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(U) HARVARD MEDICAL SCHOOL BOSTON MA M C MOORE-EDE
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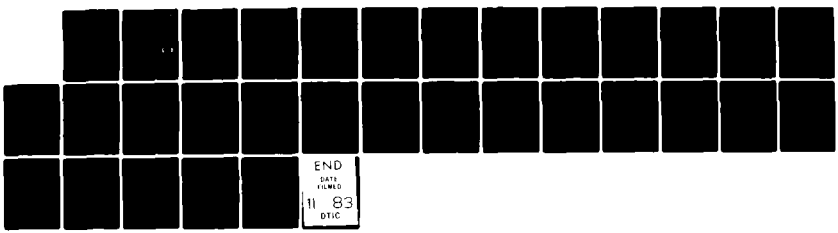

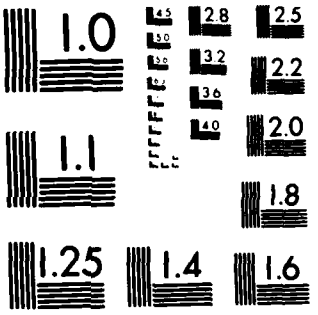

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This is the Final Scientific Report on AFOSR Grant 81-0133 which supported the Satellite Symposium on the mathematical modeling of circadian systems which was held on June 21, 1981 in conjunction with the Annual Meeting of the Association for the Psychophysiological Study of Sleep (APSS) in Cape Cod, Massachusetts. It was considered important that a meeting on the mathematical modeling of the circadian (approximately 24 hour) timing system be held at this time. In the last few years, prior to the Satellite Symposium, a large number of mathematical

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20. ABSTRACT (Continued)

models have been developed but this activity has usually been isolated so that there is none of the normal interaction that should occur between those who have thought most about this problem. Proponents of these models belong to different scientific disciplines and normally never meet at national or international meetings. For this reason, the APSS was a particularly appropriate choice as sponsor of this meeting because of the focus at their meetings on the circadian timing of the sleep-wake cycle and related biological rhythms and the relative sophistication of the audience. The Satellite Symposium brought these investigators together enabling their various proposed models to be critically reviewed and their strengths and weaknesses in predicting periodic biological phenomena to be fully understood. The papers of each participant and an edited transcription of the discussion which followed will shortly be published as a symposium volume by Raven Press, New York. This book will serve as an important source for all those who are concerned about the temporal organization of human and animal behavior and physiology.

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DEPARTMENT OF THE AIR FORCE

GRANT AFOSR-81-0133

SYMPOSIUM ON

MATHEMATICAL MODELING OF CIRCADIAN SYSTEMS

FINAL SCIENTIFIC REPORT

MAY 1, 1981 - APRIL 30, 1982

Submitted By:

Martin C. Moore-Ede, M.D., Ph.D.
Department of Physiology and Biophysics
Harvard Medical School
25 Shattuck Street
Boston MA 02115

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I. GRANT OBJECTIVES

Grant AFOSR-81-0133 was awarded by the Department of the Air Force in support of a proposed one-day satellite symposium on the mathematical modeling of circadian systems, to be held in conjunction with the meeting of the Association for the Psychophysiological Study of Sleep in Cape Cod, Massachusetts, between 17 to 21 of June, 1981. The purpose of the satellite symposium was to present and critically review recently developed mathematical models of the circadian timing system, with particular emphasis on human sleep-wake organization, as designed by various investigators from both the United States and abroad who would be invited to participate.

Through the AFOSR grant, travel and housing expenses would be defrayed for participants in the proposed satellite symposium, as well as support for publication of a volume which might result from this conference.

II. BACKGROUND

A. Circadian Timing Systems: Mechanisms and Medical Implications

Many aspects of the metabolism and behavior of living organisms are periodic. In the last twenty years, particular attention has been paid to the circadian (approximately 24 hour) rhythms which occur in many physiological functions. Indeed, in mammals virtually every physiological variable that can be measured shows circadian rhythmicity, reaching a maximum at one particular phase of the day, and a minimum at another. Examples of such rhythms include the sleep-wake cycle, and the rhythms of body temperature, plasma cortisol concentration, plasma growth hormone concentration, renal electrolyte excretion, as well as such behavioral variables as psychomotor performance and alertness. Each of these circadian rhythms is endogenous to the organism for they persist with a "free-running" period usually slightly different from 24 hours when the animal is placed in a constant environment with no time cues. The properties of these endogenous rhythms have been extensively documented over the last twenty years.

In 1972, a cluster of neurons in the hypothalamus, the suprachiasmatic nuclei (SCN), was identified as a key pacemaker of the mammalian circadian timing system. When the SCN are destroyed, circadian rhythms in a variety of physiological and behavioral functions are lost. This finding has stimulated a rapid increase in research activity on the anatomy and physiology of the circadian timing system. It has become apparent that it is a multioscillator system with oscillators in different tissues being coupled by neural and endocrine pathways. For example, certain circadian rhythms (such as body temperature in squirrel monkeys) persist

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after SCN lesions are placed, confirming that circadian oscillators exist in locations other than the SCN.

It is now apparent that there are widespread medical implications of circadian rhythmicity. For example, there are circadian rhythms in susceptibility of animals to trauma, bacterial toxins, and to drugs. Many pharmacological agents have markedly different effects depending on the time of the circadian cycle at which they are administered, and this is now contributing breakthroughs in such areas as cancer chemotherapy.

The demands of modern society have focused attention on the circadian timing system and the problems of disparity between internal and external time. With the widespread use of shift work schedules (approximately 20% of workers in industrialized nations) and the large numbers of individuals who are daily transported across multiple time zones by jet aircraft, the limits of the timing system of the body are becoming readily apparent. The problem underlying the "jet-lag syndrome" is that the circadian timing system shifts only relatively slowly after a shift in the environmental day-night cycle. Thus there are several days of desynchronization of the individual's physiology with respect to environmental demands and stimuli. More serious problems occur with repeatedly shifting schedules (e.g. rotating shift work schedules or the crews of commercial aircraft on international schedules). Indeed, animal studies have shown decreased longevity with chronic exposure to such schedules.

