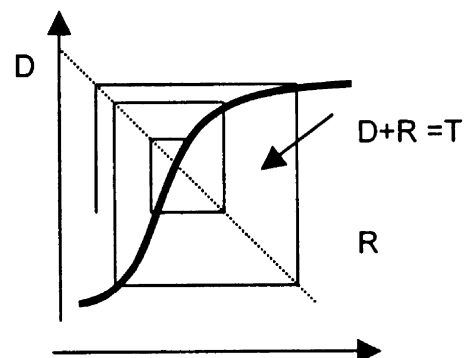
A distinction should be made before we proceed. Clinical electrophysiologists do not deal much with normal heart muscle. Scientists do because they don't know how to quantitatively describe any particular pathological condition of the variegated hearts that clinicians must regulate. Our hope is that it will not prove a waste of time to discover what fibrillation is in normal, describable heart muscle. But clinicians have a long tradition of assuming the opposite. For example, almost the only approach to this problem before the mid-1980s is based on the idea that spatially heterogeneous-parametric inhomogeneities underlie almost everything of interest about fibrillation, so the models tend to resemble cellular automata with heterogeneous parameters. In contrast, the newer models of normal heart muscle in which computational “fibrillation” is studied are parametrically uniform partial differential equations. They seem to make fibrillation just fine.

*Another distinction:* Even normal heart muscle is lots more complicated than any of the models here mentioned. My assumption is that these complications are nugatory details. I think well chosen models clarify concepts by judicious deliberate over-simplification. Hardly any medical physiologist would agree. So this is only a beginning.

*And a caveat:* Correlation of computational experiments with laboratory experiments has often been too loose, not only because the equations and their parameters remain far from sure, but also because the experimental observations keep changing. Artifacts of both computation and experiment have played prominent roles in misleading us, and they continue to do so (B J Roth,

unpublished results). But perseverance sometimes pays off in a big way. A conspicuous recent example stems from the fact that, unlike any known chemical medium, the duration,  $D$ , of the next cardiac action potential is longer when the tissue gets a longer rest interval,  $R$ , after the end of the prior action potential. That monotone increasing function  $D(R)$  is called the “restitution curve” for action potential duration. It was realized 30 years ago that if such tissue is homogeneously paced at a short enough period,  $T = R + D$ , so that the slope of this measurable function of period exceeds 1, then its response to periodic pacing becomes unstable. You can see why in figure 1.

Ten years ago it became clear that in models rotors provide a sufficiently short-period source to evoke this instability, if something like it exists in two-dimensional tissue paced not homogeneously but by wave propagation. If so, then might some such mechanism instigate fibrillation (Lewis and Guevara 1990)? But to believe that this scenario, among many alternatives, actually occurs in real heart muscle one had to ignore almost all the reproducible data on restitution curves. Of seventy curves I gleaned from published and private sources, only two, which might be suspect on other grounds, exhibited slopes  $> 1$  at periods as short as the rotor's. To me, this scenario accordingly seemed implausible (Winfree 1994b, 1997). But others adhered to this line of thinking (Courtemanche 1996; Garfinkel *et al* 1996), and their faith was rewarded. At the end of 1998 Koller *et al* (1998) reported a better way to measure these curves. Near the observed period of rotors their new assay reveals slopes that do consistently exceed 1 in situations



**Figure 1.** During regular pacing at period  $T = D + R$  the succession of  $D$ 's and  $R$ 's can be followed by reflecting off heavy curve  $D(R)$  and the dashed line of fixed sum  $D + R = T$ . Their intersection is the only periodic solution. It is stable if  $dD/dR$  at the intersection is less than 1 at the chosen  $T$ , otherwise not. A given initial  $D$  leads (leftward) to the dashed line at the next  $R$  complementary to period  $T$ , which gives (down) a next  $D$  on the curve, and so on, spiraling outward in this picture because slope at the intersection here exceeds 1.

that do go unstable in the laboratory, and only in those (Ricci *et al* 1999). This is just what was foreseen from computational models that – here is the key point I want to stress – differed sharply from laboratory experiments until only two years ago. In some sense the two-dimensional computations were right and provided the indispensable catalyst for this fundamentally important discovery. [In a further sense, a later three-dimensional computational model (Vigmond and Leon 2002) appears to re-muddle this tidy story, or maybe to underscore the need for specific further experiments to clarify a version that came out from the laboratory while still implausibly simplified.]

