Lecture Notes on Mathematical Modelling in the Life Sciences

Yoichiro Mori
Benoît Perthame
Angela Stevens *Editors*

Dynamics of Physiological Control

Contributions in Honor of Michael C. Mackey

Springer

Lecture Notes on Mathematical Modelling in the Life Sciences

The rapid pace and development of new methods and techniques in mathematics and in biology and medicine creates a natural demand for up-to-date, readable, possibly short lecture notes covering the breadth and depth of mathematical modelling, mathematical analysis and numerical computations in the life sciences, at a high scientific level.

The volumes in this series are written in a style accessible to graduate students. Besides monographs, we envision the series to also provide an outlet for material less formally presented and more anticipatory of future needs due to novel and exciting biomedical applications and mathematical methodologies.

The topics in LMML range from the molecular level through the organismal to the population level, e.g. gene sequencing, protein dynamics, cell biology, developmental biology, genetic and neural networks, organogenesis, tissue mechanics, bioengineering and hemodynamics, infectious diseases, mathematical epidemiology and population dynamics.

Mathematical methods include dynamical systems, partial differential equations, optimal control, statistical mechanics and stochastics, numerical analysis, scientific computing and machine learning, combinatorics, algebra, topology and geometry, etc., which are indispensable for a deeper understanding of biological and medical problems.

Wherever feasible, numerical codes must be made accessible.

Yoichiro Mori • Benoît Perthame • Angela Stevens
Editors

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Preface

This volume of the Lecture Notes on Mathematical Modeling in the Life Sciences (LMML) is dedicated to Michael Mackey on the occasion of his 80th birthday and is finally published on the occasion of his 82nd birthday.

It is a great pleasure for us to present this collective enterprise.

Michael Mackey is one of the two founders of LMML. With a Bachelor in Mathematics and a PhD in Physiology and Biophysics, he explored the promising and strong connections between mathematical modeling and medicine and biology early on.

His fields of research and his motto:

> "My emphasis is always on biologically realistic mathematical models, careful consideration of laboratory and/or clinical data, and achieving a reasonable concordance between the data and the modeling."

always were and still are central for this series.

Michael Mackey is consistently eager to discuss science concretely and critically, which is nicely reflected also in the contributions to this volume.

These Lecture Notes start with some personal notes about Michael Mackey's career and his research by David Dale, followed by Morgan Craig's article about data-driven models of chemotherapy-induced neutropenia, further explaining Michael Mackey's contributions and his collaborators' toward understanding this side effect of cytotoxic chemotherapy.

Then Albert Goldbeter stresses the ubiquitousness of oscillations in biological systems, and how multiple layers of regulation by feedback loops and the cooperativity of biological processes provide the sources of nonlinearity responsible for the onset of oscillatory behavior.

In his contribution about mathematical models of heterogeneous stem cell regeneration, Jinzhi Lei focuses on primary strategies for describing cell division in biological systems and on methods for modeling Waddington's epigenetic landscape. These are fundamental steps to understand tissue development and tumor progression.

Pauline Mazel, Nicolas Foray, and Laurent Pujo-Menjouet describe the effect of irradiation and antioxidants in cells affected by Alzheimer's disease, focusing on ATM kinase as a pivotal protein in the cellular response to genotoxic stress, playing a crucial role in the recognition and repair of DNA double-strand breaks.

In his article about ergodic and chaotic properties in biological models Ryszard Rudnicki discusses two classes of mathematical models, one describing, e.g., the change of population size in successive generations, and the other being partial differential equations, e.g. space-structured models or describing maturity-distribution of precursors of blood cells.

Moisés Santillán reviews mathematical models for quantitative insight into glucose regulation and addresses new challenges such as integrating glucose regulation into whole-body regulatory networks and unraveling long-term compensatory mechanisms.

Last but not least, John Milton and Tamás Insperger explain why a stick balanced at the fingertip falls, although from the mathematical point of view, the upright position of an inverted pendulum can be fully stabilized by time-delayed feedback.

This volume would not have been possible without the essential work of referees, to whom we are very grateful.

Here's to you Mike, in recognition of your extra-ordinary impact on the "mathematics in the life sciences" community.

We are all wishing you many more healthy and happy years to come!

