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Editorial

Arthur T. Winfree (1942–2002)

In this issue, 12 essays to honor the life and achievements of Art Winfree, a friend and mentor to all of us, and father to one, are collected. The essays vary from personal reminiscences to opinionated reviews to original research articles. Some essays deal with problems derived directly from Art's own work; others with problems that surely would have captured his attention and critical scrutiny. In this introduction we summarize Art's scientific career and provide an extensive bibliography of his work. The essays that follow will touch over and over again on the themes that ran through Art's research—biological oscillators, synchronization, geometrical reasoning, phaseless points, and a creative and playful approach to science. All of us, in one way or another, owe a deep debt to Art Winfree for defining a generation of important, challenging, theory-rich problems and pointing the way to their resolution.

1. Bubbles and blinkers

Art's joyful, eccentric, creative and gadget-building approach to science was evident already in his high school science project: blowing enormous, long-lasting soap bubbles (see Fig. 1). For this accomplishment he won the first of many distinctions, a Westinghouse Science Talent Search finalist in 1961 (Table 1). He went on to study engineering physics at Cornell University, and his senior thesis led to his first publication, which set off a line of scientific inquiry that continues fruitfully to this day.

Art became interested in the spontaneous synchronization of populations of biological oscillators. For example, the pacemaker region of the heart consists of thousands of cells that produce a regular, collective rhythm of electrical signals. In some species of fireflies, males congregate in a tree and flash in synchrony to the presumed delight of their lady friends. Thousands of slime mold cells secrete synchronous pulses of cyclic AMP, a molecular signal that calls them to forego their solitary existence and adopt a communal lifestyle. Sidestepping the issue of the molecular, electrical or neural bases of these rhythms, Winfree reasoned that, if it were not for some sort of interaction between them, each individual cell or organism would oscillate at its own distinctive frequency and phase, and the output of the population would be a non-periodic buzz of activity. What rules bring the separate oscillations into lock step?

In a beautiful paper published in this journal (Winfree, 1967), Art drew the world's attention to a new way of thinking about this problem. Engineers and applied mathematicians had explored the case of a single nonlinear oscillator (natural period $= T$) being driven by an external periodic signal (period $= T_o$), and they knew that, for $|T\text{-}T_o|$ sufficiently small, the oscillator would synchronize to the external signal (oscillator period $= T_o$). Art considered the case of a large population of weakly interacting oscillators. Each oscillator has a period (T_i) chosen from a random distribution with a certain mean and standard deviation.

For weak coupling, each oscillator runs at its natural period and idiosyncratic phase, and the population as a whole appears asynchronous and arrhythmic (Fig. 2A). As the coupling strength increases past a certain characteristic value (dependent on the variance of natural periods), the population of oscillators undergoes an abrupt transition to a synchronized state, where most individuals oscillate with the same period. The population shows a distribution of phases, with the naturally faster oscillations being phase advanced, and the naturally slower oscillations lagging behind (Fig. 2B).

This intriguing and insightful paper triggered a large number of studies that deeply probed the interactions of coupled oscillators in situations as diverse as the propagation of chemical waves to the locomotion of lampreys, led by Y. Kuramoto, N. Kopell, B. Ermentrout, S. Strogatz, and others. The field is nicely summarized in Steven Strogatz's popular book *Sync*, published by Hyperion in 2003.

2. Flies and phaseless states

His interest in biological oscillators led Art to pursue a Ph.D. at Princeton University, studying circadian

