A Time to Reap

Author: CASSONE, VINCENT M.

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VINCENT M. CASSONE

Poets and sages throughout the centuries have been moved to speak about the mystery of time and the poignancy of its passage, yet until recently, books about biological time and the biological clocks that record it have been scarce. Over the past half-century, however, the entire scientific field of chronobiology, the study of biological time, has been growing in both size and reputation.

Its modern inception could be traced to a pivotal meeting in 1960 on biological clocks, held at Cold Spring Harbor, New York. Many of the central questions about biological clock behavior, experimental design, and nomenclature were first enunciated at that meeting. Some terms—for example, *chronobiology* (the study of biological time) and *circadian rhythm* (from *circa,* "approximately," and *diem,* "day"; Aschoff 1960)—entered common scientific parlance as a result. Chronobiologists have since progressed from describing biological timekeeping in nearly all types of living things to identifying the structures and processes associated with it, including the biochemical and molecular genetic mechanisms responsible for it. Even more astounding, several researchers have identified mutations in human clock-related genes that result in abnormal sleep–wake cycles; some have identified disorders in clock mechanisms that predispose us to cancers and cardiovascular disease, and others are trying to determine when in the circadian cycle treatments for cancer and other diseases are most efficacious. Thus chronobiology has matured to a state that beckons the interest of the general public, calls for college courses to be taught, and attracts researchers from related disciplines. It is therefore heartening to see the field explained at different levels of sophistication in several new books.

John D. Palmer's *The Living Clock* (2002) provides an amusing and enjoyable personal journey through the study of chronobiology. Palmer, a professor at the University of Massachusetts, has over the years documented a wide array of rhythmic behaviors, primarily in marine microorganisms and invertebrates. He has shown, for example, that crabs dwelling in the intertidal zone synchronize their behavior both to the time of day and to the tide. In *The Living Clock,* his fifth book on chronobiology, Palmer introduces the subject with a discussion of what he clearly knows best, the phenomenally diverse chronobiological adaptations found among microorganisms. He follows this with three chapters devoted to biological timekeeping in humans, including an account of the formal properties of circadian rhythms, drawn from clinical studies. He describes the effects of biological clocks—and hence time of day—on patients' responses to drugs and on our attempts to adapt to unnatural shift-work schedules, to artificial lighting, and to the more modern problem of jet lag.

Surprisingly (to me, at least), Palmer concludes this section with a rather uncritical endorsement of the use of the pineal hormone melatonin for amelioration of the symptoms caused by these hazards of modern life. This is my own area of research and interest, and I was disappointed to find that Palmer's discussion included several minor inaccuracies. These seem to derive mainly from an incautious enthusiasm, but they gave me cause to wonder about the accuracy of other sections.

Subsequent chapters return to more familiar chronobiological territory: rhythmic processes in microorganisms, intertidal invertebrates, higher animals, and plants. Palmer saves the most recent advances in the field for the last, curiously short chapter, prematurely entitled "Denouement." Here, Palmer gives lamentably short shrift to studies identifying and demonstrating the activity of specialized clock-related structures in higher animals, such as the pineal organ and the suprachiasmatic nucleus in vertebrates. He also glosses over the tremendous advances made over the past 25 years as a result of developments in molecular genetics and genomics. After explaining the phenomenon of biological time with great enthusiasm, Palmer seems to relegate to an afterthought the news that science can now tell a good story about the intricate interplay of genes and accumulating proteins that drives many biological clocks. His failure to adequately explain these pathbreaking discoveries robs the denouement of much of its force. Yet despite this unsatisfactory closing and some overstatement, I could recommend Palmer's book to an intelligent lay reader looking for an introduction to the topic.

In the same vein but deeper into the lode, *Rhythms of Life,* by Russell G. Foster and Leon Kreitzman (2004), will appeal to a more technically sophisticated audience. Foster is a professor of molecular neuroscience at Imperial College, London, and a highly regarded chronobiology researcher who has made important discoveries about how light affects the biological timekeeping of many vertebrates. Kreitzman is a professional science writer and a sometime BBC radio host, which perhaps explains why the book sometimes seems to read like the transcript of a radio broadcast.

Rhythms of Life focuses primarily on mammalian clocks, with an eye to understanding human clocks and the maladies that can result when a clock goes awry. The book begins with a general description of biological rhythmicity from a historical perspective. The opening chapter is particularly engaging, because it relates seldom-told stories: the 18th-century French astronomer Jean Jacques Ortous de Mairan's discovery of an internal sense of time in plants and Charles Darwin's extensive studies of rhythmic processes in plants and earthworms. The compelling attention to historical detail is maintained over the next three chapters as the narrative advances to modern investigations of the clock mechanism responsible for rhythmicity and synchronization in response to environmental cues. It is here that the book excels, because its centerpiece—chapters 5, 6, and 7—describes the search for the clock itself and the mechanisms that drive the gears and turn the hands. Chapters 8, 9, and 10 briefly discuss clock mechanisms in a few other taxa, particularly nonmammalian vertebrates and plants, and the role of circadian clocks in seasonal rhythms, such as photoperiodic control of reproduction. There follows a discussion of "clockwork evolution." The book ends with a four-chapter vignette on clinical clock research. I found this last section the most useful, because it effectively integrates the often disparate research approaches of chronobiologists and sleep researchers.

