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2013 EPL 104 50001

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Outbreaks of coinfections: The critical role of cooperativity

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received 15 November 2013; accepted 30 November 2013

published online 16 December 2013

PACS 05.45.Xt – Synchronization; coupled oscillators

PACS 89.75.Hc – Networks and genealogical trees

PACS 87.23.Cc – Population dynamics and ecological pattern formation

Abstract – Modeling epidemic dynamics plays an important role in studying how diseases spread, predicting their future course, and designing strategies to control them. In this letter, we introduce a model of SIR (susceptible-infected-removed) type which explicitly incorporates the effect of *cooperative coinfection*. More precisely, each individual can get infected by two different diseases, and an individual already infected with one disease has an increased probability to get infected by the other. Depending on the amount of this increase, we prove different threshold scenarios. Apart from the standard continuous phase transition for single-disease outbreaks, we observe continuous transitions where both diseases must coexist, but also discontinuous transitions are observed, where a finite fraction of the population is already affected by both diseases at the threshold. All our results are obtained in a mean-field model using rate equations, but we argue that they should hold also in more general frameworks.

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Introduction. – From the Plague of Athens to the 14th century Black Death, the 1918–1919 Spanish flu, and to the recent HIV pandemic, infectious diseases have caused more deaths than any other factor, such as wars or famines [1]. Mathematical models are thus extremely important for understanding the outbreak and subsequent dynamics of epidemics [2,3]. Such models have been studied in particular by statistical physicists, who relied on the notion of *universality* in critical phenomena to describe valid features of real epidemics in terms of highly idealized and simplified models.

A pioneering work in this direction was carried out by Kermack and McKendrick [4], who introduced in 1927 the “susceptible-infective-removed” (SIR) model, in which each individual can be in one of three states (or “compartments”) S, I, and R. Infected individuals are “removed” (*i.e.*, recover or die) with fixed rate, while susceptible ones can get infected with a rate that is proportional to the fraction of infecteds. “Removed” individuals, finally, stay as they are and do not take part any more in the dynamics.

When treating this on a spatial grid with nearest-neighbor infection, starting with all sites being susceptible except for one infected would lead to a percolation cluster of removed sites [5,6]. As the infection rate passes through the percolation threshold, the average relative cluster size increases gradually from zero, implying that the onset of the epidemic is a continuous or “second-order” phase transition. In the mean-field treatment of [4], basically the same is true: an infinitesimal fraction of initially infected individuals will have no effect if the process is subcritical, while it leads to a finite fraction of removed individuals if the threshold is passed. This fraction is zero at threshold and increases continuously above it.

In recent years such models of epidemic spreading have been much studied on networks [7,8]. Also, there was much interest in mechanisms that might lead to discontinuous phase transitions where the epidemic involves a finite fraction of the epidemic already at threshold. Models that show (or were claimed to show) that the latter include “explosive percolation” [9], the Dodds-Watts model for cooperative complex contagion [10] (see also [11–13]), cascades on interdependent networks [14–16], models with long-range infection [17,18], and models with structured immunity [19].

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Surprisingly little work was, however, devoted in the statistical physics literature to the dynamics of multiple diseases. The competition between epidemics that are mutually exclusive or antagonistic was studied in [20–23]. But much more interesting is the case of *cooperative* multiple diseases, where the presence of one disease makes the other(s) more likely to spread. Such “syndemics” [24] or “coinfections” are well documented in the epidemiological literature. Cases include the increased incidence of tuberculosis during the 1918–1919 Spanish flu [25,26] and the fact that persons infected by HIV have a higher risk to be infected by other pathogens, including hepatitis B and C [27], TB [28] and malaria [29].

In such cases, as in other cases of positive feedback, one can expect much more violent outbreaks. Indeed, cooperative coinfections have been studied in the mathematics literature [29–31]. In [29] the case of HIV and malaria was modeled by a compartmental model in terms of ODEs similar to eq. (1), but the intention there was to describe the syndemic as realistic as possible, introducing a large number of parameters and disregarding any phase transitions. Recently [32], a model more in spirit of the present paper was proposed (albeit with completely different formalism). But it deals only with strongly asymmetric cases where only one of the diseases can influence the other, while we are mostly interested in symmetrical cases with mutual cooperativity, where more interesting phenomena are expected. Closest in spirit to the present work are [30,31]. There it was shown, by using also ODEs similar to eq. (1), that cooperativity can lead to “backward bifurcations”, which are just first-order mean-field transitions in physics jargon.

