MR2987767 (Review) 62L05 62-02 62J02 62L10 62P10

Bartroff, Jay (1-SCA)**; Lai, Tze Leung** (1-STF-S)**; Shih, Mei-Chiung** (1-STF-HPL)

★**Sequential experimentation in clinical trials.**
Design and analysis.
Springer Series in Statistics.
Springer, New York, 2013. *xvi*+237 *pp. ISBN* 978-1-4614-6113-5; 978-1-4614-6114-2

As reported by A. S. Hedayat [Statist. Sci. **20** (2005), no. 3, 302–315;MR2189003], when Professor Sir Ronald Fisher was asked in 1952 by the late Walt Federer "If you were a young statistician who had just received a Ph.D., what line of statistical research would you pursue today?", the great man responded: "Ah yes, if I were just starting my research career, I would work on sequential experimentation. That Abraham Wald did an ingenious thing with his work on sequential sampling."

However, no explosion of publications on the subject happened at that time, as might have been predicted from Fisher's comments. This contrasts sharply with the large number of books that followed Fisher's own work on analysis of variance and design of agricultural experiments. One can but ponder what the subject of sequential analysis would look like today if Fisher had started work in medical rather than agricultural research.

Wald himself had worked in the defense industry during WWII, but there were many ad hoc sequential methods for production and quality control already in place. For them, there was little theoretical foundation; however, they had proved to work remarkably well in practice. Of course, in the years following Wald there were published journal papers on the theoretical developments by such authors as T. W. Anderson, H. Chernoff, J. Kiefer, H. Robbins, C. Stein, J. Wolfowitz and others. An important milestone in the mathematical development of the subject was the 1985 book *Sequential analysis* [Springer Ser. Statist., Springer, New York, 1985; MR0799155 (87h:62145)] by David Siegmund, published in the same Springer Series in Statistics as the book under review. The volume of 27 contributed chapters in [*Handbook of sequential analysis*, Statist. Textbooks Monogr., 118, Dekker, New York, 1991; MR1174296 (93g:62102)] edited by B. K. Ghosh and P. K. Sen is another invaluable resource.

The explosion of research in sequential methods followed later, and this was stimulated by applications to medical trials. This had been foreseen by P. Armitage in his 1960 book *Sequential medical trials* [Charles C. Thomas, Springfield, Ill, 1960; MR0143321 (26 #880)]. Much later, in 1983, J. R. Whitehead published the first edition of his book *The design and analysis of sequential clinical trials* [Ellis Horwood Ser. Math. Appl., Horwood, Chichester, 1983; MR0793018 (88b:62151)]. At the same time, there began an emphasis on group sequential methods needed for formal interim monitoring of results accruing from long-term clinical trials. This need was instigated by the U.S. National Institutes of Health in their model of use of Data Safety Monitoring Boards (DSMBs), also known as Data Monitoring Committees (DMCs). Still there was a paucity of books on the subject. A comprehensive treatment of these methods first appeared in 2000 in the book by C. Jennison and B. W. Turnbull [*Group sequential methods with applications to clinical trials*, Chapman & Hall/CRC, Boca Raton, FL, 2000; MR1710781 (2000f:62004)], which was followed by the 2006 book by M. A. Proschan, K. K. Gordon Lan and J. T. Wittes [*Statistical monitoring of clinical trials*, Springer, New York, 2006].

The most recent explosion in sequential statistical methods has been in so-called adaptive design. In the past ten years, hundreds of articles on the subject have appeared in the literature. Adaptive designs allow for more drastic mid-course changes in the original clinical trial design, which can be based on the accumulating data and/or external information, all the while still controlling for various statistical properties. Notable books in this area include *Adaptive design methods in clinical trials* [S.-C. Chow

and M. Chang, Chapman & Hall/CRC Press, Boca Raton, FL, 2007] and especially the comprehensive *Handbook of adaptive designs in pharmaceutical and clinical development* [CRC Press, Boca Raton, FL, 2011; MR2789104 (2012d:62006)], edited by A. Pong and Chow and published in 2011. An alternate approach to adaptive sequential trial design is based on the Bayesian paradigm; an excellent book on this subject is the one by S. M. Berry et al. [*Bayesian adaptive methods for clinical trials*, Chapman & Hall/CRC Biostat. Ser., 38, CRC Press, Boca Raton, FL, 2011;MR2723582].

This brings us to 2013 and the book currently under review. As the authors point out in the introductory Chapter 1, sequential statistical methods have found a wide range of applications—e.g. stochastic approximation, simulation optimization, control theory, design of experiments and many more. However, there is no doubt that it is the clinical trials application that is driving the current interest, and this is also reflected here in their book. The book gives a thorough mathematical treatment of the subject on the level of the 1985 book by Siegmund [op. cit.] and from which it follows on naturally. However, the practitioner can also find much of interest here with the narratives, discussion and commentary that are interspersed with the mathematics. Of particular note is the fact that each chapter concludes with a section of "Supplements and Problems". This is unusual in modern books on sequential analysis and makes it particularly suitable for use as a textbook in a graduate course on mathematical statistics.

