INTERDISCIPLINARY APPLIED MATHEMATICS

MATHEMATICAL BIOLOGY

Mathematical Biology

II: Spatial Models and Biomedical Applications

生物数学 第2卷 第3版

J. D. Murray

Third Edition

Springer

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Interdisciplinary Applied Mathematics

Volume 18

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Interdisciplinary Applied Mathematics

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. . . que se él fuera de su consejo al tiempo de la general criación del mundo, i de lo que en él se encierra, i se hallá ra con él, se huvieran producido *i formado algunas cosas mejor que fueran hechas, i otras ni se hicieran, u se enmendaran i corrigieran.*

Alphonso X (Alphonso the Wise), 1221–1284
King of Castile and Leon (attributed)

If the Lord Almighty had consulted me before embarking on creation I should have recommended something simpler.

To my wife Sheila, whom I married more than forty years ago and lived happily ever after, and to our children Mark and Sarah

Preface to the Third Edition

In the thirteen years since the first edition of this book appeared the growth of mathematical biology and the diversity of applications has been astonishing. Its establishment as a distinct discipline is no longer in question. One pragmatic indication is the increasing number of advertised positions in academia, medicine and industry around the world; another is the burgeoning membership of societies. People working in the field now number in the thousands. Mathematical modelling is being applied in every major discipline in the biomedical sciences. A very different application, and surprisingly successful, is in psychology such as modelling various human interactions, escalation to date rape and predicting divorce.

The field has become so large that, inevitably, specialised areas have developed which are, in effect, separate disciplines such as biofluid mechanics, theoretical ecology and so on. It is relevant therefore to ask why I felt there was a case for a new edition of a book called simply *Mathematical Biology*. It is unrealistic to think that a single book could cover even a significant part of each subdiscipline and this new edition certainly does not even try to do this. I feel, however, that there is still justification for a book which can demonstrate to the uninitiated some of the exciting problems that arise in biology and give some indication of the wide spectrum of topics that modelling can address.

In many areas the basics are more or less unchanged but the developments during the past thirteen years have made it impossible to give as comprehensive a picture of the current approaches in and the state of the field as was possible in the late 1980s. Even then important areas were not included such as stochastic modelling, biofluid mechanics and others. Accordingly in this new edition only some of the basic modelling concepts are discussed—such as in ecology and to a lesser extent epidemiology—but references are provided for further reading. In other areas recent advances are discussed together with some new applications of modelling such as in marital interaction (Volume I), growth of cancer tumours (Volume II), temperature-dependent sex determination (Volume I) and wolf territoriality (Volume II). There have been many new and fascinating developments that I would have liked to include but practical space limitations made it impossible and necessitated difficult choices. I have tried to give some idea of the diversity of new developments but the choice is inevitably prejudiced.

As to general approach, if anything it is even more practical in that more emphasis is given to the close connection many of the models have with experiment, clinical data and in estimating real parameter values. In several of the chapters it is not yet

possible to relate the mathematical models to specific experiments or even biological entities. Nevertheless such an approach has spawned numerous experiments based as much on the modelling approach as on the actual mechanism studied. Some of the more mathematical parts in which the biological connection was less immediate have been excised while others that have been kept have a mathematical and technical pedagogical aim but all within the context of their application to biomedical problems. I feel even more strongly about the philosophy of mathematical modelling espoused in the original preface as regards what constitutes good mathematical biology. One of the most exciting aspects regarding the new chapters has been their genuine interdisciplinary collaborative character. Mathematical or theoretical biology is unquestionably an interdisciplinary science *par excellence*.

The unifying aim of theoretical modelling and experimental investigation in the biomedical sciences is the elucidation of the underlying biological processes that result in a particular observed phenomenon, whether it is pattern formation in development, the dynamics of interacting populations in epidemiology, neuronal connectivity and information processing, the growth of tumours, marital interaction and so on. I must stress, however, that mathematical descriptions of biological phenomena are not biological explanations. The principal use of any theory is in its predictions and, even though different models might be able to create similar spatiotemporal behaviours, they are mainly distinguished by the different experiments they suggest and, of course, how closely they relate to the real biology. There are numerous examples in the book.

