Chapter 16
Challenges, Opportunities and Theoretical Epidemiology

Lessons learned from the HIV pandemic, SARS in 2003, the 2009 H1N1 influenza pandemic, the 2014 Ebola outbreak in West Africa, and the ongoing Zika outbreaks in the Americas can be framed under a public health policy model that responds after the fact. Responses often come through reallocation of resources from one disease control effort to a new pressing need. The operating models of preparedness and response are ill-equipped to prevent or ameliorate disease emergence or reemergence at global scales [27]. Epidemiological challenges that are a threat to the economic stability of many regions of the world, particularly those depending on travel and trade [132], remain at the forefront of the Global Commons. Consequently, efforts to quantify the impact of mobility and trade on disease dynamics have dominated the interests of theoreticians for some time [14, 143]. Our experience includes an H1N1 influenza pandemic crisscrossing the world during 2009 and 2010, the 2014 Ebola outbreaks, limited to regions of West Africa lacking appropriate medical facilities, health infrastructure, and sufficient levels of preparedness and education, and the expanding Zika outbreaks, moving expeditiously across habitats suitable for Aedes aegypti. These provide opportunities to quantify the impact of disease emergence or reemergence on the decisions that individuals take in response to real or perceived disease risks [11, 62, 93]. The case of SARS in 2003 [40], the efforts to reduce the burden of H1N1 influenza cases in 2009 [33, 62, 80, 93] and the challenges faced in reducing the number of Ebola cases in 2014 [24, 27] are but three recent scenarios that required a timely global response. Studies addressing the impact of centralized sources of information [150], the impact of information along social connections [33, 37, 42], or the role of past disease outbreak experiences [105, 130] on the risk-aversion decisions that individuals undertake may help identify and quantify the role of human responses to disease dynamics while recognizing the importance of assessing the timing of disease emergence and reemergence. The co-evolving human responses to disease dynamics are prototypical of the feedbacks that define

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complex adaptive systems. In short, we live in a socioepisphere being reshaped by ecoepidemiology in the "Era of Information".

What are the questions and modes of thinking that should be driving ongoing research on the dynamics, evolution, and control of epidemic diseases at the population level? The challenges of SARS, Ebola, Influenza, Zika, and other diseases are immense. While we may guess which emerging or re-emerging disease may lead to the next possible catastrophe, we cannot know. The contemporary philosopher Yogi Berra is rumored to have said, "Making predictions is hard, especially about the future". There are some epidemiological topics that have already received some attention but are not yet fully developed. In the rest of this chapter we highlight some challenges, opportunities, and promising approaches in the study of disease dynamics at the population level.

16.1 Disease and the Global Commons

As has been noted, "The identification of a theoretical explanatory framework that accounts for the pattern regularity exhibited by a large number of host–parasite systems, including those sustained by host–vector epidemiological dynamics, is but one of the challenges facing the co-evolving fields of computational, evolutionary, and theoretical epidemiology" [25]. Furthermore, "The emergence of new diseases, the persistence of recurring diseases and the re-emergence of old foes, the result of genetic changes or shifts in demographic, and environmental shifts have increased due to mobility, global connectedness, trade, bird migration, poverty and long-lasting violent conflicts. These diseases often present modeling challenges which may yield to existing analytic techniques but sometimes require new mathematics" [25].

The Global Commons are continuously reshaped by the ability of an increasing proportion of the human population to live, move, or trade nearly anywhere. Therefore, understanding the patterns of interactions between humans, or between humans and vectors, as well as their relationships to patterns of individual movement, particularly those of the highly mobile, is critical to public health responses that effectively ameliorate the ability of a disease to spread. In today's world, hosts' risk knowledge (good or bad information) when combined with the ability of public health officials to measure and properly communicate, in a timely manner, real or perceived information on disease risks, limit our ability to derail the spread of emergent and re-emergent diseases, at time scales that make a difference.

16.1.1 Contagion and Tipping Points

Contagion is believed to be the direct or indirect result of interactions between individuals experiencing radically different epidemiological, or immunological, or

social states. Contagion tends to succeed within environments or communities that "facilitate" modes of infection among its members. Contagion is an "understood" or "believed" mode of disease transmission or of "socially transmitted" behaviors, popularized by Malcolm Gladwell, a journalist who made use of his general understanding of the concept of "contagion." In his construction of reasonable or plausible explanations for the observed and documented dramatic reductions in car thefts and violent crimes in New York City in the 1990s, [71] Gladwell expanded the use of the concept of contagion and tipping point in his development of a framework that captures—as the result of contagion—the spread of a multitude of social ills or virtues [72]. Specifically, contagion is seen in [71] as a force capable of starting and sustaining growth in criminal activity as long as a "critical mass" of individuals capable and willing to commit crimes is available. The growth in criminal activity in New York City is, according to Gladwell, the result of the "interactions" between a large enough pool of criminally active (infected) individuals and individuals susceptible to criminal contagion [71]. Gladwell extends the perspective pioneered by Sir Ronald Ross [141] and his "students" [90–92] to the field of social dynamics.

Gladwell concludes as Ross did in 1911 that implementing control measures (crime contact-reduction measures) that bring the size of the population of criminals (the core) below a critical threshold (tipping point), are sufficient to explain the drastic reductions in criminal activity in NYC. Gladwell concludes, "There is probably no other place [NYC] in the country where violent crime has declined so far, so fast" [71].

16.1.2 Geographic and Spatial Disease Spread

The SARS epidemic of 2002–2003 emphasized the possibility of disease transmission over long distances through air travel, and this has led to metapopulation studies that account for long-distance transmission [5–8]. A metapopulation, in this context, is a population of populations linked by travel. A metapopulation model would have an associated, independent of travel, reproduction number as well as reproduction numbers that account for travel between patches, either temporary travel or permanent migration . This is an Eulerian perspective, describing migration between patches.

