On the role of reinfection in the transmission of infectious diseases

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Abstract. *We introduce a spatial stochastic model for the spread of tuberculosis. After a primary infection an individual may become sick (and infectious) through an endogenous reinfection or through an exogenous reinfection. We show that even in the absence of endogenous reinfection an epidemic is possible if the exogenous reinfection parameter is high enough. This is in sharp contrast with what happens for a mean field model introduced by Feng et al. (2001).*

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1. Introduction. Tuberculosis is usually acquired through airborne infection from someone with active TB. After a primary infection, a small proportion of infected individuals develop active TB but most die without ever developing active TB, see for instance Enarson and Rouillon (1998). In the medical literature there is still a debate on whether developing active TB is exclusively a consequence of a primary infection or whether it may come from re-exposure to TB through individuals with active TB, see Styblo (1991), Ziegler et al. (1985) and McMurray et al. (1989). This question is especially important for some parts of the world (in particular South-East Asia) where at least 50% of individuals have had a primary infection and there is bound to have many contacts between individuals with active and individuals with dormant TB, see Dye et al. (1999).

In this paper we will analyze mathematical models with two types of reinfection. The first type is a reactivation of a dormant infection and is called an endogenous reinfection. The second type of reinfection is acquired from another individual and is called an exogenous reinfection. Both reinfections are assumed to make an individual with dormant TB develop active TB. Our aim is to examine the relative importance of the two types of reinfection in the spread of an infectious disease such as TB. We introduce a spatial stochastic model for which we show that even with no endogenous reinfection (in that case the only route to active TB is a primary infection followed by an exogenous reinfection) the infectious disease may spread provided the exogenous reinfection parameter is large enough. In contrast, following Feng et al. (2001), we show that for a mean field model (corresponding to our spatial stochastic model) with no endogenous reinfection the infectious disease cannot spread.

Our results seem interesting in at least two ways. By introducing a spatial stochastic model one sees that (at least in theory) exogenous reinfection may be crucial in the spread of an infectious disease. It is also interesting to note that this is one of the few cases for which a spatial stochastic model and its corresponding mean field model behave strikingly differently.

2. A spatial stochastic model. We consider a continuous time spatial stochastic model on $\mathbf{Z}^d$ where each site may be in one of three states: 0, 1 or 2. There is always exactly one individual at each site. If the individual at site x is healthy then we say that site x is in state 0, if the individual at x is infected but not infectious we say that site x is in state 1, if the individual at x is infected and infectious then site x is said to be in state 2. In the case of tuberculosis it is thought that the vast majority of the people infected (in state 1) die without developping the disease so they never get to state 2.

If the model is in configuration η, let $n_1(x,\eta)$ and $n_2(x,\eta)$ be the number of nearest neighbors of x (among the $2d$ nearest neighbors of x) that are in state 1 and in state 2, respectively. Assume that the model is in configuration η, then the state at a given site x

evolves as follows:

$$0 \to 1 \text{ at rate } \lambda_0 n_2(x,\eta)$$

$$1 \to 2 \text{ at rate } \gamma + \lambda_1 n_2(x,\eta)$$

$$1 \to 0 \text{ at rate } 1$$

$$2 \to 0 \text{ at rate } \delta$$

In words, infectious individuals infect nearest neighbors that are healthy at rate λ_0. Infected individuals that are not infectious may become infectious by two different routes: by an endogenous reinfection at rate γ and by an exogenous reinfection caused by an infectious nearest neighbor at rate λ_1. Infected individuals that are not infectious die at rate 1 and infectious individuals die at rate $\delta \geq 1$.

The model above is related to the contact process for which there are only two possible states, say 0 and 1, and that evolves according to

$$0 \to 1 \text{ at rate } \lambda n_1(x,\eta)$$

$$1 \to 0 \text{ at rate } 1$$

It is known that there is a critical value λ_c such that if $\lambda \leq \lambda_c$ then starting with any initial configuration the 1's die out while if $\lambda > \lambda_c$ then, for any configuration having 1's, there is a positive probability that there will always be 1's. For more on the contact process, see for instance Liggett (1999).

