Contents

L1	ist of Code Challenges	XXV
M	leet the Authors	xxxi
	Meet the Development Team	xxxi
	Meet our Adopting Institutions	xxx
	Acknowledgments	XXX
1	Where in the Genome Does DNA Replication Begin?	2
	A Journey of a Thousand Miles	. 3
	Hidden Messages in the Replication Origin	
	DnaA boxes	. 5
	Hidden messages in "The Gold-Bug"	. 6
	Counting words	
	The Frequent Words Problem	
	Frequent words in <i>Vibrio cholerae</i>	
	Some Hidden Messages are More Surprising than Others	
	An Explosion of Hidden Messages	. 14
	Looking for hidden messages in multiple genomes	. 14
	The Clump Finding Problem	. 15
	The Simplest Way to Replicate DNA	. 16
	Asymmetry of Replication	. 19
	Peculiar Statistics of the Forward and Reverse Half-Strands	. 22
	Lurking biological phenomenon or statistical fluke?	. 22
	Deamination	

	The skew diagram	25
	Some Hidden Messages are More Elusive than Others	27
	A Final Attempt at Finding <i>DnaA</i> Boxes in <i>E. coli</i>	31
	Epilogue: Complications in <i>ori</i> Predictions	32
	Open Problems	34
	Multiple replication origins in a bacterial genome	34
	Finding replication origins in archaea	36
	Finding replication origins in yeast	37
	Computing probabilities of patterns in a string	38
	Charging Stations	40
	The frequency array	40
	Converting patterns to numbers and vice-versa	42
	Finding frequent words by sorting	44
	Solving the Clump Finding Problem	46
	Solving the Frequent Words with Mismatches Problem	48
	Generating the neighborhood of a string	50
	Finding frequent words with mismatches by sorting	52
	Detours	53
	Big-O notation	53
	Probabilities of patterns in a string	53
	The most beautiful experiment in biology	58
	Directionality of DNA strands	60
	The Towers of Hanoi	61
	The overlapping words paradox	63
	Bibliography Notes	65
2	Which DNA Patterns Play the Role of Molecular Clocks?	66
	Do We Have a "Clock" Gene?	67
	Motif Finding Is More Difficult Than You Think	68
	Identifying the evening element	68
	Hide and seek with motifs	69
	A brute force algorithm for motif finding	71
	Scoring Motifs	73
	From motifs to profile matrices and consensus strings	73
	Towards a more adequate motif scoring function	75
	Entropy and the motif logo	76
	From Motif Finding to Finding a Median String	77

The Motif Finding Problem	77
Reformulating the Motif Finding Problem	78
The Median String Problem	80
Why have we reformulated the Motif Finding Problem?	
Greedy Motif Search	
Using the profile matrix to roll dice	83
Analyzing greedy motif finding	
Motif Finding Meets Oliver Cromwell	
What is the probability that the sun will not rise tomorrow?	
Laplace's Rule of Succession	
An improved greedy motif search	
Randomized Motif Search	
Rolling dice to find motifs	92
Why randomized motif search works	
How Can a Randomized Algorithm Perform So Well?	
Gibbs Sampling	
Gibbs Sampling in Action	
Epilogue: How Does Tuberculosis Hibernate to Hide from Antibiotics?	105
Charging Stations	108
Solving the Median String Problem	108
Detours	
Gene expression	
DNA arrays	
Buffon's needle	110
Complications in motif finding	113
Relative entropy	
Bibliography Notes	
How Do We Assemble Genomes?	115
Exploding Newspapers	
The String Reconstruction Problem	
Genome assembly is more difficult than you think	
Reconstructing strings from <i>k</i> -mers	
Repeats complicate genome assembly	
String Reconstruction as a Walk in the Overlap Graph	
From a string to a graph	124
The genome vanishes	127

