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Dynamics of targeted cancer therapy

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Targeted cancer therapies offer renewed hope for an eventual 'cure for cancer'. At present, however, their success is often compromised by the emergence of resistant tumor cells. In many cancers, patients initially respond to single therapy treatment but relapse within months. Mathematical models of somatic evolution can predict and explain patterns in the success or failure of anticancer drugs. These models take into account the rate of cell division and death, the mutation rate, the size of the tumor, and the dynamics of tumor growth including density limitations caused by geometric and metabolic constraints. As more targeted therapies become available, mathematical modeling will provide an essential tool to inform the design of combination therapies that minimize the evolution of resistance.

Targeted cancer therapy

Targeted cancer therapies are drugs that interfere with specific molecular structures implicated in tumor development [1]. In contrast to chemotherapy, which acts by killing both cancer cells as well as normal cells that divide rapidly, targeted therapies are a much sharper instrument and offer the prospect of more effective cancer treatment, with fewer side effects. Most targeted therapies are either small-molecule drugs that act on targets found inside the cell (usually protein tyrosine kinases) or monoclonal antibodies directed against tumor-specific proteins on the cell surface [2].

The first drug that was rationally developed to block a known oncogene was imatinib, a small-molecule drug that effectively blocks the activity of the BCR-ABL kinase protein in chronic myeloid leukemia (CML) [3]. The success of imatinib for treating CML is striking: the response rate to imatinib treatment is 90% compared with 35% that can be achieved with conventional chemotherapy [4]. Moreover, most patients taking imatinib achieve complete cytogenetic remission and those who do have an overall survival rate similar to the general population [5,6]. Unfortunately, many of the more recent targeted therapies are not as successful over time. An example is the EGFR tyrosine kinase inhibitor gefitinib, used to treat the 10% of patients with non-small cell lung cancer (NSCLC) who have EGFR-activating mutations. Patients taking gefitinib have a higher response rate and longer progression-free survival (75% and 11 months, respectively) compared with those treated with standard chemotherapy (30% and 5 months); however, after 2 years, disease progresses in more than 90% of patients who initially responded to gefitinib treatment [7].

The failures of targeted therapies in patients who initially respond to treatment are usually due to acquired resistance. This resistance is often caused by a single genetic alteration in tumor cells, arising either before or during treatment [8,9]. In the case of CML, several mutations in the *BCR-ABL* kinase domain have been shown to cause resistance to imatinib [10]. In the case of NSCLC, a mutation in *EGFR* is observed in approximately 50% of patients [11,12]. The mutation that confers resistance to targeted therapy does not necessarily arise in the gene that is targeted. For example, resistance to BRAF inhibitor PLX4032 (vemurafinib), used in the treatment of melanomas, does not occur via mutations in the *BRAF* gene [13].

The current situation has interesting parallels to the treatment of HIV with AZT (coincidentally, a failed cancer drug) in the 1990s. AZT impedes HIV progression, but during prolonged treatment the virus usually develops resistance. It was only after the introduction of combination therapies with several HIV inhibitors that the disease became controllable in most patients. The hope for cancer is that similarly, as more targeted therapies become available, combination targeted therapies will be able to achieve indefinite remission in most cancer patients. However, the situation in cancer is more complicated than in HIV: because every cancer is genetically unique, many targeted therapies are needed for effective combination therapies to be available for all cancers.

To understand why some targeted therapies succeed while others ultimately fail, it is important to study the evolutionary process by which resistance arises. Mathematical evolutionary models have previously provided great insight into the gradual escape of HIV from the immune system [14–18] and the response of HIV to treatment [19–21], and similar models can be applied to the evolution of tumors.

Modeling the evolution of resistance to cancer therapy

Evolutionary modeling of cancer has a rich history dating to the 1950s, when Nordling [22] and Armitage and Doll [23,24] showed how patterns in the age incidence of cancer could be explained by somatic evolutionary processes involving multiple mutations. Mathematical evolutionary models have elucidated important patterns in the genetic and clinical progression of cancer [25–32] and its response to treatment [33–36]. Attolini and Michor [37] provide a comprehensive review of the history and development of this field.

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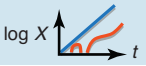
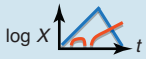
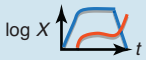
Table 1. Models of the evolution of resistance to cancer therapy

Event of interest	Model of tumor dynamics[a]	Refs
Resistant cells exist when tumor reaches detectable size	Exponential growth 	[33,36,38,40,41,43,45]
Treatment fails due to resistance acquired during treatment	Exponential decay 	[47,48]
Treatment fails due to resistance acquired before or during treatment	Exponential growth, then decay during treatment 	[35,50]
Treatment fails due to resistance acquired before or during treatment	Density-dependent growth, then decay during treatment 	This work

[a]Blue curves show the dynamics of sensitive cells, whereas red curves show a possible (stochastic) trajectory of the resistant cell population. In some cases, resistant cells may arise and subsequently disappear due to stochastic drift.