We also note that the special case $\lambda_1 = 0$ (no exogenous reinfection) was examined by Krone (1999).

We say that an epidemic is possible if starting with a single infectious individual there is a positive probability that there will be infectious individuals at all times. We are now ready to state our results.

Theorem. *We consider the spatial stochastic model on $\mathbf{Z}^d$ for any $d \geq 1$.*

(a) If $\lambda_0 \leq \lambda_c$ (the critical value of the contact process) then no epidemic may take place for any γ, λ_1 in $[0,\infty)$ and $\delta \geq 1$.

(b) If $\lambda_0 > \delta\lambda_c$ and $\delta \geq 1$, for any $\gamma \geq 0$ there is a positive probability for an epidemic provided λ_1 is large enough.

(c) There is $c > 0$ such that if $\gamma + \lambda_1 < c$ then no epidemic can take place for any λ_0.

Not surprisingly, Theorem (a) states that it is enough to control primary infections in order to avoid an epidemic. More interestingly, Theorem (b) tells us that even with no endogenous reinfection (i.e. $\gamma = 0$) an epidemic is possible provided the exogenous reinfection parameter is high enough. Finally, we see that if both reinfection parameters are below a certain threshold then no epidemic may take place even for very high primary infection rates. We will see that Theorem (b) and (c) are not true for the mean field model corresponding to our spatial stochastic model.

3. The mean field equations. Let $u_i \geq 0$ be the density of individuals in state i, for $i = 0, 1, 2$, in particular $u_0 + u_1 + u_2 = 1$. Assuming total mixing of the population we get the following system of differential equations.

$$u_1' = \lambda_0 u_0 u_2 - \gamma u_1 - \lambda_1 u_1 u_2 - u_1$$

$$u_2' = \lambda_1 u_1 u_2 + \gamma u_1 - \delta u_2$$

Note that $(u_1, u_2) = (0, 0)$ is the disease free equilibrium. The equilibrium (0,0) is said to be stable if for every neighborhood U of (0,0) there is a neighborhood $U_1 \subset U$ of (0,0) such that every solution $(u_1(t), u_2(t))$ with $(u_1(0), u_2(0))$ in U_1 is defined and in U for all $t > 0$, see for instance 9.2 in Hirsch and Smale (1974). For this model, we will say that an epidemic is possible if $(0, 0)$ is not stable. Note that this is analogous to our definition of an epidemic for the spatial stochastic model, in both cases we say that an epidemic is possible if starting close to the disease free equilibrium the disease may grow.

We now investigate the stability of the disease free equilibrium. The Jacobian at (0,0) is

$$\begin{pmatrix} -\gamma - 1 & \lambda_0 \\ \gamma & -\delta \end{pmatrix}$$

By looking at the determinant and the trace of this matrix, one sees that it has at most one positive eigenvalue. The Jacobian has exactly one positive eigenvalue if and only if its determinant is negative. That is, if and only if

$$\lambda_0 \gamma > \delta(\gamma + 1) \tag{3.1}$$

The condition above is necessary and sufficient for an epidemic to be possible (see the Theorems p 181 and p 187 in Hirsh and Smale (1974)).

We now point to two properties of the mean field model that are not true for the spatial stochastic model. Condition (3.1) cannot be met if $\gamma = 0$. That is, for the mean field model, if there is no endogenous reinfection then no epidemic is possible. In contrast Theorem (b) shows that an epidemic is possible for the spatial stochastic model even if $\gamma = 0$. Another difference with the spatial stochastic model is that even if γ is arbirarily low (but strictly positive) it is possible to pick λ_0 large enough so that (3.1) is met and an epidemic is possible for the mean field model. Theorem (c) shows that if $\gamma + \lambda_1$ is below a certain threshold then no epidemic is possible for the spatial stochastic model even for arbitrarily large λ_0.

