Perspectives on the role of mobility, behavior, and time scales in the spread of diseases

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The dynamics, control, and evolution of communicable and vector-borne diseases are intimately connected to the joint dynamics of epidemiological, behavioral, and mobility processes that operate across multiple spatial, temporal, and organizational scales. 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 coevolving fields of computational, evolutionary, and theoretical epidemiology. Host–parasite epidemiological patterns, including epidemic outbreaks and endemic recurrent dynamics, are characteristic to well-identified regions of the world; the result of processes and constraints such as strain competition, host and vector mobility, and population structure operating over multiple scales in response to recurrent disturbances (like El Niño) and climatological and environmental perturbations over thousands of years. 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. In this perspective, we touch on some of the issues calling for the identification of an encompassing theoretical explanatory framework by identifying some of the limitations of existing theory, in the context of particular epidemiological systems. Fostering the reenergizing of research that aims at disentangling the role of epidemiological and socioeconomic forces on disease dynamics, better understood as complex adaptive systems, is a key aim of this perspective.

infectious disease | risk | complex adaptive systems | mobility | behavior

Lessons learned from the HIV pandemic, 2003 severe acute respiratory syndrome (SARS) epidemic, 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, most often via the reallocation of resources from one disease control effort to the new pressing one. The operating models of preparedness and response are ill-equipped to prevent or ameliorate disease emergence or reemergence, at global scales (1). Epidemiological challenges that are a threat to the economic stability of many regions of the world, particularly those depending on travel and trade (2), remain at the forefront of the Global Commons. Consequently, efforts to quantify the impact of mobility and trade on disease dynamics have long dominated the interests of theoreticians (3, 4). Our experience with an H1N1 influenza pandemic crisscrossing the world in the months during 2009 to 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 suitable habitats to *Aedes aegypti*, 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 (5–7). The case of SARS 2003 (8), the efforts to reduce the burden of H1N1 influenza cases in 2009 (5, 7, 9, 10), and the challenges faced in reducing the number of Ebola cases in 2014 (1, 11) are but three recent scenarios that required a timely global response. Studies addressing the impact of centralized sources of information (12), the impact of information along social connections (9, 13, 14), or the role of past disease outbreak experiences (15, 16) 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 coevolving human responses to disease dynamics are prototypical of the feedbacks that define complex adaptive systems. In short, we live in a socioepisphere being reshaped by ecoepidemiology in the "Era of Information."

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 of the highly mobile, is critical in guiding public health responses to disease spread. In today's world, hosts' risk knowledge or diffuse information about risk, 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, limits our ability to derail the spread of emergent and reemergent diseases, at scales that make a difference.

Simon Levin showed that the key to understanding scale-dependent phenomena was tied to knowing how information is carried across scales. He put it all together in a seminal paper that integrated a series of joint contributions focusing on the development of techniques and models used to establish the relationships between processes operating at different scales, highlighting how macroscopic features arise from microscopic processes (17). The theory of metapopulations (18, 19) was used, for example, to establish the role that localized disturbances have had in maintaining biodiversity (20, 21). In a review article, Kareiva et al. observe that, "Models that deal with dispersal and spatially distributed populations are extraordinarily varied,

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partly because they employ three distinct characterizations of space: as 'islands' (or 'metapopulations'), as 'stepping-stones', or as a continuum" (22). We choose to deal with mobility using a metapopulation approach (7, 10, 18), that is, populations exist on discrete "patches" defined by some characteristic(s) (i.e., location, disease risk, water availability, etc.). Patches are connected by their ability to transfer relevant information between one another, 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 (23, 24).

The movement/behavior of individuals within and between these patches may be driven by real or perceived personal economic risk and accompanying social dynamics. Embedding behavioral-driven decisions within epidemiological models has shed new perspectives on the modeling of disease dynamics (25), expanding the options available to manage infectious diseases (5, 26). Economic epidemiological modeling (EEM) has previously addressed the role of individuals' behavior when facing the risk of disease, albeit it has often failed to incorporate within host–pathogen feedback mechanisms (27–33). The focus on EEMs that account for host–pathogen feedback mechanisms has propelled their study of the ways that contact decisions impact disease emergence or alter "expected" infectious disease-transmission dynamics. The class of decisions involved may include the determination to engage in trade along particular routes (34–37), or to travel to particular places (5, 38–40), or to make contact with or to avoid particular types of people (25, 41, 42). 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 (43, 44). EEMs are typically built under the assumption that associated disease risks are among the factors that individuals must consider when making decisions. Therefore, individual decision-making process, within epidemic outbreaks, may require the incorporation of humans' cost–benefit-driven adaptive responses to risk.