In the present letter, we propose what we believe to be the simplest SIR-type model with two diseases (called A and B) that leads to first-order transitions. In this model, the infection rate for disease A is increased, if the individual has or had disease B and vice versa. When recovering from disease A , say, an individual is “removed” from the population that is susceptible to A , but it still can be infected by B . We shall only treat this model in mean-field approximation (described by rate equations similar to those in [4]). Moreover, we shall mostly deal only with a very special case where there is symmetry between A and B , and where present and past infections by B have the same effect on the infection by A . In spite of these limitations we find a surprisingly rich behavior with two novel outbreak mechanisms, one continuous and the other discontinuous.

Model. – Consider a population of fixed size, where every individual can be in one of three possible states—susceptible, infective, and recovered/removed—with respect to each of the two diseases, called A and B in the following. This gives nine possible states for each individual, denoted by $S, A, B, AB, a, b, aB, Ab$ and ab . Here capital letters refer to actual infections, while lower-case letters refer to previous infections. Thus, *e.g.*, a person in

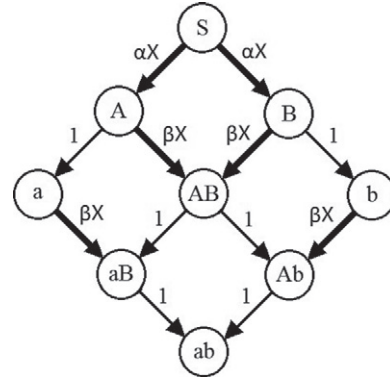


Fig. 1: Flow chart in two-disease coinfection with A, B symmetry and restrictions on the infection rates as discussed in the text. Capital letters A and B represent infective states, lower-case letters a and b stand for “recovered” ones. Infecting neighbors are not indicated explicitly, but it is assumed that all individuals infected with disease A , say, have the same chances to pass A on to another individual. Thus, every infection process occurs with a rate proportional to the fraction X of the population having the corresponding disease.

state aB has recovered from (and is thus immune to) disease A , but has presently disease B . Single letters refer to states where the person is still susceptible with respect to the other disease. We assume a well-mixed population with normal first-order “chemical” kinetics. Designing the nine states by an index $i = 0, \dots, 8$ and by x_i the corresponding fraction (with $\sum_{i=0}^8 x_i = 1$), the dynamics can thus be written as

$$\frac{dx_i}{dt} = \sum_j \mu_{ij}(x_j - x_i) + \sum_{jk} \nu_{ijk} x_k (x_j - x_i), \quad (1)$$

where μ_{ij} is the rate with which state i recovers spontaneously to state j and ν_{ijk} is the rate for i to change into j due to infection by k .

In the following we shall make several simplifying assumptions:

- 1) Diseases A and B have the same infection and recovery rates, and also the initial conditions are symmetric under the exchange $A \leftrightarrow B$.
- 2) All infected states have the same recovery rate, which we set equal to one; state AB cannot go directly to ab , but must first go to aB or Ab .
- 3) Infection rates for disease A , say, depend only on the fact whether the target has (or has had) B or not, but are independent of whether the infector has (had) B or not. Thus, we have only two different infection rates: Rate α for a target that is still susceptible for both diseases, and rate β for targets which have or have had the other disease.

Thus, we end up with the flow pattern depicted in fig. 1. At the end of the paper we shall briefly discuss more general cases where some of these restrictions are released.

Due to assumptions 1) and 3), all bilinear terms in eq. (1) are proportional to the fraction

$$X = [A] + [AB] + [Ab] = [B] + [AB] + [aB] \quad (2)$$

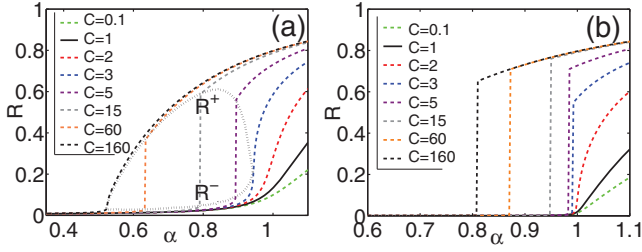


Fig. 2: (Color online) Order parameter $R = 1 - S_\infty$ plotted against α for (a) $\epsilon = 0.005$ and (b) $\epsilon = 10^{-4}$. Each curve corresponds to a different level of cooperativity C . The dotted lines in panel (a) indicate the upper and lower limits R^+ and R^- of the jumps at the first-order transitions.