3

Two graph representations	129
Hamiltonian paths and universal strings	130
Another Graph for String Reconstruction	131
Gluing nodes and de Bruijn graphs	131
Walking in the de Bruijn Graph	
Eulerian paths	134
Another way to construct de Bruijn graphs	135
Constructing de Bruijn graphs from <i>k</i> -mer composition	
De Bruijn graphs versus overlap graphs	138
The Seven Bridges of Königsberg	139
Euler's Theorem	142
From Euler's Theorem to an Algorithm for Finding Eulerian Cycles	146
Constructing Eulerian cycles	146
From Eulerian cycles to Eulerian paths	147
Constructing universal strings	148
Assembling Genomes from Read-Pairs	150
From reads to read-pairs	150
Transforming read-pairs into long virtual reads	152
From composition to paired composition	153
Paired de Bruijn graphs	155
A pitfall of paired de Bruijn graphs	156
Epilogue: Genome Assembly Faces Real Sequencing Data	158
Breaking reads into k -mers	159
Splitting the genome into contigs	160
Assembling error-prone reads	161
Inferring multiplicities of edges in de Bruijn graphs	
Charging Stations	165
The effect of gluing on the adjacency matrix	165
Generating all Eulerian cycles	166
Reconstructing a string spelled by a path in the paired de Bruijn graph .	
Maximal non-branching paths in a graph	170
Detours	
A short history of DNA sequencing technologies	171
Repeats in the human genome	
Graphs	
The icosian game	
Tractable and intractable problems	177

	From Euler to Hamilton to de Bruijn	178
	The seven bridges of Kaliningrad	179
	Pitfalls of assembling double-stranded DNA	
	The BEST Theorem	
	Bibliography Notes	182
4	How Do We Sequence Antibiotics?	184
	The Discovery of Antibiotics	
	How Do Bacteria Make Antibiotics?	186
	How peptides are encoded by the genome	186
	Where is Tyrocidine encoded in the <i>Bacillus brevis</i> genome?	188
	From linear to cyclic peptides	190
	Dodging the Central Dogma of Molecular Biology	190
	Sequencing Antibiotics by Shattering Them into Pieces	192
	Introduction to mass spectrometry	192
	The Cyclopeptide Sequencing Problem	193
	A Brute Force Algorithm for Cyclopeptide Sequencing	195
	A Branch-and-Bound Algorithm for Cyclopeptide Sequencing	196
	Mass Spectrometry Meets Golf	199
	From theoretical to real spectra	199
	Adapting cyclopeptide sequencing for spectra with errors	200
	From 20 to More than 100 Amino Acids	203
	The Spectral Convolution Saves the Day	205
	Epilogue: From Simulated to Real Spectra	207
	Open Problems	210
	The Beltway and Turnpike Problems	210
	Sequencing cyclic peptides in primates	211
	Charging Stations	213
	Generating the theoretical spectrum of a peptide	213
	How fast is CyclopeptideSequencing?	214
	Trimming the peptide leaderboard	216
	Detours	217
	Gause and Lysenkoism	217
	Discovery of codons	218
	Quorum sensing	219
	Molecular mass	219
	Selenocysteine and pyrrolysine	220

	Pseudo-polynomial algorithm for the Turnpike Problem	. 221
	Split genes	. 222
	Bibliography Notes	. 223
5	How Do We Compare Biological Sequences?	224
	Cracking the Non-Ribosomal Code	. 225
	The RNA Tie Club	. 225
	From protein comparison to the non-ribosomal code	. 226
	What do oncogenes and growth factors have in common?	. 227
	Introduction to Sequence Alignment	. 228
	Sequence alignment as a game	. 228
	Sequence alignment and the longest common subsequence	. 229
	The Manhattan Tourist Problem	. 231
	What is the best sightseeing strategy?	. 231
	Sightseeing in an arbitrary directed graph	. 234
	Sequence Alignment is the Manhattan Tourist Problem in Disguise	. 235
	An Introduction to Dynamic Programming: The Change Problem	. 238
	Changing money greedily	. 238
	Changing money recursively	. 239
	Changing money using dynamic programming	. 241
	The Manhattan Tourist Problem Revisited	. 243
	From Manhattan to an Arbitrary Directed Acyclic Graph	. 247
	Sequence alignment as building a Manhattan-like graph	. 247
	Dynamic programming in an arbitrary DAG	. 248
	Topological orderings	. 249
	Backtracking in the Alignment Graph	. 253
	Scoring Alignments	. 255
	What is wrong with the LCS scoring model?	. 255
	Scoring matrices	. 256
	From Global to Local Alignment	. 257
	Global alignment	. 257
	Limitations of global alignment	. 259
	Free taxi rides in the alignment graph	. 261
	The Changing Faces of Sequence Alignment	
	Edit distance	. 264
	Fitting alignment	. 265
	Overlan alignment	266

