# Contents in Brief

**Introduction 1** 

**CHAPTER 1/The Molecular Basis of Biology and Evolution 5 CHAPTER 2/Allele Dynamics in Populations 35 CHAPTER 3/DNA and Amino Acid Sequence Evolution 79 CHAPTER 4/Rates and Patterns of Molecular Evolution 107 CHAPTER 5/Molecular Phylogenetics and Phylogenetic Trees 165 CHAPTER 6**/Reticulate Evolution and Phylogenetic Networks 237 **CHAPTER 7 / Evolution by DNA Duplication 273 CHAPTER 8 / Evolution by Molecular Tinkering 339 CHAPTER 9/Mobile Elements in Evolution 391 CHAPTER 10/Prokaryotic Genome Evolution 451 CHAPTER 11/Eukaryotic Genome Evolution 491** CHAPTER 12 / The Evolution of Gene Regulation 575 **CHAPTER 13 / Experimental Molecular Evolution 597** 

# Table of Contents

# **Introduction 1**

# CHAPTER 1/The Molecular Basis of Biology and Evolution 5

Nucleotide Sequences 5 Genomes 7 Genome constituents 7

Somatic genome processing 7

## DNA Replication 8 Transcription and Posttranscriptional Modifications of RNA 9

#### Genes 11

Protein-coding genes 12 RNA-specifying genes 14 Nontranscribed genes 15 Pseudogenes 16

## Amino Acids 16

Proteins 19 Translation and Genetic Codes 20 Information Flow among DNA, RNA, and Proteins 24 Mutation 24 Classification of mutations 25 Point Mutations 26 Segmental Mutations 30 Recombination 30 Deletions and insertions 31 Inversions 34 Spatial distribution of mutations 34 Are Mutations Random? 34

# **CHAPTER 2/Allele Dynamics in Populations 35**

#### **Standing Genetic Variation 35**

Gene diversity 36 Nucleotide diversity 37 Structural variation 38

# What Is Evolution? 38 Changes in Allele Frequencies 39

#### **Selection 40**

Codominance 42 Dominance and recessiveness 43

Overdominance and underdominance 44

## Random Genetic Drift 47

## Census Population Size and Effective Population Size 49

Short-term effective population size 50
Coalescence and long-term effective population size 51
Factors conspiring to reduce the effective population size relative to the census population size 54

# **Gene Substitution 55**

Fixation probability 55 Fixation time 56 Rate of gene substitution 58 Mutational meltdown: The double jeopardy of small populations 58 Nearly neutral mutations 58 Second-Order Selection 60 The evolution of mutation rates 60 The evolution of mutational robustness 62 Violations of Mendel's Laws of Inheritance 63 Transmission Ratio Distortion 63 Segregation distortion 64 Postsegregation distortion 65 Converting elements 65 Sex allocation distortion 66 Autonomous replicating elements 66

# Linkage Equilibrium and Disequilibrium 66 Hitchhiking and Selective Sweep 67

Molecular signatures of selective sweeps 68 The evolution of lactase persistence in Africa and Europe 70

**Background Selection 71** 

#### Epistasis 71

#### The Driving Forces in Evolution 72

The neo-Darwinian theory and the neutral mutation hypothesis 72

The distribution of fitness effects 74

A test of neutrality based on genetic polymorphism 75

Consequences of Explosive Population Growth: Single-Nucleotide Variation in Humans 76

# CHAPTER 3 / DNA and Amino Acid Sequence Evolution 79

#### Nucleotide Substitution in a DNA Sequence 79

Jukes and Cantor's one-parameter model 80 Kimura's two-parameter model 82

#### Number of Nucleotide Substitutions between Two DNA Sequences 83

Number of substitutions between two noncoding sequences 84

Substitution schemes with more than two parameters 86

Violation of assumptions 87 Saturation 88

Number of Substitutions between Two Protein-Coding Genes 88 Number of Amino Acid Replacements between Two Proteins 93

#### Alignment of Nucleotide and Amino Acid Sequences 93

Pairwise alignment 94 Manual alignment 95 The dot matrix method 95 Scoring matrices and gap penalties 97 Alignment algorithms 100 Multiple-sequence alignment 101 Quality of alignments 104 **Alignment of Genomic Sequences 106** 

# CHAPTER 4/Rates and Patterns of Molecular Evolution 107

#### Rates of Point Mutation 107

#### **Rates of Segmental Mutations 110**

#### Rates of Nucleotide Substitution 111

Rates of substitution in protein-coding sequences 111 Rates of substitution in noncoding regions 115

