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.

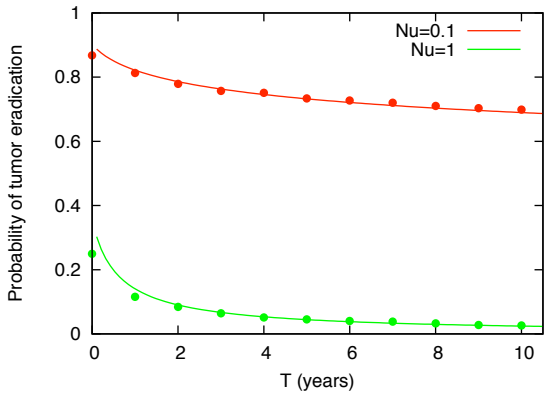

Figure S1: Comparison of formula for overall probability of treatment success (S7) and simulations. Parameter values are $r = 0.25$, $d = d' = 0.24$, $r' = 0.1$, $u = 10^{-5}$. Simulation results are averaged over $10,000$ runs.

Supplementary references

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S5 Komarova, N.L. (2006) Stochastic modeling of drug resistance in cancer. *Journal of Theoretical Biology* 239, 351–366