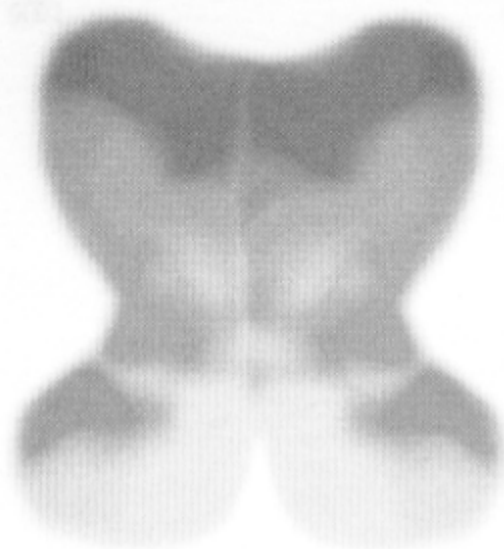




Preface

"For the geneticist there are accordingly three ways of examining anything. Through characters, he can examine function; through their changes, he can examine mutation; through their reassortment, he can examine recombination."

Francois Jacob in *The Logic of Life* (p. 224)

This book is intended for an advanced course in genetic analysis. The focus is on the basic principles that underlie genetic analysis: mutation, complementation (and its bridesmaids, suppression and enhancement), recombination, segregation, and regulation. Our goal is to provide insights into the biological and analytical processes that comprise each of these tools, and to explain their use. Our basic objective is to explain to you just what each of these tools, or operations, does, and how that operation or test can lie to you. Perhaps most importantly, the book is designed to teach you just how much you can learn when nature misunderstands your question. In other words, this is a book about genetic theory.

Although a discussion of genetic analysis inevitably requires the presentation of multiple examples, this is not to be considered as a textbook of genetic facts. Facts can sometimes change in the blink of an eye; but the basic analytical tools change rather more slowly. We have tried to be as comprehensive and catholic as possible in the choice of examples and organisms, drawing on examples from as many genetically tractable model organisms as possible, with even the occasional reference to humans. The book assumes the reader has a basic familiarity with the genetics of eukaryotes, as well as with the basic biology of prokaryotes and their viruses. We also take for granted a working knowledge of the three sirens of molecular biology: transcription, translation, and replication. In cases where specialized techniques are used or concepts required, we have endeavored to provide the essential background material.

We are obviously not the first authors to attempt to set forth the principles of genetic analysis. Indeed, this book follows in the footsteps of Pontecorvo's *Trends in Genetic Analysis* (Pontecorvo 1958) and Stahl's *The Mechanics of Inheritance*, 2nd edn. (Stahl 1969). We have also drawn heavily from courses taught by Professor Dean Parker, Professor Kenneth W. Cooper, and the late Professor Crellin Pauling at UC Riverside, and from courses taught by Drs. Jonathan Gallant, Leland Hartwell, and the late Drs. Larry Sandler and Herschel Roman at the University of Washington. RSH also acknowledges gratefully a

20-year on-going and intensive genetics tutorial with Professor Adelaide Carpenter at Cambridge.

This book had its beginnings while the authors were members of the Section of Molecular and Cellular Biology at the University of California at Davis. The support of the faculty and staff of that Section is gratefully recognized. The book was completed after RSH moved to the Stowers Institute for Medical Research in Kansas City. RSH gratefully acknowledges the support of many members of the Institute, and especially Dr. Bill Neaves, was critical to the completion of this project. His gratitude extends to Jim and Virginia Stowers, whose vision of "Hope for Life" extends far beyond the Institute they founded.

We are especially indebted to our editors at Blackwell for help during all phases of this project, but most especially for knowing when to prod and when to let us be – to Nancy Whilton and Nathan Brown, we offer a most sincere "thank you." Nancy showed a calmness that allowed us to respond to criticism in a constructive rather than a reactive fashion. RSH will long view the lessons learned from her to be the major reward of writing this book. Nathan was patient to the point of stoic and dedicated to the point of heroic.

Many people read and extensively commented on various drafts; we especially thank Professors Frank Stahl, Jim Haber, and Julia Richards. These three colleagues went far beyond anything we might have expected to help make this a "useful book." The debt to Julia Richards for thoroughly revising the section on LOD score analysis is enormous and the gratitude equally large. Our colleagues Mike Zwick, Kent Golic, Ken Burtis, Keith Maggert, Pam Geyer, Ting Wu, Mia Champion, and Kim McKim also read chapters and made important contributions. We also thank Dan Kiehart, Tim Stearns, Adelaide Carpenter, Tom Cline, Seymour Benzer, Carl Marrs, Michael Dahmus, and many others who took the time to answer questions or explain techniques. We thank David Harris, Charisse Orme, and Heather Peters for insightful comments and for proofreading the entire text. We owe a real debt to Ed van Veen for teaching us the math we should have known and for editing, re-editing, and sometimes rewriting much of chapter 7. A number of "outside reviewers" contributed significantly to the clarity and accuracy of the text: Celeste Berg, University of Washington; YiPing Chen, Tulane University; Todd Disotell, NYU; Richard Gaber, Northwestern University; Kim McKim, Rutgers University; John Osterman, University of Nebraska at Lincoln; Paul Ramsey, Louisiana Tech.

RSH also acknowledges a debt to Diana Hiebert and Nancy Lane for secretarial help, and for preserving his sanity. In that vein, he also, once again, acknowledges the muses Jewel, Harriet Schock, Meat Loaf, John Stewart, Trisha Yearwood, and Pam Tillis for keeping him company during much of the writing. RSH thanks his teenage daughter, Tara Hawley, for her assistance in creating the index.

The inception for this book was a course in Advanced Genetic Analysis taught by RSH at UC Davis. A large debt is owed to the students, and most especially the Teaching Assistants, of that course. We especially thank Shelley Force, Chris Boulton, Charisse Orme, Heather Peters, David Harris, Kara Koehler, Mike Zwick, Rachael French, Soni Lacefield, and Bill Gilliland for raising questions

that were the impetus for much of the book. Every point of clarity in this book came from wrestling with a question they asked. More than likely, it was answered badly (or gruffly) at the time. But it wasn't forgotten. The need to provide cogent answers to those questions rumbled about in our heads for years. Our effort to answer them properly is the book that is now in your hands.

Finally, the last section of this tome is a list of some 430 references. Despite every attempt to be complete, we know that we have missed citing many extremely well-done and important examples of genetic analysis. In our defense, we can say only that there came a time to stop reading and to actually write this book. Our apologies to those authors whose work was in the huge stack of "you know we really ought to discuss this" papers on the side of our desk.

"A genetic unit should be defined by a genetic experiment. The absurdity of doing otherwise can be seen by imagining a biochemist describing an enzyme as that which is made by a gene."

Seymour Benzer, *Scientific American*