



Handbook of

Statistical Genetics

Edited by

D.J. Balding | M. Bishop | C. Cannings

Contents

Editors' Preface	xxi
List of Contributors	xxiii
Part 1 BIOINFORMATICS	1
1 Chromosome Maps	3
<i>T.P. Speed and H. Zhao</i>	
1.1 Introduction	3
1.2 Genetic Maps	5
1.2.1 Mendel's Two Laws	5
1.2.2 Basic Principles in Genetic Mapping	6
1.2.3 Meiosis, Chromatid Interference, Chiasma Interference, and Crossover Interference	8
1.2.4 Genetic Map Functions	9
1.2.5 Genetic Mapping for Three Markers	9
1.2.6 Genetic Mapping for Multiple Markers	11
1.2.7 Tetrads	14
1.2.8 Half-tetrads	16
1.2.9 Other Types of Data	17
1.2.10 Current State of Genetic Maps	17
1.2.11 Programs for Genetic Mapping	18
1.3 Physical Maps	20
1.3.1 Polytene Chromosomes	20
1.3.2 Cytogenetic Maps	21
1.3.3 Restriction Maps	21
1.3.4 Restriction Mapping Via Optical Mapping	22
1.3.5 Ordered Clone Maps	23
1.3.6 Contig Mapping using Restriction Fragments	25
1.3.7 Sequence-Tagged Site Maps	25
1.4 Radiation Hybrid Mapping	27
1.4.1 Haploid Data	28
1.4.2 Diploid Data	29
1.5 Other Physical Mapping Approaches	31
1.6 Gene Maps	31

1.7	Programs for Physical Mapping	31
	Acknowledgments	32
	References	32
2	Statistical Significance in Biological Sequence Comparison	39
	<i>W.R. Pearson and T.C. Wood</i>	
2.1	Introduction	39
2.2	Statistical Significance and Biological Significance	40
2.2.1	'Molecular' Homology	41
2.2.2	Examples of Similarity in Proteins	41
2.2.3	Inferences from Protein Homology	42
2.3	Estimating Statistical Significance for Local Similarity Searches	43
2.3.1	Measuring Sequence Similarity	43
2.3.2	Statistical Significance of Local Similarity Scores	46
2.3.3	Evaluating Statistical Estimates	57
2.4	Summary: Exploiting Statistical Estimates	61
	Acknowledgments	62
	References	62
3	Probabilistic Models for the Study of Protein Evolution	67
	<i>J.L. Thorne and N. Goldman</i>	
3.1	Introduction	67
3.2	The Dayhoff Model	68
3.3	Amino Acid Composition	70
3.4	Heterogeneity of Replacement Rates Among Sites	71
3.5	Protein Structure	72
3.6	Variation of Preferred Residues Among Sites	74
3.7	Models with a Physicochemical Basis	75
3.8	Codon-Based Models	76
3.9	Covariation Among Sites	77
3.10	Conclusion	79
	Acknowledgments	79
	References	80
4	Statistical Approaches in Eukaryotic Gene Prediction	83
	<i>V. Solovyev</i>	
4.1	Structural Organization and Expression of Eukaryotic Genes	83
4.2	Methods of Functional Signal Recognition	86
4.2.1	Position-Specific Measures	87
4.2.2	Content-Specific Measures	88
4.2.3	Frame-Specific Measures	89
4.3	Performance Measures	89
4.4	Linear Discriminant Analysis	90
4.5	Prediction of Donor and Acceptor Splice Junctions	91
4.5.1	Splice-Site Characteristics	91
4.5.2	Donor Splice-Site Characteristics	95
4.5.3	Acceptor Splice-Site Recognition	98
4.6	Identification of Promoter Regions in Human DNA	99
4.7	Recognition of PolyA Signals	105
4.8	Characteristics for Recognition of 3'-Processing Sites	106
4.9	Identification of Multiple Genes in Genomic Sequences	107

