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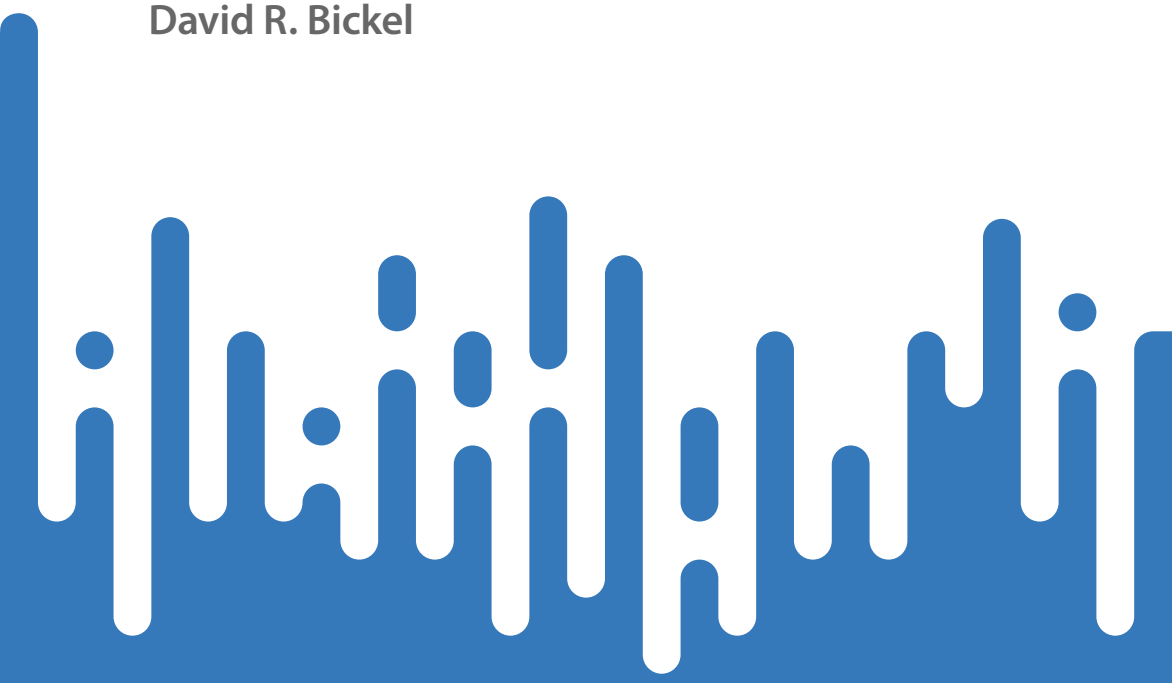
David R. Bickel



Phylogenetic Trees and Molecular Evolution

A Hands-on Introduction with Uncertainty Quantification Corrected

Springer

SpringerBriefs in Systems Biology

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To Mary Anna, beloved and highly favored

μακαρια η πιστευσασα οτι εσται τελειωσις τοις
λελαλημενοις αυτη παρα κυριου

Preface

Why This Book?

Brief Description

The book introduces molecular phylogenetics and explains how to interpret the results of evolutionary models, which by their nature only quantify a fraction of the uncertainty involved. The book is intended to introduce upper-level undergraduate and graduate students of biology to phylogenetic tree reconstruction and its dependence on models of molecular evolution. The scope encompasses basic concepts of estimating divergence times and ancestral sequences and of quantifying the uncertainty of the estimates.

Key features:

- Selective use of mathematics
  - An informal, graphical introduction to the main concepts of molecular phylogenetics
  - A competitive dice game to teach evolution modeling without equations
  - Gradual exposure to simple formulas for understanding phylogenetic methods
- Uncertainty quantification
  - Thorough explanations of sources of uncertainty in phylogenetics
  - Simple methods for quantifying uncertainty not captured by phylogenetics software
- Concepts underlying present and future software more than details of today's programs

Why the Subtitle "A Hands-On Introduction with Uncertainty Quantification Corrected*?*"

This book serves two purposes. First, it introduces biology students to phylogenetic trees and molecular evolution without requiring any mathematics beyond elementary algebra. It does so by presenting the main concepts in a variety of ways: first in graphics, then in some history of the field, next in a dice game, and finally in simple equations. Completing the exercises will prepare students for textbooks with more realistic mathematical modeling and details of current software.