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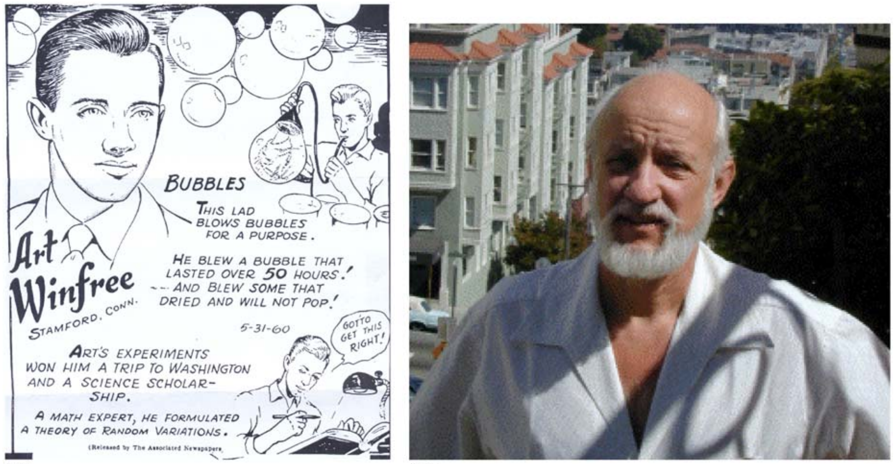

(A) (B)

Fig. 1. Arthur T. Winfree. (A) Bubble Master. From The Associated Newspapers, 1960. (B) Regents Professor.

Table 1
Brief curriculum vitae

1965	Bachelor of Engineering Physics, Cornell University
1970	Ph.D., Biology, Princeton University
1969–1972	Assistant Professor, University of Chicago
1972–1979	Associate Professor of Biological Sciences, Purdue University
1979–1986	Professor of Biological Sciences, Purdue University
1986–2002	Professor of Ecology and Evolutionary Biology, University of Arizona
1989–2002	Regents Professor, University of Arizona
Awards	
1961	Westinghouse Science Talent Search Finalist
1982	John Simon Guggenheim Memorial Fellowship
1984	John D. and Catherine T. MacArthur Prize
1989	The Einthoven Award (Netherlands Royal Academy of Sciences, InterUniversity Cardiology Institute, and Einthoven Foundation)
2000	AMS-SIAM Norbert Wiener Prize in Applied Mathematics (shared with A. Chorin)
2001	Aisenstadt Chair Lecturer (Centre de Recherche Mathématiques, Université de Montréal)

rhythms in fruit flies in the laboratory of a famous physiologist, Colin Pittendrigh. By a brilliant analysis of classical experiments on phase resetting, Art concluded that the circadian oscillator, which everyone believed to be extremely robust, could be silenced by a mild perturbation applied at just the right time. His argument was as compelling as it was unusual.

Circadian rhythms, such as our 24 h cycle of sleep and wakefulness, persist under conditions of constant darkness or low illumination. The rhythm can be phase advanced or delayed by brief light pulses. This property of circadian rhythms underlies recovery from jet lag. Examining many such experiments, Art plotted "new phase" (after the light pulse) as a function of "old phase" (at the time of the light pulse). Depending upon the intensity and/or duration of the light pulse, Art found two characteristic patterns (Fig. 3). A weak pulse causes only a small change in phase, so the line of new phases bobbles above and below the diagonal line, where new phase = old phase. For strong perturbations, the oscillator is reset to a nearly constant phase, regardless of the phase at the time of the pulse. Hence, the line of new phases bobbles above and below a horizontal line, where new phase = constant.

Next Art pointed out that, since phase is a periodic variable (0 and 2π are identical phases), the lines plotted on Fig. 3A and B are more naturally plotted on the surface of a torus, Fig. 3C and D. For a weak pulse, the line relating new phase to old phase passes once through the hole of the torus (hence, "Type 1" phase resetting); whereas, for a strong pulse the line does not pass through the hole ("Type 0"). Now, he reasoned, new phase seems to be a function of old phase and strength of the perturbing light pulse, new phase = F(old phase, intensity), but it cannot be a continuous function. There must be places on the (old phase, intensity) domain where the function F is undefined (such places are called singularities of the function). If F were a continuous function of old phase and intensity, then the topological