It is also becoming apparent that there are a number of specific malfunctions of the circadian timing system (just like any other system of the body) which show up as clinical syndromes. In the last few years, several of these have now been well-documented including a) the failure to entrain to environmental time cues, b) the ability to sleep only at an inappropriate phase of the day, a syndrome called Delayed Sleep Phase Insomnia. Many of these pathological disorders have been presented in the last few years at the meetings of the Association for the Psychophysiological Study of Sleep (APSS). This is one of the reasons why it would be so valuable to hold this particular symposium in conjunction with the APSS.

B. Contribution of Mathematical Modeling to the Study of Circadian Systems

The identification of endogenous oscillating systems within the body has led to a search for useful analogies to aid in the conceptualization of possible mechanisms that could account for the biological phenomena being observed. Hence there has been an increasing interest of circadian physiologists in oscillator theory--a subject which has long been the province of the mathematician and engineer. Just as the engineer has a need to understand oscillations in complex systems, so now too does the biologist, and yet there

is very little in the biological literature to aid in this effort.

Since 1960, mathematical models of coupled oscillators have been developed by a number of investigators which have proved useful and necessary in predicting and quantifying the complex behaviors of these biological timing systems. However, it has become increasingly clear that any model of a physiological system which neglects to consider its periodic nature may have major limitations. Accordingly, it was felt important and timely to hold a meeting on the mathematical modeling of the circadian timing system.

III. PLANNING OF THE SYMPOSIUM

Prior to this time, although a large number of mathematical models had been developed by various investigators, this activity had usually been isolated, precluding the normal interaction and exchange that should occur between those who have thought most about this problem. Since proponents of these models belong to different scientific disciplines, they rarely, if ever, meet at national or international meetings. Our proposed Satellite Symposium would overcome this deficit and bring the investigators together, ensuring that their various models would be critically reviewed and their strengths and weaknesses in predicting periodic biological phenomena fully understood.

The Association for the Physiological Study of Sleep (APSS) was considered a particularly appropriate choice as sponsor of this meeting because of the focus at their meetings on the circadian timing of the sleep-wake cycle and related biological rhythms and, concomitantly, of the relative sophistication of the audience. (It should be noted here that the APSS has undergone a change of name and is now known as the Sleep Research Society.)

Because the Satellite Symposium was to be held at the conclusion of the meeting of the APSS, all taking part would benefit from exposure to the state-of-the-art discussion of the biological properties of circadian phenomena that was programmed for the APSS meeting, and would interact with other circadian biologists present and so focus the discussion.

The following panel members were invited to take part in the Satellite Symposium as researchers who had made significant contributions to the modeling of circadian systems:

Dr. Serge Daan
Zoologisch Laboratory der Rijksuniversiteit te Groningen
Kerklaan 30, Postbus 14
Haren (Gron.), The Netherlands

Dr. Gerhard Dirlich
Max-Planck-Institut für Psychiatrie
Kraepelinstrasse 10
D-8000 Munich 40
Federal Republic of Germany

Dr. Charmane I. Eastman
University of Chicago Sleep Laboratory
5741 South Drexel
Chicago IL 60637

Dr. James T. Enright
Scripps Institution of Oceanography
University of California, San Diego
La Jolla, California 92037

Dr. Richard E. Kronauer
Division of Applied Sciences
Harvard University
Cambridge MA 02138

Dr. Rütger Wever
Max-Planck Institut für Verhaltensphysiologie
8131 Erling-Andechs
Federal Republic of Germany

Brief biographies of each invited speaker are attached as Appendix A.

Prior to the Satellite Symposium in order to maximize the critical review of the various models, each participant was requested to submit a preliminary manuscript to the Chairmen by 21 February 1981. The manuscripts were then distributed to the other speakers who were asked to respond by 21 April 1981 with a series of queries or comments. These responses, in turn, were again circulated to all so that, by the time they arrived at the meeting, each individual taking part in the presentation would have an understanding both of the models of the other participants and of the comments and criticisms that had been raised about his own model. This procedure worked extremely well since it ensured a most productive interaction at the meeting itself.

IV. CONFERENCE: MATHEMATICAL MODELING OF CIRCADIAN SYSTEMS

The APSS Satellite Symposium entitled "Circadian Timekeeping: Mathematical Models of a Biological System" was held on Sunday, June 21, 1981, at Dunfey's Hyannis Hotel in Cape Cod, Massachusetts.

Co-Chairmen were:

Charles A. Czeisler, Ph.D., M.D.
Department of Medicine
Brigham and Women's Hospital
75 Francis Street
Boston MA 02115, and

Martin C. Moore-Ede, M.D., Ph.D.
Department of Physiology and Biophysics
Harvard Medical School

whose tasks were to oversee adherence to relevance of data, to elicit issues and contrast them, and to challenge speakers on physiologic data.

At the meeting in the conference room of the Dunfey Hyannis Hotel, use was made of the same facilities that had been provided for the preceding APSS meeting. Projection facilities were provided, but simultaneous translation was not considered necessary since all participants spoke English fluently.

Each speaker was given forty minutes to provide an overview of his model for the general audience and to answer the specific problems and questions raised in writing by other participants. There then followed twenty minutes of open discussion with questions raised from the floor both from the other speakers and the general audience with the aim of focusing on the strengths and limitations of each model and the predictions it made for useful experiments to be conducted by the biological community directly on biological systems.

The meeting was conducted in two sessions with speakers presenting and discussing their work at the first session. After a break for the midday meal and informal discussion, the balance of the scheduled speakers then presented their papers. The entire meeting was recorded on tape, and the discussion of each paper subsequently transcribed and edited.

The anticipated attendance at the Satellite Symposium was fully realized with 78 registrants present (see list in Appendix B). Many attendees were young researchers with a keen interest in circadian rhythm modeling who undoubtedly benefitted from interaction with established investigators, which will be of importance for future developments in this field.

V. RESULTS

Since the entire symposium, including each speaker's paper and the

edited discussion of it which followed from the floor, was to be published as a volume, overtures were made to various publishers. The offer from the medical and scientific publishing house of Raven Press, New York, was accepted since they could produce a book at a reasonable per page charge. This would ultimately ensure a hardbound book with an approximate cost of $20. which kept the volume to a moderate price thus making it accessible to a wide audience of individuals, both professionals and students, concerned with the temporal organization of human and animal behavior.

