Evolutionary rescue by aneuploidy in tumors exposed to anti-cancer drugs

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Abstract

Evolutionary rescue happens when a population survives a sudden environmental change that initially causes the population to decline toward extinction. A prime example of evolutionary rescue is the ability of cancer to survive exposure to treatment. One evolutionary mechanism by which a population of cancer cells can adapt to chemotherapy is aneuploidy. Aneuploid cancer cells can be fitter in an environment altered by anti-cancer drugs, e.g., because aneuploidy disrupts the pathways usually targeted by the drugs. Indeed, aneuploidy is highly prevalent in tumors, and some anti-cancer drugs fight cancer by increasing chromosomal instability. Here, we model the impact of aneuploidy on the fate of a population of cancer cells. We use multi-type branching processes to approximate the probability that a tumor survives drug treatment as a function of the initial tumor size, the rates at which aneuploidy and other beneficial mutations occur, and the growth rates of the drug-sensitive and drug-resistant cells. Additionally, we investigate the effect of the pre-existent aneuploid cells on the probability of evolutionary rescue. Finally, we estimate the tumor's mean recurrence time to revert to its initial size following treatment and evolutionary rescue. We propose that aneuploidy can play an essential role in the relapse of smaller secondary tumors.

Keywords: aneuploidy, evolutionary model, adaptive evolution, cancer, drug resistance, chromosome instability

Introduction

Aneuploidy in cancer. Each year, approximately 10 million people die from cancer (Kocarnik et al., 2022). Understanding the factors that contribute to the failure of interventions is of great importance. One suggested factor is aneuploidy, in which cells are characterized by an imbalanced karyotype and alterations in the number of chromosomes (Schukken and Foijer, 2018). Aneuploidy is caused by chromosomal instability and mis-segregation of chromosomes during mitosis. Importantly, changes in the number of chromosomes and chromosome arms copies allow cancer cells to survive under stressful conditions such as drug therapy (Ippolito et al., 2021, Lukow et al., 2021, Rutledge et al., 2016). Indeed, cancer cells are often aneuploid, and aneuploidy is associated with poor patient outcomes (Ben-David and Amon, 2020, Smith and Sheltzer, 2018).

Ippolito et al. (2021) induced aneuploidy in cancer cell lines by exposing them to reversine, a small-molecule inhibitor of the mitotic kinase Mpsi1, and then to anti-cancer drugs such as vemurafenib. Reversine-treated cells had a higher proliferation rate following drug exposure than sensitive cancer cells, due to selection of specific beneficial karyotypes. Similarly, Lukow et al. (2021) induced aneuploidy in cancer cells and observed that such cells have an advantage compared to sensitive cells during drug treatment despite having lower fitness before the onset of treatment. One proposed mechanism through which aneuploidy can confer resistance to anti-cancer drugs is by antagonizing cell division, which prevents the drugs from damaging DNA and microtubules (Replogle et al., 2020). Other mechanisms are the selection for specific karyotypes that lead to reduced drug metabolism (Ippolito et al., 2021) and elevated levels of DNA damage repair due to higher basal levels of DNA damage (Zerbib et al., 2023).

An essential aspect of aneuploidy is that the rate with which cells become aneuploid, that is, the rate of chromosome missegregation, is several orders of magnitude higher than mutation rate (Bakker et al., 2023). Consequently, a cell exposed to stress, such as chemotherapeutic drugs, can acquire aneuploidy faster than a mutation. Moreover, several proposed anti-cancer drugs elevate the missegregation rate to fight cancer cells (Lee et al., 2016), as an extremely high chromosome missegregation rate is incompatible with cell survival and proliferation.

Evolutionary rescue. Populations adapted to a specific environment are vulnerable to environmental changes, which might cause the population's extinction. Examples of such environmental changes include climate change, invasive species, and the onset of drug therapies. Adaptation is a race against time as the population size decreases in the new environment (Tanaka and Wahl, 2022). *Evolutionary rescue* is the process by which the population acquires a trait that increases fitness in the new environment such that extinction is averted. It is mathematically equivalent to the problem of crossing of fitness valley (Weissman et al., 2009, 2010). There are three potential ways for a population to survive environmental change: migration to a new habitat similar to the one before the onset of environmental change (Cobbold and Stana, 2020, Harsch et al., 2014, Zhou, 2022); adaptation by phenotypic plasticity without genetic modification (Carja and Plotkin, 2017, 2019, Gunnarsson et al., 2020, Levien et al., 2021); and adaptation through genetic modifications, e.g., mutation (Gomulkiewicz and Holt, 1995, Orr and Unckless, 2014, Uecker and Hermisson, 2011, 2016, Uecker et al., 2014).

Gunnarsson et al. (2020) analyzed a model where a tumor consisting of two populations of cancer cells, one drug-resistant and the other drug-sensitive, can evade extinction by cells switching between the two phenotypes through epigenetic mutations. They found that even when drug-resistant cells are barely viable, the epimutations guarantee evolutionary rescue. Evolutionary rescue in a single step, where an initially declining population has to acquire a mutation to survive extinction after a sudden environmental change, has been studied by Orr and Unckless (2008, 2014). They analyzed a model where the mutant strain is present in small numbers at the onset of therapy. They concluded that this can significantly enhance the population's probability of survival.

Most models focus on the probability that at most one mutation rescues the population. How multiple mutations contribute to the survival of the population is less explored, but Wilson et al. (2017) have shown that evolutionary rescue is significantly enhanced by soft selective sweeps when multiple mutations contribute towards evolutionary rescue. Evolutionary rescue that requires two successive mutations (i.e., two steps) has been investigated by Martin et al. (2013), who tested their model's predictions with data from yeast and bacteria experiments. Iwasa et al. (2003, 2004) used multi-type branching process theory to approximate the probability that a population under strong selective pressure can survive extinction via succesive mutations.

Here, we study evolutionary rescue after a sudden environmental change caused by initiating anti-cancer drug treatment. We consider a range of effects of aneuploidy, from tolerance to (partial) resistance to the drug (Brauner et al., 2016). We estimate the effect of aneuploidy on the tumor's evolutionary rescue probability. When aneuploidy provides drug resistance, it can directly rescue the tumor. However, when aneuploidy provides tolerance to the drug, it may act as an evolutionary "stepping stone" or "springboard" (Martin et al., 2013, Osmond et al., 2020, Yona et al., 2015), delaying extinction, and thereby allowing the tumor more time to acquire a resistance mutation on top of the aneuploid background. As mentioned above, evidence suggests that aneuploidy may be a common strategy for tumor adaptation to drug therapy. Still, it is unknown how often aneuploidy provides tolerance and acts as a stepping stone. We also estimate the mean time until a tumor cell population reaches its pre-treatment size following drug therapy. Given that aneuploidy is present in many tumors before the onset of therapy (Ben-David and Amon, 2020, Lukow et al., 2021), we also consider the effect of pre-treatment standing genetic variation on the evolutionary dynamics. Additionally, we are interested in the timescale of evolutionary rescue and the impact that aneuploidy has on the time necessary for the tumor to overcome drug therapy.

Methods

Evolutionary model. We follow the number of cancer cells with one of three different genotypes at time t: sensitive, s_t; tolerant/resistant aneuploid, a_t; and resistant mutant, m_t. These cells divide and die with rates λ_k and μ_k (for $k = s, a, m$). The division and death rate difference is $\Delta_k = \lambda_k - \mu_k$. We assume the population of cells is under a strong stress, such as drug therapy, and therefore $\Delta_s < 0$, whereas the mutant is resistant to the stress, $\Delta_m > 0$. We consider a range of possible values for Δ_a, finding three distinct scenarios: in the first, aneuploid cells are partially resistant, $\Delta_m > \Delta_a > 0$; in the second, aneuploid cells are tolerant, $0 > \Delta_a > \Delta_s$ (see Brauner et al., 2016, for the distinction between susceptible, resistant, and tolerant); in the third, aneuploid cells are non-growing, stationary, or growing or dying only very slowly, that is, either slightly tolerant or slightly resistant, such that $\Delta_a \approx 0$, in a sense that we will make precise below.

We assume that both chromosomal missegregation and mutations occur during the process of mitosis. Sensitive cells may divide and then missegregate to become aneuploids at rate $u\lambda_s$. Both aneuploid and sensitive cells may divide and mutate to become mutants at rates $v\lambda_a$ and $v\lambda_s$, respectively. To model standing genetic variation, we assume that before the onset of therapy, sensitive cells become aneuploid with rate $\tilde{u}\lambda_s$ (which may differ from $u\lambda_s$) and that aneuploidy confers a fitness cost c in the drug-free environment, that is, we assume that aneuploid cells have an increased death rate compared to sensitive cells in a drug-free environment.

See Figure 1 for a schematic representation of the model and Figure 2 for sample trajectories of the different genotypes.

Stochastic simulations. Simulations are performed using the *Gillespie stochastic simulation algorithm* (Gillespie, 1976, 1977) implemented in Python (Van Rossum and Others, 2007). The simulation monitors the number of cells of each type: sensitive, aneuploid, and mutant. Initially, the population starts with only sensitive cells, $s_0 = N$, and the other genotypes are initially absent.

The cell population at time t is represented by the triplet (s_t, a_t, m_t). The following describes the events that may occur (right column), the rates at which they occur (middle column), and the effect these events have on the population (left column, see Figure 1):

$$
\begin{aligned}
(+1,0,0): &\quad \lambda_s s_t\,(1-u-v) \quad \text{(birth of sensitive cell)}\,,\\
(-1,0,0): &\quad \mu_s s_t \quad \text{(death of sensitive cell)}\,,\\
(0,+1,0): &\quad u\lambda_s s_t \quad \big(\text{sensitive cell divides and becomes aneuploid}\big)\,,\\
(0,0,+1): &\quad v\lambda_s s_t \quad \text{(sensitive cell divides and becomes mutant)}\,,\\
(0,+1,0): &\quad \lambda_a a_t\,(1-v) \quad \big(\text{birth of aneuploid cell}\big)\,,\\
(0,-1,0): &\quad \mu_a a_t \quad \big(\text{death of aneuploid cell}\big)\,,\\
(0,0,+1): &\quad v\lambda_a a_t \quad \big(\text{aneuploid cell divides and becomes mutant}\big)\,,\\
(0,0,+1): &\quad \lambda_m m_t \quad \text{(birth of mutant cell)}\,,\\
(0,0,-1): &\quad \mu_m m_t \quad \text{(death of mutant cell)}\,.
\end{aligned}
$$

For the remaining of this paper, we assume that the division rates of sensitive and aneuploid cells can be written as $\lambda_s s_t\,(1-u-v) \approx \lambda_s s_t$ and $\lambda_a a_t\,(1-v) \approx \lambda_a a_t$ because $u, v \ll 1$ (Table 1). Each iteration of the simulation loop starts by computing the rates ν_k of each event k. We then draw the time until the next event, Δt, from an exponential distribution whose rate parameter is the sum of the rates of all events, such that $\Delta t \sim \mathrm{Exp}(\sum_j \nu_j)$. Then, we randomly determine which event occurred, where the probability for event k is $p_k = \nu_k / \sum_j \nu_j$. Finally, we update the number of cells of each genotype according to the event that occurred and update the time from t to $t + \Delta t$. We repeat these iterations until either the population becomes extinct (the number of cells of all genotypes is zero) or the number of mutant cells is high enough so that their extinction probability is $< 0.1\%$, that is, until

$$
m_t > \left\lfloor \frac{3 \log 10}{\log\left(\lambda_m/\mu_m\right)} \right\rfloor + 1,
$$

which we obtain by solving $1 - (1-p_m)^{m_t} = 0.999$ for m_t with $p_m = \Delta_m/\lambda_m$ as the probability that a single mutant escapes stochastic extinction (Appendix A).

When simulations are slow (e.g., due to large population size) with runtimes in the order of days, we use τ-leaping (Gillespie, 2001), where we assume that the change in the number of cells of genotype k in a fixed time interval Δt is Poisson distributed with mean $\nu_k \Delta t$. If the number of cells of genotype k becomes negative, we change it to zero.

Parameterization. To parametrize the simulations, we assume that the cells under consideration are melanoma cells and rely on Rew and Wilson (2000) and Bozic et al. (2013) for the division and death rates, respectively. Rew and Wilson (2000) report *in vivo* measurements of the potential doubling times (the waiting time for the number of cells in the tumor to double, disregarding cell death) for a large set of cancer types. The division rate is obtained as $\lambda = \log 2/T \approx 0.1$ per day. We select this to be the division rate for sensitive and mutant cells.

Bozic et al. (2013) report the growth rate Δ_s for sensitive melanoma cancer cells from which they deduce the death rate $0.11 \le \mu_s \le 0.17$. We use $\mu_s = 0.14$ per day. Additionally, they observed the growth rate of cancer cells before treatment to be 0.01, which we use as the growth rate of mutant cells, which are resistant to the drug. Thus, we use $\mu_m = 0.1 - 0.01 = 0.09$ per day as the death rate for mutant cells.

Aneuploid death rate μ_a is set to the same value as the mutant death rates, $\mu_m = 0.09$ per day, given that aneuploidy increases resistance to the drug, such as cisplatin, by antagonizing cell division (Replogle et al., 2020). The aneuploid division rate is selected such that the aneuploid growth rate $\Delta_s \ll \Delta_a \ll \Delta_m$ means that $0.06 \leq \lambda_a \leq 0.1$. For most of our simulations, we use $\lambda_a = 0.0899$ per day, so that aneuploid cells are tolerant and aneuploidy can only act as an evolutionary "stepping stone" for the generation of the resistant mutant that rescues the tumor (note that this mutant will occur on the background of an aneuploid genotype).

The missegregation rate in cancer cells is estimated to be between $2.5 \times 10^{-4} - 10^{-2}$ per chromosome per cell division (Shi and King, 2005, Thompson and Compton, 2008). Ippolito et al. (2021) observed that trisomy in Chr 2 and Chr 6 are most likely to confer increased resistance against the anti-cancer drug vemurafenib for A375 cells. We assume each of these trisomies is formed at the most likely rate, and as a result, we use $\tilde{u} = 10^{-3}$ per cell division as the chromosome missegregation rate in the drug-free environment. Some drugs are known to increase chromosome instability (Mason et al., 2017, Wang et al., 2019). Specifically, Lee et al. (2016) estimated the effect of different anti-cancer drugs on the missegregation rate and found a 3-50-fold increase. We thus assume an anti-cancer drug that causes a 10-fold increase in the chromosome missegregation rate, which gives us $u = 10^{-2}$ per cell division. We assume the mutation rate is 10^{-7} per gene per cell division (Loeb, 2001), and since we assume that a single target gene confers resistance to the drug, we use $v = 10^{-7}$ per cell division.

The fitness cost c of aneuploidy before the onset of therapy is difficult to estimate as we are interested in a specific type of aneuploidy that improves the fitness of cancer cells in an environment altered by drugs. We estimate $c = \tilde{u}\lambda_s/f$, where f is the fraction of aneuploid cancer cells. To estimate f, we note that Lukow et al. (2021) mixed sensitive and aneuploid A375 melanoma cells at $1:1$ ratio, cultured them in a drug-free environment, and observed the ratio evolve as a function of time with the aneuploid cells declining to 15% after 24 days. Thus, our estimate for the fitness cost is $c = \left|\log\left[0.15/(1-0.15)\right]/24\right| \approx 0.07$ per day (Chevin, 2011), and the estimated fraction of cancer cells with the beneficial aneuploidy is $f = 10^{-3} \times 10^{-1}/0.07 = 0.14\%$, that is, 0.14% of pre-treatment cancer cells have the beneficial aneuploidy of interest.

