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Comment

Dynamically rich, yet parameter-sparse models for spatial epidemiology
Comment on "Coupled disease–behavior dynamics on complex networks: A review" by Z. Wang et al.

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Since the very inception of mathematical modeling in epidemiology, scientists exploited the simplicity ingrained in the assumption of a well-mixed population. For example, perhaps the earliest susceptible–infectious–recovered (SIR) model developed by L. Reed and W.H. Frost in the 1920s [1], included the well-mixed assumption such that any two individuals in the population could meet each other. The problem was that, unlike many other simplifying assumptions used in epidemiological modeling whose validity holds in one situation or the other, well-mixed populations are almost non-existent in reality because the nature of human socio-economic interactions is, for the most part, highly heterogeneous (e.g. [2–6]).

As stated in the comprehensive review by Z. Wang et al. [7], resorting to the theoretical framework of complex networks [8] has become a preferred way to circumvent the limitations of well-mixed populations. Adopting the framework of complex networks opened up epidemiology to contributions from physics due to the long-standing interest of physicists in graph theory as a mathematical foundation for analyzing complex networks [9]. Possibly the most surprising result arising from the "marriage" between epidemiology and physics was that any spreading rate of a disease in a scale-free network, no matter how low it is, causes the infection to spread over the whole network [10]. Given this and many other successes of theoretical epidemiology achieved by breaking free from the assumption of a

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well-mixed population, it was only natural to extend the models of disease dynamics in complex networks to include the aspects of human behavior. The outlined series of developments brought about a number of new insights and... a few "challenges" [7].

Coupled disease–behavior models in spatially structured populations are dynamically rich in the sense of exhibiting a number of critical phenomena such as phase transitions, self-organization, and pattern formation. However, this richness comes at a price [7]:

- The number of model parameters is generally quite high, leading to the so-called curse of dimensionality—a state in which any amount of practically attainable data is sparse, thus causing problems in analyses that aim to establish statistical significance of the results (e.g. the parameter estimation).
- There is a notable lack of attempts to integrate dynamic models with empirical data, although such an integration is helpful in quantifying risks inherent in complex systems (e.g. the risk of a stock market collapse [11], the risk of an economic contraction for a country and delay risk in air traffic [12], systemic risk in banking [13], and credit risk in microfinance [14] to name a few).

We argue that the above-mentioned problems could be avoided and/or resolved in the context of epidemiology. A straightforward benefit would be the ability to take advantage of available epidemiological data for the purpose of quantifying disease-related risks in the spirit of the following examples:

- During the 2014 outbreak of Ebola virus disease (EVD) in West African countries [15,16], records of world flight schedules and Ebola virus surveillance were put to good use. Combined with a mathematical model, these records predicted that, on average, 2.8 travelers infected with Ebola virus depart from the EVD affected area via commercial flights monthly [17]. Traffic reductions had a limited effect on the spread of EVD to new countries, causing the delay of only a few weeks [18].
- The concept of complex networks is gradually finding its way into host-level "epidemiology". Namely, in a human body, there are around 1000 lymph nodes that form a complex network structure [19]. Lymph nodes are tightly related to $CD4^+$ T lymphocytes which, in turn, represent a major target for human immunodeficiency virus (HIV) [20]. Consequently, gaining a deeper understanding of HIV infection dynamics and *in vivo* effects of a therapy should rely on structurally explicit models that make use of vast knowledge on the lymphoid tissue network [21], as well as the spatial-temporal data on the viral load and the amount of target cells [22–24].

In what follows, we describe a class of dynamically rich, yet parameter-sparse network models [11,14] that have the potential to resolve some, if not all, of the problems outlined in review [7].

The construction of the model is accomplished in several steps. First, we specify an adjacency matrix, $A = [a_{ij}]$, whose elements map the network of interactions in a population of agents. In the simplest case, $a_{ij} = a_{ji} = 1$ if agents i and j interact with each other and $a_{ij} = a_{ji} = 0$ if they do not. For the purpose of more detailed modeling of human behavior, elements $a_{ij} \geq 0$ can be interpreted as the number of contacts between any two agents in the network from moment t to $t + 1$ (in effect, a_{ij} become contact rates).

Second, the network of interactions is dynamical. In coupled disease–behavior models, contact rates are updated to reflect the current state of an epidemic (e.g. fear of contracting the disease, preventive measures, etc.). Such updates can be global or local. Contact rates may decrease from $a_{ij}(0)$ to, for instance, $a_{ij}(t+1) = a_{ij}(0)\exp(-\Gamma I(t))$ due to the global state of an epidemic (e.g. as reported by media), where $I(t)$ is the total number of infectious agents in the network and Γ is a model parameter representing the global responsiveness of the population. The global responsiveness is necessary because agents deal with fuzzy information—the speed with which the disease spreads is uncertain and infectious neighbors are often symptom-free for a while. In addition, contact rates may decrease due to the increasing effective exposure to the disease, $n_i(t) = \sum_{\Delta(i)} a_{ij}(t)$, which for agent i is obtained by adding contact rates across the set of i's infectious neighbors, $\Delta(i)$. Consequently, $a_{ij}(t+1) = a_{ij}(0)\exp(-\gamma n_i(t))$, where γ is the second model parameter called the local responsiveness. The combined effect of global and local updates can be accounted for with a product of the two exponentials.

