

Contents

1	Introduction	1
1.1	Aims of This Book	1
1.2	Outline of This Book	3
 Part I Stochastic Modelling		
2	Stochastic Modelling in Life Sciences	9
2.1	Compartment Models	10
2.2	Modelling the Spread of Infectious Diseases	11
2.2.1	History of Epidemic Modelling	12
2.2.2	SIR Model	13
2.2.3	Model Extensions	18
2.3	Modelling Processes in Molecular Biology, Biochemistry and Genetics	19
2.3.1	History of Chemical Reaction Modelling	20
2.3.2	Chemical Reaction Kinetics	20
2.3.3	Reaction Kinetics in the Biological Sciences	23
2.4	Algorithms for Simulation	25
2.4.1	Simulation of Continuous-Time Markov Jump Processes	25
2.4.2	Simulation of Solutions of ODEs and SDEs	26
2.5	Conclusion	27
	References	28
3	Stochastic Differential Equations and Diffusions in a Nutshell	31
3.1	Brownian Motion and Gaussian White Noise	32
3.1.1	Brownian Motion	32
3.1.2	Brownian Bridge	34
3.1.3	Gaussian White Noise	34
3.1.4	Excursus: Lévy Processes	35

3.2	Itô Calculus	35
3.2.1	Stochastic Integral and Stochastic Differential Equations	36
3.2.2	Different Stochastic Integrals	37
3.2.3	Existence and Uniqueness of Solutions	38
3.2.4	Transition Density and Likelihood Function	39
3.2.5	Itô Diffusion Processes	40
3.2.6	Sample Path Properties	41
3.2.7	Ergodicity	41
3.2.8	Kolmogorov Forward and Backward Equations	42
3.2.9	Infinitesimal Generator	43
3.2.10	Itô Formula	44
3.2.11	Lamperti Transformation	45
3.2.12	Girsanov Formula	45
3.3	Approximation and Simulation	46
3.3.1	Convergence and Consistency	47
3.3.2	Numerical Approximation	47
3.3.3	Simulation of Brownian Bridge	50
3.4	Concluding Remarks	50
	References	51
4	Approximation of Markov Jump Processes by Diffusions	55
4.1	Characterisation of Processes	56
4.2	Motivation and Purpose	61
4.3	Approximation Methods	63
4.3.1	Convergence of the Master Equation	65
4.3.2	Convergence of the Infinitesimal Generator	69
4.3.3	Langevin Approach	71
4.3.4	Kramers-Moyal Expansion	75
4.3.5	Van Kampen Expansion	77
4.3.6	Other Approaches	83
4.4	Extensions to Systems with Multiple Size Parameters	83
4.4.1	Convergence of the Master Equation	84
4.4.2	Convergence of the Infinitesimal Generator	85
4.4.3	Langevin Approach	86
4.4.4	Kramers-Moyal Expansion	87
4.4.5	Van Kampen Expansion	88
4.5	Choice of Stochastic Integral	91
4.6	Discussion and Conclusion	92
	References	97
5	Diffusion Models in Life Sciences	101
5.1	Standard SIR Model	102
5.1.1	Model	102
5.1.2	Jump Process	103

5.1.3	Diffusion Approximation	104
5.1.4	Summary	109
5.1.5	Illustration	110
5.2	Multitype SIR Model	111
5.2.1	Model	111
5.2.2	Jump Process.....	113
5.2.3	Diffusion Approximation	115
5.2.4	Summary	121
5.2.5	Illustration and Further Remarks	123
5.3	Existence and Uniqueness of Solutions	125
5.4	Conclusion.....	127
	References.....	127

Part II Statistical Inference

6	Parametric Inference for Discretely-Observed Diffusions	133
6.1	Preliminaries.....	134
6.1.1	Time-Continuous Observation	135
6.1.2	Time-Discrete Observation.....	136
6.1.3	Time Scheme	137
6.2	Naive Maximum Likelihood Approach	138
6.3	Approximation of the Likelihood Function	139
6.3.1	Analytical Approximation of the Likelihood Function ...	139
6.3.2	Numerical Solutions of the Kolmogorov Forward Equation.....	142
6.3.3	Simulated Maximum Likelihood Estimation.....	145
6.3.4	Local Linearisation	149
6.4	Alternatives to Maximum Likelihood Estimation	150
6.4.1	Estimating Functions	150
6.4.2	Generalised Method of Moments	156
6.4.3	Simulated Moments Estimation.....	157
6.4.4	Indirect Inference	158
6.4.5	Efficient Method of Moments.....	160
6.5	Exact Algorithm	160
6.6	Discussion and Conclusion	165
	References.....	167
7	Bayesian Inference for Diffusions with Low-Frequency Observations	171
7.1	Concepts of Bayesian Data Augmentation for Diffusions.....	172
7.1.1	Preliminaries and Notation	173
7.1.2	Path Update	175
7.1.3	Parameter Update.....	185
7.1.4	Generalisation to Several Observation Times	188
7.1.5	Generalisation to Several Observed Diffusion Paths.....	189
7.1.6	Practical Concerns	190

