PREFACE

For the past thirty years, due particularly to the fundamental work of Pittendrigh, Aschoff, and Wever, theoretical analysis of circadian rhythms and sleep has gone hand-in-hand with experimental and clinical studies. Circadian rhythms have been investigated at levels ranging from cell fragments to humans, from biochemistry to behavior. This experimental diversity is reflected in a diversity of modeling approaches, several of which are represented in the present volume. One class of models focuses on the circadian sleep and activity cycles of humans. Here, a number of investigators postulate pacemaker systems with two coupled oscillators, while others propose single pacemaker models. Other analyses focus upon the activity patterns of small vertebrates or upon anatomical data and physiological recordings from crucial brain sites, such as the suprachiasmatic nuclei (SCN) or the pineal organ. Mathematical formulations and analyses include nonlinear dynamical systems and stochastic models, as well as computer simulations. The articles in this volume discuss, analyze, and compare these various experimental, theoretical, and mathematical approaches.

Dr. Steven Strogatz carries out a comparative analysis of five models of human sleep-wake and temperature circadian cycles. By so doing he is able to distinguish those properties which are shared by all the models from those properties which critically test the various alternatives. Results from earlier models are tested against two new, simpler "control" models, which give results similar to those of the more complex models. Tests failed by all five systems point to new directions for modeling efforts.

Dr. Domien Beersma, Dr. Serge Daan, and Dr. Derk Jan Dijk also focus on the human sleep-wake cycle. They consider a model with a single circadian pacemaker whose output, process C, regulates preferred intervals for sleep; and a homeostatic process S that increases during wakefulness and decreases during sleep. The authors compare predictions of this model with results obtained using the two-oscillator model proposed by Kronauer and others, and use the model to help understand observed variations in sleep intensity as well as sleep timing.

The model analyzed by **Dr. Richard Kronauer** unites two more traditional modeling approaches. Each of these earlier models has two coupled oscillators. The first type, used primarily in the analysis of data from human subjects, postulates a temperature oscillator and a sleep-wake oscillator. The second type, used primarily in the analysis of data from non-human subjects, postulates a sleep-wake, activity-rest pacemaker whose internal dynamics are described by two oscillators. Dr. Kronauer's three-oscillator model consists of a two-oscillator sleep-wake pacemaker coupled with a one-oscillator temperature pacemaker. Model dynamics are compared with complex wave forms observed in data collected from both human and non-human subjects.

Dr. James Enright and Dr. Arthur Winfree also combine two earlier streams of thought. Dr. Enright has extensively developed, analyzed, and applied a set of models called coupled stochastic systems. Dr. Winfree has investigated various types of phase resetting, including the notion of a phase singularity. In this article, Dr. Enright and Dr. Winfree together study phase singularities in coupled stochastic systems. The results provide better methods for distinguishing between different types of phase resetting and make more precise the notion of phase singularity.

The gated pacemaker model in the article by **Dr. Gail A. Carpenter and Dr. Stephen Grossberg** is derived from an ecological analysis of how a pacemaker adapts to environmental changes. The model is used to analyze a variety of parametric data probing the circadian sleep-wake, activity-rest cycle of mammals. The model's basic pacemaker plays a role which is formally similar to process C described by Beersma, Daan, and Dijk; and the model's homeostatic fatigue signal is formally similar to process S. However, the gated pacemaker model has different features, including testable anatomical and physiological mechanisms and feedback, via the fatigue signal, to the pacemaker. The gated pacemaker is also used to model a different set of data than that modeled by Beersma, Daan, and Dijk.

Dr. Rütger A. Wever begins his article with a review of his pioneering work on one- and two-oscillator models of circadian rhythms. This work anticipated by many years the now widespread use of nonlinear oscillators in modeling biological systems. He traces these models, as well as related multi-oscillator systems, as they have evolved over the years and been applied to the rapidly expanding set of experimental results on circadian rhythms.

The six articles in this volume are based on lectures presented at the Twentieth Annual Symposium on Some Mathematical Questions in Biology. This symposium series seeks to foster communication between experimental and theoretical biologists and to provide a forum for the critical evaluation and comparative analysis of mathematical models in the life sciences. This year's symposium, Modeling Circadian Rhythms, was held on May 28, 1986, in Philadelphia, Pennsylvania, as part of the Annual Meeting of the American Association for the Advancement of Science. It was sponsored by the American Mathematical Society, the Society for Industrial and Applied Mathematics, and Section A of the AAAS.

The AAAS Symposium was planned under the auspices of the AMS–SIAM Committee on Mathematics in the Life Sciences. On behalf of the Committee, I would like to thank those who contributed to the Symposium and the present volume. First among these are the speakers and other authors who provided a lively day of talks and discussions and who recorded their thoughts in the present volume. The staff at the AMS office, notably Ms. Betty Verducci, Dr. James W. Maxwell, and Ms. Virginia Biber were particularly helpful and efficient in carrying out the numerous tasks associated with planning the symposium. We are also grateful to Ms. Phoebe Murdock of the AMS Publications Office, which produces the series Lectures on Mathematics in the Life Sciences. Finally, we would like to express sincere thanks to the National Science Foundation, Division of Mathematical Sciences, for the grant (NSF DMS-85-11456) which funded the Symposium.

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