Philadelphia, PA, USA — Yoichiro Mori
Paris, France — Benoît Perthame
Münster, Germany — Angela Stevens
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Contents

Mike and Me Since 1973: A Review of a Long Friendship and Research Relationship

David C. Dale

Michael Mackey and I have known each other for a long time! He was a graduate student and received his Ph.D. in Physiology from the University of Washington (UW) in 1968, now my academic home. Mike reports that he got his inspiration to study the dynamics of cell growth at the UW from a fellow graduate student, Dr. John Combs [1]. We both began working at the National Institutes of Health (NIH) in 1968 but we did not know each other then. At that time the US had an ongoing universal military draft. I, like Mike, saw benefit for my family and my career if I if I got a job at the NIH rather than going to the war in Vietnam. At the NIH Mike began studying the classic cell cycle, focusing on the rodent mammary tumor model as proposed by Burns and Tannock [2, 3].

I landed a job at the NIH Clinical Center in the Laboratory of Clinical Investigation of the National Institute of Allergy and Infectious Diseases (NIAID) under its new director, Dr. Sheldon Wolff. Shelly, as we all called him, was a visionary person who wanted to investigate every reason people have for susceptibility to infections, i.e., diseases that are often associated with recurrent fevers. One of my first patients had a rare disease that causes recurrent fevers, a disease called "cyclic neutropenia." One of the early questions was how to be sure about the diagnosis. I thought, if we just had enough serial blood counts, we could know if there was a neutrophil cycle. Because we had research beds and could invite patients to stay for long periods of time, we asked patients to stay for several weeks at the NIH Clinical Center to observe their health and have blood samples drawn at the same time every day to see if there was a regular pattern of fluctuations in their blood cell counts. I was interested in mathematics and knew a little, but I recognized that I would need help in analyzing the data to look for periodicity. At that time, I was lucky to have made

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a lasting friendship with the Institute's statistician, Dr. David Alling. He taught me about periodicity and the Lomb periodogram, and we began to work together.

It was quite fortuitous that at just about this time, researchers at Washington State University discovered that grey collie dogs, purebred collies with a grey coat rather than a true brown or black, died soon after birth due to infections [4]. Serial blood cell counts showed that there was an apparent cycle of blood neutrophils and the severe infections always coincided with severe neutropenia [4]. Shelly helped me find collie breeders who were concerned about the dying grey puppies. We created a home for these puppies at the NIH, and I became their personal physician! I cared for them with the help of many other physicians, researchers, veterinarians, and technicians and studied their disease as a model for human cyclic neutropenia for the next 40 years [5, 6]! One distinctive feature of the collies' cyclic neutropenia was the cycle length. In humans it was almost always about every 21 days, however, in the grey collies it was every 13 days [7, 8]. Bone marrow studies showed that there were regular periodic changes in the formation of neutrophils in the bone marrow in both the human and the canine form of the disease. Consistently, the marrow showed periodic interruption followed by recovery in neutrophil production [7, 8]. We started to ponder what was interrupting neutrophil production.

In Mike's paper "The story of the Mackey-Glass equation," he wrote that in 1974 John Combs pointed out to him our reports about human and canine cyclic neutropenia and another about periodic leukemia. Mike reported, "A wise suggestion as it turned out, since the study of these periodic hematological diseases became a focal point of my career" [1]. At that time, I was also trying to measure the bone marrow production of neutrophils in several ways: serial biopsies, labeling cells with radioisotopes, looking for the slope of the decline of counts to their lowest levels and then the pattern of recovery in this interesting disease. I read and reread the reports from the 1950s and the early 1960s on leukocyte kinetics by Cronkite et al. [9], Craddock et al. [10], and Athens et al. [11]. I became convinced that neutropenia was caused by an interruption in neutrophil production at an early stage in myelopoiesis. We observed that not only neutrophils, but red cells, monocytes and platelets also cycled, though not so extremely as the neutrophils. For a time, we referred to the disease as cyclic hematopoiesis, especially after we showed that the grey collies' disease could be cured by bone marrow transplantation [5, 7, 12].

Two important discoveries shifted our thinking and work. Mike and Leon Glass were then studying oscillatory dynamics. In modeling of cyclic neutropenia, Mike postulated that the fundamental problem was an inherent delay in the feedback mechanism regulating neutrophil production that caused cycling [13]. This paper in the journal *Blood* was a critical "paradigm shifting" report for understanding biological cycling. At the same time that Mike and Leon Glass were developing these concepts, I was interested in the newly discovered growth factors that could stimulate blood cell formation in the laboratory; for leukocytes these were called "colony-stimulating factors (CSFs)." We set out to measure the colony-stimulating factor levels in blood and urine of the grey collies and humans with cyclic neutropenia. We observed that the levels were highest when the marrow was

recovering from severe neutropenia and did not rise until there was neutropenia [14, 15].