We note that when we refer to drug-sensitive cells, we include those cells that have any aneuploidy other than trisomy in Chr 2 and 6, as those are the aneuploid cells that are hypothesized to have higher fitness in the environment altered by drugs such as vemurafenib.

All the parameters discussed above are shown in Table 1.

Density-dependent growth. In our analysis, we assume that cells from the initial population divide and die independently of each other. However, these cells will compete for resources. We assume this competition can be ignored because the drug will cause the cell density to rapidly drop below the carrying capacity where competition is important. To test this assumption, we simulate a logistic growth model, with division and death rates given by

$$
\begin{aligned}
\lambda_s' &= \lambda_s, \\
\mu_s' &= \mu_s, \\
\lambda_a' &= \lambda_a, \\
\mu_a' &= \mu_a + \lambda_a \frac{w+a+m}{K}, \\
\lambda_m' &= \lambda_m, \\
\mu_m' &= \mu_m + \lambda_m \frac{w+a+m}{K},
\end{aligned}
$$

where K is the tumor carrying capacity. The effective carrying capacity in this model is $K_e = K\Delta_a/\lambda_a \approx 10^6$ for $K = 10^8, \lambda_a = 0.0901, \mu_a = 0.09$, where we define the effective carrying capacity to be the population size at which the aneuploid division rate is equal to the aneuploid death rate.

Code and data availability. All source code is available online at https://github.com/yoavram-lab/EvolutionaryRescue.

Results

Evolutionary rescue probability

In our model, *evolutionary rescue* occurs when drug-resistant cells appear and establish (avoid random extinction) in the population ($m_t \gg 1$) before the population becomes extinct ($w_t = a_t = m_t = 0$). Aneuploidy may contribute to evolutionary rescue by either preventing (when $\Delta_a > 0$) or delaying (when $0 > \Delta_a > \Delta_s$) the extinction of the population before mutant cells appear and establish. We assume independence between clonal lineages starting from an initial population of N sensitive cells (we check the effect of density-dependent growth on our results below). Define p_s as the probability that a lineage starting from a single drug-sensitive cell avoids extinction by acquiring drug resistance. Thus, $N^* = 1/p_s$ is the threshold tumor size above which evolutionary rescue is very likely, and the rescue probability is given by

$$p_{\text{rescue}} = 1 - \left(1 - p_s\right)^N \approx 1 - \mathrm{e}^{-Np_s} = 1 - e^{-N/N^*}, \tag{2}$$

where the approximation $(1 - p_s) \approx e^{-p_s}$ assumes that p_s (but not necessarily Np_s) is small. Indeed, when $N < 1/p_s$, then the probability for evolutionary rescue is $p_{\text{rescue}} \approx Np_s$, and when $N > 1/p_s$, it is $p_{\text{rescue}} \approx 1$, justifying the definition of N^* as the threshold tumor size for evolutionary rescue.

We use multi-type branching-process theory to find approximate expressions eqs. (A4), (A7) and (A11) for p_s in three distinct scenarios (Appendix A). Substituting these into $N^* = 1/p_s$, we find approximations for the threshold tumor size, N^*. In these approximations, an important quantity is $T^* = \sqrt{\lambda_m/4v\lambda_a^2\Delta_m}$, which is the critical time an aneuploid lineage needs to survive to produce a resistant mutant that avoids random extinction. First, if aneuploidy is very rare ($u\lambda_a T^* < 1$), or if aneuploidy is rare ($u\lambda_a < -\Delta_a$) and very sensitive to the drug ($\Delta_a T^* < -1$), then it is likely that evolutionary rescue will occur through a direct resistance mutation in a sensitive cell without aneuploidy playing a role in the adaptive dynamics, such that

$$N_m^* \approx \frac{|\Delta_s|}{v\lambda_s}\frac{\lambda_m}{\Delta_m}. \tag{3}$$

Here, $|\Delta_s|/(v\lambda_s)$ is the ratio of the rate at which sensitive cells decrease in number and the rate at which they are mutating. Notably, the aneuploidy parameters (u, λ_a, μ_a) do not affect N_m^*.

Otherwise, aneuploidy is frequent enough ($u\lambda_a > \max\left(-\Delta_a, 1/T^*\right)$) to affect the evolution of drug resistance. The threshold tumor size can be approximated by one of the following scenarios, depending on $\Delta_a T^*$, which represents the change in the aneuploid log-population size during the critical time,

$$N_a^* \approx \frac{|\Delta_s|}{u\lambda_s} \cdot \begin{cases} \frac{|\Delta_a|}{v\lambda_a}\frac{\lambda_m}{\Delta_m}, & \Delta_a T^* \ll -1 \text{ (tolerant aneuploids)}, \\ 2\lambda_a T^*, & -1 \ll \Delta_a T^* \ll 1 \text{ (stationary aneuploids)}, \\ \frac{\lambda_a}{\Delta_a}, & \Delta_a T^* \gg 1 \text{ (resistant aneuploids)}. \end{cases} \tag{4}$$

These approximations perform very well when compared to the results of stochastic evolutionary simulations (Figures 3 and 4). The first line describes the scenario in which the treatment still effectively kills aneuploid cells but not as quickly as the sensitive cells. In the second scenario, aneuploid cells are sufficiently resistant, and the expected size of each aneuploid lineage is roughly 1. In both of these scenarios, aneuploidy increases the probability of rescue by slowing or halting the decrease in the tumor population size, allowing more opportunities to produce resistant mutants. In the third scenario, aneuploid cells are sufficiently resistant for the population to re-grow the tumor without additional resistance mutations. Notably, in this scenario the mutant parameters (v, λ_m, and Δ_m) do not affect N_a^* beyond their effect on T^*. In all scenarios, N_a^* is proportional to $1/u$ such that increasing the missegregation rate u will decrease the threshold tumor size (Figure 4B). Furthermore, increasing the aneuploid growth rate Δ_a (which appears both in the terms and in the conditions), also reduces the threshold tumor size, with a sharp decrease around $\Delta_a = 0$, but the effect is minor when $|\Delta_a|$ is small compared to T^* as this would result in the second scenario where $dN_a^*/d\Delta_a = 0$ (Figure 4A). The tumor threshold size decreases with the mutation rate in the first and second scenarios: N_a^* is proportional to $1/v$ in the first scenario (tolerant aneuploids) and to $\sqrt{1/v}$ in the second scenario (stationary aneuploids). Furthermore, the growth rate $\Delta_a < 0$ that allows tolerant aneuploids to rescue the tumor is between $-u\lambda_a$ and $-1/T^*$, which is proportional to $-\sqrt{v}$. Thus, increasing the mutation rate v will decrease the tumor threshold size N_a^*, making evolutionary rescue more likely, but only until T^* decerases to a point where $\Delta_a = 1/T^*$.

Using eqs. (3) and (4), we can find the ratio of threshold tumor size for rescue via aneuploidy (u is high) or via direct mutation (u is low),

$$\frac{N_a^*}{N_m^*} \approx \begin{cases} \frac{|\Delta_a|}{u\lambda_a}, & \Delta_a T^* \ll -1, \\ \frac{1}{u}\left(v\frac{\Delta_m}{\lambda_m}\right)^{1/2}, & -1 \ll \Delta_a T^* \ll 1, \\ v\frac{\Delta_m}{\lambda_m}\left(u\frac{\Delta_a}{\lambda_a}\right)^{-1}, & \Delta_a T^* \gg 1. \end{cases} \tag{5}$$

As expected, this ratio increases with the mutation rate v and decreases with the aneuploidy rate u. In the first scenario, $|\Delta_a|/u\lambda_a$ is the ratio of the expected time for an aneuploid lineage to appear, $1/u\lambda_a$, and the expected time until that lineage disappears, $1/|\Delta_a|$. In the third scenario, $\left(v\frac{\Delta_m}{\lambda_m}\right)/\left(u\frac{\Delta_a}{\lambda_a}\right)$ is the ratio of the rates of appearance of resistant mutants that avoid extinction and partially resistant aneuploids that avoid extinction. In the second scenario, $\frac{1}{u}\left(v\frac{\Delta_m}{\lambda_m}\right)^{1/2} = \sqrt{\frac{\Delta_a}{u\lambda_a}v\frac{\Delta_m}{\lambda_m}\left(u\frac{\Delta_a}{\lambda_a}\right)^{-1}}$, which is the geometric mean of the first and third scenarios.

Interestingly, increasing both the aneuploid division rate, λ_a, and the aneuploid death rate, μ_a, such that the growth rate Δ_a remains constant, leads to a decrease in T^*, pushing the system to the second scenario. In this scenario, increasing the division rate λ_a should also increase the mutation rate $v\lambda_a$ in aneuploid cells, as mutations mostly occur during division, so overall, the threshold tumor size N_a^* is unaffected by the division rate λ_a (i.e., $d\lambda_a T^*/d\lambda_a = 0$). Thus, if aneuploid cells rapidly die due to the drug but compensate by rapidly dividing, increasing the division rate will *not* facilitate adaptation. This is consistent with experimental findings where aneuploidy confers resistance by decreasing the division rate (Replogle et al., 2020).

We can categorize tumors by their size: small tumors with size $N < N_a^*$ that are unlikely to survive treatment, intermediate tumors with size $N_a^* < N < N_m^*$ that rely on aneuploidy for evolutionary rescue, and large tumors with size $N > N_m^*$ that could overcome the effect of drug treatment without aneuploidy. For the parameter values in Table 1 with $\lambda_a = 0.0899, \mu_s = 0.14, u = 10^{-2}, v = 10^{-7}$, we are in the tolerant aneuploid scenario, and substituting in eqs. (3) and (4), we have $N_a^* \approx 4 \times 10^6$ and $N_m^* \approx 4 \times 10^7$. Hence, we obtain the ratio $N_a^*/N_m^* \approx 0.11$ (eq. (5)), that is, aneuploidy reduces the threshold tumor size by approximately 89%. Interestingly, the threshold between small and intermediate tumors, N_a^*, is similar to the tumor detection threshold of 4.19×10^6 cells for a wide variety of tumors (Avanzini and Antal, 2019).

Aneuploidy may lead to an increased mutation rate in cancer cells(Garribba et al., 2023, Janssen et al., 2011, Passerini et al., 2016). Thus, we extended our model to account for this in Appendix H. We find that increasing the mutation rate in aneuploid cells by one order of magnitude leads to a decrease in the threshold tumor size of approximately one order of magnitude. Also, it transitions the system from the first scenario (tolerant aneuploids) to the second scenario (stationary aneuploids) without changing the aneuploid growth rate, Δ_a.

In our analysis, we used branching processes, which assume that growth (division and death) is density-independent. However, growth may be limited by resources (oxygen, nutrients, etc.) and therefore depend on cell density. Therefore, we performed stochastic simulations of a logistic growth model with a carrying capacity. We find that our density-independent approximations agree with the results of simulations with density-dependent growth for biologically relevant parameter values (Figure S1).

Standing vs. *de-novo* genetic variation. In the above, we assumed that at the onset of drug treatment, the initial tumor consisted entirely of drug-sensitive cells. However, aneuploidy is likely produced even before the onset of treatment at some rate $\tilde{u}$, which may be lower in the absence of drugs, $\tilde{u} < u$ (Mason et al., 2017, Wang et al., 2019). Moreover, aneuploidy likely confers a fitness cost c in the absence of drugs (Giam and Rancati, 2015, Replogle et al., 2020). Hence, if the number of cells in the tumor N is large (as expected if the tumor is treated with a drug), there may already be a fraction $f \approx \tilde{u}\lambda_s/c$ of aneuploid cells in the population (here we assume that the drug affects the sensitive death rate but not the division rate and therefore we use λ_s for the sensitive division rate in the drug-free environment).

Therefore, the threshold tumor size for rescue by standing generation variation, $\tilde{N}_a^*$, is similar to the threshold for rescue by de-novo variation, N_a^*, except that the sensitive growth rate $|\Delta_s|$ is replaced by the cost of aneuploidy c, such that

$$\frac{\tilde{N}_a^*}{N_a^*} = \frac{u}{\tilde{u}} \frac{c}{|\Delta_s|}. \tag{6}$$

Comparing this approximation of $\tilde{N}_a^*/N_a^*$ to results of stochastic simulations, we find that the approximations perform very well (Figure 5). Standing genetic variation will drive evolutionary rescue if sensitive cells die rapidly (growth rate Δ_s is very negative) due to a strong effect of the drug on sensitive cells or if the cost of aneuploidy in the drug-free environment, c, is small. In contrast, *de-novo* aneuploid cells will have a greater contribution to rescue if the cost of aneuploidy, c, is large, the effect of the drug on sensitive cells is weak (Δ_s is close to zero), or if the drug induces the appearance of aneuploid cells ($u > \tilde{u}$). For example, with $\lambda_s = 0.1$, $\mu_s = 0.14$, $u = 10^{-2}$, $\tilde{u} = 10^{-3}$, and $c = 0.07$, the ratio of the threshold tumor sizes for standing vs. *de-novo* variation is $\tilde{N}_a^*/N_a^* \approx 17.5$, which means that *de-novo* genetic variation is the main driver of evolutionary rescue.

Using eqs. (3), (4) and (6), we can find the ratio of threshold tumor size for rescue via standing genetic variation to the threshold for rescue via direct mutation,

$$\frac{\tilde{N}_a^*}{N_m^*} = \frac{\tilde{N}_a^*}{N_a^*}\frac{N_a^*}{N_m^*} \approx \frac{c}{|\Delta_s|}\begin{cases} \frac{|\Delta_a|}{\tilde{u}\lambda_a}, & \Delta_a T^* \ll -1, \\ \frac{1}{\tilde{u}}\left(\nu\frac{\Delta_m}{\lambda_m}\right)^{1/2}, & -1 \ll \Delta_a T^* \ll 1, \\ \nu\frac{\Delta_m}{\lambda_m}\left(\tilde{u}\frac{\Delta_a}{\lambda_a}\right)^{-1}, & \Delta_a T^* \gg 1. \end{cases} \tag{7}$$

Evolutionary rescue through direct mutation is more likely if the cost of aneuploidy, c, is very large or the effect of the drug Δ_s is small. In contrast, standing genetic variation will drive adaptation if the pre-treatment chromosome missegregation rate, $\tilde{u}$, is very large. The ratio does not depend on the rate of chromosome missegregation induced by the drug, u. However, if the aneuploid growth rate,

Δ_a, increases, evolutionary rescue is driven by standing genetic variation. For the parameter values of $\lambda_s = 0.1$, $\lambda_a = 0.0899$, $\lambda_m = 0.1$, $\mu_s = 0.14$, $\mu_a = 0.09$, $\mu_m = 0.09$, $\tilde{u} = 10^{-3}$, and $v = 10^{-7}$, we are in the first scenario (tolerant aneuploids) and obtain the ratio $\tilde{N}_a^*/N_m^* \approx 1.94$, which means that standing genetic variation does not drive evolution of drug resistance when compared to direct mutation. We note that for larger values of the pre-treatment chromosome missegregation rate, $\tilde{u}$, which are consistent with empirical studies (Table 1), standing genetic variation can drive adaptation when compared to direct mutation.

