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 8
4.4 Extensions to Systems with Multiple Size Parameters 8
4.4.1 Convergence of the Master Equation 8
4.4.2 Convergence of the Infinitesimal Generator 8
4.4.3 Langevin Approach 8
4.4.4 Kramers-Moyal Expansion 8
4.4.5 Van Kampen Expansion 8
4.5 Choice of Stochastic Integral 9
4.6 Discussion and Conclusion 9
References.... 9

5 Diffusion Models in Life Sciences 10
5.1 Standard SIR Model.... 10
5.1.1 Model 10
5.1.2 Jump Process.... 10

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

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

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 325

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