Epidemic spreading dynamics with drug-resistant and heterogeneous contacts

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Abstract

Drug resistance and strong contacts actually play crucial roles in epidemic spread in complex systems. Nevertheless, neither theoretical model or methodology is proposed to address this. We thus consider an edge-based epidemic spread model considering the two key ingredients, in which the contacts are grouped into two classes: strong contacts and normal ones. Next, we present a unified edge-based compartmental approach to the spread dynamics on Erdős-Rényi (ER) networks and validate its results by extensive numerical simulations. In case that epidemic is totally drug-resistant, we both numerically and theoretically show a slow outbreak (continuous transition) of epidemics when number of strong contacts is not enough for the emergence of null threshold. If the epidemic owns partial resistance, we would observe evident faster-growing outbreaks (discontinuous transitions) and larger final epidemic sizes for few strong contacts, instead of emergence of null threshold with increase of strong contacts. Inhibiting effect of infection threshold, positive roles of strong contacts and strength of strong contacts in promoting outbreaks are also approved. Throughout this paper, we could drive exact predictions through the analytical approach, showing good agreements with numerical simulations.

Keywords: Epidemiology, Network dynamics, Edge-based compartmental theory

1. Introduction

In field of epidemic research, an actual non-negligible case that is recently gaining attention is drug resistance arisen from abuse of substance especially antibiotics, which contributes to the problem of drug resistance. Drug resistance refers to that individually applied therapies targeted at single pathogens in individual bodies would actually
become environmental events to drive the evolution of pathogens and commensal bacteria alike far beyond bodies. Growing problems with multi-resistant pathogens such as methicillin-resistant staphylococcus aureus (MRSA) found in most European countries [1], more particularly infectious agents of tuberculosis (like multidrug-resistant tuberculosis (TB) or even extensively drug-resistant TB [2]) and gonorrhoea begin to capture much more attention than before, because these pathogens remaining high infection rates would make infected people are difficult or impossible to cure. For some extreme cases of multi-drug resistant epidemics like superbugs, even last-resort antibiotics fail [3, 4]. Therefore large amount of empirical studies have been conducted by epidemiologists, microbiologists, health economists and physicians to the drug resistance especially antibiotic resistance, aiming to develop new medicines, therapies even coping strategies in the face of this crisis [5].

In turning to studies related to epidemic spread in complex systems, lots of researchers have developed different models, estimation methods or efficient algorithms to explore the influence of spatial structure topology especially the edges on spread of epidemics, so as to design network-based prevention strategies [6]. However, designing network-based prevention strategies requires knowledge on disease transmission through network edges and statistical methods for analyzing network data. Fortunately, data-driven method such as contact tracing is very effective, because this method could identify which contacts are key to the transmission and can contribute to the so-called real time tracking of an epidemic [7]. Further, one significant research progress of contact tracing is that there exist considerable differences among contact frequencies in real complex networks [7, 8], while the frequency of contact can be used as a proxy measure for the tendency of at-risk events for infection. This means that various contact frequencies lead to multiple transmission rates (positively related to contact frequency) along different contacts. Hence, contact-based network models accessing nature of contact patterns could yielded more deep insights into infectious disease transmission, and to control their epidemiological significance.

Another important fact we could not ignore is that spread of epidemics with drug resistance is often accompanied by increasing number of some contacts with enough high strength (i.e. high contact frequency) which could be called strong contacts. And these strong contacts have been found to be widespread in reality, in forms of concurrent partnerships (spouse partnerships, cohabitation relationships and homosexual relations) [9], compact communities [10, 11], doctor-patient relationship [12, 13] and so on. For example, gay relationship is always considered as a high risk contact for being infected with HIV compared with other forms of sexual contacts, through largely increasing infection rate [14]. Another well-known case is that of tuberculosis transmissions, which could occur more easily among family members; despite the possible infection through inhalation of aerosols or small droplets for example during a conversation between strangers [15]. Besides, doctor-patient relationship has been confirmed as a nearly ‘straightway unblocked channel’ to transfer streptococci and staphylococci (even MRSA), resulting in a serious cross-infection [16]. These studies indicate that the strength of contacts and drug resistances especially antimicrobial resistances can profoundly influence the spread of disease and should thus be incorporated into applicable epidemiological models. However, it still not clear how drug resistance regulates the epidemic diffusion in complex systems in presence of strong contacts. To our knowl-
Based on the above arguments, we herein put forward an edge-based epidemic spread model to capture the two realistic mechanisms: drug resistance and strengths of contacts. In the present model, contacts are directly classified into two types: normal contacts and strong ones, which allows us to develop a unified edge-based compartmental theory so as to deeply understand the effects of drug resistance and strong contacts on the spread dynamics. We elucidate the issue in two different situations at length: (1) Epidemic is totally drug-resistant; (2) Epidemic own partial resistance. In the first case, we both numerically and theoretically show a slow outbreak (continuous transition) of epidemics when number of strong edges (i.e., strong contacts) is not sufficiently enough for the emergence of null threshold i.e., the system exhibits the lack of an epidemic threshold and always show a finite fraction of infected population [17]. We then extend the analytical approach to the latter case to derive a number of predictions, including the final infection size, the position of the threshold and the nature of the transition. Both the theoretical approach and agent-based simulations indicate the occurrences of faster-growing outbreaks (i.e., discontinuous transitions) and larger final epidemic sizes with few strong contacts in networks, instead of emergence of null threshold with increasing fraction of strong contacts. In both cases, numerical simulations perfectly fit the analytical predictions.