Recurrence time due to evolutionary rescue

When evolutionary rescue occurs, the time until the tumor recurs may still be very long. We therefore explored the time until the tumor recurs, that is, the time until the tumor reaches its original size, N. When the expected number of resistant lineages that avoid extinction is small, the expected recurrence time can be estimated by adding two terms: the *mean evolutionary rescue time*, which is the waiting time for the appearance of a resistant lineage that avoids extinction (conditioned on such an event occurring in the first place), and the *mean proliferation time*, which is the expected time for that lineage to grow to N cells. However, when the expected number of resistant lineages is large, the dynamics of the number of mutant cells is deterministic (i.e., it can be modeled by a system of ODEs, eq. (D2)), and the mean recurrence time cannot be separated into the mean evolutionary rescue time and mean proliferation time because multiple mutant lineages contribute towards the mutant population size reaching the initial tumor size. Of particular interest is the distribution of the evolutionary rescue time and recurrence time with tolerant aneuploid cells ($\Delta_a T^* \ll 1$), for which we focus on the parameter values $\lambda_s = 0.1$, $\lambda_a = 0.0899$, $\lambda_m = 0.1$, $\mu_s = 0.14$, $\mu_a = 0.09$, $\mu_m = 0.09$, $u = 10^{-2}$, and $v = 10^{-7}$.

Evolutionary rescue time. We have derived approximations for τ_m, the mean evolutionary rescue time without aneuploidy ($u = 0$), and τ_a, the mean rescue time with aneuploidy ($u > 0$), both conditioned on evolutionary rescue occurring (Appendix C). These approximations agree with simulation results for small, intermediate, and large tumor sizes (Figures S2 and S6). The mean rescue time with aneuploidy for small and large tumors follows

$$\tau_a \approx \begin{cases} -\frac{1}{\Delta_s} - \frac{1}{\Delta_a}, & N \ll N_a^*, \\ \frac{1}{v\lambda_s N}\frac{\lambda_m}{\Delta_m}, & N \gg N_m^*. \end{cases} \tag{8}$$

For small tumors ($N \ll N_a^*$), the mean rescue time is a function of the sensitive and aneuploid growth rates and independent of the other model parameters, including tumor size (blue line in Figure S6). Increasing the sensitive or aneuploid growth rates leads to an increase in the mean rescue time, because the corresponding cells will survive for longer and will produce additional rescue mutations at latter times. In our focus parameter regime, we have $\Delta_s = -0.04$ and $\Delta_a = -10^{-4}$, such that the mean rescue time is mainly determined by the aneuploid growth rate, $\tau_a \approx 10^4$ days.

For large tumors ($N \gg N_m^*$), the mean evolutionary rescue time (eq. (8)) is independent of parameters characterizing aneuploid cells or their production (u, λ_a, and Δ_a). Increasing the per division mutation rate, v leads to the faster appearance of a rescue mutation and hence reduced mean rescue time. Finally, increasing the tumor size leads to shorter mean rescue time, as more sensitive cells can mutate to become resistant.

Given that a fraction $f \approx 0.14\%$ of the initial cancer cell population is expected to have beneficial aneuploidy even before the onset of drug treatment, we want to know whether the mean evolutionary rescue time is affected by the standing genetic variation. We calculated the mean evolutionary rescue time with standing genetic variation, $\tilde{\tau}_a$ (eq. (C10)), and compared our result with simulations

(Figure S9). We note that standing genetic variation does not significantly affect the mean evolutionary rescue time.

We calculate the probability that a rescue mutation has been generated by time t in Appendix E. This allows us to examine whether aneuploidy promotes or delays evolutionary rescue. We find that aneuploidy promotes evolutionary rescue after $1/\Delta_a \approx 100$ days, at a time when no more rescue mutations are generated through mutations in sensitive cells (Figure 6A). Thus, aneuploidy increases the *window of opportunity* for evolutionary rescue. This can have a counter-intuitive outcome: conditioned on the rescue of the tumor, tumors rescued by aneuploid cells may acquire rescue mutations later than those rescued by sensitive cells.

Recurrence time. We next approximated the mean time for the population of mutant cancer cells to reach the initial, pre-treatment population size N, which we denote the recurrence time τ_a^r (Appendix D),

$$\tau_a^r \approx \begin{cases} -\frac{1}{\Delta_s} - \frac{1}{\Delta_a} + \frac{\log p_m N}{\Delta_m}, & N \ll N_a^*, \\ \frac{1}{\Delta_m} \log \frac{\Delta_m - \Delta_s}{\nu \lambda_s}, & N \gg N_m^*. \end{cases} \tag{9}$$

Figures 7 and S7 show the agreement between our approximations and simulation results. For small tumors ($N \ll N_a^*$), the mean recurrence time can be approximated as the sum of the mean time for the first rescue mutation to appear and the mean time for its lineage to reach size N. The mean recurrence time grows logarithmically with tumor size N and is the same order of magnitude as the mean evolutionary rescue time. Increasing the mutant growth rate, Δ_m, decreases the recurrence time, while increasing the sensitive and aneuploid growth rates, Δ_s and Δ_a, respectively, increases the recurrence time. For large tumors ($N \gg N_m^*$), the dynamics of the number of mutant cells is deterministic, and the mean recurrence time becomes independent of the initial tumor size N. Increasing either the mutant growth rate, Δ_m, or the mutation rate, ν, decreases the time for the tumor to rebound to its initial size. In addition, drugs that significantly increase the death rate of drug-sensitive cells, μ_s, but do not affect their division rate, λ_s, delay cancer recurrence (conditioned on evolutionary rescue). Consequently, patients treated with such drugs may require a longer period of monitoring to guarantee the effectiveness of the treatment.

We note that, for small and large tumors, when $N \ll N_a^*$ or $N \gg N_m^*$, the asymptotic expressions for the mean recurrence time are independent of the chromosome missegregation rate u, and therefore, the rate at which the drug induces aneuploidy has no effect on the time for the tumor to rebound to its initial size N.

Appendix F gives us the probability that a mutant cancer cell population has not reached size N by time t. Figure 6B shows agreement between our approximations and simulation results for various values of N. Additionally, we derive the distribution of the recurrence time for a small tumor with $N = 10^6$ cells, noting that the distribution is wide and right-skewed (Figure S4). It is highly unlikely to observe the recurrence of cancer at times smaller than $\frac{1}{\Delta_m} \log \frac{\Delta_m - \Delta_s}{\nu \lambda_s} \approx 1542$ days for the parameter values in Table 1 with $\lambda_a = 0.0899$, $\mu_s = 0.14$, and $\nu = 10^{-7}$ and independent of initial tumor size N (Figure 6B).

The detection time τ_a^M is defined as the time for the tumor size to reach detection threshold M. We derive the mean detection time for $M = 10^7$ in Appendix D. We find for small and intermediate-sized tumors, the detection size M has a negligible effect on the mean detection time τ_a^M compared to when the detection size equals the initial population size, N (i.e., $\tau_a^r \approx \tau_a^M$ for $N < N_m^*$). However, for large tumors, the mean detection time τ_a^M decreases logarithmically with tumor size N, while the recurrence time τ_a^r is constant (Figure S8). Additionally, for large tumors, we have $M < N_m^* < N$, so the mean detection time is shorter compared to the mean recurrence time, that is, the resistant tumor may be detected before recovering back to its initial size.

Discussion

We have modeled a tumor–a population of cancer cells–exposed to drug treatment that causes it to decline in size toward potential extinction. In this scenario, the tumor can be "evolutionary rescued" or escape extinction via two paths. In the direct path, a drug-sensitive cell acquires a mutation or aneuploidy that confers resistance and allows it to grow rapidly. In the indirect path, a sensitive cell first becomes aneuploid, which diminishes the drug's effect, and then an aneuploid cell acquires a mutation that confers resistance (Figure 1).

Using multi-type branching processes, we derived the probability of evolutionary rescue of the tumor under the effects of aneuploidy, ranging from tolerance to partial resistance. We obtained exact and approximate expressions for the probability of evolutionary rescue (eq. (2)). Our results show that the probability of evolutionary rescue increases with the initial tumor size N, the drug-sensitive growth rate Δ_s, the mutation rate v, and the aneuploidy rate u.

When aneuploid cells are partially resistant to the drug ($\Delta_s \ll 0 \ll \Delta_a \ll \Delta_m$), aneuploidy itself rescues the population (Figure 4A). When aneuploidy only provides tolerance to the drug ($\Delta_s \ll \Delta_a \ll 0 \ll \Delta_m$), it cannot rescue the population. Instead, it acts as a "stepping stone" through which the resistant mutant can appear more rapidly, given that the number of aneuploid cells declines slower than the number of drug-sensitive cells (Figure 2). In this scenario, aneuploidy provides two advantages. First, it delays the extinction of the population, providing more time for the appearance of the resistance mutation. Second, it increases the population size relative to a drug-sensitive population, providing more cells in which mutations can occur, i.e., it increases the mutation supply (i.e., $Nuv\lambda_s\lambda_a/|\Delta_s\Delta_a|$).

We find that aneuploidy can significantly affect evolutionary rescue as it reduces the threshold tumor size by at least an order of magnitude even when aneuploidy only provides tolerance (Figure 3). When the number of cells in the tumor is large enough (i.e., $N \gg N_m^* \approx 4 \times 10^7$), a resistance mutation will occur in drug-sensitive cells before these cells become extinct (Figure 3). Therefore, large tumors are likely to be rescued with or without aneuploidy. However, anti-cancer drugs are often used as adjuvant therapy after resection, in which case the number of cells in the tumor may be below the detection threshold of $\sim 10^7$ (Bozic et al., 2013). In these cases, aneuploidy can have a crucial role in the evolutionary rescue of the tumor and, therefore, in cancer recurrence. Indeed, secondary tumors are estimated to cause the majority of cancer-related deaths (Chaffer and Weinberg, 2011). The importance of aneuploidy in the evolutionary rescue of secondary tumors is reinforced by the fact that metastases have been shown to have a chromosome missegregation rate two to three orders of magnitude higher compared to primary tumors (Kimmel et al., 2023).

Given that the mean time for secondary tumors to adapt to anti-cancer drugs can be of the order of 1,000 days (Figure S2A), aneuploidy can explain the reappearance of cancer even after initial remission. The theoretical prediction for the mean rescue time of tumors smaller than 10^8 cells is greater than 4 years, consistent with previous estimates of the recurrence time of tumors after resection (Avanzini and Antal, 2019). We found that aneuploidy complements evolutionary rescue through direct mutation because it produces rescue mutations mostly after the number of sensitive cells has decreased to a point where a direct mutation is no longer a feasible option for evolutionary rescue (Figure 6A).

We hypothesized that standing genetic variation (the existence of aneuploid cancer cells in the tumor before the onset of therapy) could facilitate evolutionary rescue by reducing the waiting time for the appearance of aneuploid cells. We found that a drug that reduces the sensitive growth rate and does not significantly increase the chromosome missegregation rate will likely lead to evolutionary rescue through standing genetic variation (Figure 5 and eq. (6)). Furthermore, if the fraction of tumor cells that have the beneficial aneuploidy is $f \gg \frac{u\lambda_s}{|\Delta_s|} \approx 2.5\%$, then evolutionary rescue is more likely to occur via standing variation rather than through *de-novo* aneuploidy. However, for the parameter values we focus on in our examples (Table 1), this fraction is an order of magnitude lower, and therefore, we expect evolutionary rescue to occur by *de-novo* aneuploidy.

Finally, we observe from Figure 4 that only for a restricted region of the parameter space will aneuploidy act as a "stepping stone" for evolutionary rescue. If the aneuploid division rate is smaller than $\frac{\mu_a}{1+u} \approx \mu_a(1-u)$, then evolutionary rescue will occur through direct mutation. As a result, for most parameter values, aneuploidy will either not play any role in evolutionary rescue or will be the main driver of adaptation without requiring any mutation (i.e., evolutionary rescue in one step).

Directions for future research Experiments could test our model predictions. For example, to assess the effect of initial tumor size on the probability of evolutionary rescue, a large culture mass can be propagated from a single cancer cell in permissive conditions and then diluted to a range of starting tumor sizes. Then, the extinction or survival of these tumors can be monitored during exposure to anti-cancer drugs that induce aneuploidy or to saline solution for control (Ippolito et al., 2021). We can then compare the results of these experiments to predictions of our model to see if tumors with initial size below the threshold eq. (4) are more likely to become extinct due to drug exposure.

We have assumed that cancer cell lineages are independent and have verified that this is accurate under simple logistic growth. However, this assumption neglects the potential effects of spatial structure and local interactions, which may be important in solid tumors. Such tumors can be spatially heterogeneous, with different genotypes inhabiting cellular niches and immune infiltration impacting growth in affected regions (Galon et al., 2010, Varrone et al., 2023). This can potentially impact the probability of evolutionary rescue (Martens et al., 2011). In addition, our model can be extended to understand evolutionary rescue in different biological contexts, for example, how yeast populations under stress overcome extinction via aneuploidy (Kohanovski et al., 2024, Pompei and Cosentino Lagomarsino, 2023).

Conclusions Our results quantitatively suggest that aneuploidy may play an important role in tumor adaptation to anti-cancer drugs when the tumor size is small or intermediate. Large tumors are predicted to adapt to anti-cancer drugs through direct mutation. In contrast, smaller tumors are predicted to become resistant either directly by aneuploidy or by a resistance mutation occurring in aneuploid cells that serve as evolutionary "stepping stones" (Figure 3). Thus, therapies that increase the rate of aneuploidy in tumors to combat cancer may also promote drug resistance.

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	Name	Value	Units	References
N	Initial tumor size	$10^7 - 10^9$	cells	Del Monte (2009)
λ_s	Sensitive division rate	0.1	1/days	Bozic et al. (2013), Rew and Wilson (2000)
μ_s	Sensitive death rate	$0.11 - 0.17$	1/days	Bozic et al. (2013)
λ_a	Aneuploid division rate*	$0.06 - 0.1$	1/days	-
μ_a	Aneuploid death rate*	0.09	1/days	-
λ_m	Mutant division rate	0.1	1/days	Bozic et al. (2013), Rew and Wilson (2000)
μ_m	Mutant death rate	0.09	1/days	Bozic et al. (2013), Carlson (2003)
u	Missegregation rate	10^{-2}	1/cell division	Lee et al. (2016)
v	Mutation rate	$10^{-9} - 10^{-7}$	1/cell division	Bozic et al. (2013), Loeb (2001)
$\tilde{u}$	Missegregation rate in the drug free environment*	$5 \times 10^{-4} - 2 \times 10^{-2}$	1/cell division	Shi and King (2005), Thompson and Compton (2008)
s	Selection coefficient of aneuploidy in the drug free environment	0.07	1/days	Lukow et al. (2021)

Table 1: Model parameters. Parameters from Bozic et al. (2013) consider patients with melanoma treated with the anti-cancer drug vemurfenib, in which resistance is conferred by trisomy in either Chr 2 or Chr 6. We have modified the parameters from Bozic et al. (2013) such that sensitive and mutant division rates are $\lambda_s = \lambda_m = \log 2/T \approx 0.1$ instead of their value of 0.14 where T is the doubling time in the absence of cellular death obtained from Rew and Wilson (2000). For a discussion of the different interpretations of the tumor doubling times see Avanzini and Antal (2019).

Appendices

Appendix A Survival probability of a single lineage

To analyze evolutionary rescue in our model, we use the framework of *multitype branching processes* (Harris, 1963, Weissman et al., 2009). This allows us to find explicit expressions for the *survival probability*: the probability that a lineage descended from a single cell does not become extinct.

