DIMACS

Series in Discrete Mathematics and Theoretical Computer Science

Volume 71

Disease Evolution

Models, Concepts, and Data Analyses

Zhilan Feng
Ulf Dieckmann
Simon Levin
Editors

American Mathematical Society

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Center for Discrete Mathematics
and Theoretical Computer Science
A consortium of Rutgers University, Princeton University,
AT&T Labs–Research, Bell Labs (Lucent Technologies),
NEC Laboratories America, and Telcordia Technologies
(with partners at Avaya Labs, HP Labs, IBM Research,
Microsoft Research, and Stevens Institute of Technology)

American Mathematical Society

2000 Mathematics Subject Classification. Primary 34C60, 35Q80, 62P10, 92B05, 92C50, 92C60, 92D10, 92D15, 92D25, 92D30.

Library of Congress Cataloging-in-Publication Data
Disease evolution : models, concepts, and data analyses/Zhilan Feng, Ulf Dieckmann, Simon Levin, editors.
p. cm. — (DIMACS series in discrete mathematics and theoretical computer science; 71)
Includes bibliographical references
ISBN 0-8218-3753-2 (alk. paper)
1. Communicable diseases–Epidemiology. 2. Molecular epidemiology. 3. Evolutionary genetics. I. Feng, Zhilan, 1959- II. Dieckmann, Ulf, 1966- III. Levin, Simon A. IV. Series.

RA652.2.M3.D57 2006
6l4.4—dc22 2006042973

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10 9 8 7 6 5 4 3 2 1 11 10 09 08 07 06

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Foreword

This volume has its genesis in the activities of the DIMACS working group on Genetics and Evolution of Pathogens. This working group held a meeting on November 24-25, 2003 at Rutgers University, and we would like to express our appreciation to Zhilan Feng for organizing and planning this successful conference. The volume represents an expansion of the efforts of this working group, and contains papers from experts in the field who were unable to attend this initial meeting. We thank the three editors Zhilan Feng, Ulf Dieckmann and Simon Levin for their efforts in the organization of the volume, and we thank Bruce Levin for his insightful Preface and also the various authors who contributed to the volume.

The meeting was part of the 2002-2007 Special Focus on Computational and Mathematical Epidemiology, and was organized by one of a number of special focus research groups called "working groups" as part of the special focus. We extend our thanks to Martin Farach-Colton, Sunetra Gupta, Donald Hoover, David Krakauer, Simon Levin, Marc Lipsitch, David Madigan, Megan Murray, S. Muthukrishnan, David Ozonoff, Fred Roberts, Burton Singer and Daniel Wartenberg for their work as special focus organizers.

The meeting brought together researchers who approach the study of epidemiology from a variety of disciplines, some applied and some theoretical. These included computer scientists, mathematicians, statisticians, and biologists together with both descriptive and analytical epidemiologists. The goal of the working group as well as of this volume is the exploration of cross-disciplinary approaches to the study of topics related to disease evolution, and how they apply to the study of specific diseases.

DIMACS gratefully acknowledges the generous support that makes these programs possible. Special thanks go to the National Science Foundation, the James S. McDonnell Foundation, the Burroughs-Wellcome Fund, the Purdue University Mathematics Department and to DIMACS partners at Rutgers, Princeton, AT&T Labs - Research, Bell Labs, NEC Laboratories America, and Telcordia Technologies, and affiliate partners Avaya Labs, HP Labs, IBM Research, and Microsoft Research.

Fred S. Roberts
Director

Robert Tarjan
Co-Director for Princeton

Preface

Infections by microparasites (bacteria, viruses, protozoa and single celled fungi) are the primary source of human mortality in the underdeveloped world. And, despite all of the improvement in public health, hygiene, nutrition, living conditions and medical intervention over the past century, infections continue to be a major cause of morbidity and mortality in the developed world as well. Indeed, if we include people compromised by age, cancers and other diseases with immune–suppressing effects and/or treatments, coronary artery, diabetes, and other non-contagious and degenerative diseases, bacterial infections (often acquired in hospitals) may well be the major immediate cause of death even in overdeveloped countries.

