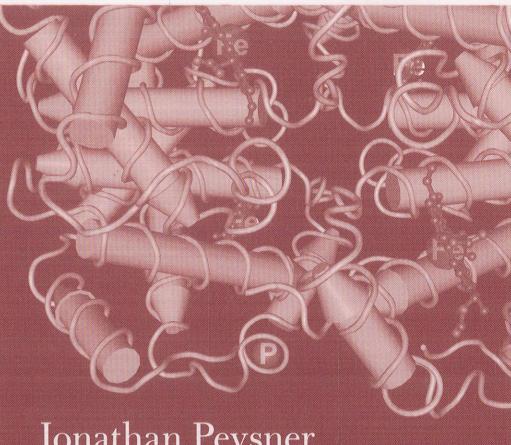
second edition

Bioinformatics and Functional Genomics





Jonathan Pevsner

Contents

	Preface to the Second Edition, xxi	Genome Survey Sequences (GSSs), 22
	Preface to the First Edition, xxiii	High Throughput Genomic
	Trotago to the vinet Edition, Axin	Sequence (HTGS), 23
	Foreword, xxvii	Protein Databases, 23
		National Center for Biotechnology
	ANNUALING BUY DIE AND DEGLEN GEOMETICE	Information, 23
PART I	ANALYZING DNA, RNA, AND PROTEIN SEQUENCES	Introduction to NCBI: Home
	III BOTH BACKS	Page, 23
	in uaiabases	PubMed, 23
1	Introduction, 3	Entrez, 24
,	Organization of The Book, 4	BLAST, 25
	Bioinformatics: The Big Picture, 4	OMIM, 25
	A Consistent Example:	Books, 25
	Hemoglobin, 8	Taxonomy, 25
	Organization of The Chapters, 9	Structure, 25
	A Textbook for Courses on	The European Bioinformatics
	Bioinformatics and	Institute (EBI), 25
	Genomics, 9	Access to Information: Accession
	Key Bioinformatics Websites, 10	Numbers to Label and Identify
	Suggested Reading, 11	Sequences, 26
	References, 11	The Reference Sequence (RefSeq) Project, 27
2	Access to Sequence Data and	The Consensus Coding Sequence
	Literature Information, 13	(CCDS) Project, 29
	Introduction to Biological	Access to Information via Entrez Gene
	Databases, 13	at NCBI, 29
	GenBank: Database of Most Known	Relationship of Entréz Gene,
	Nucleotide and Protein	Entrez Nucleotide, and Entrez
	Sequences, 14	Protein, 32
	Amount of Sequence Data, 15	Comparison of Entrez Gene and
	Organisms in GenBank, 16	UniGene, 32
	Types of Data in GenBank, 18	Entrez Gene and Homolo Gene, 33
	Genomic DNA Databases, 19	Access to Information: Protein
	cDNA Databases Corresponding	Databases, 33
	to Expressed Genes, 19	UniProt, 33
	Expressed Sequence Tags	The Sequence Retrieval System at
	(ESTs), 19	ExPASy, 34
	ESTs and UniGene, 20	Access to Information: The Three
	Sequence-Tagged Sites	Main Genome Browsers, 35
	(STSs), 22	The Map Viewer at NCBI, 35

The University of California, Santa Cruz (UCSC) Genome	Step 1: Setting Up a Matrix, 76 Step 2: Scoring the Matrix, 77
Browser, 35	Step 3: Identifying the Optimal
The Ensembl Genome Browser, 35	Alignment, 79
Examples of How to Access Sequence	Local Sequence Alignment: Smith
Data, 36	and Waterman Algorithm, 82
HIV pol, 36	Rapid, Heuristic Versions of
Histones, 38	Smith – Waterman: FASTA and
Access to Biomedical Literature, 38	BLAST, 84
PubMed Central and Movement	Pairwise Alignment with Dot
toward Free Journal Access, 39	Plots, 85
Example of PubMed Search:	The Statistical Significance of Pairwise
RBP, 40	Alignments, 86
Perspective, 42	Statistical Significance of Global
Pitfalls, 42	Alignments, 87
Web Resources, 42	Statistical Significance of Local
Discussion Questions, 42	Alignments, 89
	•
Problems, 42	Percent Identity and Relative
Self-Test Quiz, 43	Entropy, 90
Suggested Reading, 44	Perspective, 91
References, 44	Pitfalls, 94
Port of the Original All Control All	Web Resources, 94
Pairwise Sequence Alignment, 47	Discussion Questions, 94
Introduction, 47	Problems/Computer Lab, 95
Protein Alignment: Often More	Self-Test Quiz, 95
Informative Than DNA	Suggested Reading, 96
Alignment, 47	References, 97
Definitions: Homology, Similarity,	1
ldentity, 48	Basic Local Alignment Search
Gaps, 55	Tool (BLAST), 101
Pairwise Alignment, Homology, and	Introduction, 101
Evolution of Life, 55	BLAST Search Steps, 103
Scoring Matrices, 57	Step 1: Specifying Sequence of
Dayhoff Model: Accepted Point	Interest, 103
Mutations, 58	Step 2: Selecting BLAST
PAM1 Matrix, 63	Program, 104
PAM250 and Other PAM	Step 3: Selecting a
Matrices, 65	Database, 106
From a Mutation Probability Matrix	Step 4a: Selecting Optional Search
to a Log-Odds Scoring	Parameters, 106
Matrix, 69	1. Query, 107
Practical Usefulness of PAM	2. Limit by Entrez Query, 107
Matrices in Pairwise	3. Short Queries, 107
Alignment, 70	4. Expect Threshold, 107
Important Alternative to PAM:	
BLOSUM Scoring Matrices, 70	5. Word Size, 108
	5. Word Size, 108 6. Matrix, 110
Pairwise Alignment and Limits of	
Pairwise Alignment and Limits of Detection: The "Twilight	6. Matrìx, 110
~	6. Matrìx, 110 7. Gap Penalties, 110
Detection: The "Twilight Zone", 74	6. Matrix, 1107. Gap Penalties, 1108. Composition-Based Statistics, 110
Detection: The "Twilight	6. Matrix, 1107. Gap Penalties, 1108. Composition-Based Statistics, 1109. Filtering and Masking, 111
Detection: The "Twilight Zone", 74 Alignment Algorithms: Global and Local, 75	6. Matrix, 110 7. Gap Penalties, 110 8. Composition-Based Statistics, 110 9. Filtering and Masking, 111 Step 4b: Selecting Formatting
Detection: The "Twilight Zone", 74 Alignment Algorithms: Global and Local, 75 Global Sequence Alignment:	6. Matrix, 110 7. Gap Penalties, 110 8. Composition-Based Statistics, 110 9. Filtering and Masking, 111 Step 4b: Selecting Formatting Parameters, 112
Detection: The "Twilight Zone", 74 Alignment Algorithms: Global and Local, 75	6. Matrix, 110 7. Gap Penalties, 110 8. Composition-Based Statistics, 110 9. Filtering and Masking, 111 Step 4b: Selecting Formatting