The paper is organized as follows. In Sec. 2 we present a detailed description of our model. Then we give a detailed theoretical analysis of the spread dynamics by means of the unified edge-based compartmental theory in Sec 3. Sec. 4 is devoted to show a deep numerical investigation of the epidemic spread dynamics on different networks. In addition, theoretical predictions are given to give a comparison with numerical simulations. Finally, we list conclusions in Sec. 5.

2. Model

One propose a model to give a framework to curve spread of highly mutated epidemics which could avoid inhibitory effect of antibiotics, such as influenza virus, TB bacteria, staphylococci and so on. As we know, in the classical SIR model in discrete time, each individual can be in one of three different states: susceptible (S, individuals that are healthy, and could be infected), infected (I, individuals who get infected and can transmit the pathogen), or removed (R, dead or recovered and immunized individuals). At each time step, each infected individual shifts into removed state with probability $\gamma$, while she transmits the pathogen to each of her susceptible neighbors with infection probability $p$.

In the present model, the epidemic spread is formulated in the terms of a modification of the susceptible-infected-recovered (SIR) model, where one class the edges of networks into two groups: strong edges and normal ones, corresponding to the strong contacts and normal contacts which have been observed in reality. The reason that only two classes of edges are assumed in the model is to enable us to develop a unified edge-based compartmental approach to analysis the spread dynamics, without loss of one important feature of human contacts – heterogeneous contributions to epidemic
diffusion caused by different contact frequencies. At the same time, we introduce infection threshold $T$ to depict drug resistance of epidemics. Like what happens in the SAR model for social contagions [18], one susceptible individual successfully becomes infected only if it has received the pathogen from its connected infected neighbors for at least $T$ times (i.e., infection threshold). This infection rule with infection threshold is actually a nice mirror to reflect how epidemics with drug resistance diffuse in real complex systems [5]. The case $T = 1$ represents one situation that the epidemic is multi-resistant or even totally-resistant, so that it could attacked people most severely, which means that individuals would easily get infected if they receive pathogen of the epidemic from the infected guys for just one time. For the case $T > 1$, we know that people have more choices in the antibiotic lists because the epidemic owns partial resistance or even no. In this case, the epidemic could be timely suppressed or repelled by acting antibiotics so that the hosts could not infect others, until the pathogen begins to evolve certain drug-resistance under the stress of antibiotics (receive times is beyond infection threshold $T$).

Specifically, for two individuals $i$ (susceptible) and $j$ (recovered) located on two ends of one edge $e_{ij}$ in the complex network, $i$ will receive the epidemic pathogen passed from $j$ at a probability $p$ if the edge $e_{ij}$ is a normal edge. Instead, if $e_{ij}$ is a strong edge, $i$ will be more likely to get infected by the epidemic transmitted from $j$ at a raised infection probability $q$. That is why our model is edge-based. It must be stressed in our model that the individuals who are suffering the epidemic are not considered to be in infected state before they gaining the ability to infect others.

