
Preface

Modern genetic analyses, with phenomenal technological advances, now permit deeper interrogation of genomes with the intent of constructing more accurate and comprehensive genotype to phenotype maps. However, as recognized by the authors of the chapters in this volume, a key to defining this map requires inclusion of factors not always explicitly incorporated into genetic analyses—namely, epistasis or interactions. Not doing this has led, at least in part, to less than perfect descriptions of genotype to phenotype maps and has motivated the term, missing heritability, or the amount of genetic variance of a trait that is left unexplained. The key is that even with enormous quantities of data, fully explanatory genetic models evade description, if inappropriate simplifying assumptions are made. The focus of this book is to explore how we can avoid making these assumptions and do so in ways that are practical.

One key to unraveling the role of epistasis in genotype to phenotype maps is to minimize the extraordinary number of possible interactions that can be assessed in genome-wide data sets, hence predefining the set of possible models of epistasis that are to be included in analyses. Such filtering can serve as a precursor to statistical or data mining analyses, both of which are covered in this book. With respect to appropriate statistical analyses for the detection of epistasis, it is important to precisely define the meaning of epistasis to be included in analyses, as historically more than one definition has existed, and they can create ambiguities in terms of how epistasis is tested. Therefore, several of our authors take substantial space to define epistasis with respect to how to appropriately analyze it. Lastly, genomic data can be mined using a variety of computational tools that make no a priori assumptions about the underlying genetic models. These are promising but often make interpretation difficult.

As any genotype to phenotype map is determined by the history of the genome in question, it is important to define how evolutionary processes may have shaped a trait's genetic architecture. This is addressed in Chapter 1. Methods that reduce the multiple testing burden are described in Chapters 2 and 3. An alternative approach in model systems is to perturb the “natural” genetic system by generating de novo mutations and assessing their roles via quantitative trait locus mapping in multiple backgrounds (Chapter 4). In systems not amenable to such manipulation (e.g., humans) epistasis analyses may depend on well-chosen candidates, an approach shown to work for neuropsychiatric diseases where epistasis and pleiotropy appear to overlap (Chapter 5).

In Chapter 6 the authors discuss the decomposition of genetic variance into its individual components, how this underpins our understanding of epistasis, and how this may affect the outcome of selection. Measuring epistasis is a key topic of Chapter 7, where it is argued that how epistasis is measured can appear to minimize its effects in an evolutionary context. The role of measurement of epistasis is also taken up in Chapter 8, where it is shown that the arbitrariness of epistasis or interaction can be eliminated by applying measurement theoretic constraints. Extending the allelic average excess and average effect to two or more loci is proposed as a novel analytical approach in Chapter 9. By explicitly defining capacitating epistasis in Chapter 10, the authors develop means to examine its effects.

Distinct from most other chapters, the authors of Chapter 11 take an explicitly epidemiological view of what they define as “compositional” epistasis, and how to best detect it. Chapter 12 examines Boolean function interactions in Age-related Macular Degeneration data and finds relevant gene–gene and gene–environment interactions. Using information theory to detect and characterize epistasis is the focus of Chapter 13. Chapters 14 and 15 examine the application of network building to better elucidating epistasis. Agnostic data mining methods are the core of Chapters 16 and 17 where two methods, multifactor dimensionality reduction and ReliefF, are described. Lastly, artificial intelligence methods are introduced in Chapter 18 as a means to detect epistasis in association studies.

Overall, we think that the chapters provide a comprehensive set of ideas that can help us elucidate epistasis in the context of modern data availability, and thereby help us to better understand the genetic bases of complex phenotypes and their evolutionary histories.

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<http://www.springer.com/978-1-4939-2154-6>

Epistasis

Methods and Protocols

Moore, J.H.; Williams, S.M. (Eds.)

2015, X, 350 p. 61 illus., 17 illus. in color., Hardcover

ISBN: 978-1-4939-2154-6

A product of Humana Press