BLAST Algorithm Parts: List, Scan, Extend, 115 BLAST Algorithm: Local Alignment Search Statistics and E Value, 118 Making Sense of Raw Scores with Bit Scores, 121 BLAST Algorithm: Relation between E and p Values, 121 Parameters of a	PSI-BLAST Errors: The Problem of Corruption, 152 Reverse Position-Specific BLAST, 152 Pattern-Hit Initiated BLAST (PHI-BLAST), 153 Profile Searches: Hidden Markov Models, 155 BLAST-Like Alignment Tools to Search Genomic DNA
BLAST Search, 123 BLAST Search Strategies, 123 General Concepts, 123 Principles of BLAST	Rapidly, 161 Benchmarking to Assess Genomic Alignment Performance, 162 PatternHunter, 162
Searching, 123 How to Evaluate Significance of Your Results, 123 How to Handle Too Many Results, 128	BLASTZ, 163 MegaBLAST and Discontiguous MegaBLAST, 164 BLAT, 166 LAGAN, 168
How to Handle Too Few Results, 128 BLAST Searching With	SSAHA, 168 SIM4, 169 Using BLAST for Gene
Multidomain Protein: HIV-1 pol, 129 Perspective, 134	Discovery, 169 Perspective, 173 Pitfalls, 173
Pitfalls, 134 Web Resources, 135 Discussion Questions, 135 Computer Lab/Problems, 135	Web Resources, 174 Discussion Questions, 174 Problems/Computer Lab, 174 Self-Test Quiz, 175
Self-Test Quiz, 136 Suggested Reading, 137 References, 137	Suggested Reading, 176 References, 176 Multiple Sequence Alignment, 179
Advanced Database Searching, 141 Introduction, 141	Introduction, 179 Definition of Multiple Sequence Alignment, 180
Specialized BLAST Sites, 142 Organism-Specific BLAST Sites, 142	Typical Uses and Practical Strategies of Multiple Sequence Alignment, 181
Ensembl BLAST, 142 Wellcome Trust Sanger Institute, 143	Benchmarking: Assessment of Multiple Sequence Alignment Algorithms, 182 Five Main Approaches to Multiple
Specialized BLAST-Related Algorithms, 143 WU BLAST 2.0, 144 European Bioinformatics Institute	Sequence Alignment, 184 Exact Approaches to Multiple Sequence Alignment, 184
(EBI), 144 Specialized NCBI BLAST Sites, 144	Progressive Sequence Alignment, 185 Iterative Approaches, 190
Finding Distantly Related Proteins: Position-Specific Iterated BLAST (PSI-BLAST), 145	Consistency-Based Approaches, 192 Structure-Based Methods, 194
Assessing Performance of PSI-BLAST, 150	Conclusions from Benchmarking Studies, 196

