Yeast Oscillations, Belousov-Zhabotinsky Waves, and the Non-Retraction Theorem*

Steven Strogatz

When you think of scientific applications of topology, you usually think of physics: fiber bundles [1], solitons [2], and instantons in particle physics, for example. But more and more, topology is beginning to play an important role in chemistry and biology. When biochemists discuss the three-dimensional coiling of DNA, differential topology is the language of choice [3–6]. The widespread occurrence of closed *rings* of DNA leads to complex topologies: knots or even networks of interlocked rings (as in the Trypanosome parasite that causes sleeping sickness) [7, 8]. Amazing enzymes called "topoisomerases" can break DNA rings and rejoin them with altered topology [9, 10]. These feats have only recently been mimicked by man-made technology—after decades of effort, organic chemists [11, 12] have synthesized the first molecular Mobius strip.

In this spirit I present two disparate examples of science unified by a theorem of topology, the so-called non-retraction theorem. The first example should appeal to beer drinkers—it concerns a peculiarity of the yeasts' brewing schedule. Then turning from rhythms in time to patterns in space, the second example deals with chemical waves in a remarkable broth, the Belousov-Zhabotinsky reagent. Unlike the tedious chemistry of high school days, this little dish of reactions seems positively alive. Against a motionless orange backdrop, blue spiral waves rotate and spread like grassfires, each dominating its own patch of reagent, colliding with and annihilating intrusive blue waves from afar. There is much topology in these two-dimensional patterns and even more in their three-dimensional analogues, all organized around the non-retraction theorem.

1. Yeast

Yeast is most famous for its biochemical knack of converting sugar to alcohol. But with some provocation by inquisitive biologists, the cells are capable of topological tricks of timing that may surprise you.

Before discussing topology, we need a bit of biology. The full story is told in [13–15]. The relevant facts concern the yeasts' timetable. Under contrived laboratory conditions, yeast cells do not metabolize sugar through a series of monotonous steps; instead some of the intermediate reactions proceed via oscillations (though the end result is still a steady trickle of alcohol). For example, biochemists have monitored the levels of a metabolic intermediate, NADH, which conveniently fluoresces under ultraviolet light. Its blue glow brightens and dims periodically, revealing a *cycle* in the underlying biochemistry. Furthermore, the individual cells are mindful of the others; they pulse in unison, collectively synchronized in a biochemical rhythm which waxes and wanes twice per minute.
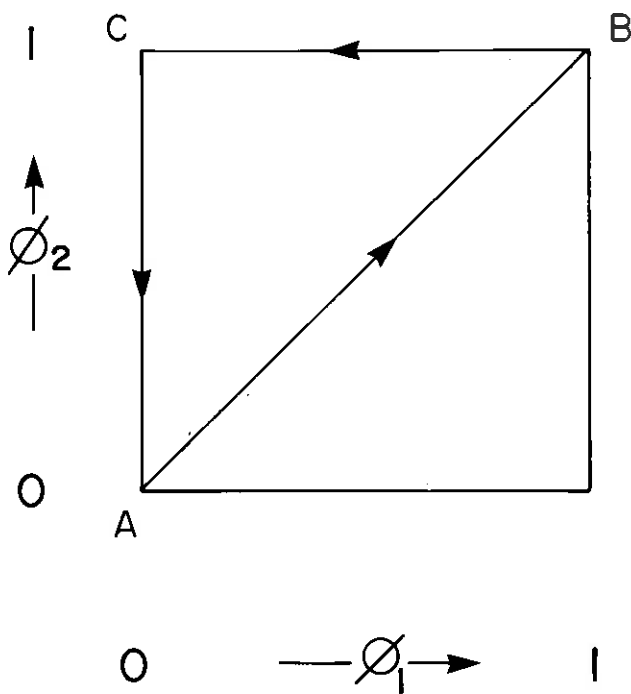
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Figure 1. A square of initial phases (ϕ_1, ϕ_2) in the phase compromise experiment for yeast glycolysis. Phases 0 and 1 represent the same point in the biochemical cycle. The contours of compromise phase $\phi = f(\phi_1, \phi_2)$ are not shown here, since this figure is for a preliminary thought experiment: according to axioms A1–A3, $\Delta\phi(AB) = 1$ and $\Delta\phi(BC) = \Delta\phi(CA) = M = $ integer. Hence $W = \Delta\phi(ABCA) = 2M + 1 \neq 0$. By the non-retraction theorem (section 2), f must be discontinuous within ABCA.

It would be extraordinary luck if all the yeast *began* in unison. So how do they manage to get in step and stay there? Presumably the cells communicate by molecular diffusion and then each accelerates or hesitates to get in step with the stirred mass.

A simple experiment [13] elucidates these adjustments. Two equal volumes of cells, each synchronous within itself, yet out of step with the other volume, are mixed together. After mixing, they rapidly resynchronize in the standard cycle, but perhaps at some compromise phase. How does the compromise phase depend on the old phases of the "parent" ingredients?