VI. SUMMARY

Publication is imminent of this book entitled "Mathematical Models of the Circadian Sleep-Wake Cycle." Galley proofs have been edited by each author and returned to the Raven Press. Included here, as Appendix C, are summations by each author which constitute the eight chapters in the book.

There remain to be done by the publisher the typesetting of the preliminary pages (a copy of which is attached as Appendix D), and preparation of a subject index.

When received, a copy of this volume will be forwarded to the Department of the Air Force as complement to this Final Scientific Report.

APPENDIX A

BIOGRAPHIES OF SYMPOSIUM PANEL

DR. MARTIN C. MOORE-EDE, CHAIRMAN

Dr. Moore-Ede has investigated the structure and function of the circadian timing system, particularly in non-human primates and in man. His particular efforts have been to identify the anatomical location of the individual oscillators of the circadian timing system and to determine the nature of the neural and endocrine modes of information transmission that ensure the internal synchronization of the system. He has published over 65 papers on the anatomy and physiology of mammalian circadian systems.

His role in the conference was to ensure that the key biological issues were addressed, that the strengths and weaknesses of each model were accurately conveyed, and to bring out the issues and contrast the positions held by the different speakers.

Key Reference: M.C. Moore-Ede, F.M. Sulzman and C.A. Fuller. *The Clocks That Time Us: Physiology of the Circadian Timing System.* Cambridge, Mass.: Harvard University Press, 1982.

DR. CHARLES A. CZEISLER, CO-CHAIRMAN

Dr. Czeisler has been one of the most active investigators of the organization and function of the human circadian system in the past few years. In collaboration with Dr. Elliot Weitzman and Dr. Moore-Ede, he set up the human isolation facility at Montefiore Hospital in New York and, as a result of that effort, he has contributed a number of significant new concepts concerning the organization of the human system. He is extraordinarily widely versed in the literature and is an extremely perceptive and insightful young scientist who kept the discussions of this meeting focused on the key issues.

Key Reference: C.A. Czeisler, E.D. Weitzman, M.C. Moore-Ede, J.C. Zimmerman and R.S. Knauer. Human sleep: its duration and organization depend on its circadian phase. *Science 210:* 1264-1267, 1980.

DR. GERHARD DIRLICH

Dr. Dirlich has pursued the question of whether stochastic processes rather than a discrete pacemaker could generate the human circadian rhythms. He has published a number of articles that relate to these issues and provided provocative alternatives to some of the more accepted models. He contributed greatly to a stimulating discussion of what can and what cannot be deduced from the biological evidence.

DR. RÜTGER WEVER

Dr. Wever has undertaken the most extensive studies of the human circadian system in isolation conditions working at the Max-Planck-Institut für Verhaltensphysiologie in collaboration with Dr. Jürgen Aschoff. Over the years of his work in circadian physiology, Dr. Wever has made a series of contributions to the modeling of circadian oscillators. His work has culminated in the publication in 1979 of a book on the circadian timing system of man. Most of his work in the past has been concerned with the interaction between the zeitgeber and the circadian rhythm generator, but he has become increasingly interested in the internal interactions between coupled oscillators in the circadian timing system and has explored a number of ways in which they can be simulated.

Key References:

Wever, R. Zum Mechanismus der biologischen 24-Stunden-Periodik. *Kybernetik 1:* 139-154, 1962.

Wever, R. Ein mathematisches Modell für biologische Schwingungen. *Zeitschrift für Tierpsychologie 21:* 359-372, 1964.

Wever, R. Virtual synchronization towards the limits of the range of entrainment. *J. Theor. Biol. 36:* 119-132, 1972.

Wever, R. *The Circadian Timing System of Man.* Springer-Verlag, New York, 1979.

DR. JAMES T. ENRIGHT

Dr. Enright has been an active investigator of circadian phenomena for over fifteen years. His development of a mathematical model of the circadian system has culminated in publication of a book which considers the substructure and dynamics of the circadian pacemakers underlining the rest-activity cycle. He proposed a model which views the pacemakers as a multicellular ensemble in which random processes and threshold effects are critical to system behavior. He argues that interactions within such a pacemaker can account for the temporal precision of circadian rhythms without making unrealistic assumptions about the behavior and properties of single neurons, and can account naturally and in detail for a large body of experimental data on influences of lighting regimens on animals.

Key Reference: J.T. Enright. *The Timing of Sleep and Wakefulness.* Springer-Verlag, New York, 1979. 263 pp.

DR. RICHARD E. KRONAUER

Dr. Kronauer has had considerable experience over many years in oscillator theory with particular applications to problems in engineering and physics. Over the last twelve years, he has focused on biological oscillators including oscillating neural circuits, respiratory pacemakers, and then over the past six years has collaborated with Dr. Moore-Ede and Dr. Czeisler in the analysis and modeling of the human circadian system. As a result of these efforts, a coupled Van Der Pol oscillator model has been developed which simulates extremely closely many of the normal and pathological features of the human circadian system. This work has interacted closely with the human isolation studies which were conducted in New York in Dr. Elliot Weitzman's laboratory by Dr. Czeisler. Dr. Kronauer's model has made very specific predictions about the mode of coupling and can explain some findings that until now were anomalous from not only Dr. Weitzman's laboratory, but also from Dr. Wever's experiments on humans in temporal isolation in West Germany.

Key References:

R.E. Kronauer, C.A. Czeisler, S.F. Pilato, M.C. Moore-Ede and E.D. Weitzman. Mathematical model of the human circadian system with two interacting oscillators. *Am. J. Physiol. 242 (11):* R3-R17, 1982.

R.E. Kronauer, C.A. Czeisler, S.F. Pilato, M.C. Moore-Ede and E.D. Weitzman. Mathematical representation of the human circadian system: two interacting oscillators which affect sleep. In: M.H. Chase, Ed., *Sleep Disorders: Basic and Clinical Research.* New York: Spectrum Publications, Inc., 1983, pp. 173-194.