Our model is simulated on Erdős-Rényi (ER) network of size $N = 10^4$ with mean degree $\langle k \rangle = 10$. In any case, an individual that get infected at time $t$ will try to transmit the infection to all its susceptible neighbors at time $t + 1$ (for exactly one time step), then it will lose interest and never transmit the infection again. i.e., the recover probability is $\gamma = 1.0$. In the simulations, $N_r$ (ranging from 500 to 2000) independent realizations are needed. Moreover, there are two initial conditions: (1) $\rho_0$ of the population are randomly chosen to be in the infected (I) state as seeds, while the remaining nodes are susceptible; (2) a proportion $\mu$ of randomly chosen edges in the networks are regarded as strong edges while the remaining edges are normal ones.

### 3. Theory analysis

Based on the edge-based compartmental theory [18], the probability that an individual owning $k$ connections has received $m$ pieces of pathogen from its infected neighbors until time $t$ is

$$\phi(k, m, t) = (1 - \rho_0) \binom{k}{m} \theta(t)^k [1 - \theta(t)]^m,$$

where $\theta(t)$ denotes the probability at which the epidemic has not been transmitted through an edge up to time $t$. Thus the probability that a individual of degree $k$ is in susceptible state is

$$S(k, t) = \sum_{m=0}^{T-1} \phi(k, m, t).$$
Then the fraction of whole susceptible population at time $t$ is

$$S(t) = \sum_{k=1}^{\infty} P(k)S(k, t).$$

(3)

According to the rules of our model, we obtain

$$\theta(t) = (1 - \mu)\theta_l(t) + \mu\theta_h(t),$$

(4)

where $\theta_l(t)$ [$\theta_h(t)$] represents the probability that up to time $t$ the epidemic has not been successfully transmitted from one end of one normal (strong) edge to the other end. Denoting $\mu$ as the fractions of strong edges in the networks. Furthermore,

$$\begin{align*}
\theta_l(t) &= \xi^S_S(t) + \xi^I_l(t) + \xi^R_l(t), \\
\theta_h(t) &= \xi^S_h(t) + \xi^I_h(t) + \xi^R_h(t),
\end{align*}$$

(5)

where $\xi^y_x(t)$ is the probability that one end of edge ($x = l$ means normal edge while $x = h$ for strong type) is in the susceptible state while the other end is in state of $y \in \{S, I, R\}$ up to time $t$.

In a similar way, for a node $\nu$ contacted with a susceptible neighbor, the probability that $\nu$ has received pathogen $m$ times until time $t$ is

$$\psi(k', m, t) = (1 - \rho_0)\left(\frac{k' - 1}{m}\right)\theta(t)^{k'-1}[1 - \theta(t)]^m.$$  

(6)

Besides, the probability that any edge in the networks contacts a node of degree $k'$ is $k'P(k')/\langle k \rangle$ in uncorrelated networks, where $\langle k \rangle$ represents the mean degree of the network. Therefore, we have

$$\xi^S_x(t) = \frac{1}{\langle k \rangle} \sum_{k'} k'P(k') \sum_{m=0}^{T-1} \psi(k', m, t).$$

(7)

Finally, the dynamics of the system could be tracked by Eq. (7) and the following equations

$$\begin{align*}
\frac{d\xi^R_x(t)}{dt} &= [1 - \lambda(x)]\xi^I_x(t), & x \in \{l, h\}, \\
\frac{d\theta_x(t)}{dt} &= -\lambda(x)\xi^I_x(t), \\
\xi^R_x &= \frac{(1 - \theta_x(t))[1 - \lambda(x)]}{\lambda(x)},
\end{align*}$$

(8)

where $\lambda(x) = \begin{cases} p, & \text{if } x = l, \\
q, & \text{if } x = h. \end{cases}$

Combining Eqs. (7) and (8), we obey

$$\frac{d\theta_x(t)}{dt} = \lambda(x)\sum_{k'} k'P(k') \sum_{m=0}^{T-1} \psi(k', m, t) + (1 - \lambda(x) - \theta_x(t)).$$

(9)
where \( \theta_h(t) \) and \( \theta_l(t) \) can be obtained by numerically integrating Eq. (9) with the initial condition \( \theta(0) = 1.0 \). Then \( \theta(t) \) is naturally derived through Eq. (4). We can thus get \( S(t) \) by submitting \( \theta(t) \) into Eqs. (2) and (3), and order parameter \( R(\infty) = 1 - S(\infty) \) as \( t \to \infty \).