<u></u>

Databases of Multiple Sequence		Stage 3: Models of DNA
Alignments, 197		and Amino Acid
Pfam: Protein Family Database of		Substitution, 246
Profile HMMs, 197		Stage 4: Tree-Building
Smart, 199		Methods, 254
Conserved Domain Database, 199		Phylogenetic Methods, 255
Prints, 201		Distance, 255
Integrated Multiple Sequence		The UPGMA Distance-Based
Alignment Resources: InterPro		Method, 256
and iProClass, 201		Making Trees by Distance-
PopSet, 202		Based Methods: Neighbor
•		-
Multiple Sequence Alignment Database Curation: Manual		Joining, 259
		Phylogenetic Inference: Maximum
versus Automated, 202		Parsimony, 260
Multiple Sequence Alignments of		Model-Based Phylogenetic
Genomic Regions, 203		Inference: Maximum
Perspective, 206		Łikelihood, 262
Pitfalls, 207		Tree Inference: Bayesian
Web Resources, 207		Methods, 264 🕺
Discussion Questions, 207		Stage 5: Evaluating Trees, 266
Problems/Computer Lab, 208		Perspective, 268
Self-Test Quiz, 208		Pitfalls, 268
Suggested Reading, 209		Web Resources, 269
References, 210		Discussion Questions, 269
·		Problems/Computer Lab, 269
Molecular Phylogeny and		Self-Test Quiz, 271
Evolution, 215		Suggested Reading, 272
Introduction to Molecular		
Evolution 215		
Evolution, 215		References, 272
Goals of Molecular		neteletices, 2/2
•		nerelences, 2/2
Goals of Molecular Phylogeny, 216	PART II	
Goals of Molecular	PART II	GENOMEWIDE ANALYSIS OF RNA AND PROTEIN
Goals of Molecular Phylogeny, 216 Historical Background, 217 Molecular Clock	PART II	GENOMEWIDE ANALYSIS OF RNA AND PROTEIN
Goals of Molecular Phylogeny, 216 Historical Background, 217 Molecular Clock Hypothesis, 221	PART II	CENOMEWIDE ANALYSIS OF RNA AND PROTEIN Bioinformatic Approaches
Goals of Molecular Phylogeny, 216 Historical Background, 217 Molecular Clock Hypothesis, 221 Positive and Negative	PART II	CENOMEWIDE ANALYSIS OF RNA AND PROTEIN Bioinformatic Approaches to Ribonucleic Acid (RNA), 279
Goals of Molecular Phylogeny, 216 Historical Background, 217 Molecular Clock Hypothesis, 221 Positive and Negative Selection, 227	PART II	GENOMEWIDE ANALYSIS OF RNA AND PROTEIN Bioinformatic Approaches to Ribonucleic Acid (RNA), 279 Introduction to RNA, 279
Goals of Molecular Phylogeny, 216 Historical Background, 217 Molecular Clock Hypothesis, 221 Positive and Negative Selection, 227 Neutral Theory of Molecular	PART II	GENOMEWIDE ANALYSIS OF RNA AND PROTEIN Bioinformatic Approaches to Ribonucleic Acid (RNA), 279 Introduction to RNA, 279 Noncoding RNA, 282
Goals of Molecular Phylogeny, 216 Historical Background, 217 Molecular Clock Hypothesis, 221 Positive and Negative Selection, 227 Neutral Theory of Molecular Evolution, 230	PART II	Bioinformatic Approaches to Ribonucleic Acid (RNA), 279 Introduction to RNA, 279 Noncoding RNA, 282 Noncoding RNAs in the Rfam
Goals of Molecular Phylogeny, 216 Historical Background, 217 Molecular Clock Hypothesis, 221 Positive and Negative Selection, 227 Neutral Theory of Molecular Evolution, 230 Molecular Phylogeny: Properties of	PART II	Bioinformatic Approaches to Ribonucleic Acid (RNA), 279 Introduction to RNA, 279 Noncoding RNA, 282 Noncoding RNAs in the Rfam Database, 283
Goals of Molecular Phylogeny, 216 Historical Background, 217 Molecular Clock Hypothesis, 221 Positive and Negative Selection, 227 Neutral Theory of Molecular Evolution, 230 Molecular Phylogeny: Properties of Trees, 231	PART II	Bioinformatic Approaches to Ribonucleic Acid (RNA), 279 Introduction to RNA, 279 Noncoding RNA, 282 Noncoding RNAs in the Rfam Database, 283 Transfer RNA, 283
Goals of Molecular Phylogeny, 216 Historical Background, 217 Molecular Clock Hypothesis, 221 Positive and Negative Selection, 227 Neutral Theory of Molecular Evolution, 230 Molecular Phylogeny: Properties of Trees, 231 Tree Roots, 233	PART II	Bioinformatic Approaches to Ribonucleic Acid (RNA), 279 Introduction to RNA, 279 Noncoding RNA, 282 Noncoding RNAs in the Rfam Database, 283 Transfer RNA, 283 Ribosomal RNA, 288
Goals of Molecular Phylogeny, 216 Historical Background, 217 Molecular Clock Hypothesis, 221 Positive and Negative Selection, 227 Neutral Theory of Molecular Evolution, 230 Molecular Phylogeny: Properties of Trees, 231 Tree Roots, 233 Enumerating Trees and	PART II	Bioinformatic Approaches to Ribonucleic Acid (RNA), 279 Introduction to RNA, 279 Noncoding RNA, 282 Noncoding RNAs in the Rfam Database, 283 Transfer RNA, 283 Ribosomal RNA, 288 Small Nuclear RNA, 291