4. Discussion. Our Theorem (b) shows that even if γ is 0 then if λ_1 is large enough an epidemic is possible for the spatial stochastic model. In contrast if $\gamma = 0$ then no epidemic may take place in the mean field model. Thus, the exogenous reinfection parameter λ_1 may be crucial for the appearance of an epidemic in the spatial stochastic model while λ_1 does not even appear in condition (3.1). However, Feng et al. (2000) show for a mean field model similar to ours the existence of a non trivial equilibrium when (3.1) does not hold but λ_1 is large enough. Therefore, in the mean field model the exogenous parameter λ_1 is not relevant to the start of an epidemic but may be important in maintaining an epidemic.

We will now explain the difference in behavior between the two models by an intuitive argument. Assume $\gamma = 0$ and start the mean field model with a very low density of 2's and a high density of 0's (no 1's). Then the 2's are going to infect 0's and 1's are going to appear. Because of the constant mixing of the population in this model the 1's and 2's are likely to be separated and the 2's are not going to be able to reinfect the 1's. So the infected individuals are going to disappear. Our intuitive scenario is confirmed mathematically by the fact that if $\gamma = 0$

$$u_2' = \lambda_1 u_1 u_2 - \delta u_2.$$

For u_1 and u_2 small $\lambda_1 u_1 u_2$ is of smaller order than $-\delta u_2$ and the 2's die out.

In contrast to what happens for the mean field model there is little mixing in the population for the spatial stochastic model. If we put a 2 in a sea of 0's then the 2 will infect its neighbors. These neighbors are now 1's and if the exogenous reinfection rate λ_1

is large then it is likely that the 2 will reinfect its neighbors before dying. The neighbors of the original 2 are now 2's as well and the infection is spreading. We believe that our results hold for spatial stochastic models with finite range interaction. We have dealt here with nearest neighbor interaction only because it is simpler to analyze mathematically.

The introduction of a spatial stochastic model has shown that (at least in theory) exogenous reinfection may be as important as endogenous reinfection in order to start an epidemic. Our results also illustrate the fact that mean field models do not always capture the whole picture. There are other examples in the mathematical biology literature of difference in qualitative behavior between mean field and low dimensional spatial models. See for instance Mollison (1977) and Schinazi (2000). However, note that in this paper we see a difference in behavior between a spatial model and the corresponding mean field model in all dimensions.

5. Proof of the Theorem We start by giving the graphical construction of our spatial stochastic process. Consider a collection of independent Poisson processes $\{N_0^{x,y}, N_1^{x,y}$,- $D_x : x, y \in Z^d, ||x-y|| = 1\}$. For x and y in Z^d such that $||x-y|| = 1$ let the intensities of $N_0^{x,y}$, $N_1^{x,y}$ and D_x be λ_0, λ_1 and δ respectively. The graphical construction takes place in the space-time region $Z^d \times (0, \infty)$. At each arrival time t of $N_0^{x,y}$ if there is a 2 in x and a 0 in y we replace the 0 in y by a 1. At each arrival time t of $N_1^{x,y}$ if there is a 2 in x and a 1 in y we replace the 1 in y by a 2. At each arrival time of D_x if there is 2 at x we replace it by a 0, if there is a 1 at x we replace it by a 0 with probability $\frac{1}{\delta}$ (with probability $1 - 1/\delta$ we leave the 1 alone). In this way we construct a version of our spatial stochastic process. The process *restricted* to a space-time region $\mathcal{A}$ is constructed by using only the arrival times inside $\mathcal{A}$. For more on graphical constructions, see for instance Liggett (1999).

Proof of (a)

Consider the contact process ξ_t that evolves according to the following rules:

$$0 \to 2 \text{ at rate } \lambda_0 n_2(x, \xi)$$

$$2 \to 0 \text{ at rate } 1$$

We construct the tuberculosis model η_t and the contact process ξ_t simultaneously by using the Poisson processes defined above. The rules for η_t have been defined above. For ξ_t we

use the following two rules. At each arrival time of $N_0^{x,y}$ if there is a 2 in x and a 0 in y we replace the 0 in y by a 2. At each arrival time of D_x if there is 2 at x we replace it by a 0 with probability $\frac{1}{\delta}$. We start ξ_t and η_t with the same initial configuration: a 2 at the origin of Z^d and 0's everywhere else. We claim that at every time t if there is 2 or a 1 at a certain site for η_t then there is a 2 at the same site for ξ_t. In order to check our claim it is enough to check that no transition in the graphical construction can make appear a 1 or a 2 for η_t without making appear a 2 for ξ_t. This is due to the fact that a 2 for the process ξ_t gives birth to a 2 while a 2 for the process η_t gives birth first to a 1 (which is not infectious). Note also that that death rates are higher for 2's in η_t than they are for 2's in ξ_t since $\delta \geq 1$.