	Penalizing Insertions and Deletions in Sequence Alignment	267
	Affine gap penalties	267
	Building Manhattan on three levels	269
	Space-Efficient Sequence Alignment	27
	Computing alignment score using linear memory	27
	The Middle Node Problem	272
	A surprisingly fast and memory-efficient alignment algorithm	276
	The Middle Edge Problem	278
	Epilogue: Multiple Sequence Alignment	280
	Building a three-dimensional Manhattan	280
	A greedy multiple alignment algorithm	
	Detours	286
	Fireflies and the non-ribosomal code	286
	Finding a longest common subsequence without building a city	287
	Constructing a topological ordering	287
	PAM scoring matrices	288
	Divide-and-conquer algorithms	292
	Scoring multiple alignments	293
	Bibliography Notes	295
6	Are There Fragile Regions in the Human Genome?	296
	Of Mice and Men	
	How different are the human and mouse genomes?	
	Synteny blocks	
	Reversals	
	Rearrangement hotspots	
	The Random Breakage Model of Chromosome Evolution	
	Sorting by Reversals	
	A Greedy Heuristic for Sorting by Reversals	
	Breakpoints	
	What are breakpoints?	
	Counting breakpoints	
	Sorting by reversals as breakpoint elimination	
	Rearrangements in Tumor Genomes	
	From Unichromosomal to Multichromosomal Genomes	
	Translocations, fusions, and fissions	316
	From a genome to a graph	317

	2-breaks	317
	Breakpoint Graphs	321
	Computing the 2-Break Distance	324
	Rearrangement Hotspots in the Human Genome	327
	The Random Breakage Model meets the 2-Break Distance Theorem	327
	The Fragile Breakage Model	328
	Epilogue: Synteny Block Construction	330
	Genomic dot-plots	330
	Finding shared k-mers	330
	Constructing synteny blocks from shared <i>k</i> -mers	334
	Synteny blocks as connected components in graphs	
	Open Problem: Can Rearrangements Shed Light on Bacterial Evolution?	
	Charging Stations	
	From genomes to the breakpoint graph	
	Solving the 2-Break Sorting Problem	343
	Detours	
	Why is the gene content of mammalian X chromosomes so conserved? .	346
	Discovery of genome rearrangements	
	The exponential distribution	
	Bill Gates and David X. Cohen flip pancakes	
	Sorting linear permutations by reversals	
	Bibliography Notes	351
7	Which Animal Gave Us SARS?	352
	The Fastest Outbreak	353
	Trouble at the Metropole Hotel	353
	The evolution of SARS	353
	Transforming Distance Matrices into Evolutionary Trees	355
	Constructing a distance matrix from coronavirus genomes	355
	Evolutionary trees as graphs	357
	Distance-based phylogeny construction	359
	Toward An Algorithm for Distance-Based Phylogeny Construction	
	A quest for neighboring leaves	362
	Computing limb lengths	
	Additive Phylogeny	
	Trimming the tree	
	Attaching a limb	369