4.10	Discriminative and Probabilistic Approaches to Multiple Gene Prediction	108
4.10.1	HMM-Based Multiple Gene Prediction	108
4.10.2	Pattern-Based Multiple Gene Prediction Approach	111
4.11	Internal Exon Recognition	111
4.12	Recognition of Flanking Exons	112
4.12.1	5'-Terminal Exon-Coding Region Recognition	112
4.12.2	3'-Exon-Coding Region Recognition	113
4.13	Performance of Gene Identification Programs	114
4.14	Using Protein Similarity Information to Improve Gene Prediction	116
4.15	Annotation of Sequences from Genome Sequencing Projects	117
4.16	Infogene: A Gene-Centered Database of Known and Predicted Genes	119
	Acknowledgments	121
	References	122
5	Protein Structure	129
	<i>W.R. Taylor</i>	
5.1	Introduction	129
5.1.1	Historical Background	129
5.1.2	Future Importance	130
5.2	Basic Principles	130
5.2.1	Hydrophobic Core	130
5.2.2	Secondary Structure	131
5.2.3	Protein Architecture and Topology	131
5.2.4	Domains	133
5.3	Structure Comparison and Classification	133
5.3.1	Limits of Structural Similarity	133
5.3.2	Protein Structure Comparison	136
5.3.3	Assessing Significance	138
5.3.4	Classification	141
5.3.5	Towards Automatic Classification	142
5.4	Protein Structure Prediction	143
5.4.1	Homology Modelling	143
5.4.2	Threading	144
5.4.3	Secondary Structure Prediction	145
5.5	Conclusions	145
5.5.1	From Deduction to Induction	145
5.5.2	Finite Biology	146
	References	146
Part 2	POPULATION GENETICS	151
6	Mathematical Models in Population Genetics	153
	<i>C. Neuhauser</i>	
6.1	A Brief History of the Role of Selection	153
6.2	Mutation, Random Genetic Drift, and Selection	154
6.2.1	Mutation	155
6.2.2	Random Genetic Drift	155

6.2.3	Selection	157
6.2.4	The Wright–Fisher Model	157
6.3	The Diffusion Approximation	158
6.3.1	Fixation	161
6.3.2	The Kolmogorov Forward Equation	162
6.3.3	Random Genetic Drift Versus Mutation and Selection	162
6.4	The Infinite Allele Model	163
6.4.1	The Infinite Allele Model with Mutation	163
6.4.2	Ewens’s Sampling Formula	165
6.4.3	The Infinite Allele Model with Selection and Mutation	165
6.5	Other Models of Mutation and Selection	166
6.5.1	The Infinitely Many Sites Model	166
6.5.2	Frequency-Dependent Selection	166
6.5.3	Overlapping Generations	167
6.6	Coalescent Theory	167
6.6.1	The Neutral Coalescent	167
6.6.2	The Ancestral Selection Graph	169
6.6.3	Varying Population Size	172
6.7	Detecting Selection	173
	Acknowledgments	175
	References	175
7	Coalescent Theory	179
	<i>M. Nordborg</i>	
7.1	Introduction	179
7.2	The Coalescent	180
7.2.1	The Fundamental Insights	180
7.2.2	The Coalescent Approximation	183
7.3	Generalizing the Coalescent	186
7.3.1	Robustness and Scaling	186
7.3.2	Variable Population Size	187
7.3.3	Population Structure on Different Time Scales	189
7.4	Geographical Structure	190
7.4.1	The Structured Coalescent	190
7.4.2	The Strong-Migration Limit	191
7.5	Segregation	192
7.5.1	Hermaphrodites	193
7.5.2	Males and Females	194
7.6	Recombination	195
7.6.1	The Ancestral Recombination Graph	195
7.6.2	Properties and Effects of Recombination	199
7.7	Selection	200
7.7.1	Balancing Selection	201
7.7.2	Selective Sweeps	203
7.7.3	Background Selection	204
7.8	Neutral Mutations	205
7.9	Conclusion	205
7.9.1	The Coalescent and ‘Classical’ Population Genetics	205
7.9.2	The Coalescent and Phylogenetics	206