An alternative approach to the modeling of the spatial spread of diseases is based on a Lagrangian perspective, which can be formulated, for example, in terms of residence times [18, 25] . This approach has been introduced in Chap. 15. In this structure, actual travel between patches is not described explicitly, and this makes the analysis less complicated. Calculation of the reproduction number and the final size relations is possible.

Another aspect of the study of the spread of diseases is the spatial spread of diseases through diffusion. This has been introduced in Chap. 14 of this book and has been examined in considerable detail in [136], with particular emphasis on epidemic waves.

16.2 Heterogeneity of Mixing, Cross-immunity, and Coinfection

In epidemics, as in the rest of biology, the role of heterogeneity plays a fundamental role and a critical question arises: what is the level of heterogeneity that must be included to address a specific question properly? For example, first-order estimates of the fraction that must be vaccinated to eliminate a communicable disease can be handled with homogeneous mixing models while the elaboration of optimal vaccination strategies in real-life situations often require an age-structured model [28, 81]. The study of nosocomial (in-hospital) infections provides an additional example of the role of heterogeneity in transmission or degree of susceptibility or resistance [38, 39, 106]. The SARS epidemic provided a timely example of the criticality of heterogeneous mixing, in nosocomial transmission [85, 152] . Since there was no treatment available during the SARS epidemic, the main management approach rested on the effectiveness of isolation of diagnosed infectives, quarantine of suspected infectives, and early diagnosis. Quarantine was decided by tracing of contacts made by infectives but in fact few quarantined individuals developed SARS symptoms. The role of early diagnosis and the effectiveness of isolation seemed to have been the key to SARS control with improvements in contact tracing also playing an important role in epidemic control.

Another set of questions arises when one considers the immunological history of individuals or populations. There are many instances in which more than one strain of a disease is circulating within a population and the possibility of cross-immunity between strains becomes important [3, 4]. Mathematically, co-strain co-circulation may lead to models that support a disease-free equilibrium (or non-uniform age distribution), equilibria in which only one strain persists, and an equilibrium in which two strains coexist. The role of cross-immunity in destabilizing disease dynamics (periodic solutions) has been studied extensively in the case of influenza models without age structure [57, 123, 124, 151] and also in age-structured models [29, 30]. Coinfections of more than one disease are also possible and their analysis requires more elaborate models. This is a real possibility with HIV and tuberculosis [96, 119, 133, 135, 140, 144, 154].

16.3 Antibiotic Resistance

In short-term disease outbreaks, antiviral treatment is one of the methods used to treat illness and also to decrease the basic reproduction number $\mathscr{R}_0$ and thus to lessen the number of cases of disease. However, many infectious pathogens can evolve and generate successor strains that confer drug resistance [55]. The evolution of resistance is generally associated with impaired transmission fitness compared to the sensitive strains of the infectious pathogen [112]. In the absence of treatment, resistant strains may be competitively disadvantaged compared to the

sensitive strains and may go extinct. However, treatment prevents the growth and spread of sensitive strains, and therefore induces a selective pressure that favors the resistant strain to replicate and restores its fitness to a level suitable for successful transmission [2]. This phenomenon has been observed in several infectious diseases, in particular for management of influenza infection using antiviral drugs [138].

Previous models of influenza epidemics and pandemics have investigated strategies for antiviral treatment in order to reduce the epidemic final size (the total number of infections throughout the epidemic), while preventing widespread drug resistance in the population [77, 107, 111, 113, 114]. Through computer simulations, these studies have shown that, when resistance is highly transmissible, there may be situations in which increasing the treatment rate may do more harm than good by causing a larger number of resistant cases than the decrease in cases produced by treatment of sensitive infections. A recent epidemic model [156] has exhibited such behavior and suggested that there may be an optimal treatment rate for minimizing the final size [107, 111, 114].

In diseases such as tuberculosis, which operate on a very long time scale, the same problems arise but the modeling scenario is quite different. It is necessary to include demographic effects such as births and natural deaths in a model. This means that there may be an endemic equilibrium, and that the disease is always present in the population. Instead of studying the final size of an epidemic to measure the severity of a disease outbreak, it is more appropriate to consider the degree of prevalence of the disease in the population at endemic equilibrium as a measure of severity. For diseases such as tuberculosis, in which there are additional aspects such as reinfection, there may be additional difficulties caused by the possibility of backward bifurcations. The importance of understanding the dynamics of tuberculosis treatment suggests that this is a topic that should be pursued [60].

Antibiotic-resistant bacterial infections in hospitals are considered one of the biggest threat to public health. The British Chief Medical Officer, Dame Sally Davies, noted that “the problem of microbes becoming increasingly resistant to the most powerful drugs should be ranked alongside terrorism and climate change on the list of critical risks to the nation.” Yet while antibiotic use is rising, not least in agriculture for farmed animals and fish, resistance is steadily growing.

The challenges posed by the persistence, evolution, and expansion of resistance to antimicrobials are critically important because the number of drugs is limited and no new ones have been created for three decades [2, 16, 38, 65, 99]. We are facing a global crisis in antibiotics, the result of rapidly evolving resistance among microbes responsible for common infections that threaten to turn them into untreatable diseases. Every antibiotic ever developed is at risk of becoming useless. Antimicrobial resistance is on the rise in Europe, and elsewhere in the world.

Dr. Margaret Chan, Director General of the World Health Organization, while addressing a meeting of infectious disease experts in Copenhagen, noted that “A post-antibiotic era means, in effect, an end to modern medicine as we know it. Things as common as strep throat or a child’s scratched knee could once again kill.

For patients infected with some drug-resistant pathogens, mortality has been shown to increase by around 50 per cent."[1]

Strategies suggested to curb the development of resistant hospital-acquired infections include antimicrobial cycling and mixing, that is, models of antibiotic use that make use of two distinct classes of antibiotics that may distributed over different schedules with the goal of slowing down the evolution of resistance. Cycling alternates both classes of drugs over pre-specified periods of time while mixing distributes both drugs simultaneously at random, that is, roughly half of the physicians would prescribe the first drug class while the other half would prescribe the second class. If the goal is to slow down single class drug resistance then "mixing" is the answer [16] while if the goal is to minimize dual resistance (if such a possibility exists) then the best option is cycling [38]. Of course, there are other factors that may accelerate resistance (physicians' compliance) or slow down resistance (quarantine and isolation). All the above questions may be addressed via the use of contagion models [38].