We could dream up all sorts of rules: "Whichever group peaked first sets the pace, and the other falls in step." But that rule is nonsense—since both groups are periodic, neither can be said to have peaked "first." Another try: "If groups 1 and 2 have progressed through fractions ϕ_1 and ϕ_2 of the cycle, then upon mixing they adopt the average, $\frac{1}{2}(\phi_1 + \phi_2)$." Nor is this rule well-defined, since the fractions depend on an arbitrary selection of the "beginning" of each cycle. In other words, the purported compromise depends unrealistically on our conventions: whether the cycle is said to begin at its peak, at its trough, or wherever.

So fix any reference point for the cycle's beginning, but stick to it. Having done so we can define the useful notion of *phase:* the cell's biochemical rhythm is at phase ϕ when it has progressed through a fraction ϕ of its cycle, as measured in equal time steps from the arbitrary zero point. Notice that phase should be regarded not as a real number, but instead as a real number (mod 1), or equivalently as a point on the unit circle S^1, because $(\phi = 0 = \text{beginning})$ and $(\phi = 1 = \text{end})$ correspond to the same part of the biochemical cycle. Now the question about phase compromise can be restated [16]. The phase ϕ of the mixture has some unknown functional dependence on the phases ϕ_1 and ϕ_2 of the ingredients.

$$\phi = f(\phi_1, \phi_2)$$
$$f : S^1 \times S^1 \to S^1$$

What can be said, *a priori*, about the function f? (Biologists [13] have actually done the experiments, and thus measured f, but that would be giving away the answer.) It is plausible that:

(A1) interchanging the *names* of groups 1 and 2 will not affect the outcome: $f(\phi_1, \phi_2) = f(\phi_2, \phi_1)$.

(A2) if the separate groups agree in phase initially, they continue at that phase, unaffected by mixture with their own kind. That is, if $\phi_1 = \phi_2$, then $\phi = \phi_1 = \phi_2$. (In science, this is usually called a "control experiment.")

(A3) Slight changes in the initial phases alter the outcome only slightly: in other words, f is continuous in each argument.

Though reasonable, these axioms probably sound weak—they don't seem to pin down the function's detailed behavior. And yet within them lurks a topological surprise, the one advertised at the outset.

They are inconsistent.

In the proof of inconsistency, the final step invokes the non-retraction theorem, discussed in the next section.

Proof:

Step 1: Instead of thinking of f as a function on the torus $T^2 = S^1 \times S^1$, regard it as a function on the unit square $I^2 = [0, 1] \times [0, 1]$. Keep track of the phase assigned to each point of the closed curve ABCA in the unit square shown in Figure 1. In particular, since the curve begins and ends at A, the compromise phase $\phi = f(\phi_1, \phi_2)$ must change by an integer number of full cycles in one counterclockwise lap around this path. This integer is the *winding number W*.

Step 2: Compute W. Along arc AB, $\phi_1 = \phi_2$, so axiom (A2) implies $\phi = \phi_1 = \phi_2$. Hence along AB, ϕ increases by one cycle. For convenience we write $\Delta\phi(AB) = 1$. Along arc BC, $\Delta\phi(BC)$ equals some integer number M of cycles (since points B and C represent the same
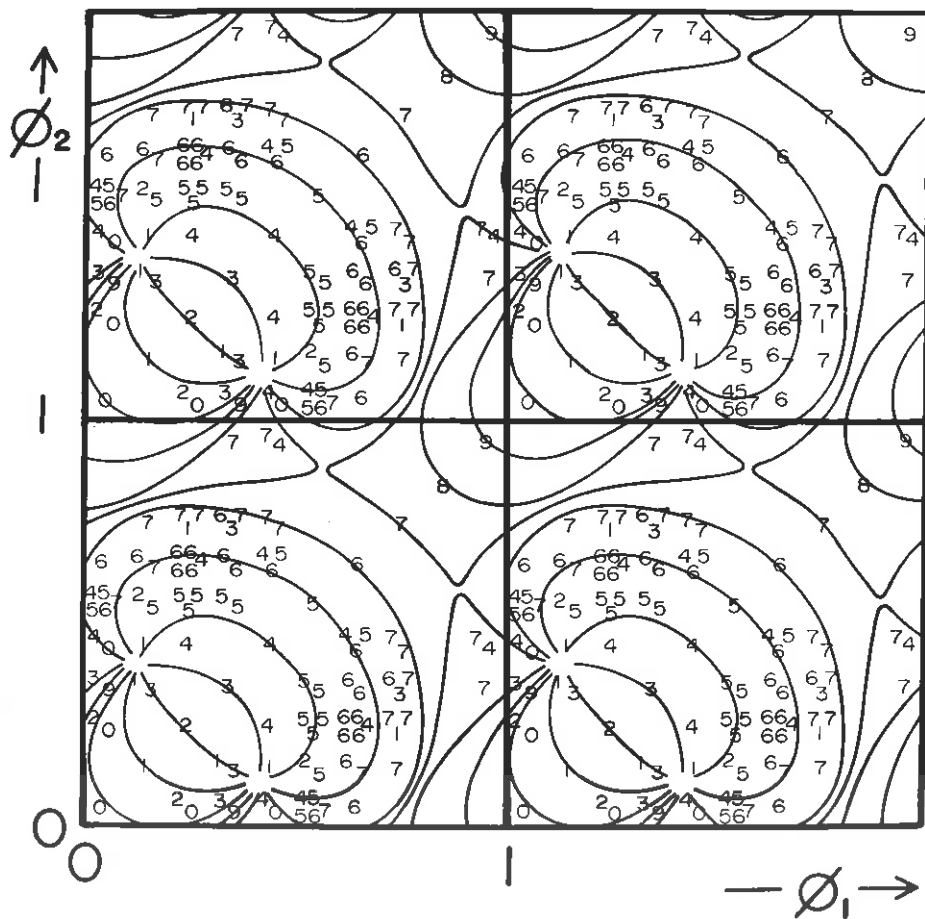
Figure 2. Phase compromise experiments, plotting compromise phase as a function of two parent phases. The digits represent observed compromise phase, plotted in one-tenth cycle intervals, using the data of Ghosh et al. [13]. Contour lines link roughly equivalent data. Note that axioms A1–A3 are satisfied, except at the predicted phase singularities, where continuity fails. From Winfree [14], p. 62. (This figure originally appeared in *The Geometry of Biological Time*, by A. T. Winfree, Springer-Verlag, 1980.)