7.9.3	Prospects	208
Acknowledgments		208
References		208
8	Inference Under the Coalescent	213
	<i>M. Stephens</i>	
8.1	Introduction	213
	8.1.1 Likelihood-based Inference	214
8.2	The Likelihood and the Coalescent	218
8.3	Importance Sampling	220
	8.3.1 Likelihood Surfaces	222
	8.3.2 Ancestral Inference	223
	8.3.3 Application and Assessing Reliability	223
8.4	Markov Chain Monte Carlo	224
	8.4.1 Introduction	224
	8.4.2 Choosing a Good Proposal Distribution	226
	8.4.3 Likelihood Surfaces	226
	8.4.4 Ancestral Inference	228
	8.4.5 Example Proposal Distributions	229
	8.4.6 Application and Assessing Reliability	232
8.5	Conclusions	235
	8.5.1 Extensions to More Complex Demographic and Genetic Models	235
	8.5.2 Choice of Method	235
	8.5.3 Software and Internet Resources	235
	Acknowledgments	236
	References	236
9	Inferences from Spatial Population Genetics	239
	<i>F. Rousset</i>	
9.1	Introduction	239
9.2	Models in Spatial Population Genetics	241
	9.2.1 Neutral Models of Geographical Variation	241
	9.2.2 Clines	242
9.3	Methods of Inference	243
	9.3.1 <i>F</i> -Statistics	243
	9.3.2 Likelihood Methods	247
9.4	Inference Under the Different Models	249
	9.4.1 Migration Matrix Models	249
	9.4.2 Island Model	250
	9.4.3 Isolation by Distance	251
	9.4.4 Inferences from Clines	254
	9.4.5 Other Methods	255
9.5	Spatial Analyses in Practice	256
	9.5.1 Objections to the Models	256
	9.5.2 How do these Methods Perform?	257
9.6	Software	258
	Acknowledgments	258

Appendix A	Analysis of Variance and Probabilities of Identity	259
Appendix B	Likelihood Analysis of the Island Model	263
	References	265
10	Analysis of Population Subdivision	271
	<i>L. Excoffier</i>	
10.1	Introduction	271
10.2	The Fixation Index F	272
10.3	Wright's F -Statistics in Hierarchic Subdivisions	274
10.3.1	Multiple Alleles	276
10.3.2	Sample Estimation of F -Statistics	277
10.3.3	G -Statistics	278
10.4	Analysis of Genetic Subdivision Under an Analysis of Variance Framework	279
10.4.1	The Model	280
10.4.2	Estimation Procedure	283
10.4.3	Dealing with Mutation and Migration Using Identity Coefficients	287
10.5	Relationship Between Different Definitions of Fixation Indexes	287
10.6	F -Statistics and Coalescence Times	290
10.7	Analysis of Molecular Data: The Amova Framework	291
10.7.1	Haplotypic Diversity	291
10.7.2	Genotypic Data	294
10.7.3	Multi-Allelic Molecular Data	294
10.7.4	Dominant Data	297
10.7.5	Relation of AMOVA to Other Approaches	298
10.8	Significance Testing	299
10.8.1	Resampling Techniques	299
10.8.2	Exact Tests	300
10.9	Related and Remaining Problems	301
10.9.1	Testing Departure from Hardy–Weinberg Equilibrium	301
10.9.2	What is the Underlying Genetic Structure of Populations?	301
	Acknowledgments	302
	References	302
11	Linkage Disequilibrium and Recombination	309
	<i>R.R. Hudson</i>	
11.1	Introduction	309
11.2	Tests of Association	311
11.2.1	Haploid Data, Two Loci	311
11.2.2	Haploid Data, More than Two Loci	314
11.2.3	Diploid Data	315
11.3	Properties of Linkage Disequilibrium Under Population Genetic Models	318
	References	323