Under the assumption $\lambda_0 \leq \lambda_c$ the 2's in ξ_t die out. Thanks to our coupling above the 2's in η_t must die out as well. This completes the proof of (a).

Proof of (b)

We write this proof in $d = 2$, the same ideas work in any $d \geq 1$. We compare our spatial stochastic model to a simple oriented percolation model. Let e_1 be the vector $(1, 0)$ and

$$\mathcal{L} = \{(m, n) \in \mathbf{Z}^2 : m + n \text{ is even}\}$$

$$B = (-4L, 4L)^2 \times [0, T] \qquad B_{m,n} = (2mLe_1, nT) + B$$

$$I = [-L, L]^2 \qquad I_m = 2mLe_1 + I$$

$$C = [-k, k]^2$$

where L and T are parameters to be chosen later and k is the largest integer smaller than $\sqrt{L}$. We declare $(m, n) \in \mathcal{L}$ wet if, for all possible time nT configurations such that there is a translate of C in I_m that is full of 2's, the spatial stochastic process restricted to $B_{m,n}$ is such that there is a translate of C in I_{m-1} and a translate of C in I_{m+1} that are both full of 2's at time $(n + 1)T$. In other words, we declare (m, n) wet if any square of side $2k + 1$ full of 2's in I_m at time nT is reproduced at time $(n + 1)T$ in both I_{m-1} and I_{m+1}. We will now show that by choosing L and T sufficiently large the probability of a site (m, n) being wet can be made arbitrarily close to 1. By translation invariance, it is enough to

show this for the site (0,0). We start by setting $\lambda_1 = \infty$ in the box B. Note that if the initial configuration η_0 has no 1's then 1's do not appear at a further time in the box B. In fact, with such an initial configuration, the process η_t with $\lambda_1 = \infty$ is a contact process that evolves according to the following rules:

$$0 \to 2 \text{ at rate } \lambda_0 n_2(x, \xi)$$

$$2 \to 0 \text{ at rate } \delta$$

Since we are assuming that $\lambda_0 > \delta\lambda_c$, this is a supercritical contact process. By taking k and therefore L large enough one can show that the probability for a supercritical contact process with k initial infected sites to survive forever can be made arbitrarily close to 1. See for instance (1.9) in p 36 in Liggett (1999). The Shape Theorem (see p 128 in Liggett (1999)) states that a supercritical contact process that does not die out spreads out at a constant speed. Thus, if the sites in state 2 do not die out, they should get to the boundary of B by time aL, where $a > 0$ depends on the linear speed of the infection. Moreover, the Shape Theorem also guarantees that the infected sites are distributed according to the upper stationary distribution of the contact process. Since this distribution is ergodic (see Proposition 2.16 p 143 in Liggett (1985)) there will be translates of C in I_1 and I_{-1} at time aL with high probability. This shows that for any $\epsilon > 0$ we may pick $T = aL$ and L large enough so that

$$P((0,0) \text{ is wet}) > 1 - \epsilon \text{ for } \lambda_1 = \infty.$$

Since B is a finite space time box, we may pick C large enough so that

$$P((0,0) \text{ is wet}) > 1 - 2\epsilon \text{ for } \lambda_1 > C.$$

We may take $\epsilon > 0$ small enough so that there is an infinite cluster of wet sites in $\mathcal{L}$ with positive probability. If we start the process η_t with at least one 2 then there is a positive probability of having a square C of sites in state 2 somewhere at time 1. We then start the construction above and there is a positive probability of an infinite cluster of wet sites. This in turn guarantees that there will be sites in state 2 at all times and completes the proof of (b).

