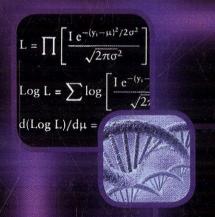
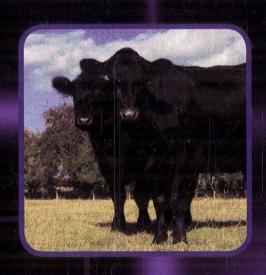
quantitative trait loci analysis in animals

2nd edition





Joel Ira Weller





Contents

	Preface: Theory Versus Results Preface to the Second Edition		
1	Histori	cal Overview	1
	1.1	Introduction	1
	1.2	From Mendel to Sax	1
	1.3	Quantitative Genetics 1920–1980, or Who Needs Mendel?	3
	1.4	QTL Detection 1930–1980, Theory and Experiments	4
	1.5	From Biochemistry to Biotechnology, or More Markers Than We Will Ever Need	4
	1.6	Genetic Mapping Functions	6
	1.7	Physical and Genetic Mapping, Questions of Scale	9
	1.8	Summary	10
	1.0	Summary	10
2	-	les of Parameter Estimation	11
	2.1	Introduction	11
	2.2	Desired Properties of QTL Parameter Estimates	12
	2.3	Moments Method of Estimation	13
	2.4	Least-squares Parameter Estimation	13
	2.5	Least-squares Solutions for a Single Parameter	14
	2.6	Least-squares Solutions for the General Linear Model	15
	2.7	Maximum Likelihood Estimation for a Single Parameter	1.5
	2.8	Maximum Likelihood Multi-parameter Estimation	17
	2.9	Confidence Intervals and Hypothesis Testing for MLE	18
	2.10	Methods to Maximize Likelihood Functions	19
	2.11	Derivative-free Methods	19
	2.12	Second Derivative-based Methods	20
	2.13	First Derivative-based Methods (Expectation-maximization)	20
	2.14	Bayesian Estimation	21
	2.15	Minimum Difference Estimation	22
	2.16	Summary	22
3	Random and Fixed Effects, the Mixed Model		24
	3.1	Introduction	24
	3.2	The Mixed Linear Model	24
	3.3	The Mixed Model Equations	25
	3.4	Solving the Mixed Model Equations	26
	3.5	Some Important Properties of Mixed Model Solutions	27
	3.6	Equation Absorption	28
	3.7	Multivariate Mixed Model Analysis	28
	3,8	The Repeatability Model	29
	3.9	The Individual Animal Model	30
	3.10	Grouping Individuals with Unknown Ancestors	31

	3.11	The Reduced Animal Model	32
	3.12	Maximum Likelihood Estimation with Mixed Models	33
	3.13	Estimation of Variance Components, Analysis of Variance-type	
		Methods	33
	3.14	Maximum Likelihood Estimation of Variance Components	34
	3.15	Restricted Maximum Likelihood Estimation of Variance	
		Components	36
	3.16	The Problem of Variance Components Outside the Parameter Space	37
	3.17	Summary	38
4	Experin	nental Designs to Detect QTL: Generation of Linkage Disequilibrium	39
	4.1	Introduction	39
	4.2	Assumptions, Problems and Types of Effects Postulated	39
	4.3	Experimental Designs for Detection of QTL in Crosses Between	
		Inbred Lines	42
	4,4	Linear Model Analysis of Crosses Between Inbred Lines	43
	4.5	Experimental Designs for Detection of QTL in Segregating	
		Populations: General Considerations	4 7
	4.6	Experimental Designs for Detection of QTL in Segregating	
		Populations: Large Families	48
	4.7	Experimental Designs for Detection of QTL in Segregating	
		Populations: Small Families	51
	4.8	Experimental Designs Based on Additional Generations:	
		Inbred Lines	54
	4.9	Experimental Designs Based on Additional Generations:	
		Segregating Populations	55
	4.10	Comparison of the Expected Contrasts for Different Experimental	
		Designs	58
	4.11	Gametic Effect Models for Complete Population Analyses	59
	4.12	Summary	60
5	QTL Pa	arameter Estimation for Crosses between Inbred Lines	63
	5.1	Introduction	63
	5.2	Moments Method of Estimation	63
	5.3	Least-squares Estimation of QTL Parameters	65
	5.4	Least-squares Estimation of QTL Location for Sib-pair Analysis with	
	· · ·	Flanking Markers	68
	5.5	Linear Regression Mapping of QTL with Flanking Markers	69
	5.6	Marker Information Content for Interval Mapping, Uninformative	
	0.0	and Missing Marker Genotypes	71
	5.7	Maximum Likelihood QTL Parameter Estimation for Crosses	
		Between Inbred Lines and a Single Marker	73
	5.8	Maximum Likelihood Tests of Significance for a Segregating QTL	74
	5.9	Maximum Likelihood QTL Parameter Estimation for Crosses	
	0.0	between Inbred Lines and Two Flanking Markers	74
	5.10	Estimation of QTL Parameters by the Expectation-maximization	
	0.10	Algorithm	75
	5.11	Biases in Estimation of QTL Parameters with Interval Mapping	77
	5.12	The Likelihood Ratio Test with Interval Mapping	78
	5.13	Summary	79
			-