Part 3 EVOLUTIONARY GENETICS	325
12 Adaptive Molecular Evolution	327
<i>Z. Yang</i>	
12.1 Introduction	327
12.2 Markov Model of Codon Substitution	329
12.3 Estimation of Synonymous and Non-Synonymous Substitution Rates Between Two Sequences	331
12.3.1 <i>Ad hoc</i> Methods	331
12.3.2 Maximum Likelihood Estimation	332
12.3.3 A Numerical Example and Evaluation of Methods	336
12.4 Likelihood Calculation on a Phylogeny	338
12.5 Detecting Adaptive Evolution Along Lineages	339
12.5.1 Likelihood Calculation Under Models of Variable ω Ratios Among Lineages	339
12.5.2 Adaptive Evolution in the Primate Lysozyme	340
12.5.3 Comparison with Methods Based on Reconstructed Ancestral Sequences	342
12.6 Inferring Amino Acid Sites Under Diversifying Selection	343
12.6.1 Likelihood Calculation Under Models of Variable ω Ratios Among Sites	343
12.6.2 Positive Selection in the HIV-1 <i>vif</i> Genes	345
12.6.3 Comparison with Methods Based on Reconstructed Ancestral Sequences	347
12.7 Limitations of Current Methods	347
12.8 Computer Software	348
Acknowledgments	348
References	348
13 Genome Evolution	351
<i>J.F.Y. Brookfield</i>	
13.1 Introduction	351
13.2 The Structure and Function of Genomes	353
13.2.1 Genome Sequencing Projects	353
13.2.2 Post-genomics	354
13.2.3 The Origins and Functions of Introns	356
13.3 The Organization of Genomes	359
13.3.1 The Relative Positions of Genes: are they Adaptive?	359
13.3.2 Functional Linkage among Prokaryotes	360
13.3.3 Gene Clusters	361
13.3.4 Gene Duplications and Gene Families	362
13.3.5 Apparent Genetic Redundancy	363
13.4 Population Genetics and the Genome	364
13.4.1 The Impact of Chromosomal Position on Population Genetic Variability	364
13.4.2 Codon Usage Bias	365
13.5 Population Genetics of Mobile DNAs	366
13.5.1 Repetitive Sequences	366
13.5.2 Transposable Elements: Parasites or Symbionts?	367

13.5.3	Copy Number Control	367
13.5.4	Selfish Transposable Elements and Sex	369
13.5.5	Phylogenies of Transposable Elements	370
13.6	Conclusions	371
	References	372
14	Virus Evolution	377
	<i>Y. Suzuki, A. Wyndham and T. Gojobori</i>	
14.1	Introduction: HIV as a Model for Virus Evolution	377
14.2	Background	378
14.2.1	HIV and AIDS	378
14.2.2	HIV Molecular Biology	378
14.2.3	HIV-1 Co-receptor Usage and Phenotype Switch	379
14.3	Evolutionary Rate	380
14.3.1	Some Common Estimation Methods	380
14.3.2	Nucleotide Substitution in HIV-1	381
14.3.3	The Mutation Rate of HIV-1	386
14.4	Natural Selection	387
14.4.1	Methods for Examining Natural Selection	387
14.4.2	What Kind of Selective Mechanisms are at Work in HIV-1?	387
14.5	Phylogenetic Relationships Between HIV and SIV Members	390
14.5.1	Virus Phylogenies	390
14.5.2	HIV-1 and the Primate Lentiviruses	390
14.5.3	HIV-1 Subtypes	391
14.6	Recombination	392
14.6.1	Escape from Muller's Ratchet	392
14.6.2	Methods for Detecting Recombination	392
14.6.3	Recombination in HIV-1	393
14.7	The Molecular Clock and Divergence Dates	394
14.7.1	Estimating Divergence Events	394
14.7.2	The Molecular Clock of HIV-1	394
14.7.3	Divergence Events Among HIV-1 Subtypes and the Primate Lentiviruses	395
14.8	Population Dynamics and Models	397
14.8.1	Stochastic or Deterministic?	397
14.8.2	HIV-1 Generation Time	398
14.8.3	Drug Resistance	399
14.8.4	Immune Response	399
14.9	Concluding Remarks	403
	References	404
15	Application of the Likelihood Function in Phylogenetic Analysis	415
	<i>J.P. Huelsenbeck and J.P. Bollback</i>	
15.1	Introduction	415
15.2	History	417
15.2.1	A Brief History of Maximum Likelihood in Phylogenetics	417
15.2.2	A Brief History of Bayesian Inference in Phylogenetics	418
15.3	Likelihood Function	418

