*The geometry of biological time*, by Arthur T. Winfree, Biomathematics, vol. 8, Springer-Verlag, New York, Heidelberg and Berlin, 1980, xiii + 530 pp., $32.00.

This book views biological periodicities through the lens of topology. It describes experiments on biological and biochemical rhythms. It interprets them in the light of topological constraints on continuous mappings between manifolds. It states only one theorem and very few equations.

A central example will illustrate the book's thrust.

A fruitfly of the species *Drosophila pseudoobscura* starts life as a fertilized egg. It develops into a larva, which eats until it matures into a pupa. The pupa acquires a hard outer cuticle, the pupal case. Within the pupal case, larval organs metamorphose into adult organs. When all is ready, a winged adult ecloses from the pupal case. The duration of eclosion is so short compared to the durations of the pupal and adult stages before and after it that eclosion is considered to occur at a discrete epoch in time.

If a population of pupae is reared under constant conditions that include bright light, eclosion times are distributed over the 24-hour day. Suppose the pupae are reared in constant bright light for some time, and then suddenly plunged into darkness. Call the epoch of this transition from light to darkness $T = 0$ hours. Within an interval of one and a half hours around $T = 17$ hours, there will be a burst of eclosion. This peak of eclosions will be followed by no

eclosions for another 24 hours. At $T = 17 + 24n$, $n = 1, 2, \ldots, 6$, there will be additional peaks of eclosions.

This observation suggests that, following a transition from bright light into steady darkness, eclosion happens under the control of a clock with a 24-hour periodicity, and that the light-dark transition sets the clock running at a phase of $7/24 = (24 - 17)/24$ of a cycle if phase 0 is defined to occur at a peak of eclosions.

Now suppose that a population of fruitfly pupae reared in bright light is suddenly darkened at $T = 0$, and at some later $T > 0$ is exposed to a dim blue light of duration $M$ seconds. Then the population again returns to darkness. The two controlled parameters of this experiment are the duration $M$ and the epoch $T$ of the blue light stimulus. (The light is so brief compared to 24 hours that it can be treated as occurring at a discrete epoch in time.)

For some hours after the blue light, no eclosion occurs. Then at first eclosions occur scattered in time. After 4 or 5 days, sharp peaks of eclosions, at 24-hour intervals, reappear. The peaks are shifted with respect to the peaks that would have occurred at $17 + 24n$ hours in the absence of the blue light. The amount of the shift depends on $M$ and $T$.

Since a clock with 24-hour periodicity seems to govern eclosion before and after the blue light, the experiment can be described in terms of the blue light duration $M$ and two phases: the phase $\phi$ of the clock (measured with respect to eclosion peaks in the absence of light) just prior to the epoch when the blue stimulus light goes on, and the phase $\phi'$ of the clock just after the blue light goes off (inferred from the interval to the next peak of eclosions).

For almost every fixed duration $M$, experiments show that the new phase $\phi'$ varies smoothly as a function of the old phase $\phi$. When $M = 0$, that is, in the absence of any blue light, $\phi'$ is proportional to $\phi$ with slope 1, since $\phi' = \phi$. Blue lights of up to 4 second durations cause minor perturbations to proportionality, but the average slope of $\phi'(\phi)$ over one cycle of $\phi$ remains 1. These curves can be plotted on a torus. If the torus lies on a table, $\phi$ runs around the hole of the torus in a plane parallel to the table top, and $\phi'$ runs around one cross section through the torus made by a plane perpendicular to the table top. Then for small values of $M$, the curves $\phi'(\phi)$ have winding number 1: their graph on the torus winds through the hole exactly once as $\phi$ varies through one cycle.

Recall, however, that the pupal eclosion clocks were synchronized in the first place by a sudden transition from bright light to darkness. It is not too surprising that a sufficiently long exposure to the dim blue light followed by darkness effectively resets all the clocks. When the duration $M$ is between 8 and 64 seconds, the winding number of $\phi'$ as a function of $\phi$ is 0. This means that as the old phase $\phi$ increases through one 24-hour cycle, the new phase $\phi'$ passes through a cumulative total of zero cycles. For long stimuli, the graph of $\phi'$ as a function of $\phi$ either does not pass through the hole of the torus at all, or comes back as often as it passes through, for a net advance of 0 cycles.