In leaving this subject, it should be mentioned that “1” is a strict criterion only for the iteration in figure 1 that supposes both strictly periodic stimuli and a spatially uniform response in a spatially uniform continuum. In real two- or three-dimensional heart muscle and in partial differential equation models a related instability does arise somewhere around slope 1, but that is only a rough rule of thumb and no one has yet figured out the appropriate analysis when propagation is involved and intervals are not regularly periodic, nor has anyone figured out why the rotor has whatever period it does. But during fibrillation in the dog F X Witkowski and I found slopes 2–3 times this steep throughout the whole range of plausible rotor period (Winfree 2001, page 507), so the details seem unlikely to matter a lot for this.

Cardiac rotors were first computed from the continuous, two-dimensional, eight-variable, ionic membrane equations of the heart in 1988 (Winfree 1989; Courtemanche and Winfree 1991). My purpose at that time was to check whether those extra degrees of freedom make any essential difference relative to more familiar simpler excitable media, and to compare the hoped-for rotors to those observed in normal heart muscle. Rotors were found, with period and size comparable to those in the heart: 100–200 ms and 1 cm along fibers (and 4–5 mm across fibers). In both media they moved in unexpectedly complicated ways. Could both be fibrillation? More realistic equations have since led to closer comparisons and more suggestive images.

Are these seemingly decisive two-dimensional computational experiments really pertinent to physiologically normal heart muscle? A strange fact suggests they might not be: all laboratories using normal three-dimensional heart muscle report that rotors immediately transition to fibrillation, but laboratories working with functionally two-dimensional tissue show stable rotors unless the tissue is also deliberately made electrophysiologically abnormal. Does this peculiarity indicate that thin-sliced, functionally two-dimensional preparations in diverse laboratories have all inadvertently become electrophysiologically abnormal? If not, then instability of rotors only

in three dimensions suggests any one of half a dozen conjectural mechanisms (Winfree 1994b, 1997), all quite different from this one involving the slope of the restitution curve – unless somehow muscle thickness determines the slope of its local restitution curve.

Some of these other conjectures stem from observation in computational models that the vortex filament, if initially straight and perpendicular the heart’s surface, has three-dimensional instabilities that develop wildly if and only if heart wall thickness exceeds a rotor diameter (4–5 mm of wall thickness). This predicted thickness threshold was checked for and found experimentally. Its relationship to theory has been probed in three-dimensional calculations of three kinds:

- Panfilov and Hogeweg (1993) found a parameter range for one excitability model in which two-dimensional rotors are stable, but filaments in three dimensions go unstable. In this model the medium is isotropic and parametrically uniform.
- By taking account of the gradient of excitability across the thickness of the heart wall one obtains rotors of different periods along the length of a filament spanning the wall, which leads to another kind of instability (Henze *et al* 1990; Pertsov *et al* 1990; Winfree 1998).
- Fenton and Karma (1998a,b) found filament instability beyond about 4 mm thickness without fine-tuning parameters or taking account of a gradient: instead they take account of the fact that myocardium is electrically anisotropic in the rotating way of a cholesteric liquid crystal.

The first two of the above computations overlook another feature of heart muscle: that it consists of two microscopically inter-penetrating volumes with different electrical properties, viz., cell insides (connected in 3d by gap junctions) and the connected spaces between cells. This “bidomain” model is like two copies of the partial differential equation above:

$$\frac{\partial \Phi_{\text{inside}}(r)}{\partial t} = D_{\text{inside}} \nabla^2 \Phi_{\text{inside}} + f(\Phi_{\text{outside}} - \Phi_{\text{inside}}, \text{channels})$$

$$\frac{\partial \Phi_{\text{outside}}(r)}{\partial t} = D_{\text{outside}} \nabla^2 \Phi_{\text{outside}} - f(\Phi_{\text{outside}} - \Phi_{\text{inside}}, \text{channels})$$

(plus subsidiary kinetic equations for ionic channel conductivity dynamics depending on the transmembrane potential,  $(\Phi_{\text{outside}} - \Phi_{\text{inside}})$ , without diffusion.

