CONTENTS

List of contributors	xi
Foreword	xiii
SECTION I. AN INTRODUCTION TO BIOINFORMATICS FOR THE GENETICIST	IE 1
Chapter 1 Introduction: The Role of Genetic Bioinformatics Michael R. Barnes and Ian C. Gray	3
1.1 Introduction	3
1.2 Genetics in the post-genome era—the role of bioinformatics	6
1.3 Knowledge management and expansion	6
1.4 Data management and mining	6
1.5 Genetic study designs	8
1.6 Physical locus analysis	12
1.7 Selecting candidate genes for analysis	14
1.8 Progressing from candidate gene to disease-susceptibility gene	14
1.9 Comparative genetics and genomics	15
1.10 Conclusions	17
References	18
Chapter 2 Internet Resources for the Geneticist Michael R. Barnes and Christopher Southan	21
2.1 Introduction	22
2.2 Sub-division of biological data on the internet	23
2.3 Searching the internet for genetic information	24
2.4 Which web search engine?	24
2.5 Search syntax: the mathematics of search engine use	26
2.6 Boolean searching	27
2.7 Searching scientific literature—getting to 'state of the art'	28
2.8 Searching full-text journals	29
2.9 Searching the heart of the biological internet—sequences and genomic	
data	30
2.10 Nucleotide and protein sequence databases	30
2.11 Biological sequence databases — primary and secondary	31
2.12 Conclusions	36
References	37

vi CONTENTS

Chapter 3 Human Genetic Variation: Databases and Concepts Michael R. Barnes	
3.1 Introduction	40
3.2 Forms and mechanisms of genetic variation	43
3.3 Databases of human genetic variation	50
3.4 SNP databases	51
3.5 Mutation databases	57
3.6 Genetic marker and microsatellite databases	60
3.7 Non-nuclear and somatic mutation databases3.8 Tools for SNP and mutation visualization — the genomic context	61 63
3.9 Tools for SNP and mutation visualization—the gene context	63
3.10 Conclusions	67
References	67
Chapter 4 Finding, Delineating and Analysing Genes Christopher Southan	71
4.1 Introduction	71
4.2 The evidence cascade for gene products	72
4.3 Shortcomings of the standard gene model	75
4.4 Locating known genes on the Golden Path	76
4.5 Gene portal inspection	79
4.6 Locating genes which are not present in the Golden Path	80
4.7 Analysing a novel gene4.8 Comprehensive database searching	81 88
4.8 Comprehensive database searching4.9 Conclusions and prospects	90
References	90
SECTION II. THE IMPACT OF COMPLETE GENOME SEQUENCES	
ON GENETICS	93
Chapter 5 Assembling a View of the Human Genome Colin A. Semple	95
5.1 Introduction	95
5.2 Genomic sequence assembly	98
5.3 Annotation from a distance: the generalities	101
5.4 Annotation up close and personal: the specifics	105
5.5 Annotation: the next generation	113
Acknowledgements	114
References	114
Chapter 6 Mouse and Rat Genome Informatics Judith A. Blake, Janan Eppig and Carol J. Bult	119
6.1 Introduction	120
6.2 The model organism databases for mouse and rat	122
6.3 Mouse genetic and physical maps	124
6.4 Rat genetic and physical maps	127

		CONTENTS	vii
6.5	Genome sequence resources		128
6.6	Comparative genomics		131
6.7	From genotype to phenotype		132
6.8	Functional genomics		135
6.9	Rodent disease models		137
6.10	Summary		137
Ack	nowledgements		137
	erences		138
	pter 7 Genetic and Physical Map Resources—An Integrated hael R. Barnes	View	143
7.1	Introduction		144
7.2	Genetic maps		145
7.3	Physical maps		148
7.4	Physical contig maps		151
7.5	The role of physical and genetic maps in draft sequence curation		152
7.6	The human genome sequence—the ultimate physical map?		153
7.7	QC of genomic DNA—resolution of marker order and gap sizes		154
7.8	Tools and databases for map analysis and integration		155
7.9	Conclusions		159
Refe	erences		160
SEC	CTION III. BIOINFORMATICS FOR GENETIC STUDY DE	SIGN	163
Ana	pter 8 From Linkage Peak to Culprit Gene: Following Up Li lysis of Complex Phenotypes with Population-based Association C. Gray	_	165
8.1	Introduction		165
8.2	Theoretical and practical considerations		166
8.3	A practical approach to locus refinement and candidate gene iden	tification	173
8.4	Conclusion	tineation	176
	nowledgements		176
	erences		177
	pter 9 Genetic Studies from Genomic Sequence hael R. Barnes		179
9.1	Introduction		180
9.2	Defining the locus		180
9.3	Case study 1: Identification and extraction of a genomic sequence two markers	between	184
9.4	Case study 2: Checking the integrity of a genomic sequence between markers	een two	185
9.5	Case study 3: Definition of known and novel genes across a gene	omic	
9.6	region Case study 4: Candidate gene selection—building biological ratio	onale	188
	around genes		190

