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On the Spread of Drug-Resistant Diseases

Rinaldo B. Schinazi[1]

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We introduce an interacting particle system to model the emergence of drug-resistant diseases, one of the most serious health problems in modern society. We are interested in diseases for which a natural strain may mutate into a drug-resistant strain. This happens, for instance, when antibiotics are misused. The main result of our analysis is that with an efficient drug against the natural strain, if there is even a small chance that the natural strain mutates into the drug-resistant one, then there will eventually be an outbreak of the drug-resistant strain throughout the population. In that case the natural strain disappears and is replaced by the drug-resistant strain. The disturbing part of this is that an efficient treatment of the natural strain gives an edge to the drug-resistant strain.

KEY WORDS: Interacting particle systems; drug resistance.

1. INTRODUCTION

One of the most serious health problems today is the emergence of drug-resistant diseases, see for instance Blower, Small and Hopewell (1996) and Castillo-Chavez and Feng (1997) and the references there for an account of the situation for tuberculosis. In this paper we will introduce a very simple stochastic model for the spread of a drug-resistant strain of a given disease. We are interested in drug-resistant strains that appear by mutation of the natural (or wild type) strain. This is the case when antibiotics are misused: incomplete treatment in the case of TB or overuse in many other cases. Our model will show that (at least in theory) for a large range of parameters it is possible for the drug-resistant strain to replace the natural strain. One case is of particular interest: if the rate of successful treatment for the natural strain is high enough then, even if the rate at which the

[1] Department of Mathematics, University of Colorado, Colorado Springs, Colorado 80933-7150; e-mail: schinazi@math.uccs.edu.

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natural strain mutates into the drug-resistant strain is very low, the drug-resistant strain will eventually sweep through the population. This possibility is somehow disturbing: it shows that an efficient treatment of the natural strain may give an edge to the drug-resistant one!

We now introduce our model. We think of our population as being spatially distributed on the square lattice $\mathbf{Z}^d$. Each site of $\mathbf{Z}^d$ is empty or occupied by at most one individual. We think of 0 as being the empty state, 1 being healthy, 2 infected with the natural strain, 3 infected with the drug-resistant strain. The state of the particle system at time t is denoted by η_t and is in $\{0, 1, 2, 3\}^{\mathbf{Z}^d}$. If the process is in state η and $x \in \mathbf{Z}^d$ then $\eta(x) = 0$ if site x is empty, $\eta(x) = 1$ if x is occupied by a healthy individual, $\eta(x) = 2$ if x is occupied by an individual infected with the natural strain of the disease and $\eta(x) = 3$ if x is occupied by an individual infected with the drug-resistant strain of the disease.

Denote by $\|\cdot\|$ the Euclidean norm and for $x \in Z^d$, $\eta \in \{0, 1\}^{\mathbf{Z}^d}$, let for $i = 1, 2, 3$

$$n_i(x, \eta) = card(\{ y \in \mathbf{Z}^d : \|y - x\| = 1, \text{ and } \eta(y) = i \})$$

That is, $n_i(x, \eta)$ is the number of nearest neighbors of x that are in state i. A site x changes its state in the configuration η according to the following transition rates:

$$0 \to 1 \text{ at rate } \beta_1$$

$$1 \to 2 \text{ at rate } \beta_2 n_2(x, \eta)$$

$$1 \to 3 \text{ at rate } \beta_3 n_3(x, \eta)$$

$$2 \to 3 \text{ at rate } \phi$$

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

$$3 \to 0 \text{ at rate } 1$$

In words, there is birth of healthy individuals at rate β_1. Healthy individuals get infected by contact at rate β_2 and β_3 by infected individuals with natural and drug-resistant strains, respectively. An individual infected with the natural strain has two possible outcomes: either his strain mutates into the drug-resistant strain at rate ϕ or he recovers at rate r. Finally, an individual with the drug-resistant strain dies at rate 1.

We now turn to a model for the disease without treatment. With not treatment, only strain 2 is present and we could have the following rules for the model ζ_t.

$$0 \to 1 \text{ at rate } \beta_1$$

$$1 \to 2 \text{ at rate } \beta_2 n_2(x, \zeta)$$

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

This model has been widely studied under the names "spatial epidemic" and "forest fire," see Kuulasmaa (1982), Durrett and Neuhauser (1991), Andjel and Schinazi (1996) and Berg, Grimmett and Schinazi (1998). In particular there is a critical value β_c (depending on the spatial dimension d) such that if $\beta_2 > \beta_c$ there exists a stationary distribution for ζ_t that concentrates on configurations with infinitely many 2's for any $\beta_1 > 0$. With our interpretation, this means that in the absence of treatment, if β_2 is high enough, then strain 2 may be endemic in the population.