Normally the body is steadily overproducing neutrophils as an always ready supplier of microbicidal substances to fight infections anywhere in the body, "a handy infection-controlling fire department." However, when production is interrupted from the early stages of myelopoiesis there could be a lag in the signal to simulate production until the bone marrow supply of these cells declines to a critical level. Based on our studies in the grey collies, we proposed that the crude colony-stimulating factor we had measured was the natural regulator for producing neutrophils [14]. Thus, we felt we were confirming Mackey and Glass' concept that cycling was due to an inherent delay in the natural feedback mechanism; the regulatory hormones were not really turned on until the neutrophil reserves were almost exhausted. Mike and I corresponded throughout this period, but we rarely met. We sent him data to analyze and criticize.

A major breakthrough for the cyclic neutropenia patients came with the cloning of genes for the colony-stimulating factors, and the biotechnology company, Amgen, producing enough of these glycoproteins for pre-clinical and clinical studies. Our first human studies were the treatment of cyclic neutropenia with the granulocyte colony-stimulating factor (G-CSF) product called "Neupogen." In 1986 I approached Amgen when it was really just a start-up company with the idea that a few weeks of G-CSF might raise the patients' counts enough to make them healthier and might stop neutrophil cycling. Of course, I did not know what would really happen. We found that daily injections of G-CSF shortened the period of severe neutropenia by shortening the neutrophil cycle from 21 to 14 days and almost completely prevented infections [16]. For the patients it was an overwhelming success! We hypothesized the shortening of the cycle was due to increased and accelerated production and more rapid delivery of neutrophils from the bone marrow to the blood. We later demonstrated these effects in normal human subjects [17]. Mike recently wrote to me reminding me that he had independently predicted these changes based upon his modeling work. He wrote that soon after I received his letter, I had replied with a preprint of our paper demonstrating these very effects.

Cyclic neutropenia is a rare disease first recognized more than a century ago. The diagnosis had always depended on a series of blood neutrophil counts over a long enough period of time to observe the regular cycles. Affected persons have regular signs and symptoms when the neutrophil counts are low, e.g., mouth ulcers, fevers, fatigue and "flu-like" symptoms, and sometimes very severe and life-threating infections. But sometimes it is not easy to distinguish the cycles because the levels are always quite low in some patients and periodicity of neutrophil cycles is not always apparent. There are also some patients who appear to have cyclic neutrophil oscillations and symptoms, but the more information you have the more uncertain you are about the diagnosis and whether the patient has another disease called "severe congenital neutropenia." One of the biggest problems for researchers and clinicians is that many patients simply have trouble getting a long series of blood cell counts to make a secure diagnosis. We discussed this problem with Mike, and he and his colleagues at McGill University developed a computer program that

clinicians could use to determine if patients had cycles of their blood neutrophil counts [18].

At the same time, we were treating our first patients with G-CSF, researchers at Sloan-Kettering Cancer Center in New York showed that G-CSF was effective for treatment of severe congenital neutropenia and a few patients with neutropenia of unknown cause, a condition called "idiopathic neutropenia". With this information, we were confident enough to conduct a randomized clinical trial to prove the effectiveness of G-CSF for various types of severe chronic neutropenia, including cyclic neutropenia, under the sponsorship of Amgen. We did the trial and it was successful, changing the lives of many patients around the world [19]. It also provided new basic research opportunities and new opportunities to collaborate with Mike and his research team.

In the late 1980s there was a flurry of interest in using genetic sequencing to discover the causes for common and rare human diseases. The human genome project was just starting but methods were sufficient to begin the search, e.g., the search for the cystic fibrosis gene and many others. In 1949 Herbert Reiman wrote an excellent paper describing cyclic neutropenia as an autosomal dominant disease [20]. When we had a treatment for congenital and cyclic neutropenia, we began to discover more patients and families with this disorder. I thought we could find the genetic and molecular cause for cyclic neutropenia, i.e., the factor that Mike predicted to interrupt neutrophil production in his 1978 modeling paper, if we could just find enough patients and families. I was overly optimistic. It took 10 years: finding families, collecting clinical information and blood samples, countless hours of tedious laboratory work by a dedicated team of collaborators and better DNA sequencing methodologies to discover that a mutation in one gene, the gene for neutrophil elastase now called *ELANE*, causes cyclic neutropenia [21]. This gene serves as a backbone for production of a very potent protease synthesized at an early stage in neutrophil development. On September 23, 1999, Mike wrote to me, "I am delighted by the recent news of the identification of the mutation causing autosomal dominant cyclic neutropenia. I like your idea of relating this abnormality of a specific granule to accelerated apoptosis of early hematopoietic cells" [personal communication]. I appreciated that this finding fitted with Mike's concepts of how cycling might occur in his 1978 paper.