in the population that has the corresponding disease. Defining in addition

$$S = [S] \quad \text{and} \quad P = [A] + [a] = [B] + [b], \quad (3)$$

eq. (1) can be rewritten as

$$\begin{aligned} \dot{S} &= -2\alpha SX, \\ \dot{P} &= (\alpha S - \beta P)X, \\ \dot{X} &= (\alpha S + \beta P)X - X. \end{aligned} \quad (4)$$

Thus, we have been able to reduce our model to three ODEs with two control parameters α, β . The *cooperativity* is defined as the ratio $C = \beta/\alpha$. In particular, we are interested in the $t \rightarrow \infty$ limit of solutions of eq. (4) with initial conditions $S_0 = 1 - \epsilon$ and $X_0 = P_0 = \epsilon/2$. This corresponds to an initial population where most of the individuals (except for a small fraction ϵ) are susceptible to both diseases, while the rest has either A or B . Including in the initial state also recovered individuals or individuals with both diseases would not give more insight. For $t \rightarrow \infty$ all activity has to die out, whence $X_\infty = 0$. Our “order parameter” is the asymptotic fraction $R = 1 - S_\infty$ of the population that has had at least one of the two diseases. We expect interesting phenomena when $C > 1$, since only then X can have an intermediate growth phase even when the single-disease infection rate α is smaller than 1. For $C = 1$ the two diseases evolve independently, and for $0 < C < 1$ we expect only minor modifications of the threshold behavior from independence.

Numerical results. – In fig. 2, we show results obtained by integrating eqs. (4) numerically. We see the following main features:

a) For $C < 2$ and $\epsilon \rightarrow 0$ there can be epidemic outbreaks only when $\alpha > 1$, corresponding to the well-known behavior of the single-disease SIR model. For $\alpha \approx 1$, the order parameter grows linearly with α , $R \sim \alpha - 1$, showing that the transition is continuous with order parameter exponent 1. For $\epsilon > 0$ the transition is rounded.

b) When $C = 2$ the transition is still continuous with threshold $\alpha^* = 1$ (in the limit $\epsilon \rightarrow 0$), but now the order parameter exponent is $1/2$.

c) For $C > 2$ we observe first-order transitions, when $1/2 < \alpha < 1$. These transitions are sharp, even when $\epsilon > 0$. On the other hand, when $\epsilon \rightarrow 0$ these transitions occur for fixed C at values $\alpha^*(C, \epsilon)$ that increase as $\epsilon \rightarrow 0$,

$$\lim_{\epsilon \rightarrow 0} \alpha^*(C, \epsilon) = 1 \quad (5)$$

for any finite C .

The behavior expressed in eq. (5) and illustrated in fig. 2(b) is an artifact of our mean-field approximation. Due to the latter, the cluster of infected neighbors created by a sick individual is immediately dispersed in the entire population, reducing thereby the chances for multiple infections. In any local model (*i.e.* on a regular lattice) we would expect that this cluster stays localized for long time, so that even an infinitesimal fraction of infective “seeds” could lead to a large epidemic.

d) Let us denote by $R^-(\alpha^*, C, \epsilon)$ and $R^+(\alpha^*, C, \epsilon)$ the lower and upper values of the jumps at the first-order transitions. When α^* decreases to $1/2$, they meet at $R^\pm(1/2, C, \epsilon) = 0$. When it increases, they both increase at first with α^* . Later they meet, for all finite $\epsilon > 0$, at nontrivial values $\alpha_c(\epsilon) < 1$ and $R_c(\epsilon) \in (0, 1)$. At these points the transition is continuous, with the order parameter exponent equal to $1/2$.

e) No epidemics are possible (for small ϵ) when $\alpha < 1/2$, as also predicted analytically by the theory discussed below.

f) As long as $\alpha^* < \alpha < 1$, the values of R are independent of ϵ within numerical accuracy, but depend weakly on C . All values of R are below the limit curve

$$R^+(\alpha) = \lim_{\epsilon \rightarrow 0} \lim_{C \rightarrow \infty} R(\alpha, C, \epsilon) \quad (6)$$

which scales as $R^+(\alpha) \sim \alpha - 1/2$ for $\alpha \searrow 1/2$.

