Biomathematics Texts

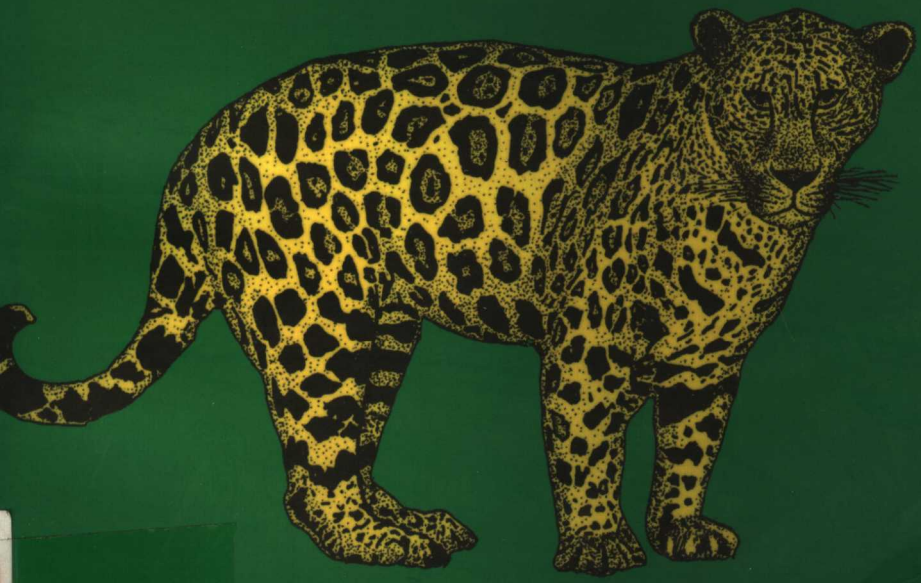
J. D. Murray

Mathematical Biology

Second, Corrected Edition

生物数学

第 2 版



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Mathematical Biology

Second, Corrected Edition
With 292 Figures

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北京・广州・上海・西安

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Cover picture: A model based on a system of reaction-diffusion equations has been suggested by the author of this book to explain how the coat markings on the leopard and other mammals are generated. In this book, he gives a whole range of animal patterning examples – from the stripes on the zebra to the eyespots on the wings of butterflies – to demonstrate the wide applicability of such models.

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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 commmensurate 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, does 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 mechanims 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 uninformed 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 summarizing, 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 developing. 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 orientated 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, January 1989 *J. D. Murray*

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

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

Table of Contents

* Denotes sections in which the mathematics is at a higher level. These sections can be omitted without loss of continuity.

1. Continuous Population Models for Single Species

The increasing study of realistic mathematical models in ecology (basically the study of the relation between species and their environment) is a reflection of their use in helping to understand the dynamic processes involved in such areas as predator-prey and competition interactions, renewable resource management, evolution of pesticide resistant strains, ecological control of pests, multi-species societies, plant-herbivore systems and so on. The continually expanding list of applications is extensive. There are also interesting and useful applications of single species models in the biomedical sciences: in Section 1.5 we discuss two practical examples of these which arise in physiology. Here, and in the following three chapters, we shall consider some deterministic models. The book edited by May (1981) gives an overview of theoretical ecology from a variety of different aspects; experts in diverse fields review their areas. The book by Nisbet and Gurney (1982) is a comprehensive account of mathematical modelling in population dynamics: a good elementary introduction is given in the textbook by Edelstein-Keshet (1988).

1.1 Continuous Growth Models

Single species models are of relevance to laboratory studies in particular but, in the real world, can reflect a telescoping of effects which influence the population dynamics. Let $N(t)$ be the population of the species at time t, then the rate of change

$$\frac{dN}{dt} = \text{births} - \text{deaths} + \text{migration}\,, \tag{1.1}$$

is a *conservation equation* for the population. The form of the various terms on the right hand side of (1.1) necessitates modelling the situation that we are concerned with. The simplest model has no migration and the birth and death terms are proportional to N. That is

$$\frac{dN}{dt} = bN - dN \quad \Rightarrow \quad N(t) = N_0\, e^{(b-d)t}$$

where b, d are positive constants and the initial population $N(0) = N_0$. Thus if $b > d$ the population grows exponentially while if $b < d$ it dies out. This

approach, due to Malthus in 1798 but actually suggested earlier by Euler, is pretty unrealistic. However if we consider the past and predicted growth estimates for the total world population from the 17th to 21st centuries it is perhaps less unrealistic as seen in the following table.

Date	Mid 17th Century	Early 19th Century	1918-27	1960	1974	1987	1999	2010	2022
Population in billions	0.5	1	2	3	4	5	6	7	8

In the long run of course there must be some adjustment to such exponential growth. Verhulst in 1836 proposed that a self-limiting process should operate when a population becomes too large. He suggested

$$\frac{dN}{dt} = rN(1 - N/K)\,, \tag{1.2}$$

where r and K are positive constants. This is called *logistic growth* in a population. In this model the per capita birth rate is $r(1 - N/K)$, that is, it is dependent on N. The constant K is the *carrying capacity* of the environment, which is usually determined by the available sustaining resources.

There are two *steady states* or *equilibrium states* for (1.2), namely $N = 0$ and $N = K$, that is where $dN/dt = 0$. $N = 0$ is unstable since linearization about it (that is N^2 is neglected compared with N) gives $dN/dt \approx rN$, and so N grows exponentially from any initial value. The other equilibrium $N = K$ is stable: linearization about it (that is $(N - K)^2$ is neglected compared with $|N - K|$) gives $d(N - K)/dt \approx -r(N - K)$ and so $N \to K$ as $t \to \infty$. The carrying capacity K determines the size of the stable steady state population while r is a measure of the rate at which it is reached, that is, it is a measure of the dynamics: we could incorporate it in the time by a transformation from t to rt. Thus $1/r$ is a representative *time scale* of the response of the model to any change in the population.