A Lagrangian Approach of Modeling Mobility and Infectious Disease Dynamics

Differences in disease risk exist between countries as a function of localized poverty, sanitary/phytosanitary conditions, access to healthcare, levels of education, cultural practices, and norms with travel and trade overcoming the natural boundaries provided by these factors in limiting the spread of pests and pathogens. The negative impact of the use of cordons sanitaires to limit the spread of Ebola in West Africa highlight the importance of developing and implementing novel approaches aimed at ameliorating the impact of disease outbreaks in areas of the world that cannot respond in a timely manner to novel disease outbreaks. Therefore, the identification of a theoretical explanatory framework that systematically disentangles the role of epidemiological and socioeconomic perspectives on disease dynamics becomes not only evident but necessary.

Classical mathematical epidemiology uses per capita contact rates (who mixes with whom or who interacts with whom) as the social dynamics currency responsible for the transmission dynamics of communicable diseases. We envision disease transmission as the result of the "collisions" between individuals or as a consequence of the movement/relocation of individuals, never identified by placed of residence, from patch to patch. This approach has had great practical and theoretical successes; the scholarly and extensive review in ref. 45 addresses this view within homogenous and (heterogeneous mixing) age-structure populations (see also ref. 46). Recent studies have also addressed the issue of homogeneity of contacts in epidemiology through network-based analyses that identify host contact patterns and clusters (refs. 47–49 and references therein). An extensive relatively recent review paper is ref. 50. This approach by focusing on how each individual is connected within the population has been able to address the effects of host behavioral response on disease prevalence (see refs. 51, 57, and 58 for a review). Other approaches included the effect behavioral changes triggered by "fear" and/or awareness of disease (52–54, 56). Although this stress-induced behavior may be of benefit to public health efforts in some cases, it can also cause somewhat unpredictable outcomes (55).

However, the fact remains that our ability to determine (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 number of contacts that an individual has while riding a packed subway in Japan or Mexico City, or what is the average number 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 a highly distinct understanding and quantification of the frequency, intensity, and levels of heterogeneity involved. In short, this perspective puts emphasis on the use of a different currency (residency 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 number contacts per passenger within the flight (see ref. 59 and references therein). Furthermore, replication studies that measure risk of infection in a given environment may indeed be possible under a residency times model. In short, the risks of acquiring an infection can be quantified as a function of the time spent (residency time) within each particular environment. The Lagrangian modeling approach builds (epidemiological) models by tracking individuals' patch-residence times or by budgeting their contacts according to the time spent on each environment (60). The value of these models increase when we have the ability to assess risk as a patch-specific characteristic. In short, the lack of preference on the use of contacts is not tied to their proven intellectual value or the use of a Lagrangian modeling perspective but rather to the difficulties that must be faced when the goal is to measure the average number 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 residency-time infection. Patch risk measurements account for environmental, health, and socioeconomic conditions. The Lagrangian approach (61–63) keeps track of the identity of the host 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 (62, 63) in the context of animal aggregation. Recently,

Lagrangian approaches have also been used to model human crowd movement and behavior (64–67) and in the context of bioterrorism (59).

Here host-residence status and mobility across patches is monitored with the help of a residence times matrix $\mathbb{P} = (p_{ij})_{1\le i,j\le n}$, 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 $\sum_{j=1}^{n} p_{ij} N_j$. That is, the effective population within each patch must account for the residents and visitors to Patch i at time t. A typical susceptible-infected-susceptible (SIS) model captures this Lagrangian approach in an n Patch setting via the following system of nonlinear differential equations:

$$\begin{cases} \dot{S}_i = b_i - d_i S_i + \gamma_i I_i - \sum_{j=1}^{n}(S_i \text{ infected in Patch } j) \\ \dot{I}_i = \sum_{j=1}^{n}(S_i \text{ infected in Patch } j) - \gamma_i I_i - d_i I_i, \end{cases} \quad [1]$$

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:

$$[S_i \text{ infected in Patch } j] = \underbrace{\beta_j}_{\text{the risk of infection in Patch } j} \times \underbrace{p_{ij} S_i}_{\text{Susceptible from Patch } i \text{ who are currently in Patch } j} \times \underbrace{\frac{\sum_{k=1}^{n} p_{kj} I_k}{\sum_{k=1}^{n} p_{kj} N_k}}_{\text{Proportion of infected in Patch } j}.$$