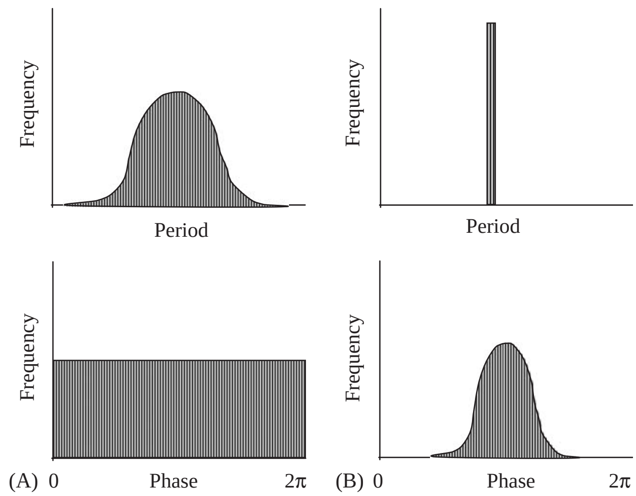

Fig. 2. Populations of weakly coupled oscillators. (A) Unsynchronized population. Each oscillator runs at its natural period, some being faster than average and others slower (top). Also, the oscillators are out of phase with one another, i.e., the phase distribution (bottom) is uniform. (B) Synchronized population. All oscillators adopt the same period (top), and each oscillator locks into the rhythm at a particular phase (bottom), the naturally faster oscillators being phase advanced and the naturally slower oscillators being phase delayed.

invariant of the curve (the integer number of times it passes through the center of the torus) could never jump discontinuously from 1 to 0 as intensity increases. Therefore, Art concluded, there must be at least one combination of old phase and intensity for which *F*(old phase*, intensity*) is undefined. In fact, he showed that on a sufficiently small circle around the special point (old phase*, intensity*) where the phase is undefined, the function *F* must adopt all values from 0 to 2π. At the critical combination of old phase* and intensity*, the rhythm is phaseless, just like, at the North or South Pole, one cannot say what time of day it is.

Art suspected that, if he could find this critical combination of old phase and intensity, then he could turn off the circadian oscillator, in the sense that a population of treated organisms would have no consistent sense of phase (i.e., time of day). To test these abstract theoretical concepts in a real example, he then designed and built an elegant "fly machine" to send fruit flies into the phaseless state. Normally, after being transferred from light to dark, fruit flies emerge from the pupal stage at about $(24n+18)$ hours, where n is an integer between 3 and 7. By delivering short light pulses