Let p_s, p_a, and p_m be the survival probabilities of a population consisting initially of single sensitive cell, aneuploid cell, or mutant cell, respectively. The complements $1 - p_s$, $1 - p_a$, and $1 - p_m$

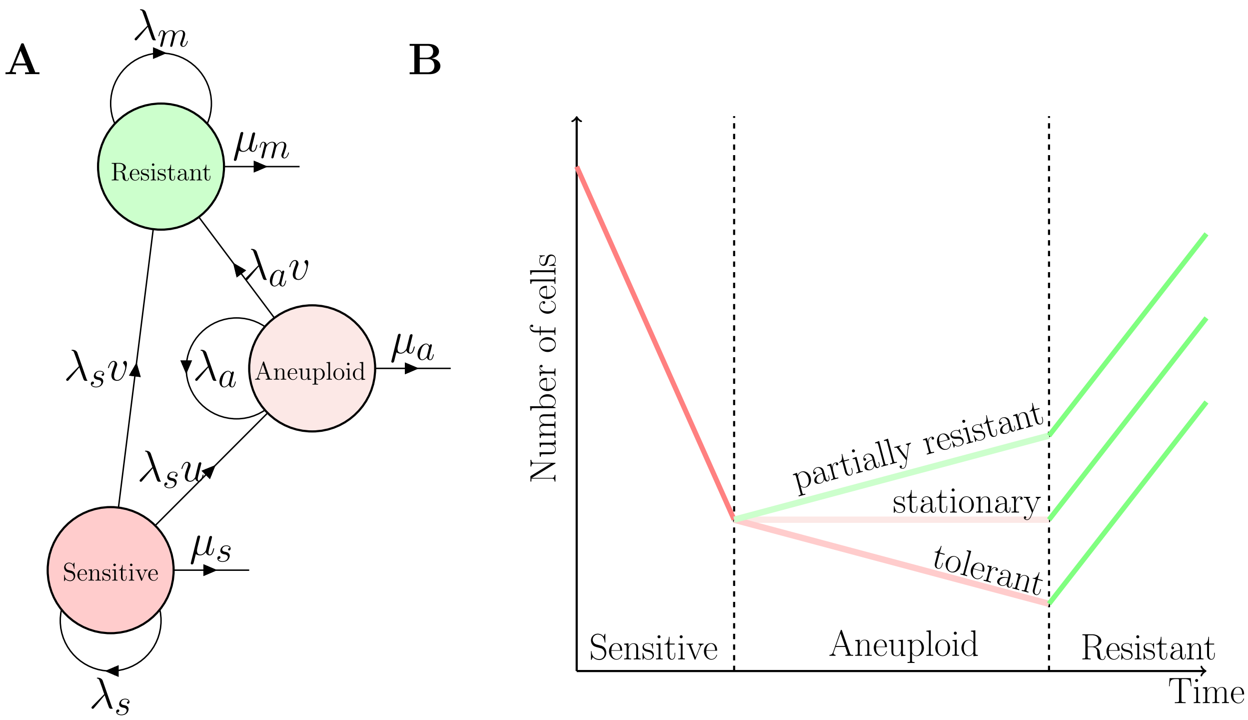

Figure 1: Model illustration. **(A)** A population of cancer cells is composed of drug-sensitive, aneuploid, and mutant cells, which divide with rates λ_s, λ_a, and λ_m and die at rates μ_s, μ_a, and μ_m, respectively. Sensitive cells can divide and become aneuploid at rate $u\lambda_s$. Both aneuploid and sensitive cells can divide and acquire a mutation with rates $v\lambda_a$ and $v\lambda_s$, respectively. Color denotes the relative growth rates of the three genotypes such that $\lambda_s - \mu_s < \lambda_a - \mu_a < \lambda_m - \mu_m$. **(B)** Sensitive cells are sensitive to the drug, while mutant cells are drug-resistant. The aneuploid may be tolerant, stationary, or partially resistant.

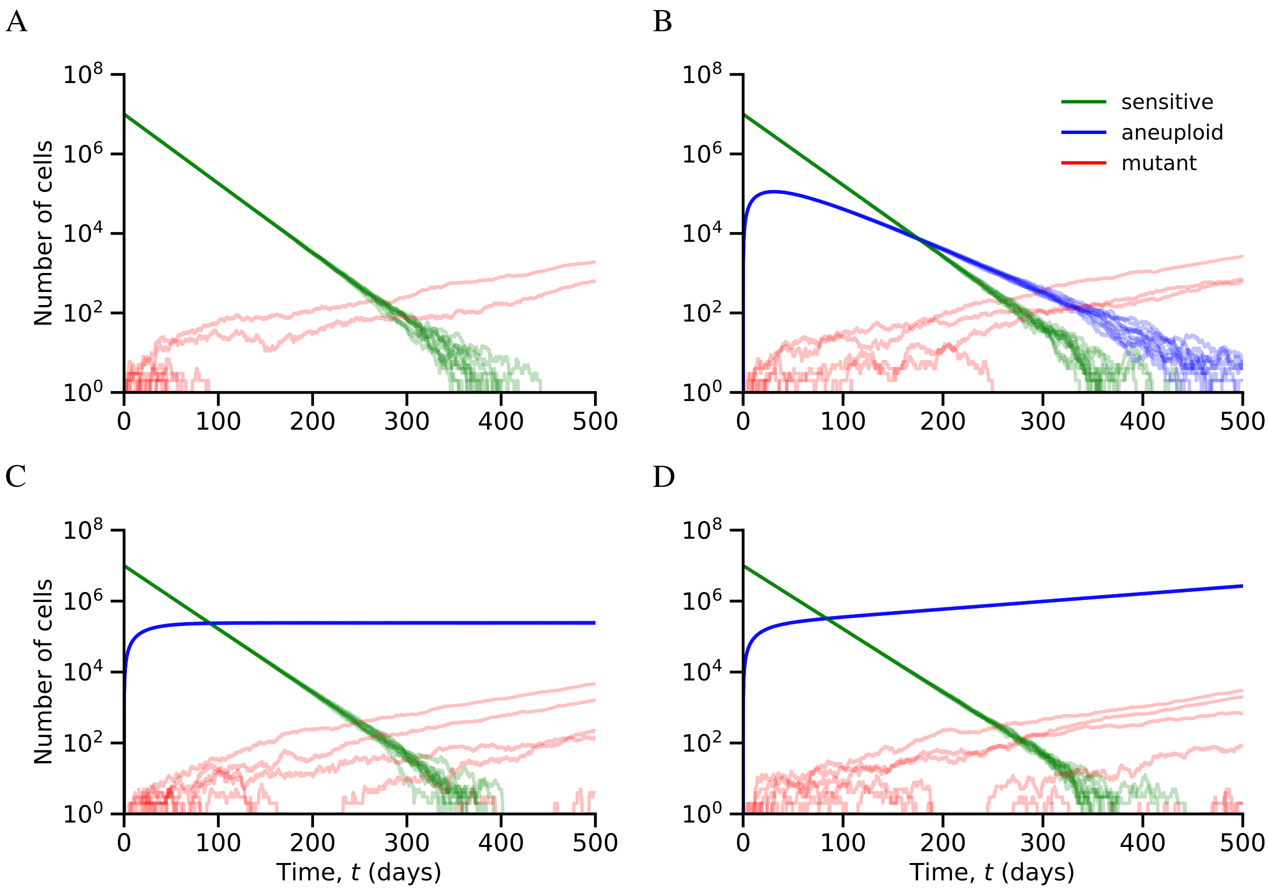

Figure 2: Sample trajectories of the genotype frequencies. (A) Without aneuploidy ($u = 0$), evolutionary rescue is possible through direct mutation, and in most scenarios, the tumor will become extinct due to the drug. (B) When aneuploid cells are tolerant ($\Delta_a < 0$), we observe, similar to A, direct mutation is the only path for evolutionary rescue. (C) When aneuploid cells are stationary ($\Delta_a \approx 0$), we observe the appearance of mutant lineages even after the sensitive population has gone extinct, thus showing that stationary aneuploidy increases the probability of evolutionary rescue. (D) When aneuploid cells are partially resistant ($\Delta_a > 0$), the tumor is rescued by the aneuploid cell population. Each plot shows 10 simulations of the number of sensitive, aneuploid, and mutant cells (s_t, a_t, m_t) over time t. Here, $\lambda_s = 0.1$, $\lambda_m = 0.1$, $\mu_s = 0.14$, $\mu_a = 0.09$, $\mu_m = 0.09$, $\nu = 10^{-7}$, $N = 10^7$; (A) $u = 0$; (B) $\lambda_a = 0.065$, $u = 10^{-2}$; (C) $\lambda_a = 0.08999$, $u = 10^{-2}$; (D) $\lambda_a = 0.095$, $u = 10^{-2}$.

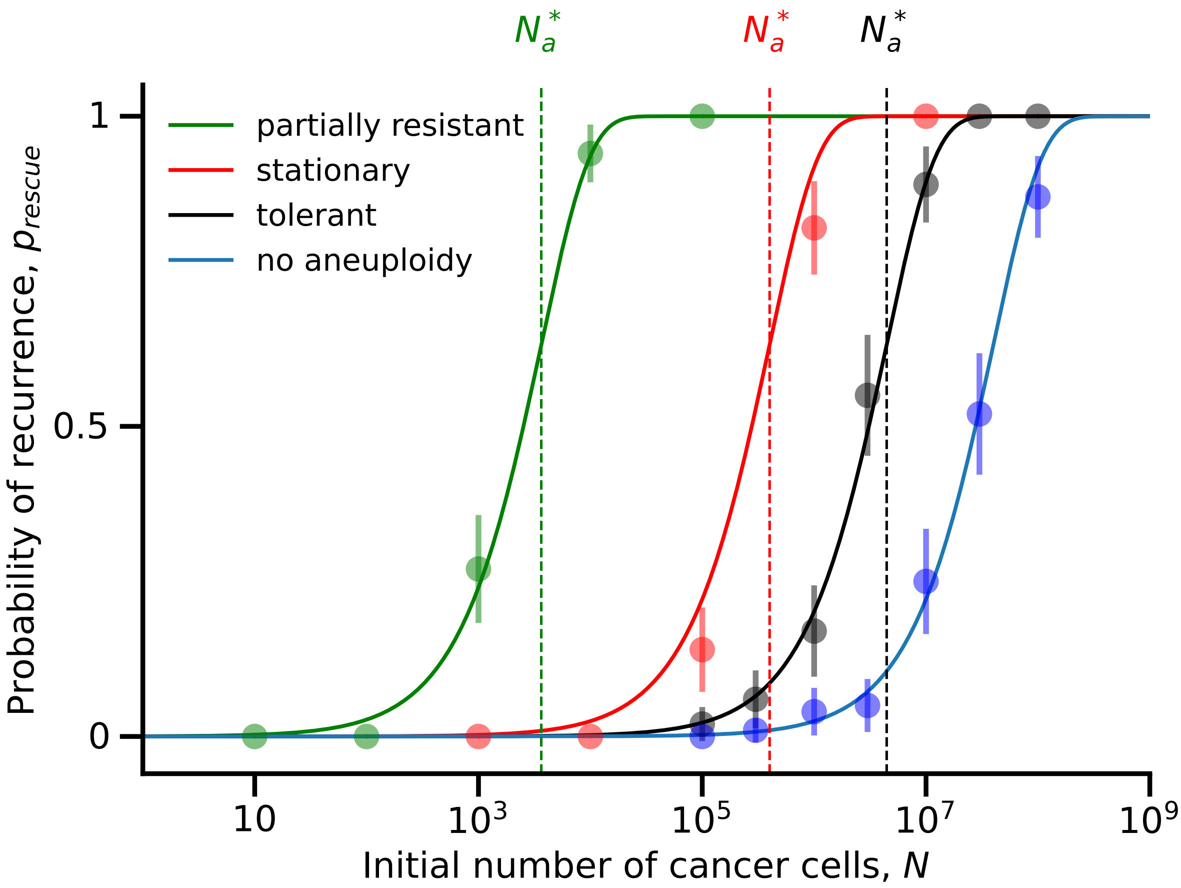

Figure 3: Aneuploidy facilitates the evolutionary rescue of cancer under drug treatment. The probability of evolutionary rescue (i.e., the probability that the population does not become extinct), p_{rescue}, as a function of the initial tumor size, N (eq. (2)). Dashed vertical line shows the threshold tumor size, N_a^*, above which the probability is very high (eq. (4)). Blue dashed line: without aneuploidy ($u = 0$). Black line: tolerant aneuploidy ($u = 10^{-2}, \lambda_a = 0.0899$). Red line: stationary aneuploidy ($u = 10^{-2}, \lambda_a = 0.08999$). Green line represents the scenario with partially resistant aneuploidy ($u = 10^{-2}, \lambda_a = 0.095$). Dots for simulations and the error bars for 95% confidence interval ($p \pm 1.96\sqrt{p\,(1-p)\,/n}$ where p is the fraction of simulations in which the tumor has been rescued, and $n = 100$ is the number of simulations). Parameters: $\lambda_s = 0.1, \lambda_m = 0.1, \mu_s = 0.14, \mu_a = 0.09, \mu_m = 0.09, v = 10^{-7}$.

A B

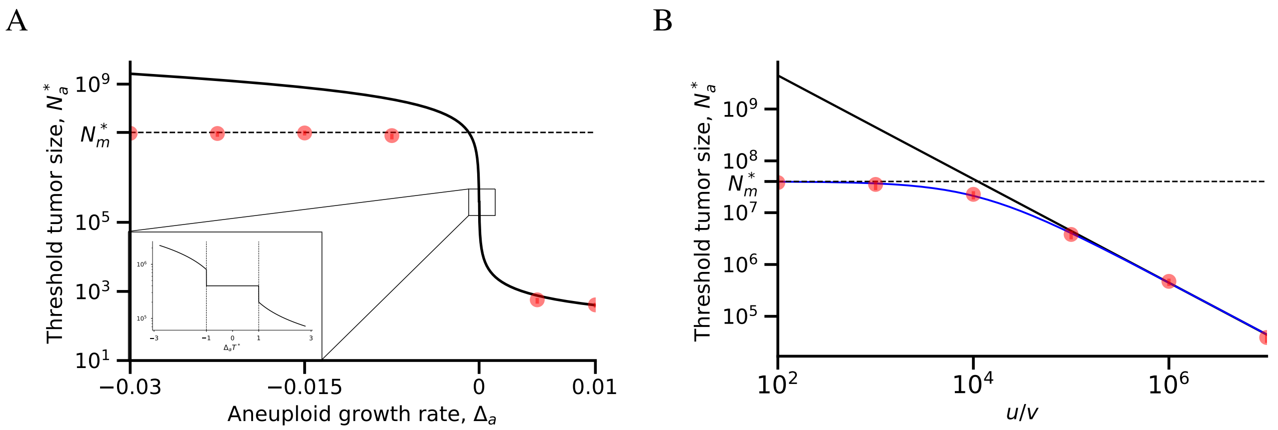

Figure 4: The effect of aneuploidy on tumor threshold size. (A) The threshold tumor size N_a^* as a function of the aneuploid growth rate Δ_a. The dashed horizontal line shows N_m^*, the threshold tumor size without aneuploidy ($u = 0$). When aneuploid growth rate is close to or higher than zero, aneuploidy decreases the threshold tumor size, facilitating evolutionary rescue. The inset highlights the scenario when aneuploid cells are stationary. Red dots for simulations and error bars for the 95% confidence intervals obtained with bootstrap (Appendix G). Parameters: $\lambda_s = 0.1, \lambda_m = 0.1, \mu_s = 0.14, \mu_a = 0.09, \mu_m = 0.09, u = 10^{-2}, v = 10^{-7}$. (B) Threshold tumor size N_a^* as a function of the ratio of aneuploidy and mutation rates, u/v. Dashed horizontal line shows N_m^*, the threshold tumor size without aneuploidy ($u = 0$). When the aneuploidy rate is much higher than the mutation rate, aneuploidy decreases the threshold tumor size, facilitating evolutionary rescue. Blue line represents the exact formula for threshold tumor size N_a^* while the solid black line represents the approximation (eq. (4)). Red dots represent simulation results, and the error bars represent the 95% confidence intervals obtained with bootstrap (Appendix G). Parameters: $\lambda_s = 0.1, \lambda_m = 0.0899, \lambda_m = 0.1, \mu_s = 0.14, \mu_a = 0.09, \mu_m = 0.09, v = 10^{-7}$.