Proof of (c)

We prove (c) under the assumption $d = 2$, in order to avoid more cumbersome notation. The same ideas work in any $d \geq 1$.

We define two space–time regions:

$$\mathcal{A} = [-2L, 2L]^2 \times [0, 2L], \qquad \mathcal{B} = [-L, L]^2 \times [L, 2L]$$

where L is an integer to be chosen later. Define $\mathcal{C}$ to be part of the 'boundary' of the box $\mathcal{A}$:

$$\mathcal{C} = \Big\{(m, n, t) \in \mathcal{A} : |m| = 2L \text{ or } |n| = 2L \text{ or } t = 0\Big\}$$

We will compare our spatial stochastic model to a certain dependent percolation process on the set $\mathcal{L} = \mathbf{Z}^2 \times \mathbf{Z}_+$, where $\mathbf{Z}_+ = \{0, 1, 2, \ldots\}$. We say that the site (k, m, n) in $\mathcal{L}$ is *wet* if for all possible states of the sites in $(kL, mL, nL) + \mathcal{C}$ there are no 1's and no 2's in $(kL, mL, nL) + \mathcal{B}$ for the process restricted to $(kL, mL, nL) + \mathcal{A}$. Sites which are not wet are called *dry*.

For any $\epsilon > 0$, we will show that there is an integer L and a constant $c > 0$ such that:

$$P\big((k, m, n) \text{ is wet}\big) \geq 1 - \epsilon \text{ if } \gamma + \lambda_1 < c$$

for any $\lambda_0 \geq 0$ and any $\delta \geq 1$. We start by showing the property when $\gamma = \lambda_1 = 0$. Then, using a continuity argument, we will deduce that the inequality remains true for small $\gamma + \lambda_1$. By translation-invariance, it suffices to consider the site $(0, 0, 0) \in \mathcal{L}$. Note that if $\gamma + \lambda_1 = 0$ then 1's cannot be reinfected and so 2's do not appear in the space-time region $\mathcal{A}$. Thus, the 2's that are in $[-2L, 2L]^2$ at time 0 will rapidly disappear. Let E be the event that there are no 2's left at time $L/2$ in $[-2L, 2L]^2$. Because there are $(4L + 1)^2$ sites in $\mathcal{A}$ and since the death rate is $\delta \geq 1$ we have that

$$P(E) \geq (1 - e^{-\delta L/2})^{(4L+1)^2} \geq (1 - e^{-L/2})^{(4L+1)^2}.$$

By taking L large enough, the r.h.s. may be made larger than $1 - \epsilon/4$ for an arbitrarily small $\epsilon > 0$.

On E there are only 0's and 1's left in $[-2L, 2L]^2$ by time $L/2$. Thereafter the only 1's that may appear in $\mathcal{A}$ are going to appear on sites (m, n) where m or n belong to

$\{-2L, 2L\}$. These 1's appear only if there are 2's in the boundary of $\mathcal{A}$ that infect 0's. However, the 1's that appear in $\mathcal{A}$ cannot infect other sites inside $\mathcal{A}$ since we are assuming that $\gamma + \lambda_1 = 0$. Therefore, the only 1's we may see in $\mathcal{B}$ are 1's that were on sites in $[-L, L]^2$ by time $L/2$ and did not die by time L. Let F be the event that there are no 1's in $\mathcal{B}$. Since the death rate of 1's is 1, we have

$$P(F|E) \geq (1 - e^{-L/2})^{(2L+1)^2}.$$

By taking L large enough the probability above may be made larger than $1-\epsilon/4$. We have

$$P\big((0,0,0) \text{ is wet}\big) \geq P(EF) = P(E)P(F|E) \geq 1 - \epsilon/2 \text{ if } \gamma + \lambda_1 = 0.$$

Since $\mathcal{A}$ is a finite box there is $c > 0$ such that with probability at least $1 - \epsilon/2$ there are no arrivals inside $\mathcal{A}$ of Poisson processes with rates γ and λ_1. Therefore, we get

$$P\big((0,0,0) \text{ is wet}\big) \geq 1 - \epsilon \text{ if } \gamma + \lambda_1 < c.$$

Note that the L we picked above depends only on ϵ and c depends only on L and therefore only on ϵ. In particular, the same c works for all λ_0 and even for $\lambda_0 = \infty$.

