Mathematical Modelling in Biomedicine

Mathematics and Its Applications

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Optimal Control of Biomedical Systems

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To Annick and Yann
for their contribution to my
inspiration and for their constant
encouragement and understanding
during the preparation of this book.

In Memory of my father

To my mother

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SERIES EDITOR'S PREFACE

Approach your problems from the right end and begin with the answers. Then one day, perhaps you will find the final question.

'The Hermit Clad in Crane Feathers' in R. van Gulik's *The Chinese Maze Murders*.

It isn't that they can't see the solution. It is that they can't see the problem.

G.K. Chesterton. *The Scandal of Father Brown* 'The point of a Pin'.

Growing specialization and diversification have brought a host of monographs and textbooks on increasingly specialized topics. However, the "tree" of knowledge of mathematics and related fields does not grow only by putting forth new branches. It also happens, quite often in fact, that branches which were thought to be completely disparate are suddenly seen to be related.

Further, the kind and level of sophistication of mathematics applied in various sciences has changed drastically in recent years: measure theory is used (non-trivially) in regional and theoretical economics; algebraic geometry interacts with physics; the Minkowsky lemma, coding theory and the structure of water meet one another in packing and covering theory; quantum fields, crystal defects and mathematical programming profit from homotopy theory; Lie algebras are relevant to filtering; and prediction and electrical engineering can use Stein spaces. And in addition to this there are such new emerging subdisciplines as "experimental mathematics", "CFD", "completely integrable systems", "chaos, synergetics and large-scale order", which are almost impossible to fit into the existing classification schemes. They draw upon widely different sections of mathematics. This programme, Mathematics and Its Applications, is devoted to new emerging (sub)disciplines and to such (new) interrelations as *exempla gratia*:

- a central concept which plays an important role in several different mathematical and/or scientific specialized areas;
- new applications of the results and ideas from one area of scientific endeavour into another;

influences which the results, problems and concepts of one field of enquiry have and have had on the development of another.

The Mathematics and Its Applications programme tries to make available a careful selection of books which fit the philosophy outlined above. With such books, which are stimulating rather than definitive, intriguing rather than encyclopaedic, we hope to contribute something towards better communication among the practitioners in diversified fields.

At the moment there are many (relatively) new areas where mathematical ideas and techniques are vigorously applied. Many of these are among the faster growing parts of mathematics. Mathematical biology and medicine (including pharmacology), or perhaps better, mathematical modeling in these areas, and the subsequent use of these models, could very well be the fastest growing ones of them all.

It does not sound too difficult: building a mathematical model of something. In reality it involves quite a lot, and there are aspects of this activity which smack of art rather than science. In particular it involves the matter of a scientist from the field in question and a mathematician getting to understand each other, a process which takes considerable amounts of time and effort and which has been described as painful.

It certainly helps in such a case to have a book available written by someone who has been through the mill several times, who has given lots of thought to the particular difficulties and pitfalls involved and who can write about it clearly.

Such are the contents of this book.

In addition biomedical mathematical models tend to generate different mathematical problems and questions compared to the more traditional physical and mechanical models, thus giving rise to new mathematical challenges. That is also what this book is about.

The unreasonable effectiveness of
mathematics in science ...

Eugene Wigner

Well, if you know of a better 'ole, go to it.

Bruce Bairnsfather

What is now proved was once only ima-
gined.

William Blake

As long as algebra and geometry pro-
ceeded along separate paths, their advance
was slow and their applications limited.

But when these sciences joined company
they drew from each other fresh vitality
and thence forward marched on at a rapid
pace towards perfection.

Joseph Louis Lagrange.

Bussum, August 1985

Michiel Hazewinkel

*"Là où est l'amour des humains,
là est aussi l'amour du métier."*

HYPPOCRATE

Préceptes, tome IX, Ed. Littré

PREFACE

This book would never have been published without the help of the open-minded and benevolent friends who have contributed to our research programme in many ways, including financing the work. Most French research organisations have not yet recognised the relevance of biomathematics, a multidisciplinary field. We have developed this field without their help.

