



Pharmacokinetic and Pharmacodynamic Data Analysis

Concepts and Applications

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5th edition
Revised and expanded

Johan Gabrielsson
Dan Weiner

 Apotekarsocieteten

This book is dedicated to Barbro and Jenny Gabrielsson for boundless patience and understanding during preparation of this and earlier editions.

Johan Gabrielsson

I am indebted to my wife Oris for her continued ongoing support.

Dan Weiner

They were “so intent on making everything numerical” that they frequently missed seeing what was there to be seen.

Barbara McClintock
Nobel Prize Laureate

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Concepts and Applications, 5th edition, revised and expanded
by Johan Gabrielsson and Dan Weiner

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Foreword

Pharmacokinetics is that branch of science, which deals with the time course of drug in the body. Specifically it is the study of drug absorption, distribution and elimination. The companion subject of pharmacodynamics deals with the time course of drug action and is intimately linked to pharmacokinetics. As Lord Kelvin said:

“When you can measure what you are speaking about, and express it in numbers, you know something about it: but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind: it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of science.”

This is especially true of pharmacokinetics/pharmacodynamics (PK/PD) and modern PK/PD has developed into a relatively sophisticated mathematical discipline.

The importance of PK/PD in drug development is becoming increasingly recognized and now permeates the program from preclinical development through to Phase IV clinical trials. Specifically in preclinical studies, PK/PD is used to support drug discovery, interpret toxicokinetic experiments and via physiological modeling to extrapolate from animal to man. In the clinical program PK/PD is used to support dose-finding and dose-escalation studies and there is at least one instance where it has been used to recommend a dose which was not originally studied in the efficacy-safety studies. More recent applications include the concentration-controlled clinical trial and population PK/PD.

However like all biological experiments, PK/PD data is noisy and one has to use sophisticated data analysis techniques to estimate parameters of interest. Therefore a scientist working with PK/PD data has frequently to fit a model to experimental data. One has to be careful about the term model as applied in PK/PD. There are a number of so-called model independent methods that have become popular recently. However in a PK/PD context model independent implies fewer assumptions about the structural PK/PD model. Even with these methods one is often faced with fitting some empirical expression to the data, for example a sum of exponentials, and when I talk about fitting models to data, it is meant in this sense.

Most models used in PK/PD are nonlinear functions of the parameters of interest and consequently severe data analysis problems arise. Therefore nonlinear regression and maximum likelihood techniques have to be used which are much more computer intensive than their linear counterparts. In addition there are several theoretical problems specific to nonlinear models, such as nonuniqueness of the solution and the estimation of confidence intervals. Weighting schemes are a particular problem for PK/PD data as it is generally impossible to get replicate measurements.

Professional scientists but amateur statisticians often carry out PK/PD data analysis. Consequently the scientist working in the PK/PD area is dependent on the availability of good software packages. Despite the lack of a complete understanding of the methodology the user of such packages needs to be convinced of their reliability and accuracy. Although it is extremely difficult to completely validate a nonlinear regression program some, perhaps even extensive, testing is required. As a final caveat I would note that it is incumbent on the PK/PD scientist to obtain a reasonable understanding of the methodology behind a software package if he or she is going to be able to correctly interpret the output and diagnostics. It is also desirable that the software producer should provide adequate user support.

The current book is an evolution of the original text, which appeared in 1994, 1997, 2000 and 2010. It has been expanded to over 1000 pages, an expansion which mirrors the growth of the subject over

the last decade. It is also testament to the increasing sophistication of PK/PD analyses being undertaken by scientists working in the drug discovery/development arena. We are seeing a growth in mechanistic rather than empirical modelling and the current text contains an extensive library of mechanistic models, particularly in the area of pharmacodynamics. In the foreword to the second edition I concluded that the book would provide a valuable introductory text to new researchers and a useful reference for established scientists. In addition the book will be a useful reference for a variety of undergraduate courses and could be used to support a graduate course in PK/PD.

Leon Aarons
Manchester, 2015

Preface to the 5th edition

The 5th edition of *Pharmacokinetic & Pharmacodynamic Data Analysis: Concepts and Applications* continues the central thesis of the first four editions: How do we go from data to insight in the most effective way? That can probably be done by exposing ourselves to a large number of real life datasets and situations, and solve these problems by pen, paper, and computer. The previous editions of the book have served as course material during a number of basic and advanced courses within academia, and at numerous pharmaceutical companies and regulatory agencies all over the globe. Therefore, a substantial effort has been invested into the new pharmacokinetics and pharmacodynamics sections, including many new and updated Case Studies.

The five most common dysfunctions of a kineticist/modeler are lack of experience with exploratory data analysis; too much trust in the modeling software; weighting away data; slavery under formulas; and, lack of holistic view of the analysis-modeling process. The book serves to remedy parts of these dysfunctions, and besides being a repository of kinetic and dynamic datasets and modeling situations, it is meant to serve as a text on points to consider in biological data analysis in general. The audience is still industrial pharmacokineticists, pharmacologists, clinical pharmacologists, bioanalytical scientists, toxicologists and scientists within academia and regulatory bodies.

The basic concepts presented here are fundamental to the pharmacokinetic and pharmacodynamic field. Most are common knowledge among professionals and have been learned through education, experience, observation and reading. Other ideas have evolved in my own practice and through the experience of teaching students and observing and evaluating their work. Some of these thoughts have been formulated in attempting to help students and colleagues overcoming common mistakes and misconceptions typical among kineticists and junior modelers. A related aim is to build knowledge of points to consider when analyzing and communicating data. The text addresses ‘What kind of data does one need to collect in order to answer a specific question?’ The text is a compilation of different viewpoints worth considering in biological data analyses. Over the years this book has evolved from focusing on the technicalities of nonlinear regression to dissecting and exploring the biology behind a concentration-time or response-time course. Having taught *pattern recognition* since the mid 80s, with an increasing interest of this topic among students, this subject is further developed within Chapter 6. A new Case Study on target mediated drug disposition is also included as a tutorial that covers different aspects of antibody kinetics and the use and abuse of the Michaelis-Menten constant K_m as an affinity parameter.

This book is envisioned as a beginning. The reader is encouraged to seek out additional sources and knowledge on all the subjects offered here. Pharmacokinetics is an exciting and challenging science, particularly when you couple it to a pharmacological response. Recommended complementary texts are *Clinical Pharmacokinetics* by Rowland and Tozer, and *Pharmacometrics* by Ette and Williams.

I would like to acknowledge colleagues in academia and pharmaceutical industry for their generosity and support towards kinetic and dynamic reasoning. The vast knowledge of professors Stephan Hjorth (pharmacology) and Bert A. Peletier (mathematics) have been invaluable throughout the work on this and earlier texts. Appreciation also goes to Björn Tillman Printografen AB for the professional book design, and to the Swedish Pharmaceutical Press for agreeing to publish the 5th edition.

Johan Gabrielsson
Gothenburg and Uppsala, November 2015

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