DR. SERGE DAAN

Dr. Daan has worked with Dr. Colin Pittendrigh at Stanford University on the properties of circadian systems in both insects and mammals, culminating in a series of papers which were a landmark in the field (*J. Comp. Physiol. 106:* 223-355, 1976). Concurrently with this effort, Dr. Daan, together with Dr. Berde, developed a coupled oscillator model to describe the rodent circadian system which is particularly useful in describing some of the characteristics of splitting of rat activity rhythms. He has also used this model to explain quantitatively the mechanisms of entrainment by the phase response curve of individual mammalian species.

Key Reference: S. Daan and C. Berde. Two coupled oscillators: simulations of the circadian pacemaker in mammalian activity rhythms. *J. Theor. Biol. 70:* 297-313, 1978.

DR. ARTHUR T. WINFREE

Dr. Winfree has been concerned with the modeling of circadian systems for over ten years and has contributed a large number of publications on this subject. He has been an inventive and prolific investigator who has contributed a number of important new concepts which enable the understanding of how biological oscillator systems function, particularly in response to environmental light inputs. Recently he has turned his attention to the question of how to model the human circadian system.

Key References:

A. Winfree. *The Geometry of Biological Time*. Vol. 8 of the Biomathematics Series. Springer-Verlag, New York, 1980.

A. Winfree. Phase control of neural pacemakers. *Science 197:* 761-762, 1977.

APPENDIX B

SYMPOSIUM PARTICIPANTS

Elliott Albers
Richard P. Allen
Bernard Bergmann
Michael Bonnet
Alexander Borbély
Ziad Boulos
E.N. Brown
Scott Campbell
Stephen Coburn
Charles Czeisler
Serge Daan
Gerhard Dirlich
Sharon Eagan
Charmane Eastman
Leland N. Edmunds
Jim Enright
Jeff Fookson
Lee Friedman
Philippa Gander
Marcia Gilliland
J.C. Gillin
Paul Glovinsky
R. Curtis Graeber
Gerard Groos
Kristyna Hartse
Jim Horne
David Hudson
Pam Hyde
Sheldon Kapen
Hiroshi Kawamura
Toshimori Kobayashi
Richard E. Kronauer
David Kupfer
Mette Larsen
Dietrich Lehmann
Juan-Carlos Lerman
Alfred J. Lewy
Franklin Lue
Reimer Lund
William Mason
Robert McCarley
Dennis McGinty
Dennis Meadows
Merrill M. Mitler
Margaret Moline
Martin Moore-Ede
Dan Mullaney
Ross H. Pastel
Nathan Phillips
Sam Pilato
Charles P. Pollak
Ruth Reinsel
Daniel L. Rickett
Joseph Ronda
Roger Rosa
Richard S. Rosenberg
Jesse Salb
Evelyn Satinoff
Hartmut Schulz
Deborah Sewitch
Joseph I. Shaffer
Jerry Siegel
Joseph Takahashi
Yasuro Takahashi
Philip Teitelbaum
Don Tepas
Michael J. Thorpy
Irene Tobler-Kost
Barry Trencher
Johanna van den Hoed
Ennio A. Vivaldi
Thomas Wehr
Elliot Weitzman
Rütger Wever
Art Winfree
Jacqueline Winter
Anna Wirz-Justice
Janet Zimmerman

APPENDIX C

Summations of chapters by individual authors in " Mathematical Models of the Circadian Sleep-Wake Cycle"

Chapter 1: "Mutual Excitation..." by J.T. Enright

Chapter 2: "Toward a Mathematical..." by R.A. Wever

Chapter 3: "Are Separate Temperature..." by C. Eastman

Chapter 4: "Modeling Principles..." by R.E. Kronauer

Chapter 5: "Circadian Gating..." by S. Daan and D. Beersma

Chapter 6: "Looking at Human..." by G. Dirlich

Chapter 7: "Exploratory Data..." by A.T. Winfree

Chapter 8: "Sleep Duration..." by J.T. Enright

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C A Czeisler Raven Press New York © 1983

Mutual Excitation of Damped Oscillators and Self-sustainment of Circadian Rhythms

J. T. Enright

Scripps Institution of Oceanography, University of California, La Jolla, California 92093

When an animal is placed under constant environmental conditions that are appropriate for the expression of endogenous circadian rhythmicity, the rhythm will usually persist indefinitely without any appreciable damping. This property of circadian systems, known as self-sustainment, is so general that when a circadian rhythm is seen to damp out under a given set of circumstances, one is apt to suspect that the wrong experimental conditions have been chosen, i.e., too cold, too much light, inappropriate monitoring equipment, and so on. It therefore seems entirely appropriate that the various sorts of single-oscillator models that have been proposed for circadian systems have embodied the capacity for self-sustainment as an essential characteristic. From a mathematical point of view, this represents a strong assumption; it focuses our attention on a relatively restricted set of oscillatory systems to the neglect of the much broader class of mechanisms and processes that can give rise only to damped oscillations.

As the modeling of circadian systems has become more sophisticated, many researchers have been led by their experimental data to propose two-oscillator models. In this case as well, it seems perfectly natural to assume that at least one of those oscillators is capable of persistent, self-sustained rhythmicity (2,10,11). Building on that tradition, it has also become customary, when proposing formulations for larger ensembles of mutually coupled oscillators, to assume that each element in the array has the capacity for self-sustainment (4,5,8,14,15). The question this article addresses is whether or not that assumption remains necessary in a multioscillator model. Suppose, instead, that each oscillator of a mutually coupled group, if it could be observed in isolation, would show only strongly damped rhythmicity: Given an impulse that sets it in motion, its rhythm will completely decay within a few cycles. Suppose, further, however, that when an oscillator is in resonance with the mutually synchronized activity of other elements in the ensemble, it receives a "push" that enhances its amplitude. Can the ensemble then show self-sustained rhythmicity? This question has both relevance and importance for circadian systems, but I will not initially invoke any evidence whatever on that point, postponing such matters to the Discussion.

Toward a Mathematical Model of Circadian Rhythmicity

Rütger A. Wever

Chronobiology Laboratory. Max Planck Institute for Psychiatry, D-8138 Andechs, West Germany

Mathematical Models of the Circadian Sleep-Wake Cycle, edited by M. C. Moore Ede and C. A. Czeisler Raven Press, New York © 1983.

