

Kwantitatieve Methoden

Book Review Section

Book Review Editor: Alex J. Koning

Book review 72B41

MOYÉ, LEMUEL A. (2003).

Multiple Analyses in Clinical Trials. Fundamentals for Investigators.

Statistics for Biology and Health. Springer-Verlag, Berlin.

ISBN 0-387-00727-X, XXIII, 436 p. 33 illus., Hardcover, EUR 89,95.

According to the preface, this book is written for clinical investigators and research groups within the pharmaceutical industry, medical students and regulators.

The author discusses many aspects of the design, the execution and the analysis of clinical investigations. Special attention is paid to the handling of multiple tests and subgroup analyses. His discussions concern theoretical backgrounds, implementations and actual examples.

I admire the eloquency of the author. In the book he pictures in great detail the difference between biostatistics and epidemiology. The epidemiologists are the whiz kids who ingeniously analyse case studies and come to their conclusion about cause and effect. There have been historical successes where the cause effect relations were so unambiguous that mathematics played no role. The finding of false conclusions is more or less reduced by existing explicit criteria used to construct causality arguments. These are summarized in an appendix. In contrast biostatisticians make a mathematical model of systematic and random effects, and then investigate this by means of some sampling design. The author does a remarkable job in spending several pages to soften the minds of the nonmathematical readers to make them appreciate the results of mathematics. For example, where probability would have started as an experimental science, he argues that the mathematization by Kolmogorov a.o. lead to new results that were not detected yet. His message is, that mathematics is useful to indicate interesting phenomena worth while to look at.

The message that investigations must be set up properly, and must be executed according to plan, is made clear not only on mathematical grounds. An example is given where some treatment for heart failure is investigated, where the primary goal was to show that the treatment lead to fewer complications and as a secondary goal resulting mortality was analysed. It happened that the treatment did not lead to significant less complications, and the regulators did not accept the significantly reduced mortality as a criterion to approve the treatment. The pharmaceutical firm was so convinced about the reduced mortality that it did a new investigation to show the mortality reducing

effect. Unfortunately for the firm, this effect did not show up any more. That is, regulators are not merely an inconvenience, they may be right in their rejections more often than you think.

In the discussion about multiple hypotheses, that is more than one hypothesis each of which to be tested against a corresponding alternative, the author argues that prospectively distributing the total available significance level additively over the different hypotheses, as one would do in a Bonferroni approach, is often wasteful in clinical investigations. Moyé works out a concept of dependency of the family of hypotheses in the sense that given two hypotheses, false rejection of one hypothesis may favor false rejection of the other. Subsequently the dependency of the total family of hypothesis is expressed in terms of one number, the dependency parameter. This idea comes back in further discussions. One of the more mathematical references is the article by Hochberg and Westfall in Handbook of Statistics Vol. 18 (P.K. Sen and C.R. Rao Eds.). In this light one might consider the book as an elaboration for the intended audience, together with a lot of details how to handle the techniques in practice. According to the preface, the book is an essentially nonmathematical discussion. Nevertheless the mathematics in it are clearly stated and expressed in syntactically correct formulas. That makes it easy to see what the author has in mind. The only point where I felt uncomfortable was the discussion leading to the dependency parameter, where the author considers the conditional probability of no Type I error for one test given no Type I error for an other test (or even no Type I error for several other tests). The reader has to find out himself, what the author has in mind as the actual probability space.

Without any doubt, the book is a valuable source of ideas for the intended audience. For statisticians it is an interesting source of experimental setups, that are actually used in practice and that consequently are worth while to be studied. Each chapter contains a list of problems to be solved by the reader. They range from conceptual questions, to simple calculus exercises, given the theory. The chapters conclude with a list of references. The book contains 5 appendices, about causality criteria, "random research" and sample size calculations, one with excerpts from the Code of Federal Regulations, and one with more results on dependency of hypotheses.

*dr H. W. M. Hendriks
Subfaculteit Wiskunde
Katholieke Universiteit Nijmegen*