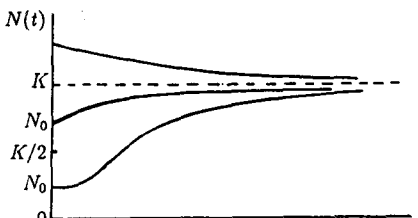

Fig. 1.1. Logistic population growth. Note the qualitative difference for the two cases $N_0 < K/2$ and $K > N_0 > K/2$.

If $N(0) = N_0$ the solution of (1.2) is

$$N(t) = \frac{N_0 K e^{rt}}{[K + N_0(e^{rt} - 1)]} \to K \quad \text{as} \quad t \to \infty \,, \tag{1.3}$$

and is illustrated in Fig. 1.1. From (1.2), if $N_0 < K$, $N(t)$ simply increases monotonically to K while if $N_0 > K$ it decreases monotonically to K. In the former case there is a qualitative difference depending on whether $N_0 > K/2$ or $N_0 < K/2$: with $N_0 < K/2$ the form has a typical sigmoid character, which is commonly observed.

In the case where $N_0 > K$ this would imply that the per capita birth rate is negative! Of course all it is really saying is that in (1.1) the births plus immigration is less than the deaths plus emigration. The point about (1.2) is that it is more like a metaphor for a class of population models with density dependent regulatory mechanisms – a kind of compensating effect of overcrowding – and must not be taken too literally as the equation governing the population dynamics. It is a particularly convenient form to take when seeking qualitative dynamic behaviour in populations in which $N = 0$ is an unstable steady state and $N(t)$ tends to a finite positive stable steady state. The logistic form will occur in a variety of different contexts throughout the book.

In general if we consider a population to be governed by

$$\frac{dN}{dt} = f(N) \,, \tag{1.4}$$

where typically $f(N)$ is a *nonlinear* function of N then the equilibrium solutions N^* are solutions of $f(N) = 0$ and are linearly stable to small perturbations if $f'(N^*) < 0$, and unstable if $f'(N^*) > 0$. This is clear from linearizing about N^* by writing

$$n(t) \approx N(t) - N^*, \quad |n(t)| \ll 1$$

and (1.4) becomes

$$\frac{dn}{dt} = f(N^* + n) \approx f(N^*) + nf'(N^*) + \dots \,,$$

which to first order in $n(t)$ gives

$$\frac{dn}{dt} \approx nf'(N^*) \quad \Rightarrow \quad n(t) \propto \exp[f'(N^*)t] \,. \tag{1.5}$$

So n grows or decays according as $f'(N^*) > 0$ or $f'(N^*) < 0$. The time scale of the response of the population to a disturbance is of the order of $1/|f'(N^*)|$: it is the time to change the initial disturbance by a factor e.

There may be several equilibrium, or steady state populations N^* which are solutions of $f(N) = 0$: it depends on the system $f(N)$ models. Graphically plotting $f(N)$ against N immediately gives the equilibria. The gradient $f'(N^*)$

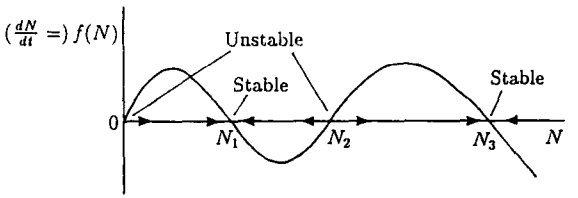

Fig. 1.2. Population dynamics model $dN/dt = f(n)$ with several steady states. The gradient $f'(N)$ at the steady state, that is where $f(N) = 0$, determines the linear stability.

at each steady state then determines its linear stability. Such steady states may, however, be unstable to finite disturbances. Suppose, for example, that $f(N)$ is as illustrated in Fig. 1.2. The gradients $f'(N)$ at $N = 0, N_2$ are positive so these equilibria are unstable while those at $N = N_1, N_3$ are stable to small perturbations: the arrows symbolically indicate stability or instability. If, for example, we now perturb the population from its equilibrium N_1 so that N is in the range $N_2 < N < N_3$ then $N \to N_3$ rather than returning to N_1. A similar perturbation from N_3 to a value in the range $0 < N < N_2$ would result in $N(t) \to N_1$. Qualitatively there is a threshold perturbation below which the steady states are always stable, and this threshold depends on the full nonlinear form of $f(N)$. For N_1, for example, the necessary threshold perturbation is $N_2 - N_1$.

1.2 Insect Outbreak Model: Spruce Budworm

A practical model which exhibits two positive linearly stable steady state populations is that for the spruce budworm which can, with ferocious efficiency, defoliate the balsam fir: it is a major problem in Canada. Ludwig et al. (1978) considered the budworm population dynamics to be governed by the equation

$$\frac{dN}{dt} = r_B N \left(1 - \frac{N}{K_B}\right) - p(N) .$$

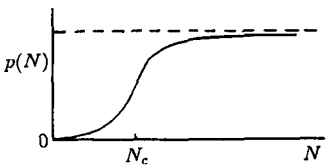

Fig. 1.3. Typical functional form of the predation in the spruce budworm model: note the sigmoid character. The population value N_c is an approximate threshold value. For $N < N_c$ predation is small, while for $N > N_c$ it is "switched on".