The likelihood of infection in each patch is tied in to the environmental risks, defined by the "transmission/risk" vector $\mathcal{B} = (\beta_1, \beta_2, \ldots, \beta_n)^t$ and the proportion of time spent in particular area. Letting $I = (I_1, I_2, \ldots, I_n)^t$, $\bar{N} = \left(\frac{b_1}{d_1}, \frac{b_2}{d_2}, \ldots, \frac{b_n}{d_n}\right)^t$, $\tilde{N} = \mathbb{P}^t \bar{N}$, $d = (d_1, d_2, \ldots, d_n)^t$, and $\gamma = (\gamma_1, \gamma_2, \ldots, \gamma_n)^t$ allows to rewrite System **1** in the following single vectorial form

$$\dot{I} = \text{diag}(\bar{N} - I)\mathbb{P}\text{diag}(\mathcal{B})\text{diag}(\tilde{N})^{-1}\mathbb{P}^t I - \text{diag}(d + \gamma) I. \quad [2]$$

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 $\mathcal{R}_0$ is less than or greater than unity (24). $\mathcal{R}_0$ is given by

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

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

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

The disease persists in Patch i whenever $\mathcal{R}_0^i(\mathbb{P}) > 1$, whereas the disease dies out in Patch i if $p_{kj} = 0$ for all $k = 1, .., n$, and $k \neq i$, provided $p_{ij} > 0$ and $\mathcal{R}_0^i(\mathbb{P}) < 1$. Patch-specific disease persistence can be established using the average Lyapunov theorem (68) (see ref. 24 for more details).

In Model **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 $\frac{p_{ij}(I_i, I_j)}{\partial I_j} \le 0$ and $\frac{p_{ij}(I_i, I_j)}{\partial I_i} \ge 0$, 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. 1 and 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. 1 and 2).

The speed at which the vector-borne Zika virus disease has spread throughout Latin America, Central America, and the Caribbean (now hitting Mexico and the United States) is strongly linked to human mobility patterns. Travelers transport the disease and infect native mosquitoes. Here, it is assumed that vector mobility is negligible and proceeds to incorporate the life history

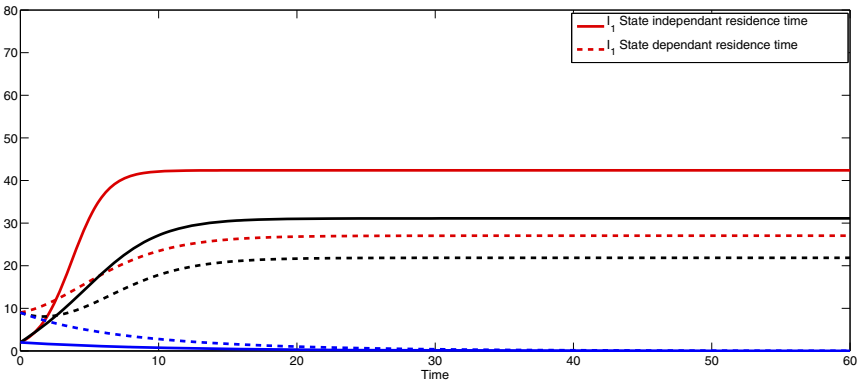

Fig. 1. Dynamics of the disease in Patch 1 for three special cases. The symmetric residence times ($p_{12} = p_{21} = \sigma_{12} = \sigma_{21} = 0.5$) are described by the solid and dashed black curves. The blue curves represent the case where there is no movement between patches, that is, $p_{12} = p_{21} = \sigma_{12} = \sigma_{21} = 0$. The red curves represent the high-mobility case for which $p_{12} = p_{21} = \sigma_{21} = \sigma_{21} = 1$. If there is no movement between the patches (blue curves), the disease dies out in the low risk Patch 1 in both approaches with $R_0^1 = \frac{\beta_1}{d_1 + \gamma_1} = 0.7636$. The vertical axis represents the prevalence of the disease in Patch 1. Figure courtesy of ref. 24.