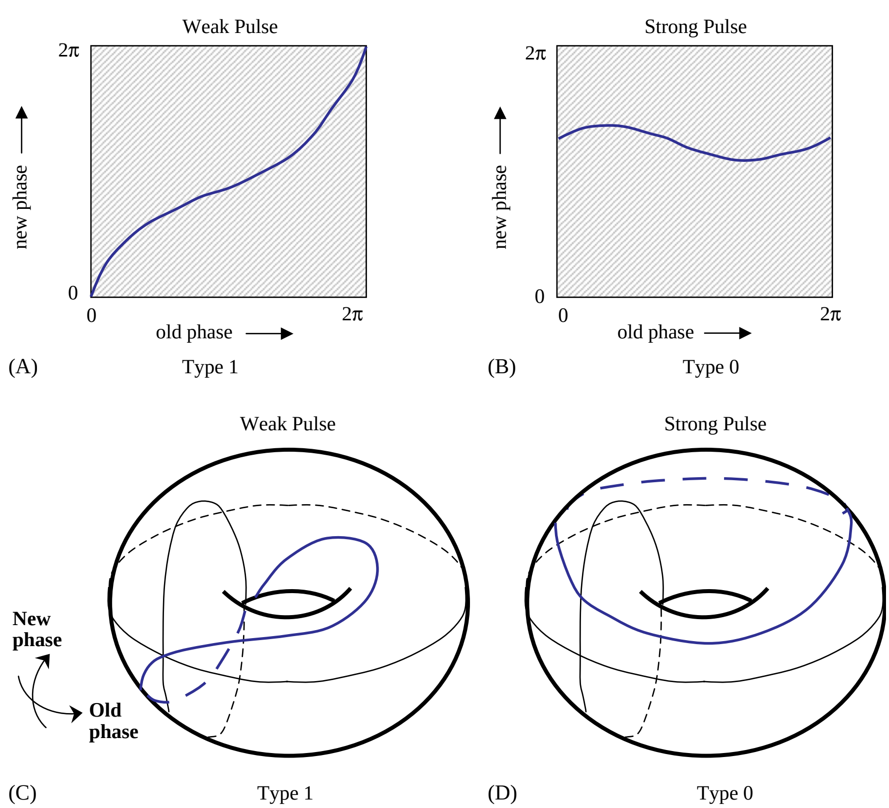

Fig. 3. Types 1 and 0 phase resetting. (A and B) After being perturbed transiently, an oscillator is allowed to return to its natural rhythm, and the "new phase" (after the perturbation has subsided) of the oscillator is plotted (blue curve) against its phase at the moment the perturbation started ("old phase"). For a weak perturbation, new phase is not much different from old phase, and the blue curve lies close to the diagonal line, new phase = old phase. For a strong perturbation, new phase is set to nearly the same value, regardless of old phase, and the blue curve lies close to a horizontal line, new phase = constant. (C and D) Because phase is a periodic variable (0 and 2π are identical), the curves in panels A and B are more naturally plotted on the surface of a donut. For a weak perturbation, the blue curve passes one time through the hole in the donut (hence, "Type 1"). For a strong perturbation, the blue curve does not pass through the hole in the donut ("Type 0").

of precise timing and duration to populations of flies, Art probed the three-dimensional surface that related the new phase to the time of perturbation and the light intensity and found the critical combination (old phase*, intensity*) that desynchronizes the eclosion rhythm. This work is beautifully described in Winfree (1970a,b). Art's insight that the topological properties of the curves describing the resetting of nonlinear oscillators should be universal, and not depend on the particular oscillator being studied, has stimulated a large number of investigations by J. Jalife, M. Guevara, A. Shrier, D. Paydarfar, C. Czeisler, R. Kronauer, and others. Art's Scientific American book, *The Timing of Biological Clocks* (Winfree, 1986), provides a popularized introduction to the concepts of biological clocks and how they manifest themselves in our everyday lives.

3. Spirals and scrolls

Before completing his Ph.D. dissertation, Art was offered an Assistant Professorship in the Program in Theoretical Biology at the University of Chicago, headed then by Jack Cowan. It was here that we authors fell under the spell of Art Winfree and another young Assistant Professor, Stuart Kauffman. Along with his flies, Art brought to Chicago a new experimental system: the Belousov–Zhabotinsky reaction (BZR). The BZR is a relatively simple oxidation–reduction reaction (dicarboxylic acid + $BrO_3^- \rightarrow CO_2 + Br_2$ + other products). In a well-stirred beaker, as chemists are wont to carry out their reactions, the BZR exhibits unusual sustained oscillations in oxidation state (periodic production and removal of $HBrO_2$ and other intermediate oxidation states).

Art realized that, if the reaction were carried out in a thin layer of unstirred solution, then each local region of space would function as an oscillator loosely coupled to its neighbors by diffusion. Like his fly machine, the unstirred BZR could function as a singularity trap. Art reasoned that if the singular phaseless point of the oscillator could somehow be trapped in space, it would form the center of a rotating spiral wave (Fig. 4), and he set out to find rotating spiral waves in thin layers of the BZR. In fact, he rediscovered spiral waves (Winfree, 1972); Zhabotinsky first described them in a 1970 Russian report. Later, Zhabotinsky and Zaikin published their first English description of spiral waves in this journal in 1973.

