Book Review

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Genetic Dissection of Complex Traits. Edited by D. C. Rao and Michael A. Province. San Diego: Academic Press, 2001. Pp. 583. $119.95.

Genetic Dissection of Complex Traits provides an extensive overview of contemporary methods for statistical gene mapping. It is definitely not intended to be a cookbook. Rather, it aims to provide balanced views of the merits and weaknesses of various methods, as a way to promote further discussion. The book includes discussions of model-based and model-free linkage analysis, candidate gene and linkage disequilibrium approaches, gene-environment interaction, rates of false-positive results, and power. The work is based on a symposium held in honor of Newton Morton, one of the major figures in genetic epidemiology. To benefit the most from this book, readers should have had some prior exposure to genetic epidemiology and/or statistical genetics. Proofs and mathematical details are kept at a minimum.

Better genotyping and faster computers have allowed the application of a wide array of statistical methods to specific problems in genetic epidemiology. The flip side of the coin is that the availability of so many choices has made study design and data analysis far more complicated. The choice is not limited to purely statistical matters, such as selecting one estimation or testing procedure over another. It reaches further into fundamental matters, such as deciding between linkage or association studies.

Unfortunately for the practitioner, the information that could help in such a choice is often scattered throughout the literature. Individual research papers are subject to space limitations. Consequently, for example, the power of a linkage test is determined for a limited number of sampling schemes, none of which may be applicable to a particular situation. To make the situation more complex, the "optimality" of a particular sampling scheme depends on both the test statistic and the genetic model under consideration. Multiple sampling schemes will thus have the same efficiency. Given these circumstances, it not surprising that the evaluation of the relative merits of competing approaches to a given problem all too often concludes with a resounding "it depends" or that the word "optimal" is usually followed by a long disclaimer.

While we await that magical flowchart that will take us from a set of easily identifiable conditions to the best study or test for the situation at hand, we welcome books, such as *Genetic Dissection of Complex Traits,* that outline some of the major findings from several years of study. Generally, the book does take the view that the added methodological complexity is well balanced by the promises (listed on the back cover) of being able to "dissect complex traits" and "fulfill the promise of the human genome project." At the same time, the book makes it quite clear that genetic epidemiology remains an expensive proposition and that hard choices must be made during both the design of the study and the analysis of the data.

Genetic Dissection of Complex Traits is a selection of independent chapters, rather than a systematic introduction to genetic epidemiology. It is organized in 32 chapters that are grouped in nine sections. The first section and the Appendix review Newton Morton's contributions to genetic epidemiology. Section 2 provides background material. Section 3 focuses on phenotyping and genotyping issues. Sections 4 and 5 cover model-based and model-free linkage analysis. Sections 7 and 8 discuss approaches to efficient study design and the problem of false-positive results. Section 9, which, in a way, should be read first, consists of two chapters. One shows the difficulties involved in the study of complex traits, with essential hypertension as an illustration. The other is an overview, written by Morton, regarding what has been achieved in methods for genetic epidemiology and what could be expected.

The background material is found in chapters 4–6. Chapter 7 provides a very neat and compact introduction to genotyping issues, including availability of resources, estimates of cost, and methods of quality control. In addition, each additional chapter provides some background, as well as extensive reference lists, on the method it examines. Chapters 4 and 5 introduce the basic concepts of familial resemblance, heritability, linkage, and association that are explored in more detail in the remainder of the book. Chapter 6 focuses on phenotype definition, a key issue in genetic epidemiology. In particular, the authors show the great decrease in power that occurs with poor phenotype definition.

Section 4 covers model-based approaches (i.e., conducting the analyses under an assumed mode of inheritance). The chapters include direct comparisons to the model-free methods covered in section 5. Chapters 8 and 9 introduce the LOD-score and the MOD-score methods. Chapter 10 sumarizes the advantages and disadvantages of the model-based methods.

Methods for model-free quantitative-trait linkage analysis are discussed in sections 5 and 6. Chapter 11 reviews the Haseman-Elston method for quantitative-trait linkage analysis. Chapter 12 is a thorough overview of variance-component approaches, with a discussion of robustness and power. An implementation is described in chapter 13. Quantitative-trait methods are further elaborated upon in later sections of the book, with a chapter on approaches that use genomic region sharing (chapter 21) and one on data reduction strategies in multivariate linkage analysis (chapter 22).

Case-control studies are discussed in chapter 14, with strong emphasis on the effects of allelic heterogeneity. Chapter 16

reviews the use of transmission/disequilibrium tests for the detection of gene-environment interactions. Chapter 25 considers the effect of population structure on the performance of linkage disequilibrium mapping.

Although most of the chapters of this book focus on a statistical method and then address implications for study design, the book also includes several chapters that specifically focus on the latter topic. For example, chapter 15 compares the cost of linkage and association methods, for both continuous and discrete traits. Chapter 23 examines the resolution of genome-scan approaches. Chapter 27 compares one-stage and two-stage genotyping strategies. Chapters 28–30 provide a lucid description of issues related to false-positive results in linkage and association studies. These include a discussion from a strict frequentist point of view (chapter 28) and a discussion of a sequential analytic approach (chapter 30).

Lastly, the book devotes three chapters to emerging methodologies: meta-analysis (chapter 18), classification method for heterogeneity by use of recursive partitioning and regression trees (chapter 19), and application of neural networks for gene finding (chapter 20).

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