Third, we describe the use of mathematical formalism in characterizing the disease at hand. To generate the index case(s) of an outbreak, there must be a (however tiny) probability, p_{ex}, for susceptible agents to contract the disease from an exogenous source. Thereafter, the infectivity of the disease drives the epidemic, whereby the probability of

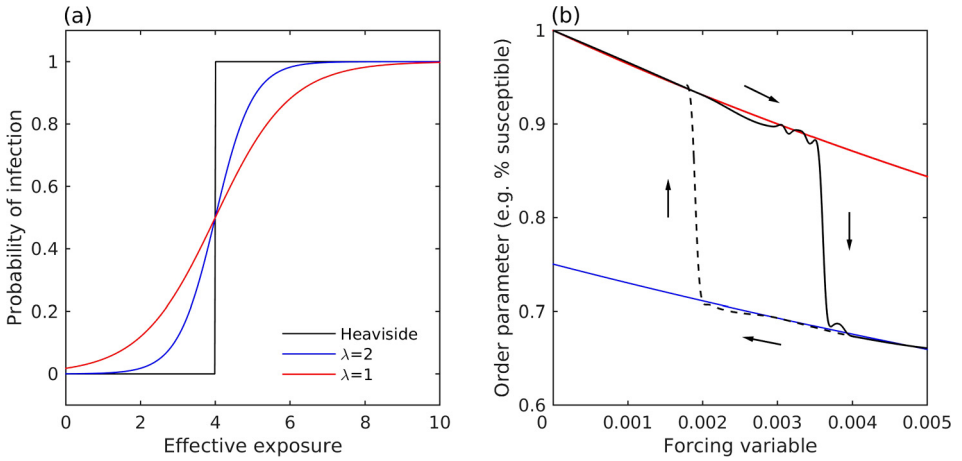

Fig. 1. Characteristics of the proposed model. (a) Probability of infection as a function of the effective exposure, i.e. $p = p(n_i)$. Parameters other than the steepness, λ, are $n_c = 4$ and $p_0 = 1$. (b) Equilibrium states of the dynamical network may form a hysteresis loop in an SIS model. This panel was adapted with permission from [14].

infection is specified as a function of the effective exposure, i.e. $p = p(n_i)$. The simplest possible choice, resulting in so called Watts model [25], sets the probability of infection proportional to Heaviside step-function (Fig. 1a), $p(n_i) = p_0 H(n_i - n_c)$, where n_c is a critical threshold below which the disease cannot infect susceptible individuals and p_0 is a constant probability of infection if $n_i \geq n_c$. Although Watts model may be overly stylized for epidemiology, the mentioned functional form *is* instructive as a limiting case of a set of more realistic sigmoid functions (Fig. 1a). With such functions (i) the infection can occur even if a susceptible agent has only one infectious neighbor and (ii) the probability of infection increases more-or-less gradually alongside the effective exposure. An example of a candidate sigmoid function is $p(n_i) = p_0 \left[1 - \exp(-\lambda(n_i - n_c))\right]^{-1}$, where λ is the steepness parameter.

The fourth and the last assumption of the model deals with recoveries [11]. Namely, an agent is assumed to simply exit from the infectious state after a period of time denoted τ. Depending on the specifics of the disease, the agent can return to a susceptible state (SIS model) or enter a new, recovered state (SIR model) in which recurrent infections are impossible. Quantity τ is a random variable, whose values for each infectious agent are drawn from an appropriate probability distribution. If, for instance, the exponential distribution is selected, then the cumulative density function is given by single parameter β, i.e. $\Pr(\tau < t) = 1 - \exp(t/\beta)$.

The class of models introduced herein, primarily with applications to epidemiology in mind, exhibits a range of interesting dynamic phenomena. These include (i) multiple dynamic regimes, (ii) severe non-linearity during regime switching, (iii) a hysteresis analogous to phase transitions near a critical point (Fig. 1b), (iv) critical slowing down, and (v) spontaneous recoveries [11,14]. More importantly, though, once the spatial structure of the population is represented by an adequate network, there are only six or so parameters (Γ, γ, n_c, p_0, λ, and β; p_{ex} is a forcing variable) that need to be estimated from the data. Although valid concerns remain as to whether the adjacency matrix, $A = \left[a_{ij}\right]$, is knowable, these can be at least partly addressed by capturing the statistical properties of complex networks such as the degree distribution and the degree correlation (see e.g. [9,26]).

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