We now define a percolation process on $\mathcal{L}$ for which the probability that a given site is wet is $1-\epsilon$. We position oriented edges between sites in $\mathcal{L}$ in order to obtain a percolation model. For (k, m, n) and (x, y, z) in $\mathcal{L}$, we draw an oriented edge from (k, m, n) to (x, y, z) if $n \leq z$ and if the intersection between $(kL, mL, nL) + \mathcal{A}$ and $(xL, yL, zL) + \mathcal{A}$ is not empty. Note that the event $\{(k, m, n) \text{ is wet}\}$ depends only on the graphical construction within $(kL, mL, nL) + \mathcal{A}$. Given (k, m, n) in $\mathcal{L}$ there is only a fixed number of sites (j, r, s) in $\mathcal{L}$ such that $(kL, mL, nL) + \mathcal{A}$ and $(jL, rL, sL) + \mathcal{A}$ intersect. Given that events that depend on disjoint regions of the graphical construction are independent, the percolation process we have defined in $\mathcal{L}$ although dependent, has an interaction with only finite range.

A path of dry sites for this model is a connected oriented path which moves along oriented edges (in the direction of the edge) and through dry sites only.

Since $\epsilon > 0$ can be taken arbitrarily small, it is not difficult to see that the probability of a path of dry sites between sites x and y in the percolation process decreases

exponentially fast with $||x-y||$, see (8.2) in Berg et al. [12]. Notice that a 1 or 2 at x at time t implies an infection path from time 0 to time t. This infection path for the spatial stochastic process corresponds to a path of dry sites for the percolation process. But long dry paths for the percolation process are very unlikely. By using this comparison it is possible to show that for any fixed site, after a finite random time, there will never be a 1 or a 2 at that site if $\gamma + \lambda_1 < c$ for the spatial stochastic process. See the proof of Theorem 4.4 in Berg et al. (1998) for more details. This completes the proof of Theorem (c).

References

L.F. Ayvazian (1993). History of tuberculosis. In *Tuberculosis. A comprehensive international approach.* Reichman and Hershfield, editors. Marcel Dekker, New York.

J. van den Berg, G. Grimmett, R.Schinazi (1998). Dependent random graphs and spatial epidemics. *The Annals of Applied Probability*, **8**, 317-336.

C.Dye, S. Sheele, P.Dolin, V. Pathania, M.C.Ravigione (1999). Global burden of tuberculosis, estimated incidence, prevalence, and mortality by country. *JAMA*, **282**, 677-686.

D.A.Enarson and A.Rouillon (1998). The epidemiological basis of tuberculosis control. *Clinical Tuberculosis*, edited by P.D.O. Davies, Chapman and Hall, London.

Z. Feng, C. Castillo-Chavez and A. Capurro (2000). A model for tuberculosis with exogenuous reinfection. *Theoretical Population Biology*, **57**, 235-247.

T. Liggett (1985).*Interacting particle systems*, Springer-Verlag.

T. Liggett (1999). *Stochastic interacting systems: contact, voter and exclusion processes.* Springer.

McMurray D.N., Bartow R.A. qnd Mintzer C.L. (1989). Impact of protein malnutrition on exogenous reinfection with mycobacterium tuberculosis. *Infect. Immun.* 57, 1746-1749.

D. Mollison. (1977) Spatial contact models for ecological and epidemic spread. J. Roy.Statist. Soc. Ser. B 39, 283-326.

R.B.Schinazi (2000) Horizontal versus vertical transmission of parasites in a stochastic spatial model. Mathematical Biosciences 168, 1-8.

Styblo K (1991). *Selected papers, epidemiology of tuberculosis.* Royal Netherlands Tuberculosis Association.

Ziegler J.E., Edwards M.L. and Smith D.W. (1985). Exogenous reinfection in experimental airborne tuberculosis, Tuberculosis 66, 121-128.