Arthur T. Winfree, the author of this book, was apparently the first to study experimentally the implication of a necessarily discontinuous transition, with

increasing $M$, from winding number 1 to winding number 0 in the graph of $\phi'$ as a function of $\phi$: there must exist a stimulus time $T^*$ or phase $\phi^*$ and a duration $M^*$ such that after an exposure to the dim blue light of $M^*$ seconds, no phase $\phi'$ can be assigned to the population of eclosion clocks. Winfree calls such a $(T^*, M^*)$ a phase singularity. In a series of ingenious, simple experiments that used approximately one megafly, Winfree demonstrated that a phase singularity does exist. At a phase singularity, the subsequent pupal eclosions become arrhythmic, probably because the eclosion clocks enter or approach nonoscillating steady state.

The theorem that lies beneath the existence of a phase singularity may be stated informally: the only continuous maps from a disk to a circle have winding number 0 around the border of the disk. If the winding number is other than 0, then the map cannot be continuous. (It is remarkable and yet unexplained that all observed winding numbers in Winfree's biological examples are 0 or 1—nothing else.)

The two crucial ingredients in this theorem, and in the example of fruitfly eclosion, are smoothness (continuity) and periodicity (the disk boundary and the circle). In roughly the first half of this book, Winfree reviews model time-keeping mechanisms in biology that share these two ingredients and describes what is known about the topologically inevitable phase singularities in each.

In the second half of the book, which Winfree calls his "Bestiary," he describes electronic, chemical, and biological examples of the various time-keeping mechanisms and their corresponding phase singularities. The biological examples include cellular anaerobic sugar metabolism, pacemaker neurons, slime-mold amoebae, amphibian limbs, roach legs, circadian rhythms both generally and in the eclosion of insects other than fruitflies, the flower of *Kalanchoe*, the cell mitotic cycle, and the female ovulatory cycle.

Winfree occasionally interprets data in ways that are, and are labelled as, potentially controversial. The contributors to Aschoff [**1981**] offer other, more descriptive than analytical, views of biological rhythms. Winfree also indicates what experimentation could resolve controversy. For the mathematically trained reader, he provides enough biological background to make his descriptions and the contested issues intelligible. He offers opportunities for mathematical research in questions raised throughout the book (see "Queries" in the Index).

In spite of the breadth of biological examples chosen, Winfree concentrates exclusively on periodic aspects of biological time. Linear biological time figures in the healing of wounds (Lecomte du Noüy, [**1937**]), aging (Behnke et al., [**1978**]), and evolution (Blum, [**1968**]). See also Whitrow [**1980**] for an overview and Krudy et al. [**1976**] for a bibliography. In large part, the linear aspects of biological time still await a geometer like Winfree.

At the transition (p. 276) from the theoretical part of the book to the "Bestiary," Winfree remarks that "topological notions are in principle incapable of rigorous application to empirical science." Perhaps I do not grasp his meaning of "rigorous," for I find the bulk of his clear-headed book to be a sound and constructive use of topological notions in biology. The evidence supports his introductory statement (p. 3): "It is my belief that the life sciences

in particular have much to gain from, and perhaps something to contribute to, mathematical developments in the general area of topology."

## REFERENCES

Jürgen Aschoff (ed.) [**1981**], *Biological rhythms*, Handbook of Behavioral Neurobiology, vol. 4, Plenum, New York.

John A. Behnke, C. E. Finch and G. B. Moment [**1978**], *The biology of aging*, Plenum, New York.

Harold F. Blum [**1968**], *Time's arrow and evolution*, 3rd ed., Princeton Univ. Press, Princeton, New Jersey.

Elmer S. Krudy, B. Bacon and R. Turner (eds.) [**1976**], *Time: A bibliography*, Information Retrieval, London and Washington.

Pierre Lecomte du Noüy [**1937**], *Biological time*, Macmillan, New York.

G. J. Whitrow [**1980**], *The natural philosophy of time*, 2nd ed., Clarendon Press, Oxford and Oxford Univ. Press, New York.

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