## **Causes of Variation in Substitution Rates 116**

The concept of functional constraint 116 Quantifying the degree of protein tolerance toward amino acid replacements 116

Synonymous versus nonsynonymous rates 117 Variation among different gene regions 117

Variation among genes 119

Variables associated with protein evolutionary rates 120

Evolutionary conservation and disease 121

Relaxation of selection 122

Selective intolerance toward indels 123

Identifying positive and purifying selection 123 Estimating the intensity of purifying selection 124 Are slowly evolving regions always important? 125

#### Male-Driven Evolution: Mutational Input and Slow-X Evolution 126

Rates of Evolution under Positive Selection 128

Prevalence of positive selection 129

#### Fast-X evolution 130

Rates of Evolution under Balancing Selection 130

#### Patterns of Substitution and Replacement 130

Patterns of spontaneous mutation 131
Patterns of mutation and strand asymmetry 134
Clustered multinucleotide substitutions: Positive selection or nonrandomness of mutation? 135
Patterns of amino acid replacement 137
What protein properties are conserved in protein evolution? 138
Heterotachy 139
Nonrandom Usage of Synonymous Codons 139

Measures of codon usage bias 140

Species-specific and universal patterns of codon usage 141

#### **Determinants of Codon Usage 142**

Interspecific variation in codon usage and amino acid usage 142

Intragenomic variation in codon usage 142 Translational efficiency and translation accuracy 143

The tRNA adaptation index 145

Intragenic variation in codon usage 147

Indirect selection on codon usage 148

- Why do only some organisms have biased codon usages? 148
- Codon usage in unicellular and multicellular organisms 148

Codon usage and population size 149

# Molecular Clocks 149 Relative Rate Tests 151 Local Clocks 154

Nearly equal rates in mice and rats 154 Lower rates in humans than in monkeys 154 Higher rates in rodents than in other mammals 155 Evaluation of the molecular clock hypothesis 156 "Primitive" versus "advanced": A question of rates 157

#### Causes of Variation in Substitution Rates among Evolutionary Lineages 157

The DNA repair hypothesis 158 The generation-time effect hypothesis The metabolic rate hypothesis 159 The varying-selection hypothesis 159

# Are Living Fossils Molecular Fossils Too? 160 Phyletic Gradualism, Punctuated Equilibria, and Episodic Molecular Evolution 160

# Rates of Substitution in Organelle DNA 161

Mitochondrial rates of evolution 161 Plastid rates of evolution 162 Substitution and rearrangement rates 162

# Rates of Substitution in Viruses 163

Human immunodeficiency viruses 163

# **CHAPTER 5 / Molecular Phylogenetics and Phylogenetic Trees 165**

#### Impacts of Molecular Data on Phylogenetic Studies 165

Advantages of Molecular Data in Phylogenetic Studies 167

## **Species and Speciation 167**

The species concept 167 Speciation 168 Terminology 170

# Phylogenetic Trees 170

Rooted and unrooted trees 171 Scaled and unscaled trees 172 The Newick format 173 Number of possible phylogenetic trees 174 Tree balance 175 True and inferred trees 177 Gene trees and species trees 177 Taxa and clades 178

# Types of Molecular Homology 179 Types of Data 180

Character data 180 Assumptions about character evolution 181 Polarity and taxonomic distribution of character states 182

Distance data 183

# Methods of Tree Reconstruction 184 Distance Matrix Methods 184

Unweighted pair-group method with arithmetic means (UPGMA) 184

Sattath and Tversky's neighbors-relation method 186 Saitou and Nei's neighbor-joining method 187 Maximum Parsimony Methods 187 Weighted and unweighted parsimony 191 Searching for the maximum parsimony tree 191 Maximum Likelihood Methods 194 **Bayesian Phylogenetics 197 Topological Comparisons** 198 Topological distance 199 Consensus trees 199 Supertrees 200 **Rooting Unrooted Trees 201** Outgroup rooting 202 Midpoint rooting 202 **Estimating Branch Lengths 204** Calibrating Phylogenetic Trees and Estimating **Divergence Times 205** Assessing Tree Reliability 207 The bootstrap 208 Tests for two competing trees 209 **Problems Associated with Phylogenetic Reconstruction 211** Strengths and weaknesses of different methods 211 Minimizing error in phylogenetic analysis 212 Genome Trees 214 Genome trees based on shared gene content 214 Genome trees from BLASTology 214 Molecular Phylogenetic Examples 214 Phylogeny of apes 215