Next, Art realized that a rotating two-dimensional spiral wave is just a slice through a three-dimensional spatiotemporal structure, which he called a scroll wave (Winfree, 1973a). Just as a spiral wave rotates around a phaseless point, a scroll wave rotates around a phaseless filament. In a thin layer of BZR, the filament is a

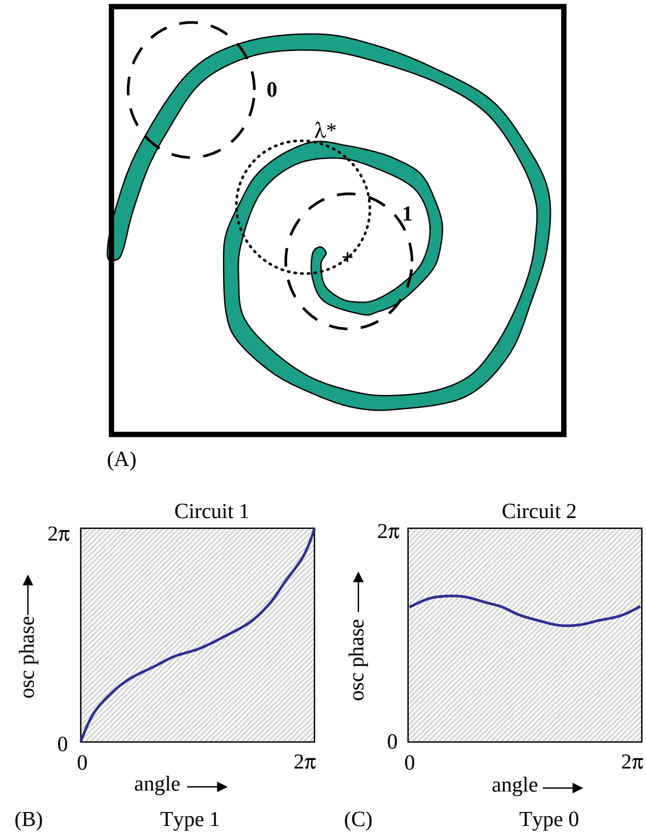

Fig. 4. The topology of spiral waves. (A) Snapshot of a two-dimensional excitable medium containing a rotating spiral wave. Most points in the domain (but not necessarily every point) undergo periodic oscillations of the state variables with common period, T_o; hence, to each oscillatory point we can assign a certain phase angle between 0 and 2π. (B and C) For circuits 1 and 0 in panel A, we plot the local phase of oscillation (ordinate) against the phase angle of position on the circuit (abscissa). Proceeding around circuit 1, we see all phases of the oscillation from 0 to 2π. Proceeding around circuit 0, we see only some phases, say from π to $3\pi/2$. Let us introduce a parameter λ that continuously transforms circuit 1 (at $\lambda = 1$) into circuit 0 (at $\lambda = 0$). The phase function F(phase angle, λ) cannot be a continuous function of its two arguments, because it has topological type 1 at $\lambda = 1$ and topological type 0 at $\lambda = 0$. There must be at least one phaseless point, where *F*(phase angle*, λ*) is undefined. In the figure the phaseless point is marked by a +. For a rigidly rotating spiral, the phaseless point (+) stays fixed in space as time proceeds. But nothing in the topological argument precludes the phaseless point from moving continuously in space as time proceeds. This phenomenon, called "meander," was clearly described by Winfree in observations of the BZR and in computer simulations of excitable media.

straight-line segment standing upright in the solution (perpendicular to the two interfaces). In a deeper solution, Art wondered, what might become of the filament? Might it break loose from the interfaces and connect with itself to form a closed ring in the interior of the solution? Might the filament tie itself in a knot before closing?

Art looked for scroll rings in a most ingenious fashion. After soaking filter papers in BZR, he stacked them like pancakes and initiated a rotating scroll wave. To capture and dissect the "beast," he quickly unstacked the filter papers and dropped them into a chemical fixative to stop the reaction. Then, by examining the patterns of oxidized and reduced regions in each slice of the reaction, he could reconstruct the three-dimensional shape of the scroll wave. In this way he proved the existence of scroll rings (Winfree, 1974). As a side effect of these experiments, Art realized that he could enliven his lectures by passing out small disks of millipore filter soaked in BZR, so that everyone could see with their own eyes the beautiful spiral waves that rotate sedately in the immobilized reaction. For a fuller description of the BZR on millipore filters, see *The Geometry of Biological Time* (Winfree, 1980) p. 302, or the Second Edition (2001) on p. 370, with references to some more recent work.

