good texts out there with excellent chapters on specific topics but no single textbook has met the needs of a full semester course that provides an appropriate background and focuses on current methods. Instead, I have cobbled together lectures from multiple sources. For instance, I have used selected chapters from classic texts by Sham (1998) and Lange (2002), but overall their focus is on linkage rather than association methods and are highly mathematical, which can be difficult for a mixed student audience. I have also used Thomas (2004) and Ziegler and Konig (2006), both of which are excellent texts but are focused more on genetic epidemiology rather than statistics. Foulkes (2009) is a great resource but with a primary emphasis on implementation in R. Hence, I was delighted to see that Nan Laird and Christoph Lange, both leaders in the field and with multiple years of combined teaching experience at Harvard, have deftly and bravely set forth to rectify this situation with their slim but comprehensive tome *The Fundamentals of Modern Statistical Genetics*.

The text is logically organized starting with a thorough yet highly accessible review of molecular genetics. Chapters 1–4 provide a fascinating history of Mendel's experiments and laws and seamlessly incorporate discussions of meiosis, crossover, and haplotypes. From the start, the authors wisely introduce a generalized linear models framework to discuss penetrance functions and various genetic models. I also commend the authors for presenting the concepts of population stratification and admixture up front rather than reserving these topics for later discussion in the context of association studies. Chapter 5 provides a thorough discussion of gene mapping concepts including an excellent explanation of linkage disequilibrium. Chapter 6 gives a brief introduction to linkage analysis. The primary intention of this chapter is to provide a better understanding of genetics rather than a comprehensive treatment of methods for linkage analysis, which are no longer common in the study of complex human diseases. Chapters 7–9 focus on recent developments in the analysis of family- and population-based association studies. Not surprisingly, since Laird and Lange developed and published the bulk of these methods (e.g., FBAT/PBAT) over the past decade, these chapters are simply outstanding and are the highlight of the book. Uniquely, the last chapter provides a very clear step-by-step discussion for designing and analyzing GWAS. This chapter could easily serve as a stand-alone tutorial for investigators who desire a concise introduction to GWAS.

Each chapter concludes with relevant exercises that provide an opportunity to obtain a more in-depth understanding of the material presented in the chapter. The level of the problems is ideal for a graduate level biostatistics course because no assumption is made of prior training in genetics but does assume a previous intermediate level course in statistics. Examples throughout the text are drawn from interesting and significant genetic studies of human disease; the authors played a key role on many of these studies including those in asthma and Alzheimer's. Most of the figures in the text are essential and quite informative; unfortunately, a handful of figures (e.g., figures 4.3, 5.3, 5.7, 10.1, and 11.1) are of poorer quality (presumably power point slides or screen snapshots did not translate well into publication quality illustrations) and are difficult to read.

An inevitable limitation of *The Fundamentals of Modern Statistical Genetics* is that it does not cover more recent advancements and ends with GWAS. The title perhaps is unfortunate in that nothing stays "modern" for long in this field. Recently, NGS studies have taken center stage in investigations of genetics and complex human disease; however, this text does not cover analytic strategies for these types of data. Hence, in any full semester course, the last few lectures will need to draw from other sources in order to cover relevant new types of genetic/genomic technologies and corresponding methodological advancements.

In their book, Laird and Lange strike a sensible balance between molecular genetics background, statistical theory, and genetic epidemiologic principals. The text is concise and very well written, thoughtfully organized, and provides clear and relevant examples with useful exercises. *The Fundamentals of Modern Statistical Genetics* is destined to become a classic textbook for introductory courses in statistical genetics. It can also serve as a valuable resource for investigators new to the field of statistical genetics.

References

Foulkes, A. (2009). *Applied Statistical Genetics with R: For Population-Based Association Studies*. New York: Springer.

Lange, K. (2002). *Mathematical and Statistical Methods for Genetic Analysis*. 2nd edition. New York: Springer.

Thomas, D. (2004). *Statistical Methods in Genetic Epidemiology*. New York: Oxford University Press.

Sham, P. (1998). *Statistics in Human Genetics*. New York: Oxford University Press.

Ziegler, A. and Konig, I. R. (2006). *A Statistical Approach to Genetic Epidemiology*. Weinheim: Wiley-VCH Verlag.

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YIN, G. **Clinical Trial Design: Bayesian and Frequentist Adaptive Methods.** John Wiley & Sons, New York, 2012. Xi + 354 pp. $115.00/€99.90, ISBN 9780470581711.

Knowledge explosion in modern medicine and disease biology is changing the way of drug development. There is great interest in clinical trials designed with adaptive features (i.e., changes in design or analyses guided by examination of the accumulated data at an interim time point during the course of the trial). There are many potential advantages of running clinical trials in an adaptive fashion such as producing shorter trial duration, requiring fewer patients, more likely selecting or demonstrating an effect if there exists one, treating more patients with more effective drugs according to their biomarker profiles, etc.

The book starts with an introduction of key components of clinical trials (Chapter 2), and a comparison between frequentist and Bayesian statistics (Chapter 3), and then moves to designs with adaptive methods with both frequentist and Bayesian approaches for phase I–IV clinical studies.