Evolutionary modeling is particularly useful for understanding the emergence of acquired resistance to treatment, either conventional chemotherapy or targeted therapy (Table 1). Investigations of this question usually model tumor growth and evolution as a branching process – a stochastic process in which cells divide and die at random. Mutations that confer resistance appear at random during cell divisions. In most models, the tumor and its clonal subpopulations (including those resistant to treatment) grow exponentially on average. However, many clones that arise subsequently disappear due to stochastic drift – fluctuations caused by randomness in cell division and death.

Goldie and Coldman [38–44] were the first to mathematically investigate the evolution of resistance to cancer therapy (chemotherapy, in their case). Specifically, they calculated the probability that resistant cells exist in a tumor that has grown exponentially to a certain size. One assumption made in their models is that resistance mutations are neutral (that is, they have no effect on fitness in the absence of treatment). Later work by Iwasa *et al.* [36], Haeno *et al.* [45], and Durrett and Moseley [46] relaxed this assumption by including the possibility that resistance mutations also confer a fitness advantage or disadvantage. A common feature of these investigations is their focus on the question of whether resistant cells exist in a tumor of detectable size. Although this is a valuable question, it does not fully address whether treatment will eradicate the tumor because resistant cells may disappear during treatment due to stochastic drift, especially if they are only present in small numbers when treatment begins.

More recent work [47–49] has addressed the probability that a treatment will eradicate a tumor, if a given number of resistant cells are present at the start of treatment. In these models, the number of sensitive cells declines exponentially due to treatment. The number of resistant cells is expected to grow exponentially on average, but they may be eliminated due to stochastic drift. In these studies, the probability of eradication was calculated in a variety of situations, including cases in which multiple mutations are required for resistance (e.g., when combination therapies are used). The formulas derived there provide an important component for calculating the overall probability of tumor eradication.

Komarova and Wodarz [35,50] derived an overall formula for the probability of tumor eradication in a fully stochastic model. They considered a tumor cell population that grows exponentially up to a certain size until treatment begins. During treatment, the number of sensitive cells declines exponentially, as in previous models. In their model, resistance can arise either before or during treatment. The authors calculated the probability of tumor eradication, based on the size of the tumor at the start of treatment and the rate at which resistance mutations appear. They found that resistance is more likely to arise during tumor growth rather than treatment. This effect is magnified if resistance requires multiple mutations (e.g., in the case of several drugs). A limiting assumption in this model is that tumors grow exponentially until treatment is initiated. Although tumors are believed to initially grow exponentially, their growth can slow as they expand, due to nutrient shortages or geometric constraints [51–53]. Because of these restrictions, tumors often reach a steady state, with little or no tumor growth until further mutations arise [54–56].

Effects of density dependence on the evolution of resistance

We present a method for quantifying the evolution of resistance in tumors that grow subject to density limitations. We assume that tumor growth is initially exponential, but this growth slows as the tumor size increases, and the tumor eventually reaches a steady state. In this steady state, density constraints prevent further growth, unless new mutations arise that allow the tumor to overcome these constraints. The key parameters of our model are the number N of tumor cells at steady state; the time T that the tumor remains at steady state before treatment; the initial rates of division (r) and death (d) of tumor cells; the rate u at which resistance mutations are produced; and the division and death rates (r' and d', respectively) of sensitive cells under treatment, in the absence of density constraints.

Mathematically, this method is based on a density-dependent branching process model of tumor growth. In this model, tumor evolution starts with a single sensitive cell. Sensitive cells divide at rate $r/(1 + \eta X)$ and die at rate d, where X is the current total number of cells in the tumor and $\eta = (r - d)/(Nd)$. From these formulas we can see that tumor growth is initially exponential with rate $r - d$, but that the division rate decreases as the tumor approaches size N. The net growth rate, $r/(1 + \eta X) - d$, is positive for $X < N$ and negative for $X > N$, thus the tumor will remain at approximately size N (steady state), with small fluctuations, until treatment starts. At every division, one of the daughter cells will, with probability u, receive a mutation conferring resistance to treatment. We initially assume that resistance mutations are selectively neutral before treatment. After the tumor has been at steady state for time T, treatment is initiated. We assume that treatment affects only sensitive cells, reducing their division rate to $r'/(1 + \eta X)$ with $r' \leq r$, and increasing the death rate to $d' \geq d$. We assume that $r' < d'$, so that the sensitive cell population declines approximately exponentially during treatment (otherwise the treatment is ineffective).

The dynamics of tumor size in this model can be approximately described by three phases: (i) expansion (up to size N); (ii) steady state (for time T); and (iii) treatment (Figure 1).

Resistance mutations can arise during any of the three phases. However, the majority of resistance mutations will die out shortly after being produced, due to stochastic drift. For example, during the expansion and treatment phases, new resistance mutations disappear with probability approximately d/r, and those resistance mutations that do not survive drift have a median lifetime of $\log(2-d/r)/(r-d)$ days [57]. For the parameter values $r = 0.25$/day, $d = 0.24$/day [31,54], only one out of every 25 resistance mutations survives stochastic drift, and the majority disappear within 5 days. Even resistant clones that grow to 20 cells still have a 44% $[=(d/r)^{20}]$ chance of disappearing due to drift. Resistance mutations arising during steady state have even slimmer chances: such a mutation has probability $1/(1 + dt)$ of surviving for t days after being produced. This probability decreases to zero as t increases.

