Contents

	Notat	ion	page xii	
	Prefac	ce	xvii	
Part I	Prelimina	ries	1	
1	Molec	Molecular biology and high-throughput sequencing		
	1.1	DNA, RNA, proteins	3	
	1.2	Genetic variations	6	
	1.3	High-throughput sequencing	7	
	Exerc	ises	9	
2	Algori	10		
	2.1	Complexity analysis	10	
	2.2	Data representations	12	
	2.3	Reductions	13	
	2.4	Literature	17	
	Exerc	17		
3	Data s	20		
	3.1	Dynamic range minimum queries	20	
	3.2	Bitvector rank and select operations	22	
	3.3	Wavelet tree	24	
		3.3.1 Balanced representation	24	
		3.3.2 Range queries	26	
	3.4	Literature	27	
	Exerc	Exercises		
4	Graph	30		
	4.1	Directed acyclic graphs (DAGs)	30	
		4.1.1 Topological ordering	30	
		4.1.2 Shortest paths	31	

	4.2		ry directed graphs	33
		4.2.1	Eulerian paths	33
		4.2.2	Shortest paths and the Bellman–Ford method	34
	4.3	Literatu	ire	38
	Exerc	ises		38
5	Netwo	rk flows		41
	5.1	Flows a	and their decompositions	41
	5.2	Minimu	nm-cost flows and circulations	45
		5.2.1	The residual graph	47
		5.2.2	A pseudo-polynomial algorithm	50
	5.3	Bipartit	e matching problems	51
		5.3.1	E	52
		5.3.2	Matching with capacity constraints	54
		5.3.3	Matching with residual constraints	56
	5.4	Coverin	ng problems	58
		5.4.1	Disjoint cycle cover	58
		5.4.2	Minimum path cover in a DAG	60
	5.5	Literatu	ire	64
	Exerc	ises		65
Part II F	undame	ntals of B	Biological Sequence Analysis	69
6	Alignn	nents		71
	6.1	Edit dis	tance	72
	0.1	6.1.1	Edit distance computation	73
		6.1.2	-	76
		*6.1.3	Myers' bitparallel algorithm	78
	6.2		t common subsequence	83
		6.2.1	Sparse dynamic programming	84
	6.3		imate string matching	86
	6.4	Biological sequence alignment		88
		6.4.1	Global alignment	89
		6.4.2	Local alignment	90
		6.4.3	Overlap alignment	92
		6.4.4	Affine gap scores	94
		6.4.5	The invariant technique	97
	6.5		ignment	98
	6.6		e alignment	101
	0.0	6.6.1	Scoring schemes	101
		6.6.2	Dynamic programming	103
		6.6.3	Hardness	103
		6.6.4	Progressive multiple alignment	104

		6.6.5	DAG alignment	105
		6.6.6	Jumping alignment	107
	6.7	Literature	e	108
	Exerci	ses		109
7	Hidde	n Markov m	nodels (HMMs)	113
	7.1	Definition	n and basic problems	114
	7.2	The Viter	rbi algorithm	118
	7.3	The forw	ard and backward algorithms	118
	7.4	Estimatir	ng HMM parameters	120
	7.5	Literature	e	122
	Exerci	ses		123
Part III	Genome-	Scale Inde	ex Structures	127
8	Classi	cal indexes		129
	8.1	k-mer inc	lex	129
	8.2	Suffix arr	ray	132
		8.2.1	Suffix and string sorting	133
	8.3	Suffix tre	ee	140
		8.3.1	Properties of the suffix tree	142
		8.3.2	Construction of the suffix tree	143
	8.4	Applicati	ons of the suffix tree	145
		8.4.1	Maximal repeats	145
		8.4.2	Maximal unique matches	147
		8.4.3	Document counting	149
		8.4.4	Suffix-prefix overlaps	151
	8.5	Literature	e	151
	Exerci	ses		153
9	Burrov	vs-Wheele	r indexes	157
	9.1	9.1 Burrows–Wheeler transform (BWT)		158
	9.2	BWT ind	lex	160
		9.2.1	Succinct LF-mapping	160
		9.2.2	Backward search	162
		9.2.3	Succinct suffix array	163
		9.2.4	Batched locate queries	165
	*9.3	-	ficient construction of the BWT	166
	9.4		onal BWT index	171
		*9.4.1	Visiting all nodes of the suffix tree with just one BWT	175
	*9.5		lex for labeled trees	177
		*9.5.1	Moving top-down	179
		*9.5.2	Moving bottom-up	181

