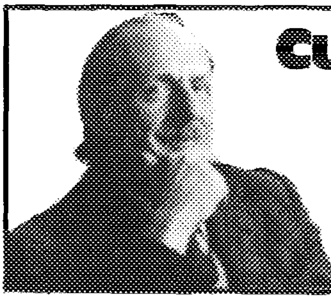
Essays of an Information Scientist: Science Literacy, Policy, Evaluation, and other Essays, Vol:11, p.1, 1988
Current Contents, #1, p.3-9, January 4, 1988



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EUGENE GARFIELD
INSTITUTE FOR SCIENTIFIC INFORMATION®
3501 MARKET ST., PHILADELPHIA, PA 19104

Chronobiology: An Internal Clock for All Seasons. Part 1. The Development of the Science of Biological Rhythms

Number 1 — January 4, 1988

The lives of virtually all plants and animals, from the simplest one-celled organisms to humans, are governed by a variety of internal biological rhythms. This essay (the first of two parts) discusses chronobiology, the study of these biological clocks. Biological periodicities may range from ultradian and circadian to circalunar and circannual cycles. Using ISI® data, we trace the development of the field from its earliest underpinnings in botany and zoology and identify the authors of *Citation Classics®*, such as Jürgen Aschoff, Erwin Bünning, and Colin S. Pittendrigh.

Living organisms exhibit myriad cycles. Annually, the leaves of deciduous trees in the temperate zones turn brilliant hues of yellow, orange, and red as the days shorten and winter approaches. Each year, animals go through cycles related to reproduction; most of those in the temperate zones also experience rhythms that prepare them for the period of inactivity that comes with winter.

Cycles that take less than a year to complete are also plentiful. Daily rhythms include the folding and unfolding of the leaves of certain plants, such as the "sensitive plant" (*Mimosa pudica*) and the tamarind tree (*Tamarindus indicus*), and the rise and fall of the body temperature of animals (including humans).[1] (p. 5, 14) Numerous organisms inhabiting the earth's tidal zones, from plankton and diatoms to crabs and seabirds, exhibit cycles of physical and behavioral change ranging from 12 hours to two weeks to a month in length, matching the complex, interacting effects of the sun and the moon on the tides.[2] In fact, even cells exhibit some type of periodicity in their activities, often in cycles lasting fractions of a second.[3-5]

The importance of rhythms in nature has been appreciated for thousands of years:[6] people plant their crops in tune with the cycle of the seasons and eat and sleep according to the daily rise and fall of the sun. Indeed, so familiar are these rhythms that, according to pharmacologists Joseph S. Takahashi and Martin Zatz, Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, Maryland, they did not elicit systematic, scholarly investigation until the 1700s.[7] Since that time, however, the study of these biological rhythms has slowly coalesced into the science of chronobiology.

Some of the foundations of chronobiology were laid in the 1930s. But as the first part of this essay shows, activity in this field remained fairly constant at a relatively low level until the 1950s and 1960s. Since then, according to a review by Alain Reinberg, director of research, National Center of Scientific Research, Paris, France, and Michael H. Smolensky, associate professor of environmental sciences, University of Texas Health Sciences Center, Houston, chronobiology has been an active, rapidly growing, multidisciplinary field.[6] The second part of this essay focuses on the latest research in this dynamic science.

Biological Rhythms and Their Significance

A vast array of periodicities in functions or activities are exhibited by virtually every organism, from single-celled plants and animals to such complex creatures as human beings.[8] These rhythms are intrinsic to the organism and enable it to measure the passage of time. For many organisms, the most important interval measured by their internal clocks is the 24-hour cycle of light and dark. Rhythms that coincide with this cycle are called "circadian," from the Latin *circa* (about) and *dies* (day).[9] (p. 2, 10)

Other important biological periodicities include "circatidal" rhythms, matching the period of daily high and low tides, and "circasyzygic" rhythms, which match the cycle of unusually high and low tides occurring each fortnight, when the sun and moon are in the proper alignment. "Circalunar" rhythms are synchronized with the monthly waxing and waning of the moon. "Circannual" periodicities are cycles of about a year.[9] (p. 9-10) It should be noted, however, that circannual rhythms are not the end of the story; for example, the 7-year and 17-year locusts that emerge from their long pupal incubation in the ground are cycles that span longer periods.