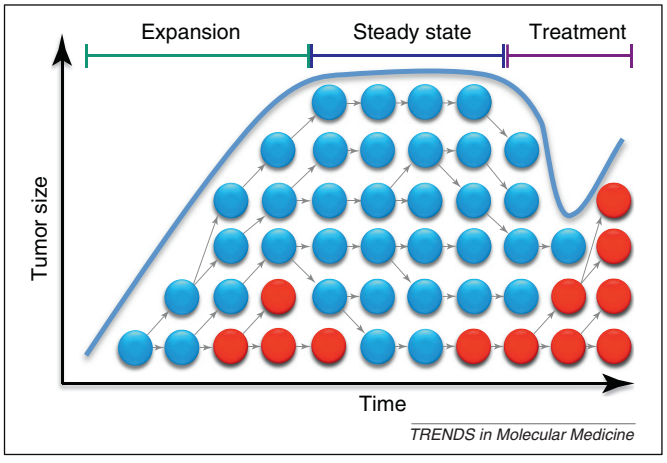


Figure 1. Density-dependent model of the evolution of acquired resistance. Sensitive cells (blue) initially grow exponentially, but this growth slows due to density constraints. Resistant cells (red) arise through mutation. When treatment begins the sensitive cells decline, leaving room for resistant cells to grow.

Treatment will eradicate the tumor as long as no resistance mutations survive long enough to cause treatment failure. Considering that resistance mutations can arise during any phase, we write the overall probability P of tumor eradication as:

$$P = P_1 P_2 P_3.$$

Here P_1, P_2, and P_3 are the probabilities that no resistance mutations leading to treatment failure arise during expansion, steady state, and treatment, respectively.

P_1, the probability that no resistance mutation leading to treatment failure arises during expansion, is calculated in the supplementary material as:

$$P_1 = \exp\left(-Nu\frac{1-\xi}{d/r-\xi}\log\left(\frac{1-\xi}{1-d/r}\right)\right),$$

$$\xi = \frac{d(r-d)T+d}{d(r-d)T+r}.$$

P_2, the probability that no resistance mutation leading to treatment failure arises during steady state, is also calculated in the supplementary material as:

$$P_2 = \left(1+\frac{d}{r}(r-d)T\right)^{-Nu}.$$

P_3, the probability that no resistance mutation leading to treatment failure arises during treatment, was calculated in previous work [47–49]:

$$P_3 = \exp\left(-Nu\frac{r-d}{r}\frac{r'}{d'-r'}\right).$$

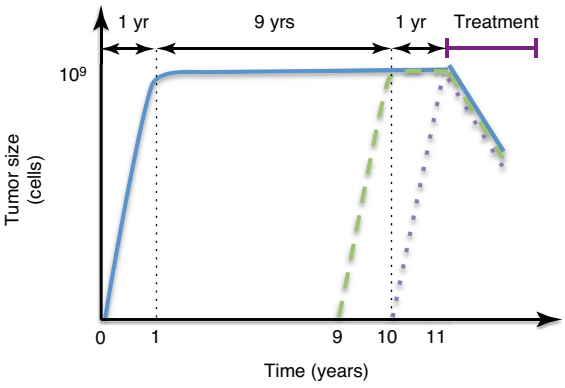
The accuracy of our formula for the probability of tumor eradication, using the above expressions for P_1, P_2, and P_3, is verified by simulations in the supplementary material (Figure S1).

The formulas above apply to the case that resistance mutations are selectively neutral. In the supplementary material, we also consider resistance mutations that carry a fitness cost, so that resistant cells divide at a reduced rate $\hat{r}/(1 + \eta X)$, with $\hat{r} < r$. The analysis is similar in this case, but the formulas for P_1, P_2, and P_3 are more complicated.

These formulas allow us to compare the relative importance of the three phases to the overall probability of eradication (Figure 2). Suppose, for example, that a tumor remains in steady state for a long period of time ($T \to \infty$). In this case, if resistance mutations are neutral (before treatment), P_1 increases to 1 and P_2 decreases to zero, while P_3 remains constant. Thus, treatment failure is probable in this case, due to resistance acquired during steady state. The outcome is similar if resistance mutations are costly, except that P_2 decreases not to zero but to an intermediate value:

$$P_2 \to \left(\frac{r-d}{\hat{r}-d}\right)^{-Nur/\hat{r}}.$$

In the opposite scenario, if treatment begins while the tumor is expanding (i.e., $T = 0$ and there is no steady state), our method reproduces results obtained by Komarova and Wodarz [35] using their biphasic (expansion then treatment) model. Their results (and ours) indicate that acquired resistance leading to treatment failure is more