Traditionally, the study of infectious diseases and their prevention and treatment has been the purview of epidemiologists, microbiologists, immunologists and clinicians – people who generally have little background in or appreciation for mathematics beyond statistics, if that. While the importance of quantitative reasoning for studies of the epidemiology of infectious diseases has been recognized for some time, this has been less so for investigations of the course of infections and their treatment within individual patients. For the most part, protocols for preventing the spread of infections in hospitals and communities and for the treatment of individual patients are based on qualitative considerations, experience and intuition, with money being the primary quantitative element in their design and implementation.

During the past two decades, studies of the epidemiology, evolution and within-host biology of infectious diseases and the development of methods for their prevention and treatment have been increasingly infiltrated by quantitative methods beyond statistics. A number of applied and not-so-applied mathematicians, mathematically trained and oriented epidemiologists, microbiologists, immunologists, ecologists, population and evolutionary biologists and even real doctors have been using mathematical and numerical models (computer simulations) to study the epidemiology, evolution and within-host dynamics of infectious diseases and to develop and evaluate protocols for their prevention and treatment. This collection is an impressive sampling of the nature and diversity of this epidemic of mathematical and numerical modelling for the studies of infectious diseases. It illustrates some of the delicious problems and opportunities for mathematicians and mathematical biologists that infectious diseases pose – problems that have the virtues of being important to human health and well-being and, at the same time, being challenging and intriguing even from the precious heights of academe.

For generality, tractability and the aesthetic appeal of closed-form mathematical analysis, traditional models of the epidemiology and evolution of infectious diseases have been deterministic and give little or no consideration to the spatial, temporal and other heterogeneities of human and other host communities and those of the microbes that infect them. In recent years, increasing numbers of modelers have been confronting these inconveniences and the unfortunate finiteness of the real world and exploring how they affect the inferences about the epidemiology and evolution of infectious diseases drawn from simpler models. Three of the chapters in this collection illustrate this trend. Mike Boots and his collaborators consider the

effects of the spatial structure of host populations on the evolution of the virulence of the microparasites that infect them. The two chapters by Wayne Getz and his cohorts examine, in a pedagogically useful as well as scholarly way, the consequences of spatial structure and stochastic processes on the spread of infectious diseases. Their chapters illustrate the utility of modelling to understanding the ascent and spread of emerging and reemerging diseases like SARS and tuberculosis, predicting their emergence and evaluating methods to control their dissemination.

In a commentary with a title that should appeal to this audience, "In Theory", Sidney Brenner referred to molecular biology as the "great leveler" and suggested that for many it has made thinking unnecessary, a position I do not challenge. On the other side, the ease with which data and particularly those on the nucleotide sequences of DNA can be and have been gathered has also provided an opportunity for the quantitative study of evolutionary history through phylogenies. God is no longer the only one who can make a tree. Phylogenies generated from DNA sequence data – molecular phylogenies – have been the largest growth industry in the evolution business for the past decade. And, the development (if not always the application) of methods for generating, analyzing and interpreting these trees is an activity that requires serious thinking. The chapter by Charleston and Galvani is a fine example of this thinking applied to ascertaining the evolutionary relationship between interacting organisms like parasites and their hosts. "Co-phylogenetic" methods of the sort they are developing are of practical as well as academic interest. They can be used to determine the origins (original hosts) of newly emerging infectious diseases like HIV/AIDS and in that way better understand the conditions responsible for their emergence.

A prominent approach to drawing inferences about the nature and direction of evolution of parasites and their virulence has been to study their ecology (population dynamics and demography) within individual hosts or communities of hosts. In this perspective, the fitness of the microparasites is proportional to their reproductive number, R_0 – the number of secondary infections in a largely (or better yet, wholly) uninfected population of cells or tissues in an infected host or among individuals in a community of hosts. While this ecological approach to evolutionary inferences is explicit about nature and functional form of the selection pressures responsible for evolution, it does not consider the genetic basis of the variability upon which that selection is operating. In different ways and with different foci, two chapters consider ways to meld the ecological approach to the study of the evolution of microparasites and their virulence with those of population and quantitative genetics in situations where the nature of inheritance is explicit but where the ecological basis of selection is not. In their chapter, Troy Day and Silvain Gandon consider how to apply classy population genetic approaches, like the Price equation, to studies of the evolution of microparasites and their virulence in communities of hosts. In his chapter, John Kelly uses a combination of ecological and population genetic methods to explore the contribution of tissue heterogeneity to the evolution of viruses in within infected hosts.