Goals of Molecular Phylogeny, 216 Historical Background, 217 Molecular Clock Hypothesis, 221 Positive and Negative Selection, 227 Neutral Theory of Molecular Evolution, 230 Molecular Phylogeny: Properties of Trees, 231 Tree Roots, 233 Enumerating Trees and Selecting Search	PART II	Bioinformatic Approaches to Ribonucleic Acid (RNA), 279 Introduction to RNA, 279 Noncoding RNA, 282 Noncoding RNAs in the Rfam Database, 283 Transfer RNA, 283 Ribosomal RNA, 288 Small Nuclear RNA, 291 Small Nucleolar RNA, 292
Goals of Molecular Phylogeny, 216 Historical Background, 217 Molecular Clock Hypothesis, 221 Positive and Negative Selection, 227 Neutral Theory of Molecular Evolution, 230 Molecular Phylogeny: Properties of Trees, 231 Tree Roots, 233 Enumerating Trees and Selecting Search Strategies, 234	PART II	Bioinformatic Approaches to Ribonucleic Acid (RNA), 279 Introduction to RNA, 279 Noncoding RNA, 282 Noncoding RNAs in the Rfam Database, 283 Transfer RNA, 283 Ribosomal RNA, 288 Small Nuclear RNA, 291 Small Nucleolar RNA, 292 MicroRNA, 293
Goals of Molecular Phylogeny, 216 Historical Background, 217 Molecular Clock Hypothesis, 221 Positive and Negative Selection, 227 Neutral Theory of Molecular Evolution, 230 Molecular Phylogeny: Properties of Trees, 231 Tree Roots, 233 Enumerating Trees and Selecting Search Strategies, 234 Type of Trees, 238	PART II	Bioinformatic Approaches to Ribonucleic Acid (RNA), 279 Introduction to RNA, 279 Noncoding RNA, 282 Noncoding RNAs in the Rfam Database, 283 Transfer RNA, 283 Ribosomal RNA, 288 Small Nuclear RNA, 291 Small Nucleolar RNA, 291 Small Nucleolar RNA, 292 MicroRNA, 293 Short Interfering RNA, 294
Goals of Molecular Phylogeny, 216 Historical Background, 217 Molecular Clock Hypothesis, 221 Positive and Negative Selection, 227 Neutral Theory of Molecular Evolution, 230 Molecular Phylogeny: Properties of Trees, 231 Tree Roots, 233 Enumerating Trees and Selecting Search Strategies, 234 Type of Trees, 238 Species Trees versus Gene/Protein	PART II	Bioinformatic Approaches to Ribonucleic Acid (RNA), 279 Introduction to RNA, 279 Noncoding RNA, 282 Noncoding RNAs in the Rfam Database, 283 Transfer RNA, 283 Ribosomal RNA, 288 Small Nuclear RNA, 291 Small Nucleolar RNA, 291 Small Nucleolar RNA, 292 MicroRNA, 293 Short Interfering RNA, 294 Noncoding RNAs in the UCSC
Goals of Molecular Phylogeny, 216 Historical Background, 217 Molecular Clock Hypothesis, 221 Positive and Negative Selection, 227 Neutral Theory of Molecular Evolution, 230 Molecular Phylogeny: Properties of Trees, 231 Tree Roots, 233 Enumerating Trees and Selecting Search Strategies, 234 Type of Trees, 238 Species Trees versus Gene/Protein Trees, 238	PART II	Bioinformatic Approaches to Ribonucleic Acid (RNA), 279 Introduction to RNA, 279 Noncoding RNA, 282 Noncoding RNAs in the Rfam Database, 283 Transfer RNA, 283 Ribosomal RNA, 288 Small Nuclear RNA, 291 Small Nucleolar RNA, 291 Small Nucleolar RNA, 292 MicroRNA, 293 Short Interfering RNA, 294 Noncoding RNAs in the UCSC Genome and Table
Goals of Molecular Phylogeny, 216 Historical Background, 217 Molecular Clock Hypothesis, 221 Positive and Negative Selection, 227 Neutral Theory of Molecular Evolution, 230 Molecular Phylogeny: Properties of Trees, 231 Tree Roots, 233 Enumerating Trees and Selecting Search Strategies, 234 Type of Trees, 238 Species Trees versus Gene/Protein Trees, 238 DNA, RNA, or Protein-Based	PART II	Bioinformatic Approaches to Ribonucleic Acid (RNA), 279 Introduction to RNA, 279 Noncoding RNA, 282 Noncoding RNAs in the Rfam Database, 283 Transfer RNA, 283 Ribosomal RNA, 288 Small Nuclear RNA, 291 Small Nucleolar RNA, 291 Small Nucleolar RNA, 292 MicroRNA, 293 Short Interfering RNA, 294 Noncoding RNAs in the UCSC Genome and Table Browser, 294
Goals of Molecular Phylogeny, 216 Historical Background, 217 Molecular Clock Hypothesis, 221 Positive and Negative Selection, 227 Neutral Theory of Molecular Evolution, 230 Molecular Phylogeny: Properties of Trees, 231 Tree Roots, 233 Enumerating Trees and Selecting Search Strategies, 234 Type of Trees, 238 Species Trees versus Gene/Protein Trees, 238 DNA, RNA, or Protein-Based Trees, 240	PART II	Bioinformatic Approaches to Ribonucleic Acid (RNA), 279 Introduction to RNA, 279 Noncoding RNA, 282 Noncoding RNAs in the Rfam Database, 283 Transfer RNA, 283 Ribosomal RNA, 288 Small Nuclear RNA, 291 Small Nucleolar RNA, 291 Small Nucleolar RNA, 292 MicroRNA, 293 Short Interfering RNA, 294 Noncoding RNAs in the UCSC Genome and Table Browser, 294 Introduction to Messenger RNA, 296