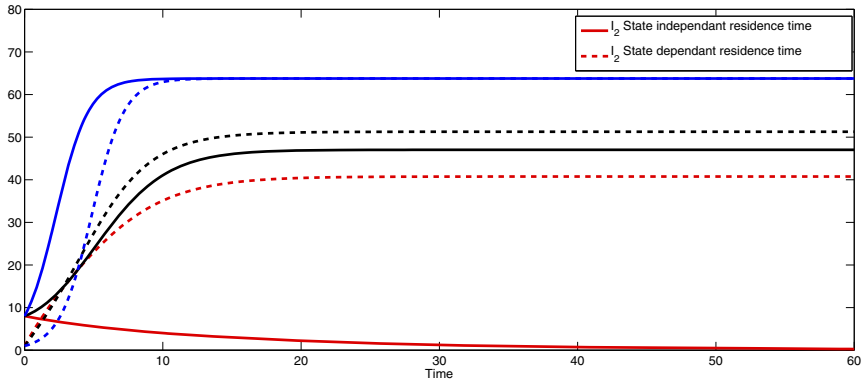

Fig. 2. Dynamics of the disease in Patch 2. In the high-mobility case $p_{12} = p_{21} = \sigma_{12} = \sigma_{21} = 1$ (and then $p_{11} = p_{22} = \sigma_{11} = \sigma_{22} = 0$), the disease dies out (solid red curve) for $\mathbb{P}$ constant, with $\tilde{R}_0^2 = \frac{\beta_1}{\gamma_2+d_2} = 0.8571$. For the constant residence times 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 $\tilde{R}_0^2 = \frac{\beta_1}{\gamma_2+d_2}$ and the disease dies out because $\tilde{R}_0^2 = 0.8571$. 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. 24.

and epidemiology of mosquitoes (69–74), which can be effectively captured by decoupling host–vector mobility (71, 75). Fig. 3 and System **3** illustrate the approach. A Lagrangian model based on residence times has been proposed recently for vector-borne diseases like Dengue, malaria, and Zika (23). 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 (75).

Lagrangian approaches have been used to model vector-borne diseases (refs. 76–80 and other references contained therein), albeit these researchers have not considered the impact that the residency–time matrix $\mathbb{P}$ may have on patch effective population size. Specifically, in refs. 76 and 78, 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 ref. 77, 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 **3** the relationship between each patch population and mobility are dynamic and explicitly formulated. Moreover, the limited (vector 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 residency habitat division can be particularly useful in the study of the impact of target control strategies.

The model in ref. 23 describes the interactions of n host groups in m patches via System **3**, where $I_h = [I_{h,1}, I_{h,2}, \ldots, I_{h,n}]^t$, $I_v = [I_{v,1}, I_{v,2}, \ldots, I_{v,m}]^t$, $N_h = [N_{h,1}, N_{h,2}, \ldots, N_{h,n}]^t$, $\bar{N}_v = [\bar{N}_{v,1}, \bar{N}_{v,2}, \ldots, \bar{N}_{v,m}]^t$, $\delta = [\delta_1, \delta_2, \ldots, \delta_m]^t$, $a = [a_1, a_2, \ldots, a_m]^t$, and $\mu = [\mu_1, \mu_2, \ldots, \mu_n]^t$. The infected hosts are denoted by the vector I_h and the host population by N_h. The infected vectors are 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 β_{hv}. 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 $\mathcal{R}_0^2(m, n) = \rho(M_{vh}M_{hv})$, where

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

and

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

If the host–vector network configuration is irreducible, then System **3** is cooperative and strongly concave with an irreducible Jacobian, and so the theory of monotone systems, particularly Smith's results (81), guarantee the existence of a sharp threshold. That is, the disease-free equilibrium is globally asymptotically stable if $R_0^2(m, n)$ 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 has been explored in ref. 23, 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, albeit the irreducibility of the host–vector network configuration is necessary for such property (23).

$$\begin{cases} \dot{I}_h = \beta_{vh}\text{diag}(N_h - I_h)\mathbb{P}\text{diag}(a)\text{diag}(\mathbb{P}^t N_h)^{-1} I_v - \text{diag}(\mu+\gamma) I_h \\ \dot{I}_v = \beta_{hv}\text{diag}(a)\text{diag}(N_v - I_v)\text{diag}(\mathbb{P}^t N_h)^{-1}\mathbb{P}^t I_h - \text{diag}(\mu_v+\delta) I_v \end{cases}. \quad [3]$$

The Lagrangian approach of disease modeling can use contacts (60) or residency 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

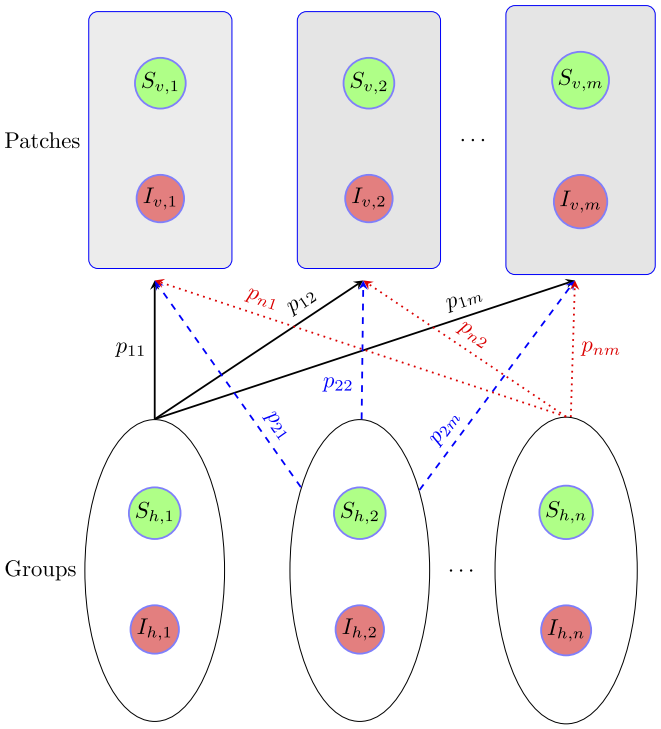

Fig. 3. Flow diagram of a Lagrangian model in which the host structure is decoupled from the vectors' structure. Figure courtesy of ref. 23.