The contribution of the heterogeneity of the within-host habitat to the population and evolutionary dynamics of microparasites is also the focus of three other chapters in this collection. While modelers as well as experimentalists have the convenience of separately studying microparasite ecology and evolution within infected host and in communities of hosts, in the real world microbes have no choice but

to deal with both of these elements of their ecology and evolution. Although their models focus primarily on the within-host population and evolutionary dynamics of viruses and the contribution of within-host heterogeneity to that evolution, in their chapter Robert Holt and Michael Barfield consider how the within-host biology of microparasites contributes to their evolution in communities of hosts. In the chapter by Zhilan Feng and Libin Rong, the within-host heterogeneity of concern is comprised of the selective environments imposed by treatment with multiple drugs that act at different stages in the microparasite replication cycle. Using an age-structured model, they consider the treatment of HIV/AIDS with reverse-transcriptase – and protease – inhibitors, and how this treatment contributes to the evolution of resistance and rates of viral replication. Antimicrobial chemotherapy, heterogeneity and resistance are also the subjects of the chapter by David Smith and his collaborators. In their case, the drugs are antibacterial (antibiotics) rather than antiviral; the heterogeneity is both spatial and in the extent to which the drugs are employed; and the focus is the epidemiology and evolution of resistance in communities of hosts rather than in individual treated patients.

Investigators studying the evolution of infectious disease are almost invariably adaptationists; they assume that selection in the host, parasite or both populations is responsible for the virulence of the parasite and for maintaining genetic diversity in the parasite population. In their article on the serological diversity of the rhinoviruses responsible for the common cold, William Koppelman and Frederick Adler consider the neutral, null hypothesis alternative – that the 100 or so serotypes of Rhinoviruses responsible for colds are consequences of a high mutation rate and genetic drift rather than immune-mediated selection. Rhinoviruses and the cross-immunity they engender are also stage center in the chapter by Alun L. Lloyd and Dominik Wodarz, but the focus of their investigation of these ubiquitous and annoying, albeit rarely lethal, viruses is chemotherapy and the contribution of the host immune response to the evolution of resistance to the antiviral drugs employed.

This collection can be and I believe should be seen as a testimony to the work of Roy Anderson and Robert May. While they are not the discoverers of infectious diseases (at least I don't think they are) or even the first to use mathematical models to investigate them, their research more than that of any other investigators has been responsible for the renaissance (epidemic) in the use of models for studying infectious diseases and their control. The research reported in almost all of the chapters in this volume have antecedents in Anderson and May's work. While there is no formal dedication to them in the front matter of this volume, that dedication is where it really counts. The contributions of either Robert May and/or Roy Anderson are acknowledged at least once in every chapter and now, appropriately, in this Preface.

Enjoy,
Bruce R. Levin
Atlanta, September 2005

Editors' introduction

The goal of this volume is to show how to use mathematical tools to understand the evolution of infectious diseases. Inspiration for this project comes from work of the DIMACS Working Group on Genetics and Evolution of Pathogens, which is organized under the auspices of DIMACS' Special Focus on Computational and Mathematical Epidemiology.

This volume is divided into two sections: Model Infrastructure and Applications to Specific Diseases. Section I discusses the impact on disease evolution of various factors, including spatial structure, transient dynamics, coupling of within-host and between-host dynamics, heterogeneity in host populations, and drug resistance. Section II is concerned with investigations associated with specific infectious diseases such as rhinovirus, HIV/AIDS, tuberculosis, and malaria.

We thank Bruce Levin for his excellent Preface. We also express our gratitude to members of DIMACS' staff who kindly helped with the support of the workshop and the preparation of this volume. The leadership of Red Roberts in developing the multi-year epidemiology program has been an inspiration to many researchers, and this volume owes its existence to his efforts. We also thank all the Purdue Mathematics Department for providing technical support. Finally, we thank the authors for their outstanding contributions.