Goals of Molecular Phylogeny, 216 Historical Background, 217 Molecular Clock Hypothesis, 221 Positive and Negative Selection, 227 Neutral Theory of Molecular Evolution, 230 Molecular Phylogeny: Properties of Trees, 231 Tree Roots, 233 Enumerating Trees and Selecting Search Strategies, 234 Type of Trees, 238 Species Trees versus Gene/Protein Trees, 238 DNA, RNA, or Protein-Based Trees, 240 Five Stages of Phylogenetic	PART II	Bioinformatic Approaches to Ribonucleic Acid (RNA), 279 Introduction to RNA, 279 Noncoding RNA, 282 Noncoding RNAs in the Rfam Database, 283 Transfer RNA, 283 Ribosomal RNA, 288 Small Nuclear RNA, 291 Small Nucleolar RNA, 291 Small Nucleolar RNA, 292 MicroRNA, 293 Short Interfering RNA, 294 Noncoding RNAs in the UCSC Genome and Table Browser, 294 Introduction to Messenger RNA, 296 mRNA: Subject of Gene
Goals of Molecular Phylogeny, 216 Historical Background, 217 Molecular Clock Hypothesis, 221 Positive and Negative Selection, 227 Neutral Theory of Molecular Evolution, 230 Molecular Phylogeny: Properties of Trees, 231 Tree Roots, 233 Enumerating Trees and Selecting Search Strategies, 234 Type of Trees, 238 Species Trees versus Gene/Protein Trees, 238 DNA, RNA, or Protein-Based Trees, 240 Five Stages of Phylogenetic Analysis, 243	PART II	Bioinformatic Approaches to Ribonucleic Acid (RNA), 279 Introduction to RNA, 279 Noncoding RNA, 282 Noncoding RNAs in the Rfam Database, 283 Transfer RNA, 283 Ribosomal RNA, 288 Small Nuclear RNA, 291 Small Nucleolar RNA, 291 Small Nucleolar RNA, 292 MicroRNA, 293 Short Interfering RNA, 294 Noncoding RNAs in the UCSC Genome and Table Browser, 294 Introduction to Messenger RNA, 296 mRNA: Subject of Gene Expression Studies, 300
Goals of Molecular Phylogeny, 216 Historical Background, 217 Molecular Clock Hypothesis, 221 Positive and Negative Selection, 227 Neutral Theory of Molecular Evolution, 230 Molecular Phylogeny: Properties of Trees, 231 Tree Roots, 233 Enumerating Trees and Selecting Search Strategies, 234 Type of Trees, 238 Species Trees versus Gene/Protein Trees, 238 DNA, RNA, or Protein-Based Trees, 240 Five Stages of Phylogenetic Analysis, 243 Stage 1: Sequence	PART II	Bioinformatic Approaches to Ribonucleic Acid (RNA), 279 Introduction to RNA, 279 Noncoding RNA, 282 Noncoding RNAs in the Rfam Database, 283 Transfer RNA, 283 Ribosomal RNA, 288 Small Nuclear RNA, 291 Small Nucleolar RNA, 291 Small Nucleolar RNA, 292 MicroRNA, 293 Short Interfering RNA, 294 Noncoding RNAs in the UCSC Genome and Table Browser, 294 Introduction to Messenger RNA, 296 mRNA: Subject of Gene Expression Studies, 300 Analysis of Gene Expression in
Goals of Molecular Phylogeny, 216 Historical Background, 217 Molecular Clock Hypothesis, 221 Positive and Negative Selection, 227 Neutral Theory of Molecular Evolution, 230 Molecular Phylogeny: Properties of Trees, 231 Tree Roots, 233 Enumerating Trees and Selecting Search Strategies, 234 Type of Trees, 238 Species Trees versus Gene/Protein Trees, 238 DNA, RNA, or Protein-Based Trees, 240 Five Stages of Phylogenetic Analysis, 243 Stage 1: Sequence Acquisition, 243	PART II	Bioinformatic Approaches to Ribonucleic Acid (RNA), 279 Introduction to RNA, 279 Noncoding RNA, 282 Noncoding RNAs in the Rfam Database, 283 Transfer RNA, 283 Ribosomal RNA, 288 Small Nuclear RNA, 291 Small Nucleolar RNA, 291 Small Nucleolar RNA, 292 MicroRNA, 293 Short Interfering RNA, 294 Noncoding RNAs in the UCSC Genome and Table Browser, 294 Introduction to Messenger RNA, 296 mRNA: Subject of Gene Expression Studies, 300 Analysis of Gene Expression in cDNA Libraries, 302
Goals of Molecular Phylogeny, 216 Historical Background, 217 Molecular Clock Hypothesis, 221 Positive and Negative Selection, 227 Neutral Theory of Molecular Evolution, 230 Molecular Phylogeny: Properties of Trees, 231 Tree Roots, 233 Enumerating Trees and Selecting Search Strategies, 234 Type of Trees, 238 Species Trees versus Gene/Protein Trees, 238 DNA, RNA, or Protein-Based Trees, 240 Five Stages of Phylogenetic Analysis, 243 Stage 1: Sequence	PART II	Bioinformatic Approaches to Ribonucleic Acid (RNA), 279 Introduction to RNA, 279 Noncoding RNA, 282 Noncoding RNAs in the Rfam Database, 283 Transfer RNA, 283 Ribosomal RNA, 288 Small Nuclear RNA, 291 Small Nucleolar RNA, 291 Small Nucleolar RNA, 292 MicroRNA, 293 Short Interfering RNA, 294 Noncoding RNAs in the UCSC Genome and Table Browser, 294 Introduction to Messenger RNA, 296 mRNA: Subject of Gene Expression Studies, 300 Analysis of Gene Expression in