Time spent at steady state (years)	Probability that treatment fails due to resistance acquired during…			Probability of treatment success ($P = P_1P_2P_3$)
	Growth ($1\text{-}P_1$)	Steady state ($1\text{-}P_2$)	Treatment ($1\text{-}P_3$)	
0	0.63	0	0.03	0.36
1	0.35	0.78	0.03	0.14
10	0.10	0.97	0.03	0.02

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Figure 2. Treatment failure due to resistance acquired during three phases of tumor dynamics. Top: sample growth trajectories of three tumors, which spend different amounts of time at steady state ($N = 10^9$) before treatment. Bottom: probabilities of treatment failure due to resistance acquired during each of the three phases, and overall probability of treatment success, for these three trajectories. As more time is spent in steady state, treatment failure becomes increasingly probable, due to resistance acquired during this phase.

likely to arise during expansion than during treatment (in symbols, $P_3 > P_1$). This is true as long as the decline of sensitive tumor cells during treatment is faster than their growth during the expansion phase – a reasonable assumption for most targeted cancer therapies.

A common feature of all our results is that the probability of tumor eradication can be expressed as M^{-Nu}, where M is a positive quantity that depends on T, r, r', and d, but not on N or u. From this insight, we reason that (a) for $Nu \ll 1$, tumor eradication is almost certain; (b) for $Nu \gg 1$, treatment failure is almost certain; and (c) in between these two regimes, the probability of eradication declines sharply as Nu increases. A useful rule of thumb is that doubling the value of Nu has the effect of squaring the probability of treatment success. (For example, a 60% success probability would become 36% if Nu were doubled.) This exponential dependence on the product of tumor size and mutation rate was first noticed by Goldie and Coldman [38], who considered only the more limited question of whether resistant cells exist after a tumor grows exponentially up to a certain size. Our findings extend this principle to the entire process of density-dependent tumor growth and treatment.

In Table 2 we show numerical results for the probability of treatment success as a function of the number of cells at steady state, N, and time spent there, T. These results illustrate points (a), (b), and (c) above. Additionally, they show that when N and $1/u$ are of similar orders of magnitude, the time spent at steady state has a significant effect on probability of treatment success. For example,

Table 2. The probability of treatment success, depending on tumor size and time spent at steady state[a]

	$T = 0$	$T = 1$ year	$T = 10$ years
Neutral			
$N = 10^7$	0.990	0.981	0.964
$N = 10^8$	0.902	0.822	0.690
$N = 10^9$	0.357	0.140	0.024
$N = 10^{10}$	0.0	0.0	0.0
Deleterious			
$N = 10^7$	0.992	0.987	0.986
$N = 10^8$	0.925	0.881	0.867
$N = 10^9$	0.459	0.283	0.241
$N = 10^{10}$	0.0	0.0	0.0

[a]Parameter values: $r = 0.25$, $r' = 0.1$, $d = d' = 0.24$, $u = 10^{-9}$. A deleterious resistant cell has a fitness disadvantage of 1% before treatment compared with sensitive cells ($\hat{r} = 0.99\ r$).

when $N = 10^9$ (which corresponds to a tumor of approximately 1 cm^3) and resistance mutations arise at rate $u = 10^{-9}$, waiting to treat for a year after the tumor reaches the carrying capacity decreases the probability of treatment success from 36% to 14%. Waiting for 9 more years further decreases this chance to only 2%. This result reveals that treatment success depends critically not only on the size of the tumor but also its age, underscoring the importance of early detection and treatment.

Another important question is how long the treatment should last in order to eradicate all sensitive cells in the tumor. In the supplementary material we calculate the time until there is probability p that all sensitive cells have been eradicated:

$$t = \frac{1}{d' - r'} \log\left(\frac{-d' + r' p^{1/N}}{-d' + d' p^{1/N}}\right).$$

For example, in a tumor with $N = 10^9$ cells, using parameter values $r' = 0.22$, $d' = 0.24$, it will take 3.1 years of treatment to achieve a 99% probability that all sensitive cells have been eradicated. If treatment effectiveness is increased so that $r' = 0.1$, $d' = 0.24$, it will only take 0.5 years to achieve a 99% probability of eradication of sensitive cells. We caution, however, that eradication may take significantly longer if there are latent tumor cells unaffected by treatment.

Applications and extensions

We believe our model may be useful in understanding resistance to many targeted therapies, and provides an important correction to models that assume exponential growth. The parameter values, including the division rate, death rate, rate of resistance mutation, and tumor size at steady state, may vary significantly among different types of cancer. Additionally, it may be appropriate to vary the functional form of the density limitation depending on the type of cancer (e.g., density limitations may apply differently in liquid versus solid tumors). However, our results remain applicable to other forms of density dependence as long as the three-phase approximation (exponential growth, steady state, treatment) is reasonably accurate.

Another important consideration in applying our model to different treatments is that some tumor cells may be

incapable of regrowing a tumor, even if they carry a resistance mutation. This situation can be addressed by considering an 'effective population size' – equal to the number of cells that could seed or regrow a tumor – in place of the actual number of cells.

We note that many of our results can also be applied to the evolution of resistance to conventional chemotherapy. However, failures of chemotherapy are often due to factors other than acquired resistance, such as toxicity to the patient.