The workshop and the preparation of this volume were partially supported by an NSF grant to DIMACS, and by NSF and James S. McDonnell Foundation grants to ZF.

Zhilan Feng (Purdue University)
Ulf Dieckmann (International Institute for Applied Systems Analysis, Austria)
Simon Levin (Princeton University)

Section I

Model Infrastructure

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Volume **71**, 2006

The implications of spatial structure within populations to the evolution of parasites

Mike Boots, Masashi Kamo, and Akira Sasaki

Abstract. It is well understood that the spatial structure inherent in most if not all populations can have important implications to the evolutionary dynamics of a wide range of traits. One of the best developed areas of evolutionary theory focusses on the evolution of parasites and spatially explicit models have illustrated the importance of structure within the host to the selection of the infectious organisms. Here we review this theory and show how approximation techniques may be useful in addressing the problem. We show that transmission can be constrained without trade-offs and there is the possibility of multiple stable states due to interactions with self-generated population structures. Models intermediate between local and the mean-field have demonstrated that these effects are not only the result of extreme local interactions and may therefore be applicable not only to plant populations with rigidly local interactions. Advances in this field have mostly been driven by the use of computer simulation, but moment closure approximations offer an opportunity to develop our analytical understanding of these processes. However, advances in these approximation techniques are required for models with extreme local interactions.

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Insights from Price's equation into evolutionary epidemiology

Troy Day and Sylvain Gandon

Abstract. We present an alternative theoretical framework for modeling the evolutionary and epidemiological dynamics of host-parasite interactions that is based on using the instantaneous rate of change of infected hosts as a measure of pathogen fitness, rather than the more commonly used quantity, R0. This alternative approach leads to a number of re-interpretations of predictions derived from previous theory, and it thereby provides a more thorough perspective on how various factors affect pathogen evolution. It also provides a relatively straightforward approach for modeling the dynamics of evolutionary change in pathogen populations when it cannot be assumed that the epidemiological dynamics occur on a time scale that is fast relative to that of the evolutionary dynamics.

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Within-host pathogen dynamics: Some ecological and evolutionary consequences of transients, dispersal mode, and within-host spatial heterogeneity

Robert D. Holt and Michael Barfield

Abstract. The ecology and evolution of infectious disease occur at multiple spatial scales. In this paper, we explore some consequences of transient dynamics of pathogens within individual hosts. If infected hosts die quickly, relative to internal equilibration in pathogen dynamics, within-host transients may influence between-host transmission and spread. We develop a formulation for characterizing the overall growth rate of an infectious disease, which includes both within-host dynamics and between-host transmission, when the disease is sufficiently rare that the supply of available hosts can be viewed as a constant. This formulation is analogous to the familiar Euler equation in age-structured demography. We suggest that the pathogen growth rate estimated this way may be a better measure of pathogen fitness than is R_0. We point out that even simple models of within-host pathogen dynamics can have phases in which numbers overshoot the final equilibrium, and that such phases may influence pathogen evolution. We touch on the potential importance of within-host spatial heterogeneities in pathogen dynamics, and suggest that an interesting question for future work is understanding the interplay of spatial structure and transient dynamics in the within-host infection process.

DIMACS Series in Discrete Mathematics
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Evolutionary and dynamic models of infection with internal host structure

John K. Kelly

Abstract. A large body of mathematical theory has been developed to characterize persistent viral infections within vertebrate hosts. Most of the theory can be classified as either "dynamical models" that predict the population dynamic interaction between virus and host cells or "population genetic models" that predict gene sequence evolution of the pathogen. These two bodies of theory can be linked by considering the demography of the viral population. Gene sequence evolution is usually modeled as a mutation-limited process in which the rate of evolution is proportional to the mutation rate per replication cycle and the number of replication cycles (pathogen generations) per unit time. The latter is clearly dependent on dynamical parameters such as the clearance rate of free virus or the death rate of infected cells. Here, I review analytical methods that explicitly link dynamical and population genetic theories. These methods are extended to consider the evolutionary consequences of internal host structure, the tendency for a virus to infect multiple different compartments (e.g. tissue types). Infection of multiple compartments, coupled with virus migration, may establish "sources" and "sinks" of viral production within the host. Paradoxically, the existence of reproductive sinks can simultaneously reduce the number of viruses within a host and accelerate the genetic evolution of the viral population.