biochemistry, and so are assigned the same ϕ.) The number M is unknown, but we *do* know $\Delta\phi(BC) = \Delta\phi(CA) = M$. (This follows from the symmetry (A1).) These contributions imply a winding number of $W = 2M + 1$, around ABCA.

Step 3: Since M is an integer, W is odd. In particular, $W \neq 0$. That's all we need to derive a contradiction. For if phase is to be assigned continuously (Axiom 3) throughout the triangular region bounded by ABCA, then the non-retraction theorem (next section) implies that $W = 0$ along this boundary.

Which axiom is the culprit? The experiments implicate A3, the continuity axiom. Indeed, the data seem to show the most localized breakdown possible: a "phase singularity" [14], a single point at which all phase contours converge. Elsewhere, all three axioms appear to be obeyed (Figure 2).

Near the singularity, the experimental results are extremely sensitive to initial conditions, and therefore practically irreproducible. One must sympathize with the pioneering experimenters [13]; at least three times, they meticulously probed the zone here claimed to be singular, each time obtaining a different compromise phase. Their dogged conclusion:

The synchronization does not follow any clear pattern. The reason . . . is not understood at this time. Much more experimentation is probably needed before the effects can be correlated to some variable in the system.

At the time, "more experimentation" may have seemed the only recourse. In retrospect, the yeast were merely behaving as they had to, single-celled creatures abiding by the non-retraction theorem.

2. The Non-Retraction Theorem

The non-retraction theorem forbids certain kinds of mappings from a space to its boundary. In its simplest form it merely states a familiar fact about intervals: a closed interval cannot be mapped continuously onto its two endpoints. All the points in the interval must go one way or the other—otherwise, the interval is ripped.

Stated more formally, let $I = [0, 1]$, and let $\partial I = \{0, 1\}$ be its boundary. By a *retraction* of I, we mean a continuous function $r: I \rightarrow \partial I$ such that $r|\partial I =$ identity. In other words, r leaves the boundary pointwise fixed. Of course, there *is* no retraction of I, since I is connected and its image $r(I)$ must be connected as well.

It might appear that the disconnectedness of the boundary is essential for this result; it is not. Consider,
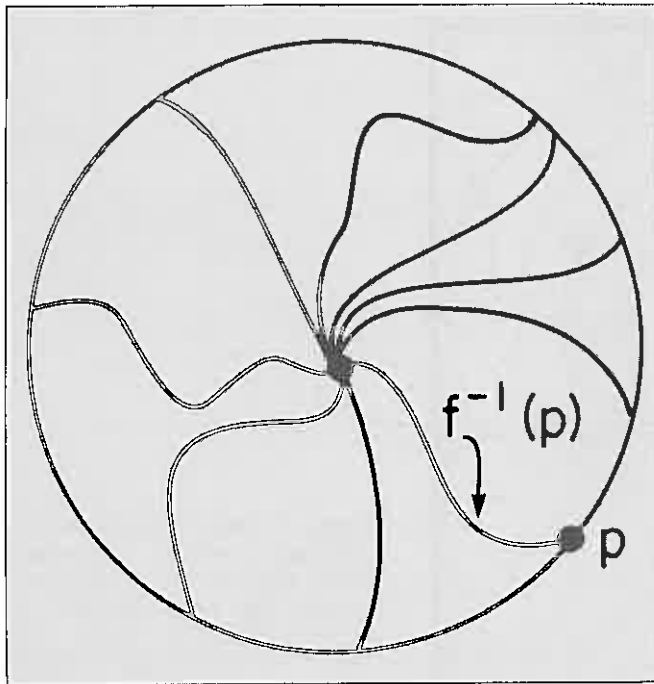
Figure 3. Any function $f:D^2 \to S^1$ which leaves the boundary $\partial D^2 = S^1$ pointwise-fixed must be discontinuous. Wiggly curves in the disk represent loci of constant phase, i.e., the contours $\{f^{-1}(p) : p \in S^1\}$. Here the contours converge to a "phase singularity," the most localized discontinuity possible.

for example, the closed unit disk $D^2 = \{(x, y) \in \mathbf{R}^2 | x^2 + y^2 \leq 1\}$ and its boundary $\partial D^2 = S^1$. The non-retraction theorem still holds, even though S^1 is connected. *There is no continuous function $r: D^2 \to S^1$ that leaves the boundary pointwise fixed* (Figure 3).