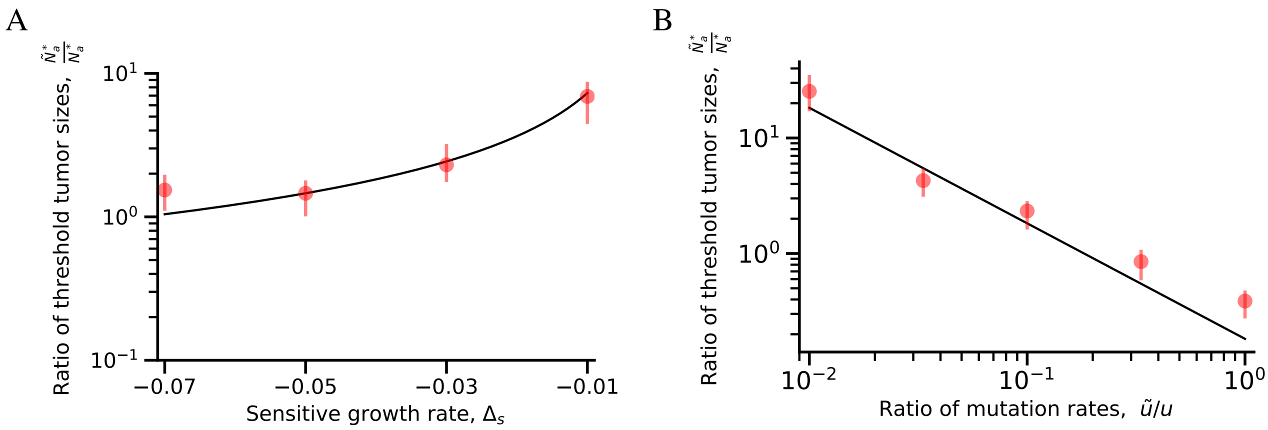

Figure 5: Standing genetic variation facilitates the evolutionary rescue of cancer. (A) Ratio of threshold tumor sizes for rescue by standing genetic variation and by de-novo variation, $\tilde{N}_a^*/N_a^*$, when a fraction $\frac{\tilde{u}\lambda_s}{c}$ is aneuploid at the start of treatment, as a function of the sensitive growth rate Δ_s. Standing genetic variation will drive adaptation to the drug if the sensitive population is rapidly declining ($\Delta_s \ll 0$) due to a stronger effect of the drug on sensitive cells. Red dots represent simulation results, and the error bars represent the 95% confidence intervals obtained with bootstrap (Appendix G). Parameters: $\lambda_s = 0.1, \lambda_a = 0.0899, \lambda_m = 0.1, \mu_a = 0.09, \mu_m = 0.09, \tilde{u} = 10^{-3}, u = 10^{-2}, v = 10^{-7}$. (B) Ratio of threshold tumor size $\tilde{N}_a^*$, when a fraction $\frac{\tilde{u}\lambda_s}{c}$ is aneuploid at the start of treatment, and N_a^* as a function of the ratio of aneuploidy rates $\tilde{u}/u$. *De-novo* aneuploids will have a larger contribution to the appearance of drug resistance if the drug induces the appearance of aneuploid cells ($u \gg \tilde{u}$). Red dots represent simulation results, and the error bars represent the 95% confidence intervals obtained with bootstrap (Appendix G). Parameters: $\lambda_s = 0.1, \lambda_a = 0.0899, \lambda_m = 0.1, \mu_s = 0.14, \mu_a = 0.09, \mu_m = 0.09, \tilde{u} = 10^{-3}, v = 10^{-7}$.

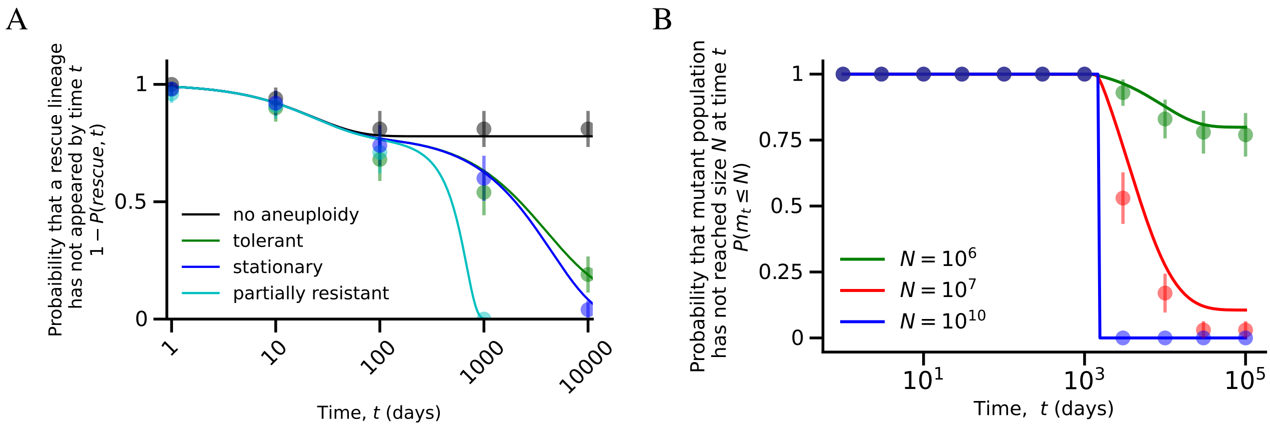

Figure 6: Aneuploidy extends the window of opportunity for evolutionary rescue. (A) The probability that a successful mutant has not appeared by time t. Green line: tolerant aneuploidy ($u > 0, \lambda_a = 0.0899$). Blue line: stationary aneuploidy ($u > 0, \lambda_a = 0.089999$). Cyan line: partially resistant aneuploidy ($u > 0, \lambda_a = 0.095$). Black line: no aneuploidy ($u = 0$). Aneuploidy plays an important role in rescuing the tumor cell population as the sensitive population becomes extinct. Markers represent simulation results, and the error bars represent 95% confidence interval ($p \pm 1.96\sqrt{p\,(1-p)\,/n}$ where p is the fraction of simulations in which a successful mutant has not been generated, and $n = 100$ is the number of simulations). Parameters: $\lambda_s = 0.1, \lambda_m = 0.1, \mu_s = 0.14, \mu_a = 0.09, \mu_m = 0.09, u = 10^{-2}, v = 10^{-7}, N = 10^7$. (B) Probability that a mutant cancer cell population has not reached size N at time t. Green line: $N = 10^6$ (small tumor). Red line: $N = 10^7$ (intermediate-sized tumor). Blue line: $N = 10^{10}$ (large tumor). Increasing the initial tumor size guarantees that the cancer will relapse. Markers represent simulations, and the error bars represent 95% confidence interval ($p \pm 1.96\sqrt{p\,(1-p)\,/n}$ where p is the fraction of the simulations in which the mutant population size has not reached N and $n = 100$ is the number of simulations). Parameters: $\lambda_s = 0.1, \lambda_a = 0.0899, \lambda_m = 0.1, \mu_s = 0.14, \mu_a = 0.09, \mu_m = 0.09, u = 10^{-2}, v = 10^{-7}$.

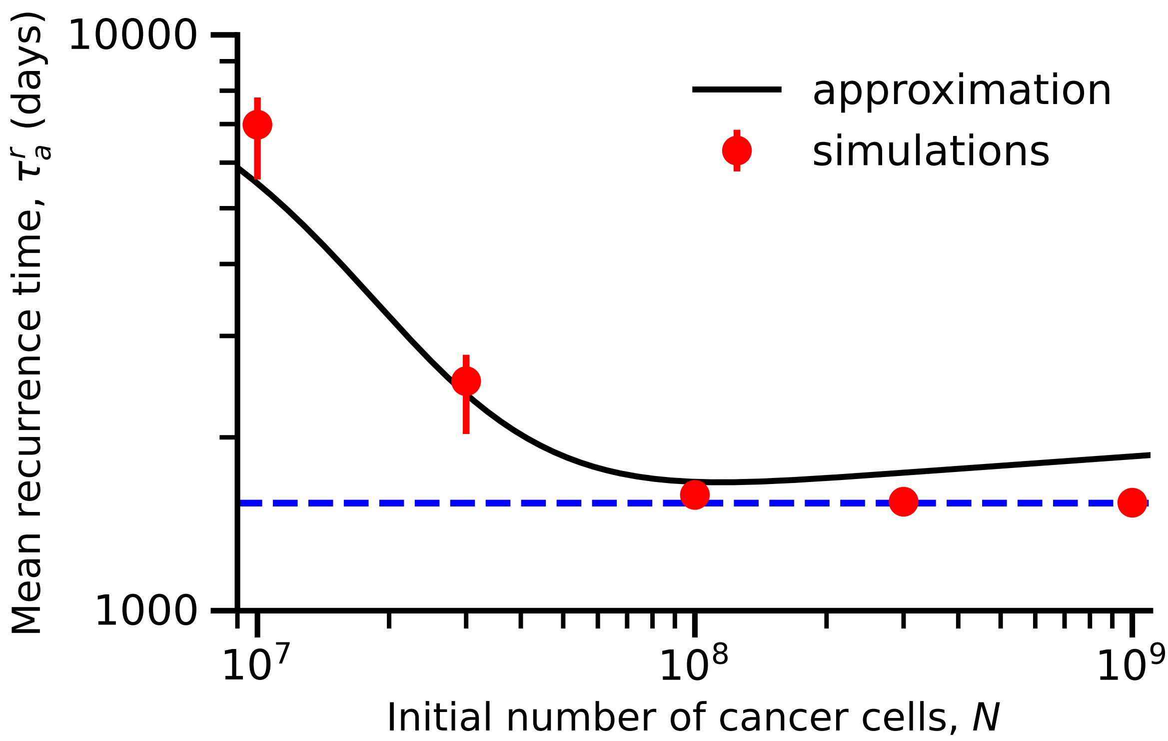

Figure 7: Tumor size decreases the mean recurrence time. The mean time for the mutant cell population to reach size N, the initial number of cancer cells. Our inhomogeneous Poisson-process approximation (solid black line, eq. (D1)) is in agreement with simulation results (red markers with 95% confidence interval obtained with bootstrapping, see Appendix G) for intermediary N. The simulations converge to eq. (D4) (blue dashed line) for large values of N. Parameters: $\lambda_s = 0.1, \lambda_a = 0.0899, \lambda_m = 0.1, \mu_s = 0.14, \mu_a = 0.09, \mu_m = 0.09, u = 10^{-2}, v = 10^{-7}$.

are the extinction probabilities, which satisfy each its respective equation (Harris, 1963),

$$
\begin{aligned}
1-p_s =&\frac{\mu_s}{\lambda_s+\mu_s+u\lambda_s+v\lambda_s}+\frac{u\lambda_s}{\lambda_s+\mu_s+u\lambda_s+v\lambda_s}\left(1-p_a\right)\left(1-p_s\right)+\\
&\frac{\lambda_s}{\lambda_s+\mu_s+u\lambda_s+v\lambda_s}\left(1-p_s\right)^2+\frac{v\lambda_s}{\lambda_s+\mu_s+u\lambda_s+v\lambda_s}\left(1-p_m\right)\left(1-p_s\right),\\
1-p_a =&\frac{\mu_a}{\lambda_a+\mu_a+v\lambda_a}+\frac{v\lambda_a}{\lambda_a+\mu_a+v\lambda_a}\left(1-p_m\right)\left(1-p_a\right)+\frac{\lambda_a}{\lambda_a+\mu_a+v\lambda_a}\left(1-p_a\right)^2,\\
1-p_m =&\frac{\mu_m}{\lambda_m+\mu_m}+\frac{\lambda_m}{\lambda_m+\mu_m}\left(1-p_m\right)^2.
\end{aligned}
\tag{A1}
$$

The survival probabilities are given by the smallest solution for each quadratic equation (Uecker et al., 2015). Therefore we have

$$
\begin{aligned}
p_s &= \frac{\lambda_s-\mu_s-u\lambda_s p_a-v\lambda_s p_m+\sqrt{\left(\lambda_s-\mu_s-u\lambda_s p_a-v\lambda_s p_m\right)^2+4\lambda_s^2\left(up_a+vp_m\right)}}{2\lambda_s},\\
p_a &= \frac{\lambda_a-\mu_a-v\lambda_a p_m+\sqrt{\left(\lambda_a-\mu_a-v\lambda_a p_m\right)^2+4\lambda_a^2 v p_m}}{2\lambda_a},\\
p_m &= \frac{\lambda_m-\mu_m}{\lambda_m}.
\end{aligned}
\tag{A2}
$$

Note that the equation for p_s depends on both p_a and p_m, and the equation for p_a depends on p_m. To proceed, we can plug the solution for p_m and p_a into the solution for p_s. We perform this for three different scenarios.

Scenario 1: Aneuploid cells are partially resistant

We first assume that aneuploidy provides partial resistance to drug therapy, $\lambda_a > \mu_a$, and that this resistance is significant, $\left(\lambda_a-\mu_a-v\lambda_a p_m\right)^2 > 4\lambda_a^2 v p_m$. We thus rewrite eq. (A2) as

$$
\begin{aligned}
p_s &= \frac{\lambda_s-\mu_s-u\lambda_s p_a-v\lambda_s p_m}{2\lambda_s}\left(1-\sqrt{1+\frac{4\lambda_s^2\left(vp_m+up_a\right)}{\left(\lambda_s-\mu_s-u\lambda_s p_a-v\lambda_s p_m\right)^2}}\right), \text{ and}\\
p_a &= \frac{\lambda_a-\mu_a-v\lambda_a p_m}{2\lambda_a}\left(1+\sqrt{1+\frac{4\lambda_a^2 v p_m}{\left(\lambda_a-\mu_a-v\lambda_a p_m\right)^2}}\right).
\end{aligned}
$$

Using the Taylor expansion $\sqrt{1+x}=1+x/2+O(x^2)$ and assuming $u, v \ll 1$, we obtain the following approximation for the survival probability of a population initially consisting of a single sensitive cell,

$$
\begin{aligned}
p_s &\approx -\frac{v\lambda_s p_m+u\lambda_s p_a}{\lambda_s-\mu_s-u\lambda_s p_a-v\lambda_s p_m}\\
&\approx -\frac{1}{\lambda_s-\mu_s}\left[\frac{u\lambda_s\left(\lambda_a-\mu_a\right)}{\lambda_a}+\frac{uv\lambda_s\lambda_a\left(\lambda_m-\mu_m\right)}{\lambda_m\left(\lambda_a-\mu_a\right)}+\frac{v\lambda_s\left(\lambda_m-\mu_m\right)}{\lambda_m}\right].
\end{aligned}
\tag{A3}
$$

Now uv is very small, and if we use the fact that $v \ll u$, we have:

$$
p_s \approx \frac{u\lambda_s}{|\Delta_s|}\frac{\Delta_a}{\lambda_a}. \tag{A4}
$$

However, if aneuploidy is very rare such that

$$\frac{u\lambda_s\Delta_a}{\lambda_a} < \frac{v\lambda_s\Delta_m}{\lambda_m} \Rightarrow u\lambda_a < \frac{v\lambda_a^2\Delta_m}{\lambda_m}\frac{1}{\Delta_a} < \frac{v\lambda_a^2\Delta_m}{\lambda_m}\frac{1}{\sqrt{4\lambda_a^2 v p_m}} \Rightarrow u\lambda_a < T^*,$$

where $T^* = (4v\lambda_a^2\Delta_m/\lambda_m)^{-1/2}$ and in the second inequality we used the fact that $\Delta_a^2 > 4\lambda_a^2 v p_m$. In this scenario adaptation is through direct mutation and:

$$p_s \approx \frac{v\lambda_s}{|\Delta_s|}\frac{\Delta_m}{\lambda_m}.$$

Scenario 2: Aneuploid cells are tolerant.

