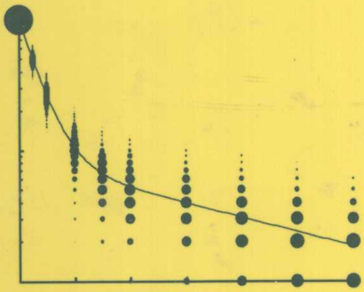
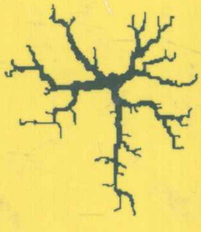
INTERDISCIPLINARY APPLIED MATHEMATICS

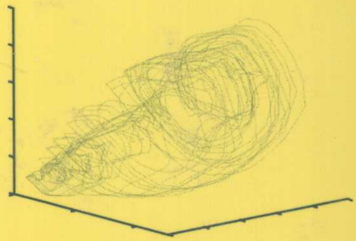
MATHEMATICAL BIOLOGY

Modeling in Biopharmaceutics, Pharmacokinetics, and Pharmacodynamics

Homogeneous and Heterogeneous Approaches







Panos Macheras
Athanassios Iliadis

Springer

Panos Macheras Athanassios Iliadis

Modeling in Biopharmaceutics, Pharmacokinetics, and Pharmacodynamics

Homogeneous and Heterogeneous Approaches

With 131 Illustrations

Springer

Panos Macheras
School of Pharmacy
Zographou 15771
Greece
Macheras@pharm.uoa.gr

Athanassios Iliadis
Faculty of Pharmacy
Marseilles 13385 CX 0713284
France
Iliadis@pharmacie.univ-mrs.fr

Cover illustration: *Left panel: Stochastic description of the kinetics of a population of particles, Fig 9.15. Middle panel: Dissolution in topologically restricted media, Fig. 6.8B (reprinted with permission from Springer). Right panel: A pseudophase space for a chaotic model of cortisol kinetics, Fig.11.11.*

Mathematics Subject Classification (2000): 92C 45 (main n°), 62P10, 74H65, 60K20.

Library of Congress Control Number: 2005934524

ISBN-10: 0-387-28178-9
ISBN-13: 978-0387-28178-0

Printed in the United States of America. (MVY)

9 8 7 6 5 4 3 2 1

springeronline.com

Interdisciplinary Applied Mathematics

Volumes published are listed at the end of the book

Interdisciplinary Applied Mathematics

Volume 30

Problems in engineering, computational science, and the physical and biological sciences are using increasingly sophisticated mathematical techniques. Thus, the bridge between the mathematical sciences and other disciplines is heavily traveled. The correspondingly increased dialog between the disciplines has led to the establishment of the series: *Interdisciplinary Applied Mathematics.*

The purpose of this series is to meet the current and future needs for the interaction between various science and technology areas on the one hand and mathematics on the other. This is done, firstly, by encouraging the ways that that mathematics may be applied in traditional areas, as well as point towards new and innovative areas of applications; and, secondly, by encouraging other scientific disciplines to engage in a dialog with mathematicians outlining their problems to both access new methods and suggest innovative developments within mathematics itself.

The series will consist of monographs and high-level texts from researchers working on the interplay between mathematics and other fields of science and technology.

- To our ancestors who inspired us
- To those teachers who guided us
- To our families

Preface

Η μεγάλη τέχνη βρίσκεται οπουδήποτε ο άνθρωπος κατορθώνει ν'αναγνωρίζει τον εαυτόν του και να τον εκφράζει με πληρότητα μες στο ελάχιστο.

Great art is found wherever man achieves an understanding of self and is able to express himself fully in the simplest manner.

Odysseas Elytis (1911-1996)
1979 Nobel Laureate in Literature
The magic of Papadiamantis

Biopharmaceutics, pharmacokinetics, and pharmacodynamics are the most important parts of pharmaceutical sciences because they bridge the gap between the basic sciences and the clinical application of drugs. The modeling approaches in all three disciplines attempt to:

- describe the functional relationships among the variables of the system under study and
- provide adequate information for the underlying mechanisms.

Due to the complexity of the biopharmaceutic, pharmacokinetic, and pharmacodynamic phenomena, novel physically physiologically based modeling approaches are sought. In this context, it has been more than ten years since we started contemplating the proper answer to the following complexity-relevant questions: Is a solid drug particle an ideal sphere? Is drug diffusion in a well-stirred dissolution medium similar to its diffusion in the gastrointestinal fluids? Why should peripheral compartments, each with homogeneous concentrations, be considered in a pharmacokinetic model? Can the complexity of arterial and venular trees be described quantitatively? Why is the pulsatility of hormone plasma levels ignored in pharmacokinetic-dynamic models? Over time we realized that questions of this kind can be properly answered only with an intuition about the underlying heterogeneity of the phenomena and the dynamics of the processes. Accordingly, we borrowed geometric, diffusional, and dynamic concepts and tools from physics and mathematics and applied them to the analysis of complex biopharmaceutic, pharmacokinetic, and pharmacodynamic phenomena. Thus, this book grew out of our conversations with fellow colleagues, correspondence, and joint publications. It is intended to introduce the concepts of fractals, anomalous diffusion, and the associated nonclassical kinetics, and stochastic modeling, within nonlinear dynamics and illuminate with their use the intrinsic complexity of drug processes in homogeneous and heterogeneous media. In parallel fashion, we also cover in this book all classical models that have direct relevance and application to the biopharmaceutics, pharmacokinetics, and pharmacodynamics.