Besides, at the end of the spreading process \( d\theta_x(t)/dt = 0 \). Hence the asymptotic value of \( \theta_x(\infty) \) obeys

\[
\theta_x(\infty) = \lambda(x) \left( \frac{\sum_{k'} k' P(k') \sum_{m=1}^{T-1} \psi(k', m, \infty)}{\langle k \rangle} \right) + 1 - \lambda(x) \quad (10)
\]

Combing with Eq. (4), we obtain

\[
\theta(\infty) = [\mu q + (1 - \mu) p]\left( \frac{\sum_{k'} k' P(k') \sum_{m=1}^{T-1} \psi(k', m, \infty)}{\langle k \rangle} - 1 \right) + 1 \quad (11)
\]

and

\[
g(p, \theta(\infty)) = [\mu q + (1 - \mu) p]\left( \frac{\sum_{k'} k' P(k') \sum_{m=1}^{T-1} \psi(k', m, \infty)}{\langle k \rangle} - 1 \right) - \theta(\infty) \quad (12)
\]

Next, we further explore the critical behaviors of the systems under different parameter situations. When \( T = 1 \) and \( \rho_0 \approx 0 \) (i.e., the epidemic is multi-resistant or even totally-resistant), there exists one solution trivial \( \theta(\infty) = 1 \) of Eq. (11). At the critical point, \( f(p, \theta(\infty)) \) is tangent to horizontal axis at \( \theta(\infty) = 1 \). Accordingly, we could obtain the continuous critical condition of the model as

\[
\frac{dg(p, \theta(\infty))}{d\theta(\infty)} \bigg|_{\theta(\infty)=1} = 0 \quad (13)
\]

Based on Eq. (13), we can elicit the following relationship

\[
[\mu q + (1 - \mu) p] \left( \frac{\langle k^2 \rangle - \langle k \rangle}{\langle k \rangle} \right) = 1 \quad (14)
\]

Naturally, the critical transmission probability can be calculated. In detail, the critical point \( p_{c}^{\text{II}} = (\langle k \rangle)/(\langle k^2 \rangle - \langle k \rangle) \) if \( p = q \), being in agreement with the threshold of the classical SIR spreading model [20]. While there are two cases to be considered for the more widely existed relationship \( p \neq q \) in reality

\[
p_{c}^{\text{II}} \text{ or } q_{c}^{\text{II}} = \frac{\langle k \rangle}{\langle k^2 \rangle - \langle k \rangle}, \text{ if } \mu = 0 \text{ or } 1,
\]

\[
p_{c}^{\text{II}} = \frac{\langle k \rangle}{(\langle k^2 \rangle - \langle k \rangle) - (1 - \mu)} - \frac{\mu q}{1 - \mu}, \text{ otherwise.} \quad (15)
\]

According to Eq. (14), we could further expected that null threshold \( p_{c}^{\text{II}} = 0 \) would arises when \( \mu \geq \mu_{c}^{\text{II}} = -b + \sqrt{b^2 + 4q\langle k \rangle}/2q \), where \( b = (\langle k^2 \rangle - \langle k \rangle - 1)q \).
For the case of $T > 1$ and $\rho_0 \approx 0$ (i.e., the epidemic owns partial drug-resistance), $\theta(\infty)$ is still the trivial solution of Eq. (12), but $f(\theta(\infty))$ will not be tangent to horizontal axis at the point $\theta(\infty) = 1.0$. With increase of $\rho_0$, $\theta(\infty) = 1.0$ is not a solution of the Eq. (11) any more. If Eq. (11) has two stable fixed points, only the largest one is physical meaningful since $\theta(t)$ decreases with $t$ from 1. As shown in Fig. 1, the physical meaningful solution of Eq. (11) is the only one stable fixed point when $p$ is small. At the critical point $p^I_c$, the physical meaningful solution of Eq. (11) is the tangent point. To determine the value of $p^I_c$, we can numerically solve Eq. (11) and

$$
\frac{dg(p, \theta(\infty))}{d\theta(\infty)} |_{\theta_c(\infty)} = 0,
$$

where $\theta_c(\infty)$ is the critical value that the infection has not transmitted through an edge. We can further calculate the final expression of critical transmission probability

