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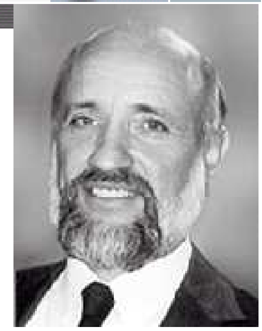

Arthur T. Winfree
1942-2002

Obituary

Arthur T. Winfree

When Art Winfree died in Tucson on November 5, 2002, at the age of 60, the world lost one of its most creative scientists. I think he would have liked that simple description: scientist. After all, he made it nearly impossible to categorize him any more precisely than that. He started out as an engineering physics major at Cornell (1965), but then swerved into biology, receiving his PhD from Princeton in 1970. Later, he held faculty positions in theoretical biology (Chicago, 1969-72), in the biological sciences (Purdue, 1972-1986), and in ecology and evolutionary biology (University of Arizona, from 1986 until his death).

So the eventual consensus was that he was a theoretical biologist. That was how the MacArthur Foundation saw him when it awarded him one of its "genius" grants (1984), in recognition of his work on biological rhythms. But then the cardiologists also claimed him as one of their own, with the Einthoven Prize (1989) for his insights about the causes of ventricular fibrillation. And to further muddy the waters, our own community honored his achievements with the 2000 AMS-SIAM Norbert Wiener Prize in Applied Mathematics, which he shared with Alexandre Chorin.

Aside from his versatility, what made Winfree so special (and in this way he was reminiscent of Wiener himself) was the originality of the problems he tackled; the sparkling creativity of his methods and results; and his knack for uncovering deep connections among previously unrelated parts of science, often guided by geometrical arguments and analogies, and often resulting in new lines of mathematical inquiry.

Let me illustrate these features of his work by focusing on three of his best contributions, taken in chronological order.

Collective Synchronization

Winfree’s first paper [4] concerned the mutual synchronization of biological oscillators. How is it that thousands of neurons or fireflies or crickets can suddenly fall into step with one another, all firing or flashing or chirping at the same time, without any leader or signal from the environment? Norbert Wiener had posed this problem in his book Cybernetics [3], but he did not make significant mathematical progress on it, nor did anyone else until Winfree came along. In work that grew out of his senior thesis at Cornell (1965), Winfree studied the nonlinear dynamics of a large population of weakly coupled limit-cycle oscillators. Since variability is inevitable in any real biological population, he assumed that the oscillators’ intrinsic frequencies were distributed about some mean value, according to some prescribed probability distribution.

Now here was a mathematical challenge. All the classical work on nonlinear oscillators, by Van der Pol, Cartwright and Littlewood, Levinson, and others, had been restricted to a single forced oscillator, or two coupled oscillators. No one had ever dared to consider gigantic systems of oscillators with randomly distributed frequencies. Winfree cut to the essence of the problem, and introduced an approximation that has been the standard approach to the study of biological oscillators for the past thirty-five years. He argued that in the limit of weak coupling, amplitude variations could be neglected and the oscillators could be described solely by their phases along their limit cycles. This "phase model" reduction stimulated later mathematical work by Guckenheimer, Neu, Kuramoto, Kopell and Ermentrout, and others, who justified it rigorously via invariant manifold theory and averaging theory.

Working within the framework of a mean-field model, Winfree discovered that such oscillator populations can exhibit a remarkable cooperative phenomenon. As the variance of the frequencies is reduced, the oscillators remain incoherent, each running near its natural frequency, until a certain threshold is crossed. Then the oscillators begin to synchronize spontaneously. (The effect is somewhat like the outbreak of synchronous applause after a magnificent concert.) Winfree pointed out that this phenomenon is strikingly reminiscent of a thermodynamic phase transition, but with a twist: The oscillators align in time, not space. This deep analogy has since been explored by many statistical physicists interested in non-equilibrium phase transitions, most notably Kuramoto, and is still a thriving area of research [2]. In the past decade, Winfree's synchronization transition has also shed new light on other collective phenomena in physics, such as Landau damping in plasmas and the onset of phase locking in superconducting Josephson junction arrays.