We can provide an intuitive proof of this fact using the winding number. Let $C = \partial D^2$. Then r assigns a "phase" $r(P)$ to each point P on C. Now r is the identity on C; when P executes one anticlockwise circuit of C, $r(P) = P$ executes one anticlockwise cycle of phase in S^1. Hence, along C, the winding number is 1.

Now deform C, shrinking it radially (Figure 4). The winding number must change continuously throughout the deformation. But since the winding number is an integer, it must be constant and hence is identically 1, even when C becomes arbitrarily small. This is a contradiction: on small circles the winding number is zero, as in Figure 4.

The winding number argument suggests a refinement of the theorem. The contradiction arose because the winding number was nonzero on ∂D^2; the stronger assumption that $r|\partial D^2 = $ identity is needlessly restrictive. Paring down to essentials, we see that *any continuous function $r:D^2 \to S^1$ must have winding number zero around ∂D^2*. This is most easily proved using fundamental groups [17].
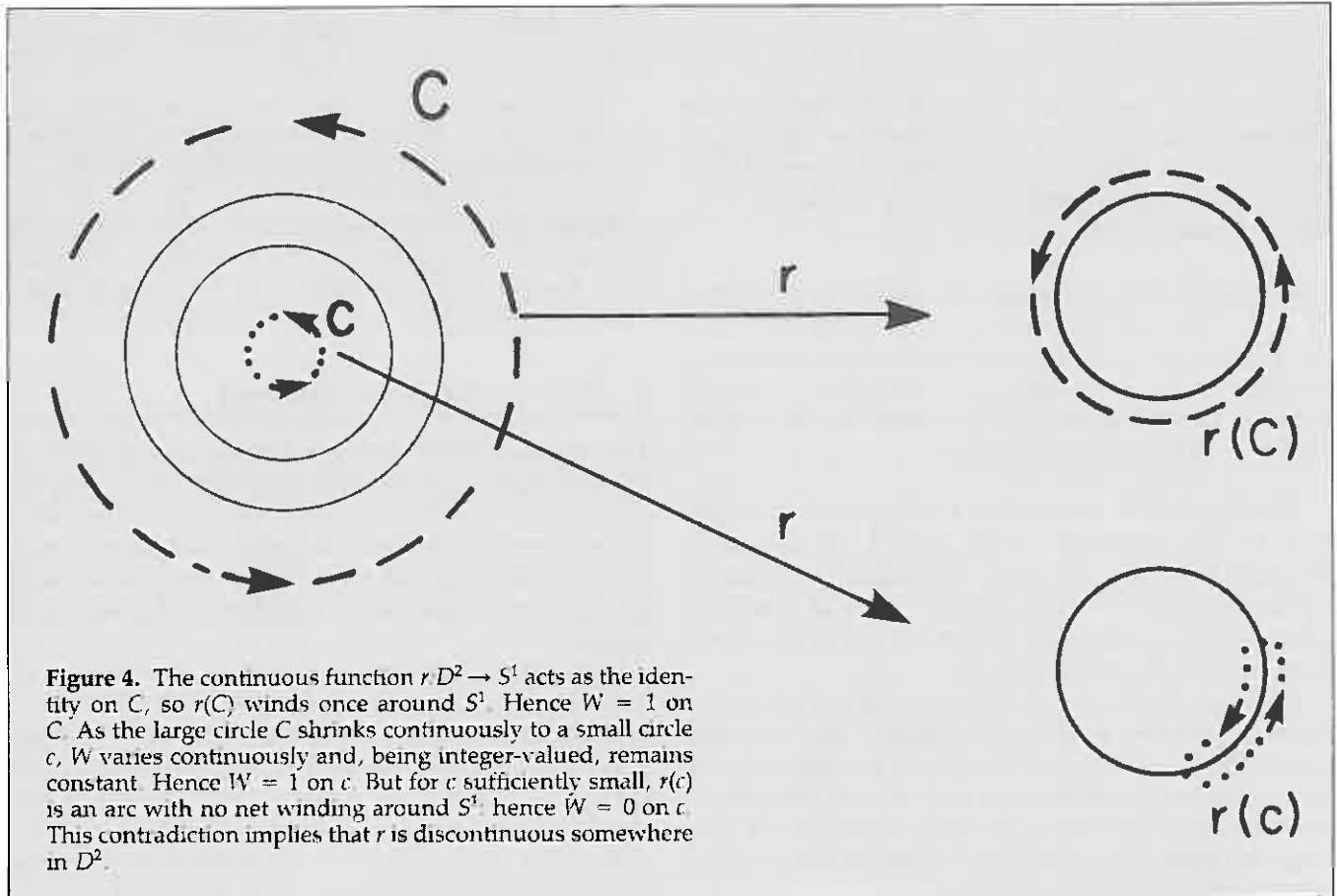
It was this form of the theorem that we invoked

Figure 4. The continuous function $r:D^2 \to S^1$ acts as the identity on C, so $r(C)$ winds once around S^1. Hence $W = 1$ on C. As the large circle C shrinks continuously to a small circle c, W varies continuously and, being integer-valued, remains constant. Hence $W = 1$ on c. But for c sufficiently small, $r(c)$ is an arc with no net winding around S^1, hence $W = 0$ on c. This contradiction implies that r is discontinuous somewhere in D^2.

when discussing yeast, and we will invoke it twice more when discussing BZ reagent.