Why use mathematics to study something as intrinsically complicated and ill understood as development, angiogenesis, wound healing, interacting population dynamics, regulatory networks, marital interaction and so on? We suggest that mathematics, rather theoretical modelling, must be used if we ever hope to genuinely and realistically convert an understanding of the underlying mechanisms into a predictive science. Mathematics is required to bridge the gap between the level on which most of our knowledge is accumulating (in developmental biology it is cellular and below) and the macroscopic level of the patterns we see. In wound healing and scar formation, for example, a mathematical approach lets us explore the logic of the repair process. Even if the mechanisms were well understood (and they certainly are far from it at this stage) mathematics would be required to explore the consequences of manipulating the various parameters associated with any particular scenario. In the case of such things as wound healing and cancer growth—and now in angiogensesis with its relation to possible cancer therapy—the number of options that are fast becoming available to wound and cancer managers will become overwhelming unless we can find a way to simulate particular treatment protocols before applying them in practice. The latter has been already of use in understanding the efficacy of various treatment scenarios with brain tumours (glioblastomas) and new two step regimes for skin cancer.

The aim in all these applications is not to derive a mathematical model that takes into account every single process because, even if this were possible, the resulting model would yield little or no insight on the crucial interactions within the system. Rather the goal is to develop models which capture the essence of various interactions allowing their outcome to be more fully understood. As more data emerge from the biological system, the models become more sophisticated and the mathematics increasingly challenging.

In development (by way of example) it is true that we are a long way from being able to reliably simulate actual biological development, in spite of the plethora of models and theory that abound. Key processes are generally still poorly understood. Despite these limitations, I feel that exploring the logic of pattern formation is worthwhile, or rather essential, even in our present state of knowledge. It allows us to take a hypothetical mechanism and examine its consequences in the form of a mathematical model, make predictions and suggest experiments that would verify or invalidate the model; even the latter casts light on the biology. The very process of constructing a mathematical model can be useful in its own right. Not only must we commit to a particular mechanism, but we are also forced to consider what is truly essential to the process, the central players (variables) and mechanisms by which they evolve. We are thus involved in constructing frameworks on which we can hang our understanding. The model equations, the mathematical analysis and the numerical simulations that follow serve to reveal quantitatively as well as qualitatively the consequences of that logical structure.

This new edition is published in two volumes. Volume I is an introduction to the field; the mathematics mainly involves ordinary differential equations but with some basic partial differential equation models and is suitable for undergraduate and graduate courses at different levels. Volume II requires more knowledge of partial differential equations and is more suitable for graduate courses and reference.

I would like to acknowledge the encouragement and generosity of the many people who have written to me (including a prison inmate in New England) since the appearance of the first edition of this book, many of whom took the trouble to send me details of errors, misprints, suggestions for extending some of the models, suggesting collaborations and so on. Their input has resulted in many successful interdisciplinary research projects several of which are discussed in this new edition. I would like to thank my colleagues Mark Kot and Hong Qian, many of my former students, in particular Patricia Burgess, Julian Cook, Tracé Jackson, Mark Lewis, Philip Maini, Patrick Nelson, Jonathan Sherratt, Kristin Swanson and Rebecca Tyson for their advice or careful reading of parts of the manuscript. I would also like to thank my former secretary Erik Hinkle for the care, thoughtfulness and dedication with which he put much of the manuscript into LaTeX and his general help in tracking down numerous obscure references and material.

I am very grateful to Professor John Gottman of the Psychology Department at the University of Washington, a world leader in the clinical study of marital and family interactions, with whom I have had the good fortune to collaborate for nearly ten years. Without his infectious enthusiasm, strong belief in the use of mathematical modelling, perseverance in the face of my initial scepticism and his practical insight into human interactions I would never have become involved in developing with him a general theory of marital interaction. I would also like to acknowledge my debt to Professor Ellworth C. Alvord, Jr., Head of Neuropathology in the University of Washington with whom I have collaborated for the past seven years on the modelling of the growth and control of brain tumours. As to my general, and I hope practical, approach to modelling I am most indebted to Professor George F. Carrier who had the major influence on me when I went to Harvard on first coming to the U.S.A. in 1956. His astonishing insight and ability to extract the key elements from a complex problem and incorporate them into a realistic

and informative model is a talent I have tried to acquire throughout my career. Finally, although it is not possible to thank by name all of my past students, postdoctorals, numerous collaborators and colleagues around the world who have encouraged me in this field, I am certainly very much in their debt.

Looking back on my involvement with mathematics and the biomedical sciences over the past nearly thirty years my major regret is that I did not start working in the field years earlier.

Bainbridge Island, Washington
January 2002

J.D. Murray

Preface to the First Edition

Mathematics has always benefited from its involvement with developing sciences. Each successive interaction revitalises and enhances the field. Biomedical science is clearly the premier science of the foreseeable future. For the continuing health of their subject, mathematicians must become involved with biology. With the example of how mathematics has benefited from and influenced physics, it is clear that if mathematicians do not become involved in the biosciences they will simply not be a part of what are likely to be the most important and exciting scientific discoveries of all time.