Gene Expression: Microarray Data Analysis, 331

Suggested Reading, 325

References, 325

Introduction, 331 Microarray Data Analysis Software and Data Sets, 334 Reproducibility of Microarray Experiments, 335 Microarray Data Analysis: Preprocessing, 337 Scatter Plots and MA Plots, 338 Global and Local Normalization. 343 Accuracy and Precision, 344 Robust Multiarray Analysis 345 (RMA), Microarray Data Analysis: Inferential Statistics. 346 Expression Ratios, 346 Hypothesis Testing, 347

Corrections for Multiple Comparisons, 351 Significance Analysis of Microarrays (SAM), 351 From t-Test to ANOVA. 353 Microarray Data Analysis: Descriptive Statistics, 354 Hierarchical Cluster Analysis of Microarray Data, 355 Partitioning Methods for Clustering: k-Means Clustering, Clustering Strategies: Self-Organizing Maps, 363 Principal Components Analysis: Visualizing Microarray 364 Data. Supervised Data Analysis for Classification of Genes or Samples, 367 Functional Annotation of Microarray 368 Data. Perspective, 369 Pitfalls. 370 Discussion Questions, 370 Problems/Computer Lab, 371 Self-Test Quiz, 372 Suggested Reading, 373 References, 373

Protein Analysis and

Proteomics. 379 379 Introduction, Protein Databases, 380 Community Standards for Proteomics Research, 381 Techniques to Identify Proteins, Direct Protein Sequencing, Gel Electrophoresis, Mass Spectrometry, Four Perspectives on Proteins, 388 Perspective 1. Protein Domains and Motifs: Modular Nature of 389 Proteins. Added Complexity of Multidomain Proteins, 394 Protein Patterns: Motifs or Fingerprints Characteristic of Proteins, 394 Perspective 2. Physical Properties of Proteins. 397 Accuracy of Prediction Programs, 399

Proteomic Approaches to

Phosphorylation, 401

11

Proteomic Approaches to Transmembrane Domains, 401	Fold Recognition (Threading), 450 Ab Initio Prediction (Template-Free Modeling), 450
Introduction to Perspectives 3 and 4:	A Competition to Assess
Gene Ontology	Progress in Structure
Consortium, 402	Prediction, 451
Perspective 3: Protein	Intrinsically Disordered
Localization, 406	Proteins, 453
Perspective 4: Protein	Protein Structure and Disease, 453
Function, 407	Perspective, 454
Perspective, 411	Pitfalls, 455
Pitfalls, 411	Discussion Questions, 455
Web Resources, 412	Problems/Computer Lab, 455
Discussion Questions, 414	Self-Test Quiz, 456
Problems/Computer Lab, 415	Suggested Reading, 457
Self-Test Quiz, 415	References, 457
Suggested Reading, 416	110101041003, 407
References, 416	ll Functional Genomics, ∞ 461
neteralices, 410	Introduction to Functional
Protein Structure, 421	Genomics, 461
Overview of Protein	·
	The Relationship of Genotype and
Structure, 421	Phenotype, 463
Protein Sequence and	Eight Model Organisms for
Structure, 422	Functional Genomics, 465
Biological Questions Addressed by	The Bacterium Escherichia
Structural Biology:	coli, 466
Globins, 423	The Yeast Saccharomyces
Principles of Protein	cerevisiae, 466
Structure, 423	The Plant <i>Arabidopsis</i>
Primary Structure, 424	thaliana, 470
Secondary Structure, 425	The Nematode Caenorhabditis
Tertiary Protein Structure:	elegans, 470
Protein-Folding Problem, 430	The Fruitfly <i>Drosophila</i>
Target Selection and Acquisition	melanogaster, 471
of Three-Dimensional Protein	The Zebrafish Danio rerio, 471
Structures, 432	The Mouse Mus musculus, 472
Structural Genomics and the	Homo sapiens: Variation in
Protein Structure	Humans, 473
Initiative, 432	Functional Genomics Using Reverse
The Protein Data Bank, 434	Genetics and Forward
Accessing PDB Entries at the NCBI	Genetics, 473
Website, 437	Reverse Genetics: Mouse
Integrated Views of the	Knockouts and the β-Globin
Universe of Protein	Gene, 475
Folds, 441	Reverse Genetics: Knocking Out
Taxonomic System for Protein	Genes in Yeast Using Molecular
Structures: The SCOP	Barcodes, 480
Database, 441	Reverse Genetics: Random
The CATH Database, 443	Insertional Mutagenesis
The Dali Domain	(Gene Trapping), 483
Dictionary, 445	Reverse Genetics: Insertional
Comparison of Resources, 446	
Protein Structure Prediction, 447	
·	Reverse Genetics: Gene
Homology Modeling (Comparative	Silencing by Disrupting
Modeling), 448	RNA, 489

Forward Genetics: Chemical Mutagenesis, 491 Functional Genomics and the Central Dogma, 492 Functional Genomics and DNA: The ENCODE Project, Functional Genomics and RNA. 492 Functional Genomics and Protein, 493 Proteomics Approaches to Functional Genomics, 493 Protein - Protein Interactions, 495 The Yeast Two-Hybrid System, 496 Protein Complexes: Affinity Chromatography and Mass Spectrometry, 498 The Rosetta Stone Approach, 500 Protein - Protein Interaction Databases. 501 Protein Networks, 502 Perspective, 507 Pitfalls. 508 Discussion Questions, Problems/Computer Lab, 509 Self-Test Quiz, 509 Suggested Reading, 510 References, 510

PART III GENOME ANALYSIS

Completed Genomes, 517

Introduction, 517

Five Perspectives on

Genomics, 519

Brief History of

Systematics, 520

History of Life on Earth,

Molecular Sequences as the Basis

of the Tree of Life, 523

Role of Bioinformatics in

Taxonomy, 524

Genome-Sequencing Projects:

Overview, 525

Four Prominent Web

Resources, 525

Brief Chronology, 526

First Bacteriophage and

Viral Genomes

(1976 - 1978).