The quantitative predictions of our model are empirically testable. For instance, our model predicts a negative exponential relationship between the number of tumor cells and the probability of tumor eradication. This can be tested using data on treatment success rates for different tumor sizes. If, in addition, the tumor age [32], resistance mutation rate, and other parameters can be estimated, the formulas we present for tumor eradication probabilities can be tested directly.

Concluding remarks and future perspectives

Mathematical modeling is an important tool for understanding the failure of targeted cancer therapies due to acquired resistance. Previous research on this question has focused mostly on resistance arising either during exponential tumor growth or during treatment. We show that phases of slow or no tumor growth are also clinically important in that they present an opportunity for resistance mutations to arise, thereby decreasing the chance of treatment success. Future models might incorporate more complex tumor dynamics, including different forms of density dependence [51,52] and/or alternating phases of growth and stasis.

As in the case of HIV, successful treatment of most cancers will probably require combination targeted therapy [58–61]. As more and more targeted therapies become available, the major challenge will be formulating effective combination therapies that minimize both the likelihood of resistance and toxicity to the patient. Mathematical models can help predict the success of potential combination therapies in advance of clinical trials.

Appendix A. Supplementary material

Supplementary material associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molmed.2012.04.006.

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Supplementary Material

Dynamics of Targeted Cancer Therapy

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1 Model of tumor growth and evolution of resistance

Here we present a mathematical model for the evolution of resistance to target cancer therapy in tumors with density-dependent growth. Our model is a two-type density dependent branching process. (See Athreya and Ney [S1] for background on branching processes.)

We consider two cancer cell types: *sensitive* and *resistant*. The numbers of sensitive and resistant cells present at any given time t are represented by the random variables $X_{\rm s}(t)$ and $X_{\rm r}(t)$, respectively. The total number of cells is denoted $X(t) = X_{\rm s}(t) + X_{\rm r}(t)$.

We initially suppose that, prior to treatment, sensitive and resistant cells have the same division and death rates. (We will relax this assumption in Section 5 to include the possibility that resistance comes with an associated fitness cost.) Each cell divides stochastically at rate $r/(1+\eta X)$ per unit time, where the constant η quantifies the extent of density dependence. Cell death also occurs stochastically, at rate d per cell.

From these division and death rates, we calculate the that the tumor has an overall carrying capacity of $N = \eta^{-1}(r/d - 1)$ cells. At carrying capacity, the expected size of the tumor remains constant, though stochastic fluctuations will occur.

We suppose that the tumor is initiated by a single sensitive cell. Mutation from sensitive to resistant type occurs at rate u, so that with each division of a sensitive cell, there is probability u that one of the daughter cells will be resistant. We disregard the possibility of back-mutation from resistant to sensitive cells.

When treatment begins, the division rate of sensitive cells is reduced to $r'/(1+\eta X)$ with $r' \leq r$, and their death rate is increased to $d' \geq d$, with $r' < d'$. The resistant cells are unaffected by treatment.

2 Three-phase approximation

To mathematically analyze this model, we approximate the process of tumor growth, evolution, and treatment by three phases:

- *Expansion:* The tumor grows exponentially. Both types divide at rate r and die at rate d. This phase lasts until the tumor reaches its carrying capacity N.
- *Steady state:* The tumor has reached carrying capacity. The division and death rates of both types are equal to d. The tumor is in steady state for time T.
- *Treatment:* When treatment is occurring, sensitive types have division rate r' and death rate d', while resistant types have birth rate r and death rate d.

We approximate each of these phases as a density-*independent* branching process, with different birth and death rates for each phase, as described

above. This allows us to use established results in calculating the probability of treatment success. This three-phase scheme is an approximation to the model, because it does not include the transitions between the first and second or second and third phases. During these transitions, the tumor is near but not at carrying capacity, and thus the birth rates take on intermediate values between r and d.

We now investigate these three phases in further detail, highlighting previous results that we will use in our analysis.

2.1 Expansion

For our density-independent branching process approximation to the expansion phase, Iwasa et al. [S2] derived the following generating function for the number of resistant cells at the termination of this process:

$$G_1(\xi) \equiv \mathrm{E}\left[\xi^{X_\mathrm{r}}\right] = \exp\left(-Nu\frac{1-\xi}{d/r-\xi}\log\left(\frac{1-\xi}{1-d/r}\right)\right). \tag{S1}$$

2.2 Steady state

In our approximation of the steady state phase, the branching process is critical with birth rate d (or r in the alternate convention). The generating function for such a branching process is [S1]:

$$G_2(\xi,t) \equiv \mathrm{E}\left[\xi^{X_\mathrm{r}(t)}\right] = \frac{dt(1-\xi)+\xi}{dt(1-\xi)+1}, \tag{S2}$$

In the alternate convention in which density dependence affects death, d is replaced by r in the above expression for $G_2(\xi,t)$.