15.4	Developing an Intuition of Likelihood	424
15.5	Method of Maximum Likelihood	426
15.6	Bayesian Inference	429
15.7	Markov Chain Monte Carlo	431
15.8	Assessing Uncertainty of Phylogenies	435
15.9	Hypothesis Testing and Model Choice	436
15.10	Comparative Analysis	437
15.11	Conclusions	438
	References	439
16	Phylogenetics: Parsimony and Distance Methods	445
	<i>D. Penny and M. Hendy</i>	
16.1	Introduction	445
16.2	Data	446
16.2.1	Character State Matrix	447
16.2.2	Genetic Distances	447
16.2.3	Splits (bipartitions)	452
16.2.4	Sampling Error	455
16.3	Theoretical Background	456
16.3.1	Terminology for Graphs and Trees	456
16.3.2	Computational Complexity, Numbers of Trees	458
16.3.3	Three Parts of an Evolutionary Model	461
16.3.4	Stochastic Mechanisms of Evolution	464
16.4	Methods for Inferring Evolutionary Trees	466
16.4.1	Five Desirable Properties for Methods	467
16.4.2	Optimality Criteria	470
16.5	Search Strategies	478
16.5.1	Complete or Exact Searches	478
16.5.2	Heuristic Searches I: Limited (local) Searches	479
16.5.3	Heuristic Searches II: Hill-climbing and Related Methods	481
16.5.4	Quartets and Supertrees	482
16.6	Overview and Conclusions	482
	References	483
Part 4	GENETIC EPIDEMIOLOGY	485
17	Nonparametric Linkage	487
	<i>P. Holmans</i>	
17.1	Introduction	487
17.2	Pros and Cons of Model-Free Methods	488
17.3	Model-Free Methods for Dichotomous Traits	489
17.3.1	Affected Sib-Pair Methods	489
17.3.2	Parameter Estimation and Power Calculation using Affected Sib Pairs	491
17.3.3	Typing Unaffected Relatives in Sib-Pair Analyses	492
17.3.4	Application of Sib-Pair Methods to Multiplex Sibships	493
17.3.5	Methods for Analysing Larger Pedigrees	494

17.3.6	Extensions to Multiple-Marker Loci	495
17.3.7	Inclusion of Covariates	495
17.3.8	Multiple Disease Loci	496
17.3.9	Strategies for Genome Scans	497
17.4	Model-Free Methods for Quantitative Traits	498
17.4.1	Sampling Considerations	499
17.5	Conclusions	499
	References	500
18	The Transmission/Disequilibrium Test	507
	<i>W.J. Ewens and R.S. Spielman</i>	
18.1	Introduction	507
18.2	The Case–Control Test	508
18.3	The Transmission/Disequilibrium Test	509
18.4	Statistical Properties of the TDT	510
18.4.1	Validity	510
18.4.2	Data	511
18.4.3	Form of the Test Statistic	511
18.4.4	Mode of Inheritance	511
18.4.5	Inferring Parental Genotypes	511
18.4.6	Continuous Traits	511
18.4.7	Power	512
18.5	The TDT as a Test of Association	512
18.6	Generalizations of the TDT: More than Two Marker Alleles	513
18.7	Generalizations of the TDT: Unaffected Sibs	514
18.8	The S-TDT Used as a Test of Association	517
	References	518
19	Population Association	519
	<i>D. Clayton</i>	
19.1	Introduction	519
19.2	Measures of Association	520
19.3	Case–Control Studies	522
19.4	Tests for Association	524
19.5	Logistic Regression and Log-Linear Models	527
19.6	Stratification and Matching	529
19.7	Unmeasured Confounding	532
19.8	Multiple Alleles	534
19.9	Haplotype Analysis	537
19.10	Discussion	538
	References	539
20	Linkage Analysis	541
	<i>E.A. Thompson</i>	
20.1	Introduction	541
20.2	The Early Years	542
20.3	The Development of Human Genetic Linkage Analysis	544
20.4	The Pedigree Years: Segregation and Linkage Analysis	546
20.5	Likelihood and Location Score Computation	548