16.4 Mobility

The Global Commons are continuously reshaped by the ability of an increasing proportion of the human population to live, move, or trade nearly anywhere. Therefore, understanding the patterns of interactions between humans, between humans and vectors, and the patterns of individuals' movement, particularly those who are highly mobile, is critical in guiding public health responses to disease spread. In today's world, hosts' knowledge of information about risk, combined with the ability of public health officials to measure and properly communicate, in a timely manner, real or perceived information on disease risks, affects our ability to derail the spread of emergent and re-emergent diseases, at scales that make a difference.

Simon Levin showed that understanding scale-dependent phenomena is intimately tied in to our understanding on how information at particular scales impact other scales. His four decade old seminal paper establishing the relationships between processes operating at different scales that highlighted how macroscopic features arise from microscopic processes open the door to the theoretical advances that have dominated the study of ecological and epidemiological systems [101]. Specifically, the theory of metapopulations, common to the study of the models in this book [104, 155], was used to establish the role that localized disturbances have had in maintaining biodiversity [103, 127]. Kareiva et al. observe that there is a multitude of frameworks to study the role of disturbance, noting that, "Models that deal with dispersal and spatially distributed populations are extraordinarily varied, partly because they employ three distinct characterizations of space: as

[1]The Independent, Friday 16 March 2012.

'islands' (or 'metapopulations'), as 'stepping-stones', or as a continuum" [88]. We choose to deal with mobility in Chap. 15 and this chapter uses a metapopulation approach [80, 93, 104], with populations that exist on discrete "patches" defined by some characteristic(s) (i.e., location, disease risk, water availability, etc.). As is customary, patches are connected by their ability to transfer relevant information among themselves, which, in the context of disease dynamics, is modeled by the ability of individuals to move between patches. Patches may be constructed (defined) by species (human and mosquito) with movement explicitly modeled via patch-specific residence times and under a framework that sees disease dynamics as the result of location-dependent interactions and location characteristic average risks of infection [17, 18].

We observed that "It is therefore important to identify and quantify the processes responsible for observed epidemiological macroscopic patterns: the result of individual interactions in changing social and ecological landscapes" [25]. In the rest of this chapter, we touch on some of the issues calling for the identification of an encompassing theoretical explanatory framework or frameworks. We do this by identifying some of the limitations of existing theory, in the context of particular epidemiological systems. The goal is fostering and re-energizing research that aims at disentangling the role of epidemiological and socioeconomic forces on disease dynamics. In short, epidemic models on social landscapes are better formulated as complex adaptive systems. Now the question becomes, "How does such a perspective help our understanding of epidemics and our ability to make informed adaptive decisions?" These are huge complex questions whose answers have engaged a large number of interdisciplinary and trans-disciplinary teams of researchers. What may be promising directions? In what follows, we discuss some of the modeling used to address some of the challenges and opportunities that we believe must be considered in the field of theoretical epidemiology.

16.4.1 A Lagrangian Approach to Modeling Mobility and Infectious Disease Dynamics

The deleterious impact of the use of cordons sanitaires [58, 100] to limit the spread of Ebola in West Africa points to the importance of developing and implementing novel approaches that may ameliorate the impact of disease outbreaks in areas where timely response to the emergence of novel pathogens is not possible at this time.

Disease risk is a function of the scale and the level of heterogeneity considered. Risk varies by countries and within a country by areas of localized poverty, or as a function of the availability and quality of sanitary/phytosanitary conditions, or as a result of access and the quality of health care, or variability on the levels of individual education, or as a result of engrained cultural practices and norms. Travel and trade, easily bypassing in today's world the natural or cultural boundaries defined by many of factors just outlined, are now seen as engines that

drive the spread of pests and pathogens across regional and global scales. Hence, the identification of explanatory frameworks that help to disentangle the role of epidemiological, socioeconomic, and cultural perspectives on disease dynamics becomes evident and necessary in the Global Commons. Further, since the work of Sir Ronald Ross over a century ago [141], efforts to develop a mathematical framework that allow us to tease out the role of various mechanisms on disease spread while enhancing our understanding of what may be the most effective measures to manage or eliminate a disease, the fields of mathematical and theoretical epidemiology have developed into rich and useful fields of their own. Their role in the development of public health policy and the study of disease evolution within hosts (immunology) and between populations and its relationship to the study of host–pathogen interactions within ecology or community ecology are now integral components of the education and training of theoreticians and practitioners alike [1, 12, 19–23, 26, 41, 53, 54, 59, 74, 76, 82, 102, 122, 157].

The use of (per capita) contact or activity rates in modeling the interactions between individuals, that is, who mixes with whom or who interacts with whom, has been the natural social dynamics currency used to model human-to-human or vector-to-human interactions in the context of the transmission dynamics of communicable diseases. The "physics or chemistry traditions" are used to model disease transmission as the result of the "collisions" between individuals (with different energy or activity levels) in different epidemiological states. Further, movement, typically modeled using a metapopulation approach, is seen as the relocation between patches of non-identifiable individuals. The scholarly and extensive review in [83] addresses this perspective within homogeneous and heterogeneous mixing (age-structured) population models (see also [30]). Weakening the assumption of homogeneous mixing via contacts in epidemiology has been addressed using network-based analyses that identify host contact patterns and clusters [13, 120, 121, 128] (and references therein with [121] offering an extensive review). Focusing on how each individual is connected within the population has been used to address the effects of host behavioral response on disease prevalence (see [67, 68, 110] for a review). Other approaches have included the effects of behavioral changes triggered by "fear" and/or awareness of disease [56, 66, 131, 134]. Although this stress-induced behavior may benefit public health efforts in some cases, it can also cause somewhat unpredictable outcomes [75].