2.3 Treatment

According to our approximation of the treatment phase, each resistant lineage which is present at the beginning of the treatment phase will go extinct during treatment with probability d/r. Thus if there are x resistant cells present at the start of treatment, then the probability that all the lineages of these cells will go extinct during treatment is $(d/r)^x$.

If no resistant cells are present when treatment starts, the probability that resistant cells will arise during and survive through treatment was calculated

by Michor et al. [S3], using a model that coincides with our approximation to the treatment phase. This probability is given by

$$P_3 = \exp\left(-Nu\frac{r-d}{r}\frac{r'}{d'-r'}\right). \tag{S3}$$

3 Analytical calculation of treatment success probability

We are interested in the probability of treatment success. This is equivalent to the probability that no ultimately successful lineages of resistant cells arise—where "ultimately successful" means that the lineage survives through the entire process, including treatment. Since resistant cells can arise during any of the three phases, we express the overall probability of treatment success as

$$P = P_1 P_2 P_3, \tag{S4}$$

where P_1, P_2 and P_3 represent the probabilities that no ultimately successful lineages of resistant cells arise during the expansion, steady state, and treatment phases, respectively. P_3 is given by (S3). We calculate P_1 and P_2 in the following subsections.

3.1 Lineages arising during expansion

To calculate P_1, we first consider a single resistant lineage that is present at the start of the steady state phase. The number of cells present in this lineage at the end of steady state is the random variable $X_{\mathrm{r}}(T)$, which has generating function $G_2(\xi, T) = \mathrm{E}\left[\xi^{X_{\mathrm{r}}(T)}\right]$. For a particular value of $X_{\mathrm{r}}(T)$, the lineage will be extinct by the end of the treatment phase with probability $(d/r)^{X_{\mathrm{r}}(T)}$ (see Section 2.3). So overall, the probability that the lineage is extinct by the end of treatment phase is

$$\mathrm{E}\left[(d/r)^{X_{\mathrm{r}}(T)}\right] = G_2(d/r, T) = \frac{dT(r-d)+d}{dT(r-d)+r}.$$

To find the probability that no lineages arising in stationary phase survive through treatment phase, we plug this value into the generating function G_1—defined in (S1)—corresponding to the expansion phase:

$$P_1 = G_1\big(G_2(d/r, T)\big). \tag{S5}$$

3.2 Lineages arising during steady state

To calulate P_2, we consider a single lineage that arises at time $t_0 < T$. By the reasoning used in the previous section, the probability that this lineage is extinct by the end of treatment phase can be expressed as

$$G_2(d/r, T-t_0) = \mathrm{E}\left[(d/r)^{X_\mathrm{r}(T-t_0)}\right] = \frac{d(T-t_0)(r-d)+d}{d(T-t_0)(r-d)+r}.$$

Since new resistant lineages arise at rate dNu, the probability that an ultimately successful lineage arises during the time interval $[t, t+dt)$ is

$$dNu\left(1 - \frac{d(T-t)(r-d)+d}{d(T-t)(r-d)+r}\right) dt.$$

Thus the probability that no ultimately successful lineage arises during steady state can be obtained as

$$\begin{aligned} P_3 =& \exp\left(-\int_0^T dNu\left(1 - \frac{d(T-t)(r-d)+d}{d(T-t)(r-d)+r}\right) dt\right) \\ =& \left(1 + \frac{d}{r}(r-d)T\right)^{-Nu}. \end{aligned} \tag{S6}$$

3.3 Overall probability of treatment success

Combining (S4), (S3), (S5), and (S6), we obtain the overall probability of treatment success as

$$\begin{aligned} P =& P_1 P_2 P_3 \\ =& G_1\big(G_2(d/r, T)\big) \times \left(1 + \frac{d}{r}(r-d)T\right)^{-Nu} \times \exp\left(-Nu\frac{r-d}{r}\frac{r'}{d'-r'}\right). \end{aligned} \tag{S7}$$

We note that, as stated in the main text, P_1, P_2 and P_3—and therefore the overall probability P—can all be expressed in the form M^{-Nu}, where M does not depend on N or u. The same is true in the case that resistance mutations carry a fitness cost (Section 5).

4 Limiting cases

4.1 The case $T = 0$

$T = 0$ represents the case that treatment begins while the tumor is still growing exponentially. In this case, N represents the number of tumor cells present at the start of treatment, rather than the carrying capacity. This case was analyzed by Komarova and Wodarz [S4,S5], and the results we present here coincide with theirs.

For $T = 0$, we calculate

$$P_1 = G_1\big(G_2(d/r, 0)\big) = \lim_{\xi \to d/r} G_1(\xi) = e^{-Nu}.$$

P_2 is clearly equal to 1 for $T = 0$ (that is, since the steady state phase is bypassed in the case $T = 0$, resistant lineages cannot arise during steady state). The overall probability P of resistance in the case $T = 0$ is equal to

$$P = P_1 P_3 = \exp\left[-Nu\left(1 + \frac{r-d}{r}\frac{r'}{d'-r'}\right)\right].$$

We note that if the condition

$$\frac{r'}{r}\frac{r-d}{d'-r'} < 1$$

is satisfied, then resistance leading to treatment failure is more likely to arise during growth than during treatment ($P_1 < P_3$). Since $r' \leq r$, the condition $d' - r' > r - d$ (that is, the decline of sensitive cells during treatment is faster than their growth during expansion) is sufficient to imply $P_1 < P_3$.