The utility of polarized character states: Cetartiodactyla and SINE phylogeny 220

#### Molecular Phylogenetic Archeology 222

The disextinction of the quagga 224

The dusky seaside sparrow: A lesson in conservation biology 225

## Molecular Phylogenetics and the Law 227

At the Limits of the Tree Metaphor: The Phylogeny of Eukaryotes and the Origin of Organelles 228

The phylogeny of eukaryotes 228

Origin of organelles 230

#### Phylogenetic Trees as a Means to an End 232

Parallelism and convergence as signifiers of positive selection 232

Detecting amino acid sites under positive selection 233 Reconstructing ancestral proteins and inferring paleoenvironments 234

Mapping nonmolecular characters onto molecular trees 234

# CHAPTER 6 / Reticulate Evolution and Phylogenetic Networks 237

### Networks 237

## Phylogenetic and Phylogenomic Networks 238

The median network method 239

The conditioned-reconstruction method 240 Inferred reticulations: Are they real? 243

### Examples of Real-Life Phylogenetic Networks 243

Reticulate evolution by recombination: A resurrected blood-group allele in humans 244

Speciation by hybridization: The reticulate evolution of woodferns 246

# The Tree of Life Hypothesis 247

The Vertical and Horizontal Components of Prokaryote Evolution 249

Prokaryote taxonomy and the meaning of "species" in prokaryotes 250

# The Phylogeny of Everything 253

The eukaryote-prokaryote divide and the taxonomic validity of Procaryota 253

The Eubacteria-Archaebacteria divide 253 The tripartite tree of life and its inadequacy 255

# The Origin of Eukaryotes 257

The gradual origin hypothesis 258

The fateful encounter hypothesis 259

Eukaryotes as an "organizational upgrade" 262

- The nonrandom origin of operational and informational genes in eukaryotes 263
- Why genes in pieces? The origin of the nuclear membrane 264
- All complex life is eukaryotic: The energetics of gene expression 266

The eukaryotic cell as a one-off innovation and a possible solution to the Fermi paradox 268

Archaebacterial Systematics: Clade-Specific Archaebacterial Genes and Clade-Specific Horizontal Gene Imports from Eubacteria 269

The Two Primary Domains of Life 271 The Public Goods Hypothesis 271

# **CHAPTER 7 / Evolution by DNA Duplication 273**

Types of DNA Duplication 274 Mechanisms of DNA Duplication 274 Dating Duplications 275 Gene Duplication and Gene Families 276 The Prevalence of Gene Duplication 278 Modes of Evolution of Multigene Families 278 Divergent Evolution of Duplicated Genes 279 Nonfunctionalization and gene loss 280 Nonfunctionalization time 281 Retention of original function following gene duplication 283 Evolution of rRNA-specifying genes 284

Neofunctionalization 285

Multifunctionality and subfunctionalization 287 Neosubfunctionalization 294

# **Rates of Evolution in Duplicated Genes 295**

Rates and patterns of expression divergence between duplicated genes 295

## Human Globins 297

# **Concerted Evolution 299**

Unequal crossing over 301

Gene conversion 302

Examples of gene conversion 304

The relative roles of gene conversion and unequal crossing over 306

# Factors Affecting Concerted Evolution 308

Number of repeats 308 Arrangement of repeats 308 Structure of the repeat unit 308 Functional requirements and selection 309 Population size 310

## Evolutionary Implications of Concerted Evolution 310

Spread of advantageous mutations 311 Retardation of paralogous gene divergence 311 Generation of genic variation 311

Methodological pitfalls due to concerted evolution 311 Positive selection or biased gene conversion? The curious histories of *HAR1* and *FXY* 312

#### **Birth-and-Death Evolution 314**

Expansion and contraction of gene families 314 Examples of birth-and-death evolution 315 The death of gene families 325

## Mixed Concerted Evolution and Birth-and-Death Evolution 325

## Polysomy 326

Polyploidy 326

Diploidization 330

Distinguishing between gene duplication and genome duplication 331

# CHAPTER 8 / Evolution by Molecular Tinkering 339

# Protein Domains 339

#### Internal Gene Duplication 340

Properties and prevalence of internal gene duplication 343

# Exon-Domain Correspondence 348 Mosaic Proteins 349

## Exon Shuffling 351

Phase limitations on exon shuffling 352

Prevalence of domain shuffling and the evolutionary mobility of protein domains 353