However, the fact remains that our ability to determine (and hence define) what an effective contact is in the context of communicable diseases, that is, our ability to measure the average number of contacts that a typical patch resident has per unit of time and where, has been hampered by high levels of uncertainty. Therefore, when we ask, what is the average rate of contacts that an individual has while riding a packed subway in Japan or Mexico City, or what is the average rate of contacts that an individual has at a religious event involving hundreds of thousands of people, including pilgrimages, one quickly arrives at the conclusion that different observers are extremely likely to arrive at very distinct understandings and quantifications of the frequency, intensity, and levels of heterogeneity involved. In short, this perspective puts emphasis on the use of a different currency (residence

times) because measuring contacts at the places where the risk of infection is the highest, pilgrimages, massive religious ceremonies, "Woodstock time events", packed subways, and other forms of mass gathering or transportation have not been done to the satisfaction of most researchers. The risk of acquiring an infectious disease within a flight can be measured at least in principle as a function of the time that each individual of x-type spends flying, the number of passengers, and the likelihood that an infectious individual is on board. For example, measuring the risk of acquiring tuberculosis, an airborne disease that may spread by air circulation in a flight, may be more a function of the duration of the flight and the seating arrangement than the average rate of contacts per passenger within the flight (see [31] and references therein). Furthermore, replication studies that measure risk of infection in a given environment may indeed be possible under a residence time model. In short, the risks of acquiring an infection can be quantified as a function of the time spent (residence time) within each particular environment. The Lagrangian modeling approach builds (epidemiological) models by tracking individuals' patch-residence times and estimating their contacts according to the time spent in each environment [32]. The value of these models increases when we have the ability to assess risk as a patch-specific characteristic. In short, the use of a Lagrangian modeling perspective rather than the use of contacts is tied to the difficulties that must be faced when the goal is to measure the average rate of contacts per type-x individual in the environments that facilitate transmission the most.

The Lagrangian approach is highlighted here via the formulation of a disease model involving the joint dynamics of an n-patch geographically structured population with individuals moving back and forth from their place of residence to other patches. Each of these patches (or environments) is defined by its associated risk of residence-time infection. Patch risk measurements account for environmental, health, and socioeconomic conditions. The Lagrangian approach [73, 125, 126] keeps track of the identity of hosts regardless of their geographical/spatial position. The use of Lagrangian modeling in living systems was, to the best of our knowledge, pioneered and popularized by Okubo and Levin [125, 126] in the context of animal aggregation. Recently, Lagrangian approaches have also been used to model human crowd movement and behavior [15, 49, 78, 79] and in the context of bioterrorism [31].

Here, host-residence status and mobility across patches are monitored with the help of a residence times matrix $\mathbb{P} = (p_{ij})_{1\leq i,j\leq n}$, where p_{ij} is the proportion of time residents of Patch i spend in Patch j. Letting N_i denote the population of Patch i predispersal, that is, when patches are isolated, we conclude that effective population size in Patch i, at time t, is given by $\sum_{j=1}^{n} p_{ji}N_j$. That is, the effective population within each patch must account for the residents and visitors to Patch i at time t. A typical SIS model captures this Lagrangian approach in an n - patch setting via the system of nonlinear differential equations:

$$\begin{aligned}\dot{S}_i &= b_i - d_i S_i + \gamma_i I_i - \sum_{j=1}^{n}(S_i \text{ infected in Patch } j)\\ \dot{I}_i &= \sum_{j=1}^{n}(S_i \text{ infected in Patch } j) - \gamma_i I_i - d_i I_i,\end{aligned} \tag{16.1}$$

where b_i, d_i, and γ_i denote the constant recruitment, the per capita natural death, and recovery rates, respectively, in Patch i. The effective population $\sum_{j=1}^{n} p_{ij} N_j$ in each Patch $i, i = 1, \ldots, n$ includes $\sum_{j=1}^{n} p_{ij} I_j$ infected individuals. Therefore, the infection term is modeled as follows:

$$S_i \text{ infected in patch } j = \beta_j \times p_{ij} S_i \times \frac{\sum_{k=1}^{n} p_{kj} I_k}{\sum_{k=1}^{n} p_{kj} N_k}.$$

The likelihood of infection in each patch is tied to the environmental risks, defined by the "transmission/risk" vector $\mathscr{B} = (\beta_1, \beta_2, \ldots, \beta_n)^t$ and the proportion of time spent in particular area. Letting $I = (I_1, I_2, \ldots, I_n)^t$, $\bar{N} = (\frac{b_1}{d_1}, \frac{b_2}{d_2}, \ldots, \frac{b_n}{d_n})^t$, $\tilde{N} = \mathbb{P}t\bar{N}$, $d = (d_1, d_2, \ldots, d_n)^t$, and $\gamma = (\gamma_1, \gamma_2, \ldots, \gamma_n)^t$ allows to rewrite System 16.1 in the following single vectorial form

$$\dot{I} = diag(\bar{N} - I)\mathbb{P}diag(\mathscr{B})diag(\tilde{N})^{-1}\mathbb{P}^t I - diag(d + \gamma)I. \tag{16.2}$$

The dynamics of the disease in all of the patches depends on the patch connectivity structure. Therefore, if the residence-time matrix $\mathbb{P}$ is irreducible, patches are strongly connected, then system 2 supports a sharp threshold property. That is, the disease dies out or persists (in all patches) whenever the basic reproduction number $\mathscr{R}_0$ is less than or greater than unity [18]. $\mathscr{R}_0$ is given by

$$\mathscr{R}_0 = \rho(diag(\bar{N})\mathbb{P}diag(\mathscr{B})diag(\tilde{N})^{-1}\mathbb{P}^t V^{-1}),$$

where ρ denotes the spectral radius and $V = -diag(d + \gamma)$. The dynamics of the system when the matrix $\mathbb{P}$ is not irreducible can be characterized using the following patch-specific basic reproduction numbers:

$$\mathscr{R}_0^i(\mathbb{P}) = \frac{\beta_i}{\gamma_i + d_i} \times \sum_{j=1}^{n}\left(\frac{\beta_j}{\beta_i}\right) p_{ij}\left(\frac{p_{ij}\left(\frac{b_i}{d_i}\right)}{\sum_{k=1}^{n} p_{kj} b_k d_k}\right).$$