7.1.7	Example: Ornstein-Uhlenbeck Process	192
7.1.8	Discussion	197
7.2	Extension to Latent Data and Observation with Error	217
7.2.1	Latent Data	217
7.2.2	Observation with Error	225
7.3	Convergence Problems	229
7.4	Improvements of Convergence	233
7.4.1	Changing the Factorisation of the Dominating Measure ..	233
7.4.2	Time Change Transformations	235
7.4.3	Particle Filters	238
7.4.4	Innovation Scheme on Infinite-Dimensional State Spaces	239
7.5	Discussion and Conclusion	272
	References	277

Part III Applications

8	Application I: Spread of Influenza	281
8.1	Simulation Study	281
8.1.1	Data	282
8.1.2	Parameter Estimation	284
8.2	Example: Influenza in a Boarding School	287
8.2.1	Data	288
8.2.2	Parameter Estimation	288
8.3	Example: Influenza in Germany	294
8.3.1	Data	294
8.3.2	Parameter Estimation	299
8.4	Conclusion and Outlook	301
	References	302
9	Application II: Analysis of Molecular Binding	305
9.1	Problem Statement	306
9.1.1	Data Acquisition by Fluorescence Recovery After Photobleaching	306
9.1.2	Research Questions	307
9.2	Preliminary Analysis	309
9.2.1	Impact of Binding	309
9.2.2	Impact of Diffusion	310
9.3	General Model	311
9.3.1	Compartmental Description	311
9.3.2	Diffusion Approximation	314
9.3.3	Deterministic Approximation	318
9.3.4	Simulation Study	319
9.4	Refinement of the General Model	325
9.4.1	Compartmental Description	326

9.4.2	Diffusion Approximation	326
9.4.3	Deterministic Approximation	328
9.4.4	Simulation Study	328
9.5	Extension of the General Model to Multiple Mobility Classes	330
9.5.1	Compartmental Description	331
9.5.2	Diffusion Approximation	333
9.5.3	Deterministic Approximation	335
9.5.4	Simulation Study	336
9.6	Data Preparation	347
9.6.1	Triple Normalisation	348
9.6.2	Double Normalisation	352
9.6.3	Single Normalisation	353
9.7	Application	355
9.7.1	Data	356
9.7.2	Bayesian Estimation	356
9.7.3	Least Squares Estimation	359
9.7.4	Conclusion	364
9.8	Diffusion-Coupled FRAP	364
9.9	Conclusion and Outlook	367
	References	368

Conclusion and Appendix

10	Summary and Future Work	371
10.1	Summary	371
10.2	Future Work	372
A	Benchmark Models	375
A.1	Geometric Brownian Motion	375
A.2	Ornstein-Uhlenbeck Process	376
A.3	Cox-Ingersoll-Ross Process	376
	References	377
B	Miscellaneous	379
B.1	Difference Operators	379
B.2	Lipschitz Continuity for SIR Models	385
B.2.1	Standard SIR Model	385
B.2.2	Multitype SIR Model	386
B.3	On the Choice of the Update Interval	387
B.4	Posteriori Densities for the Ornstein-Uhlenbeck Process	388
B.5	Inefficiency Factors	397
B.6	Path Proposals in the Latent Data Framework	398
B.7	Derivation of Radon-Nikodym Derivatives	402
B.8	Derivation of Acceptance Probability	409
	References	409

C Supplementary Material for Application II 411

 C.1 Diffusion Approximations 411

 C.1.1 One Mobility Class 411

 C.1.2 Multiple Mobility Classes 413

 C.2 Calculation of Deterministic Process 415

 C.3 Estimation Results 416

 C.4 Diffusion-Coupled Model 417

Index 425