Here the  $\Phi$ ’s are scalar electrical potentials,  $f$  is the dependence of ionic conductivities on potential difference across the membrane separating the two potentials, and the  $D$ ’s are  $3 \times 3$  diagonal matrices of distinct electrical conductivity components determined by the geographical distribution of gap junctions, etc. This pair of equations would reduce to the single equation above if

both domains had the same anisotropy, but they don't. How much does it matter? Not much for propagation far from boundaries. But for calculating the effects of externally applied electric current it matters a lot. A particularly nice demonstration of this is due to Sepulveda *et al* (1989) (see also Wikswo *et al* 1995), who showed that the neighbourhood of a point where current is injected divides into criss-crossed patterns of excitatory and inhibitory effect. One consequence is that two successive pulses applied at the same point can evoke a tetrad of doubly mirrored rotors (Roth 1998)! "Monodomain" models, or bidomain with equal anisotropies in the two intermingled domains, in contrast, require appropriately spaced successive adjacent stimuli. These qualitatively different and counter-intuitive effects of electrical stimuli in bidomain media were not anticipated. They were discovered entirely by computation, and then confirmed dramatically in the laboratory (Lin *et al* 1999).

A vitally important problem that seems approachable only through bidomain computation is the quantification of mechanisms whereby strong electric shock erases rotors or fibrillation. This is the only known therapy, and its contemporary protocols are shockingly crude and not always effective. They could probably be improved dramatically if we understood their mechanism. There are several clear possibilities, e.g. that local inhomogeneities of resistivity create hot spots without which not much would happen. Another is that the cm-scale curvature of muscle fibers facilitates their penetration by external currents, as nicely demonstrated in recent computations of Trayanova *et al* (1998). But it seems that no single one of several suggested biophysical mechanisms can quantitatively account for the measured shock strength thresholds of effectiveness. "The answer" may require superposition of several contributory effects, all essentially involving bidomain physics (Roth and Krassowska 1998). It seems hard at present to imagine how laboratory experiments could tease apart these subtle factors; meanwhile computation seems to be converging on the needed understanding.

Medicine based on the completely dominant sole paradigm of the past 30 years seems not to be converging on the needed understanding. It turns out that the pharmaceuticals routinely prescribed during the past few decades were actually causing about 40,000 more deaths per year in the USA alone than would have occurred in their absence. FDA approval does not require prior demonstration of benefit to patients and does not guarantee that a profitable drug will do its users more good than harm (Moore 1995).

#### 4. Bottom line

The reaction diffusion equations deployed in chemistry and electrophysiology have illuminated those areas in

ways that experiment probably never would have done. While the field of chemistry has persisted 40 years in showing almost no interest, a tiny handful of determined investigators discovered the (formerly denied) existence and delightfully surprising properties of chemical Turing patterns, oscillations, and waves, and the capacity of reaction-diffusion media to organize themselves in topologically exotic life-like three-dimensional patterns. While the field of electrophysiology unswervingly ignored the parallel development (by computational theorists) applied to heart muscle, a few physics-oriented biologists undermined the central dogma of that field, according to which (since about 1964) therapy should be based on stochastic models of parametric heterogeneity. Predictions from recent theory for engineering design of cardiac pacemakers and defibrillators are proving themselves and providing clinically useful improvements during a time when drugs selected under the former dogma are proving themselves worse than useless.

Two main problems limit achievement in this area:

First of all, looseness of inference connecting computations to laboratory experience deprives both of their dialectical potential. From the viewpoint of experimentalists, ignoring computations often seems justified, since computations tend to be highly idealized and may seem even frivolously so, and often don't replicate well (in part because they are seldom fully specified in publications, and then with multiple typos). And ignoring experiments often seems justified from the viewpoint of theorists, since experiments also often don't replicate well or they pertain to such unrepresentative special cases that one hardly knows what general lesson to draw from their outcomes. The utility of both seems greatly enhanced when the same individual or laboratory does both computations and experiments, taking both seriously to refine the other in the next iteration, and when the prominence of artifacts in both methods is given due attention (B J Roth unpublished results).

Secondly, the magnitude of the computational challenge has always been a problem. Fortunately, most of the investigations mentioned here transpired during the 30-year rule of Moore's Law that machine capacity doubles every year and a half. Every one of the five or six order-of-magnitude increases of machine capacity so far has revealed fundamental inadequacies in prior efforts in this area. Going from zero to one to two to three dimensions, from smooth kinetics at low temporal resolution to shock waves representable only at small steps, from monodomain to bidomain, and from single cell to uniform tissue to whole heart, even with hydrodynamics included now – but not yet including the effect of stress and mechanical deformation on electrical behaviour – has at each step introduced qualitatively new phenomena that turned out

to be essential, not just refinements of detail. Presumably a plateau of diminishing returns will be found, and maybe we are already on it, but we don't yet know.