20.6	Linkage Analysis of Complex Traits	553
20.7	Map Estimation, Map Uncertainty, and the Meiosis Model	556
20.8	The Future	559
	Acknowledgment	560
	References	560
Part 5 ANIMAL AND PLANT GENETICS		565
21 Quantitative Trait Loci in Inbred Lines		567
<i>R.C. Jansen</i>		
21.1	Introduction	567
21.1.1	Mendelian Factors and Quantitative Traits	567
21.1.2	The Genetics of Inbred Lines	568
21.1.3	Phenotype, Genotype and Environment	569
21.2	Segregation Analysis	570
21.2.1	Visualization of Quantitative Variation in a Histogram	570
21.2.2	Plotting Mixture Distributions on Top of the Histogram	572
21.2.3	Fitting Mixture Distributions	573
21.2.4	Wanted: QTLs!	574
21.3	Dissecting Quantitative Variation with the Aid of Molecular Markers	575
21.3.1	Molecular Markers	575
21.3.2	Mixture Models	576
21.3.3	Alternative Regression Mapping	580
21.3.4	Highly Incomplete Marker Data	581
21.3.5	ANOVA and Regression Tests	581
21.3.6	Maximum Likelihood Tests	582
21.3.7	Analysis-of-deviance Tests	583
21.3.8	How Many Parameters Can we Fit Safely?	584
21.4	QTL Detection Strategies	585
21.4.1	Model Selection and Genome Scan	585
21.4.2	Single-marker Analysis and Interval Mapping	586
21.4.3	Composite Interval Mapping	588
21.4.4	Multiple-QTL Mapping	589
21.4.5	Uncritical use of Model Selection Procedures	592
21.4.6	Final Comments	592
21.5	Bibliographic Notes	593
	Acknowledgments	594
	References	594
22 Mapping Quantitative Trait Loci in Outbred Pedigrees		599
<i>I. Hoeschele</i>		
22.1	Introduction	599
22.2	Linkage Mapping via Least Squares or Maximum Likelihood and Fixed Effects Models	601
22.2.1	Least-Squares	601
22.2.2	Maximum Likelihood	604

22.3	Linkage Mapping via Residual Maximum Likelihood and Random Effects Models	605
22.3.1	Identity-by-Descent Probabilities of Alleles	605
22.3.2	Mixed Linear Model with Random QTL Allelic Effects	609
22.3.3	Mixed Linear Model with Random QTL Genotypic Effects	610
22.3.4	Relationship with other Likelihood Methods	612
22.4	Linkage Mapping via Bayesian Methodology	614
22.4.1	General	614
22.4.2	Bayesian Mapping of a Monogenic Trait	615
22.4.3	Bayesian QTL Mapping	616
22.5	Genotype Sampling in Complex Pedigrees	625
22.6	Fine Mapping of Quantitative Trait Loci	636
22.6.1	Fine Mapping Using Current Recombinations	636
22.6.2	Fine Mapping Using Historical Recombinations	637
22.7	Concluding Remarks	639
	Acknowledgments	639
	References	639
23	Inferences About Breeding Values	645
	<i>D. Gianola</i>	
23.1	Introduction	645
23.2	Landmarks	646
23.2.1	Statistical Genetic Models	646
23.2.2	Best Linear Unbiased Prediction	648
23.2.3	Variance and Covariance Component Estimation	651
23.2.4	BLUP and Unknown Dispersion Parameters	654
23.2.5	Bayesian Procedures	654
23.2.6	Nonlinear, Generalized Linear Models, and Longitudinal Responses	657
23.2.7	Effects of Selection on Inferences	661
23.2.8	Computing Software	663
23.3	Future Developments	664
	Acknowledgments	666
	References	666
24	Marker-Assisted Selection and Introgression	673
	<i>J.C. Whittaker</i>	
24.1	Introduction	673
24.2	Marker-Assisted Selection: Inbred Line Crosses	674
24.2.1	Results	676
24.2.2	Refinements	679
24.3	Marker-Assisted Selection: Outbred Populations	681
24.3.1	MAS via BLUP	682
24.3.2	Comments	683
24.3.3	Within-family MAS	685
24.4	Marker-Assisted Introgression	686
24.4.1	Inbred Line Crosses	687
24.4.2	Outbred Populations	688

24.5	Discussion	689
	Acknowledgments	690
	References	690
Part 6 APPLICATIONS		695
25	Ethics in the Use of Statistics in Genetics	697
	<i>D. Byleveld</i>	
25.1	Introduction	697
25.2	What is Ethics?	698
	25.2.1 Uses of the Term 'Ethics'	698
	25.2.2 Morality	699
25.3	Normative Moral Theories and Institutionalized Consensus	700
	25.3.1 Normative Moral Theories	700
	25.3.2 Adjudicating Between Normative Moral Theories	702
	25.3.3 Consensus and Legitimation	704
25.4	Uses of Statistics	709
	25.4.1 Use of DNA Analysis as Forensic Evidence	709
	25.4.2 Heritability Studies	715
25.5	Concluding Remarks	718
	References	719
26	Forensics	721
	<i>B.S. Weir</i>	
26.1	Introduction	721
26.2	Principles of Interpretation	722
26.3	Profile Probabilities	724
	26.3.1 Allelic Independence	724
	26.3.2 Allele Frequencies	726
	26.3.3 Joint Profile Probabilities	727
	26.3.4 Dirichlet Distribution	730
26.4	Mixtures	730
26.5	Sampling Issues	733
	26.5.1 Allele Probabilities	733
	26.5.2 Coancestry	734
26.6	Other Forensic Issues	735
	26.6.1 Common Fallacies	735
	26.6.2 Relevant Population	736
	26.6.3 Database Searches	736
	26.6.4 Uniqueness of Profiles	736
26.7	Conclusion	737
	References	738
27	Pharmacogenetics	741
	<i>N.J. Schork, D. Fallin, H.K. Tiwari and M.A. Schork</i>	
27.1	Introduction: The Scope of Pharmacogenetics	742
27.2	General Issues in the Pharmacogenetic Analysis of Clinical Trials	743