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 tradeoffs, within systems that account for the overall population disease dynamics has been recently addressed (2, 25) and is discussed in *Economic Epidemiology*.

Economic Epidemiology

Simple EEMs are 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 further 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 values' connections to individualized cost–benefit analyses of disease risk is central to the building of potentially useful EEMs and is quite challenging.

EEM approaches have precursors in the epidemiological literature (82–84). EEM construction has been strongly influenced by past and ongoing work on the exploitation of species (85–87), 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 all motivations for mitigation against infection are not monetary in nature, we continue to call them economic, in keeping with previous published literature.

Modeling whether or not an individual undertakes infection causing behavior provides a classic starting point, because 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 number of new infections at a given time is 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 (5, 88). 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

$$U^h = U(h, C^h). \quad \textbf{[4]}$$

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 number of contacts, the optimal choice of contacts is the solution to a dynamic programing problem:

$$V_t(h) = \max_{C^s} \left\{ U_t\left(h_t, C_t^h\right) + r \sum_j \rho^{hj} V_{t+1}(j) \right\}, \quad \textbf{[5]}$$

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. **4** and **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 (25, 26, 89, 90). 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 (41). 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.

Lagrangian and EEMs

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 rather succinct and biased perspective, we expand on alternative ways for modeling disease transmission that can use contacts as its currency or residency times or both. Despite the overwhelming use of contacts as the most common currency of transmission and its undeniable theoretical value, it seems evident to these researchers that contacts, in the context of influenza, Ebola, tuberculosis, or other communicable diseases (as opposed to sexually transmitted diseases), 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, if we are to advance the role of theory, we need models that are informed by data, and the need to reinvest efforts to bring forth alternative modes of modeling becomes pressing (Lagrangian approaches that extends the functionality of classical models while requiring only "functional contacts" whenever infection takes place). Modeling approaches that require parameters like residence times and average time to infection for a given environment (risk), that is, parameters that can be measured, should be further investigated and their analyses contrasted to those that involve contacts. We believe that the use of Lagrangian models parametrized in this fashion are likely to increase the give and take necessary for theory and data to modify, expand, or even reinvent the way that we look and think about the dynamics and evolution of infectious diseases.

