

## 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 angiogenesis 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 L<sup>A</sup>T<sub>E</sub>X 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.

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*J.D. Murray*



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Murray, J.D.

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