The author wishes to acknowledge the help of:

- M.G.E.N. (Mr. Pélinaud and Mr. Lajeunie), which has financed our work for several years.
- Some pharmaceutical laboratories, specifically Sandoz and Servier (Dr. Kiechel, Miss Lavene, Mrs. Guerret, Dr. Poirier, Dr. J. F. Prost) that have signed contracts with the Medimat laboratory in order to develop the field of pharmacological mathematics.
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- The Pierre and Marie Curie University (Paris VI), which has always fostered our field (Prof. Dry, Prof. Astier, Prof. Garnier, Prof. Proteau).
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- D. Reidel Publishing Company (Dr. Larner) and Prof. Hazewinkel (Centre for Mathematics and Computer Studies, Amsterdam), who asked me to write this book as they were interested in the field of biomathematics.
- Annick Cherruault for her essential bibliographical research work and her share in our work.

We thank all these people and companies, among others.
We owe them an important debt with respect to our scientific
work. We hope that our work will be developed further by
the young open-minded scientists interested in our book.

Paris, 1985

Y. CHERRUAULT

*"D'abord, une grande racine de foi,
ensuite, une grande boule de doute,
enfin, une grande fermeté de dessein."*

HAKUIN

Maître ZEN (1685-1768)

FOREWORD

Yves Cherruault is one of the founders of Biomathematics. This book contains important new developments in this field, introduces new ideas, and opens up new areas of research.

Yves Cherruault has succeeded in combining theory and practice to develop methods and procedures which connect mathematics to biology, medicine, and pharmacology. These interrelationships are illustrated by means of practical examples, coming from the author's experience as head of the Medimat laboratory, where these problems are approached and treated both from a theoretical viewpoint and by means of practical applications.

The problems considered are deterministic or statistical, and it is necessary to increase the number of tools and techniques available to scientists and engineers working in this field.

Chapter 1 of the book is an introduction. Here the author presents general problems of modelling and various techniques. He gives some examples and illustrates the difficulties involved.

Chapters 2 to 4 chiefly concern pharmacological applications, compartmental systems, dose-effects and concentration-effect relationships. These topics provide all the information necessary to define and solve the corresponding differential systems, linear or not, with or without internal delays, and their controls. Some new mathematical methods are developed, such as the Alienor method, that enable one to find the absolute extrema.

Therapeutical applications are covered in Chapter 5 and 6. Chapter 5 covers the first modelling methods in medicine and the treatment of hormonal equilibrium by Dr. Bernard Weil's equations, the optimal control of this system is treated by an original mathematical method. The regulation of glucose using insulin is presented in Chapter 6.

Chapters 7 to 9, in which the more classical problems are examined, introduce many novel approaches. Chapters 7 and 8 illustrate some applications of integral equations in biomedicine, in particular, their use in the

problems of catheter utilisation, knee articulation and diffusion of oxygen from the kidneys. New and powerful methods for defining and solving integral equations or mathematical systems are introduced, such as Caron's method. These methods can be implemented on microcomputers. Chapter 9 treats partial differential equations and systems, which model Kernevez's problem for membranes, gas exchange during breathing and other related topics.

Chapter 10 presents the important problem of optimality in human physiology. Professor J. Brocas has provided useful information on minimum necessary energy consumption. Applications are presented; for example, the problem of thermo-regulation.

Chapter 11 treats errors in computation and modelling. These errors, arising from computers and measurements, can be estimated using the methods of Vignes and sensitivity theory.

Chapter 12 treats several open problems: biological delayed systems, retrocontrolled systems, the simultaneous action of two or more drugs, numerical techniques for global optimization, optimization of industrial processes, and optimality criteria in physiology. Case studies are described for some of these problems.

Chapter 13 describes the present situation in the field and looks into the future of biomathematics.

The nervous system is not explicitly treated, but the chapters on hormonology and pharmacology can be used by neurologists and psychiatrists.

The interest and importance given to biomathematics varies from country to country. This book will outline our methods and concepts for mathematicians, biologists, physicians, pharmacologists and engineers. Applied mathematical problems originating in the fields of medicine and biology not only lead to new applications of existing algorithms but also to the creation of new ones. These, in turn, lead to new models, because none are available in most cases.

Dr. A. Guillez, Chairman
Symposium of mathematical modelling in Medicine
and Biology,
International Congress of Cybernetics, Namur, 1983