An innate ability to measure the passage of time has adaptive significance. A sense of time helps birds to accurately use the sun, moon, and stars as navigational aids during migration. Internal clocks also enable organisms to synchronize their breeding behaviors with one another as well as with the most favorable environmental conditions for raising young. In fact, biological rhythms help organisms match a number of activities to the times when those activities can be carried out most effectively. For example, as noted by zoologist David S. Saunders, University of Edinburgh, Scotland, circadian rhythms allow animals of different species to share the same food sources without direct competition because some animals are active only during hours of darkness (i.e., they are *nocturnal*) while others are active only during the day (*diurnal*). The advantage to having a built-in method of responding to light and darkness, rather than relying on actual changes in light as a cue, is that, in effect, the organism is prevented from "sleeping late" and missing the optimal time of day for foraging.[9] (p. 12)

Environmental Influences on Biological Rhythms

For centuries it was believed that biological periodicities were *caused* by the environmental rhythms with which they were synchronized.[6] But in 1729 French astronomer Jean Jacques d'Ortous de Mairan (1678-1771) conducted an experiment showing that, even in total darkness, the leaves of a "sensitive heliotropic plant"—probably *Mimosa pudica*[1] (p. 5)—continue to fold and unfold in a 24-hour cycle that was previously thought to be in response to daylight.[10]

The idea that the circadian movements of plants are independent of the daily light-dark cycle was confirmed by a series of experiments performed by the German botanist, Wilhelm F.P. Pfeffer (1845-1920),[6,11] (p. 61-2) in the late 1800s[12] and early 1900s.[13] As Reinberg and Smolensky note, however, it was not until the 1950s "that Pfeffer's findings were clearly understood and appreciated."[6]

It was another German botanist, Erwin Bünning, University of Tübingen, who first conclusively established the accepted foundations of chronobiology: that organisms use their biological rhythms to measure the passage of time and that these rhythms are inherent to the organism. Bünning proved the genetic origin of biological rhythms in the mid-1930s while working at the Botanical Institute of the University of Jena. He found that circadian rhythms persisted in the bean plant *Phaseolus*[14] and the fruit fly *Drosophila*,[15] even though generation after generation had been raised in environments completely lacking cues to the passage of time.[6,11] (p. 146-8) The 1936 paper on fruit flies has been cited over 180 times, according to the *Science Citation Index*® (*SCI*®). A *Citation Classic*®,[16] it is the most-cited paper ever published by *Berichte der Deutschen Botanischen Gesellschaft*, the journal of the German Society of Botanists.

Bünning's work with *Drosophila* eventually led him to conclude that the fruit fly "knew" when to emerge from the pupal stage of its development because its circadian rhythm had cycled a given number of times, indicating that a season had passed.

His work has been extensively cited. A definitive, German-language edition of Bünning's work in this area, entitled *Die physiologische Uhr* (*The Physiological Clock*),[17] was originally published in 1958 and reprinted in 1963. Using the 1955-1964 *SCI*,[18] we determined that the former has received about 100 citations. The reprint has been cited at least 120 times. An English translation appeared in 1964[19] and has been reprinted twice since then. The various editions have been explicitly cited in almost 700 publications, making *The Physiological Clock* a *Citation Classic*.[20]

Although biological rhythms are innate, they nevertheless function to keep organisms in tune with their environment and are thus responsive to various environmental, or exogenous, cues. In 1954 Jürgen Aschoff, professor of physiology and director, Max Planck Institute for Behavioral Physiology, Seewiesen über Starnberg, Federal Republic of Germany,[21] and Franz Halberg, University of Minnesota Medical School, Minneapolis, and Cambridge State School and Hospital, Minnesota, and colleagues[22] independently and almost simultaneously developed an explanation of the role that environmental factors play in the functioning of internal clocks.[6]