Chapter 1 gives a brief overview of the different phases I–IV of clinical trials, and a short introduction to sequential and group sequential designs. It also provides a succinct commentary comparing the frequentist and Bayesian approaches. The chapter concludes with an overview of relevant available computer software.

Chapter 2 discusses statistical dose-finding methods for early phase clinical trials. These include: nonlinear regression models; models for pharmacokinetics and pharmacodynamics such as the Emax model; theory of optimal design; up-and-down, $3+3$ and CRM designs.

Chapter 3 starts with a treatment of Wald's classic sequential probability ratio test (SPRT). Asymptotic results are developed to handle composite hypotheses using sequential generalized likelihood ratio (GLR) tests. Ideas of dynamic programming and Bayes sequential tests are introduced. This facilitates the proof of the Wald-Wolfowitz theorem on the optimality of the SPRT. The chapter continues with a discussion of asymptotic approximations to Bayes sequential tests and their properties. It concludes with a treatment of approximate dynamic programming (ADP) and some applications.

Chapter 4 begins with a brief description of standard group sequential methods. This summary is too short to be useful, and the reader would be well advised to refer to the books by Jennison and Turnbull [op. cit.] or Proschan, Lan and Wittes [op. cit.], which the authors cite. The remainder of the chapter describes the results of a somewhat different approach introduced by T. L. Lai and M.-C. Shih [Biometrika **91** (2004), no. 3, 507–528; MR2090619 (2005c:62139)], which modifies the fully sequential GLR tests of Chapter 3 for the group sequential setting.

Chapter 5 describes applications of sequential methods described in the earlier chapters to the testing of incidence rates of adverse events in vaccine clinical trials and in post-marketing safety evaluation. The last section discusses the application of the methodology to the sequential change-point detection problem.

Chapter 6 concerns the special case of clinical trials with failure time or time-to-event endpoints that are subject to random censoring. For the reader, some previous knowledge of survival analysis is advisable. The chapter starts with brief descriptions of the Kaplan-Meier estimator of a survival function, two-sample rank tests, and the Cox hazard rate regression model. This is followed by an in depth discussion of the

well-known Beta-Blocker Heart Attack Trial (BHAT) published in 1982, including such issues as error spending, choice of time scales and the role of conditional power. Sections 6.5 and 6.6 give a detailed summary of the asymptotic distribution theory that is needed.

An important issue is inference (p-values, point estimates and confidence intervals) upon termination of a trial that permits early stopping. Unlike the case of a fixed sample design, this problem is not straightforward because of (i) the inherent bias of the maximum likelihood estimator and (ii) the two-dimensional nature of the sample space. Section 7.1 gives an overview of popular methods while Section 7.2 features the hybrid resampling method, proposed by C.-S. Chuang and Lai [Biometrika **85** (1998), no. 2, 317–332; MR1649116 (2000f:62103)], for constructing confidence intervals. The later sections look at the specific case of censored survival data. The discussion includes tests on a secondary parameter such as the regression coefficient of a concomitant explanatory variable in a Cox model. It should be noted that this method is not easily generalized to the case of true multiple endpoints (which may be of equal importance or hierarchically ordered). Then such testing issues as family-wise error rates become relevant [see e.g. D.-I. Tang and N. L. Geller, Biometrics **55** (1999), no. 4, 1188–1192, doi:10.1111/j.0006-341X.1999.01188.x].

The last chapter is entitled "Adaptive Design of Confirmatory Trials". This has recently become a very broad subject with an increasingly large literature. Thus it is impossible to cover the subject in just one chapter. Naturally the authors concentrate on their own work in this area on mid-course modification of sample size. For example, J. Bartroff and Lai [Stat. Med. **27** (2008), no. 10, 1593–1611;MR2420330] used the GLR statistics introduced in Chapter 3 in an efficient adaptive 3-stage test. In a later section, the authors look at the adaptive choice between superiority and non-inferiority trials. The chapter does not cover other important issues of adaptive design in confirmatory trials. These include adaptive choice of target population ("enrichment" trials); adaptive choice of treatments or dose levels ("seamless" designs); adaptive choice of test statistic as information on assumptions emerge; adaptive allocation to assign fewer patients to inferior treatment arms; and other goals.

In summary, the practitioner may not benefit much from this book, but it is definitely a "must read" for anyone doing research into the theory or methodology of modern sequential statistical analysis.   *Bruce W. Turnbull*