Contents

Contributing Authors xiv
List of Boxes xvi
Notational Standards xvii

1 Introduction 1
Karl Sigmund, Maurice W. Sabelis, Ulf Dieckmann, and Johan A. J. Metz

A Setting the Stage 7
Introduction to Part A 8

2 Alternative Transmission Modes and the Evolution of Virulence 10
Paul W. Ewald and Giulio De Leo
2.1 Introduction: Historical Background 10
2.2 Virulence Depending on Transmission Modes 11
2.3 Effects of Transmission Mode on Virulence 18
2.4 Model of Virulence Evolution and Waterborne Transmission 19
2.5 Discussion: Applications and Implications 24

3 Wildlife Perspectives on the Evolution of Virulence 26
Giulio De Leo, Andy Dobson, and Andy Goodman
3.1 Introduction 26
3.2 Microparasites versus Macroparasites 27
3.3 Impact of Parasitism on Community Structure 29
3.4 Example: The pan-African Rinderpest Epidemic 31
3.5 Role of Genetic Diversity 32
3.6 Myxomatosis and the Coevolution of Virulence Traits 33
3.7 Evolutionary Race Between Host and Parasite 34
3.8 Multiple Infection Alters the Evolution of Virulence 35
3.9 Interspecific Transmission Influences Virulence 35
3.10 Example: Pasteurella Outbreaks in Bighorn Sheep 36
3.11 Potential Impact of Wildlife Diseases on Human Health 37
3.12 Discussion 38

4 Adaptive Dynamics of Pathogen–Host Interactions 39
Ulf Dieckmann
4.1 Introduction 39
4.2 Limitations of $R_0$ Maximization 40
4.3 Adaptive Dynamics Theory 44
4.4 Pathogen Evolution 45
4.5 Pathogen–Host Coevolution 54
4.6 Discussion 57
# 5 Dilemmas in Virulence Management
Minus van Baalen

5.1 Introduction .................................................. 60
5.2 Optimal Antiparasite Strategies .......................... 62
5.3 Parasite Evolutionary Responses ......................... 65
5.4 Discussion .................................................... 68

# B Host Population Structure
Introduction to Part B ............................................ 71

# 6 Variation in Susceptibility: Lessons from an Insect Virus
Greg Dwyer, Jonathan Dushoff, Joseph S. Elkinton, John P. Burand, and Simon A. Levin

6.1 Introduction .................................................. 74
6.2 Theory of Multigenerational Epidemics .................. 75
6.3 Controlling Gypsy Moths by Genetically Engineered Viruses 77
6.4 Discussion .................................................... 84

# 7 Contact Networks and the Evolution of Virulence
Minus van Baalen

7.1 Introduction .................................................. 85
7.2 Epidemics on Contact Networks .......................... 90
7.3 Mean-field Dynamics ....................................... 91
7.4 Across-network Dynamics ................................. 92
7.5 Pair Dynamics ................................................. 94
7.6 Implications of Network Structure ....................... 97
7.7 Evolutionary Stability ..................................... 99
7.8 Discussion .................................................... 101

# 8 Virulence on the Edge: A Source–Sink Perspective
Robert D. Holt and Michael E. Hochberg

8.1 Introduction .................................................. 104
8.2 Sources and Sinks: Pervasive in Host–Pathogen Systems? 107
8.3 A Limiting Case: Two Coupled Patches .................. 108
8.4 On to Praxis .................................................. 116
8.5 Discussion .................................................... 118

# C Within-Host Interactions
Introduction to Part C ............................................ 121

# 9 Super- and Coinfection: The Two Extremes
Martin A. Nowak and Karl Sigmund

9.1 Introduction .................................................. 124
9.2 Superinfection ............................................... 125
9.3 Coinfection ................................................... 131
9.4 Discussion .................................................... 135
10 Super- and Coinfection: Filling the Range
Frederick R. Adler and Julio Mosquera Losada
10.1 Introduction .............................................. 138
10.2 Coinfection and the Superinfection Limit ............... 139
10.3 Coexistence and the Superinfection Function ............ 143
10.4 Discussion ............................................. 147

11 Multiple Infection and Its Consequences for Virulence Management
Sylvain Gandon and Yannis Michalakis
11.1 Introduction .............................................. 150
11.2 Multiple Infection, Virulence, and Dispersal .......... 153
11.3 Indirect Effects .......................................... 157
11.4 Virulence Management .................................. 161
11.5 Discussion ............................................. 163

12 Kin-selection Models as Evolutionary Explanations of Malaria
Andrew F. Read, Margaret J. Mackinnon, M. Ali Anwar,
and Louise H. Taylor
12.1 Introduction .............................................. 165
12.2 Kin-selection Models of Virulence ...................... 166
12.3 Conditional Virulence Strategies ...................... 167
12.4 Genetically Fixed Virulence Strategies ............... 171
12.5 Within-host Competition and Between-host Fitness .... 172
12.6 Management Implications .............................. 177
12.7 Discussion ............................................. 178

D Pathogen–Host Coevolution
Introduction to Part D ........................................ 180