I think there are lessons in this adventure both for computational physicists and for experimental biologists: basically, they are more fruitful when working together than when disparaging one another.

## References

- Bar M and Eiswirth M 1993 Turbulence due to Spiral Break-up in a Continuous Excitable Medium; *Phys. Rev. E* **48** 1635–1637
- Barkley D 1992 Linear Stability Analysis of Rotating Spiral Waves in Excitable Media; *Phys. Lett.* **68** 2090–2093
- Barkley D 1994 Euclidean Symmetry and Dynamics of Rotating Spiral Waves; *Phys. Rev. Lett.* **72** 164–166
- Barkley D 1995 Spiral Meandering; in *Chemical waves and patterns* (eds) R Kapral and K Showalter (Dordrecht: Kluwer) pp 163–190
- Barkley D, Kness M and Tuckerman L S 1990 Spiral Wave Dynamics in a Simple Model of Excitable Media: Transition from Simple to Compound Rotation; *Phys. Rev. A* **42** 2489–2492
- Beaumont J, Davidenko N, Davidenko J M and Jalife J 1998 Spiral Waves in Two-dimensional Models of Ventricular Muscle: Formation of a Stationary Core; *Biophys. J.* **75** 1–14
- Biktashev V N and Holden A V 1998 Deterministic Brownian Motion in the Hypermeander of Spiral Waves; *Physica D* **116** 342–354
- Boissonade J, Dulos E and De Kepper P 1995 Turing Patterns: From Myth to Reality; in *Chemical waves and patterns* (eds) R Kapral and K Showalter (Dordrecht: Kluwer) pp 221–268
- Castets V, Dulos E, Boissonade J and De Kepper P 1990 Experimental evidence of a sustained standing Turing-type nonequilibrium chemical pattern; *Phys. Rev. Lett.* **64** 2953–2956
- Courtemanche M 1996 Complex Spiral Wave Dynamics in a Spatially Distributed Ionic Model of Cardiac Electrical Activity; *Chaos* **6** 579–600
- Courtemanche M and Winfree A T 1991 Re-entrant rotating waves in a Beeler-Reuter based model of two-dimensional cardiac conduction; *Int. J. Bif. Chaos* **1** 431–444
- Diks C 1996 *On Nonlinear Time Series Analysis: Spatiotemporal Complexity and Noise*, Ph.D. dissertation, University of Leiden, The Netherlands
- Diks C, Hoekstra B and DeGoede J 1995 Spiral Wave Dynamics; *Chaos Sol. Fract.* **5** 646–660
- Fenton F and Karma A 1998a Fiber-Rotation-Induced Vortex Turbulence in Thick Myocardium; *Phys. Rev. Lett.* **81** 481–484
- Fenton F and Karma A 1998b Vortex Dynamics in Three-Dimensional Continuous Myocardium with Fiber Rotation: Filament Instability and Rotation; *Chaos* **8** 20–47
- Fiedler B and Mantel R M 2000 Crossover Collision of Scroll Wave Filaments; *Documenta Math.* **5** 695–731
- Garfinkel A, Chen P S, Walter D, Karagueuzian H, Kogan B and Weiss J 1996 Quasiperiodicity and Chaos in Cardiac Fibrillation; *J. Clin. Invest.* **99** 305–314
- Gul'ko F B and Petrov A A 1972 Mechanism of the Formation of Closed Pathways of Conduction in Excitable Media in Russian; *Biofizika* **17** 261–270
- Henze C 1993 *Stable Organizing Centers*, Ph.D. dissertation, University of Arizona, University Microfilms #9333307