The SARS, influenza, and Ebola epidemics have shown the dramatic role that individual decisions play on the dynamics of infectious diseases. 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 what we have described here as EEMs seems promising, albeit computationally and mathematically challenging. However, as discussed in ref. 91, 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 individual in a poor community/country to do actually more risk mitigation. In fact, the need for richer communities or nations to find ways to incentivize greater levels of disease-risk mitigation in poor countries may be, in fact, 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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1. Castillo-Chavez C, et al. (2015) Beyond Ebola: Lessons to mitigate future pandemics. *Lancet Glob Health* 3(7):e354–e355.
2. Perrings C, et al. (2014) Merging economics and epidemiology to improve the prediction and management of infectious disease. *Ecohealth* 11(4):464–475.
3. Baroyan OV, et al. (1971) Computer modelling of influenza epidemics for the whole country (USSR). *Adv Appl Probab* 3(2):224–226.
4. Rvachev LA, Longini IM (1985) A mathematical model for the global spread of influenza. *Math Biosci* 75(1):3–22.
5. Fenichel EP, Kuminoff NV, Chowell G (2013) Skip the trip: Air travelers' behavioral responses to pandemic influenza. *PLoS One* 8(3):e58249.
6. Bajardi P, et al. (2011) Human mobility networks, travel restrictions, and the global spread of 2009 H1N1 pandemic. *PLoS One* 6(1):e16591.
7. Khan K, et al. (2009) Spread of a novel influenza a (H1N1) virus via global airline transportation. *N Engl J Med* 361(2):212–214.
8. Chowell G, Fenimore PW, Castillo-Garsow MA, Castillo-Chavez C (2003) SARS outbreaks in Ontario, Hong Kong and Singapore: The role of diagnosis and isolation as a control mechanism. *J Theor Biol* 224(1):1–8.
9. Cauchemez S, et al. (2011) Role of social networks in shaping disease transmission during a community outbreak of 2009 H1N1 pandemic influenza. *Proc Natl Acad Sci USA* 108(7):2825–2830.
10. Herrera-Valdez MA, Cruz-Aponte M, Castillo-Chavez C (2011) Multiple outbreaks for the same pandemic: Local transportation and social distancing explain the different "waves" of A-H1N1pdm cases observed in Mexico during 2009. *Math Biosci Eng* 8(1):21–48.
11. Castillo-Chavez C, et al. (2016) Modeling Ebola at the Mathematical and Theoretical Biology Institute (MTBI). *Not Am Math Soc* 63(4):366–371.
12. Towers S, et al. (2015) Mass media and the contagion of fear: The case of Ebola in America. *PLoS One* 10(6):e0129179.
13. Chew C, Eysenbach G (2010) Pandemics in the age of Twitter: Content analysis of Tweets during the 2009 H1N1 outbreak. *PLoS One* 5(11):e14118.
14. Chowell G, Hyman JM, Eubank S, Castillo-Chavez C (2003) Scaling laws for the movement of people between locations in a large city. *Phys Rev E Stat Nonlin Soft Matter Phys* 68(6 Pt 2):066102.
15. Pennings JME, Wansink B, Meulenberg MTG (2002) A note on modeling consumer reactions to a crisis: The case of the mad cow disease. *Int J Res Market* 19(1):91–100.
16. Levinthal DA, March JG (1993) The myopia of learning. *Strat Manag J* 14(S2):95–112.
17. Levin SA (1992) The problem of pattern and scale in ecology: The Robert H. MacArthur Award lecture. *Ecology* 73(6):1943–1967.
18. Levins R (1969) Some demographic and genetic consequences of environmental heterogeneity for biological control. *Bull Entomol Soc Am* 15(3):237–240.
19. Wilson EO (1973) Group selection and its significance for ecology. *Bioscience* 23(11):631–638.
20. Levin SA, Paine RT (1974) Disturbance, patch formation, and community structure. *Proc Natl Acad Sci USA* 71(7):2744–2747.
21. Paine RT, Levin SA (1981) Intertidal landscapes: Disturbance and the dynamics of pattern. *Ecol Monogr* 51(2):145–178.
22. Kareiva P, Mullen A, Southwood R (1990) Population dynamics in spatially complex environments: Theory and data [and discussion]. *Philos Trans R Soc Lond B Biol Sci* 330(1257):175–190.
23. Bichara D, Castillo-Chavez C (2016) Vector-borne diseases models with residence times-A Lagrangian perspective. *Math Biosci* 281:128–138.
24. Bichara D, Kang Y, Castillo-Chavez C, Horan R, Perrings C (2015) SIS and SIR epidemic models under virtual dispersal. *Bull Math Biol* 77(11):2004–2034.
25. Fenichel EP, et al. (2011) Adaptive human behavior in epidemiological models. *Proc Natl Acad Sci USA* 108(15):6306–6311.