The efficiency of a model describing biological phenomena, such as circadian rhythmicity, can be measured by the ratio between the basic preconditions put into the modeling process and the predictions deduced from different model applications and confirmed by the results of biological experiments. No single model can describe all the different aspects of a biological phenomenon equally well; rather, there will be several models complementing one another, each of which will describe specific aspects of the system. In order to critically examine any model, the basic preconditions used for constructing the model should be listed, and the predictions tested through biological experimentation. If possible, these predictions should be formulated quantitatively.

Models have been developed that simulate the dynamics of biological systems; these are usually "hardware" models that consist of mechanical, hydraulic, or electrical devices. Their mechanisms have, in principle, no direct relation to biological mechanisms. Such models are rarely flexible enough to simulate all biological conditions, and applications of such models run the risk of inappropriately representing biological mechanisms. Other models are based on features of the biological systems under consideration, e.g., on neuronal interconnections, properties of membranes, or structural transformations. These simplifications of the structural processes of the biological phenomena under consideration can lead to a more thorough understanding of them. However there is a danger in such models that correlation between model predictions and experimental data may suggest a similar correlation between the structural mechanisms of the model and the biological system; knowledge of the mechanisms underlying circadian rhythmicity is as yet insufficient to apply these hardware models effectively.

Thorough understanding of the dynamics of biological processes is a precondition for subsequent analysis of their underlying mechanisms. It is therefore advantageous to use "software," or mathematical, models that describe these dynamics without assuming their anatomical basis. Of relevance here are kinetic models that render the dynamics of the system; special wave shapes are then the result of computations describing the behavior of the system under varying external conditions. The mathematical expression of such a dynamic type of model is a differential equation, and the expressions of peculiarities in biological results are nonlinearities.

A mathematical model describing circadian rhythmicity will be presented based on a simple differential equation. The method of deducing the model is that of trial and error. Alternative models and modifications are formulated and tested, based on relevant biological experiments, in successive iterative steps (31). After establishing the relevant model equations, solutions of this model will be presented, as computed under varying external conditions, constituting predictions for the behavior of the biological system under various environmental conditions. Different types of equations have the capacity to describe correlations between separated rhythm parameters and experimental conditions when the coefficients are selected properly. More powerful is the prediction of summarizing multifold correlations and, in particular, of interdependences between different rhythm parameters in both the steady state and during transient states. Therefore, of special relevance is the determination of many different rhythm parameters in both the mathematical analysis and the biological experiment.

Mathematical Models of the Circadian Sleep-Wake Cycle edited by M. C. Moore-Ede and C. A. Czeisler. Raven Press, New York © 1983.

Are Separate Temperature and Activity Oscillators Necessary to Explain the Phenomena of Human Circadian Rhythms?

Charmane Eastman

University of Chicago Sleep Laboratory, Chicago, Illinois 60637

TWO TYPES OF MULTIPLE-OSCILLATOR THEORIES

It is generally accepted that circadian systems are composed of multiple oscillators. This chapter describes a single-oscillator model of human circadian rhythms. This does not necessarily represent a contradiction. The potential for confusion stems from the fact that there are two different types of multiple-oscillator theories based on different types of experimental evidence.

In the first type of theory, multiple oscillators interact to control a single rhythmic variable, usually locomotor activity (17,18,23,24,28,35–38,42, 50,51). Evidence for this type of organization is provided by various sets of data, including the "splitting" of locomotor-activity rhythms in various animal species (37), the breakdown of circadian rhythms after lesions of the suprachiasmatic nuclei (SCN) (38,42), coexisting free-running and food-entrained activity rhythms in rodents (12), and the demonstration of circadian rhythms in isolated mammalian organs and tissues (13,26,39,43).

In the second type of multiple-oscillator theory, separate oscillators are responsible for the control of different physiological and behavioral circadian rhythms. The strongest evidence for this type of multiple-oscillator organization has been "spontaneous internal desynchronization" in the human, which has been attributed to the uncoupling of separate temperature and activity oscillators (9,10,30,34,48,49) (See R. E. Kronauer, *this volume*).

The single-oscillator model presented here is an alternative to the second type of multiple-oscillator theory, in that all the various circadian rhythms are controlled by the same circadian oscillator. This model does not dispute the multiple-oscillator organization proposed by the first type of multiple-oscillator theory; in fact, the single oscillator may itself be composed of multiple oscillators (23,24). However, the model demonstrates that spontaneous internal desynchronization, as well as other human circadian phenomena, can be explained with the single oscillator remaining intact, i.e., without a desynchronization or breakdown of the circadian system into its component parts.

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Modeling Principles for Human Circadian Rhythms

Richard E. Kronauer

Division of Applied Sciences, Harvard University,
Cambridge, Massachusetts 02138

The objective of this chapter is to present a review of features of human circadian rhythms that must affect any attempt to model the human circadian system. It is unfortunate but true that direct physiological knowledge of this system is so rudimentary as to afford almost no basis for model construction. This means that models are merely mathematical constructs that serve to organize our view of system performance. One model has an advantage over another only if it matches more data features or is more economical in form.

ESSENTIAL MODEL COMPLEXITY

Perhaps the most important single experimental observation is that the sleep–wake cycle and the body-temperature rhythm of the free-running human can exhibit two different circadian periods at the same time (1). Furthermore, these periods do not appear to be related by any ratio of low integers, so that one oscillation cannot be supposed to derive from the other by any relatively simple frequency multiplication/demultiplication scheme. Within the family of models described by ordinary differential equations it is possible to generate two incommensurate oscillating frequencies with a third-order system (2), but only when special care is exercised. The ordinary third-order system generates frequencies that are rationally related. The mathematical distinction between these two situations is that in the former the limit set is a toroidal surface, whereas in the latter the limit set is a line that spirals about the torus and ultimately closes in a finite number of cycles. If one wishes to avoid mathematical oddities and still retain the differential-equation form, it makes sense to advance to the fourth-order system. This also permits a kind of parity between the two rhythms in that each can be viewed as originating principally in its own second-order system, while mathematically identifiable mechanisms generate interactions between these two subsystems. Thus, whereas a general fourth-order system is intrinsically more complex than a third-order system, the reduced fourth-order system represented by two coupled second-order systems can actually be the more economical form. Furthermore, the idea that the full system is a conjunction of two oscillatory subsystems is given physiological support by studies in which lesions destroying the suprachiasmatic nuclei (SCN) in squirrel monkeys disrupt the rest–activity cycle but leave a persisting body-temperature rhythm (3). Other experiments in rats have shown that knife cuts in the hypothalamus that isolate the SCN neurally do not abolish circadian rhythmicity within the SCN (4). Thus, the SCN appear to act as a discrete pacemaker, but other oscillating centers also exist in the organism. When the sleep–wake cycle and body-temperature rhythm show different circadian periods, the two subsystems are understood to have lost internal synchrony.

