

# Contents

---

<b>1 Genetic Polymorphisms</b>	<b>1</b>
1.1 Genetic and Molecular Background	2
Genotype and Phenotype	2
Gene Expression	2
1.2 Major Types of Polymorphisms	5
DNA Polymorphisms	5
Utility of DNA Polymorphisms	7
1.3 Allele and Genotype Frequencies	8
1.4 Populations and Models	11
Models	11
Utility of Mathematical Models	13
Discrete-Time Models	13
Continuous-Time Models	15
How Models are Tweaked	16
<b>2 Organization of Genetic Variation</b>	<b>21</b>
2.1 Random Mating	21
The Hardy–Weinberg Principle	22
Constancy of Allele Frequencies	23
Chi-square Test for Hardy–Weinberg Equilibrium	24
Statistical Power of the Chi-square Test for Hardy–Weinberg Equilibrium	26
Recessive Alleles Hidden in Heterozygotes	28
Multiple Alleles and DNA Typing	29
2.2 X-Linked Genes	31
2.3 Multiple Loci: Linkage and Linkage Disequilibrium	33
Linkage Disequilibrium, Genetic Associations, and the Problem of Multiple Comparisons	37
2.4 Linkage Disequilibrium in Natural Populations	38
Linkage Disequilibrium as a Correlation Between Alleles of Different Genes in Gametes	39
Linkage Disequilibrium Due to Population Admixture	41
Wahlund’s Principle	42
<b>3 Inbreeding and Population Structure</b>	<b>47</b>
3.1 Genotype Frequencies with Inbreeding	47
3.2 The Inbreeding Coefficient	49
Inbreeding Depression and Heterosis	51
Effects of Inbreeding on Rare Harmful Alleles	52
Inbreeding Effects in Human Populations	53

## CONTENTS

3.3	Calculation of the Inbreeding Coefficient from Pedigrees	54
3.4	Regular Systems of Mating	57
	Partial Selfing	58
	Repeated Sib Mating	59
	Recombinant Inbred Lines	61
3.5	Remote Inbreeding in Finite Populations	62
	Identity by Descent in Finite Populations	63
	Decreased Heterozygosity in Admixed Populations	65
	Hierarchical Population Structure	68
	Mating Between Relatives in a Structured Population	70
<b>4</b>	<b>Mutation, Gene Conversion, and Migration</b>	<b>75</b>
4.1	Mutation	75
	Irreversible Mutation	76
	Reversible Mutation	77
	Gene Duplication and Functional Divergence	78
	Equilibrium Heterozygosity with Mutation	81
4.2	The Coalescent	82
	Coalescence in the Wright-Fisher Model	83
	Nucleotide Polymorphism	85
	Nucleotide Diversity	86
	Estimating $\theta$ and $\pi$ from Sequence Data	86
	The Moran Model	88
	Effective Population Number	90
4.3	Gene Conversion	94
	Biased Gene Conversion	94
	A Model of Biased Gene Conversion	95
4.4	Migration	97
	Models of Migration	97
	One-Way Migration	98
	The Island Model of Migration	98
	How Migration Limits Genetic Divergence	99
	The Fixation Index $F_{ST}$ in Relation to Coalescence	101
	Stepping-Stone Models	103
<b>5</b>	<b>Natural Selection in Large Populations</b>	<b>109</b>
5.1	Selection in Haploids	109
	Continuous-Time Model of Haploid Selection	109
	Discrete-Generation Model of Haploid Selection	111
5.2	Selection in Diploids	112
	Directional Selection	112
	Time Required for Changes in Allele Frequency	115
	Selective Sweeps: Hard Sweeps and Soft Sweeps	117
	Probability of Survival of a Favorable Mutation	118
	Overdominance and Heterozygote Inferiority	121
	Evolutionary Change in Fitness	125