An algorithm for distance-based phylogeny construction	369
Constructing an evolutionary tree of coronaviruses	370
Using Least Squares to Construct Approximate Distance-Based Phylogenies .	372
Ultrametric Evolutionary Trees	373
The Neighbor-Joining Algorithm	377
Transforming a distance matrix into a neighbor-joining matrix	377
Analyzing coronaviruses with the neighbor-joining algorithm	381
Limitations of distance-based approaches to tree construction	383
Character-Based Tree Reconstruction	383
Character tables	383
From anatomical to genetic characters	384
How many times has evolution invented insect wings?	385
The Small Parsimony Problem	387
The Large Parsimony Problem	392
Epilogue: Evolutionary Trees Fight Crime	398
Detours	401
When did HIV jump from primates to humans?	401
Searching for a tree fitting a distance matrix	401
The four point condition	403
Did bats give us SARS?	404
Why does the neighbor-joining algorithm find neighboring leaves?	406
Computing limb lengths in the neighbor-joining algorithm	411
Giant panda: bear or raccoon?	412
Where did humans come from?	
Bibliography Notes	415
How Did Yeast Become a Wine Maker?	416
An Evolutionary History of Wine Making	
How long have we been addicted to alcohol?	
The diauxic shift	
Identifying Genes Responsible for the Diauxic Shift	
Two evolutionary hypotheses with different fates	
Which yeast genes drive the diauxic shift?	419
Introduction to Clustering	
Gene expression analysis	
Clustering yeast genes	422
The Good Clustering Principle	424

8

Clustering as an Optimization Problem	426
Farthest First Traversal	
k-Means Clustering	430
Squared error distortion	430
<i>k</i> -means clustering and the center of gravity	
The Lloyd Algorithm	
From centers to clusters and back again	433
Initializing the Lloyd algorithm	
k-means++ Initializer	
Clustering Genes Implicated in the Diauxic Shift	
Limitations of <i>k</i> -Means Clustering	438
From Coin Flipping to <i>k</i> -Means Clustering	
Flipping coins with unknown biases	
Where is the computational problem?	
From coin flipping to the Lloyd algorithm	
Return to clustering	
Making Soft Decisions in Coin Flipping	
Expectation maximization: the E-step	
Expectation maximization: the M-step	448
The expectation maximization algorithm	
Soft <i>k</i> -Means Clustering	
Applying expectation maximization to clustering	449
Centers to soft clusters	
Soft clusters to centers	451
Hierarchical Clustering	452
Introduction to distance-based clustering	452
Inferring clusters from a tree	455
Analyzing the diauxic shift with hierarchical clustering	457
Epilogue: Clustering Tumor Samples	459
Detours	460
Whole genome duplication or a series of duplications?	460
Measuring gene expression	460
Microarrays	461
Proof of the Center of Gravity Theorem	462
Transforming an expression matrix into a distance/similarity matrix	463
Clustering and corrupted cliques	464
Bibliography Notes	467

9	How Do We Locate Disease-Causing Mutations?	468
	What Causes Ohdo Syndrome?	469
	Introduction to Multiple Pattern Matching	470
	Herding Patterns into a Trie	471
	Constructing a trie	471
	Applying the trie to multiple pattern matching	473
	Preprocessing the Genome Instead	
	Introduction to suffix tries	475
	Using suffix tries for pattern matching	475
	Suffix Trees	479
	Suffix Arrays	482
	Constructing a suffix array	482
	Pattern matching with the suffix array	483
	The Burrows-Wheeler Transform	484
	Genome compression	484
	Constructing the Burrows-Wheeler transform	485
	From repeats to runs	487
	Inverting the Burrows-Wheeler Transform	488
	A first attempt at inverting the Burrows-Wheeler transform	488
	The First-Last Property	490
	Using the First-Last property to invert the Burrows-Wheeler transform	493
	Pattern Matching with the Burrows-Wheeler Transform	496
	A first attempt at Burrows-Wheeler pattern matching	496
	Moving backward through a pattern	497
	The Last-to-First mapping	499
	Speeding Up Burrows-Wheeler Pattern Matching	502
	Substituting the Last-to-First mapping with count arrays	502
	Getting rid of the first column of the Burrows-Wheeler matrix	503
	Where are the Matched Patterns?	505
	Burrows and Wheeler Set Up Checkpoints	506
	Epilogue: Mismatch-Tolerant Read Mapping	508
	Reducing approximate pattern matching to exact pattern matching	508
	BLAST: Comparing a sequence against a database	510
	Approximate pattern matching with the Burrows-Wheeler transform	511
	Charging Stations	514
	Constructing a suffix tree	
	Solving the Longest Shared Substring Problem	517

