Drug Resistance always Depends on the Turnover Rate

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Abstract— **Resistance to drugs is a fundamental problem in the treatment of many diseases. In this work we consider the problem of drug resistance in cancer, focusing on random genetic point mutations.**

A recent result obtained by Komarova is that for the case of a single drug treatment, the probability to have resistant mutants generated before the beginning of the treatment (and present, including their progeny, at some given time afterward) does not depend on the cancer turnover rate. This implies that the treatment success will not depend on such rate.

In this paper we show that the number of such resistant mutants must depend on the turnover rate, which will also be the case for the success of the treatment.

Keywords— **Drug resistance, Cancer, Ordinary differential equations.**

I. Introduction

One of the main reasons for the failure of cancer treatment is the development of drug resistance. There are multiple mechanisms by which drug resistance may develop.

One type of resistance is "kinetic resistance". Many drugs are indeed effective only during one specific phase of the cell cycle, e.g., the S phase, when the DNA is synthesized. Thus, in the case of a short exposure to the drug, the cell will not be affected if during that time it is in a different phase. Even more importantly, the cell will be substantially invulnerable if it is out of the cell division cycle, i.e., in a "resting state". Such resistance is generally only temporary.

Resistance to drugs may instead develop as a consequence of genetic events such as mutations. This category includes both "point mutations" and "chromosomal mutations", also known as "gene amplifications". Point mutations are random genetic changes that occur during cell division. These mutations cause the replacement of a single base nucleotide or pair, with another nucleotide or pair in the DNA or RNA. This is a random event with a very small probability that modifies the cellular phenotype, making any of its daughter cells resistant to the drug. Gene amplification is the consequence of an overproduction of a particular gene or genes. This means that a limited portion of the genome is reproduced to a much greater extent than normal, essentially providing the cell with more copies of a particular gene than the drug is able to cope with. For a more comprehensive picture we refer to the book by Teicher [1] and to the references therein.

In the following we will focus only on random point mutations, given the main role they have in causing drug resistance (see Luria and Delbrück [2]). Thus we will consider a growing cancer cell population for which, at each division, a random point mutation may occur, conferring drug resistance to a daughter cell.

The first models of resistance caused by point mutations in cancer are due to Goldie and Coldman [3-6]. Using stochastic processes, Goldie and Coldman show for example how the probability of having no drug resistance is larger in smaller tumors. A recent work on point mutations is by Iwasa et al. [7], in which continuous-time branching processes are used to calculate the probability of having resistance at the time of detection of the cancer.

We will focus on another recent work on point mutations due to Komarova [8-9]. There, probabilistic methods and a hyperbolic PDE are used to show for example how the pretreatment phase is more significant in the development of resistance than the treatment phase. This is a very natural, intuitive result given that during treatment the cancer population cannot be able to divide nearly as frequently, due to the presence of the drug. However, the main result obtained by Komarova is the following. In the case of a single drug treatment, the probability to have resistant mutants generated before the beginning of the treatment and present, including their progeny, at some given time afterward, does not depend on the cancer turnover rate. A consequence of such result is that also the probability of treatment success will not depend on such rate. For the case of a multi-drug treatment, instead, Komarova shows how there appears to be a strong dependence of the probability to have resistant mutants on the turnover rate (see [9]), and therefore also the probability of treatment success will strongly depend on such rate.

Our goal is to understand the reason for such a difference between the single and multi-drug cases. This is accomplished by using a different, much simpler approach, based on an elementary compartmental system of ordinary differential equations rather than on stochastic processes. In particular we would like to understand if it is true that in the case of single drug treatment, drug resistance (and therefore

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treatment success) is independent of the cancer's turnover rate.

II. An elementary model

Consider the case of resistance to a single drug. Accordingly, we have two populations. The first group is composed of wild-type cancer cells (cells that are sensitive to the drug). We denote the number of wild-type cancer cells at time t, by $N(t)$. The second group is composed by cells that have undergone a mutation, and therefore are resistant to the drug. The number of mutated cells at time t is denoted by $R(t)$.

We assume that cancer grows exponentially and also that the drug therapy starts at time t^*. Our model can then be written as:

$$\begin{cases} N'(t) = (L-D)N(t), \\ R'(t) = (L-D)R(t) + uN(t). \end{cases} \qquad t \le t^*, \tag{1}$$

and

$$\begin{cases} N'(t) = (L-D-H)N(t), \\ R'(t) = (L-D)R(t) + uN(t). \end{cases} \qquad t > t^*. \tag{2}$$

System (1) describes the pre-treatment phase, while system (2) follows the dynamics after the treatment starts. The difference between both systems is the introduction of H, the drug-induced death rate. In both systems, L, D, and u denote the birth, death, and mutation rates, respectively. We assume that $0 \le D < L$ and $0 < u = 1$.

The initial conditions for the pre-treatment system (1) are given as constants $N(0) = N_0 \neq 0$ and $R(0) = 0$. The initial conditions for the system (2) are $N(t^*)$ and $R(t^*)$, which are the solutions of (1) at $t = t^*$.