Time dependence and theoretical explanations.

– In order to better understand the dynamics, we first define $Y(t) = \alpha S(t) + \beta P(t)$, whose time dependence is

$$\dot{Y} = [(\beta - 2\alpha)\alpha S - \beta^2 P]X \quad (7)$$

$$= [2(\beta - \alpha)\alpha S - \beta Y]X \quad (8)$$

According to eq. (4), $\dot{X} = (Y - 1)X$. Therefore, $X(t)$ can only grow when $Y(t) > 1$. But, due to eq. (7), Y can grow for small ϵ only iff $\beta > 2\alpha$. This explains immediately why normal SIR threshold behavior is seen if and only if $C < 2$. Assume now that $\alpha < 1$ and that C is sufficiently large so that $(\beta - 2\alpha)\alpha > 1$. Then Y will start to grow for sufficiently small ϵ . If it grows to a value 1, there will be an outbreak. This might be prevented by two mechanisms: Either S decreases so fast and Y increases so fast that the first factor on the r.h.s. of eq. (8) becomes zero, or X —the second factor in eq. (8)— vanishes. As we shall see, these two alternatives give rise to first- and second-order phase transitions.

To proceed we use the exact inequality $\alpha S \leq Y$ in order to eliminate S from eq. (8), and obtain for small times (as

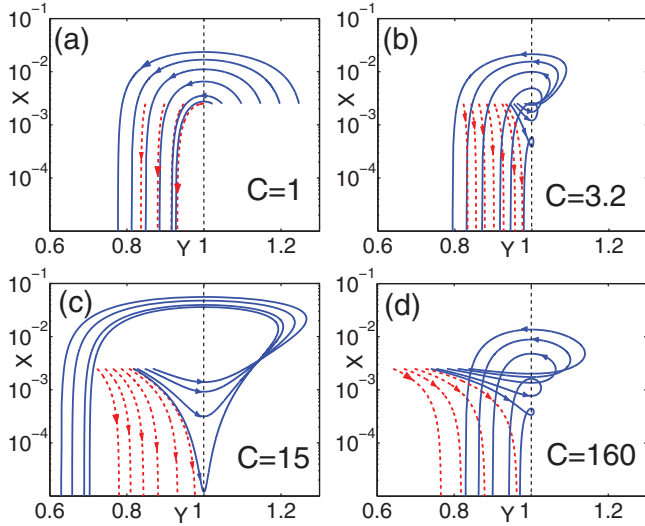


Fig. 3: (Color online) Phase portraits of near-critical trajectories obtained by plotting $X(t)$ against $Y(t)$, for four different levels of cooperativities. The initial conditions are the same as in fig. 2(a). Blue solid lines indicate the cases with epidemic outbreaks (supercritical), in contrast to red dashed lines (subcritical). The latter never cross the threshold $Y = 1$ (black dashed lines). Within each panel, different trajectories correspond to different infection rates α .

long as $Y < 1$)

$$\frac{1-Y}{Y} \dot{Y} \leq -(\beta - 2\alpha) \dot{X}. \quad (9)$$

This can be integrated to give an upper bound $X_+(Y)$ on X that decreases monotonically with Y . If $X_+(Y = 1) < 0$, we know that there cannot be an outbreak. If $X_+(Y = 1) > w$, where w is a positive constant independent of ϵ , we must have a first-order phase transition for sufficiently small ϵ (where the inequality becomes practically tight), provided $\dot{Y} > 0$ when $Y = 1$. Finally, if $X_+(Y = 1) \geq 0$ but $\dot{Y} = 0$ when $Y = 1$, we have a second-order transition.

These cases are illustrated in fig. 3. In each panel of this figure, we show trajectories of the flow by plotting $X(t)$ against $Y(t)$. Panel (a) shows a standard SIR transition where the critical point corresponds to $\alpha = 1$ and Y decreases monotonically. Panel (c) shows the generic case of strong cooperativity, where Y increases beyond $Y = 1$, provided that X does go to zero before. If Y passes through $Y = 1$, it continues to $Y \gg 1$ (even close to the transition point), indicating a first-order transition. Panels (b) and (d) show cases where Y goes only infinitesimally beyond $Y = 1$ at the transition point, corresponding to second-order transitions. Panel (d) shows the case of ultra-strong cooperativity, corresponding to the uppermost curve in fig. 2(a), where $\alpha^* = 1/2$. Panel (b), finally, corresponds to the special case of moderately weak cooperativity where $R^-(\alpha^*, C, \epsilon) = R^+(\alpha^*, C, \epsilon)$, so that the jump height in fig. 2 just vanishes.