viii CONTENTS

9.7	Case study 5: Known and novel marker identification	195
9.8	Case study 6: Genetic/physical locus characterization and marker	
	panel design	199
9.9	Conclusions	201
Refe	rences	201
Cha	pter 10 SNP Discovery and PCR-based Assay Design: From In Silico	
	a to the Laboratory Experiment	203
	ı Vieux, Gabor Marth and Pui Kwok	
10.1	Introduction	204
10.2	SNP identification	205
10.3	PCR primer design	207
10.4	Broader PCR assay design issues	208
10.5	Primer selection	210
10.6	Problems related to SNP assay validation	212
10.7	Conclusion	213
Refe	rences	213
Cha	pter 11 Tools for Statistical Analysis of Genetic Data	217
	a Bansal, Peter R. Boyd and Ralph McGinnis	
11.1	Introduction	218
11.2	Linkage analysis	218
	Association analysis	223
	Haplotype Reconstruction	226
	Linkage disequilibrium	229
	Quantitative Trait Locus (QTL) mapping in experimental crosses	235
Ackı	nowledgements	240
Refe	rences	240
SEC	TION IV. BIOLOGICAL SEQUENCE ANALYSIS AND	
	ARACTERIZATION	247
Cha	pter 12 Predictive Functional Analysis of Polymorphisms:	
	Overview	249
Mich	nael R. Barnes	
12.1	Introduction	250
12.2	Principles of predictive functional analysis of polymorphisms	252
12.3	The anatomy of promoter regions and regulatory elements	257
12.4	The anatomy of genes	258
12.5	Pseudogenes and regulatory mRNA	264
12.6	Analysis of novel regulatory elements and motifs in nucleotide	
	sequences	264
12.7		266
12.8	*	
100	laboratory investigation	268
12.9		268
Refe	rences	269

CONTENTS	IX
CONTLINIO	

-	oter 13 Functional In Silico Analysis of Non-coding SNPs	273
1 nom	as werner	
13.1	Introduction	273
13.2	General structure of chromatin-associated DNA	275
13.3	General functions of regulatory regions	276
13.4	Transcription Factor binding sites (TF-sites)	276
13.5	Structural elements	276
13.6	Organizational principles of regulatory regions	277
	RNA processing	279
13.8	SNPs in regulatory regions	279
	Evaluation of non-coding SNPs	280
	SNPs and regulatory networks	281
	SNPs may affect the expression of a gene only in specific tissues	281
	In silico detection and evaluation of regulatory SNPs	281
	Getting promoter sequences	282
	Identification of relevant regulatory elements	283
	Estimation of functional consequences of regulatory SNPs	284
13.16	Conclusion	285
Refer	ences	285
_	oter 14 Amino Acid Properties and Consequences of Substitutions new J. Betts and Robert B. Russell	289
14.1	Introduction	291
14.2	Protein features relevant to amino acid behaviour	292
14.3	Amino acid classifications	296
14.4	Properties of the amino acids	298
14.5	Amino acid quick reference	299
14.6	Studies of how mutations affect function	311
14.7	A summary of the thought process	313
	rences	314
an ar		245
SEC'.	TION V. GENETICS/GENOMICS INTERFACES	317
	oter 15 Gene Expression Informatics and Analysis	319
	ne H. C. van Kampen, Jan M. Ruijter, Barbera D. C. van Schaik, Huib N. n and Rogier Versteeg	
15.1	Introduction	320
15.2	Technologies for the measurement of gene expression	322
15.3	The Cancer Genome Anatomy Project (CGAP)	324
15.4	Processing of SAGE data	325
15.5	Integration of biological databases for the construction of the HTM	334
15.6	The Human Transcriptome Map	336
15.7	Regions of Increased Gene Expression (RIDGES)	339
15.8	Discussion	340
Refer	rences	341

X CONTENTS

Chapter 16 Proteomic Informatics	345
Jérôme Wojcik and Alexandre Hamburger	
16.1 Introduction	346
16.2 Proteomic informatics	347
16.3 Experimental workflow: classical proteomics	347
16.4 Protein interaction networks	351
16.5 Building protein interaction networks	354
16.6 False negatives and false positives	354
16.7 Analysing interaction networks	355
16.8 Cell pathways	356
16.9 Prediction of protein networks	359
16.10 Assessment and validation of predictions	363
16.11 Exploiting protein networks	366
16.12 Deducing prediction rules from networks	367
16.13 Conclusion	368
Acknowledgements	369
References	369
Chapter 17 Concluding Remarks: Final Thoughts and Future Trends	373
Michael R. Barnes and Ian C. Gray	
17.1 How many genes?	374
17.1 How many genes? 17.2 Mapping the genome and gaining a view of the full depth of human	3/4
variation	375
17.3 Holistic analysis of complex traits	376
17.4 A final word on bioinformatics	376
Acknowledgements	376
References	376
References	370
Appendix I	379
Appendix II	381
Glossary	387
Index	391