These environmental factors—such as light and dark, ambient temperature, noise, and even interactions with other members of the same species[6]—act to keep biological cycles in phase with periodic fluctuations in the environment. In the absence of such cues (which occurs when plants and animals are removed to controlled laboratory conditions), the cycles continue but begin to drift out of phase with clock time and become "free-running." Within their own free-running cycles, though, they are remarkably resistant to perturbation.[6] In fact, several studies by Aschoff demonstrated that, beyond certain narrow limits, the presence or lack of environmental cues has no effect on biological rhythms.[23-25] One of these papers, entitled "Exogenous and endogenous components in circadian rhythms,"[24] is Aschoff's most-cited paper; published in 1960, this *Citation Classic* has been cited over 470 times.

To describe the environmental cues from which biological rhythms are derived, Aschoff coined the word "Zeitgeber," meaning "time giver."[21] Colin S. Pittendrigh, Stanford University, California, later introduced the term "entraining agent";[26] still later, Halberg and colleagues proposed the word "synchronizer."[27] Although these authors each give a somewhat different definition of their terms, it has become common practice in the field to use them interchangeably.[6]

The Emergence of the Discipline of Chronobiology

Despite the discoveries of Pfeffer, Bünning, Aschoff, and others, chronobiology did not really begin to coalesce as a distinct discipline until the 1960s.[6] In part, according to Reinberg and Smolensky, this was because chronobiology lacked some of the attributes that help a field establish its own identity. For example, until recently chronobiology was not taught in schools as a subject in its own right, and no departments or chairs of chronobiology existed. This meant that those who studied chronobiology necessarily came to the subject from other fields, often by accident. As a result, the authors write, "the number of active and well-trained chronobiologists was quite small."[6] Again, until recently, there were few scholarly societies devoted to chronobiology, which may have hampered communication between the widely scattered members of the chronobiological community.

It is often believed that the true emergence of a specialty is hampered by a lack of journals focused on that field. Until recently no journals devoted exclusively to chronobiology were being published. In this respect, it is worth quoting Victor A. McKusick[28] and Frank H. Ruddle, editors-in-chief of *Genomics*, on their justification for launching a new journal. In an editorial in the first issue, they said that they viewed the journal "as a common meeting ground for molecular biologists and biochemists, human and somatic cell geneticists, cytogeneticists, population and evolutionary biologists, genetic epidemiologists, clinical geneticists, theo-

Table 1: Selected list of journals reporting on basic and applied study of physiological rhythms. A = title and publisher. B = 1986 impact factor.

A	B
American Journal of Physiology American Physiological Society Bethesda, MD	3.29
Brain Research Elsevier Science Publishers Amsterdam, The Netherlands	2.86
Chronobiologia Casa Editrice Milan, Italy	0.72
Chronobiology International Pergamon Press, Inc. Elmsford, NY	–
International Journal of Chronobiology Gordon & Breach Science Publishers Ltd. London, United Kingdom	–
Journal of Biological Rhythms Guilford Publications New York, NY	–
Journal of Clinical Endocrinology and Metabolism Endocrine Society Baltimore, MD	4.20
Journal of Comparative Physiology A—Sensory, Neural, and Behavioral Physiology Springer-Verlag New York, Inc. New York, NY	0.90
Journal of Insect Physiology Pergamon Press, Inc. Oxford, United Kingdom	1.60
Journal of Interdisciplinary Cycle Research Swets & Zeitlinger BV Lisse, The Netherlands	1.46
Journal of Pineal Research Alan R. Liss, Inc. New York, NY	1.25
Physiology and Behavior Pergamon Press, Inc. Elmsford, NY	1.43
Psychiatry Research Elsevier Scientific Publishers Ireland Ltd. Shannon, Ireland	2.30
Sleep Raven Press New York, NY	1.50

retical biologists, and computational scientists, all interested in the biology and genetics of human and other complex genomes."[29] However, not every field best serves itself by jumping into separate publication. As long as the most important articles remain in the bigger, multidisciplinary journals, the smaller, new journals will have a tough time.