We mention in passing only one of the vast generalizations of the results above. If M is *any* compact manifold with boundary, then there is no smooth map $r: M \rightarrow \partial M$ that leaves ∂M pointwise fixed. The argument can be found in [18] and uses an elegant idea of Hirsch [19]. Essentially it says the following. If such an r exists, then for any regular value $x \in \partial M$, $r^{-1}(x)$ must be a one-dimensional manifold (with boundary). But the boundary of $r^{-1}(x)$ is precisely $r^{-1}(x) \cap \partial M$ and consists of the point x itself. There are, however, no one-dimensional manifolds with only one boundary component.

3. Belousov-Zhabotinsky reagent

Figure 5 shows an example of "Pa Ndau." In this ritual needlework embroidered by one of the Hmong women of Laos, the spirals are said to hold a magic spell; the borders guard the magic of the inner images. All Hmong children begin life strapped to their mothers' backs in carriers elaborately decorated with Pa Ndau, and Pa Ndau honors the dead on their final journeys [20].

Nature too stitches the spiral patterns of Pa Ndau. In a dish of motionless BZ reagent (Figure 6), a blue spiral wave of "fire" (actually, chemical oxidation) spreads across a medium of orange "grass" (quiescent, unoxidized reagent). The wavefront advances relentlessly, oxidizing its neighbors in front and thus turning them blue. The visual effect is striking: thanks to the spiral geometry [21], the wave appears to rotate rigidly, slowly turning like the spray from a lawn sprinkler. Meanwhile its passage leaves a "burnt out," refractory region behind. Gradually the exhausted region recovers. Its color returns to deep orange, indicating its renewed susceptibility to another oxidizing pulse from its neighbors. Because of this renewal, the pattern is *self-regenerating*: it propagates round and round, like a dog chasing its own tail, until the energy resources in the medium are spent (after about an hour.)

BZ reagent has become a Rorschach inkblot test. Applied mathematicians [22, 23] see it as an analog computer for demonstrating rotating wave solutions to reaction-diffusion equations. Chemists point to it as an oscillating [24] oxidation-reduction reaction. And for physiologists, it mimics pernicious rotating electrical waves on the heart [25, 26], believed to be involved in certain forms of heart attack.

Here it is recruited in the name of topology. The existence of rotating waves in BZ reagent entails some weird topological consequences, in the form of "phase singularities." First we must adapt the earlier notion of phase.

Figure 5. A "snail" motif in Pa Ndau, needlework of the Hmong people of Laos.

Figure 6. The Belousov-Zhabotinsky chemical reagent, seen by blue light transmitted through a 1 mm depth. The bright spirals mark loci of maximum concentration of ferriin (Belousov's blue indicator dye); the intervening darkness is deep orange. Waves of oxidation propagate from the spiral centers at a few mm per minute, the spirals turning in about one minute. The dish is 90 mm in diameter. From Winfree and Strogatz [29], Figure 2. (This figure originally appeared in an article by A. T. Winfree and S. H. Strogatz, *Physica-8D* (1983), pp. 35–49, North-Holland Physics Publishing, Amsterdam.)
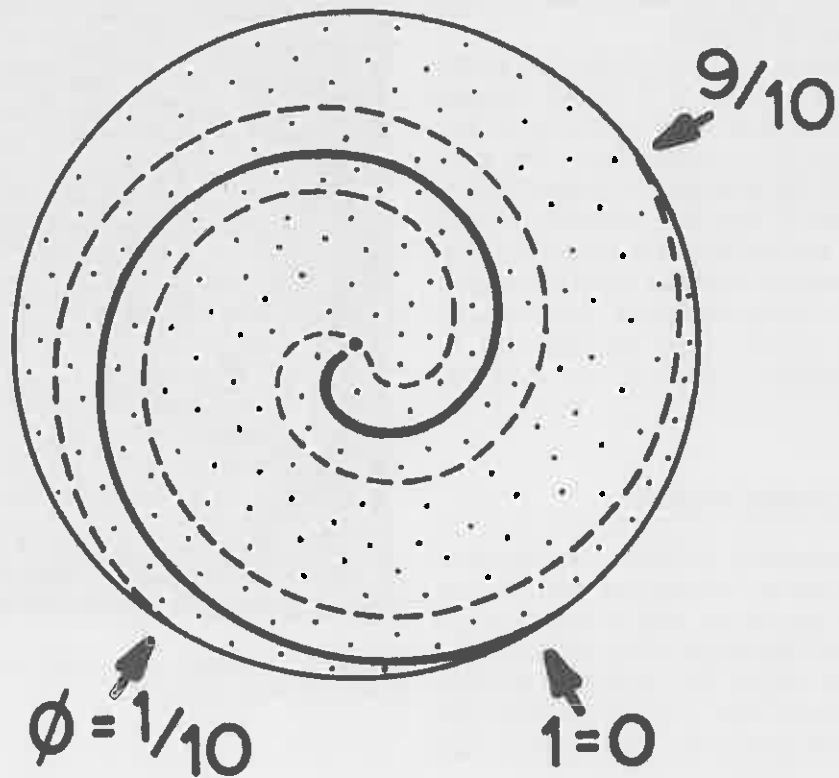
9/10