First Eukarvotic Organellar

Genome (1981), 527

(1986), 528 First Eukaryotic Chromosome (1992), 529Complete Genome of Free-Living Organism (1995), 530 First Eukaryotic Genome (1996). 532 Escherichia coli (1997), 532 First Genome of Multicellular Organism (1998), 532 Human Chromosome (1999), 533Fly, Plant, and Human Chromosome 21 (2000), 534 Draft Sequences of Human Genome (2001), 535 Continuing Rise in Completed Genomes (2002), 535 **Expansion of Genome Projects** (2003-2009), 536Genome Analysis Projects, 537 for Sequencing, 538 Genome Size, 539 Cost. 540 Relevance to Human

Criteria for Selection of Genomes

Disease, 541

Questions, 541

Relevance to

Agriculture, 541

Should an Individual from a Species, Several Individuals,

or Many Individuals Be

Sequenced,

Resequencing Projects,

Ancient DNA Projects,

Metagenomics Projects, 543

DNA Sequencing

Technologies,

Sanger Sequencing,

Pyrosequencing, 545

Cyclic Reversible Termination:

Solexa, 547

The Process of Genome

Sequencing, 547

Genome-Sequencing

Centers, 547

Sequencing and Assembling

Genomes: Strategies,

Genomic Sequence Data: From

Unfinished to Finished, 549

Finishing: When Has a Genome
Been Fully Sequenced, 551
Repository for Genome
Sequence Data, 552
Role of Comparative
Genomics, 552
Genome Annotation: Features of
Genomic DNA, 555
Annotation of Genes in
Prokaryotes, 556
Annotation of Genes in
Eukaryotes, 558
Summary: Questions from
Genome-Sequencing
Projects, 558
Perspective, 559
Pitfalls, 559
Discussion Questions, 560
Problems/Computer Lab, 560
Self-Test Quiz, 560
Suggested Reading, 561
References, 561
11010101000, 001
Completed Genomes:

Viruses, 567

Introduction, 567 Classification of Viruses, 568 Diversity and Evolution of Viruses, 571 Metagenomics and Virus Diversity, 573 Bioinformatics Approaches to Problems in Virology, 574 Influenza Virus, 574 Herpesvirus: From Phylogeny to Gene Expression, 578 Human Immunodeficiency Virus, 583 Bioinformatic Approaches to HIV-1, 585 Measles Virus, 588 Perspectives, 591 Pitfalls. 591 Web Resources, 591 Discussion Questions, Problems/Computer Lab. 592 Self-Test Quiz, 593 Suggested Reading, 593 References, 593

Completed Genomes: Bacteria and Archaea, 597 Introduction, 598 Classification of Bacteria and

Archaea, 598

Classification of Bacteria by Morphological Criteria, 599 Classification of Bacteria and Archaea Based on Genome Size and Geometry, 602 Classification of Bacteria and Archaea Based on Lifestyle, 607 Classification of Bacteria Based on Human Disease Relevance, 610 Classification of Bacteria and Archaea Based on Ribosomal RNA Sequences, 611 Classification of Bacteria and Archaea Based on Other Molecular Sequences, Analysis of Prokaryotic Genomes, 615 Nucleotide Composition, 615 Finding Genes, 617 Lateral Gene Transfer. 620 Functional Annotation: COGs, 622 Comparison of Prokaryotic Genomes, 625 TaxPlot, 626 MUMmer, 628 Perspective, 629 Pitfalls, 630 Web Resources, 630 Discussion Questions, 630 Problems/Computer Lab, 631 Self-Test Quiz, 631 Suggested Reading, 632

The Eukaryotic Chromosome, 639

References, 632

Introduction, 640 Major Differences between Eukaryotes and Prokaryotes, General Features of Eukarvotic Genomes and Chromosomes, 643 C Value Paradox: Why Eukaryotic Genome Sizes Vary So Greatly, 643 Organization of Eukaryotic Genomes into Chromosomes, 644 Analysis of Chromosomes Using

Genome Browsers, 645

Analysis of Chromosomes by the	Techniques to Measure
ENCODE Project, 647	Chromosomal Change, 682
Repetitive DNA Content of	Array Comparative Genomic
Eukaryotic Chromosomes, 650	Hybridization, 682
Eukaryotic Genomes Include	Single Nucleotide Polymorphism
Noncoding and Repetitive DNA	(SNP) Microarrays, 683
Sequences, 650	Perspective, 687
1. Interspersed Repeats	Pitfalls, 687
(Transposon-Derived	Web Resources, 688
Repeats), 652	Discussion Questions, 688
2. Processed	Problems/Computer Lab, 688
Pseudogenes, 653	Self-Test Quiz, 689
3. Simple Sequence	Suggested Reading, 690
Repeats, 657	References, 690
4. Segmental	Eukaryotic Genomes:
Duplications, 658	-
5. Blocks of Tandemly	Fungi, 697
Repeated Sequences Such as	Introduction, 697
Are Found at Telomeres,	Description and Classification of
Centromeres, and Ribosomal	Fungi, 698
Gene Clusters, 660	Introduction to Budding Yeast
Gene Content of Eukaryotic	Saccharomyces cerevisiae, 700
Chromosomes, 662	Sequencing the Yeast
Definition of Gene, 662	Genome, 701
Finding Genes in Eukaryotic	Features of the Budding Yeast
Genomes, 663	Genome, 701
EGASP Competition and	Exploring a Typical Yeast
JIGSAW, 666	Chromosome, 704
Protein-Coding Genes in	Gene Duplication and Genome
Eukaryotes: New	Duplication of <i>S. cerevisiae</i> , 708
Paradox, 668	Comparative Analyses of
Regulatory Regions of Eukaryotic	Hemiascomycetes, 712
Chromosomes, 669	Analysis of Whole Genome
Transcription Factor Databases	Duplication, 712
and Other Genomic DNA	Identification of Functional
Databases, 669	Elements, 714
Ultraconserved Elements, 672	Analysis of Fungal Genomes, 715
Nonconserved Elements, 673	Aspergillus, 715
Comparison of Eukaryotic	Candida albicans, 718
DNA, 673	Cryptococcus neoformans: Model
Variation in Chromosomal	Fungal Pathogen, 719
DNA, 674	Atypical Fungus: Microsporidial
Dynamic Nature of Chromosomes:	Parasite Encephalitozoon
Whole Genome	cuniculi, 719
Duplication, 675	Neurospora crassa, 719
Chromosomal Variation in	First Basidiomycete:
Individual Genomes, 676	Phanerochaete
Chromosomal Variation in	chrysosporium, 720
Individual Genomes:	Fission Yeast Schizosaccharomyces
Inversions, 678	pombe, 721
Models for Creating Gene	Perspective, 721
Families, 678	Pitfalls, 722
Mechanisms of Creating	Web Resources, 722
Duplications, Deletions, and	Discussion Questions, 722
Inversions, 680	Problems/Computer Lab, 723