We now assume that aneuploidy provides tolerance to drug therapy, that is, the number of aneuploid cells significantly declines over time, but at a lower rate than the number of sensitive cells, $\lambda_s - \mu_s < \lambda_a - \mu_a < 0$. We also assume that the decline are significant, $\left(\lambda_a - \mu_a - v\lambda_a p_m\right)^2 > 4\lambda_a^2 v p_m$. We rewrite eq. (A2) as

$$\begin{aligned} p_s &= \frac{\lambda_s - \mu_s - u\lambda_s p_a - v\lambda_s p_m}{2\lambda_s}\left(1 - \sqrt{1 + \frac{4\lambda_s^2\left(vp_m + up_a\right)}{\left(\lambda_s - \mu_s - u\lambda_s p_a - v\lambda_s p_m\right)^2}}\right), \\ p_a &= \frac{\lambda_a - \mu_a - v\lambda_a p_m}{2\lambda_a}\left(1 - \sqrt{1 + \frac{4\lambda_a^2 v p_m}{\left(\lambda_a - \mu_a - v\lambda_a p_m\right)^2}}\right). \end{aligned} \tag{A5}$$

Since $u, v \ll 1$, the term in the root can be approximated using a Taylor expansion. So, substituting the expressions for p_a and p_m, we have

$$\begin{aligned} p_s &\approx -\frac{v\lambda_s p_m + u\lambda_s p_a}{\lambda_s - \mu_s - u\lambda_s p_a - v\lambda_s p_m} \\ &\approx \frac{1}{\lambda_s - \mu_s - u\lambda_s p_a - v\lambda_s p_m}\left[\frac{uv\lambda_s\lambda_a\left(\lambda_m - \mu_m\right)}{\lambda_m\left(\lambda_a - \mu_a - v\lambda_a\right)} - \frac{v\lambda_s\left(\lambda_m - \mu_m\right)}{\lambda_m}\right] \\ &\approx \frac{v\lambda_s\left(\lambda_m - \mu_m\right)}{\lambda_m\left(\lambda_s - \mu_s\right)}\left[\frac{u\lambda_a}{\left(\lambda_a - \mu_a\right)} - 1\right] \\ &= \frac{v\lambda_s\Delta_m}{\lambda_m|\Delta_s|}\left(\frac{u\lambda_a}{|\Delta_a|} + 1\right). \end{aligned} \tag{A6}$$

If we assume that aneuploidy is not rare ($u\lambda_a > |\Delta_a|$) then we have:

$$p_s \approx \frac{u\lambda_s}{|\Delta_s|}\frac{v\lambda_a}{|\Delta_a|}\frac{\Delta_m}{\lambda_m}. \tag{A7}$$

Scenario 3: Aneuploid cells are stationary

We now assume that the growth rate of aneuploid cells is close to zero (either positive or negative), such that $\left(\Delta_a - v\lambda_a p_m\right)^2 \ll 4\lambda_a^2 v p_m$. We rewrite eq. (A2) as

$$p_a = \frac{\lambda_a - \mu_a - v\lambda_a p_m + 2\sqrt{\lambda_a^2 v p_m}\left(1 + \frac{\left(\lambda_a - \mu_a - v\lambda_a p_m\right)^2}{4\lambda_a^2 v p_m}\right)^{\frac{1}{2}}}{2\lambda_a}. \tag{A8}$$

Using a following Taylor series expansion for small $\left(\lambda_a - \mu_a - v\lambda_a p_m\right)^2 / 4\lambda_a^2 v p_m$,

$$\left(1 + \frac{\left(\lambda_a - \mu_a - v\lambda_a p_m\right)^2}{4\lambda_a^2 v p_m}\right)^{\frac{1}{2}} = 1 + \frac{\left(\lambda_a - \mu_a - v\lambda_a p_m\right)^2}{8\lambda_a^2 v p_m} + \cdots ,$$

we obtain the approximation

$$\begin{aligned} p_a &\approx \frac{\lambda_a - \mu_a - v\lambda_a p_m + 2\sqrt{\lambda_a^2 v p_m}\left[1 + \frac{\left(\lambda_a - \mu_a - v\lambda_a p_m\right)^2}{8\lambda_a^2 v p_m}\right]}{2\lambda_a} \\ &= \frac{\lambda_a - \mu_a - v\lambda_a p_m + 2\sqrt{\lambda_a^2 v p_m} + \frac{\left(\lambda_a - \mu_a - v\lambda_a p_m\right)^2}{4\sqrt{\lambda_a^2 v p_m}}}{2\lambda_a} \\ &= \frac{\left(\lambda_a - \mu_a - v\lambda_a p_m + 2\sqrt{\lambda_a^2 v p_m}\right)^2 + 4\lambda_a^2 v p_m}{8\lambda_a\sqrt{\lambda_a^2 v p_m}} \\ &= \frac{4\lambda_a^2 v p_m + 4\lambda_a^2 v p_m\left(1 + \frac{\lambda_a - \mu_a - v\lambda_a p_m}{2\sqrt{\lambda_a^2 v p_m}}\right)^2}{8\lambda_a\sqrt{\lambda_a^2 v p_m}} \\ &= \frac{1}{2\lambda_a}\left(\lambda_a - \mu_a - v\lambda_a p_m + 2\sqrt{\lambda_a^2 v p_m}\right). \end{aligned} \tag{A9}$$

Plugging this in eq. (A3), the survival probability of a population starting from one sensitive cell is

$$\begin{aligned} p_s &\approx -\frac{1}{\lambda_s - \mu_s - u\lambda_s p_a - v\lambda_s p_m}\left[v\lambda_s\frac{\lambda_m - \mu_m}{\lambda_m} + \frac{u\lambda_s}{2\lambda_a}\left(\lambda_a - \mu_a - v\lambda_a p_m + 2\sqrt{\lambda_a^2 v p_m}\right)\right] \\ &= -\frac{1}{\lambda_s - \mu_s - u\lambda_s - v\lambda_s}\left[v\lambda_s\frac{\lambda_m - \mu_m}{\lambda_m} + \frac{u\lambda_s}{2\lambda_a}\left(\lambda_a - \mu_a - v\lambda_a p_m\right) + u\lambda_s\sqrt{\frac{v\left(\lambda_m - \mu_m\right)}{\lambda_m}}\right] \\ &\approx -\frac{1}{\Delta_s}\left[v\lambda_s\frac{\Delta_m}{\lambda_m} + \frac{u\lambda_s\left(\Delta_a - v\lambda_a\right)}{2\lambda_a} + u\lambda_s\sqrt{\frac{v\Delta_m}{\lambda_m}}\right]. \end{aligned} \tag{A10}$$

Using the fact that

$$\left(\Delta_a - v\lambda_a p_m\right)^2 \ll 4\lambda_a^2 v p_m \Rightarrow \frac{\Delta_a - v\lambda_a p_m}{2\lambda_a} \ll \sqrt{\frac{v\lambda_a\Delta_m}{\lambda_m}},$$

and $v \ll u$ we obtain:

$$p_s \approx \frac{u\lambda_s}{|\Delta_s|}\sqrt{\frac{v\lambda_a\Delta_m}{\lambda_m}}. \tag{A11}$$

Appendix B Evolutionary rescue probability

Using the fact that $\Delta_a - v\lambda_a p_m \approx \Delta_a$ we write the condition $\left(\Delta_a - v\lambda_a p_m\right)^2 \ll 4\lambda_a^2 v p_m$ as:

$$\Delta_a^2 \ll 4\lambda_a^2 v p_m \Rightarrow -1 \ll \Delta_a T^* \ll 1,$$

where $T^* = (4v\lambda_a^2\Delta_m/\lambda_m)^{-1/2}$. Substituting eqs. (A4), (A7) and (A11) into eq. (2), the evolutionary rescue probability can be approximated by

$$p_{\text{rescue}} \approx \begin{cases} 1 - \exp\left[-\frac{u\lambda_a}{|\Delta_s|}\frac{v\lambda_s}{|\Delta_a|}\frac{\Delta_m}{\lambda_m}N\right], & \Delta_a T^* \ll -1, \\ 1 - \exp\left[-\frac{u\lambda_s}{|\Delta_s|}\sqrt{\frac{v\lambda_a\Delta_m}{\lambda_m}}N\right], & -1 \ll \Delta_a T^* \ll 1, \\ 1 - \exp\left[-\frac{u\lambda_s}{|\Delta_s|}\frac{\Delta_a}{\lambda_a}N\right], & 1 \ll \Delta_a T^*. \end{cases} \tag{B1}$$

Appendix C Evolutionary rescue time

We first calculate the expected time for the appearance of the first mutant that rescues the cell population. This can occur either through the evolutionary trajectory *sensitive* → *mutant* or through the trajectory *sensitive* → *aneuploid* → *mutant*. We start with the former.

Assuming no aneuploidy ($u = 0$), we define T_m to be the time at which the first mutant cell appears that will avoid extinction and will therefore rescue the population. Note that if extinction occurs, that is the frequency of mutants after a very long time is zero, $m_\infty = 0$, then it is implied that $T_m = \infty$, and vice versa if $T_m < \infty$ then $m_\infty > 0$.

The number of successful mutants generated until time t can be approximated by an inhomogeneous Poisson process with rate $R_m(t) = v\lambda_s p_m w_t$, where $s_t = N\mathrm{e}^{\Delta_s t}$ is the number of sensitive cells at time t. Note that

$$\int_0^t R_m(z)\mathrm{d}z = v\lambda_s p_m N \frac{\exp[\Delta_s t] - 1}{\Delta_s} \approx v\lambda_s p_m N t, \tag{C1}$$

by integrating the exponential and because $\frac{\exp[\Delta_s t]-1}{\Delta_s} = \frac{1+\Delta_s t + O(t^2)-1}{\Delta_s} = t + O(t^2)$. The probability density function of T_m is thus $R_m(t)\exp\left(-\int_0^t R_m(z)\mathrm{d}z\right)$ (Allen, 2010). Therefore, the probability density function of the conditional random variable $(T_m \mid T_m < \infty)$ is $f_m(t) = \frac{R_m(t)\exp\left(-\int_0^t R_m(z)\mathrm{d}z\right)}{p_{\text{rescue}}}$.

We are interested in the mean conditional time, $\tau_m = \mathbb{E}\left[T_m \mid T_m < \infty\right]$, which is given by

$$\tau_m = \int_0^\infty t f_m(t)\mathrm{d}t = \frac{\int_0^\infty t R_m(t)\exp\left(-\int_0^t R_m(z)\mathrm{d}z\right)\mathrm{d}t}{p_{rescue}}, \tag{C2}$$

Therefore, plugging eqs. (2) and (C1) in eq. (C2),

$$\tau_m = \int_0^\infty t v\lambda_s N\mathrm{e}^{\Delta_s t}\frac{\mathrm{e}^{-v\lambda_s N p_m \frac{\mathrm{e}^{\Delta_s t}-1}{\Delta_s}}}{1 - \left(1 - p_s\right)^N}\mathrm{d}t \approx \int_0^\infty t v\lambda_s N\mathrm{e}^{\Delta_s t}\frac{\mathrm{e}^{-v\lambda_s N p_m t}}{1 - \mathrm{e}^{-Np_s}}\mathrm{d}t. \tag{C3}$$

Figure S2B show the agreement between this approximating and simulation results.
Assuming aneuploidy is possible ($u > 0$), we define T_a to be the time at which the first mutant cell appears that will rescue the population. We are interested in the mean conditional time, $\tau_a = \mathbb{E}\left[T_a \mid T_a < \infty\right]$.

When $Nu\lambda_s/|\Delta_s| \gg 1$ the aneuploid frequency dynamics is roughly deterministic and therefore can be approximated by

$$a_t \approx \frac{Nu\lambda_s}{\Delta_s - \Delta_a}\left(\mathrm{e}^{\Delta_s t} - \mathrm{e}^{\Delta_a t}\right). \tag{C4}$$

As a result, the number of successful mutants created by direct mutation and via aneuploidy can be approximated by inhomogeneous Poisson processes with the rates

$$r_1(t) = v\lambda_a p_m \int_0^t a_z \mathrm{d}z = \frac{uv\lambda_s\lambda_a N p_m}{\Delta_s - \Delta_a}\left(\frac{\mathrm{e}^{\Delta_s t} - 1}{\Delta_s} - \frac{\mathrm{e}^{\Delta_a t} - 1}{\Delta_a}\right), \tag{C5}$$

$$r_2(t) = v\lambda_s p_m \int_0^t s_z \mathrm{d}z = v\lambda_s N p_m \frac{\mathrm{e}^{\Delta_s t} - 1}{\Delta_s}. \tag{C6}$$

For large initial population sizes we assume that the two processes are independent and as a result, they can be merged into a single Poisson process with rate $R_a(t) = (r_1 + r_2)(t)$. Consequently, the mean time to the appearance of the first rescue mutant is

$$\begin{aligned}\tau_a &= \frac{\int_0^\infty t R_a(t)\exp\left(-\int_0^t R_a(z)\mathrm{d}z\right)\mathrm{d}t}{p_{rescue}}\\ &= \int_0^\infty t\left(v\lambda_a p_m a_t + v\lambda_s p_m s_t\right)\frac{\exp\left[-\frac{uv\lambda_s\lambda_a N p_m}{\Delta_s - \Delta_a}\left(\frac{\mathrm{e}^{\Delta_s t}-1}{\Delta_s} - \frac{\mathrm{e}^{\Delta_a t}-1}{\Delta_a}\right) - v\lambda_s N p_m \frac{\mathrm{e}^{\Delta_s t}-1}{\Delta_s}\right]}{1 - \mathrm{e}^{-Np_s}}\mathrm{d}t, \end{aligned}\tag{C7}$$

which we plot in Figure S2A as a function of the initial population size, N.

Paradoxically, we observe from Figure S2 that the mean time of a rescue mutation to appear is significantly shorter for the scenario when $u = 0$ when compared to the scenario $u > 0$, however this can be explained by the fact this mean time is conditioned on evolutionary rescue and, as a result, aneuploidy increase the *window of opportunity* in which a rescue mutation could appear thus increasing the mean time as well (Figure 2).