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Basic Methods for Modeling the Invasion and Spread of Contagious Diseases

Wayne M. Getz and James O. Lloyd-Smith

Abstract. The evolution of disease requires a firm understanding of heterogeneity among pathogen strains and hosts with regard to the processes of transmission, movement, recovery, and pathobiology. In this and a companion chapter (Getz et al. this volume), we focus on the question of how to model the invasion and spread of diseases in heterogeneous environments, without making an explicit link to natural selection–the topic of other chapters in this volume. We begin in this chapter by providing an overview of current methods used to model epidemics in homogeneous populations, covering continuous and discrete time formulations in both deterministic and stochastic frameworks. In particular, we introduce Kermack and McKendrick's SIR (susceptible, infected, removed) formulation for the case where the removed (R) disease class is partitioned into immune (V class) and dead (D class) individuals. We also focus on transmission, contrasting mass-action and frequency-dependent formulations and results. This is followed by a presentation of various extensions including the consideration of the latent period of infection, the staging of disease classes, and the addition of vital and demographic processes. We then discuss the relative merits of continuous versus discrete time formulations to model real systems, particularly in the context of stochastic analyses. The overview is completed with a presentation of basic branching process theory as a stochastic generation-based model for the invasion of disease into populations of infinite size, with numerical extensions generalizing results to populations of finite size. In framework of branching process theory, we explore the question of minor versus major stochastic epidemics and illuminate the relationship between minor epidemics and a deterministic theory of disease invasion, as well as major epidemics and the deterministic theory of disease establishment. We conclude this chapter with a demonstration of how the basic ideas can be used to model containment policies associated with the outbreak of SARS in Asia in the early part of 2003.

Section II

Applications to Specific Diseases

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Modeling the Invasion and Spread of Contagious Diseases in Heterogeneous Populations

Wayne M. Getz, James O. Lloyd-Smith, Paul C. Cross, *Shirli Bar-David, Philip L. Johnson, Travis C. Porco, and María S. Sánchez

Abstract. The evolution of disease requires a firm understanding of heterogeneity among pathogen strains and hosts with regard to the processes of transmission, movement, recovery, and pathobiology. In this chapter, we build on the basic methodologies outlined in the previous chapter to address the question of how to model the invasion and spread of diseases in heterogeneous environments, without making an explicit link to natural selection—the topic of other chapters in this volume. After a general introdution in Section 1, the material is organized into three sections (Sections 2–4). Section 2 covers heterogeneous populations structured into homogeneous subgroups, with application to modeling TB and HIV epidemics. Section 3 reviews a new approach to analyzing epidemics in well-mixed populations in which individual-level variation in infectiousness is represented by a distributed reproductive number [**51**]—in particular, the expected number of secondary cases due to each individual is drawn from a gamma distribution, yielding a negative binomial offspring distribution after stochasticity in transmission is taken into account. In Section 3, we discuss ideas relating to superspreading events, as well as the best way to characterize the heterogeneity associated with transmission in real epidemics, including SARS, measles, and various pox viruses. Section 4 deals with individual-based approaches to modeling the spread of disease in finite populations with group structure, focusing on several issues including interactions among movement, transmission, and demographic time-scales, the effects of network connectivity on the spread of disease, and the spread of disease in invading or colonizing hosts. The applications in Section 5 focus on bovine TB (BTB) in an African buffalo population and the potential for BTB to invade a colonizing Persian fallow deer population.