$$
p^I_c = \frac{H(\theta_c, \rho_0, T, \langle k \rangle) - \mu q}{1 - \mu},
$$

where $H(\theta_c, \rho_0, T, \langle k \rangle) = \langle k \rangle / (1 - \rho_0) \sum_k kP(k) \sum_{m} (\theta_c^{-m - 2} (1 - \theta_c)^{m - 1} (k - 1)(1 - \theta_c) - m)$. From Eq. (17), we know that $p^I_c$ is correlated with $\mu$, $q$, $T$, $\rho_0$, and $\langle k \rangle$. When $p > p^I_c$, we find that Eq. (11) has only one small stable fixed point. From the above statements, the physical meaningful solution of Eq. (11) decreases discontinuously from a large value to a small one. From the perspective of nonlinear dynamics, the system exhibits a bifurcation phenomenon, which indicates $\theta(\infty)$ decreases discontinuously with $p$, that is $R(\infty)$ increases discontinuously with $p$. If Eq. (11) has only one stable fixed point, $R(\infty)$ increases continuously with $p$. The critical point
Fig. 2: The final steady density of removed individuals versus $p$ for four different values of raised infection probability $q$ of each $\mu$, where four different fractions of edges are initially set as strong ones: (a) $\mu = 0.07$, (b) $\mu = 1/\langle k \rangle = 0.1$, (c) $\mu = 0.3$ and (d) $\mu = 0.8$. The results are averaged over $N_r = 1000$ independent realizations. The other parameter is taken as $\rho_0 = 0.1$.

that the growth pattern of $R(\infty)$ changes can be determined by simultaneously solving Eqs. (11), (16) and

$$\frac{d^2 g(p, \theta_s(\infty))}{d\theta_s(\infty)^2} \bigg|_{\theta_s(\infty)} = 0. \quad (18)$$

4. Results

In this section, we perform extensive numerical simulations for our proposed model with totally ($T = 1$) and partial ($T > 1$) drug-resistant respectively.

4.1. Totally drug-resistant

We first study the model with totally drug-resistant, i.e., $T = 1$. In this situation, individuals would easily get infected if they receive the epidemic from the neighbors for one time. This case corresponds to the diffusion of an epidemic that is difficult to treat, or with total drug resistance; where our model is equivalent to the classical SIR model, but with two types of connections along which epidemics spread at different probability.

It is obvious in Fig. 2 that the phase transitions for case $q < 1.0$ and $\mu \leq 1/\langle k \rangle$ and case $q < 1/\langle k \rangle$ and $\mu > 1/\langle k \rangle$ belong to continuous class. While null threshold (exhibit the lack of an epidemic threshold and always show a finite fraction of infected population) occurs if and only if $q > 1/k$ for $\mu > 1/\langle k \rangle$. For continuous transitions, the threshold decrease with increasing $q$, and the fractions of strong edges $\mu$ in the networks. In contrast to the case $q > 1/\langle k \rangle$, the networks with a large number of strong
Fig. 3: The final stationary distributions of removed individuals as a function of $p$ and $\mu$ for $T = 1$, where the final results are respectively obtained from (a) simulations and (b) numerical integration of Eq. (9), combining with Eqs. (7) and (8). The numerically obtained critical values of transmission probability $p$ are illustrated as white inverted triangles to enable a comparison with the solid black line from theoretical prediction based on Eq. (15). The results are obtained by averaging over $N_r = 1000$ independent realizations. Moreover, the light blue solid line gives the critical value of $\mu_c = \frac{(-b + \sqrt{b^2 + 4q\langle k \rangle})}{2q}$, where $b = \langle k^2 \rangle - \langle k \rangle - 1$.

edges actually instead suppress the epidemic spread when $q < \frac{1}{\langle k \rangle}$. Based on above results, there exists a threshold of raised transmission probability $q_{c}^{11} = \frac{1}{\langle k \rangle}$ predicted from the bond percolation [21, 22, 23], beyond which strong edges are considered to be strong enough to facilitate the epidemic spread, by speeding up the transmissions of pathogen along them.

The theoretical value of outbreak threshold for $T = 1$ could be calculated from Eq. (15), so one can make a comparison with the numerical critical value corresponding to the position of susceptibility peak [20]. The analytical threshold by means of edge-based compartmental theory shows a good agreement with the numerically evaluated threshold. The results illustrated in Fig. 2 and Fig. 3 prove that the edge-based compartmental theory provides hence a good tool to portray the dynamics of our model in theory, with a high accuracy.