6	Advanc	ed Statistical Methods for QTL Detection and Parameter Estimation	80
	6.1	Introduction	80
	6.2	Higher-order QTL Effects	80
	6.3	QTL Interaction Effects	81
	6.4	Simultaneous Analysis of Multiple Marker Brackets	83
	6,5	Principles of Composite Interval Mapping	84
	6.6	Properties of Composite Interval Mapping	85
	6.7	Derivation of Maximum Likelihood Parameter Estimates by	
		Composite Interval Mapping	85
	6,8	Hypothesis Testing with Composite Interval Mapping	86
	6.9	Multi-marker and QTL Analysis by Regression of Phenotype on	
		Marker Genotypes	87
	6.10	Estimation of QTL Parameters in Outbred Populations	88
	6.11	Analysis of Field Data, Daughter and Granddaughter Designs	89
	6.12	Maximum Likelihood Analysis of QTL Parameters for the Daughter	
		Design with Linkage to a Single Marker	91
	6.13	Non-linear and Linear Regression Estimation for Complex Pedigrees	93
	6.14	Estimation of QTL Allelic Frequencies in Segregating Populations	94
	6.15	Maximum Likelihood Estimation with Random Effects Included in	
		the Model	96
	6.16	Incorporation of Genotype Effects into Animal Model Evaluations	
		When Only a Small Fraction of the Population Has Been Genotyped	97
	6.17	Maximum Likelihood Estimation of QTL Effects on Categorical	
		Traits	98
	6.18	Estimation of QTL Effects with the Threshold Model	100
	6.19	Estimation of QTL Effects on Disease Traits by the Allele-sharing	
		Method	101
	6.20	Summary	101
7	Analysis	s of QTL as Random Effects	103
	7.1	Introduction	103
	7.2	ML Estimation of Variance Components for the Haseman–Elston	103
	7.2	Sib-pair Model	104
	7.3	The Random Gametic Model of Fernando and Grossman,	104
	7.5	Computing G _v	106
	7.4	Computing the Inverse of G _v	107
	7.5	Analysis of the Random Gametic Model by a Reduced Animal Model	108
	7.6	Analysis of the Random Gametic QTL Model with Multiple QTL and	100
		Marker Brackets	110
	7.7	Computation of the Gametic Effects Variance Matrix	110
	7.8	The Gametic Effect Model for Crosses Between Inbred Lines	111
	7.9	REML Estimation of the QTL Variance and Recombination for the	111
	•	Model of Fernando and Grossman	112
	7.10	REML Estimation of the QTL Variance and Location with	112
		Marker Brackets	113
	7.11	Bayesian Estimation of QTL Effects, Determining the Prior	113
		Distribution	114
	7.12	Formula for Bayesian Estimation and Tests of Significance of a	117
		Segregating QTL in a Simulated Granddaughter Design	117
	7.13	Comparison of ML and Bayesian Analyses of a Simulated	11/
		Granddaughter Design	119
			-1/