The disease persists in Patch i whenever $\mathscr{R}_0^i(\mathbb{P}) > 1$, whereas the disease dies out in Patch i if $p_{kj} = 0$ for all $k = 1, \ldots, n$, and $k \neq i$,provided $p_{ij} > 0$ and $\mathscr{R}_0^i(\mathbb{P}) < 1$.

Patch-specific disease persistence can be established using the average Lyapunov theorem [86] (see [18] for more details).

In Model 16.2, human behavior is crudely incorporated through the use of a constant mobility matrix $\mathbb{P}$. The role that adaptive human behavior may play in response to disease dynamics is captured, also rather crudely, via a phenomenological approach that assumes that individuals avoid or spend less time in areas of high prevalence. This effect is captured by placing natural restrictions on the entries of $\mathbb{P}$. The inequalities $\frac{p_{ij}(I_i,I_j)}{\partial I_j} \leq 0$ and $\frac{p_{ij}(I_i,I_j)}{\partial I_i} \geq 0$, for $(i, j) \in 1, 2$, guarantee the expected behavioral response. An example of such dependency could be captured by the following functions: $p_{ii}(I_i, I_j) = \frac{\sigma_{ii}+\sigma_{ii}I_i+I_j}{1+I_i+I_j}$ and $p_{ij}(I_1, I_j) = \sigma_{ij}\frac{1+I_i}{1+I_i+I_j}$, for $(i, j) \in 1, 2$ and $\sigma_{ij} = p_{ij}(0, 0)$, are such that $\sum_{j=1}^{2} \sigma_{ij} = 1$. The simulation below shows how a crude, density-dependent modeling mobility approach can alter the expected disease dynamics from those generated under constant $\mathbb{P}$ (Figs. 16.1 and 16.2). In the special case, where there is no movement between patches ($p_{12} = p_{21} = \sigma_{12} = \sigma 21 = 0$), that is, there is no behavioral change, the two populations support, as expected, the same dynamics (see the blue curves in Figs. 16.1 and 16.2).

The speed at which the vector-borne Zika virus disease spread throughout Latin America, Central America, and the Caribbean (then hitting Mexico and the United States) was strongly linked to human mobility patterns. Travelers transport the disease and infect native mosquitoes. Here, it is assumed that vector mobility is negligible and the assumptions proceed to incorporate the life history and epidemiology of mosquitoes [10, 84, 98, 108, 109, 141], which can be effectively captured

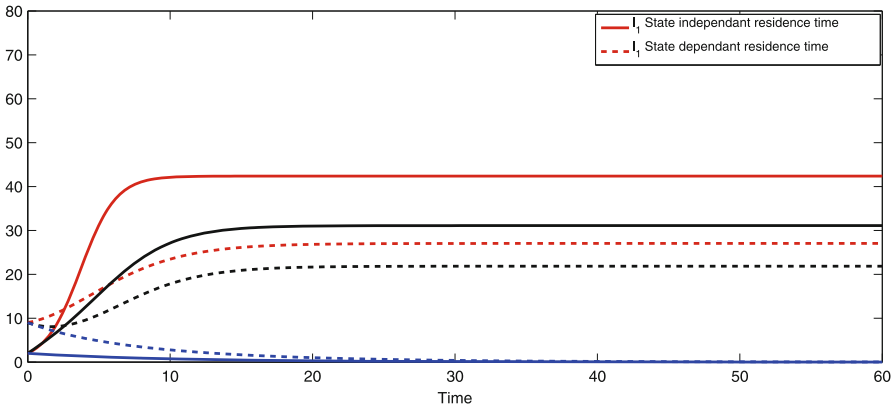

Fig. 16.1 Dynamics of the disease in Patch 1 for three special cases. The symmetric residence times ($p_{12} = p_{21} = \sigma_{12} = \sigma_{21} = 0.5$) are described by the solid and dashed black curves. The blue curves represent the case where there is no movement between patches, that is, $p_{12} = p_{21} = \sigma_{12} = \sigma_{21} = 0$. The red curves represent the high-mobility case for which $p_{12} = p_{21} = \sigma_{12} = \sigma_{21} = 1$. If there is no movement between the patches (blue curves), the disease dies out in the low risk Patch 1 in both approaches with $\mathscr{R}_0^1 = \frac{\beta_1}{d_1+\gamma_1} = 0.7636$. The vertical axis represents the prevalence of the disease in Patch 1. Figure courtesy of Ref. [18]