- Henze C, Lugosi E and Winfree A T 1990 Stable Helical Organizing Centers in Excitable Media; *Can. J. Phys.* **68** 683–710
- Henze C and Winfree A T 1991 A Stable Knotted Singularity in an Excitable Medium; *Int. J. Bifurc. Chaos* **1** 891–922
- Hodgkin A L and Huxley A F 1952 A Quantitative Description of Membrane Current and Its Application to Conduction and Excitation in Nerve; *J. Physiol.* **117** 500–544
- Jahnke W, Skaggs W and Winfree A T 1989 Chemical vortex dynamics in the Belousov-Zhabotinsky reaction and in the 2-Variable Oregonator model; *J. Phys. Chem.* **93** 740–749
- Jahnke W and Winfree A T 1991 A survey of spiral wave behavior in the Oregonator model; *Int. J. Bif. Chaos* **1** 445–466
- Kapral R and Showalter K 1995 *Chemical waves and patterns* (Dordrecht: Kluwer)
- Karma A 1990 Meandering Transition in Two-dimensional Excitable Media; *Phys. Rev. Lett.* **65** 2824–2827
- Koller M L, Riccio M L and Gilmour R F 1998 Dynamic Restitution of Action Potential Duration during Electrical Alternans and Ventricular Fibrillation; *Am. J. Physiol.* **275** H1635–1642
- Kuramoto Y 1984 *Chemical oscillations, waves and turbulence* (Berlin: Springer)
- Lee K J, Cox E C and Goldstein R E 1996 Competing Patterns of Signaling Activity in *Dictyostelium discoideum*; *Phys. Rev. Lett.* **76** 1174–1177
- Lengyel I, Kadar S and Epstein I R 1993 Transient Turing structures in a gradient-free closed system; *Science* **259** 493–495
- Lewis T J and Guevara M R 1990 Chaotic Dynamics in an Ionic Model of the Propagated Cardiac Action Potential; *J. Theor. Biol.* **146** 407–432
- Lin S F, Roth B J and Wikswo J P 1999 Quatrefoil Reentry in Myocardium: An Optical Imaging Study of the Induction Mechanism; *J. Cardiovasc. Electrophysiol.* **10** 574–586
- Lugosi E 1989 Analysis of Meandering in Zykov-Kinetics; *Physica D* **40** 331–337
- Moore T J 1995 *Deadly medicine* (New York: Simon and Schuster)
- Nandapurkar P J 1988 Computation of Three Dimensional Waves in Supercomputers; in *Simulation of wave processes in excitable media* translation V S Zykov (Manchester: University Press)
- Nandapurkar P J and Winfree A T 1989 Dynamical Stability of Untwisted Scroll Rings in Excitable Media; *Physica D* **35** 277–288
- Ouyang Q, Flesselles J-M 1996 Transition from Spirals to Defect Turbulence; *Nature (London)* **379** 143–146
- Ouyang Q and Swinney H L 1991 Transition from a uniform state to hexagonal and striped Turing patterns; *Nature (London)* **352** 610–612
- Panfilov A V and Hogeweg P 1993 Spiral Break-up in a Modified FitzHugh-Nagumo Model; *Phys. Lett. A* **176** 295–299
- Panfilov and Holden A V 1997 *Computational biology of the heart* (Chichester: John Wiley)
- Panfilov A V and Winfree A T 1985 Dynamical Simulations of Twisted Scroll Rings in Active Three-Dimensional Media; *Physica D* **17** 323–330
- Pertsov A M, Aliev R R and Krinsky V I 1990 Three-dimensional Twisted Vortices in an Excitable Chemical Medium; *Nature (London)* **345** 419–421