Domain shuffling and protein-protein interaction networks 356

Gene Fusion and Fission 356

**Domain Accretion 360** 

Strategies of Multidomain Gene Assembly 361

Evolution by Exonization and Pseudoexonization 362

**Evolution of Overlapping Genes 364** 

## **Alternative Splicing 368**

Sex determination and alternative splicing 369 Evolution of alternative splicing 370

Increasing proteome diversity: Alternative splicing or gene duplication? 372

## **De Novo Origination of Genes 373**

#### **Nested and Interleaved Genes 375**

Gene Loss and Unitary Pseudogenes: A Molecular Revisiting of the "Law of Use and Disuse" 376

#### **Functional Convergence 382**

Origin and Evolution of Spliceosomal Introns 383

#### A Grand View of Molecular Tinkering: Suboptimality and Gratuitous Complexity 385

Tinkering in action: The patchwork approach to the evolution of novel metabolic pathways 386

Irremediable complexity by constructive neutral evolution 388

# **CHAPTER 9/Mobile Elements in Evolution 391**

Mobile Elements, Transposable Elements, and Transposition 391

## **Classification of Transposable Elements 393**

Conservative and replicative transposition 393 DNA- and RNA-mediated transposition 394 Enzymatic classification of transposable elements 394 Autonomous and nonautonomous transposable elements 394

Active and fossil transposable elements 394

Taxonomic, developmental, and target-site specificity of transposition 394

# **DNA-Mediated Transposable Elements 395**

Insertion sequences 395 Transposons 396 Nonautonomous DNA-mediated transposable elements 397

## **Retroelements 398**

Retrons 398 *TERT* genes 399 Mitochondrial retroplasmids 399 Group II introns and twintrons 400 Retrotransposons 400 Retroviruses 401 Pararetroviruses 402 Evolutionary origin of retroelements 402 Nonautonomous and fossil retrotransposable elements 403

#### LINEs and SINEs 405

SINEs derived from 7SL RNA 405 SINEs derived from tRNAs and SINEs containing 5S rRNA 407

SINEs containing snRNA 408

Mosaic SINEs 408

Where there's a SINE, there's a LINE 408 Rate of SINEs evolution 410

#### **Retrosequences 410**

Retrogenes 411

Semiprocessed retrogenes 413

Retropseudogenes 413

Endogenous non-retroviral fossils 416

#### The "Ecology" of Transposable Elements 417

Transposable elements and the host genome: An evolutionary tug-of-war 417

Transposable elements and segregation distortion 418 Evolutionary dynamics of transposable-element copy number 419

#### Genetic and Evolutionary Effects of Transposition 420

Transposable elements as mutagens 420 Transposable elements and somatic mosaicism 424 The molecular domestication of transposable elements 424

#### Transposition and Speciation 430 Horizontal Gene Transfer 431

Telltale signs of horizontal gene transfer 431 Mechanisms of horizontal gene transfer among prokaryotes 432

Prevalence and limitations of horizontal gene transfer in prokaryotes 435

Genomic consequences of gene transfer among prokaryotes 437

Clinical consequences of gene transfer among prokaryotes 437

#### Horizontal Gene Transfer Involving Eukaryotes 438

Horizontal gene transfer from eukaryotes to prokaryotes 438

Horizontal gene transfer from prokaryotes to eukaryotes 438

- Horizontal transfer among eukaryotes 440
- Horizontal gene transfer among plants 441

Horizontal transfer of a functional gene from fungi to aphids 441

Horizontal transfer of transposable elements among animals 442

#### Promiscuous DNA 446

Transfer of intact functional genes to the nucleus 447 Transfer of nonfunctional DNA segments from

organelles to the nucleus: *numts* and *nupts* 447 Rates and evolutionary impacts of norgDNA insertion 448

# CHAPTER 10 / Prokaryotic Genome Evolution 451

#### Genome Size in Prokaryotes 452

The pangenome, the core genome, and the accessory genome 453

Increases and decreases in prokaryotic genome sizes 455

#### Genome Miniaturization 457

- Genome size reduction in intracellular symbionts and parasites 457
- The miniaturization of organelle genomes 459

The evolution of mitochondrial genome sizes 460

The evolution of plastid genome sizes 462

#### The Minimal Genome 463

- The comparative genomics approach: Identifying the core genome of all life forms 464
- Probabilistic reconstruction of gene content in the last universal ancestor of life 466
- The experimental gene inactivation approach: Gene essentiality 466

#### GC Content in Prokaryotes 467

Possible explanations for variation in GC content 468 Chargaff's parity rules 470