As expected, Fig. 3 implies that lack of effective treatment or serious disease of totally drug-resistant could facilitate the outbreak of epidemics because individuals are
doomed to be infected if they contact the patients with high frequency and receive the pathogen only once. Fig. 2 shows that the transitions are continuous for $T = 1$, which is further supported by the smooth color bitmap transitions for $\mu < \mu_c$ showed in Fig. 3. As expected, the boundary illustrated in Fig. 3 reveals the favored role of strong edges to outbreaks of epidemic. Besides, both numerical simulations and theoretical analysis manifest the existence of null threshold when there are more than $\frac{N(k)\mu_c}{\mu_c}$ strong edges in the network. This indicates that a small number of infected individuals ($\rho_0$ of the whole population) could still spread the totally drug-resistant epidemic out to capture the whole population, merely relying on few ($\mu_c \simeq 10^{-2}$) strong contacts of the network. On the other hand, continuous transitions reveals that a slow growth of the epidemic activity for increasing spreading rates makes epidemic less threatening, which could leave us enough time to take measures for the treatment and control of these infectious diseases.

4.2. Partial drug-resistant

We further study the situations that epidemic is partial drug-resistant, i.e., $T > 1$. A larger value of $T$ requires the individual to be exposed with more infection from distinct neighbors to affirm the attack ability of the epidemic. The model for $T > 1$ is assumed to describe a society where good medical treatment especially antibiotic therapy is available for the individuals once the epidemic is diagnosed.

![Fig. 4: The final density of removed individuals versus $p$ for three different values of raised infection probability $q$. In detail, $T = 2$ in (a) while $T = 3$ in (b). $\mu = 0.25$ of the total edges are initially set as strong edges while the others are normal ones. The simulation results represented by open markers are obtained by averaging $N_r = 2000$ independent realizations, in comparison with the corresponding solid lines from analytical predictions based on Eq. 9.](image-url)

We firstly present both the simulation results and numerical integration of Eq. 9 in Fig. 4 to investigate how the spread of epidemics depend on the strength of the strong edges (value of $q$) and infection threshold $T$. We find that the edge-based compartmental theory also gives accurate estimates of the size of epidemic spread on ER networks for $T > 1$. Besides, it is found that stronger edges of higher $q$ could impel the outbreak of epidemics to take place, which is in accordance with what we have observed in Fig. 5. Sharp jumps of infection sizes from numerical simulations and theoretical predictions presented in Fig. 4 indicate discontinuous transitions. Furthermore, more
sharp transitions could be observed for higher $T$. The type of transition can be determined by using bifurcation analysis of Eq. (12).

The occurrence of discontinuous transitions with $T > 1$ could be attributed to occurrence of avalanche outbreaks as $p$ is beyond the threshold $T_4$ $T_5$. In the present model, one consider that the spread dynamics of the epidemics start with a small number $\rho_0$ of nodes which have initially received the pathogen and become infected, regardless of the infection threshold $T$. In the following, some of neighbors of these initial seeds, due to the incoming pathogen brought about by enough high infection probability $p \geq p_c$, may receive the pathogen for more than $T$ times; next, these newly fully infected sites also spread pathogen, during the same time step, again to their own neighbors which have received the pathogen below threshold $T$. Although large number of the left nodes are still susceptible, they have received the pathogen for some times; which means that only one or two more arrival of pathogen would trigger more new infections to make all of them infected. In other words, these susceptible nodes are in critical state. The process can go on and lasts until none of the neighbor nodes goes above the infection threshold, thus this avalanche stops; which showing a massive expansion of infection population in the networks. Moreover, in comparison with the case $T = 2$, larger number of susceptible nodes are in critical state for $T = 3$, leading to a more drastic avalanche which indicates a more obvious discontinuous transition (see Fig. 4). Since the susceptible nodes in critical state could be in one of two critical states for $T = 3$: have received the pathogen either once or twice; rather than only one critical state for $T = 2$. Meanwhile thresholds of outbreaks are greatly increased for $T = 3$ (see Fig. 4), owing to the fact that larger infection probability $p$ are needed to drive the pathogen to reach more susceptible areas to make the nodes there be in critical states in the avalanche process. Overall, a necessary condition for discontinuous transitions is an abundance of susceptible nodes in the critical state on the underlying network.

The theoretical value of $p_c$ for $T > 1$ can be calculated from Eqs. (13) and (18), while the numerical critical value can be estimated by identifying the number of iterations (denoted as NOI) at which at least one individual get infected $T_6$ $T_8$. In Fig. 5, it could be observed that the NOI exhibits a peak of maximum value; which shows a remarkable agreement between theory and numerics in terms of the quantities $\rho_R$ and $p_c^l$. This provides further proof of the correctness of analysis based on edge-based compartmental theory. Also, Fig. 5 provides a important evidence both in numerical simulations and in theory about the role of strong contacts in governing spread of epidemics, that is, more strong edges could not only facilitate the outbreaks of epidemics by reducing outbreak threshold but also promote the spread of epidemics (because more strong edges in the networks means higher equivalent infection probability of epidemics). Again, the integration of analytical equations not only predicts the position of the threshold, but also identifies discontinuous types of the transitions.