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Circadian Gating of Human Sleep–Wake Cycles

*Serge Daan and **Domien Beersma

*Zoological Laboratory and **Department of Biological Psychiatry, University of Groningen, 9713 EZ Groningen, The Netherlands

CIRCADIAN MODELING: AIMS AND STRATEGY

The temporal organization of behavior in animals, including humans, presents one of the major challenges today for both physiological and functional analysis. Circadian processes play a key role by their function in integrating behavioral organization into the predictable time patterns of the environment on a rotating planet. Two aspects of circadian rhythmicity make its analysis exceedingly complicated: first, the fact that such rhythms behave as self-sustained, nonlinear oscillations (40); second, the recognition that they may be the combined output of several structures (probably a multitude of structures) with such oscillatory capacity, in continuous interaction with each other and with environmental periodicities. This complexity has called for extensive mathematical modeling of the circadian system (19,22,32,38,39,51,53,55) to help in understanding the relationships among empirical results and occasionally to suggest new experimental designs. Of the many models developed, few have been refuted by subsequent experimental analysis. Most models still survive in peaceful coexistence, albeit with fluctuating popularity. Indeed, the mainstream of current physiological research in circadian rhythms is hardly influenced by mathematical simulations. In our view, this is because of a superabundance of parameters in many of the models and because of the absence of specific hypotheses regarding the physiological equivalents of those parameters [with the notable exception of Enright's model (22)]. The physiologist hoping to gain further insight into a system is left without guidance from the mathematicians as to how to test their models. There is a continuing danger of overcomplication and overabstraction in mathematical modeling. A useful model should be minimally complex to account for an existing set of data and maximally specific about what its parameters mean in physiological terms. It should not aim at completeness. The essence of a model's usefulness is in being a simplification of nature, rather than in approaching the complexity of nature itself.

The aim of this chapter is to propose a simple hypothesis of the generation of human sleep–wake rhythms and to follow its complex consequences with the help of mathematical simulations. There are several precursors of this model, and their essential characteristics can be summarized as follows:

Enright (22) designed an elegant model of a circadian pacemaker, composed of a multitude of neuronal elements, each capable of rather imprecise circadian firing oscillations, and together forming an ensemble with very precise self-sustained circadian properties, matching in great detail what is known of vertebrate activity rhythms. Enright's assumption is that the activity of such a pacemaker will directly elicit activity of the organism, whereas rest of the pacemaker will lead to rest of its bearer.

Wever (53), in addition to extensively reviewing the main body of data obtained in 20 years of isolation experiments, proposed a general mechanism for the generation of human circadian rhythms. In this concept, there are at least two self-sustained oscillators involved, one stronger than the other, and

mutually interacting in such a way that they are normally running in synchrony. The strong oscillator controls rhythms in body temperature, the weak oscillator controls rhythms in sleep and wakefulness. The latter oscillator, although normally synchronized to the frequency of the stronger one, may in free-running conditions occasionally dissociate from the latter and exhibit its own frequency.

Kronauer et al. (32) presented simulations based on a mathematical formulation of this model using two coupled Van der Pol oscillators. Using six variable parameters, these authors were able to select values such that a reasonable approximation of observed sleep–wake rhythms was obtained.

Eastman (21; and *this volume*) stated that the assumption of a second oscillator is not required to explain these observed patterns. In her view, occasional spontaneous extensions of the activity time, together with a strong feedback effect of sleep and wakefulness on the single basic oscillator, may be sufficient assumptions to account for the data. If such extensions occur regularly, however, such as in "circabidian" rhythms, Eastman's model also requires a second oscillator (the "phase-shifting oscillator").

Of these models, Enright's is the only one that makes specific assumptions about the (neuronal) structure generating sleep and wakefulness. The other models are abstract, and their specific parameters, insofar as defined, have no obvious physiological counterparts. Enright's model, designed as a general hypothesis of circadian sleep–wake pacemakers, is also the only one at variance with the human data, unless an additional oscillator, controlling body temperature and interacting with the sleep–wake pacemaker, is invoked. None of the models considers the body of knowledge on sleep per se, its temporal structure, and experimental manipulation of sleep. The simple fact that sleep in humans is not fixed exclusively by deterministic oscillatory structures, but may to a large extent be modified consciously, is also rarely considered (however, see C. Eastman, *this volume*).

Dissatisfied with this situation, we have attempted to formulate a minimally complex hypothesis incorporating known homeostatic properties of sleep with a circadian regulatory mechanism. The model formulated and used for simulations to study its behavior invokes a single circadian oscillator or pacemaker, as suggested by Eastman (21; and *this volume*). In addition, it includes a homeostatic regulatory process of sleep and wakefulness with empirically estimated parameters along the lines proposed by Borbély (9). This model, essentially using two free parameters, is able to match most of the available data. We see no evidence in the literature at variance with the model, but we hope it will help to generate such evidence in the future.

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Looking at Human Circadian Phenomena from a Framework of Simple Stochastic Models

Gerhard Dirlich

Max Planck Institute for Psychiatry, 8000 Munich, West Germany

PRELIMINARY REMARKS

Self-sustaining Circadian Rhythm: A Universal Phenomenon?

Research in circadian systems was initiated by the discovery of self-sustaining, approximately periodic rest-activity cycles under constant environmental conditions. Rest-activity cycles have been observed in some animal species under certain experimental conditions, and these are some of the temporally most precise biological rhythms known thus far (4, p. 16).