We also need to introduce the contact process in order to formulate our results. The contact process ξ_t has only two possible states per site, say 1 and 2, and evolves according to the following rules

$$1 \to 2 \text{ at rate } \lambda n_2(x, \xi)$$

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

Moreover, there is a critical parameter λ_c (depending on the spatial dimension d) such that if $\lambda > \lambda_c$ there is a stationary distribution for he contact process that concentrates on configurations with infinitely many 2's. If $\lambda \leqslant \lambda_c$ the unique stationary distribution is the trivial one: the all 1's configuration, see Bezuidenhout and Grimmett (1990) for more on the contact process.

We are now ready to state the main result of this paper:

Theorem 1. Assume that $\beta_2/(\phi + r) < \lambda_c$, $\phi > 0$, $\beta_1 > 0$ and $\beta_3 > \beta_c$. Then, there is an epidemic of the drug-resistant strain in the following sense. If the initial configuration has infinitely many 2's then, with probability 1, there is a spatial region with no 2's and with 3's in it that grows through the whole space $\mathbf{Z}^2$.

In an ideal scenario the treatment rate of the natural strain r is much higher than the mutation rate from the natural strain to the drug-resistant strain ϕ. Theorem 1 shows that even in this ideal scenario an epidemic of the drug-resistant strain will eventually happen, if $\phi + r$ (which is essentially r in this case) is high enough. This poses the question of the ultimate effectiveness of any drug that may provoke the appearance of a mutated drug-resistant strain.

In reality, we are far from the ideal scenario described above. As noted by Blower, Small and Hopewell (1996) the treatment rate for tuberculosis can be rather low (r and ϕ could than be of the same order of magnitude) and then the perverse effects of treatment may make the treatment an undesirable option.

Theorem 1 is proved assuming that we have infinitely many individuals infected with the natural strain to start with. This is, of course, an approximation of an endemic state. The proof works if we start with only finitely many infected individuals but then the conclusion is that there is a strictly positive probability (instead of probability 1) of an epidemic of the drug-resistant strain. It seems intuitively clear, but might be difficult to prove, that the probability of an epidemic increases rapidly with the number of infected individuals we start with.

We may think of the two strains as competing for the same susceptibles. Under the conditions $\beta_2/(\phi+r)<\lambda_c$ and $\beta_3>\beta_c$, the natural strain is out competed by the resistant strain. The mean-field analysis of the next section will show that there are probably other conditions under which the natural strain is out competed by the resistant strain. The paradoxical result of our analysis is that it is when the treatment is most effective, and r is large, that the population is more at risk of a major outbreak of the drug-resistant strain. It is when the treatment is effective and the natural strain is rapidly disappearing that we will have an epidemic of the drug-resistant strain.

The following is another possible application of our model. It has been observed that after a few weeks of lamivudine treatment, HIV infected patients are subjected to a large increase in lamivudine resistant virus. This is analogous to the large epidemic of drug-resistant strain our model predicts when the treatment of the natural strain is efficient. See Bonhoeffer, Coffin and Nowak (1997), in particular Fig. 2 there.

Our other result is that if $\phi+r$ is low enough then coexistence of strains 2 and 3 is possible.

Theorem 2. If $\phi+r$ is low enough and $\phi>0$, coexistence is possible. That is, there is a stationary distribution for η_t on $\mathbf{Z}^d$ $(d\geqslant 1)$ that concentrates on configurations with infinitely many 2's and 3's.

Note that if $\beta_2>\beta_c$ and $\beta_2/(\phi+r)<\lambda_c$ then the 2's would persist in the process ζ_t (the model with no treatment) and would die out in the process η_t (the model with treatment). In other words, for this range of parameters, strain 2 would survive in the absence of treatment but would be eliminated by strain 3 as a consequence of the treatment. However, Theorem 2 shows that coexistence is possible for $\phi+r$ small in the model with treatment,

confirming the results that Castillo-Chavez and Feng (1997) obtained for their deterministic non-spatial model.