- Plessner T and Muller K H 1994 Fourier Analysis of the Complex Motion of a Spiral Tip in Excitable Media; *Int. J. Bif. Chaos* **5** 1071–1084
- Rashevsky N 1940 An Approach to the Mathematical Biophysics of Biological Self-Regulation and of Cell Polarity; *Bull. Mathe. Biophys.* **2** 15–25
- Riccio M L, Koller M L and Gilmour R F 1999 Electrical Restitution and Spatiotemporal Organization during Ventricular Fibrillation; *Circ. Res.* **84** 955–963
- Rössler O E and Kahlert C 1979 Winfree Meandering in a 2-Dimensional 2-Variable Excitable Medium; *Z. Naturforsch.* **34** 565–570
- Roth B J 1998 The Pinwheel Experiment Revisited; *J. Theor. Biol.* **190** 389–393
- Roth B J and Krassowska W 1998 The Induction of Reentry in Cardiac Tissue. The Missing Link: How Electric Fields Alter Transmembrane Potential; *Chaos* **8** 204–220
- Sepulveda N G, Roth B J and Wikswo J P 1989 Current Injection into a Two-dimensional Anisotropic Bidomain; *Biophys. J.* **55** 987–999
- Shcherbunov A I, Kukushkin N I and Sakson M Y 1973 Reverberator in a System of Interrelated Fibers Described by the Noble Equation in Russian; *Biofizika* **18** 519–525
- Trayanova N, Scouibine K and Aguel F 1998 The Role of Cardiac Tissue Structure in Defibrillation; *Chaos* **8** 221–233
- Vigmond E J and Leon L J 2002 Restitution Curves and the Stability of Reentry in Three-dimensional Simulations of Cardiac Tissue; *Comput. Visual. Sci.* **5** 1–11
- Wikswo J P, Lin S-F and Abbas R A 1995 Virtual Electrodes in Cardiac Tissue: A Common Mechanism for Anodal and Cathodal Stimulation; *Biophys. J.* **69** 2195–2210
- Winfree A T 1972 Spiral Waves of Chemical Activity; *Science* **175** 634–636
- Winfree A T 1973 Scroll-shaped waves of chemical activity in three dimensions; *Science* **181** 937–939
- Winfree A T 1974a Rotating Chemical Reactions; *Sci. Am.* **230** 82–95
- Winfree A T 1974b Rotating Solutions to Reaction/Diffusion Equations; *S.I.A.M./A.M.S. Proc.* **8** 13–31 (ed. D Cohen, *Am. Math. Soc.*: Providence R I)
- Winfree A T 1977 Spatial and Temporal Organization in the Zhabotinsky Reaction; *Adv. Biol. Med. Phys.* **16** 115–136 (1973 *Aharon Katchalsky Memorial Symposium* eds J H Lawrence, J W Gofman, T L Hayes)
- Winfree A T 1980 The geometry of biological time (New York: Springer-Verlag) (and second edition 2001)
- Winfree A T 1985 Organizing Centers for Chemical Waves in Two and Three Dimensions; in *Oscillations and traveling waves in chemical systems* (eds R Field and M Burger (New York: Wiley) ch. 12, pp 441–472
- Winfree A T 1989 Electrical Instability in Cardiac Muscle: Phase Singularities and Rotors; *J. Theor. Biol.* **138** 353–405
- Winfree A T 1990 Discrete Spectrum of Rotor Periods in an Excitable Medium; *Phys. Lett. A* **149** 203–206
- Winfree A T 1991a Varieties of Spiral Wave Behavior in Excitable Media; *Chaos* **1** 303–334
- Winfree A T 1991b Alternative Stable Rotors in an Excitable Medium; *Physica D* **49** 125–140
- Winfree A T 1994a Persistent Tangled Vortex Rings in Generic Excitable Media; *Nature (London)* **371** 233–236
- Winfree A T 1994b Electrical Turbulence in 3-Dimensional Heart Muscle; *Science* **266** 1003–1006
- Winfree A T 1995 Persistent Tangles of Vortex Rings in Excitable Media; *Physica D* **84** 126–147
- Winfree A T 1997 Rotors, Fibrillation, and Dimensionality; in *Computational Biology of the Heart* (eds A V Panfilov and A V Holden (Chichester: John Wiley) Chapter 4, pp 101–135
- Winfree A T 1998 Evolving Perspectives during Twelve Years of Electrical Turbulence; *Chaos* **8** 1–19
- Winfree A T 2001 The geometry of biological time (New York: Springer-Verlag) (and first edition 1980)
- Winfree A T 2002 A Prime Number of Prime Questions about Vortex Dynamics in NonLinear Media; in *Where do we go from here?* (eds J Hogan *et al* (Bristol: Institute of Physics Press)
- Winfree A T and Guilford W 1988 The Dynamics of Organizing Centers: Numerical Experiments in Differential Geometry; in *Biomathematics and related computational problems* 697–716 (ed. L M Riccardi) (Dordrecht: Kluwer Academic Publishers)
- Winfree A T and Strogatz S H 1984 Organizing Centers for Three-Dimensional Chemical Waves; *Nature (London)* **311** 611–615
- Zaikin A N and Zhabotinsky A M 1970 Concentration wave propagation in two-dimensional liquid-phase self-oscillating systems; *Nature (London)* **225** 535–537
- Zhang H and Holden A V 1995 Spiral wave breakdown in an excitable medium model of cardiac tissue; *Chaos Soliton Fractals* **5** 661–672
- Zykov V S 1986 Cycloidal circulation of spiral waves in excitable medium; *Biofizika* **31** 862–865