At about this time, Art left Chicago for Purdue University, where he put together his masterpiece, *The Geometry of Biological Time* (Winfree, 1980), in which he drew together all the ideas that had been fermenting in his mind for 15 years. True to form, he did not write a dry synopsis of well-established results but rather a lively hodge–podge of questions, answers, puzzles, partial solutions, and future directions.

In the early 1980s Art was joined at Purdue by a talented young mathematician, Steven Strogatz, who worked with Art briefly before embarking on a graduate degree at Harvard. Together they published a series of groundbreaking articles on the topological rules governing scroll wave filaments in three-dimensional oscillatory and excitable media (Winfree and Strogatz, 1982, 1983, 1984a–c).

4. Flutter and fibrillation

Although rotating spiral and scroll waves in the BZR were nothing more than curious distractions to the majority of chemists, suitable mainly for classroom wizardry, Art recognized that the same waves might arise in heart muscle, where they would manifest themselves as pernicious rapid heart beats. Although this idea was not his own creation—as early as 1948 Wiener and Rosenblueth had expressed a similar notion, and the analysis of spiral autowaves was undergoing active development by Valentin Krinsky and colleagues in the USSR—Art pursued it diligently from his characteristic topological perspective. He wanted to know how rotating waves could appear suddenly in a heart that had hitherto been beating normally. He showed that certain aberrant electrical stimuli, of just the right strength at just the right time (or should we say "just the wrong strength and wrong time"), could create a pair of phase singularities, around which a pair of counter-rotating spirals would spontaneously form (Winfree, 1983, 1989). This brilliant prediction was soon verified in many cardiology laboratories, and led eventually to Art's receipt of the Einthoven Award for Cardiology in 1989.

One or two rotating scroll waves or spiral waves in heart tissue would be recognized by a clinician as a fast heart rate (rapid, inefficient heart contractions)—a tachycardia. However, hearts also exhibit fibrillatory rhythms that are associated with highly irregular dynamics. Fibrillation can occur in the upper chambers of the heart (the atria) leading to a non-fatal but potentially disabling arrhythmia, or in the lower chambers (the ventricles) leading to a fatal arrhythmia. These fibrillatory rhythms might be associated with multiple rotating waves that arise from the spontaneous fractionation of regular waves into myriad small foci of rotating scroll waves.

To understand the origins of fibrillation and potential treatments, Art initiated several different lines of enquiry. In careful numerical and experimental studies of two-dimensional excitable media, Art demonstrated that rotating spiral waves often meander in space—the exact geometry of the meander depending on the parameters of the differential equations or the experimental preparation (Winfree, 1990a). Moreover, in some instances, spiral waves spontaneously break up, leading to many independently rotating spiral waves (Courtemanche and Winfree, 1991).

In order to investigate the stability of the twisted and knotted scroll waves that he and Steve Strogatz predicted to exist and to determine initial conditions that might lead to these waves, Art and his students began an ambitious project of super-computer calculations of three-dimensional scroll wave dynamics (Nandapurkar and Winfree, 1987; Winfree, 1990b,1994; Henze and Winfree, 1991). To determine the geometry of wave propagation in intact heart, Art collaborated with the late Frank Witkowski, a brilliant cardiologist who was building an optical mapping apparatus to study wave propagation in heart during fibrillatory rhythms by measuring the fluorescence of heart tissue stained with voltage-sensitive dyes. This work led to the observation of rotating spiral waves from the surface of a sheep heart during ventricular fibrillation (Witkowski, et al., 1998). Art's ideas about cardiac arrhythmias and their relationship to rotating spiral and scroll waves are summarized in his book, *When Time Breaks Down* (Winfree, 1987). This book helped to shape experimental and theoretical work by many investigators, including R. Ideker, J. Jalife, J. Keener and A. Karma.