	Self-Test Quiz, 723	The Road to Chordates: The Sea
	Suggested Reading, 724	Urchin, 766
	References, 724	750 Million Years Ago: <i>Ciona</i>
1በ		<i>intestinalis</i> and the Road to
18	Eukaryotic Genomes: From	Vertebrates, 767
	Parasites to Primates, 729	450 Million Years Ago:
	Introduction, 729	Vertebrate Genomes of
	Protozoans at the Base of	Fish, 768
	the Tree Lacking	310 Million Years Ago: Dinosaurs
	Mitochondria, 732	and the Chicken
	Trichomonas, 732	Genome, 771
	Giardia lamblia: A Human	180 Million Years Ago: The
	Intestinal Parasite, 733	Opposum Genome, 772
	Genomes of Unicellular Pathogens:	100 Million Years Ago:
	Trypanosomes and	Mammalian Radiation from
	Leishmania, 735	Dog to Cow, 773
	Trypanosomes, 735	80 Million Years Ago: The Mouse
	Leishmania, 736	and Rat, 774 🏸
	The Chromalveolates, 738	5 to 50 Million Years Ago:
	Malaria Parasite <i>Plasmodium</i>	Primate Genomes, 778
	falciparum and Other	Perspective, 781
	Apicomplexans, 738	Pitfalls, 781
	Astonishing Ciliophora:	Web Resources, 782
	Paramecium and	Discussion Questions, 782
	Tetrahymena, 742	Problems/Computer Lab, 782
	Nucleomorphs, 745	Self-Test Quiz, 783
	Kingdom Stramenopila, 746	Suggested Reading, 783
	Plant Genomes, 748	References, 784
	Overview, 748	Human Genome, 791
	Green Algae (<i>Chlorophyta</i>), 748	•
	Arabidopsis thaliana	Introduction, 791 Main Conclusions of Human
	Genome, 751 The Second Plant Genome:	Genome Project, 792
	Rice, 753	The ENCODE Project, 793
	The Third Plant Genome:	Gateways to Access the Human
	Poplar, 755	Genome, 794
	The Fourth Plant Genome:	NCBI, 794
	Grapevine, 755	Ensembl, 794
	Moss, 756	University of California at Santa
	Slime and Fruiting Bodies at the	Cruz Human Genome
	Feet of Metazoans, 756	Browser, 798
	Social Slime Mold Dictyostelium	NHGRI, 800
	discoideum, 756	The Wellcome Trust Sanger
	Metazoans, 758	Institute, 800
	Introduction to	The Human Genome Project, 800
	Metazoans, 758	Background of the Human
	Analysis of a Simple Animal: The	Genome Project, 800
	Nematode Caenorhabditis	Strategic Issues: Hierarchical
	elegans, 759	Shotgun Sequencing to
	The First Insect Genome:	Generate Draft
	Drosophila melanogaster, 761	Sequence, 802
	The Second Insect Genome:	Features of the Genome
•	Anopheles gambiae, 764	Sequence, 805
	Silkworm, 765	The Broad Genomic

Honeybee, '765

Landscape, 806

xix

Human Disease, 841

Garrod's View of Disease, 842 Classification of Disease. NIH Disease Classification: MeSH Terms. 845 Four Categories of Disease, 846 Monogenic Disorders, 847 Complex Disorders, Genomic Disorders, 852 **Environmentally Caused** 855 Disease, Other Categories of Disease, 857 Disease Databases, 859 **OMIM: Central Bioinformatics** Resource for Human Disease, 859 Locus-Specific Mutation Databases, 862 The PhenCode Project, Four Approaches to Identifying Disease-Associated Genes, 866 Linkage Analysis, 866 Genome-Wide Association Studies, 867 Identification of Chromosomal Abnormalities, Genomic DNA Sequencing, Human Disease Genes in Model Organisms, 870 Human Disease Orthologs in Nonvertebrate Species, 870 Human Disease Orthologs in Rodents, 876 Human Disease Orthologs in Primates. 878 Human Disease Genes and Substitution Rates, 878 Functional Classification of Disease Genes, 880 Perspective, 882 Pitfalls, 882 Web Resources, 882 Discussion Questions. 884 Problems, 884 Self-Test Quiz. 885 Suggested Reading, 885 References, 886

Glossary, 891

Answers to Self-Test Quizzes, 909

Author Index, 911

Subject Index, 913