Second, the book explores the interface between molecular evolution and uncertainty quantification, of potential benefit to both fields. For not only does phylogenetics clearly illustrate the need for uncertainty quantification in science, but quantifying the uncertainty involved in estimating phylogenetic trees can lead to reliable biological interpretations. This book equips students with statistical tools for correcting uncertainty quantification for the study of evolutionary relationships between DNA and protein sequences.

Chapter-by-Chapter Synopsis

1. Chapter 1 starts slow, without assuming more than a basic knowledge of biology or mathematics. Readers are exposed to the main concepts of the book through graphics and an easy-to-read, conversational exposition. The absence of formulas facilitates comprehension for readers intimidated by mathematics. The chapter ends with simple exercises to reinforce the basic ideas.
2. This chapter continues to expose readers to the main concepts of the book. It does so by sketching a history of the main developments of molecular phylogenetics and molecular evolution since the 1960s. All mathematical formulas related to this chapter are postponed until Appendix B and Appendix C. The exercises at the end of the chapter encourage reflection, especially on how the history can inform assessments of the uncertainty in estimated trees.
3. The third chapter covers a probability model of molecular evolution in a way designed to engage readers with little interest in mathematics. That is accomplished by stating the model in terms of a competitive game rather than mathematical formulas: one team rolls dice to simulate molecular evolution, and the other team then uses the resulting simulated sequence data to estimate the phylogenetic tree. The description of the game rules gradually eases the readers into some simple mathematical formulas needed to understand how evolutionary distances are corrected for multiple substitutions. Exercises provided at the end of the chapter give readers hands-on experience with the sequence simulation and tree reconstruction methods.
4. The fourth chapter goes into more detail about estimating divergence times from molecular sequence data. It explains the inadequacy of confidence intervals for

quantifying the uncertainty in divergence times. A simple method of improving the uncertainty quantification is provided. Exercises at the end of the chapter give readers experience with quantifying the uncertainty in divergence times.
5. The fifth chapter explains three ways to infer ancestral sequences from sequence data. After explaining a heuristic approach to build the intuition of the readers, the chapter explains maximum likelihood estimation and Bayesian estimation with some simplifications to keep the formulas minimal. To adjust the results for uncertainty not quantified in the models, the previous chapter's method of uncertainty quantification is adapted. Exercises provided at the end of the chapter give readers practical experience with estimating ancestral sequences and intuition about the uncertainty involved.
6. This chapter lifts the uncertainty quantification of the previous chapters up to the level of molecular evolution hypotheses. A relatively recent rival to the neutral theory of molecular evolution is explained in terms of how its predictions differ. The exercises at the end of the chapter give readers experience with quantifying the extent to which sequence data support one evolutionary hypothesis more than another.
7. The last chapter is a guide to further reading on molecular phylogenetics, uncertainty quantification, and other topics encountered in the book.

The three appendices fill in some mathematical gaps.

Acknowledgments

Molecular evolution models were the subject of my PhD research, which would not have been possible without the mentorship of Bruce J. West. This book started in the form of lecture notes at the Medical College of Georgia. I drafted Appendices B and C at the University of Ottawa. Teaching computational biology courses at the University of North Carolina at Greensboro led to many updates and additions, and I am grateful to all the students who provided feedback.

The comments of the anonymous reviewers on the book proposal led to the addition of Chap. 7 and to an expansion of Sect. 2.7. I thank Shi Huang for carefully reading a draft of Chap. 6 and for suggesting corrections.

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Greensboro, NC, USA David R. Bickel
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Contents