After finding that mutant *ELANE* caused cyclic neutropenia, it took many more years of work to show that the mutant protein triggers the death of developing neutrophils by the unfolded protein response and apoptosis [22]. We also discovered that some of our confusion about distinguishing severe cyclic neutropenia from severe congenital neutropenia is because both diseases are caused by mutations in *ELANE*, but there are many, more than 200, different *ELANE* mutations associated with cyclic and congenital neutropenia [23, 24]. There are a few overlapping mutations, mutations associated with both diseases. Through genotype-phenotype studies we discovered that there are mild and severe mutations, reflected by the dose of G-CSF to increase blood neutrophils and the risk of leukemic transformation [24]. As Mike predicted in 1978, some mutations cause severe disease with no apparent cycling, presumably because of very severe suppression of cells advancing beyond

the promyelocyte stage, the stage in development when the neutrophil elastase protein is templated from the mutant gene. We believe now that with less severe mutations, cycling occurs because of the time required for myeloid recovery and the intrinsic delay in the response to neutropenia by the master endogenous regulator of neutrophil production, G-CSF.

About 20 years ago, I began to work with several young investigators in Mike's research group at McGill University. They were interested in both the methods for analyzing data to look for periodicity and looking for periodicity in other hematological diseases. It was fruitful work. From my perspective it was delightful to work with such bright young researchers who worked so hard to teach me advanced mathematics. It was also important because it strengthened our understanding that cyclic biological phenomena can be a consequence of diverse underlying physiological and pathological processes. The difference between the diseases we call severe cyclic neutropenia and severe congenital neutropenia (originally called "Kostmann's syndrome") are primarily due to variations in the mutations of the *ELANE* gene.

In 2008, I nominated Michael Mackey to return to Seattle as the University of Washington's Walker-Ames Lecturer. Members of the Departments of Medicine, Physiology, and Biophysics and Mathematics joined me for this invitation. In my letter to the chair of the selection committee, I wrote about the significance of his book, co-authored with Leo Glass, "From Clocks to Chaos: The Rhythms of Life." Mike was selected. He came and gave a superb lecture on "Bifurcations at the Bedside: How Non-linear Dynamics Can Help to Understand Periodic and Dynamical Diseases" [25]. His friends from his graduate school days, as well as many others, enjoyed being with him again.

In 2013 I participated in a symposium at the University of León to honor Mike on his 70th birthday. I believe I was the only non-mathematician attendee. We were all friends of Mike's, friends from all around the world. The talks were diverse and interesting. Equally impressive was the collegiality and appreciation for Michael Mackey's work. It is now 10 years later, and we are both less active but not retired or retiring. It has been so meaningful to me to have this long-term friendship.

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Michael Mackey and Data-Driven Models of Chemotherapy-Induced Neutropenia

Morgan Craig

Abstract During his research career, Michael Mackey, Joseph Morley Drake Professor Emeritus of Physiology in the Department of Physiology at McGill University, Canada, made numerous consequential insights into biological mechanisms of dynamic hematologic diseases and gene regulatory networks. Throughout, he emphasized the importance of data on mathematical model conceptualization, development, calibration, and validation. This brief review describes contributions by Michael Mackey and his collaborators toward understanding and treating chemotherapy-induced neutropenia, a frequent and serious toxic side effect of cytotoxic chemotherapy, using data-driven mathematical models.

1 Introduction

The human body maintains homeostasis through multiple overlapping networks, implying that physiological data are inherently multiscale and multidimensional [1, 2]. Accordingly, revealing mechanistic drivers of physiological responses requires a multipronged approach integrating mathematical and computational modelling [3]. Historically, one of the greatest difficulties faced by mathematical modellers in biomedicine is a lack of data. It was not until recent advances in data collection and analysis that mathematical models in physiology could become strongly anchored within experimental and clinical paradigms.

During his career, Michael Mackey worked on a variety of problems ranging from the abstract [4–7] to those with concrete applications for patient care [8–11]. Throughout, he placed a special emphasis on "*biologically realistic mathematical models, careful consideration of laboratory and/or clinical data, and achieving*

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