Chapter 4 introduces a variety of statistical methods for dose finding, which can be classified into two classes: rule-based (e.g., the 3 + 3 design) and model-based (e.g., the continual reassessment method). Due to small sample size in a typical phase I trial, model-based designs provide more advantages because they can borrow information or strength across the doses.

Chapter 5 covers both single-arm and randomized phase II trial design methods. In particular, adaptive randomization may be incorporated to phase II designs to enhance trial ethics by assigning more patients to better treatment arms. The seamless phase I/II trial may also be designed to fully utilize the data collected in both phase I and phase II trials, in which toxicity and efficacy are jointly evaluated for the drug's risk and benefit trade-offs.

In Chapter 6 of the book the author covers many topics in phase III trial designs, such as sample size versus power, sample size for survival data and correlated data, group sequential methods, and multiple testing issues. Differences in superiority and noninferiority trials are neatly summarized from a practical design point of view. The principle of intent-to-treat analysis is clearly explained. Limitations of phase I–III trials and reasons to initiate phase IV trials are summarized as well.

Randomization remains the gold standard to control potential bias in evaluating treatment effect across different arms. Chapter 7 is devoted to various randomization procedures that can be classified into two buckets: One fixes allocation probabilities and the other allows the randomization probabilities to change throughout the trial. The later, called adaptive randomization, can be covariate-adaptive to balance the baseline prognostic factors or outcome-adaptive to assign more patients to better treatment arms. This chapter concludes with a comparison between fixed and adaptive randomization.

More advanced topics that are receiving more and more attention in the recent decades are late-onset toxicity, combination therapies, and targeted therapy designs. Chapter 8 discusses the fractional 3 + 3 design and several continual reassessment methods to meet the needs when toxicity outcomes cannot be quickly observed in a dose finding study. These methods allow for delayed response and continuous accrual, and they can substantially shorten the trial duration.

Disease biology is very complicated and often involves various biological mechanisms. To optimize the treatment strategy, a combination of drugs is often under investigation to target multiple disease pathways. Chapter 9 covers a broad range of statistical methods for dose finding in drug-combination trials. These methods can also be applied to other situations: One is to jointly search for the optimal dose level and dose schedule, and the other is dose finding with ordered groups.

With the ground-breaking concept of personalized medicine, identification and validation of biomarkers for therapeutical use become increasingly important. Chapter 10 focuses on the most updated development in targeted therapy designs that are either all-comers or enrichment designs, depending on the depth of understanding on the biomarkers and assay development at the time of trial design.

All the chapters start with background information and motivating examples, and end with a summary of the key considerations for each design option. The book explains when to use Bayesian and when to use frequentist approaches to clinical trial design. It clearly characterizes the meaning of "adaptive design" from both perspectives. This is a distinctive feature from other clinical trial books, which are either all Bayesian or all frequentist. Exercises at the end of each chapter are prepared in a step-by-step fashion, which makes it very practical and handy for statisticians in industry. The book accompanied with software developed at MD Anderson Cancer Center provides an excellent reference for everyone who works in clinical trial field.

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ANDO, T. **Bayesian Model Selection and Statistical Modeling.** CRC Press, Boca Raton, Florida, 2010. Xiv + 286 pp. $89.95/£59.99, ISBN 9781439836149.

This book is about model selection from the Bayesian viewpoint. The author is Associate Professor of Management Science at Keio University in Japan. He has been a visiting scholar in Chicago, UC Berkeley, and UCLA. The aim of the author is to "provide comprehensive explanations of the concepts and derivations" of the different model selection criteria together with a range of practical examples. In many ways the book satisfies these aims but I feel it would benefit from more comparison between methods and discussion of their advantages and disadvantages in addition to the description and examples he gives.

The first four chapters give a fairly standard account of Bayesian analysis, largely of a single model. Chapter 1 is a short introduction to statistical modeling and describes how the book is organized. Chapter 2 discusses the basics of Bayesian analysis, including the likelihood and the prior and calculating the posterior analytically. There is a brief discussion of how you might use the marginal likelihood to choose between different multiple regression models. Chapter 3 is about asymptotics and Laplace's method to calculate integrals. The fourth Chapter is about different simulation-based approaches to calculate the posterior distribution. The remainder of the book is about choosing between competing models. Chapter 5 is by far the longest in the book. It considers model selection and emphasizes the marginal likelihood and Bayes factors but also considers the Bayesian information criterion (BIC) and the generalized BIC. Chapter 6 discusses computing the marginal likelihood using various simulation techniques. Chapter 7 describes various information criteria including the author's own Bayesian predictive information criterion, the Deviance information criterion, and other generalizations and modifications. A theoretical derivation of some of the information criteria is given in Chapter 8. The final section of that chapter gives a brief comparison of some of the properties of the model selection methods. The final chapter gives a short treatment of Bayesian model averaging.

This book is good at describing the various methods, which have been proposed in this area. It also gives good examples of the use of most of the methods, albeit with a preponderance