Fig.6 presents a comprehensive review about the dependence of the infection size on both fractions of strong edges $\mu$ and infection probability $p$ for $T > 1$; containing numerical simulations and theoretical estimations. It could be found that simulation results [see Figs. 6(a) and (b)] and numerical integration [see Figs. 6(c) and (d)] show a good accordance with each other. In the same figure, the thresholds obtained from theoretical predictions are also plotted to make a comparison with numerical estimation of
Fig. 5: (a) The final density of removed individuals versus $p$ for three different values of $\mu$, where both simulation results (open markers) and theoretical predictions (solid lines) are plotted to make a comparison. (b) Simulation results of NOI (number of iterations) as a function of $p$ with three difference values of $\mu$. The raised transmission probability is $q = 1.0$, and $T = 3$. The results are obtained by averaging $N_r = 2000$ independent realizations.

Fig. 6: The final stationary distributions of removed individuals as function of $p$ and $\mu$ for $T = 2$ (a)(c) and $T = 3$ (b)(d), where the final results are respectively obtained from simulations (shown in (a)(b)) and numerical integration of Eqs. 9, 7 and 8, as shown in (c-d). The numerically obtained critical values of transmission probability $p$ through NOI method are illustrated as white inverted triangles to enable a comparison with the solid black (for $T = 2$) or yellow (for $T = 3$) line from theoretical prediction based on Eq. 15. The results are obtained by averaging over $N_r = 1000$ independent realizations. The other parameter are taken as $q = 1.0$ and $\rho_0 = 0.1$. 
Fig. 7: The final density of removed individuals as function of $\rho_0$ for five different values of $p$. In detail, $T = 2$ in (a) while $T = 3$ in (b). $\mu = 0.01$ of the total edges are initially set as strong edges while the others are normal ones. The simulation results represented by open markers are obtained by averaging $N_r = 2000$ independent realizations, in comparison with the corresponding solid lines from theoretical predictions based on Eq. (9). The other parameter is taken as $q = 1.0$.

NOI, revealing a rather satisfactory agreement. As the infection threshold grows from $T = 2$ to $T = 3$, both $\mu_c$ and position of the threshold $p_c$ are greatly increased; however, the nature of the transition remains unchanged. In addition, despite of infection threshold $T$, the emergence of null threshold with $\mu > \mu_c$ tells us that large number of strong contacts in the society could make the prevalence of pathogens critical easy all the time by forming sizable cluster (larger than giant cluster of the network because $\mu_c > \frac{1}{\langle k \rangle}$) which could reach most of the nodes, without help of the transmissions along normal edges. Notice that the dependence of the threshold boundary (indicated by both solid lines and inverted triangles) is another piece of evidence in favor of the understand of what roles strong edges, infection probability and infection threshold play in favoring epidemic diffusion. In detail, compared with $T = 2$ [Figs. 6(a) and (c)], more edges even the majority of total edges (nearly 60%) when $p = 0$, are needed to be strong for $T = 3$ [Figs. 6(b) and (d)] so that the whole population are occupied by the epidemic. This means that high infection threshold $T$ indeed delay the outbreak of epidemics and emergence of null threshold, in contrast with the acceleration of strong edges on the spread of epidemic. This is what is observed in Fig. 6.

4.3. Roles of initial seeds

In this subsection, we turn to elucidating the effect of number of initial seeds on epidemic spread dynamics. We note that the transitions shown in Fig. 7 are discontinuous when infection probability $p$ is large enough. Furthermore, Fig. 7 displays a degree of independence of infection sizes on number of initial seeds as $\rho_0 \geq 0.1$. Since only 0.01 of total edges are assumed to be normal ones in Fig. 7. By combing with the illustration in Fig. 5, we can deduce that the outbreaks and prevalence of epidemics are more relatively independent of the number of initial seeds as $\rho_0$ getting larger than 0.1 for higher fractions of strong edges. This is why we adopt $\rho_0 = 0.1$ throughout this paper. It is also interesting that the epidemic does not spread out immediately even if the individuals would inevitably received the pathogen on condition that their neighbors get infected, i.e., $p = 1.0$. The reason for this is that one susceptible individual
would probably get infected only when more than one neighbors are in the infected state. This is to say there exists a critical value of $\rho_0$ above which initial seeds could promote the outbreak of epidemics.