∅ = 1/10   **1 = 0**

Figure 7. Contours of uniform phase on a disk periodically excited by a clockwise rotating wave. During one circuit of the boundary, at fixed time, phase changes through a full cycle. Hence a phase singularity lurks within the disk. From Winfree and Strogatz [29], Figure 5. (This figure originally appeared in an article by A. T. Winfree and S. H. Strogatz, *Physica-8D* (1983), pp. 35–49, North-Holland Physics Publishing, Amsterdam.)
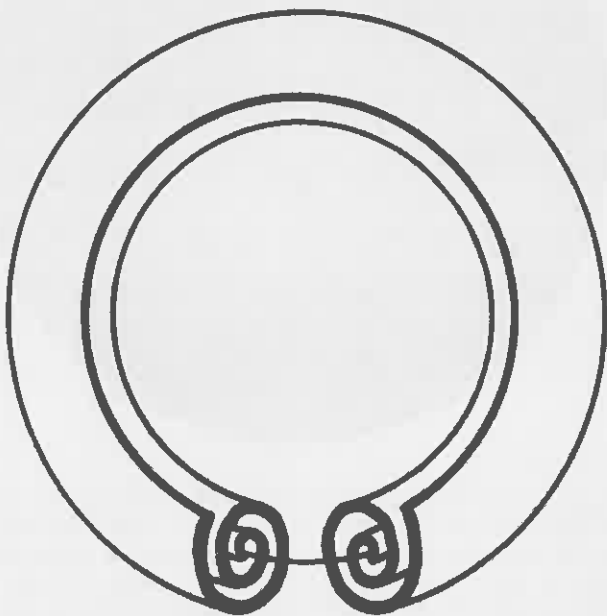

Figure 8a. A scroll-shaped wave surface formed from spirals. The singular point of a spiral wave is here replaced by a singular filament about which the scroll is coiled. Without violating local chemical continuity, the scroll may be closed in an untwisted ring.
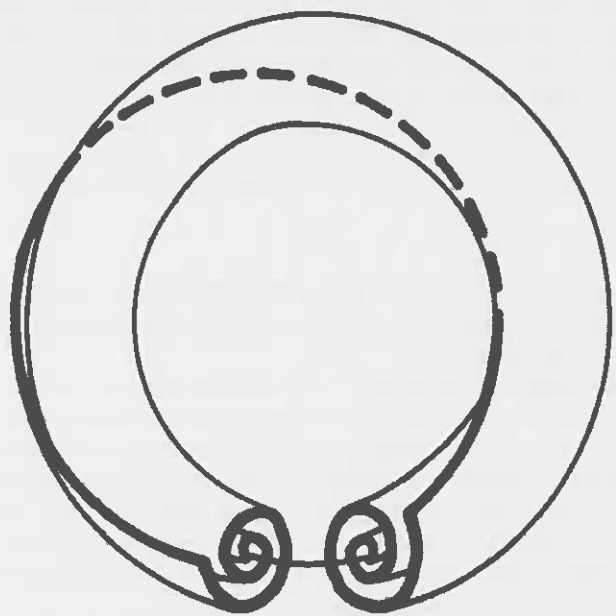
Fig. 8b. As in (a), but a 360° twist is imparted along the length of the scroll before joining its ends. Both figures from Winfree [14], p. 253. (These figures originally appeared in The *Geometry of Biological Time*, by A. T. Winfree, Springer-Verlag, 1980.)
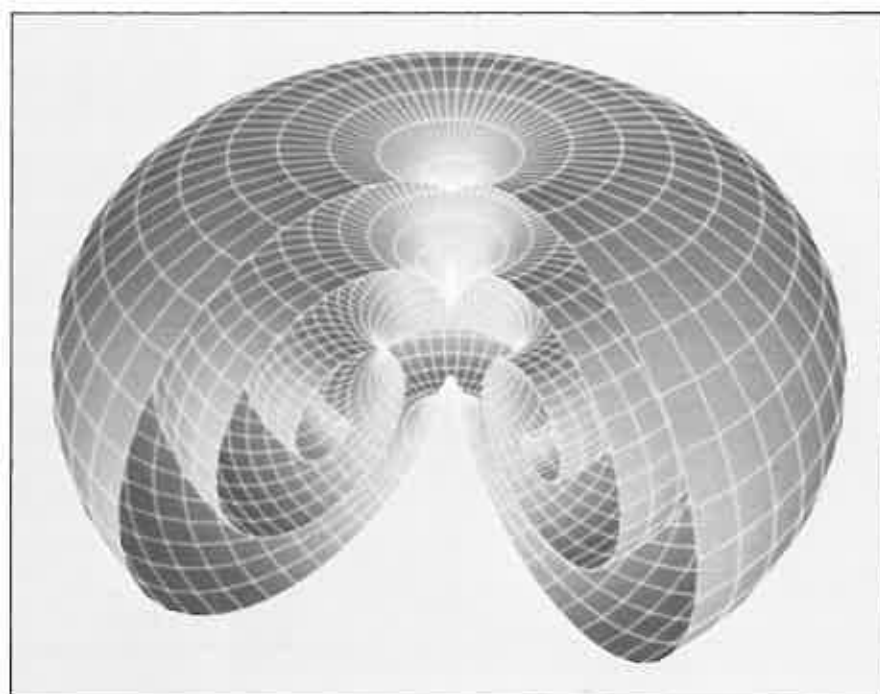
Figure 9. Computer image of an "untwisted scroll ring," obtained from Figure 8a by adding more turns to the spirals. A wide sector has been removed to make the insides visible. The inner piece of the wave is attached to the singular ring; the outer piece has budded off, and is formed by the collision of spirals with their diametrically opposite counterparts. Real chemical scroll rings [31, 32] look less symmetric, but are topologically similar to this figure.