Foster and Kreitzman's book does a better job than Palmer's of integrating the history of chronobiology with recent advances in research, although because it requires more scientific background, it would probably not be the best choice for someone with no training in biology. The book falls awkwardly on the border between popular scientific books and technical treatises, making it not quite ideal either for casual lay readers or for researchers with a strong background in biological clocks. Yet its entertaining and informative style make it an excellent choice for advanced students and researchers in other fields who are interested in the subject.

The third book under review is *Chronobiology: Biological Timekeeping* (2004), which provides the first college-level textbook for the field. Jay Dunlap and Jennifer Loros, of Dartmouth Medical School, and Patricia DeCoursey, of the University of South Carolina, are the book's editors, and they have done an admirable job of stylistically reworking and significantly updating the contributions to the volume, which stem from a conference held in 1995 at Dartmouth Medical School. Although symposium proceedings are often uneven in both style and content, this text reads seamlessly from start to finish. The book is a tour de force.

Dunlap and Loros are well-known chronobiologists who are largely responsible for the successful use of the filamentous fungus *Neurospora crassa* as a model system for the study of molecular aspects of circadian clocks. DeCoursey's credentials are also beyond reproach, as she has published widely cited studies on formal aspects of clock behavior in flying squirrels, some of them in the classic Cold Spring Harbor Symposium mentioned earlier. More recently, she has addressed questions about the adaptive value of clocks in free-living rodents.

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Dunlap, Loros, and DeCoursey lucidly describe the history of the field while deftly explaining the complex processes of rhythm generation and synchronization to environmental light cues, and their physiological significance. They cover the wide array of organisms that express circadian rhythmicity, from cyanobacteria to humans. The text draws on the expertise of some 50 of the brightest minds in the field, so there is no chapter that stands out as being shallow or bereft of detail. *Chronobiology* is appropriate for upper-division university students or introductory graduate courses. It has a glossary (an excellent one) and provides review questions at the end of each chapter, like most textbooks, yet it reads more easily than standard textbooks. It is good enough to recommend to anyone with a serious interest in biological rhythmicity.

A recent special issue of *Methods in Enzymology* entitled "Circadian Rhythms," prepared by guest editor Michael W. Young (2005), is the most advanced of the volumes under discussion here, offering methodological and theoretical approaches to chronobiological research for professional scientists interested in biological clocks. Young is a well-known clock researcher who codiscovered the molecular nature of the first "clock gene," named *period,* in the fruit fly *Drosophila melanogaster.* Young's research has advanced knowledge of the molecular genetics of the *Drosophila* clock at many levels.

This text is authored by 115 of the world's most productive chronobiologists, both graduate students and the grand old bears of the field. The book is divided into 12 sections, with most chapters devoted to methodological approaches to a wide variety of experimental systems. Several chapters have a more standard focus on both research and data, though, and I found these chapters somewhat disappointing, because they do not fit comfortably with the theme of the series in general or this book in particular.

The first, and largest, section, "Genetic Approaches to Circadian Clocks," documents forward and reverse genetic screens in a wide array of species, ranging from *Neurospora* to humans. The second section comprises six chapters that arguably represent the body of current genomics analysis of circadian clocks, delineating gene expression techniques in several model systems, such as luciferase reporter imaging and DNA microarray analysis. This section is useful, although it describes work that is largely complete, at least in the major model systems in the field. In contrast, the third section describes what is likely to be in the forefront of molecular analyses of clock research—of all biological research, for that matter—in the next 5 to 10 years: the analysis of protein dynamics, or proteomics, of clock proteins. This section is incomplete in both the breadth of model systems and proteomics approaches, but this is largely because this area is in its infancy. As such, it is a seed around which new approaches may grow.

The remaining sections and chapters contain a wide array of approaches, some of which may be generally useful to all researchers in the field and some of which are specific to certain model systems. I found chapter 34, by Charles Weitz's group at Harvard, particularly useful, because it describes an experimental approach for identifying unknown signaling molecules that regulate oscillator coupling or output using a yeast signal sequence trap. However, many other chapters are of equal utility.

The book as a whole is an extremely useful desk reference for the engaged researcher in the field and provides an excellent snapshot of the state of play in 2005, although, as with many edited texts, the quality of individual chapters varies.

These various recent offerings on time are worth the time of many readers. Given the rapid rate of discoveries in chronobiology and their importance to so many human endeavors, let us hope there will be more such useful volumes in years to come.

Vincent M. Cassone (e-mail: vmc@mail.bio.tamu.edu) studies comparative aspects of biological clock function at Texas A&M University. His research interests are the evolution of biological clocks and the mechanisms by which the vertebrate clock regulates behavior.

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