In this model we assume that both the wild-type and the resistant (mutated) cells have the same birth and death rates, as assumed in Komarova [9].

The time of the beginning of the treatment, t^*, is related to the size of the tumor at that time. If we assume that the total number of cancer cells at time t^* is M, we can use the exponential growth of cancer and the fact that the mutation rate u is relatively small, to estimate t^* as

$$t^* \approx \frac{1}{L-D} \ln \frac{M}{N_0}. \tag{3}$$

III. Analysis and results

By solving the linear system (1), and using (3), we find that the solution for $R(t)$ is given by:

$$R(t^*) = N_0 u t^* e^{(L-D)t^*} \approx \frac{Mu \ln(M/N_0)}{L(1-D/L)}. \tag{4}$$

Here M is the total number of cancer cells when the therapy begins.

The expression for $R(t^*)$ contains the turnover ratio D/L. Therefore we see that the amount of resistant mutants generated before the beginning of the treatment clearly depends on the turnover rate. The slower the growth of the cancer is (i.e., the closer the turnover rate D/L is to 1) the larger is the amount of pre-treatment drug resistance. Conversely, the faster the tumor grows (i.e., the closer the turnover rate is to zero) the smaller is the resistance that develops prior to the beginning of the treatment. The result is natural since a tumor having a lower death rate will reach detection size with fewer divisions (and therefore fewer mutations) than a tumor with a higher death rate.

Now, assume that mutations could be terminated after time t^*, the time at which the therapy starts, so that the only drug resistance that is present after t^* would be the "progeny" of the resistance generated before therapy started. We refer to such resistance as the "pre-treatment resistance at time t", where t is the time from the start of the treatment, and denote it by $R^p(t)$. Note that $R^p(t)$ is simply the solution of system (1) at time t^* that is then multiplied by an exponential term $e^{(L-D)t}$ that accounts for the growth of this resistance during treatment, that is

$$R^p(t) = \frac{Mu \ln(M/N_0)}{L(1-D/L)} e^{(L-D)t}. \tag{5}$$

Equation (5) clearly shows how the amount of resistance generated before the beginning of the treatment and present, including its progeny, at any given time afterward depends on the turnover rate. Using the same methods, such dependence can be shown to be present also in the case of a multi-drug therapy. We would like to note the simplicity of our mathematical approach with respect to the much more sophisticated one taken by Komarova. Of course our result is only about the average behavior of the drug resistant population, given our deterministic approach.

IV. Discussion

A puzzling issue is the source of the apparent contradiction between our result and the result of Komarova [9]. A possible cause could be found in the different mathematical techniques used: while in this work we use a deterministic approach that deals with numbers of cells, in [9] the quantities of interest are probabilities. Can this be the source of the contradicting results?

Clearly, the answer must be negative. The reason for this difference is due to the fact that Komarova studies the probability to have such resistance in the limit, as $t \to \infty$. It is actually only at $t = \infty$ that the results of [9] show a lack of dependence of the resistance on the turnover rate (see page 365, equation (49) and the following discussion in [9]). Therefore these results do not hold at any finite time.

This result can be further understood by the following argument. Using techniques of branching processes we were able to calculate the probability to have resistant mutants generated before the beginning of the treatment and present, including their progeny, at some given time afterward. This probability is given by the following formula

$$P_R(t) = 1 - \exp\left(-uM \frac{L}{De^{-(L-D)t}} ln\left(\frac{1}{1 - \frac{De^{-(L-D)t}}{L}} \right) \right). \quad (6)$$

Here the time t is measured from the start of the treatment. Once again it is clear that this probability given by (6) does depend on the cancer turnover rate for any finite time t. It is only asymptotically that such dependence will disappear. The strength of such dependence will depend on the actual values of the parameters.

Furthermore, the conclusion in [9] that, in the single drug case, the probability of treatment success does not depend on the turnover rate (see page 352, [9]), is related to the definition of a successful treatment as a complete extinction of the tumor as time becomes infinite. Different definitions of a successful treatment (such as allowing tumors not to exceed a certain size or simply considering finite times) will lead to a dependence on the turnover rate also in the single drug case.

While from a mathematical point of view, it is a common practice to compute asymptotics as $t \to \infty$, in our opinion it is more desirable in the problem of drug resistance (and its related concept of treatment success) to study the dynamics for finite time, a time that is at most of the order of several years.

V. Conclusions

Our goal was to understand the reasons behind the difference in the results of Komarova [9] for the single and multi-drug cases. In order to accomplish this goal we have used a different, much simpler approach, based on an elementary compartmental system of linear ordinary differential equations, rather than on stochastic processes. In particular we wanted to understand if it is true that in the case of a single drug treatment, drug resistance (and therefore treatment success) is independent of the cancer's turnover rate.

We have shown that for the single drug case, Komarova's results do not hold at any finite time. This is due to the fact that all quantities of interest are defined only as $t \to \infty$ in [9]. The dependence on the turnover rate in the single drug case is simply weaker that the dependence in the multi-drug case. The asymptotic analysis in [9] loses this information.

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