If $N \gg N_m^*$ then the mean time τ_a can be written as:

$$\tau_a = \int_0^\infty \mathrm{e}^{-R_a(\tau)}\,\mathrm{d}\tau = \int_0^\infty \exp\left[-\frac{uv\lambda_s\lambda_a N p_m}{\Delta_s - \Delta_a}\left(\frac{\mathrm{e}^{\Delta_s \tau} - 1}{\Delta_s} - \frac{\mathrm{e}^{\Delta_a \tau} - 1}{\Delta_a}\right) - v\lambda_s N p_m \frac{\mathrm{e}^{\Delta_s \tau} - 1}{\Delta_s}\right]\mathrm{d}\tau,$$

and we use the following Taylor series expansions:

$$\begin{aligned}\frac{\mathrm{e}^{\Delta_s \tau} - 1}{\Delta_s} &= \frac{1 + \Delta_s\tau + O(\tau^2) - 1}{\Delta_s} = \tau + O(\tau^2).\\ \frac{\mathrm{e}^{\Delta_a \tau} - 1}{\Delta_a} &= \frac{1 + \Delta_a\tau + O(\tau^2) - 1}{\Delta_a} = \tau + O(\tau^2),\end{aligned}$$

to obtain a simpler approximation for τ_a:

$$\tau_a \approx \int_0^\infty \mathrm{e}^{-v\lambda_s N p_m \tau}\,\mathrm{d}\tau = \frac{1}{v\lambda_s N p_m}. \tag{C8}$$

If $N \ll N_a^*$ then we can write Equation (C7) as:

$$\begin{aligned}\tau_a &\approx \frac{\int_0^\infty t v\lambda_a p_m a_\tau\,\mathrm{d}\tau}{1 - \mathrm{e}^{-Np_s}} \approx \frac{uv\lambda_a\lambda_s p_m|\Delta_s + \Delta_a|}{p_s\Delta_a^2\Delta_s^2}\\ &= \frac{1}{|\Delta_s|} + \frac{1}{|\Delta_a|},\end{aligned}\tag{C9}$$

where in the last line we used the fact that $1/p_s = N_a^*$ and Equation (4).

If a fraction f of the cancer cells are aneuploid when the drug is administered then the rates at which the rescue mutations are generated can be written as:

$$r_1^f(t) = v\lambda_a p_m \int_0^t a_z \mathrm{d}z = (1-f)\frac{uv\lambda_s\lambda_a N p_m}{\Delta_s - \Delta_a}\left(\frac{\mathrm{e}^{\Delta_s t}-1}{\Delta_s} - \frac{\mathrm{e}^{\Delta_a t}-1}{\Delta_a}\right) + f v\lambda_a N p_m \frac{\mathrm{e}^{\Delta_a t}-1}{\Delta_a},$$

$$r_2^f(t) = v\lambda_s p_m \int_0^t s_z \mathrm{d}z = (1-f)\, v\lambda_s N p_m \frac{\mathrm{e}^{\Delta_s t}-1}{\Delta_s},$$

and the mean evolutionary rescue time is given by:

$$\tilde{\tau}_a = \frac{\int_0^\infty t R_a^f(t)\exp\left(-\int_0^t R_a^f(z)\mathrm{d}z\right)\mathrm{d}t}{p_{rescue}}, \tag{C10}$$

where $R_a^f(t) = r_1^f(t) + r_2^f(t)$ and $p_{rescue} = 1 - \exp\left[-(1-f)\, p_s N - f p_a N\right]$. We plot our approximation in Figure S9 together with simulated data.

Appendix D Recurrence time

We define the proliferation time τ_a^p to be the time it takes the population of mutant cancer cells to reach the initial tumor size N. The number of rescue lineages generated by the sensitive population is given by eq. (C5) (see Figure S3):

$$r_1(\infty) = \frac{uv\lambda_s\lambda_a N p_m}{|\Delta_s||\Delta_a|} = \frac{N}{N_a^*},$$

where we ignore lineages created by direct mutation because we assumed $u\lambda_a > \max(-\Delta_a, 1/T^*)$, $N \ll N_m^*$ and used Equation (4).

This helps us distinguish between two scenarios for the proliferation time. Firstly, when we have at most one lineages which rescues the cancer cell population:

$$N \ll N_a^*.$$

As a result, the recurrence time is given by (Avanzini and Antal, 2019):

$$\tau_a^r \approx \tau_a + \frac{\log p_m N}{\Delta_m}. \tag{D1}$$

The factor of p_m in the second term of eq. (D1) is due to the fact that the lineage is conditioned to survive genetic drift and the time to reach N is shorter then the scenario without this property.

The second scenario is when the sensitive population produces a large number of rescue lineages in a short period of time. This is given by the condition:

$$N \gg N_a^*.$$

As a result, the recurrence time is obtained by solving the following system of ODEs:

$$\begin{aligned}\frac{ds}{dt} &= \Delta_s s,\\ \frac{da}{dt} &= \Delta_a a + u\lambda_s s,\\ \frac{dm}{dt} &= \Delta_m m + v\lambda_a a + v\lambda_s s.\end{aligned} \tag{D2}$$

Solving the system of ODEs for initial condition $\left(s(0), a(0), m(0)\right) = (N, 0, 0)$ we obtain:

$$m\left(t\right) = \frac{Nuv\lambda_a\lambda_s}{\Delta_s - \Delta_a}\left[\frac{\mathrm{e}^{\Delta_s t} - \mathrm{e}^{\Delta_m t}}{\Delta_s - \Delta_m} - \frac{\mathrm{e}^{\Delta_a t} - \mathrm{e}^{\Delta_m t}}{\Delta_a - \Delta_m}\right] + Nv\lambda_s\frac{\mathrm{e}^{\Delta_s t} - \mathrm{e}^{\Delta_m t}}{\Delta_s - \Delta_m}.$$

We obtain τ_a^r such that $m\left(\tau_a^r\right) = N$ by solving:

$$1 = \frac{uv\lambda_a\lambda_s}{\Delta_s - \Delta_a}\left[\frac{\mathrm{e}^{\Delta_s \tau_a^r} - \mathrm{e}^{\Delta_m \tau_a^r}}{\Delta_s - \Delta_m} - \frac{\mathrm{e}^{\Delta_a \tau_a^r} - \mathrm{e}^{\Delta_m \tau_a^r}}{\Delta_a - \Delta_m}\right] + v\lambda_s\frac{\mathrm{e}^{\Delta_s \tau_a^r} - \mathrm{e}^{\Delta_m \tau_a^r}}{\Delta_s - \Delta_m}. \tag{D3}$$

This is a transcendental equation which cannot be solved exactly but we can obtain an approximation by noting that for large τ_a^r the above equation can be written as:

$$1 = v\lambda_s\frac{\mathrm{e}^{\Delta_m \tau_a^r}}{|\Delta_s - \Delta_m|},$$

which has solution:

$$\tau_a^r \approx \frac{1}{\Delta_m}\log\frac{\Delta_m - \Delta_s}{v\lambda_s}. \tag{D4}$$

We observe that the terms given by the evolutionary trajectory $sensitive \rightarrow aneuploid \rightarrow mutant$ do not contribute to the above approximation and, as a result, we deduce that it accurate only for $N \gg N_m^* > N_a^*$.

Additionally, we note that if we are interested in the time until the tumor reaches a detectable size M then our above analysis is valid but in Equation (D1) we change:

$$\tau_a^{r,M} \approx \tau_a + \frac{\log p_m M}{\Delta_m}, \tag{D5}$$

and Equation (D4) becomes:

$$\tau_a^{r,M} \approx \frac{1}{\Delta_m}\log\frac{M\left(\Delta_m - \Delta_s\right)}{v\lambda_s N}, \tag{D6}$$

which we plot in Figure S8 and observe that our approximations are in agreement with simulations.

Appendix E Distribution of evolutionary rescue time

The probability that a successful mutant has been generated by time t is given by:

$$\begin{aligned} P\left(rescue, t\right) &= P\left(T_a < t\right) \\ &= 1 - \exp\left\{-\left[r_1\left(t\right) + r_2\left(t\right)\right]\right\} \\ &= 1 - \exp\left\{-\left[\frac{uv\lambda_s\lambda_a N p_m}{\Delta_s - \Delta_a}\left(\frac{\mathrm{e}^{\Delta_s t} - 1}{\Delta_s} - \frac{\mathrm{e}^{\Delta_a t} - 1}{\Delta_a}\right) + v\lambda_s N p_m\frac{\mathrm{e}^{\Delta_s t} - 1}{\Delta_s}\right]\right\}, \end{aligned}$$

where T_a is the time at which the first mutant cell appears that will avoid extinction and which was defined in appendix C.

As a result, the probability that a successful mutant has not been generated by time t is:

$$1 - P\left(rescue, t\right) = \exp\left\{-\left[\frac{uv\lambda_s\lambda_a N p_m}{\Delta_s - \Delta_a}\left(\frac{\mathrm{e}^{\Delta_s t} - 1}{\Delta_s} - \frac{\mathrm{e}^{\Delta_a t} - 1}{\Delta_a}\right) + v\lambda_s N p_m\frac{\mathrm{e}^{\Delta_s t} - 1}{\Delta_s}\right]\right\}. \tag{E1}$$

Appendix F Distribution of recurrence time

The probability distribution of the time that a lineage, consisting initially of a single cell, will reach size N as time t is given by the Gumbel distribution $\text{Gumb}_{max}\left(\frac{\log N p_m}{\Delta_m}, \frac{1}{\Delta_m}\right)$ (Avanzini and Antal, 2019) with probability density function:

$$G\left(t\right) = \mathrm{e}^{-p_m N \mathrm{e}^{-\Delta_m t}}.$$

A mutant lineage initiated at time s, through aneuploidy, at rate $v\lambda_a p_m a_s$ reaches size N before time t with probability $G\left(t - s\right)$ where $s \leq t$. As a result, the number of successful mutant lineages which reach size N by time t can be approximated by inhomogeneous Poisson random variable with rate:

$$r\left(t\right) = v\lambda_a p_m \int_0^t a_s G\left(t - s\right)\, \mathrm{d}s$$

where a_s is aneuploid population size at time s defined in eq. (C4). The proliferation time is defined as the first time the size of all lineages reaches N. When $N \ll \left|\Delta_s\right|\left|\Delta_a\right| / uv\lambda_s\lambda_a p_m$ there is at most a single mutant lineage that will survive and reach size N (Figure S3) and the probability that the size of that lineage has not reached N by time t is given by:

$$\begin{aligned} P\left(m_t \leq N\right) &= \exp\left[-r\left(t\right)\right] \\ &= \exp\left[-\frac{Nuv\lambda_s\lambda_a p_m}{\Delta_s - \Delta_a}\int_0^t \left[\mathrm{e}^{\Delta_s x} - \mathrm{e}^{\Delta_a x}\right]\mathrm{e}^{-p_m N \mathrm{e}^{-\Delta_m (t-x)}}\, \mathrm{d}x\right]. \end{aligned} \tag{F1}$$

When $N \gg \left|\Delta_s\right|\left|\Delta_a\right| / uv\lambda_s\lambda_a p_m$ the dynamics of the cancer cell populations is deterministic and approximated by the system of ODEs shown in eq. (D2). As a result, the size of the mutant cell population will always be below N until time τ_a^r and will always be greater after:

$$P\left(m_t \leq N\right) = 1 - H\left(t - \tau_a^r\right), \tag{F2}$$

where $H(x)$ is the Heaviside function:

$$H\left(x\right) = \begin{cases} 0, & x < 0, \\ 1, & x \geq 0. \end{cases}$$

We plot eq. (F1) and eq. (F2) in Figure Figure 6B and compare with stochastic simulations and observe that our approximation are in agreement.

We observe that for $N = 10^7$ our formula overestimates the probability that the mutant population will be smaller then N at time t. This can be explained by the fact that $N = 10^7$ is an intermediary scenario where the sensitive population produces a number of rescue lineages that is greater then one but still sufficiently small such that stochasticity plays an important role in the population dynamics. As a result, the number of mutant cancer cells will reach N faster then the scenario with a single mutant lineage. Additionally, we observe from Figure 6B that the probability of the mutant cell population reaching size N is approximately zero before time τ_a^r which is the recurrence time for the deterministic scenario. This can be explained as follows: in the deterministic scenario there is a sufficient number of lineages produced such that there exists a lineage where each descendant will only reproduce and not die; the time it takes for this lineage to reach N is the lower bound for the time of all other lineages to reach N and this time cannot be smaller then τ_a^r by definition. Given that for small values of N we expect that at most a single lineage will rescue the tumor, this lineage cannot reach N before τ_a^r for the deterministic scenario eq. (D4).

From eq. (F2) we obtain the distribution of the recurrence time conditional of evolutionary rescue:

$$f(t) = \frac{d}{dt}\left[\frac{P(m_t \geq N)}{p_{rescue}}\right] = r'(t)\,\frac{\exp\left[-r(t)\right]}{p_{rescue}}, \tag{F3}$$

which we plot in Figure S4 and compare with simulations. We note that in the scenario $N \gg |\Delta_s||\Delta_a| / uv\lambda_s\lambda_a p_m$ the distribution becomes the Dirac δ-function (Barton, 1989).

Appendix G Bootstrapping

For the mean times the 95% confidence interval is obtained through bootstrapping in the following steps: (1) we simulate T 100 times; (2) we sample with replacement which we store in T'; (3) for each element of this sample we obtain $\tau = \mathbb{E}[T']$; (4) we repeat steps (2)-(3) 100 times to obtain τ and we select the upper and lower limits such that 95% of the values of τ lie in the interval given by the bounds.

For the threshold tumor sizes the 95% confidence interval is obtained through bootstrapping in the following steps: (1) we simulate p_{rescue} 100 times; (2) we sample with replacement which we store in S; (3) for each element of this sample we obtain $N_a^* = 1/p_s$ using $p_s = -1/N_e \log\left(1 - \bar{S}\right)$ where $\bar{S}$ is the mean of S and N_e is an arbitrary value of the initial population size we selected in order to calculate p_{rescue}; (4) we repeat steps (2)-(3) 100 times to obtain N_a^* and we select the upper and lower limits such that 95% of the values of N_a^* lie in the interval given by the bounds.

For the ratio of the threshold tumor sizes the 95% confidence interval is obtained through bootstrapping in the following steps: (1) we simulate p_{rescue} 100 times for both the scenario when $f = \tilde{u}\lambda_s/c$ and $f = 0$; (2) we sample with replacement which we store in S_f and S_0; (4) for each element of S_0 we obtain $N_a^* = 1/p_s$ using $p_s = -1/N_e \log\left(1 - \bar{S}\right)$ where $\bar{S}$ is the mean of S_0 and N_e is an arbitrary value of the initial population size we selected in order to calculate p_{rescue}; (5) for each element of S_f we obtain $\tilde{N}_a^* = 1/p_a$ using $p_a = -f/N_e \log\left(1 - \bar{S}\right)$ where $\bar{S}_f$ is the mean of S_f and N_e is an arbitrary value of the initial population size we selected in order to calculate p_{rescue}; (6) we repeat steps (2)-(5) 100 times to obtain $\tilde{N}_a^*/N_a^*$ and we select the upper and lower limits such that 95% of the values of $\tilde{N}_a^*/N_a^*$ lie in the interval given by the bounds.