	Partial suffix array construction	519
	Detours	520
	The reference human genome	520
	Rearrangements, insertions, and deletions in human genomes	520
	The Aho-Corasick algorithm	521
	From suffix trees to suffix arrays	522
	From suffix arrays to suffix trees	524
	Binary search	527
	Bibliography Notes	528
10	Why Have Biologists Still Not Developed an HIV Vaccine?	530
	Classifying the HIV Phenotype	531
	How does HIV evade the human immune system?	531
	Limitations of sequence alignment	533
	Gambling with Yakuza	534
	Two Coins up the Dealer's Sleeve	536
	Finding CG-Islands	537
	Hidden Markov Models	538
	From coin flipping to a Hidden Markov Model	538
	The HMM diagram	540
	Reformulating the Casino Problem	540
	The Decoding Problem	543
	The Viterbi graph	543
	The Viterbi algorithm	546
	How fast is the Viterbi algorithm?	547
	Finding the Most Likely Outcome of an HMM	548
	Profile HMMs for Sequence Alignment	550
	How do HMMs relate to sequence alignment?	550
	Building a profile HMM	552
	Transition and emission probabilities of a profile HMM	555
	Classifying proteins with profile HMMs	559
	Aligning a protein against a profile HMM	559
	The return of pseudocounts	560
	The troublesome silent states	561
	Are profile HMMs really all that useful?	568
	Learning the Parameters of an HMM	569
	Estimating HMM parameters when the hidden path is known	569

	Viterbi learning	571
	Soft Decisions in Parameter Estimation	573
	The Soft Decoding Problem	573
	The forward-backward algorithm	574
	Baum-Welch Learning	577
	The Many Faces of HMMs	579
	Epilogue: Nature is a Tinkerer and not an Inventor	580
	Detours	582
	The Red Queen Effect	582
	Glycosylation	582
	DNA methylation	582
	Conditional probability	583
	Bibliography Notes	585
	W. W. A. D. Cl. I. A.	=0.6
11	Was T. rex Just a Big Chicken?	586
	Paleontology Meets Computing	
	Which Proteins Are Present in This Sample?	
	Decoding an Ideal Spectrum	
	From Ideal to Real Spectra	
	Peptide Sequencing	
	Scoring peptides against spectra	
	Where are the suffix peptides?	
	Peptide sequencing algorithm	
	Peptide Identification	
	The Peptide Identification Problem	
	Identifying peptides in the unknown <i>T. rex</i> proteome	
	Searching for peptide-spectrum matches	
	Peptide Identification and the Infinite Monkey Theorem	
	False discovery rate	
	The monkey and the typewriter	
	Statistical significance of a peptide-spectrum match	
	Spectral Dictionaries	
	T. rex Peptides: Contaminants or Treasure Trove of Ancient Proteins?	
	The hemoglobin riddle	
	The dinosaur DNA controversy	
	Epilogue: From Unmodified to Modified Peptides	
	Post-translational modifications	617

Searching for modifications as an alignment problem	618
Building a Manhattan grid for spectral alignment	620
Spectral alignment algorithm	623
Detours	626
Gene prediction	626
Finding all paths in a graph	627
The Anti-Symmetric Path Problem	628
Transforming spectra into spectral vectors	629
The infinite monkey theorem	630
The probabilistic space of peptides in a spectral dictionary	631
Are terrestrial dinosaurs really the ancestors of birds?	632
Solving the Most Likely Peptide Vector Problem	633
Selecting parameters for transforming spectra into spectral vectors	634
Bibliography Notes	636
	600
Appendix: Introduction to Pseudocode	639
What is Pseudocode?	
Nuts and Bolts of Pseudocode	
The if condition	
The for loop	
The while loop	
Recursive algorithms	
Arrays	647
Glossary	649
Bibliography	671
Image Courtesies	683