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A cophylogenetic perspective on host-pathogen evolution

Michael A. Charleston and Alison P. Galvani

Abstract. Cophylogeny reconstruction is an increasingly important component of the study of evolution, as it pertains to the relationships among ecologically linked organisms, particularly those of hosts and pathogens. Cophylogenetic models have enhanced our understanding of the evolution of many pathogens, including malaria, adenoviruses and lyssaviruses. These models have also been used to infer the conditions surrounding the emergence of HIV. We compare the primary techniques used in cophylogenetic analysis, and survey some of the insights that cophylogenetic analysis has yielded about host-pathogen interactions and the emergence of new diseases.

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The influence of anti-viral drug therapy on the evolution of HIV-1 pathogens

Zhilan Feng and Libin Rong

Abstract. An age-structured model is used to study the possible impact of drug treatment of infections with the human immunodeficiency virus type 1 (HIV-1) on evolution of the pathogen. Inappropriate drug therapy often leads to the development of drug-resistant mutants of the virus. Previous studies have shown that natural selection within a host favors viruses that maximize their fitness. By demonstrating how drug therapy may influence the within host viral fitness we show that while a higher treatment efficacy reduces the fitness of the drug-sensitive virus, it may provide a stronger force of selection for drug-resistant viruses allowing a wider range of resistant strains to invade.

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Do rhinoviruses follow the neutral theory? The role of cross-immunity in maintaining the diversity of the common cold

William J. Koppelman and Frederick R. Adler

Abstract. Over 100 serotypes of rhinoviruses, one of the primary causes of the common cold, co-circulate in the human population. This high diversity makes it effectively impossible to develop a vaccine, even for those at risk of complications due to asthma or cystic fibrosis. Is the high mutation rate of these viruses sufficient to explain this diversity? We use parameters estimated from the literature to study whether immune interactions between different rhinovirus serotypes also play an important role in maintaining diversity. Our mathematical models indicate that high mutation rates alone may well be responsible for the observed levels of diversity. However, careful studies of a few communities have found that some serotypes persist for many years, in conflict with the predictions of the simplest models, hinting that there might be more to the story than is yet known.

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Drug Resistance in Acute Viral Infections: Rhinovirus as a Case Study

Alun L. Lloyd and Dominik Wodarz

Abstract. The emergence and spread of drug resistant virus variants reflects both within-host and between-host processes. We develop an epidemiological model that can be used to address the spread of resistance at the population level, and a virus dynamics model that can be used to study the dynamics of virus over the time course of an individual's infection. The dynamics depend in an important way on the competition between drug sensitive and drug resistant virus strains. A key observation is that the strength of competition between strains is strongly modulated by the degree of cross-immunity that infection with one strain confers against infection with the other. At the within-host level, we see that an efficient immune response can reduce the likelihood of the emergence of resistant virus. Consequently, resistance poses more of a problem for chronic infections in which there is significant immune impairment than for acute infections. These findings are discussed in the setting of rhinovirus infections, which are an important cause of infection in humans and for which novel antiviral drugs are being developed.

DIMACS Series in Discrete Mathematics
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Dynamics and Control of Antibiotic Resistance in Structured Metapopulations

David L. Smith, Maciej F. Boni, and Ramanan Laxminarayan

Abstract. The evolution of resistance to antimicrobial drugs is a major public health concern. Mathematical models for the spread of resistance have played an important role as a conceptual tool for understanding how and why resistance emerges and spreads. Here, we present a new, general mathematical model for the spread of resistance within a population that accounts for several biologically plausible effects of antimicrobial drug use. Except for the evolution of *de novo* resistance, the model is mathematically identical to Lotka-Volterra competition. The simple model is extended to include the spread of resistance among several patches, and the evolution of multi-drug resistance. The models are used to illustrate some simple ideas about the spatial spread and spatial control of resistance and the evolution of multi-drug resistance.

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Infectious diseases are continuing to threaten humankind. While some diseases have been controlled, new diseases are constantly appearing. Others are now reappearing in forms that are resistant to drug treatments. A capacity for continual re-adaptation furnishes pathogens with the power to escape our control efforts through evolution. This makes it imperative to understand the complex selection pressures that are shaping and reshaping diseases. Modern models of evolutionary epidemiology provide powerful tools for creating, expressing, and testing such understanding.

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ISBN 0-8218-3753-2

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DIMACS/71