In 1987, Art moved from Purdue to the University of Arizona, where he continued his research on chemical reactions and cardiac muscle, somewhat incongruously, in the Department of Ecology and Evolutionary Biology.

5. Back to BZ

Though good at it, Art was never truly comfortable with computer simulations. To him they were guides to his intuition, geometric vision, and experimental tinkering. How would it be possible to confirm experimentally the predicted existence of stable scroll rings and other more exotic, three-dimensional, rotating structures? Although it seemed likely that scroll rings could rotate deep in the heart, optical studies of wave propagation in heart tissue were only capable of imaging a thin surface layer, so it was impossible to observe scroll rings directly.

Hoping to find sound experimental evidence for the subtle and spectacular patterns playing out in his computer simulations, Art designed and built a system to measure with high resolution the concentration patterns of BZR intermediates in space and time. It was essentially a high-tech version of his stacked filter papers. By shining a light through the BZR and scanning the absorption of light at different angles, he used tomographic reconstruction techniques to determine the geometry of the three-dimensional rotating structure. In Winfree et al. (1996), he described the many technical hurdles that had to be overcome and presented unequivocal evidence that the detailed anatomy of rotating scroll waves could in fact be observed in real systems. In what we believe is Art's last paper on this problem, published post-humously, he addressed some of these matters computationally (Sutcliffe and Winfree, 2003). Unfortunately, following the demonstration of optical tomographic imaging of the BZR, the projected use of this method to study a host of other problems (such as the initial conditions needed to seed various three-dimensional structures, and the dynamics and stability of knotted and twisted scroll rings in real systems) was never completed. Those problems, many of which are sketched out in a recent review (Winfree, 2001), remain a part of Art's legacy to future generations.

6. Scientist and visionary

Although many people regard Art Winfree primarily as a theoretician, the essence of his science really emerges from the lively way his theorizing led to predictions that could be tested experimentally. His experimental designs wove deep topological notions into the thinking of circadian physiologists, physical chemists, and cardiologists. Before Winfree's analysis, many people had done experiments in which stimuli were used to reset circadian clocks or perturb cardiac rhythms. But the unexpected results found by Winfree and others when his theoretical ideas were confirmed by experimental observations remain landmark studies elucidating the universal properties of biological rhythms.

Art Winfree was perhaps the most self-sufficient scientist we have known. In contrast to today's environment that often favors large research groups and selects for scientists who are good managers, Art preferred to work alone or at most with a small group of select students. He developed the theory, built the equipment (usually from his collections of miscellaneous electrical and mechanical parts scavenged from discarded equipment), managed the computers, wrote the code, drew the figures, and composed the papers. Although his research was usually funded, the amounts requested were purposefully small, enough to pay the bills for the next few years.

Art's influence derives not only from his own work but also from the way he interacted with colleagues, friends, and strangers, urging them to dig deeper. In the days before email, sending a draft of a paper to Art would lead a few days later to a returned copy, filled with markings in green felt-tipped pen, pointing out where ideas were vague or where new directions could be taken, as well as giving enthusiastic bravos for new discoveries. The degree of care he took critiquing the ideas of his colleagues is witnessed by a host of papers that end with "Thanks to A. T. Winfree for helpful conversations."

Art reveled in thinking about all aspects of nature. Although we have focused on the work for which he is best known, his curiosity extended in many directions. What controls the spiral rings in *Nectria* (Winfree, 1973b), or the patterns in arthropod cuticles (Gordon and Winfree, 1978), or the flowering of morning glories (Winfree, 1976)? Each of these topics, having captured his fancy for a time, was put aside in favor of investigations into the dynamics of cardiac arrhythmias in the 1980s and 1990s. Who knows what important new science these passing fancies may lead to someday?

Art was a scientist who played in many fields of science, wherever his deep geometric insights revealed new and subtle properties of the spatial and temporal organization of living and non-living systems. He has had a strong influence on his friends and colleagues, and he is sorely missed.

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