		*9.5.3	Construction and space complexity	182
	*9.6	BWT in	dex for labeled DAGs	182
		*9.6.1	Moving backward	185
		*9.6.2	Moving forward	186
		*9.6.3	Construction	187
	9.7	BWT in	dexes for de Bruijn graphs	188
		9.7.1	Frequency-oblivious representation	190
		9.7.2	Frequency-aware representation	192
		9.7.3	Space-efficient construction	193
	9.8	Literatu	re	194
	Exerci	ses		196
Part IV	Genome-	Scale Alg	porithms	199
10	Read a	lignment		201
	10.1	Pattern 1	partitioning	202
	10.2	Dynami	c programming along suffix tree paths	204
	10.3	Backtra	cking on BWT indexes	204
		10.3.1	Prefix pruning	206
		10.3.2	Case analysis pruning with the bidirectional BWT index	208
	10.4	Suffix fi	ltering for approximate overlaps	209
	10.5	Paired-e	and and mate pair reads	211
	10.6		gnment of reads	212
	10.7	_	ent of reads to a pan-genome	214
			Indexing a set of individual genomes	214
			Indexing a reference genome and a set of variations	215
		Literatu	re	216
	Exerci	ses		217
11	Genom	e analysis	s and comparison	220
	11.1	Space-e	fficient genome analysis	221
		11.1.1	Maximal repeats	221
		11.1.2	Maximal unique matches	223
		11.1.3	Maximal exact matches	225
	11.2	Compar	ing genomes without alignment	229
		11.2.1	Substring and <i>k</i> -mer kernels	232
		*11.2.2	Substring kernels with Markovian correction	238
		11.2.3		244
		11.2.4	Mismatch kernels	251
		11.2.5	<u>.</u>	253
	11.3	Literatu	re	255
	Exercises			

12	Genom	ne compression	262
	12.1	Lempel–Ziv parsing	263
		12.1.1 Basic algorithm for Lempel–Ziv parsing	264
		12.1.2 Space-efficient Lempel–Ziv parsing	265
		*12.1.3 Space- and time-efficient Lempel–Ziv parsing	266
	*12.2	Bit-optimal Lempel–Ziv compression	270
		*12.2.1 Building distance-maximal arcs	275
		*12.2.2 Building the compact trie	278
	12.3	Literature	279
	Exerci	ses	280
13	Fragment assembly		
	13.1	Sequencing by hybridization	282
	13.2	Contig assembly	284
		13.2.1 Read error correction	285
		13.2.2 Reverse complements	286
		13.2.3 Irreducible overlap graphs	287
	13.3	Scaffolding	291
	13.4	Gap filling	297
	13.5	Literature	299
	Exerci	ses	301
Part V	Application	ons	305
14	Genomics		307
	14.1	Variation calling	308
		14.1.1 Calling small variants	308
		14.1.2 Calling large variants	309
	14.2	Variation calling over pan-genomes	313
		14.2.1 Alignments on a set of individual genomes	313
		14.2.2 Alignments on the labeled DAG of a population	314
		14.2.3 Evaluation of variation calling results	315
	14.3	_	315
	14.4	Literature	322
	Exerci	ses	323
15	Transc	riptomics	325
	15.1	Estimating the expression of annotated transcripts	325
	15.2	Transcript assembly	329
		15.2.1 Short reads	329
		15.2.2 Long reads	330
		15.2.3 Paired-end reads	335

	15.3	Simultan	neous assembly and expression estimation	337
	15.4 Transcript alignment with co-linear chaining15.5 Literature			
	Exercises			346
16	Metage	enomics		350
	16.1	Species of	estimation	351
		16.1.1	Single-read methods	351
		16.1.2	Multi-read and coverage-sensitive methods	353
	16.2	Read clu	stering	357
		16.2.1	Filtering reads from low-frequency species	357
		16.2.2	Initializing clusters	359
		16.2.3	Growing clusters	363
	16.3 Comparing metagenomic samples		364	
		16.3.1	Sequence-based methods	365
		16.3.2	Read-based methods	365
		16.3.3	Multi-sample methods	366
	16.4	Literatur	re	366
	Exercises			367
	Refere	nces		370
	Index			386