# THE PROBABILITY OF TREATMENT INDUCED DRUG RESISTANCE

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### ABSTRACT

We propose a discrete time branching process to model the appearance of drug resistance under treatment. Under our assumptions at every discrete time a pathogen may die with probability $1 - p$ or divide in two with probability $p$. Each newborn pathogen is drug resistant with probability $\mu$. We start with $N$ drug sensitive pathogens and with no drug resistant pathogens. We declare the treatment successful if all pathogens are eradicated before drug resistance appears. The model predicts that success is possible only if $p < 1/2$. Even in this case the probability of success decreases exponentially with the parameter $m = \mu N$. In particular, even with a very potent drug (i.e. $p$ very small) drug resistance is likely if $m$ is large.

**Key Words**: drug resistance, mathematical model, branching process, mutation

## 1. INTRODUCTION

Drug resistance is a constant threat to the health of individuals who are being treated for a variety of ailments: HIV, tuberculosis, cancer. It is also a threat to the population as a whole since there is a risk that a treatable disease may be replaced by a non treatable one. See for instance the case of tuberculosis in Castillo-Chavez and Feng (1997) and the spatial stochastic model in Schinazi (1999).

In this paper we are interested in evaluating the risk of a treatment induced drug resistance. We assume that in the absence of treatment a drug resistant pathogen is outcompeted by the drug sensitive pathogen and it rapidly dies out if it appears. However, in the presence of a drug the drug sensitive strain is weakened (how much it is weakened depends on the efficacy of the drug) and this gives an edge to the drug resistant strain if it appears before the drug is able to eradicate all pathogens. Therefore, under the assumptions of this model, what determines the treatment outcome is whether total eradication takes place before the appearance of a drug resistance mutation. We propose a model to compute the probability of pathogen eradication before drug resistance appears.

## 2. THE MODEL

We use a very simple branching process to model the dynamics of drug sensitive pathogens under treatment. We assume that at every unit time a given pathogen may die with probability $1 - p$ or divide in two with probability $p$. Thus, the mean offspring per pathogen is $2p$. We assume that $p$ is strictly between 0 and 1. If $2p > 1$ then there is a positive probability for the family tree of a single drug sensitive pathogen to survive

forever. If $2p \leq 1$ then eradication is certain for drug sensitive pathogens. For this and other results regarding branching processes, see Harris (1989). The parameter $p$ is a measure of efficacy of the drug. The smaller the $p$ the more efficient the drug is and the more likely eradication of the drug sensitive pathogen is.

As always for branching processes, we assume that the number of pathogens each pathogen gives birth to is independent of the number of pathogens any other pathogen gives birth to at the same time. We also assume that for each birth of pathogen there is a probability $\mu$ that the new pathogen is drug resistant. We denote by $N$ the number of pathogens at the beginning of treatment.

We first deal with the case $N = 1$ for mathematical convenience. That is, treatment starts when we have a single pathogen. Let $Z$ be the total (random) number of pathogens in the family tree of a single initial pathogen: $Z$ counts the initial pathogen in addition to all successive offspring. Note that if $p > 1/2$ then there is a positive probability that $Z$ is infinite. However, in order to have no drug resistance mutation $Z$ must be finite and none of the total $Z - 1$ offspring may have the drug resistance mutation. Let $M$ be the number of births (among the total $Z - 1$) with the drug resistant mutation. Assuming that a drug resistant mutation occurs with probability $\mu$ at each birth and that mutations occur independently of each other we get

$$P_1(M = 0 \mid Z = k) = (1 - \mu)^{k-1}$$

where the subscript 1 indicates that $N = 1$. Thus,

$$P_1(M = 0) = E((1 - \mu)^{Z-1}).$$

It turns out that the distribution of $Z$ can be computed exactly (see the Computations Section below) and used to compute the probability above. We get

$$P_1(M = 0) = \frac{1}{2p(1 - \mu)^2}(1 - \sqrt{1 - 4p(1 - p)(1 - \mu)^2})$$

for all $p$ in $(0, 1)$. If at the start of the treatment there are in fact $N$ pathogens, by stochastic independence we get

$$q(N, \mu, p) \equiv P_N(M = 0) = (q(1, \mu, p))^N$$

and so

$$q(N, \mu, p) = \left(\frac{1}{2p(1 - \mu)^2}(1 - \sqrt{1 - 4p(1 - p)(1 - \mu)^2})\right)^N.$$