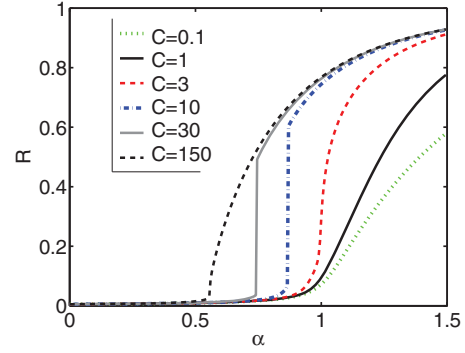


Fig. 4: (Color online) Order parameter R plot for a general case where both diseases have different infection rates, and where also the chances for getting infected depend on whether the target still has the other disease or has already recovered from it. More specifically we used initial conditions $[S] = 0.995$, $[A] = 0.002$, $[B] = 0.003$, with infection rates α for $S \rightarrow A$; $\alpha' = 0.9\alpha$ for $S \rightarrow B$; $\beta = C\alpha$ for $A \rightarrow AB$; $\beta' = 2C\alpha'$ for $B \rightarrow AB$; $\gamma = 0.7\beta$ for $a \rightarrow aB$; and $\gamma' = 0.8\beta'$ for $b \rightarrow Ab$.

Up to now we have dealt with the special case with perfect symmetry between the two diseases, and where the infection rate increase due to cooperativity is the same for targets that are still infected and those which have already recovered from the other disease. In more general cases, where all parameters in eq. (1) are different, we cannot give similarly detailed mathematical results, but we still can make numerical simulations. We have found similar behaviors in all cases. One such case is shown in fig. 4. There we still assume that all recovery rates are equal, but all other symmetry restrictions are removed. We see the same type of phase transitions as in fig. 2. We thus conjecture that the behavior discussed above is indeed robust and prevails also in more general cases.

Conclusions. – As we have shown, the cooperativity of coinfections can not only decrease the thresholds for epidemic outbreaks, but it can also change the outbreak from continuous (“second order”) to discontinuous (“first order”). This may pose a much more serious problem in real situations. In second-order transitions the size of the epidemic grows gradually as conditions become more favorable for an outbreak, and one has precursors which may be used to initiate countermeasures. In a first-order transition such precursors are absent, and the epidemic develops immediately its full size, once the threshold has been overcome, leaving much less time to react. Intuitively, the discontinuity of the phase transitions results from the fact that the “basic reproduction ratio” [2,19] (which applies to infinitesimally small initial epidemic seeds) is smaller than the reproduction ratio that applies when the fraction of infecteds is finite.

Our results were only obtained in a very crude mean-field treatment, and moreover our analytical results dealt only with very special cases. But we checked numerically that they were robust in a wider setting, and we conjecture

that similar phenomena are seen when more sophisticated mathematical modeling is used, such as spreading of the epidemics on spatial grids or methods similar to belief propagation on (locally) loopless networks [7,12,16]. Obviously much more work has to be done, and the present letter should be seen only as a first small step towards mathematically modeling more general and realistic situations.

In preliminary studies of a stochastic version [33] we found no first-order transitions on regular d -dimensional lattices in $d = 2$ and $d = 3$, if infections are local (between nearest or next-nearest neighbors), but they do occur in $d = 4$. They also occur in $d = 2$, if infection can happen with probability $P(\mathbf{x})$ between nodes that are a distance \mathbf{x} apart, provided $P(\mathbf{x}) \sim |\mathbf{x}|^{-d-\sigma}$ for large \mathbf{x} with small enough σ . As expected, we found first-order transitions also in Erdős-Rényi (ER) and small-world networks. In all these cases, we assumed that both diseases spread on the same set of links. If we had used two independent networks, spreading on ER networks would have been identical to mean field. It is only the assumption that both diseases use the same network which makes spreading on ER networks different from mean field, and which allows epidemics in the first-order regime to spread already from infinitesimal seeds.

Finally, we should point out that cooperative coinfections are not only important for epidemiology in the narrow sense, but also for the spreading of computer malware, rumors, fashions, innovations, political opinions [34] or social unrest [35].

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