Such highly regular rest-activity patterns inspired the creation of the term *circadian clock*; moreover, they became the inductive basis of several mathematical models of circadian systems (4,10,13,14). These models are all aimed at explaining recurrent phenomena of high cycle-to-cycle precision; more randomly organized rhythms, which also exist, have to be treated by incorporation of sources of perturbation into the models. This is due to the intrinsic philosophy of these models, according to which circadian rhythms are basically periodic phenomena that under the influence of perturbing factors may appear more or less veiled or distorted (14, p. 99) (see R. A. Wever, *this volume*).

This implicit assumption may lead a layperson in this field of research to the conjecture that circadian fluctuations of life functions in general are distinct and temporally precise phenomena. No expert in the field, however, would deny the fact that this is not true. There are three important factors for the observation of circadian rhythms in constant environments, namely, the chosen species, the given experimental conditions, and the observed life function.

Persistent circadian rhythms can be observed only for certain configurations of these factors; i.e., for a given species, certain species-specific environmental conditions and an appropriate choice of the observed life function are required (5, p. 14).

For example, it has been shown experimentally that rest-activity behavior is not always organized in the form of circadian cycles (8). Moreoever, it has been explored systematically how self-sustainment of precise circadian rhythms

depends on certain environmental variables. For instance, rest–activity cycles persist only when the light intensity lies between critical lower and upper thresholds. With values of the intensity outside this interval, the animals develop more or less irregular rest–activity patterns.

The existence of regular 24-hr fluctuations has been demonstrated in many biological and behavioral variables (13, p. 3). However, despite the vast literature on experiments under constant conditions, our knowledge about circadian rhythms under these circumstances is still limited with respect to the entire spectrum of candidate variables: the majority of investigations in animals have been concerned with the rest–activity behavior; a much smaller amount of data on body temperature is available, and there are relatively few data on endocrine variables. In humans, the observational data comprise the rest–activity cycle, the body temperature, some parameters of the blood-circulating system, some ingredients of blood plasma and urine, and finally some psychometric variables.

Thus, circadian rhythms as distinct and temporally precise phenomena are *not universal, but rather an indication of some special mode of operation* of the biological timing mechanisms in cases of favorable configurations of species, environment, and observed variable. For certain other configurations of these factors it has been demonstrated that the circadian rhythms degenerate in constant environments.

This delimits the validity of oscillator models of circadian systems. They are suitable only for approximately periodic phenomena; they do not allow for the description of aperiodically recurring events.

In this situation it appears attractive to consider the possibility of developing a more general biological theory of the temporal organization of life functions, whose range of validity includes the case of ongoing distinct and precise circadian rhythms as a special case. Some elements of a theory of this kind would certainly have to be borrowed from mathematics, just like the concept of oscillators, which was borrowed from physics. This chapter is concerned with a class of mathematical models that might be useful for such an approach. They are based on the concept of stochastic processes. This type of model is suitable for the description of irregular, random phenomena, as well as for almost perfectly periodic rhythms. Thus, in contrast to oscillator models of the circadian clock, periodicity is here not an assumption but a property resulting from a special choice of model parameters or the special structure of the model.

Exploratory Data Analysis: Published Records of Uncued Human Sleep–Wake Cycles

Arthur T. Winfree

Department of Biological Sciences, Purdue University, West Lafayette, Indiana 47907; and Institute for Natural Philosophy, West Lafayette, Indiana 47906

Everything should be made as simple as possible . . .
but not simpler..
Albert Einstein

I am exploring that limit, in the case of modeling human circadian rhythms by taking the risk that I may err on the side of oversimplification. I shall attempt to redescribe some recordings of human sleep and waking made in several laboratories in the past decade. My objective is to avoid models as far as possible, then to compare only the sketchiest versions of them against published data in order to find out what further elaborations the data seem to require. A first look at the data suggests that under some conditions there may be an interesting discontinuity in the dependence of wake-up time on prior sleep-onset time. This feature may find simple interpretation in terms of circadian variation in a threshold process that initiates wake-up. It may therefore help to clarify the connection between the continuous variables of oscillator models and the discrete events of sleep onset and wake-up. Also, I have observed none of the regularities in the timing of sleep onset that would be expected according to the dozen or so models currently under consideration.

Curious and elusive regularities lurk in records of sleep and wake transition times. Among the most intriguing are the following:

1. Aschoff and Wever (9, and citations therein) have observed that sleep and wake timing need not stay synchronous with the steadier beating of our circadian clock, as reflected in the ups and downs of core temperature.

2. The more recent discoveries by Czeisler (1,2) have shown that there is a natural periodic time base to which to refer human sleep–wake transitions, that the time of awakening depends mainly on the time of prior falling asleep when both times are referred to that natural period, and that something about human sleep–wake behavior is slowly changing week after week and month after month during temporal isolation.

3. Kronauer (6,7) has demonstrated that a two-oscillator analogy descended from that of Wever, with several critical mutations, does reproduce many of the curious regularities of human sleep–wake timing.

Because I am not in a position to do my own experiments in this area, I have chosen to begin with the published data. In particular, it struck me that one feature of the data—a feature that I have often seen in my own experiments and in those of others on invertebrates—has not been emphasized in manuscripts available to me at this writing. Because it may have an important bearing on contemporary interpretations, I would like to draw attention to it here.

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Sleep Duration for Human Subjects During Internal Desynchronization

J. T. Enright

Scripps Institution of Oceanography, University of California, La Jolla, California 92093

Zulley [in Czeisler et al. (2)] and Czeisler et al. (1), in their analyses of data from circadian studies of isolated human subjects, have noted that when a subject shows dissociation of the wake–sleep rhythm from the core-temperature rhythm, there is a systematic relationship between the phase of the temperature cycle at which the subject falls asleep and the duration of the ensuing sleep. On the basis of these data, as well as of his own analyses of similar data, Winfree (*this volume*) has suggested that this quantitative relationship may well involve a discontinuity: If sleep onset occurs at a certain critical phase of the underlying endogenous pacemaker rhythm (as indexed by the temperature cycle), the result can be either a very short sleep or a very long one, with intermediate values being unlikely. A slightly earlier sleep onset leads consistently only to very short sleep, and a slightly later sleep onset only to very long sleep. Both Winfree (*this volume*) and Daan and Beersma (*this volume*) have proposed models, of differing complexity, in which such a discontinuity is predicted to occur because of interactions between a cumulative renewal process and a rhythmically fluctuating threshold. In this chapter I shall outline a possible alternative explanation for that phenomenon.