2. MEAN-FIELD ANALYSIS

We do a mean-field analysis of our model in order to get a more complete picture of what the phase diagram of the spatial model might be. Let us start at time 0 with a translation invariant distribution, with a positive density of 1's, 2's, and 3's. Then at all times t, the distribution of $\eta_t(x)$ is translation invariant, and $u_i(t) = P(\eta_t(x) = i)$ does not depend on x, for $i = 1, 2, 3$. From the dynamics and the approximation that the states at different sites are independent it is straightforward to derive the system of differential equations

$$u_1'(t) = \beta_1(1 - u_1 - u_2 - u_3) - \beta_2 u_1 u_2 - \beta_3 u_1 u_3 + r u_2$$

$$u_2'(t) = \beta_2 u_1 u_2 - r u_2 - \phi u_2$$

$$u_3'(t) = \beta_3 u_1 u_3 + \phi u_2 - u_3$$

We now look for an equilibrium that concentrates on 1's, 2's, and 3's. Using that $u_i' = 0$ for $i = 1, 2, 3$, we get from the second equation that

$$u_1 = \frac{r + \phi}{\beta_2}$$

The third equation yields

$$u_2 = \frac{\phi}{1 - \beta_3 u_1} u_3$$

Plugging the expressions for u_1 and u_2 in the first equation yields u_3. In order to have u_i in $(0, 1)$ for $i = 1, 2, 3$ it is easy to check that it is necessary and sufficient to have the following conditions:

$$\phi > 0, \qquad \beta_2 > r + \phi, \qquad \frac{\beta_2}{r + \phi} > \beta_3$$

As for the spatial model we get that if $\beta_2/(r + \phi)$ is not large enough then the 2's do not survive. We also get a new interesting condition: if β_3 is larger than $\beta_2/(r + \phi)$ then the 2's die out. This makes us conjecture that in the spatial model too strain 3 is going to out compete strain 2 if $\beta_2/(r + \phi) < \beta_3$.

Since it is so easy to derive results for the mean-field model the reader may wonder at this point what is gained in terms of biological insight by the analysis of the interacting particle system. Spatial and mean-field models have different advantages and drawbacks. A Mean-field model is usually simple to analyze and in this case it gives precise conditions for coexistence. On the other hand spatial models are usually more difficult to analyze and computations of precise critical values are very difficult. However, in this particular case the analysis of the interacting particle system gives a precise pathwise analysis of how 2's that are endemic, in the initial configuration, will be driven out by 3's under certain conditions, see Theorem 1. This type of precise description is not available for the mean-field model. The mean-field model only tells us that under certain conditions 2's and 3's cannot coexist. This is a result about possible equilibria but there is no information about the underlying dynamics. Moreover, space seems quite important in the spread of epidemics and is completely ignored by mean-field models. Of course, our spatial model is a caricature of reality but we believe it is a first step in incorporating space into the model.

3. PROOF OF THEOREM 1

Throughout this paper, we think of the epidemic process as being generated by Harris' graphical representation. That is to say, we are given appropriate families of independent Poisson processes which may be used to couple together different processes. Such constructions are standard; see for instance Durrett (1995).

Note that in the absence of 2's the process of 3's behaves like a forest fire model (i.e., the process ζ_t) introduced above. That is,

$$0 \to 1 \text{ at rate } \beta_1$$

$$1 \to 3 \text{ at rate } \beta_3 n_3(x, \eta)$$

$$3 \to 0 \text{ at rate } 1$$

Durrett and Neuhauser (1991) have proved that for $\beta_3 > \beta_c$ and $\beta_1 > 0$ there is a stationary distribution that concentrates on configurations with infinitely many 3's, for the forest fire model in dimension 2. The crucial point of their proof is that starting with enough 3's there is a positive probability that 3's will persist forever in a growing spatial region (see Lemma 1.1 in their paper). We need to show that this is still true in the presence of 2's.

In order to control the influence of the 2's, consider the following contact process

$$1 \to 2 \text{ at rate } \beta_2 n_2(x, \xi)$$

$$2 \to 1 \text{ at rate } \phi + r$$

We say that configuration ξ has more i's ($i=1$ or $i=2$) than configuration η if $\eta(x)=i$ implies that $\xi(x)=i$ for every x in $\mathbf{Z}^2$. Using the graphical construction, one can couple (that is, construct on the same probability space) η_t to ξ_t in such a way that if ξ_0 has more 1's and 2's than η_0 then ξ_t has more 1's and 2's than η_t at all times $t>0$. But if

$$\frac{\beta_2}{r+\phi} < \lambda_c$$

the 2's die out in the process ξ_t and therefore in the process η_t as well. Moreover, the 2's die out exponentially fast, see Bezuidenhout and Grimmett (1991). The exponential decay of the 2's implies the following.