4.2 The limit $T \to \infty$

4.2.1 Resistance arising during growth

As $T \to \infty$, $G_2(d/r, T) \to 1$, and hence $P_1 = G_1\big(G_2(d/r, T)\big) \to G_1(1) = 1$. This expresses the fact that, as time spent in steady state goes to infinity, the probability that a resistant lineage will arise during growth and survive through treatment goes to zero.

4.2.2 Resistance arising during steady state

For the probability that no resistant types arise during steady state and survive through treatment, we have:

$$\lim_{T\to\infty} P_2 = \lim_{T\to\infty} \left(1 + \frac{d}{r}(r-d)T\right)^{-Nu} = 0.$$

Thus the overall treatment success probability $P = P_1P_2P_3$ also goes to zero as $T \to \infty$.

5 The case of deleterious resistant types

The above analysis assumes that resistant cells are selectively neutral in the absence of treatment. However, treatment resistance may be costly; for example, it may expend energy that could otherwise be put towards reproduction. It is therefore important to consider deleterious resistance mutations.

For this section we suppose that resistant types reproduce at rate $\hat{r}/(1+\eta X)$, while sensitive types divide at rate $r/(1+\eta X)$. The death rate is d for both types. We suppose resistant types are less fit than sensitive types, but still fit enough to grow in the absence of density-dependent constraints; that is, $d < \hat{r} < r$.

For the treatment phase we suppose, as above, that the resistant types are unaffected, while the sensitive types have their division rate reduced to $r'/(1+\eta X)$, with $r' \leq r$ and their death rate increased to $d' \geq d$, with $r' < d'$.

The mathematical analysis of this case proceeds along the same lines as the neutral case. We again use a three-phase approximation and calculate the probability of treatment success as $P = P_1P_2P_3$, where P_1, P_2, and P_3 have the same meanings as above. The only difference lies in the generating functions that are used.

5.1 Generating functions

5.1.1 Expansion

In the expansion phase, For the expansion phase, we have from [S2]

$$G_1(\xi) \equiv \mathrm{E}\left[\xi^{X_\mathrm{r}}\right] = \exp\left[-\frac{Nu}{1-d/r}\left(1 - \int_0^1 g_{Nx}(\xi)\, dx\right)\right],$$

where $g_{Nx}(\xi)$ is the generating function for a resistant lineage that arises when there are Nx sensitive cells:

$$g_{Nx}(\xi) = \frac{(\xi - 1)\, d/\hat{r}\, x^{-\alpha} - (\xi - d/\hat{r})}{(\xi - 1)x^{-\alpha} - (\xi - d/\hat{r})},$$

and

$$\alpha = \frac{\hat{r} - d}{r - d}$$

is the ratio of resistant cell growth rate to sensitive cell growth rate. The generating function $G_1(\xi)$ can also be expressed in terms of the hypergeometric function ${}_2F_1$:

$$G_1(\xi) = \exp\left[-Nu\alpha\frac{r}{d}\ {}_2F_1\left(1, \alpha^{-1}, 1 + \alpha^{-1}, \frac{\hat{r} - d\xi}{d(1 - \xi)}\right)\right]. \tag{S8}$$

5.1.2 Steady state

For the equilibrium phase, we have $r/(1 + \eta X) = d$. Thus the reproduction rate of resistant types is

$$\hat{r}/(1 + \eta X) = \hat{r}\, d/r.$$

The generating function for resistant cells in the steady state phase is therefore [S1]:

$$G_2(\xi, t) \equiv \mathrm{E}\left[\xi^{X_r(t)}\right] = \frac{(\xi - 1)\frac{r}{\hat{r}} \exp\left(\frac{d(\hat{r}-r)}{r}t\right) - (\xi - \frac{r}{\hat{r}})}{(\xi - 1)\exp\left(\frac{d(\hat{r}-r)}{r}t\right) - (\xi - \frac{r}{\hat{r}})}. \tag{S9}$$

5.1.3 Treatment

In the treatment phase, resistant types divide at rate $\hat{r}$ and die at rate d. The extinction probability of each lineage is therefore $d/\hat{r}$.

5.2 Treatment success probability

5.2.1 Lineages arising during expansion

Following the logic of Section 3.1, the probability that no ultimately successful lineage arises during expansion is

$$P_1 = G_1\big(G_2(d/\hat{r}, T)\big), \tag{S10}$$

using the formulas (S8) and (S9).