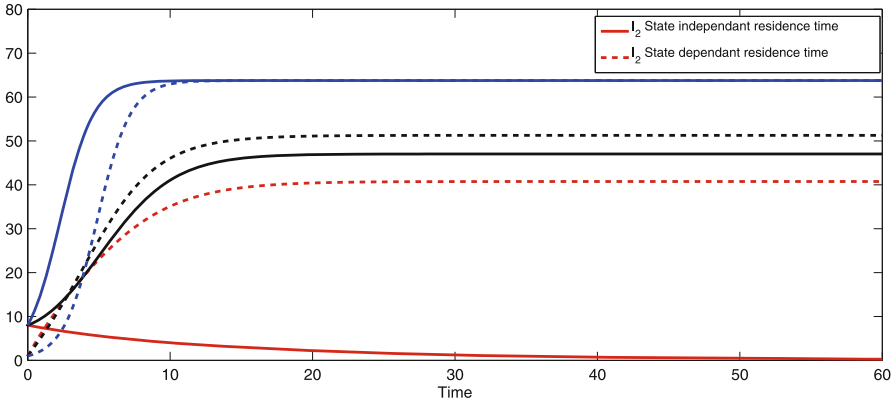

Fig. 16.2 Dynamics of the disease in Patch 2. In the high-mobility case $p_{12} = p_{21} = \sigma_{12} = \sigma_{21} = 1$ (and then $p_{11} = p_{22} = \sigma_{11} = \sigma_{22} = 0$), the disease dies out (solid red curve) for $\mathbb{P}$ constant, with $\tilde{\mathscr{R}}_0^2 = \frac{\beta_1}{\gamma_2 + d_2} = 0.8571$. For the constant residence-time matrix, the system is strangely decoupled because individuals of Patch 1 spend all their time in Patch 2, whereas individuals of Patch 2 spend all their time in Patch 1. Hence, Patch 2 individuals (d_2 and μ_2) are subject exclusively to the environmental conditions that define Patch 1 (β_1), and so the basic reproduction of the "isolated" Patch 1 is $\tilde{\mathscr{R}}_0^2 = \frac{\beta_1}{\gamma_2 + d_2}$ and the disease dies out because $\tilde{\mathscr{R}}_0^2 = 0.8571$. The disease persists if $\mathbb{P}$ state-dependent (dashed red curve) as $p_{12}(I_1, I_2) = \frac{1+I_1}{1+I_1+I_2}$, $p_{21}(I_1, I_2) = \frac{1+I_2}{1+I_1+I_2}$, $p_{11}(I_1, I_2) = \frac{I_2}{1+I_1+I_2}$, and $p_{22}(I_1, I_2) = \frac{I_1}{1+I_1+I_2}$. Figure courtesy of Ref. [18]

by decoupling host and vector mobility [98, 145]. Figure 16.3 and System 16.3 illustrate the approach. A Lagrangian model based on residence times has been proposed recently for vector-borne diseases like dengue, malaria, and Zika [17]. The appropriateness of the Lagrangian approach for the study of the dynamics of vector-borne diseases lies also in its assessment of the life-history specifics of the vector involved [145].

$$\begin{aligned} \dot{I}_h &= \beta_{vh} diag(N_h - I_h)\mathbb{P} diag(a) diag(\mathbb{P}^t N_h)^{-1} I_v - diag(\mu + \gamma) I_h \\ \dot{I}_v &= \beta_{hv} diag(a) diag(N_v - I_v) diag(\mathbb{P}^t N_h)^{-1} \mathbb{P}^t I_h - diag(\mu_v + \delta) I_v. \end{aligned} \tag{16.3}$$

Lagrangian approaches have been used to model vector-borne diseases (see [48, 87, 139, 142, 153] and other references contained therein), although these researchers have not considered the impact that the residence-time matrix $\mathbb{P}$ may have on patch effective population size. Specifically, in [48, 142], the effects of movement on patch population size at time t are ignored, namely, the population size in each Patch j is fixed at N_j. In [139], it is assumed that human mobility across patches does not produce any "net" change on the patch population size. On the other hand, in Model 16.3 the relationship between each patch population and mobility is dynamic and explicitly formulated. Moreover, the limited (vector

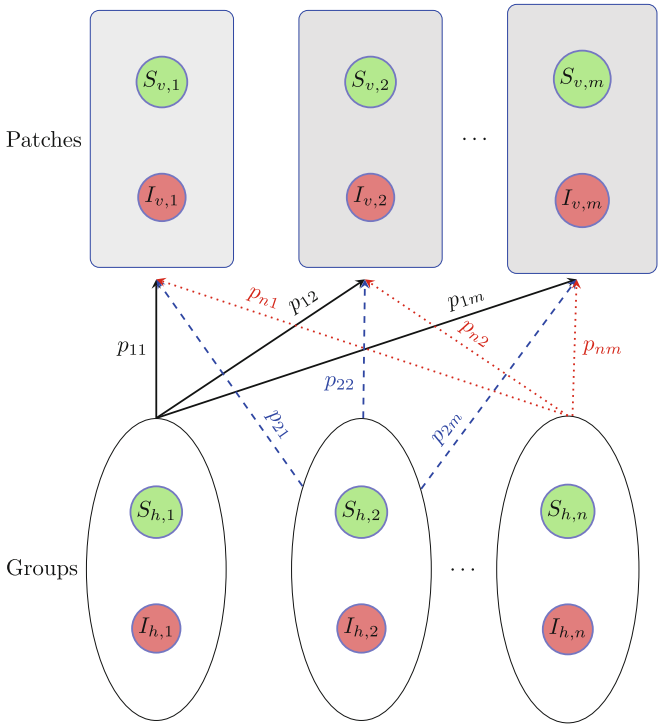

Fig. 16.3 Flow diagram of a Lagrangian model in which the host structure is decoupled from the vectors' structure. Figure courtesy of Ref. [17]

mobility is ignored) Lagrangian approach used here to model the dynamics of vector-borne diseases captures some unique features because the "spatial" structure of mosquitoes is not the same as that of humans. Mosquitoes are stratified into m patches (that may represent, for example, oviposition or breeding sites or forests) with infection taking place still within each Patch j, characterized by its particular risk $\beta_{vh}a_j$ for $j = 1, \ldots, m$. Here, β_{vh} represents the infectiousness of human to mosquitoes bite with a_j denoting the per capita biting rate in Patch j. Hosts, on the other hand, are structured by social groups or age classes (n). This residence habitat division can be particularly useful in the study of the impact of target control strategies.