26. Chowell G, Viboud C, Wang X, Bertozzi SM, Miller MA (2009) Adaptive vaccination strategies to mitigate pandemic influenza: Mexico as a case study. *PLoS One* 4(12):e8164.
27. Chen FH (2004) Rational behavioral response and the transmission of STDs. *Theor Popul Biol* 66(4):307–316.
28. Del Valle S, Hethcote H, Hyman J, Castillo-Chavez C (2005) Effects of behavioral changes in a smallpox attack model. *Math Biosci* 195(2):228–251.
29. Klein E, Laxminarayan R, Smith DL, Gilligan CA (2007) Economic incentives and mathematical models of disease. *Environ Dev Econ* 12(5):707–732.
30. Chen FH (2009) Modeling the effect of information quality on risk behavior change and the transmission of infectious diseases. *Math Biosci* 217(2):125–133.
31. Reluga TC (2010) Game theory of social distancing in response to an epidemic. *PLoS Comput Biol* 6(5):e1000793.
32. Chen F, Jiang M, Rabidoux S, Robinson S (2011) Public avoidance and epidemics: Insights from an economic model. *J Theor Biol* 278(1):107–119.
33. Gersovitz M (2011) The economics of infection control. *Annu Rev Resour Economics* 3(1):277–296.
34. Karesh WB, Cook RA, Bennett EL, Newcomb J (2005) Wildlife trade and global disease emergence. *Emerg Infect Dis* 11(7):1000–1002.
35. Kilpatrick AM, Chmura AA, Gibbons DW, Fleischer RC, Marra PP, Daszak P (2006) Predicting the global spread of H5N1 avian influenza. *Proc Natl Acad Sci USA* 103(51):19368–19373.
36. Kimball AM (2012) Risky Trade: Infectious Disease in the Era of Global Trade (Ashgate Publishing, New York).
37. Pavlin BI, Schloegel LM, Daszak P, et al. (2009) Risk of importing zoonotic diseases through wildlife trade, United States. *Emerg Infect Dis* 15(11):1721–1726.
38. Tatem AJ (2009) The worldwide airline network and the dispersal of exotic species: 2007–2010. *Ecography (Cop.)* 32(1):94–102.
39. Tatem AJ, Hay SI, Rogers DJ (2006) Global traffic and disease vector dispersal. *Proc Natl Acad Sci USA* 103(16):6242–6247.
40. Tatem AJ, Rogers DJ, Hay SI (2006) Global transport networks and infectious disease spread. *Adv Parasitol* 62:293–343.
41. Fenichel EP, Wang X (2013) The mechanism and phenomena of adaptive human behavior during an epidemic and the role of information. Modeling the Interplay Between Human Behavior and the Spread of Infectious Diseases (Springer, New York), pp 153–168.
42. Morin BR, Fenichel EP, Castillo-Chavez C (2013) SIR dynamics with economically driven contact rates. *Nat Resour Model* 26(4):505–525.
43. Daszak P, et al. (2006) The emergence of Nipah and Hendra virus: Pathogen dynamics across a wildlife-livestock-human continuum. Disease Ecology: Community Structure and Pathogen Dynamics (Oxford Univ Press, New York), pp 186–201.
44. Daszak P, Tabor GM, Kilpatrick AM, Epstein J, Plowright R (2004) Conservation medicine and a new agenda for emerging diseases. *Ann N Y Acad Sci* 1026(1):1–11.
45. Hethcote HW, Yi L, Zhujun J (1999) Hopf bifurcation in models for pertussis epidemiology. *Math Comput Model* 30(11-12):29–45.
46. Castillo-Chavez C, Hethcote HW, Andreasen V, Levin SA, Liu WM (1989) Epidemiological models with age structure, proportionate mixing, and cross-immunity. *J Math Biol* 27(3):233–258.
47. Bansal S, Grenfell BT, Meyers LA (2007) When individual behaviour matters: Homogeneous and network models in epidemiology. *J R Soc Interface* 4(16): 879–891.
48. Newman MEJ (2002) Spread of epidemic disease on networks. *Phys Rev E Stat Nonlin Soft Matter Phys* 66(1 Pt 2):016128.
49. Pastor-Satorras R, Vespignani A (2001) Epidemic dynamics and endemic states in complex networks. *Phys Rev E Stat Nonlin Soft Matter Phys* 63(6):066117.
50. Newman MEJ (2003) The structure and function of complex networks. *SIAM Rev* 45(2):167–256.
51. Funk S, Gilad E, Watkins C, Jansen VAA (2009) The spread of awareness and its impact on epidemic outbreaks. *Proc Natl Acad Sci USA* 106(16):6872–6877.
52. Epstein JM, Parker J, Cummings D, Hammond RA (2008) Coupled contagion dynamics of fear and disease: Mathematical and computational explorations. *PLoS One* 3(12):e3955.
53. Funk S, Gilada E, Jansen VAA (2010) Endemic disease, awareness, and local behavioural response. *J Theor Biol* 264(2) 501–509.
54. Perra N, Balcan D, Gonçalves B, Vespignani A (2011) Towards a characterization of behavior-disease models. *PLoS One* 6(8):e23084.
55. Hadeler KP, Castillo-Chavez C (1995) A core group model for disease transmission. *Math Biosci* 128(1):41–55.
56. Preisser EL, Bolnick DI (2008) The many faces of fear: Comparing the pathways and impacts of nonconsumptive predator effects on prey populations. *PLoS One* 3(6):e2465.
57. Meloni S, et al. (2011) Modeling human mobility responses to the large-scale spreading of infectious diseases. *Sci Rep* 1:62.