13 Coevolution of Virus and Host Cell-death Signals
David C. Krakauer
13.1 Introduction .............................................. 183
13.2 Mathematics of Cell Death .............................. 184
13.3 Evolutionary Dynamics of Cell-death Signals .......... 187
13.4 Threshold Reversals ..................................... 188
13.5 Experimental Case Studies .............................. 189
13.6 Lessons from Case Studies .............................. 192
13.7 Testing the Model ....................................... 193
13.8 Medical Implications ................................... 194
13.9 Discussion ............................................. 195

14 Biogeographical Perspectives on Arms Races
Michael E. Hochberg and Robert D. Holt
14.1 Introduction .............................................. 197
14.2 Importance of Species and Space in Population Dynamics . . . 198
14.3 (Co)Evolution of Impact by Natural Enemies .......... 199
14.4 Discussion ............................................. 204
20.4 Population Genetics of Senescence Plasmids: A Model 282
20.5 Intragenomic Conflict and Virulence Management 283
20.6 Discussion: Host Senescence and Pathogen Virulence 284

21 Ecology and Evolution of Chestnut Blight Fungus 286
Douglas R. Taylor
21.1 Introduction 286
21.2 Ecology and Evolution of Virulence with Hyperparasites 287
21.3 Chestnut Blight as a Pandemic in the USA 291
21.4 Hyperparasitism in the Chestnut Blight System 291
21.5 Previous Efforts at Virulence Management 292
21.6 Virulence Management: Suggestions from Theory 294
21.7 Discussion 296

22 Evolution of Exploitation and Defense in Tritrophic Interactions 297
Maurice W. Sabelis, Minus van Baalen, Bas Pels, Martijn Egas, and Arne Janssen
22.1 Introduction 297
22.2 Spatial and Temporal Scales of Interaction 299
22.3 Predator–Herbivore Dynamics on Individual Plants 300
22.4 Tritrophic Game Theory and Metapopulation Dynamics 307
22.5 Discussion 318
22.A Evolutionarily Stable Herbivore Emigration Rate 320

F Vaccines and Drugs 323
Introduction to Part F 324

Sebastian Bonhoeffer
23.1 Introduction 326
23.2 Evaluation of Drug Treatment Strategies 327
23.3 Dynamics of Infection: A Simple Model 327
23.4 The Steady State 328
23.5 Gauging Antibiotic Therapy 328
23.6 Treatment with Two Antibiotics: An Extended Model 331
23.7 Multiple Antibiotic Therapy 333
23.8 Discussion 335

24 Evolution of Vaccine-resistant Strains of Infectious Agents 339
Angela R. McLean
24.1 Introduction 339
24.2 Theoretical Framework 339
24.3 Case Studies from Infectious Diseases of Humans 344
24.4 Discussion 346
25 Pathogen Evolution: The Case of Malaria 347
Sunetra Gupta
25.1 Introduction ........................................ 347
25.2 Maintenance of Pathogen Diversity in Single-locus Systems .... 347
25.3 Multilocus Antigenic Diversity with Genetic Exchange .......... 349
25.4 *Plasmodium falciparum*: A Case Study .......................... 353
25.5 Impact of Vaccination .................................. 358
25.6 Discussion ............................................ 360

26 Vaccination and Serotype Replacement 362
Marc Lipsitch
26.1 Introduction ........................................ 362
26.2 Biology, Diversity, and Impact of Two Pharyngeal Pathogens .... 363
26.3 Conjugate Vaccines ................................... 364
26.4 Serotype Replacement .................................. 365
26.5 Role of Mathematical Models ................................ 366
26.6 Pneumococcal Conjugate Vaccines versus Hib Vaccines ......... 368
26.7 Detection of Replacement: Design of Clinical Trials ............. 370
26.8 Is Serotype Replacement Always Bad? ........................ 370
26.9 Limitations of the Models and Areas for Future Work .......... 372
26.10 Discussion ........................................... 374

G Perspectives for Virulence Management 375
Introduction to Part G ...................................... 376

27 Taking Stock: Relating Theory to Experiment 379
Maurice W. Sabelis and Johan A.J. Metz
27.1 Introduction ........................................ 379
27.2 Panoramic View of Virulence Evolution ........................ 380
27.3 Conceptual Issues ...................................... 386
27.4 The Dialogue between Theorists and Empiricists .................. 389
27.5 Gaps in Current Knowledge ................................ 393
27.6 Discussion: Toward Virulence Management ...................... 397

28 Virulence Management in Humans 399
Paul W. Ewald
28.1 Conceptual Basis for Virulence Management ....................... 399
28.2 Virulence Management of Diarrheal Diseases ..................... 399
28.3 Virulence Management of Vectorborne Diseases ................ 404
28.4 Virulence Management in Dwellings ................................ 409
28.5 Discussion: The Intervention Spectrum ........................ 409

29 Virulence Management in Wildlife Populations 413
Giulio De Leo and Andy Dobson
29.1 Introduction ........................................ 413
29.2 Time Needed for Resistance to Evolve ........................ 413
29.3 Drugs and the Development of Resistance ....................... 414
29.4 Problems in Managing Virulence in Wildlife .................... 415