The model in [17] describes the interactions of n host groups in m patches via System 16.3, where

$$
\begin{aligned}
I_h &= [I_{h,1}, I_{h,2}, \ldots, I_{h,n}]^t, I_v = [I_{v,1}, I_{v,2}, \ldots, I_{v,m}]^t \\
N_h &= [N_{h,1}, N_{h,2}, \ldots, N_{h,n}]^t, \bar{N}_v = [\bar{N}_{v,1}, \bar{N}_{v,2}, \ldots, \bar{N}_{v,m}]^t \\
\delta &= [\delta_1, \delta_2, \ldots, \delta_m]^t, a = [a_1, a_2, \ldots, a_m]^t, and \mu = [\mu_1, \mu_2, \ldots, \mu_n]^t.
\end{aligned}
$$

The infected host population is denoted by the vector I_h and the host population by N_h. The infected vector population is denoted by I_v and the mosquito population by N_v. The parameters a_i, δ_i, and μ_v denote the biting, death rate of control, and natural death rate of mosquitoes in Patch j, for $j = 1, \ldots, m$. The infectiousness of human to mosquitoes is β_{vh}, whereas the infectiousness of mosquitoes to humans is given by $\beta_h v$. The host recovery and natural mortality rates are given, respectively, by γ and μ. Finally, the matrix $\mathbb{P}$ represents the proportion of time host of group i, $i = 1, \ldots, n$, spend in Patch j, $j = 1, \ldots, m$. The basic reproduction number of Model 3, with m patches and n groups, is given by $\mathscr{R}_0^2(m, n) = \rho(M_{vh} M_{hv})$, where

$$M_{hv} = \beta_{hv} diag(a) diag(\mathbb{P}^t N_h)^{-1} diag(N_v) \mathbb{P}^t diag(\mu + \gamma)^{-1}$$

and

$$M_{vh} = \beta_{vh} diag(Nh) \mathbb{P} diag(\mathbb{P}^t N_h)^{-1} diag(a) diag(\mu_v + \delta)^{-1}.$$

If the host–vector network configuration is irreducible, then System 16.3 is cooperative and strongly concave with an irreducible Jacobian, hence the theory of monotone systems, particularly Smith's results [146], guarantee the existence of a sharp threshold. That is, the disease-free equilibrium is globally asymptotically stable if $\mathscr{R}_0^2(m, n)$ is less than unity and a unique globally asymptotic stable interior endemic equilibrium exists otherwise. The effects of various forms of heterogeneity on the basic reproduction number have been explored in [17], and we have found, for example, that the irreducibility of the residence-time matrix $\mathbb{P}$ is no longer sufficient to ensure a sharp threshold property, although the irreducibility of the host–vector network configuration is necessary for such property [17].

The Lagrangian approach to disease modeling can use contacts [32] or times or both as its currency. Here, we choose time-spatial-dependent risk, that is, we choose to handle social heterogeneity by keeping track of individuals' social or geographical membership. In this context, it is possible to include adaptive responses, for example, via the inclusion of prevalence-dependent dispersal coefficients. In this setting, the underlying hypothesis is that host behavioral responses to disease are automatic: either constant or following a predefined function. The average residence time $\mathbb{P}$ incorporates the average behavior of all hosts in each patch. This assumption is rather crude because it implicitly assumes that hosts have accurate information on health status and patch prevalence and respond to risk of infection accordingly. The incorporation of the role that human decisions, as a function of what individuals value and the cost that individuals place on these choices and trade-offs, within systems that account for the overall population disease dynamics has been addressed recently [61, 132] and discussed in economic epidemiology.

16.5 Behavior, Economic Epidemiology, and Mobility

The movement/behavior of individuals within and between patches may be driven by real or perceived personal economic risk and associated social dynamics. Embedding behavioral-driven decisions in epidemiological models has shed new perspectives on the modeling of disease dynamics [61], expanding available option to manage infectious diseases [44, 62]. Economic epidemiological modeling (EEM) has a history of addressing the role of individuals' behavior when facing the risk of disease. However, it has often failed to incorporate within host-pathogen feedback mechanisms [34–36, 52, 70, 97, 137]. EEMs that account for host-pathogen feedback mechanisms has propelled the study of the ways that contact decisions impact disease emergence or alter infectious disease-transmission dynamics. Decisions involved may include the determination to engage in trade on particular routes [89, 94, 95, 129], or to travel to specific places [62, 147–149], or to make contact with or to avoid particular types of people [61, 63, 116]. EEMs advance the view that the emergence of novel zoonotic diseases, such as SARS or the Nipah virus, depend on the choices that bring people into contact with other species [50, 51]. EEMs are usually built under the assumption that associated disease risks are among the factors that individuals must consider when making decisions. Individual decision-making processes, within epidemic outbreaks, must incorporate the humans' cost–benefit-driven adaptive responses to risk.

16.5.1 Economic Epidemiology

Simple EEMs are, by mathematical necessity, initially built on classical compartmental epidemiological models that account for the orderly transition of individuals facing a communicable disease, through the susceptible, infected, and recovered disease stages: the result of social and environmental interactions. EEMs assume that the amount of activity one participates in, with whom, and where may all be envisioned as the solutions to an individual decision problem. It is assumed that individual decision problems are generated by rational-value formulations based on (driven by) personal, real or perceived, cost of disease, and disease avoidance: decisions constrained by underlying population-level disease dynamics. Thus, finding effective ways of modeling rational value connections to individualized cost–benefit analyses of disease risk is fundamental to the building of useful EEMs. It is a quite challenging enterprise.

EEM approaches have precursors in the epidemiological literature [9, 64, 69]. EEM construction has been strongly influenced by past and ongoing work on the exploitation of species [45–47], a literature that addresses optimal harvesting questions in the context of wild species, or the control of invasive pests, or the management of forestry system. The methodology for modeling behavior within an EEM rests on a proper specification of behavioral costs and a description of

the payoffs linked to such behaviors; the stipulation of an appropriate objective function, congruent with the decision-makers' goals; the coupling to the dynamics of the natural resource and/or infectious human capital; and the mechanisms available for a decision-maker to alter his or her behavior and the behaviors of those around him or her. Although not all motivations for mitigation against infection are monetary in nature, we choose to refer to them as economic.