The book is divided into four sections, with Part I, Chapters 1–3, presenting the basic new concepts: fractals, nonclassical diffusion-kinetics, and nonlinear dynamics; Part II, Chapters 4–6, presenting the classical and nonclassical models used in drug dissolution, release, and absorption; Part III, Chapters 7–9, presenting empirical, compartmental, and stochastic pharmacokinetic models; and Part IV, Chapters 10 and 11, presenting classical and nonclassical pharmacodynamic models. The level of mathematics required for understanding each chapter varies. Chapters 1 and 2 require undergraduate-level algebra and calculus. Chapters 3–8, 10, and 11 require knowledge of upper undergraduate to graduate-level linear analysis, calculus, differential equations, and statistics. Chapter 9 requires knowledge of probability theory.

We would like now to provide some explanations in regard to the use of some terms written in italics below, which are used extensively in this book starting with *homogeneous* vs. *heterogeneous* processes. The former term refers to kinetic processes taking place in well-stirred, Euclidean media where the classical laws of diffusion and kinetics apply. The term *heterogeneous* is used for processes taking place in disordered media or under topological constraints where classical diffusion-kinetic laws are not applicable. The word *nonlinear* is associated with either the kinetic or the dynamic aspects of the phenomena. When the kinetic features of the processes are nonlinear, we basically refer to Michaelis–Menten-type kinetics. When the dynamic features of the phenomena are studied, we refer to nonlinear dynamics as delineated in Chapter 3.

A *process* is a real entity evolving, in relation to time, in a given environment under the influence of internal mechanisms and external stimuli. A *model* is an image or abstraction of reality: a mental, physical, or mathematical representation or description of an actual process, suitable for a certain purpose. The model need not be a true and accurate description of the process, nor need the user have to believe so, in order to serve its purpose. Herein, only mathematical models are used. Either processes or models can be conceived as boxes receiving inputs and producing outputs. The boxes may be characterized as gray or black, when the internal mechanisms and parameters are associated or not with a physical interpretation, respectively. The *system* is a complex entity formed of many, often diverse, interrelated elements serving a common goal. All these elements are considered as *dynamic processes* and *models*. Here, deterministic, random, or chaotic real processes and the mathematical models describing them will be referenced as *systems*. Whenever the word "system" has a specific meaning like *process* or *model*, it will be addressed as such.

For certain processes, it is appropriate to describe globally their properties using numerical techniques that extract the basic information from measured data. In the domain of linear processes, such techniques are correlation analysis, spectral analysis, etc., and in the domain of nonlinear processes, the correlation dimension, the Lyapunov exponent, etc. These techniques are usually called *nonparametric models* or, simply, indices. For more advanced applications, it may be necessary to use models that describe the functional relationships among the system variables in terms of mathematical expressions like difference or differential equations. These models assume a prespecified parametrized structure. Such models are called *parametric models.*

Usually, a mathematical model simulates a process behavior, in what can be termed a *forward problem.* The *inverse problem* is, given the experimental measurements of behavior, what is the structure? A difficult problem, but an important one for the sciences. The inverse problem may be partitioned into the following stages: hypothesis formulation, i.e., model specification, definition of the experiments, identifiability, parameter estimation, experiment, and analysis and model checking. Typically, from measured data, nonparametric indices are evaluated in order to reveal the basic features and mechanisms of the underlying processes. Then, based on this information, several structures are assayed for candidate parametric models. Nevertheless, in this book we look only into various aspects of the forward problem: given the structure and the parameter values, how does the system behave?

Here, the use of the term "model" follows Kac's remark, "models are caricatures of reality, but if they are good they portray some of the features of the real world" [1]. As caricatures, models may acquire different forms to describe the same process. Also, Fourier remarked, "nature is indifferent toward the difficulties it causes a mathematician," in other words the mathematics should be dictated by the biology and not vice versa. For choosing among such competing models, the "parsimony rule," Occam's "razor rule," or Mach's "economy of thought" may be the determining criteria. Moreover, modeling should be dependent on the purposes of its use. So, for the same process, one may develop models for process identification, simulation, control, etc. In this vein, the tourist map of Athens or the system controlling the urban traffic in Marseilles are both tools associated with the real life in these cities. The first is an identification model, the second, a control model.

Over the years we have benefited enormously from discussions and collaborations with students and colleagues. In particular we thank P. Argyrakis, D. Barbolosi, A. Dokoumetzidis, A. Kalampokis, E. Karalis, K. Kosmidis, C. Meille, E. Rinaki, and G. Valsami. We wish to thank J. Lukas whose suggestions and criticisms greatly improved the manuscript.

A. Iliadis
Marseilles, France
August 2005

P. Macheras
Piraeus, Greece
August 2005

Contents

List of Figures