Since the 1960s, however, several changes have begun to take place that have enabled chronobiology to gain recognition and influence as a discipline in its own right. Three journals that report solely on chronobiological research, the *International Journal of Chronobiology*, *Chronobiologia*, and *Chronobiology International*, have been founded. Table 1 lists these and other journals in which chronobiologists publish. The Society for the Study of Biological Rhythm, founded in 1937 but relatively dormant until 1953, changed its name to the International Society for Chronobiology in 1971 and has been highly active ever since. Other scholarly societies and associations that promote chronobiological research are listed in Table 2.

A favorable intellectual climate also played a role in helping to establish chronobiology as a distinct discipline. Reinberg and Smolensky refer to the 1960s as the "golden age of molecular biology" and note that it coincided with a flowering of chronobiological research.[6] In part, they say, the emergence of chronobiology was aided by the burgeoning interest of molecular biologists in cellular periodicities. At the same time, as both a cause and an interactive result of this heightened interest, new statistical approaches for detecting and measuring biological periodicities were being developed. These were especially useful in studying ultradian rhythms, which include cycles that range from a fraction of a second to a fraction of a day.

Pittendrigh organized a symposium at Cold Spring Harbor, New York, in 1960 to address the standards that chronobiology had to meet to develop further as a modern, quantitative biological science.[6] Among the topics discussed were more rigorous methods of data sampling and gathering and statistical analysis.[24,26,30] The 1960 paper Pittendrigh wrote for the symposium, entitled "Circadian rhythms and the circadian organization of living systems,"[26] is his most-cited work. This *Citation Classic* has been cited in over 450 works.

Table 2: Selected list of associations promoting research and providing information on various aspects of chronobiology and circadian rhythms.

International Commission on Circadian Rhythms and Sleep
Department of Physiology
Harvard Medical School
25 Shattuck Street
Boston, MA 02115

International Society of Mathematical Biology
11 bis avenue de la Providence
F-92160 Antony
France

International Society for Chronobiology
Chronobiology Laboratories
University of Minnesota School of Medicine
380 Lyon Laboratories
Minneapolis, MN 55455

This symposium and the subsequent activity and debate that surrounded the establishment of chronobiology as a discipline have been the objects of considerable interest among historians and sociologists of science, according to Alberto Cambrosio and Peter Keating, Institute of History and Sociopolitics of Science, University of Montreal, Quebec, Canada.[31] We discussed some of the characteristics of the emergence of a new discipline in a previous essay on biomedical engineering.[32]

As a result of the founding of journals and societies and advances in techniques, the number of researchers engaged in chronobiology and, consequently, the number of papers concerning various aspects of it have greatly increased since the 1960s. This has enabled chronobiologists to produce what Reinberg and Smolensky call "a critical mass of experimental evidence" that has overcome previous theories that "slowed or inhibited the advance of chronobiologic hypotheses and concepts."[6]

These theories included the idea, taught to "generations of students," as Reinberg and Smolensky note, that the regulatory mechanisms of biological systems are processes that attempt to maintain a constant, or steady, state, called homeostasis. Although Reinberg and Smolensky do not discount the importance of homeostatic regulatory mechanisms, they point out that the body's "set points" fluctuate within a narrow range in a distinct rhythm. Such physiological phenomena as the levels of plasma cortisol, testosterone, circulating lymphocytes, and blood pressure and body temperature, to mention just a few, vary in predictable rhythms over a 24-hour period.[6]

This concludes our discussion of the development of chronobiology as a distinct discipline. In Part 2 of this essay, we will describe current chronobiology research.

* * * * *

My thanks to Stephen A. Bonaduce and C.J. Fiscus for their help in the preparation of this essay.

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