	7.14 7.15	Markov Chain Monte Carlo Algorithms, Gibbs Sampling Summary	119 120
8	Statistic	al Power to Detect QTL, and Parameter Confidence Intervals	122
	8.1	Introduction	122
	8.2	Estimation of Power in Crosses Between Inbred Lines	123
	8.3	Replicate Progeny in Crosses Between Inbred Lines	124
	8.4	Estimation of Power for Segregating Populations	126
	8.5	Power Estimates for Likelihood Ratio Tests: General Considerations	128
	8.6	The Effect of Statistical Methodology on the Power of QTL Detection	129
	8.7	Estimation of Power with Random QTL Models	130
	8.8	Confidence Intervals for QTL Parameters, Analytical Methods	130
	8.9	Simulation Studies of Confidence Intervals	132
	8.10	Empirical Methods to Estimate Confidence Intervals, Parametric and Nonparametric Bootstrap and Jackknife Methods	132
	8.11	Summary	133
9	Optimiz	zation of Experimental Designs	135
	9.1	Introduction	135
	9.2	Economic Optimization of Marker Spacing When the Number of	
		Individuals Genotyped Is Non-limiting	135
	9.3	Economic Optimization with Replicate Progeny	136
	9.4	Selective Genotyping	137
	9.5	Sample Pooling: General Considerations	140
	9.6	Estimation of Power with Sample Pooling	140
	9.7	Comparison of Power and Sample Sizes with Random Genotyping, Selective Genotyping and Sample Pooling	142
	9.8	Sequential Sampling	143
	9.9	Summary	144
10	Fine Ma	apping of QTL	145
	10.1	Introduction	145
	10.2	Determination of the Genetic Map Critical Interval for a Marker	
		Locus with a Saturated Genetic Marker Map	145
	10.3	Confidence Interval for QTL Location with a Saturated Genetic	
		Marker Map	146
	10.4	Fine Mapping of QTL via Advanced Intercross Lines	150
	10.5	Selective Phenotyping	151
	10.6	Recombinant Progeny Testing	151
	10.7	Interval-specific Congenic Strains	152
	10.8	Recombinant Inbred Segregation Test	152
	10.9	Fine Mapping of QTL in Outcrossing Populations by Identity	150
	10.10	by Descent	153
	10.10	Estimation and Evaluation of Linkage Disequilibrium in	151
	10.11	Animal Populations Linkson Dissoullibrium OTL Manning Regio Principles	154
	10.11 10.12	Linkage Disequilibrium QTL Mapping, Basic Principles	155 156
	10.12 10.13	Linkage Disequilibrium Mapping, Advanced Topics Summary	156
		·	13/
11		ete Genome QTL Scans: The Problem of Multiple Comparisons	159
	11.1	Introduction	159
	11.2	Multiple Markers and Whole-genome Scans	159