58. Funk S, Salathé M, Jansen VAA (2010) Modelling the influence of human behaviour on the spread of infectious diseases: A review. *J R Soc Interface* 7(50):1247–1256.
59. Castillo-Chavez C, Song B (2004) Dynamical models of tuberculosis and their applications. *Math Biosci Eng* 1(2):361–404.
60. Castillo-Chavez C, Song B, Zhangi J (2003) An epidemic model with virtual mass transportation: The case of smallpox. Bioterrorism: Mathematical Modeling Applications in Homeland Security (Society for Industrial and Applied Mathematics, Philadelphia), Vol 28, pp 173–198.
61. Grünbaum D (1994) Translating stochastic density-dependent individual behavior with sensory constraints to an Eulerian model of animal swarming. *J Math Biol* 33(2):139–161.
62. Okubo A (1980) Diffusion and ecological problems: Mathematical models. Biomathematics, Vol 10.
63. Okubo A, Levin SA (2013) Diffusion and Ecological Problems: Modern Perspectives (Springer Science & Business Media, New York), Vol 14.
64. Cristiani E, Piccoli B, Tosin A (2014) Multiscale Modeling of Pedestrian Dynamics (Springer, New York), Vol 12.
65. Bellomo N, Piccoli B, Tosin A (2012) Modeling crowd dynamics from a complex system viewpoint. *Math Model Meth Appl Sci* 22(supp02):1230004.
66. Helbing D, Farkas I, Vicsek T (2000) Simulating dynamical features of escape panic. *Nature* 407(6803):487–490.
67. Helbing D, Keltsch J, Molnar P (1997) Modelling the evolution of human trail systems. *Nature* 388(6637):47–50.
68. Hutson V (1984) A theorem on average Liapunov functions. *Mon Hefte Math* 98: 267–275.
69. Bailey NTJ, et al. (1982) The Biomathematics of Malaria. The Biomathematics of Diseases (Charles Griffin and Company, High Wycombe, UK), Vol 1.
70. Honório NA, et al. (2003) Dispersal of *Aedes aegypti* and *Aedes albopictus* (*Diptera: Culicidae*) in an urban endemic dengue area in the state of Rio de Janeiro, Brazil. *Mem Inst Oswaldo Cruz* 98(2):191–198.
71. Koram KA, Bennett S, Adiamah JH, Greenwood BM (1995) Socio-economic risk factors for malaria in a peri-urban area of The Gambia. *Trans R Soc Trop Med Hyg* 89(2): 146–150.
72. Macdonald G (1956) Epidemiological basis of malaria control. *Bull World Health Organ* 15(3–5):613.
73. Macdonald G (1956) Theory of the eradication of malaria. *Bull World Health Organ* 15(3–5):369.
74. Ross R (1911) The Prevention of Malaria (John Murray, New York).
75. Smith DL, Dushoff J, McKenzie FE (2004) The risk of a mosquito-borne infection in a heterogeneous environment. *PLoS Biol* 2(11):e368.
76. Cosner C, et al. (2009) The effects of human movement on the persistence of vector-borne diseases. *J Theor Biol* 258(4):550–560.
77. Rodríguez DJ, Torres-Sorando L (2001) Models of infectious diseases in spatially heterogeneous environments. *Bull Math Biol* 63(3):547–571.
78. Ruktanonchai NW, Smith DL, De Leenheer P (2016) Parasite sources and sinks in a patched Ross-Macdonald malaria model with human and mosquito movement: Implications for control. *Math Biosci* 279:90–101.
79. Wesolowski A, et al. (2012) Quantifying the impact of human mobility on malaria. *Science* 338(6104):267–270.
80. Iggidr A, Sallet G, Souza MO (2016) On the dynamics of a class of multi-group models for vector-borne diseases. *J Math Anal Appl* 441(2):723–743.
81. Smith HL (1986) Cooperative systems of differential equations with concave nonlinearities. *Nonlinear Anal Theor Meth Appl* 10:1037–1052.
82. Geoffard PY, Philipson T (1996) Rational epidemics and their public control. *Int Econ Rev* 37(3):603–624.
83. Auld MC (2003) Choices, beliefs, and infectious disease dynamics. *J Health Econ* 22(3):361–377.
84. Ferguson N (2007) Capturing human behaviour. *Nature* 446(7137):733–733.
85. Clark CW (1973) Profit maximization and the extinction of animal species. *J Polit Econ* 81(4):950–961.
86. Clark CW (1976) A delayed-recruitment model of population dynamics, with an application to baleen whale populations. *J Math Biol* 3(3-4):381–391.
87. Clark CW (1979) Mathematical models in the economics of renewable resources. *SIAM Rev* 21(1):81–99.
88. Morin BR, Perrings C, Levin S, Kinzig A (2014) Disease risk mitigation: The equivalence of two selective mixing strategies on aggregate contact patterns and resulting epidemic spread. *J Theor Biol* 363:262–270.
89. Morin B, Perrings C, Levin S, Kinzig A, Economic instruments for the socially optimal management of infectious disease. *EcoHealth*, in press.
90. Chowell G, Nishiura H, Bettencourt LM (2007) Comparative estimation of the reproduction number for pandemic influenza from daily case notification data. *J R Soc Interface* 4(12):155–166.
91. Morin BR, Perrings C, Kinzig A, Levin S (2015) The social benefits of private infectious disease-risk mitigation. *Theor Ecol* 8(4):467–479.