Lemma 3.1. Consider the contact process ξ_t under the condition $\beta_2/(r+\phi) < \lambda_c$. For any $R>0$ and any $\varepsilon>0$ there is L such that if there are no 2's in $[-2L, 2L]^2$ at time 0 then there are no 2's in $[-Rt, Rt]^2$ at all times $t>0$, with probability at least $1-\varepsilon$.

For a proof of Lemma 3.1, see the proof of Theorem 3 in Schinazi (1996).

Recall that η_0 has infinitely many 2's. Since the mutation rate ϕ is strictly positive there is, with probability one at time 1, somewhere in space a translation of $[-L, L]^2$ denoted by $[-L, L]^2 + z$ (for some z in $\mathbf{Z}^2$) full of 3's and with no 2's in $[-2L, 2L]^2 + z$. We start, at time 1, the construction of Durrett and Neuhauser (1991). There is a positive probability that the 3's, originally in $[-L, L]^2 + z$, will generate a spatial growing region, B_t, that will take over the whole space. To be more precise, we may think of B_t as being the smallest Euclidean ball that contains all the 3's, at time t, whose line of infection goes back to $[-L, L]^2 + z$. Moreover, it is easy to see that B_t grows at most linearly. Therefore, for any $\varepsilon>0$ there is an $R_1>0$ such that the event

$$\mathscr{A} = \{B_t \subset [-R_1 t, R_1 t]^2 \text{ for all } t \geqslant 1\}$$

has probability at least $1-\varepsilon$. On the other hand, by Lemma 3.1 we have that the event

$$\mathscr{B} = \{\text{there are no 2's in } [-R_2 t, R_2 t]^2 \text{ for all } t \geqslant 1\}$$

has probability at least $1-\varepsilon$, for R_2 large enough. Take $R_2 > R_1$. Observe that $\mathscr{A}$ and $\mathscr{B}$ depend on Poisson processes that are in distinct space-time regions. Thus, $\mathscr{A}$ and $\mathscr{B}$ are independent. Therefore the probability that the construction succeeds, that is, that B_t grows forever and that $\mathscr{A}$ and $\mathscr{B}$ occur has a strictly positive probability. If the construction fails, i.e., the 3's die out or come into contact with the 2's we can try this construction again. Since the trials are independent and the probability of success of each trial is bounded below by the same constant, the construction will eventually succeed. This proves Theorem 1.

4. PROOF OF THEOREM 2

We will only sketch this proof because it is very similar to the proof of Theorem 1 in Schinazi (1997). It is enough to work in $d=1$ because the construction that follows may be embedded in higher dimensional spaces.

Consider the process η_t with $\phi = r = 0$ restricted to some finite box $[-4L, 4L]$ and with 2's on every site of the interval $[-L, L]$. In the case $\phi = r = 0$ the 2's do not die and the rightmost 2, denoted by r_t, can only go to the right. We now describe one of the ways r_t may jump at least one unit to the right. Assume that $r_t = x$ and that there is a death with rate 1 at $x+1$ (so that if there is 3 at $x+1$ it is killed), followed by a birth of a 1 at $x+1$ and finally an infection from x to $x+1$ before anything else happens. After this succession of events $r_t = x+1$. This shows that we may couple r_t to a renewal process in such a way that r_t is always larger than the renewal process. Thus, by the Renewal Theorem we see that

$$\liminf_{t\to\infty} \frac{r_t}{t} \geqslant \frac{1}{1+(1/\beta_1)+(\beta_2/(\beta_2+\beta_3)^2)} \tag{4.1}$$

Let $\mathscr{C}$ be the following event. Starting η_t with 2's at every site of $[-L, L]$ there will be 2's at every site of $[-3L, -L]$ and $[L, 3L]$ at time cL ($c>0$ depending on the edge speed of r_t) for the process η_t restricted to $[-4L, 4L]$. By (4.1), for every $\varepsilon > 0$ here is L such that

$$P(\mathscr{C}) \geqslant 1-\varepsilon \qquad \text{for} \quad \phi = r = 0$$

Since we are dealing with the process restricted to a finite space time region, we have by continuity that

$$P(\mathscr{C}) \geqslant 1-2\varepsilon \qquad \text{for} \quad \phi + r > 0 \text{ small enough}$$

This is enough to show that the 2's in η_t dominate a supercritical oriented percolation model. Starting with 2's on every site of Z, standard arguments

show that a subsequence of the Cesaro average of the distributions converges to a stationary distribution that concentrates on configurations with infinitely many 2's. Since $\phi > 0$, this stationary distribution must concentrate on configurations with infinitely many 3's as well. There is coexistence for $\phi + r$ small enough and this proves Theorem 2.

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