Winfree's work on coupled oscillators provided one of the first tractable examples of a self-organizing system. It began as a problem in biology but has had a major impact on dynamical systems theory and statistical physics.

Stopping a Biological Clock

Perhaps the most surprising of Winfree's discoveries is that biological clocks can be stopped by relatively mild perturbations. The claim is that a stimulus of appropriate timing and duration can drive the clock to a "phase singularity," roughly analogous to a biological North Pole at which all the phases of the cycle converge and the rhythm's amplitude vanishes. He predicted this in the late 1960s, based on ingenious topological reasoning, and then confirmed it experimentally for the circadian rhythm of hatching in populations of fruitflies (that was his PhD work at Princeton).

Before I explain the reasoning, let me stress how shocking this prediction was. The prevailing dogma about circadian rhythms emphasized their robustness: They persist in the absence of light-dark cycles, their period is essentially independent of temperature, and so on. So the idea that they could be stopped at all, let alone by mild stimuli, seemed absurd. But Winfree's experiments showed that it is true.

Winfree's prediction was based on thinking about maps between circles. He viewed a biological rhythm as a periodic motion through an unknown, high-dimensional state space. Associating a "phase" to each state corresponds to a mapping from the state space to a circle. An experimental perturbation, such as a pulse of light, takes an old phase and maps it to a new phase, and thus induces a circle map. Experimentally, this circle map is often found to be continuous, and to have degree (i.e., winding number) equal to 1 for weak perturbations, but degree 0 for very strong perturbations. Winfree was the first to recognize the significance of the resetting map's degree. He argued that the map could not be continuous for all phases and intermediate perturbation strengths (otherwise, its degree could not change from 1 to 0). In this way, he was led to devise an experimental protocol that he called a "singularity trap," and through dozens of careful experiments varying perturbation strength and timing, he zeroed in on the critical stimulus that stopped the clock.

Winfree's work here changed the way we think about biological rhythms and arrhythmias. Subsequent studies (reviewed in [5]) have shown that mild perturbations can also quench other kinds of biological oscillations, including breathing rhythms, neural pacemaker oscillations, and the human circadian rhythm of body temperature, in each case by driving them to a phase singularity. Such findings may ultimately have medical relevance for disorders involving the loss of a biological rhythm, such as sudden infant death or certain types of cardiac arrhythmias.

In any case, these discoveries would not have occurred if Winfree hadn't introduced topological ideas into the study of biological rhythms. His work here went beyond mathematical modeling; it showed that mathematics can play a genuinely heuristic, predictive role in biological inquiry.

Phase Singularities in Space: Spiral Waves and Scroll Waves

After 1972 much of Winfree's work concerned propagating waves of activity in excitable media. He focused on a chemical system, the Belousov-Zhabotinsky reaction, which has many qualitative similarities to nerve tissue, heart muscle, and other biological excitable media. The virtue of the BZ reaction is that the activity patterns are visible, appearing as bright blue waves of oxidation spreading through an orange sea of quiescent, reduced reagent.

In 1972 Winfree discovered experimentally that thin layers of BZ reagent could display self-sustained rotating spiral waves [6]. Ever since, this example of pattern formation has fascinated researchers in applied mathematics, physics, chemistry, cardiology, and several branches of biology. Other examples of spiral waves have been found in heart tissue (where they are associated with tachycardias and other arrhythmias, thus accounting for much of the applied interest in spiral waves); in aggregation patterns of slime mold (a key example in developmental biology); in surface catalysis; and in calcium dynamics in cells.

Winfree’s discovery of spiral waves was no accident. Once again, topological thinking played a guiding role. He had initially wondered whether rotating waves were possible in a two-dimensional medium with no holes in it. Norbert Wiener had looked into a related question in the 1940s, with his cardiologist collaborator Rosenblueth. They had studied rotating waves in a cellular automaton model of heart tissue, but their model was a one-dimensional ring, not a two-dimensional sheet. It was an open problem to demonstrate rotating waves in two dimensions. Winfree realized that any such wave would necessarily entail a phase singularity at its core (a spatial version of the temporal phase singularities discussed earlier).