5.2.2 Lineages arising during steady state

Following the logic of Section 3.2, the probability that no ultimately successful lineage arises during steady state can be obtained as

$$\begin{aligned} P_2 &= \exp\left(-\int_0^T dNu\big(1-G_2(d/\hat{r},T-t)\big)\,dt\right) \\ &= \left(\frac{r-d-(\hat{r}-d)\exp\left(\frac{-dT(r-\hat{r})}{r}\right)}{r-\hat{r}}\right)^{-Nur/\hat{r}} . \end{aligned} \tag{S11}$$

5.2.3 Lineages arising during treatment

The probability that no successful resistant lineages arise during treatment is given by [S3]:

$$P_3 = \exp\left(-Nu\frac{\hat{r}-d}{\hat{r}}\frac{r'}{d'-r'}\right). \tag{S12}$$

5.2.4 Overall treatment success probability

We calculate the overall treatment success probability $P = P_1P_2P_3$, using (S10), (S11), and (S12), as

$$P = G_1\big(G_2(d/\hat{r},T)\big) \times \left(\frac{r-d-(\hat{r}-d)\exp\left(\frac{-dT(r-\hat{r})}{r}\right)}{r-\hat{r}}\right)^{-Nur/\hat{r}} \times \exp\left(-Nu\frac{\hat{r}-d}{\hat{r}}\frac{r'}{d'-r'}\right).$$

5.3 Limiting cases

5.3.1 The case $T = 0$

For $T = 0$ we have $G_2(d/\hat{r},0) = d/\hat{r}$, thus

$$\begin{aligned} P_1 &= \exp\left[-Nu\alpha\frac{r}{d}\,{}_2F_1\left(1,\alpha^{-1},1+\alpha^{-1},\frac{\hat{r}-d^2/\hat{r}}{d(1-d/\hat{r})}\right)\right] \\ &= \exp\left[Nu\frac{r}{d}\left(1+\frac{\hat{r}}{d}\right)^{-\alpha^{-1}}\beta_{1+\hat{r}/d}(\alpha^{-1},0)\right], \end{aligned}$$

where β is the incomplete Euler beta-function:

$$\beta_x(a,b) = \int_0^z \frac{y^{a-1}}{1-y^{b-1}}\, dy$$
$$\beta_{1+\hat{r}/d}(\alpha^{-1},0) = \int_0^{1+\hat{r}/d} \frac{y^{(r-\hat{r})/(\hat{r}-d)}}{1-y}\, dy.$$

As explained in Section 4.1, $P_2 = 1$ for $T = 0$. P_3 is again given by (S12).

5.3.2 The limit $T \to \infty$

For the limit $T \to \infty$ we have $P_1 = 1$ as explained in Section 4.2.1. For the steady state phase we calculate

$$\begin{aligned} P_2 &= \lim_{T\to\infty} \left(\frac{r-d-(\hat{r}-d)\exp\left(\frac{-dT(r-\hat{r})}{r}\right)}{r-\hat{r}} \right)^{-Nur/\hat{r}} \\ &= \left(\frac{r-d}{r-\hat{r}}\right)^{-Nur/\hat{r}}. \end{aligned}$$

Formula (S12) for P_3 is again unchanged.

6 Length of treatment

In this section we calculate the amount of time needed for treatment to eradicate all sensitive cells in a tumor. We approximate the behavior of sensitive cells during the treatment phase with a subcritical branching process with division rate r' and death rate d'. In this process, a single cell will die by time t with probability [S1]

$$q(t) = \frac{-d' + d'e^{(d'-r')t}}{-r' + d'e^{(d'-r')t}}.$$

If there are N sensitive cells in a tumor, they will die out by time t with probability

$$Q(t) = \left(\frac{-d' + d'e^{(d'-r')t}}{-r' + d'e^{(d'-r')t}}\right)^N.$$

Thus the time needed for all sensitive cells to be eradicated by treatment in a fraction p of tumors that had N cells when treatment started is

$$t = \frac{1}{d' - r'} \log \left(\frac{-d' + r' p^{1/N}}{-d' + d' p^{1/N}} \right).$$

7 Simulations

We employ exact computer simulations of the density-dependent branching process defined in Section 1 of the Appendix in order to test the accuracy of our analytical calculations. In simulations, we assume that the population has reached steady state when the total number of cells in the tumor is 90% of the carrying capacity. In Fig. 1 we show the excellent agreement between the formula for overall probability of treatment (S7) success and simulations.

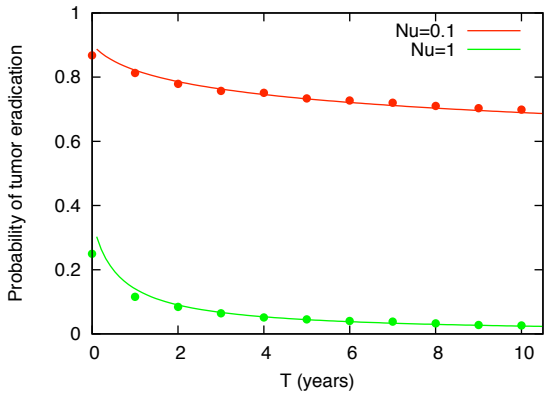

Figure S1: Comparison of formula for overall probability of treatment success (S7) and simulations. Parameter values are $r = 0.25$, $d = d' = 0.24$, $r' = 0.1$, $u = 10^{-5}$. Simulation results are averaged over $10,000$ runs.

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