	11.3	QTL Detection by Permutation Tests	161
	11.4	QTL Detection Based on the False Discovery Rate	162
	11.5	A Priori Determination of the Proportion of False Positives	165
	11.6	Analysis of Multiple Pedigrees	166
	11.7	Biases with Estimation of Multiple QTL	167
	11.8	Bayesian Estimation of QTL from Whole-genome Scans, Theory	168
	11.9	Bayesian Estimation of QTL from Whole-genome Scans, Simulation	
		Results	171
	1 1.10	Summary	172
12	Multitra	ait QTL Analysis	173
	12.1	Introduction	173
	12.2	Problems and Solutions for Multitrait QTL Analyses	173
	12.3	Multivariate Estimation of QTL Parameters for Correlated Traits	174
	12.4	Comparison of Power for Single and Multitrait QTL Analyses	175
	12.5	Pleiotropy Versus Linkage	178
	12.6	Estimation of QTL Parameters for Correlated Traits by Canonical	
		Transformation	179
	12.7	Determination of Statistical Significance for Multitrait Analyses	180
	12.8	Selective Genotyping with Multiple Traits	182
	12.9	Multitrait LD Mapping	184
	12.10	Summary	184
13	From th	ne QTL to the Gene	186
	13.1	Introduction	186
	13.2	The Molecular Basis of QTL Discovered So Far	187
	13.3	Determination of QTL Candidate Genes	188
	13.4	Determination of Concordance	189
	13.5	QTN Validation by Other Statistical Methods	190
	13.6	QTN Validation by Functional Studies	192
	13.7	Summary	193
14	Principl	es of Selection Index and Traditional Breeding Programmes	194
	14.1	Introduction	194
	14.2	Selection Index for a Single Trait	194
	14.3	Changes in QTL Allelic Frequencies Due to Selection	196
	14.4	Multitrait Selection Index	197
	14.5	The Value of Genetic Gain	198
	14.6	Dairy Cattle Breeding Programmes, Half-sib and Progeny Tests	199
	14.7	Nucleus Breeding Schemes	202
	14.8	Summary	203
15	Marker	-assisted Selection: Theory	204
	15.1	Introduction	204
	15.2	Situations in which Selection Index Is Inefficient	204
	15.3	Potential Contribution of MAS for Selection Within a Breed: General	
		Considerations	205
	15.4	Phenotypic Selection Versus MAS for Individual Selection	206
	15.5	MAS for Sex-limited Traits	207
	15.6	Two-stage Selection: MAS on Juveniles, and Phenotypic Selection	207
	157	of Adults	207
	15.7	MAS Including Marker and Phenotypic Information on Relatives	208

	15.8	Maximum Selection Efficiency of MAS with All QTL Known, Relative to Trait-based Selection, and the Reduction in RSE Due to	
		Sampling Variance	209
	15.9	Marker Information in Segregating Populations	210
	15.10	Inclusion of Marker Information in 'Animal Model' Genetic Evaluations	210
	15.11	Genetic Evaluation Based on Dense Whole-genome Scans	212
	15.12	Velogenetics: the Synergistic Use of MAS and Germ-line Manipulation	214
	15.13	Summary	215
16	Marker	-assisted Selection: Current Status and Results of Simulation Studies	216
	16.1	Introduction	216
	16.2	Modelling the Polygenic Variance	216
	16.3	The Effective Number of QTL	217
	16.4	Proposed Dairy Cattle Breeding Schemes with MAS: Overview	218
	16.5	Inclusion of Marker Information into Standard Progeny Test and MOET Nucleus Breeding Schemes	219
	16.6		2.19
	10.0	Progeny Test Schemes, in Which Information on Genetic Markers is Used to Preselect Young Sires	220
	16.7	The Current Status of MAS in Dairy Cattle	220
			222
	16.8	Selection of Sires Based on Marker Information Without a Progeny Test	223
	16.9	Computation of Reliabilities of Genetic Evaluations Based on	
		Complete Genome Scans	224
	16.10	Long-term Considerations, MAS Versus Selection Index	225
	16.11	MAS for a Multitrait Breeding Objective with a Single Identified QTL	228
	16.12	MAS for a Multitrait Breeding Objective with Multiple	
	4642	Identified QTL	230
	16.13	Summary	231
17		-assisted Introgression	232
	17.1	Introduction	232
	17.2	Marker-assisted Introgression: General Considerations	233
	17.3	Marker-assisted Introgression of a Major Gene into an Inbred Line	234
	17.4	Marker-assisted Introgression of a QTL into a Donor Population Under Selection	235
	17.5	Marker-assisted Introgression for Multiple Genes	237
	17.6	Summary	237
Glos	sary of Sy	mbols	238
	Latin Sy	ymbols .	238
	Greek S		242
	Other S		243
Refe	rences		244
Auth	or Index		258
	ect Index		261