Assuming that $\mu > 0$ is small compared to the other parameters we may approximate the formula above by

$$q(N, \mu, p) \sim \exp\left(-\frac{2p}{1 - 2p}N\mu\right) \quad \text{for } p < 1/2$$

and

$$q(N, \mu, p) \sim \left(\frac{1 - p}{p}\right)^N \exp\left(-2\frac{1 - p}{2p - 1}N\mu\right) \quad \text{for } p > 1/2.$$

Thus, the behavior of $q$ depends crucially on whether $p < 1/2$. For fixed $p < 1/2$ the probability that the treatment succeeds depends only on the parameter $m \equiv N\mu$ and decreases exponentially as $m$ increases. See Figure 1.
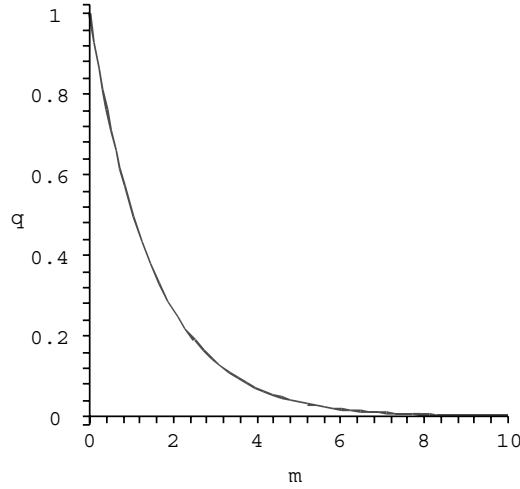
**Figure 1.** This is the probability of no drug resistant mutation as a function of $m = \mu N$ when $p = 0.2$.

If $p > 1/2$ then the probability of success decreases exponentially in $m$ and also in $N$. In particular, if $p > 1/2$ then

$$q(N, \mu, p) < \left(\frac{1-p}{p}\right)^{N}.$$

Since $N$ is usually very large, it is extremely unlikely to avoid drug resistance in this case.

## 3. DISCUSSION

We propose a simple branching process to model the appearance of drug resistance under treatment. Under our assumptions at every discrete time a pathogen may die with probability $1 - p$ or divide in two with probability $p$. Each newborn pathogen is drug resistant with probability $\mu$. We start with $N$ drug sensitive pathogens and with no drug resistant pathogens. We declare the treatment successful if all pathogens are eradicated before drug resistance appears.

There are two possible cases. If $p > 1/2$ then, under treatment, it is more likely for a pathogen to divide than to die. That is, the effect of the treatment is to lower $p$ but not enough for eradication to be certain. Then the probability that no drug resistance will appear is less than $(\frac{1-p}{p})^{N}$. Since $N$ is huge, drug resistance is almost certain to appear.

The other case is $p < 1/2$. In this case a pathogen is more likely to die than to divide. In Figure 1 we plot the graph of $q$ (the probability of no drug resistance) as a function of $m = \mu N$ in the case $p = 0.2$. We see that $q$ decreases exponentially and is essentially 0 when $m \geq 10$. If $p = 0.01$ then the drug is much more efficient. The shape of the graph is the same as in Figure 1 but $q$ is essentially 0 only for $m$ above 250.

In summary, our model predicts that treatment should be tried only if the drug is potent enough to ensure eradication of drug sensitive pathogens. It also predicts that the essential parameter is $m = \mu N$. Even with a very potent drug (i.e. $p$ very small) resistance is likely to appear during treatment if $m = \mu N$ is large.