5. Conclusion

In this paper we have proposed a biologic spread model considering not only drug resistance curved by infection threshold $T$, but also heterogeneous contributions of connections by simply classing the edges of the networks into two classes: normal edges and strong ones. Then we have performed both numerical simulations and theoretical analysis employing edge-based compartmental theory to deeply investigate the system behaviors. In detail, we have firstly explored the spread dynamics of our model for $T = 1$. Furthermore, we deduce the kinetic equations to curve the spread dynamics to allow us to give a precise prediction of final infection size. By means of edge-based compartmental theory, we also have obtained the expressions for the threshold of continuous transitions, revealing a good agreement with the numerical estimations. Overall, both simulations and theoretical analysis show two main results: (1) for $\mu < \mu_c$, the system gives a evidence for a continuous transition which is vulnerable to the possibility of outbreaks (low threshold); (2) while abundant strong edges themselves could promote the outbreaks and prevalence of epidemics, i.e., null threshold begin to emerge as $\mu > \mu_c$. Overall, the results for $T = 1$ suggest that the populations are vulnerable to the epidemics with total resistance. Whereas continuous transition indicates a slow growth of the epidemic activity that makes epidemic less threatening, leaving us enough time to take measures for the treatment and control of epidemic.

In the following we extend our study to the situations of $T > 1$ to map the spread of epidemic with partial drug resistance. By means of edge-based compartmental theory, we have further developed a method to find the positions of thresholds for discontinuous transitions, as well as an exact expression for the epidemic threshold. Both numerical simulations and analytical predictions show that the infection size depends on the fractions of strong edges of network $\mu$, the strength of strong edges $q$ and infection threshold $T$. The thresholds obtained from theoretical approach are found be in good accordance with numerical estimations of NOI. Differing from the case $T = 1$, we find a confirmation that the discontinuous transition occurs when sufficient initial infected nodes are seeded in the network and the strength of strong contacts is high enough, but at a more larger threshold. Meanwhile we have given the interpretation about the origin of the discontinuous epidemic transition occurring in this kind of system for large $T$, that is occurrence of avalanche outbreak [24, 25] brought about by large number of susceptible individuals in critical state. Taken together with the results from agent-based simulations and the theoretical predictions, we have concluded that both the strength of strong contacts $q$ and the fractions of strong edges $\mu$ play important positive roles in promoting the outbreak and prevalence of epidemics with drug resistance. Nevertheless higher $T$ corresponding to sophisticated antibiotic resources or more simply accessible specific medicines actually hinder or delay the coming of epidemic prevalence; but that if the strong contacts are not abundant enough the true, inhibiting effect of the $T$ becomes evident.
It is also worth noticing that our theoretical model does not take more realistic complex mechanisms such as dynamic changes of infection threshold, individual variation in resisting different epidemics owning drug resistance into account. Also, the correlation between strong contacts and drug resistance has not been considered in the model because of lack of empirical data. However, these findings of our study lead directly to two important suggestions for a logical treatment of epidemics: (1) imposing contact restrictions on connections especially strong contacts to inhibit the spread such as the shutdown of individual connections or isolation of cities, which has gained wide acceptance \cite{27, 28, 29}; (2) keeping persistent development of new wonder medicines or new therapies (such as medicine cocktail therapy) to sustain high values of infection threshold $T$. Of course, sustainable research inputs for the development are indispensable.

What is more important this study has revealed is that, despite of enough and good medical resources to enable members of developed society repel the epidemics more than one time, sharp massive outbreaks of epidemics resulting from drug resistences mutations seems to be still a possible serious threat. Even worse, economic recession in developed regions would greatly aggravate contagion of epidemics which have developed partial or even complete resistance to antibiotics; leaving people in a more dangerous situation.

Drug resistance and contact connections are two very important ingredients for biological spreading processes. The investigation of epidemic diffusion with the two mechanisms in general complex contagion situations remains a very important and interesting avenue for future research activity. Our approach may be considered a basic reference framework for the further description and exploration of epidemics spread with other ingredients, in addition to drug resistance and heterogeneous contacts.

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