APPENDIX D

MATHEMATICAL MODELS OF THE CIRCADIAN SLEEP-WAKE CYCLE

Edited by

Martin C. Moore-Ede

Department of Physiology and Biophysics
Harvard Medical School
Boston, Massachusetts

and

Charles A. Czeisler

Department of Medicine
Harvard Medical School
Brigham and Women's Hospital
Boston, Massachusetts

&

Division of Health Policy Research and Education
Harvard University
Boston, Massachusetts

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PREFACE

It may seem presumptuous to attempt to model so fundamental a human behavior as sleep. The time when one falls asleep appears to be so complexly dependent on subjective decisions--how absorbing is the book one is reading; on prior behavior--how hard one worked that day; and on one's constitutional predilection as a "morning" or "evening" person, that the very idea of mathematical description might seem preposterous to all but the most foolhardy.

Yet what led each of us to resort to modeling were the data themselves--the striking regularity of the circadian rhythms in sleep and wakefulness, body temperature, hormone levels and many other functions, especially in environments where human subjects have no knowledge of the time of day. Even more intriguing were the characteristic but complex patterns in the timing of sleep episodes that can develop in environments devoid of 24-hour time cues. Different physiological variables may display different "free-running" non-24 hour periods which interact within the same individual, providing glimpses of internal counterpoint within the human body.

In 1972, a cluster of neurons in the hypothalamus, the suprachiasmatic nuclei (SCN), was identified as a key pacemaker of the mammalian circadian timing system. When the SCN are destroyed, circadian rhythms in a variety of physiological and behavioral functions are lost. This finding has stimulated a rapid increase in research activity on the anatomy and physiology of the circadian timing system. It has become apparent that it is a multioscillator system with oscillators in different tissues being coupled by neural and endocrine pathways.

The identification of endogenous oscillating systems within the body has

led to a search for useful analogies to aid in the conceptualization of possible mechanisms that could account for the biological phenomena being observed. Hence, circadian physiologists have become increasingly interested in oscillator theory--a subject which has long been the province of the mathematician and engineer. Just as the engineer has a need to understand osillations in complex systems, so now too does the biologist, and yet there is very little in the biological literature to aid in this effort.

Attempts to model circadian systems have been made since 1960. However, only a few individuals made serious theoretical efforts until Pavlidis wrote his book, "Biological Oscillators: Their Mathematical Analysis," in 1973. Since that time there has been an intensification of interest in oscillator models which can describe circadian phenomena. Recently, books by Winfree, Enright and Wever, and articles by each of the other contributors to this symposium, have presented coupled oscillator models of the circadian timing system.

These works have represented major syntheses of oscillator theory and physiological evidence with the attempt being made to develop mathematical models of the circadian timing system which are useful in defining experimental questions, and conceptualizing potential mechanisms that may account for the behaviors being observed. They are now making it possible to model many aspects of periodic human and animal behavior. Indeed, it is becoming increasingly clear that any model of a physiological system which does not take into account its periodic nature may have major limitations.

With each of the mathematical models of the circadian timing system that have been proposed, the author has typically presented a <u>prima facie</u> case with little consideration of other modeling attempts. When each model has been presented at a scientific conference, it has usually been presented to an

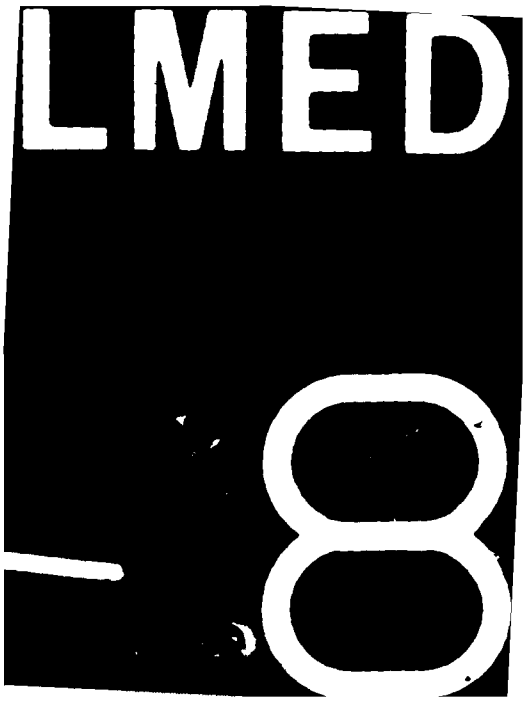
audience which does not include other investigators who have modeled circadian systems. While each model has attracted much interest from biologists who are concerned with the strengths and the failures of prediction of the models, there has usually never been more than one proponent of a circadian mathematical model at any given meeting. It has thus been impossible to get a productive interaction and meaningful debate at such meetings, particularly since the mathematical subtleties are not readily appreciated in a brief presentation.

Hence, the modeling of circadian systems has been an isolated activity with none of the normal interaction that should occur between those who have thought most about a scientific problem. The reason for this is that the proponents of the models belong to different scientific disciplines and normally never meet at national or international meetings. The Satellite Symposium at the Association for the Psychophysiological Study of Sleep, which forms the basis for this volume, brought together the various investigators who have developed models of the circadian system and allowed them to interact in a productive environment where there were also many circadian biologists present who could help focus the discussion on whether the various models depicted the research data gathered in actual experiments.

The meeting was lively and informative. Besides providing a review of the state of the art of circadian modeling, the discussion, which we record at the end of each chapter, provided critical insights into the strengths and weaknesses of each approach. The reverberations of the debate will be heard for many years, and this book should provide a stimulating starting point for all those who wonder what determines when we sleep and when we wake.

Martin C. Moore-Ede
Charles A. Czeisler

Boston, October 1982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