After discovering spiral waves experimentally, Winfree also showed that a nonlinear reaction-diffusion partial differential equation could support such solutions. His numerical experiments clarified the structure of the spiral core, and triggered a mathematical hunt for spiral wave solutions to PDEs. Cohen, Neu, and Rosales [1] were the first to construct such a solution, and over the intervening decades, many other applied mathematicians and mathematical physicists (Greenberg, Kopell and Howard, Kuramoto, Keener and Tyson, Barkley, Karma, Levine and Kessler, among others) have investigated the existence and stability of spiral waves in reaction-diffusion PDEs. It’s still a vigorous area of applied mathematics.

In 1973, Winfree conceived of the three-dimensional analog of spiral waves, which he called scroll waves. He demonstrated experimentally that these waves typically close in rings and that the central singular core becomes extended into a singular filament. Winfree’s work in the 1980s concerned the remarkable topologies that these scroll rings can take---they can be twisted, knotted, or linked through each other, but only in certain topologically permissible ways, governed by an "exclusion principle" [7]. This exclusion principle was later proved rigorously by Sumners, using the theory of framed links.

The next questions concerned the stability of scroll ring solutions to three-dimensional reaction-diffusion PDEs. For instance, could such solutions untie themselves, or do they have some sort of topological permanence? Winfree and his students performed a number of supercomputer simulations to probe the behavior of these waves, and showed that they could indeed be stable, at least numerically. But despite stimulating theoretical work by Keener, Tyson, Ott, and others, the dynamics of scroll waves is still not understood. To learn more, Winfree returned to the lab bench and developed what he called "optical tomography," an experimental method for probing the internal structure of scroll waves in the BZ reaction.

Much of the motivation for Winfree’s work on spiral and scroll waves came from cardiology. He spent the latter half of his career trying to crack the mystery of cardiac fibrillation, the arrhythmia that causes sudden cardiac death. He believed that it might be an essentially three-dimensional phenomenon, with the scroll waves playing a pernicious role in disrupting the heart’s normal electrical rhythm.

Art Winfree changed the way we think about several entire subfields of science, ranging from coupled oscillators and circadian rhythms to chemical waves and cardiac arrhythmias. Although he was not a mathematician in the conventional sense, his work was always influenced by mathematical ideas, often of a topological nature, and his brilliant intuitions repeatedly opened new lines of mathematical investigation.

Memories of a Friend and Teacher

Art was also a wonderful mentor. I had the great fortune to be able to work with him at Purdue and Los Alamos in the summers of 1982 and 1983, just after I'd graduated from college. His book The Geometry of Biological Time had entranced me, and when I wrote to him asking for a summer job, he shocked me by saying he would be "super-delighted to enlist my partnership." When I inquired about who else would be working in the lab with us, he wrote back, "Now I could make up tales about the other students + co-workers. But truth to tell, I have none. Maybe I am away too much to form relationships, maybe I have body odor, dunno. . . . but population density = 1 in my lab. You will be a singular event. Does that undermine your confidence?"

Every moment of our collaboration was a thrill. I call it a collaboration because he always treated me like a fellow scientist, never as a student. I was awed by the way he seemed to roam freely from biology to chemistry, from physics to mathematics, working just as happily at the lab bench or the computer, though his favorite mode of operation was always geometrical. I can still picture him at his desk, cheerfully ensconced with a sketchpad and Magic Marker, doodling, playing, drawing complicated knots and their spanning surfaces, wrestling in his mind's eye with the questions that were consuming us at the time.

Of the many things he taught me, the most valuable was a lesson about how to do science. Just before we started working together, he wrote me a long letter with a list of dozens of unsolved problems, fun things he thought we could work on together. Most of them were way over my head, but he anticipated that and told me not to worry. The important thing, he said, was for us to choose a problem that "irrationally grips you (and me) by the imagination, else nothing remarkable can be expected to happen."

Over the years since then, first as a fledgling graduate student and now as a professor tending my own flock, I've taken that lesson to heart and tried to pass it along. By his own example, Art Winfree demonstrated what spectacular things can be achieved when you love the problem you're chasing, when it irrationally grips you by the imagination.

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