Modeling whether or not an individual undertakes infection-causing behavior provides a natural starting point since it is connected to the rate of generation of secondary cases of infection per unit of time, the so-called incidence rate. A simple incidence function that captures the instantaneous expectation of the rate of new infections at a given time is therefore given by

$$S(t)cP_{SI}(t)\rho,$$

where $S(t)$ is the number of individuals susceptible to the disease, c is the average amount of activity they engage in, $P_{SI}(t)$ is the probability that a unit of such activity takes the susceptible individual in contact with infectious individuals/material, and ρ is the probability that such contact successfully infects.

A decision to reduce the volume of activity one engages in (lowering c) has been shown in many cases to be phenomenologically identical to reducing one's chances of coming in contact with infection (lowering $P_{SI}(t)$) by altering where the activity takes place and with whom one engages or by substituting a particular behavior for a riskier one [62, 118]. The modeling assumes that individuals derive benefits from making contacts but may incur costs associated with an infection. Hence, the modeling assumes that activity volume or contacts are chosen to maximize expected utility (rudimentarily, benefit less cost), balancing the marginal value of a contact against the increased risk of infection. The utility function is assumed to depend on the health status of the individual and the contacts that they make, that is, the utility of a representative individual of health status h is given, for example, by the function

$$U_h = U(h, C^h). \tag{16.4}$$

The utility function is assumed to be concave, decreasing in illness and increasing in contacts. If the probability of transitioning from susceptible to infected health status depends on the rate of contacts, the optimal choice of contacts is the solution to a dynamic programming problem:

$$V_t(h) = \max_{C_s} \left\{ U_t(h_t, C_t^h) + r \sum_j \rho^{hj} V_{t+1}(j) \right\}, \tag{16.5}$$

where r is the discount rate and ρ^{hj} is the probability of transition from health state h to health state j. This probability depends on the current state of the system, $\{S(t), I(t), R(t)\}$, the behavior of individuals in other health classes, C^{-h}, and

the behavior of individuals in the decision-makers' own health class, $\bar{C}^h$. In short, we have a complex adaptive system where individuals within the model, in this example, impact disease outcomes (through changes in the incidence). Eqs. (16.4) and (16.5) are both optimized from an individual perspective. Within this individual context, EEMs have shown that individual distancing, conditional on health status, plays an important role in the spread of infectious disease. However, it has also been shown that the provision of incentives for infectious individuals to self-quarantine is likely to be welfare-enhancing [43, 44, 61, 115]. Thus, understanding how the individual responds to relative costs of disease and disease prevention is critical to the design of public policy that affects those costs. Indeed, the role of recovered individuals in protecting susceptible individuals has been generally overlooked in public health interventions, and yet it is known that their behavior is, in fact, critical to disease management due to the positive externality the individuals' contacts generate once in an immune, non-disease-transmitting state [63]. The benefits of herd immunity include the positive externality associated with acquired immunity but may, in turn, be nullified by nontargeted social-distancing policies that induce such immune individuals to reduce contacts. By incentivizing the maintenance of contacts by recovered individuals policy may lower the probability of susceptible individuals contacting infected individuals and/or allow susceptible and infected individuals to individually increase contacts without changing the probability of infection.

16.5.2 Lagrangian and Economic Epidemiology Models

Theoretical epidemiology aims to disentangle the role of epidemiological and socioeconomic forces on disease dynamics. However, the role of behavior and individual decisions in response to a changing epidemic landscape has not been tackled systematically. In this chapter, we highlight alternative ways for modeling disease transmission that can use contacts as its currency or residence times or both. It seems evident that the use of contacts, in the context of influenza, Ebola, tuberculosis, or other communicable diseases (as opposed to sexually transmitted diseases), while intellectually satisfying, fails to recognized the fact that contacts cannot be measured effectively in settings where the risk of acquiring such infections is the highest. In fact, when contact-based models are fitted to data, it has become clear that contact rates play primarily the role of fitting parameters; in other words, if the goal is connecting models to data that include transmission mechanisms, then the use of contacts has serious shortcomings. Therefore, in order to advance the role of theory, we need models that are informed by data. Hence, the need to invest on efforts that bring forth alternative modes of modeling. While Lagrangian approaches are not a panacea, their use extends the possibilities because they depend on parameters like residence times and average time to infection for a given environment (risk), that is, parameters that can be measured. Frameworks should be explored and compared

and their analyses contrasted. We have revisited recent work that equates behavior with cost–benefit decisions, which, in turn, are linked, within our framework, to health status and population-level dynamics, the components of a complex adaptive system. Connecting the Lagrangian movement-modeling approach with EEMs seems promising, albeit computationally and mathematically challenging. However, as discussed in [117], the perception that the benefits of disease control are limited by the capacity of the weakest link in the chain to respond effectively is not a basic result of EEM models, which actually show that it may not be in within the ability of an individual in a poor community/country to do more risk mitigation. The need for richer communities or nations to find ways to incentivize greater levels of disease-risk mitigation in poor countries may be the best approach.

Simon Levin, in his address as the 2004 recipient of the Heineken award, placed our narrow perspective in a broader powerful context:

> A great challenge before us is thus to understand the dynamics of social norms, how they arise, how they spread, how they are sustained and how they change. Models of these dynamics have many of the same features as models of epidemic spread, no great surprise, since many aspects of culture have the characteristics of being social diseases. 1998 Heineken award winner Paul Ehrlich and I have been directing our collective energies to this problem, convinced that it is as important to understand the dynamics of the social systems in which we live as it is to understand the ecological systems themselves. Understanding the links between individual behavior and societal consequences, and characterizing the networks of interaction and influence, create the potential to change the reward structures so that the social costs of individual actions are brought down to the level of individual payoffs. It is a daunting task, both because of the amount we still must learn, and because of the ethical dilemmas that are implicit in any form of social engineering. But it is a task from which we cannot shrink, lest we squander the last of our diminishing resources.

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