27.3	Phenotypic and Outcome Assessment via Mixture Distribution Analysis	746
27.3.1	The Basic Normal Mixture Model	746
27.3.2	Hypothesis Testing	748
27.4	Optimal Genotyping Protocols via Extreme Sampling	749
27.5	Multilocus and Haplotype Analysis	752
27.5.1	The Potential Advantages of Studying Haplotypes	752
27.5.2	Haplotypes: Estimation and Testing	753
27.6	Assessing Sample Homogeneity	755
27.7	Sequential Pharmacogenetic Designs	757
27.7.1	The Basic Model	757
27.7.2	Matched Pair Sequential Pharmacogenetic Trial	758
27.8	Conclusions	762
	Acknowledgments	762
	References	762
28	Statistical Basis of Risk Calculations	765
	<i>R. Chakraborty</i>	
28.1	Introduction	765
28.2	Concept of Risk in the Formulation of Bayesian Inference	766
28.3	Various Stages of Risk Estimation	767
28.3.1	Population-based Risk Estimate	767
28.3.2	Conditional Probability	768
28.3.3	Joint and Posterior Risk Probability	768
28.4	Major Advances in Estimating the Conditional Probability	768
28.4.1	Conditional Risks for Single or Major Gene Defects	768
28.4.2	Conditional/Recurrence Risk for Multifactorial Diseases	769
28.4.3	Factors Affecting the Information Content of Conditional Risk Evaluation	769
28.5	Use of Genetic Data in Other Types of Risk Estimation	772
28.5.1	Radiation-induced Risk	772
28.5.2	Pharmacogenetic and Ecogenetic Aspects of Risk Evaluation	773
28.6	Summary and Concluding Remarks	774
	Acknowledgments	774
	References	774
29	Conservation Genetics	779
	<i>M.A. Beaumont</i>	
29.1	Introduction	779
29.2	Estimating Effective Population Size	780
29.2.1	Estimating N_e Using Two Samples from the Same Population: the Temporal Method	781
29.2.2	Estimating N_e from Two Derived Populations	785
29.2.3	Estimating N_e Using One Sample	790
29.2.4	Inferring Past Changes in Population Size: Population Bottlenecks	793
29.3	Hybridization	798
29.3.1	Admixture	798
29.3.2	Genetic Mixture Modelling	802
	References	808

30 Genetic History of the Human Species	813
<i>J.H. Relethford</i>	
30.1 Introduction	813
30.2 Models of Modern Human Origins	814
30.2.1 Replacement – The Recent African Origin Model	815
30.2.2 Continuity – The Multiregional Evolution Model	815
30.2.3 Is There a Middle Ground?	816
30.2.4 The Genetic Evidence	817
30.3 Gene Trees	818
30.3.1 Mitochondrial DNA	819
30.3.2 Other Gene Trees	821
30.3.3 Interpretations of Gene Trees	822
30.3.4 Neandertal DNA	822
30.4 African Genetic Diversity	824
30.4.1 Bottlenecks and Population Age	825
30.4.2 Variation in Effective Population Size	825
30.5 Genetic Distances Between Living Human Populations	828
30.5.1 Levels of Genetic Differentiation	828
30.5.2 Patterns of Genetic Distances	830
30.6 Genetic Demography of the Human Species	832
30.6.1 Species Effective Population Size	832
30.6.2 Temporal Changes in Species Effective Size	834
30.6.3 Species Effective Size-What Does it Mean?	835
30.7 Conclusion	838
Acknowledgments	840
References	840
Index	847