5.3	Mutation–Selection Balance	126
	Equilibrium Allele Frequencies for Recessive and Partially Dominant Mutations	127
	Degree of Dominance of Severely Versus Mildly Deleterious Mutations	128
	Background Selection	129
	Balance Between Migration and Selection	131
5.4	Gametic Selection and Meiotic Drive	132
	Gametic Selection	133
	Meiotic Drive	134
	Gene Drive	135
5.5	Other Modes of Selection	137
<b>6</b>	<b>Random Genetic Drift in Small Populations</b>	<b>147</b>
6.1	Differentiation of Subpopulations Under Random Drift	147
	Random Drift in Small Experimental Populations	148
	The Probability Process Underlying the Wright–Fisher Model	149
	Transition Matrix for the Moran Model	151
	Change in Average Allele Frequency Among Subpopulations	152
	Decrease in Average Heterozygosity Among Subpopulations	154
6.2	Diffusion Approximations	155
	The Forward Equation: An Approach Looking Forward in Time	156
	The Backward Equation: Musing on the First Step	159
6.3	Fixation Probabilities and Times to Fixation	159
	Probability of Fixation	160
	Times to Fixation or Loss	162
6.4	Equilibrium Distributions of Allele Frequency	164
	An Equation for the Stationary Distribution	164
	Reversible Mutation	165
	Multiple Alleles and the Ewens Sampling Formula	167
	Migration	169
	Mutation–Selection Balance	170
	Protein Polymorphisms	171
<b>7</b>	<b>Molecular Population Genetics</b>	<b>179</b>
7.1	Rates of Nucleotide Substitution	180
	Nucleotide Substitutions in Noncoding DNA	180
	Synonymous and Nonsynonymous Substitutions	182
	Nucleotide Divergence Between Species	182
	Correction for Multiple Mutational Hits	184
	Amino Acid Divergence Between Species	186
	Molecular Clockwork	187
7.2	Analysis of the Site Frequency Spectrum	189
	The Unfolded Site Frequency Spectrum	189
	The Folded Site Frequency Spectrum	193
	Codon Usage Bias	194
	Selection for Optimal Codons and Amino Acids	195

## CONTENTS

7.3 Polymorphism and Divergence	197
The McDonald–Kreitman Test	197
Refinements of the McDonald–Kreitman Test	200
Polymorphism and Divergence as a Poisson Random Field	201
The Hudson–Kreitman–Aguadé Test	204
Neutrality Versus Selection: An Emerging Consensus	205
7.4 Demographic History	206
Changes in Population Size Through Time	206
Population Splits and Fusions	207
Estimating Parameters in Demographic Models	208
7.5 Ancient DNA in Studies of Human Populations	209
Human Origins	209
Technical Challenges of Ancient DNA	210
Insights into Human History from Ancient DNA	210
7.6 Transposable Elements	213
Insertion Sequences and Transposons in Bacteria	214
Transposable Elements in Eukaryotes	215
<b>8 Population Genetics of Complex Traits</b>	<b>225</b>
8.1 Phenotypic Variation in Complex Traits	225
Three Types of Complex Traits	226
Phenotypic Variation	226
Properties of the Normal Distribution	227
8.2 Genes and Environment	229
Genotypic Variance and Environmental Variance	230
Broad-Sense Heritability	231
Genotype-by-Environment and Other Interactions	232
Genetic Effects on Complex Traits	233
Components of Genotypic Variation	234
Physiological Epistasis Versus Statistical Epistasis	236
8.3 Artificial Selection	238
Prediction Equation for Individual Selection	240
Intensity of Selection	242
Genetic Basis of the Prediction Equation	243
Change in Mean Phenotype from One Generation of Selection	245
Effect of Selection on a Constituent Locus of a Complex Trait	246
Genomic Selection	247
Correlated Response to Selection	248
8.4 Resemblance Between Relatives	249
Parent–Offspring Covariance	249
Covariance Between Relatives	250
Heritability Estimates from Covariance	251
Heritability Estimates from Regression	251
8.5 Complex Traits with Discrete Expression	253
Threshold Traits: Genes as Risk Factors	253
Heritability of Liability	253
Applications to Human Disease	256

<b>9 Complex Traits in Natural Populations</b>	<b>263</b>
9.1 Genetic Variation and Phenotypic Evolution	263
Mutational Variance and Standing Variance	264
Phenotypic Evolution Under Directional Selection	265
Phenotypic Evolution Under Stabilizing Selection	267
9.2 Searching for the Genes Affecting Complex Traits	269
Quantitative Trait Loci	269
Candidate Genes	272
Genome-Wide Association Studies	274
Number of Genes and Magnitude of Effects	275
Genetic and Environmental Risk Factors in Complex Traits	277
9.3 Complex Traits in Evolutionary Adaptation	278
Evolutionary Pathways of Drug Resistance	279
Genomic Changes Under Domestication	280
Local Selection Versus Gene Flow	281
9.4 Complex Traits in Speciation	281
Reinforcement of Mating Barriers	282
Reproducibility of Phenotypic and Genetic Changes in Speciation	282
Accumulation of Genetic Incompatibilities	283
<i>Index</i>	291