Since every area element in the domain of a spiral wave is periodically excited by its recurrent passage, each element may be assigned a phase. As before, a phase is a point on S^1; now it represents the fraction of a cycle elapsed since the arrival of the previous wavefront (at the point in question).

This phase description breaks down in an informative way: it detects a point to which phase cannot be meaningfully assigned (hence, one which is not periodically excited). The proof relies on the non-retraction theorem, as applied to a closed curve C that encircles the spiral's inner portions (Figure 7). The winding number of phase around C is $W = \pm 1$. (Why? Because as time advances, the wave periodically rotates through all locations along C. Hence, at fixed time, one point is just now being excited, those ahead of the wave are in varying stages of anticipation, and those behind are in varying stages of recovery, running through all phases *once* in a circuit of C.)

As before, the key point is that $W \neq 0$ around C. Now if we idealize the assignment of phase throughout the dish of reagent as a mapping $f:D^2 \rightarrow S^1$, the non-retraction theorem requires that f be discontinuous. The alternative is that f fails to be defined somewhere in D^2, i.e., some point is not periodically excited. The latter option is physically reasonable; molecular diffusion smears the observed wavefront, and the inner end of the spiral appears to thrash about, or "meander" [27].

Of course, the actual medium is three-dimensional. In thick layers of BZ reagent, the spirals are seen to be slices of a wave surface shaped like a *scroll* [14, 28]. The singular point elongates to a *thread* of phaselessness (Figure 8a). For chemical reasons [29, 30], the

thread generically closes in a ring, and the scroll closes in a toroidal "scroll ring" wave.

The closure might occur in many topologically distinct ways: the ends could be joined directly (Figure 8a), or the scroll could first be twisted along its length through 360° (Figure 8b), or it could even be knotted. What would these structures look like, and would they be chemically viable?

The simplest is shown in Figure 9. It is a surface of revolution swept out by a spiral orbiting a distant axle. The spirals all intersect and terminate at a common kink. (They terminate because of the empirical observation that such colliding waves annihilate, just as colliding grassfires cannot continue through each other's ashes.) These waves have been observed [31] and photographed recently [32]. Their chemical viability is indisputable.

On the other hand, the once-twisted scroll ring (Figure 8b) is chemical nonsense. Though *locally* a normal scroll wave, its *global* behavior is unphysical. (Scroll rings are reminiscent of fiber bundles [1] in this interplay of local and global properties.) To visualize a twisted scroll ring, imagine extending the surface's edge in Figure 8b, stopping its development whenever bits of edge collide.

Not easy, is it?

A more indirect approach is instructive. Encase the twisted scroll ring with an imaginary torus. The intersection of the wavefront with the toroid is a ring which threads the hole exactly once (since the generating spiral twists once as it orbits the hole axis.) The past and future positions of this ring constitute the instantaneous contours of constant phase on the torus (Figure 10). In a circuit around the toroid's inner
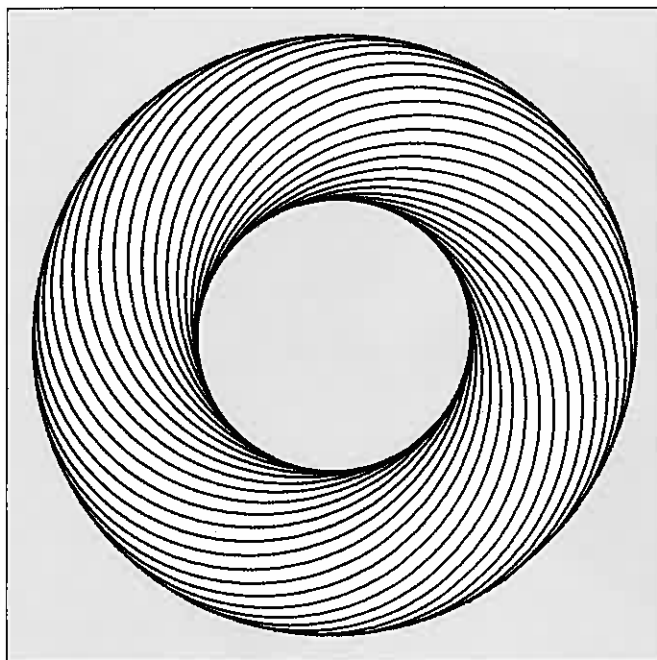
Figure 10. Curves of constant phase on an imaginary torus encasing a twisted scroll ring. One of the curves represents the position of the moving wavefront. Because of the scroll's twist, the curves link the toroid's hole. Only half of each curve is visible. From Winfree [14], p. 255. (This figure originally appeared in The *Geometry of Biological Time*, by A. T. Winfree, Springer-Verlag, 1980.)