#### GC Skew and Gene-Density Asymmetries Are Related to DNA Replication Biases 471

Replichores and chirochores 471

The location of genes in leading and lagging strands 474

#### **Chromosomal Evolution in Prokaryotes 477**

Evolution of chromosome number in prokaryotes 478 Estimating the number of gene order rearrangement events 480

Gene order evolution 483

Operon evolution 483

The Emergence of Alternative Genetic Codes 486

# **CHAPTER 11 / Eukaryotic Genome Evolution 491**

# Functionality and nonfunctionality in eukaryotic genomes 492

What is "function" in an evolutionary context? 492

What do genomes do? An evolutionary classification of genomic function 494

Changes in functional affiliation 496

Detecting functionality at the genome level 496

# Phenotypic validation of positive selection 499

What proportion of the human genome is functional? 503

How much garbage DNA is in the human genome? 503

# Genome Size, DNA Content, and C Value 505

Genome size variation and genomic content in eukaryotes 505

Intraspecific variation in genome size 507

# Mutations That Increase or Decrease Genome Size 507

The contribution of genome duplication to genome size 508

The contribution of transposable elements to genome size 509

Deletions and genome size 510

# Genomic Paradoxes in Eukaryotes 511

The C-value paradox 511

Possible solutions to the C-value paradox 513

Why so much of the genome is transcribed—or is it? 516

## Life History and Cellular Correlates of Genome Size 517

The nucleocytoplasmic ratio 518 The coincidence hypothesis 519 Nucleotypic hypotheses 519 The nucleoskeletal hypothesis 520 Is small genome size an adaptation to flight? 521 **The C-Value Paradox: The Neutralist Hypothesis 522** Selfish DNA 523 The mutational hazard hypothesis 524

Is it junk DNA or is it indifferent DNA? 526

# Trends in Genome Size Evolution 527

Is there an upper limit to genome size? 527 Genome miniaturization in eukaryotes 528

# Protein-Coding Gene Number Variation and the G-Value Paradox 532

Possible solutions to the G-value paradox 534 The I value 535

# **Gene Number Evolution 536**

# Methodologies for Studying Gene Repertoire Evolution 537

Gene-family cluster analysis 538 Functional clustering of proteins 539 Supervised machine learning and the subcellular localization of proteins 541

Gene ontology 542

# **Chromosome Number and Structure 544**

Chromosome number variation 544 Chromosome morphology and chromosome types 545 Chromosome size variation 546 Euchromatin and heterochromatin 547

# **Chromosomal Evolution 548**

Chromosome number evolution 548 Chromosomal rearrangements 551 Evolutionary patterns of chromosomal rearrangements 555 Is gene order conserved? 555

# Gene Distribution Between and Within Chromosomes 556

Gene density 556 Do genes cluster by function? 557

# The Repetitive Structure of the Eukaryotic Genome 558

Tandemly repeated sequences 560

Mutational processes affecting repeat-unit number in tandemly repeated DNA 562

The contribution of tandem repeats to genome size 564

Do tandemly repeated DNA sequences have a function? 564

Centromeres as examples of indifferent DNA 565

# **Genome Compositional Architecture 565**

Segmentation algorithms and compositional domains 568

Compositional architectures of mammalian nuclear genomes 570

The origin and evolution of compositional domains 572

# **CHAPTER 12/The Evolution of Gene Regulation 575**

# **Pretranscriptional Regulation 576**

Regulation by covalent modifications of histones 576 DNA methylation 576

# **Regulation at the Transcriptional Level 577**

Promoters 577 Promoter evolution 580 Divergent transcription 581 Enhancers 582 Shadow enhancers 585 Insulators 591

# **Posttranscriptional Regulation 592**

RNA interference 593 Patterns of evolution of miRNAs 594 Do miRNAs have a deep evolutionary history? 595 Does translational regulation contribute to phenotypic evolution? 595

# **CHAPTER 13 / Experimental Molecular Evolution 597**

# What Is Experimental Evolution? 598

The basic design of evolutionary experiments 599 How to measure fitness and changes in fitness in evolutionary experiments 600

## The Contribution of Experimental Evolution to Evolutionary Biology 601

Population divergence and the adaptive landscape metaphor 602

Historical contingency 604 Epistasis 607

# **Mutation Dynamics 608**

Neutral mutation rates 608 Non-neutral mutation rates 608 Targets of Selection 610

Literature Cited LC-1 Index I-1

THOMAS HUXLEY PALEONTOLOGY AND THE DOCTRINE OF EVOLUTION" (1870)