Many different classes of mathematical models for the emergence of drug resistance exist in the literature. Examples of differential equations models are McLean and Nowak (1992), Bonhoeffer and Nowak (1997), Bonhoeffer *et al.* (1997) and Nowak and May (2000). Ribeiro and Bonhoeffer (2000) use a deterministic model to compare two possible scenarios for the outgrowth of drug resistant pathogens: either a drug resistant strain exists before the treatment or it appears after the treatment starts. They also use stochastic simulations to compare the two possibilities. Our point of view is different: we assume that new strains are rapidly outcompeted by the wild type in the absence of treatment and that there is no drug resistant strain when the treatment starts.

As pointed out by several anonymous referees there are also many examples in the literature of stochastic models. There are in particular several stochastic models dealing with drug resistance in cancer treatment, see in particular Harnevo and Agur (1992) and (1993), Axelrod *et al.* (1993) and Kimmel and Axerold (1990). Our present model is close to these models, however our objective is different. In these papers the authors concentrate in drug resistance caused by gene amplification in a cancerous cell. Their models allow them to suggest several possible molecular processes involved in gene amplification. Our objective is different. We ignore the different possible routes to drug resistance and we compute the probability of a successful treatment as a function of the probability of drug resistance mutation.

Kimmel *et al.* (1998) and Polanski *et al.* (1997) examine differential equations models for coexistence of (infinitely) many drug resistant strains of a given pathogen and find stability criteria for their model. Closer to us is the work of Goldie and Coldman (1998) on drug resistance in cancer. They compute the probability of no resistance at time $t$ in function of the number of cells at time $t$ (see their Section 5.4 and also 10.9 in Wheldon (1988)). The main difference with our model is that they do not include the dynamics of tumor growth under treatment and its influence on the probability of successful treatment. In this sense our result completes theirs.

Iwasa *et al.* (2003) and (2004) use a multi-type branching process to model the sequence of mutants that leads to a drug resistant mutant. They use their model to understand the importance of different mutation networks in the appearance of a drug resistant mutant. Understanding the evolutionary dynamics of drug resistance is a complex problem that requires a complex model with many parameters. However, they also use their model to compute the probability of drug resistance. It is our opinion that to compute the probability of drug resistance a simple model such as ours (with only two parameters) is at least as useful. In particular, one can think of the probability $\mu$ of a drug resistant mutation in our model as being the probability of a sequence of mutations leading to drug resistance. For that it is not necessary to model the exact path that leads to a drug resistant mutation. Finally, note that even in the simplest case, when the wild type mutates to a drug resistant type in one step the model in Iwasa *et al.* (2004) is not the same as ours (see their Section 2.2). They still have a two-type branching process and we have a one-type branching process.

## 4. COMPUTATIONS

Set $Z_0 = 1$ and let $Z_1$ be the number of offspring of the initial pathogen. Under our assumptions we may have $Z_1 = 0$ or 2. Let $Z_n$ be the offspring of the pathogens present at time $n - 1$ where $n \geq 1$. We assume that the number of offspring for a given pathogen is stochastically independent of the offspring of any other pathogen. Let $f$ be the moment generating function of the offspring distribution. We have for all $s$

$$f(s) = \sum_{k=0}^{2} P(Z_1 = k \mid Z_0 = 1)s^k = 1 - p + ps^2.$$

Let $Z$ be the total number of pathogens in the family tree of the single initial pathogen. That is,

$$Z = \sum_{n=0}^{\infty} Z_n.$$

The distribution of $Z$ has been known since at least Otter (1949), see Example 1 in that paper. In order to compute the probability of no drug resistance $q$ we need part of the computation used to derive $Z$ so we first compute the distribution of $Z$ and then $q$.