equator, the contours are encountered in succession, running through a full cycle after one lap, so that $W = \pm 1$.

Hence, around the inner equatorial circle, $W \neq 0$. This circle bounds a disk that plugs the toroid's hole. As in earlier arguments, there must be a phase singularity within the disk. Here's a new wrinkle: since the theorem applies to *any* disk-like diaphragm bounded only by the equator, each such diaphragm is pierced by a singular point. Following the singularity from one diaphragm to another, we trace a *new* singularity, an unforeseen filament threading the original singular ring.

Computer graphics replaces this existence proof with a picture (Figure 11). The wavefront is a screw surface, a gnarled helicoid built from spirals. As in a parking garage, we can move from one level to the next by staying on the surface and circulating around the central axle. Chemically the axle would be a sink, a collision locus for waves emanating from the original singular ring. However, sinks have never been observed in BZ reagent.

The non-retraction theorem spawns a prediction: a twisted scroll ring is not chemically viable. Indeed, further investigation shows that scroll ring topology is *quantized*; the only configurations of linked, twisted, and knotted rings which are potentially realizable are those for which a certain mathematical index vanishes

[29, 33–35]. On topological grounds, it seems that waves in BZ reagent are like atoms—they fall into a periodic table, not of chemistry but of shape.

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Figure 11a (right). Similar to Figure 9, but obtained instead by extending the twisted scroll ring of Figure 8b. Unlike Figure 9, this wave is in one piece, attached to the inner singular ring—strictly speaking, the wavefront must be continued to infinity so that it will not have to end along an artifactual edge. No such structure could exist chemically. (In the computer construction, the edge was placed in the invisible sector.) From Winfree [36], Figure 14a.
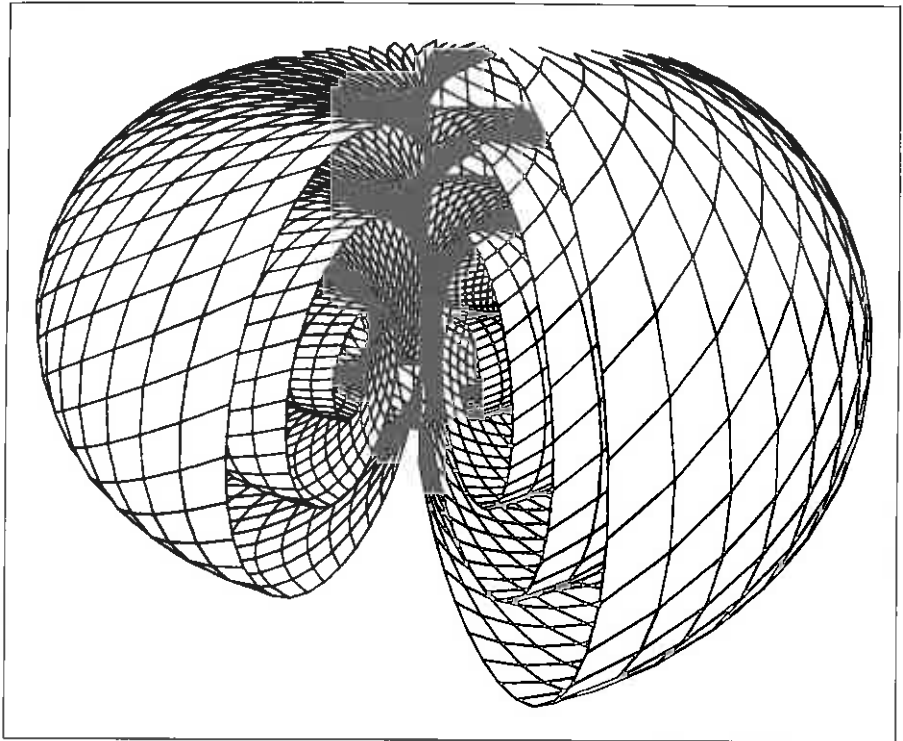
Figure 11b (below). The screw-like surface near the vertical axle is viewed through several windows in the fully evolved wave. The original singular filament is horizontal, near the center; note that it is threaded by the axle singularity, as predicted by the non-retraction theorem. From Winfree [36], Figure 14b. (These figures originally appeared in "Wavefront Geometry in Excitable Media" by A. T. Winfree, an article in *Fronts, Interfaces, and Patterns*, ed. by A. Bishop, 1984, North-Holland, Amsterdam.)