Mathematical biology is a fast-growing, well-recognised, albeit not clearly defined, subject and is, to my mind, the most exciting modern application of mathematics. The increasing use of mathematics in biology is inevitable as biology becomes more quantitative. The complexity of the biological sciences makes interdisciplinary involvement essential. For the mathematician, biology opens up new and exciting branches, while for the biologist, mathematical modelling offers another research tool commensurate with a new powerful laboratory technique but *only* if used appropriately and its limitations recognised. However, the use of esoteric mathematics arrogantly applied to biological problems by mathematicians who know little about the real biology, together with unsubstantiated claims as to how important such theories are, do little to promote the interdisciplinary involvement which is so essential.

Mathematical biology research, to be useful and interesting, must be relevant *biologically*. The best models show how a process works and then predict what may follow. If these are not already obvious to the biologists *and* the predictions turn out to be right, then you will have the biologists' attention. Suggestions as to what the governing mechanisms are may evolve from this. *Genuine* interdisciplinary research and the use of models can produce exciting results, many of which are described in this book.

No previous knowledge of biology is assumed of the reader. With each topic discussed I give a brief description of the biological background sufficient to understand the models studied. Although stochastic models are important, to keep the book within reasonable bounds, I deal exclusively with deterministic models. The book provides a toolkit of modelling techniques with numerous examples drawn from population ecology, reaction kinetics, biological oscillators, developmental biology, evolution, epidemiology and other areas.

The emphasis throughout the book is on the practical application of mathematical models in helping to unravel the underlying mechanisms involved in the biological processes. The book also illustrates some of the pitfalls of indiscriminate, naive or un-

informed use of models. I hope the reader will acquire a practical and realistic view of biological modelling and the mathematical techniques needed to get approximate quantitative solutions and will thereby realise the importance of relating the models and results to the real biological problems under study. If the use of a model stimulates experiments—even if the model is subsequently shown to be wrong—then it has been successful. Models can provide biological insight and be very useful in summarising, interpreting and interpolating real data. I hope the reader will also learn that (certainly at this stage) there is usually no 'right' model: producing similar temporal or spatial patterns to those experimentally observed is only a first step and does not imply the model mechanism is the one which applies. Mathematical descriptions are *not* explanations. Mathematics can never provide the complete solution to a biological problem on its own. Modern biology is certainly not at the stage where it is appropriate for mathematicians to try to construct comprehensive theories. A close collaboration with biologists is needed for realism, stimulation and help in modifying the model mechanisms to reflect the biology more accurately.

Although this book is titled *mathematical biology* it is not, and could not be, a definitive all-encompassing text. The immense breadth of the field necessitates a restricted choice of topics. Some of the models have been deliberately kept simple for pedagogical purposes. The exclusion of a particular topic—population genetics, for example—in no way reflects my view as to its importance. However, I hope the range of topics discussed will show how exciting intercollaborative research can be and how significant a role mathematics can play. The main purpose of the book is to present some of the basic and, to a large extent, generally accepted theoretical frameworks for a variety of biological models. The material presented does not purport to be the latest developments in the various fields, many of which are constantly expanding. The already lengthy list of references is by no means exhaustive and I apologise for the exclusion of many that should be included in a definitive list.

With the specimen models discussed and the philosophy which pervades the book, the reader should be in a position to tackle the modelling of genuinely practical problems with realism. From a *mathematical* point of view, the art of good modelling relies on: (i) a sound understanding and appreciation of the biological problem; (ii) a realistic mathematical representation of the important biological phenomena; (iii) finding useful solutions, preferably quantitative; and what is crucially important; (iv) a biological interpretation of the mathematical results in terms of insights and predictions. The mathematics is dictated by the biology and not vice versa. Sometimes the mathematics can be very simple. Useful mathematical biology research is not judged by mathematical standards but by different and no less demanding ones.

The book is suitable for physical science courses at various levels. The level of mathematics needed in collaborative biomedical research varies from the very simple to the sophisticated. Selected chapters have been used for applied mathematics courses in the University of Oxford at the final-year undergraduate and first-year graduate levels. In the U.S.A. the material has also been used for courses for students from the second-year undergraduate level through graduate level. It is also accessible to the more theoretically oriented bioscientists who have some knowledge of calculus and differential equations.

I would like to express my gratitude to the many colleagues around the world who have, over the past few years, commented on various chapters of the manuscript, made

valuable suggestions and kindly provided me with photographs. I would particularly like to thank Drs. Philip Maini, David Lane, and Diana Woodward and my present graduate students who read various drafts with such care, specifically Daniel Bentil, Meghan Burke, David Crawford, Michael Jenkins, Mark Lewis, Gwen Littlewort, Mary Myerscough, Katherine Rogers and Louisa Shaw.

Oxford *J.D. Murray*
January 1989

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