Since the offspring is always even and we start with a single pathogen $Z$ is always odd. Let $F$ be the moment generating function of $Z$:

$$F(s) = \sum_{n=1}^{\infty} P(Z = 2n - 1 \mid Z_0 = 1)s^{2n-1}$$

for $|s| < 1$. $F$ is the solution of the following equation:

$$F(s) = sf(F(s)) = s(1 - p + pF(s)^2)$$

for all $|s| < 1$, see Otter (1949). Solving this quadratic equation in $F(s)$ yields

$$F(s) = \frac{1}{2ps} - \sqrt{\frac{1}{4p^2s^2} - \frac{1-p}{p}}$$

where we pick this solution of the quadratic equation because $F$ must be finite for $s$ near 0. We have

$$F(s) = \frac{1}{2ps}(1 - \sqrt{1 - 4p(1-p)s^2}).$$

Using the binomial expansion we get

$$1 - \sqrt{1 - x} = \sum_{n=1}^{\infty} c_n x^n \quad \text{for } |x| < 1$$

where

$$c_n = \frac{(2n-2)!}{2^{2n-1}n!(n-1)!} \quad \text{for } n \geq 1.$$

Thus,

$$F(s) = \frac{1}{2ps} \sum_{n=1}^{\infty} c_n (4p(1-p)s^2)^n = \sum_{n=1}^{\infty} \frac{(2n-2)!}{n!(n-1)!}(1-p)^n p^{n-1} s^{2n-1}.$$

In particular we get for $n \geq 1$

$$P(Z = 2n - 1 \mid Z_0 = 1) = \frac{(2n - 2)!}{n!(n - 1)!}(1 - p)^n p^{n-1}.$$

We now compute the probability of no drug resistance starting with one pathogen.

$$q(1, \mu, p) = E((1 - \mu)^{Z-1}) = \sum_{n=1}^{\infty}(1 - \mu)^{2n-2}\frac{(2n - 2)!}{n!(n - 1)!}(1 - p)^n p^{n-1}.$$

A little algebra yields

$$q(1, \mu, p) = \frac{1}{2p(1 - \mu)^2} \sum_{n=1}^{\infty} \frac{(2n - 2)!}{2^{2n-1}n!(n - 1)!}(4(1 - \mu)^2(1 - p)p)^n.$$

We get

$$q(1, \mu, p) = \frac{1}{2p(1 - \mu)^2} \sum_{n=1}^{\infty} c_n(4(1 - \mu)^2(1 - p)p)^n.$$

Thus,

$$q(1, \mu, p) = \frac{1}{2p(1 - \mu)^2}(1 - \sqrt{1 - 4p(1 - p)(1 - \mu)^2}).$$

Since each pathogen multiplies independently of the others we get, starting with $N$ pathogens

$$q(N, \mu, p) = (q(1, \mu, p))^N = \left(\frac{1}{2p(1 - \mu)^2}(1 - \sqrt{1 - 4p(1 - p)(1 - \mu)^2})\right)^N.$$

In order to obtain a friendlier expression we compute a linear approximation in $\mu$. Note that the linear approximation for $(1 - \mu)^{-2}$ is $1 + 2\mu$ and that

$$\sqrt{1 - 4p(1 - p)(1 - \mu)^2} \sim |1 - 2p|\left(1 + \frac{4p(1 - p)}{(1 - 2p)^2}\mu\right)$$

where $f \sim g$ means that

$$\lim_{\mu \to 0} \frac{f(\mu) - g(\mu)}{\mu} = 0.$$

For $p < 1/2$ we get

$$q(1, \mu, p) \sim 1 - \frac{2p}{1 - 2p}\mu.$$

Therefore,

$$q(N, \mu, p) \sim \left(1 - \frac{2p}{1 - 2p}\mu\right)^N \sim \exp\left(-\frac{2p}{1 - 2p}N\mu\right) \quad \text{for all } p < 1/2.$$

For $p > 1/2$ we may do a similar approximation but more importantly we have

$$q(N, \mu, p) < \left(\frac{1 - p}{p}\right)^N$$

which may be obtained directly as follows. Starting with one pathogen the probability of eradication is $\frac{1-p}{p}$: it is the solution of $f(s) = s$ which is not 1 (see Harris, 1989). If among the $N$ initial pathogens at least one generates a family tree which survives forever then drug resistance is certain (there are infinitely many births and each one has

the constant probability $\mu > 0$ of being resistant). Thus, in order to avoid drug resistance it is necessary (but not sufficient) that all $N$ initial pathogens generate family trees that are eradicated. This implies the inequality above.

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