Appendix H Aneuploidy-induced mutation rate

The mutation rate may be increased in aneuploid cells. To account for an increased mutation rate in cells with the aneuploidy that provides a fitness advantage in the presence of a drug, we extend our model such that sensitive cells mutate with rate v_s and aneuploid cells mutate with rate v_a. Note that sensitive cells include those cells with any other aneuploidy, including those that may cause an increased mutation rate, and therefore those cases are already covered by the model presented in the main text. We then calculate the survival probabilities p_s, p_a and p_s as in Appendix A,

$$\begin{aligned}
1 - p_s =& \frac{\mu_s}{\lambda_s + \mu_s + u\lambda_s + v_s\lambda_s} + \frac{u\lambda_s}{\lambda_s + \mu_s + u\lambda_s + v_s\lambda_s}\left(1 - p_a\right)\left(1 - p_s\right) + \\
& \frac{\lambda_s}{\lambda_s + \mu_s + u\lambda_s + v_s\lambda_s}\left(1 - p_s\right)^2 + \frac{v_s\lambda_s}{\lambda_s + \mu_s + u\lambda_s + v_s\lambda_s}\left(1 - p_m\right)\left(1 - p_s\right), \\
1 - p_a =& \frac{\mu_a}{\lambda_a + \mu_a + v_a\lambda_a} + \frac{v_a\lambda_a}{\lambda_a + \mu_a + v_a\lambda_a}\left(1 - p_m\right)\left(1 - p_a\right) + \frac{\lambda_a}{\lambda_a + \mu_a + v_a\lambda_a}\left(1 - p_a\right)^2, \\
1 - p_m =& \frac{\mu_m}{\lambda_m + \mu_m} + \frac{\lambda_m}{\lambda_m + \mu_m}\left(1 - p_m\right)^2.
\end{aligned} \tag{H1}$$

Solving the above equations we obtain

$$
\begin{aligned}
p_s &= \frac{\lambda_s - \mu_s - u\lambda_s p_a - v_s\lambda_s p_m + \sqrt{\left(\lambda_s - \mu_s - u\lambda_s p_a - v_s\lambda_s p_m\right)^2 + 4\lambda_s^2\left(u p_a + v_s p_m\right)}}{2\lambda_s}, \\
p_a &= \frac{\lambda_a - \mu_a - v_a\lambda_a p_m + \sqrt{\left(\lambda_a - \mu_a - v_a\lambda_a p_m\right)^2 + 4\lambda_a^2 v_a p_m}}{2\lambda_a}, \\
p_m &= \frac{\lambda_m - \mu_m}{\lambda_m}.
\end{aligned}
\tag{H2}
$$

Consequently, the threshold population size can be written as

$$
N_a^* \approx \frac{|\Delta_s|}{u\lambda_s} \cdot \begin{cases} \frac{|\Delta_a|}{v_a\lambda_a}\frac{\lambda_m}{\Delta_m}, & \Delta_a T^* \ll -1 \text{ (tolerant aneuploids)}, \\ 2\lambda_a T^*, & -1 \ll \Delta_a T^* \ll 1 \text{ (stationary aneuploids)}, \\ \frac{\lambda_a}{\Delta_a}, & \Delta_a T^* \gg 1 \text{ (resistant aneuploids)}, \end{cases}
\tag{H3}
$$

where $T^* = \left(4 v_a \lambda_a^2 p_m\right)^{-\frac{1}{2}}$. This is the same as in eq. (4) except with v_a instead of v.

The probability of evolutionary rescue is

$$
p_{\text{rescue}} = 1 - \left(1 - p_s\right)^N \approx 1 - \mathrm{e}^{-N p_s} = 1 - e^{-N/N_a^*},
\tag{H4}
$$

which we plot in Figure S10 for multiple values of v_a. We note that when $v_a = 10^{-5}$, we are in the case of stationary aneuploidy (i.e., $\Delta_a T^* \approx -0.55$).

Supplementary Figures

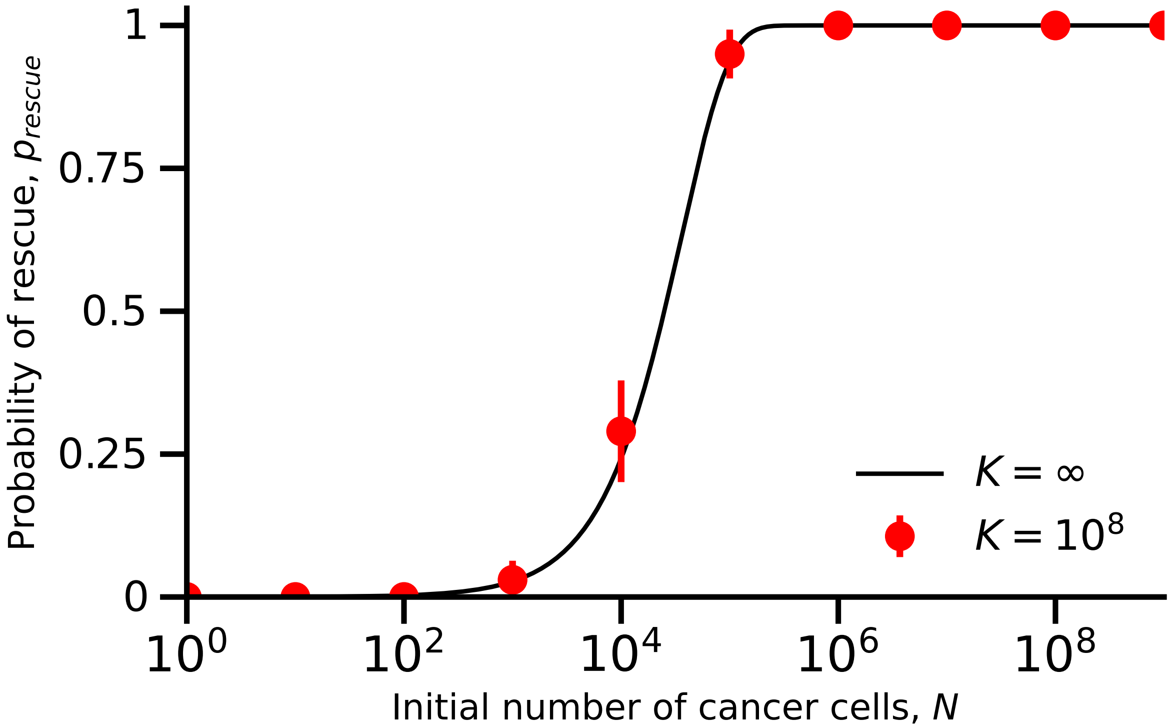

Figure S1: Density dependent growth does not affect the accuracy of our model. Comparison of results of simulations with density-dependent growth (red markers with with 95% CI) and the approximation formula (black line, eq. (4) in eq. (2)) with maximum carrying capacity $K = 10^8$ and effective carrying capacity $K_e = K\Delta_a/\lambda_a \approx 10^6$. The error bars represent 95% confidence interval of the form $p \pm 1.96\sqrt{p\,(1-p)\,/n}$ where p is the fraction of simulations in which the tumor has adapted to the stress and $n = 100$ is the number of simulations. Parameters: $\lambda_s = 0.1, \lambda_a = 0.0901, \lambda_m = 0.1, \mu_s = 0.14, \mu_a = 0.09, \mu_m = 0.09, u = 10^{-2}, v = 10^{-7}, K = 10^8$.

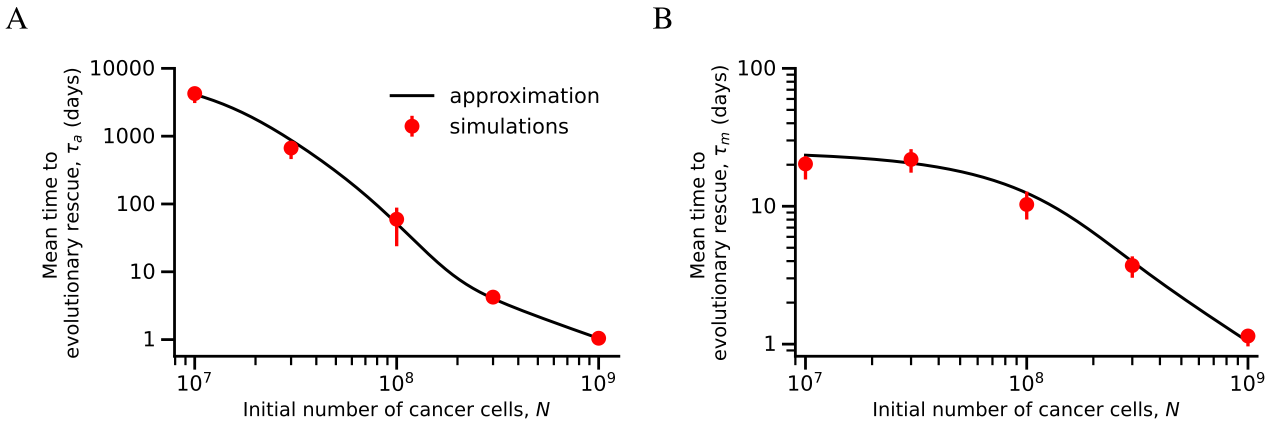

Figure S2: Evolutionary rescue time. Shown is the mean time for appearance of a resistance mutation the leads to evolutionary rescue (A) with aneuploidy ($u > 0$) and (B) without aneuploidy ($u = 0$). Our inhomogeneous Poisson-process approximations (solid black lines, right: eq. (C2), left: eq. (C7)) is in agreement with simulation results (red markers with 95% quantile intervals obtained with bootstrapping, see see Appendix G). Parameters: $\lambda_s = 0.1, \lambda_m = 0.0899, \lambda_m = 0.1, \mu_s = 0.14, \mu_a = 0.09, \mu_m = 0.09, u = 10^{-2}, v = 10^{-7}$.

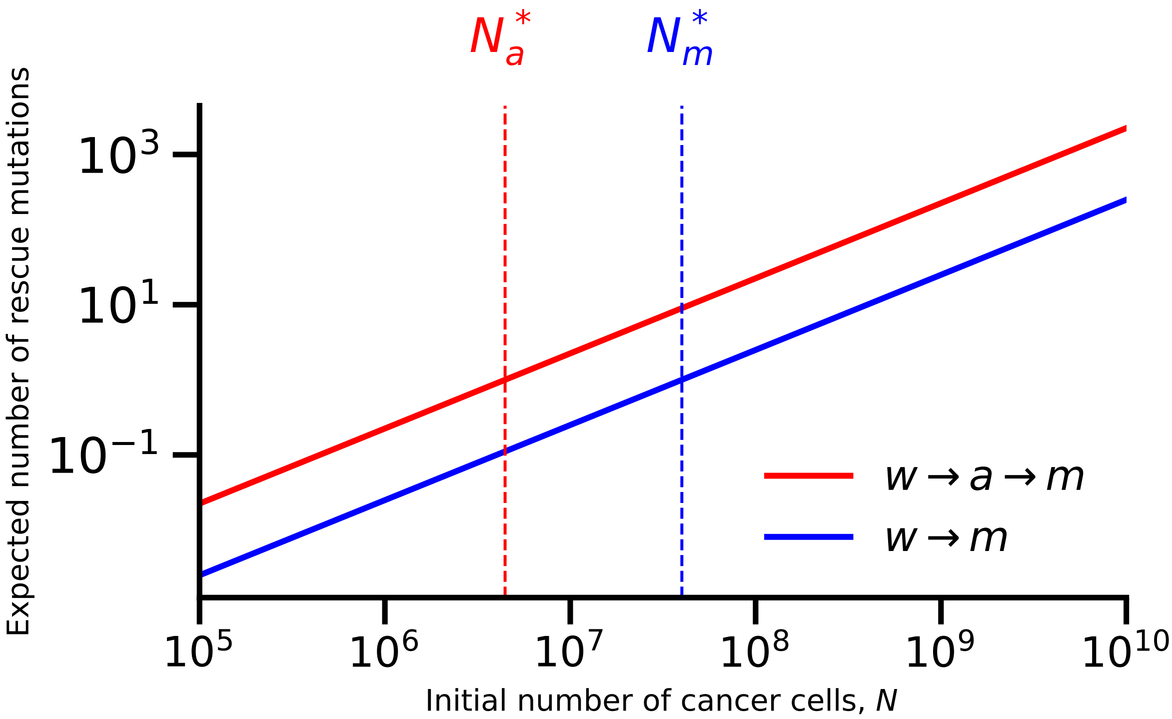

Figure S3: Aneuploidy increases the number of mutations which rescue the tumor. Shown is the expected number of mutation, which will rescue the cancer cell population, produced through the evolutionary trajectory $sensitive \to mutant$ (blue line, eq. (C6)) or through the trajectory $sensitive \to aneuploid \to mutant$ (red line, eq. (C5)). Dashed vertical red line represents the threshold tumor size above which evolutionary rescue is very likely through aneuploidy eq. (4) and the dashed vertical blue line represents the threshold tumor size above which evolutionary rescue is very likely through direct mutation eq. (3). Parameters: $\lambda_s = 0.1, \lambda_m = 0.0899, \lambda_m = 0.1, \mu_s = 0.14, \mu_a = 0.09, \mu_m = 0.09, u = 10^{-2}, v = 10^{-7}$.

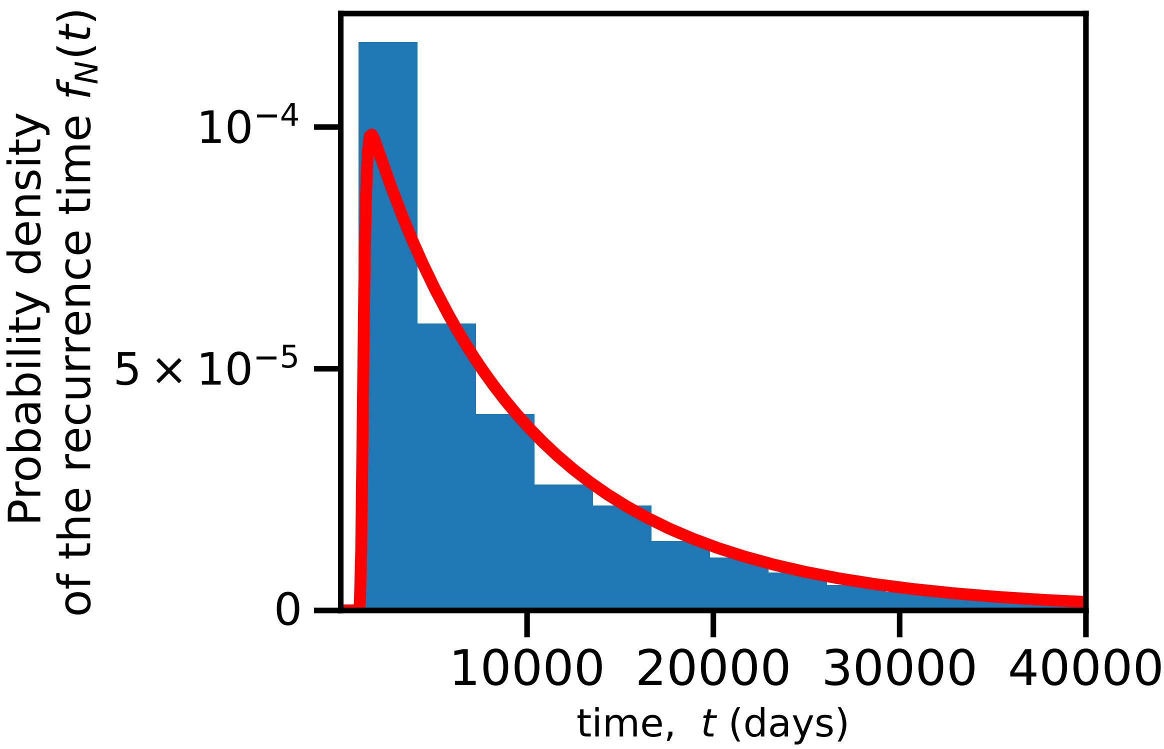

Figure S4: Distribution of the recurrence time. Shown is the distribution of the time for the mutant cell population to reach size N, where N is the initial number of cancer cells. The red line is analytic result eq. (F3) overlaid over the histogram of simulations. Parameters: $N = 10^6, \lambda_s = 0.1, \lambda_a = 0.0899, \lambda_m = 0.1, \mu_s = 0.14, \mu_a = 0.09, \mu_m = 0.09, u = 10^{-2}, v = 10^{-7}$.

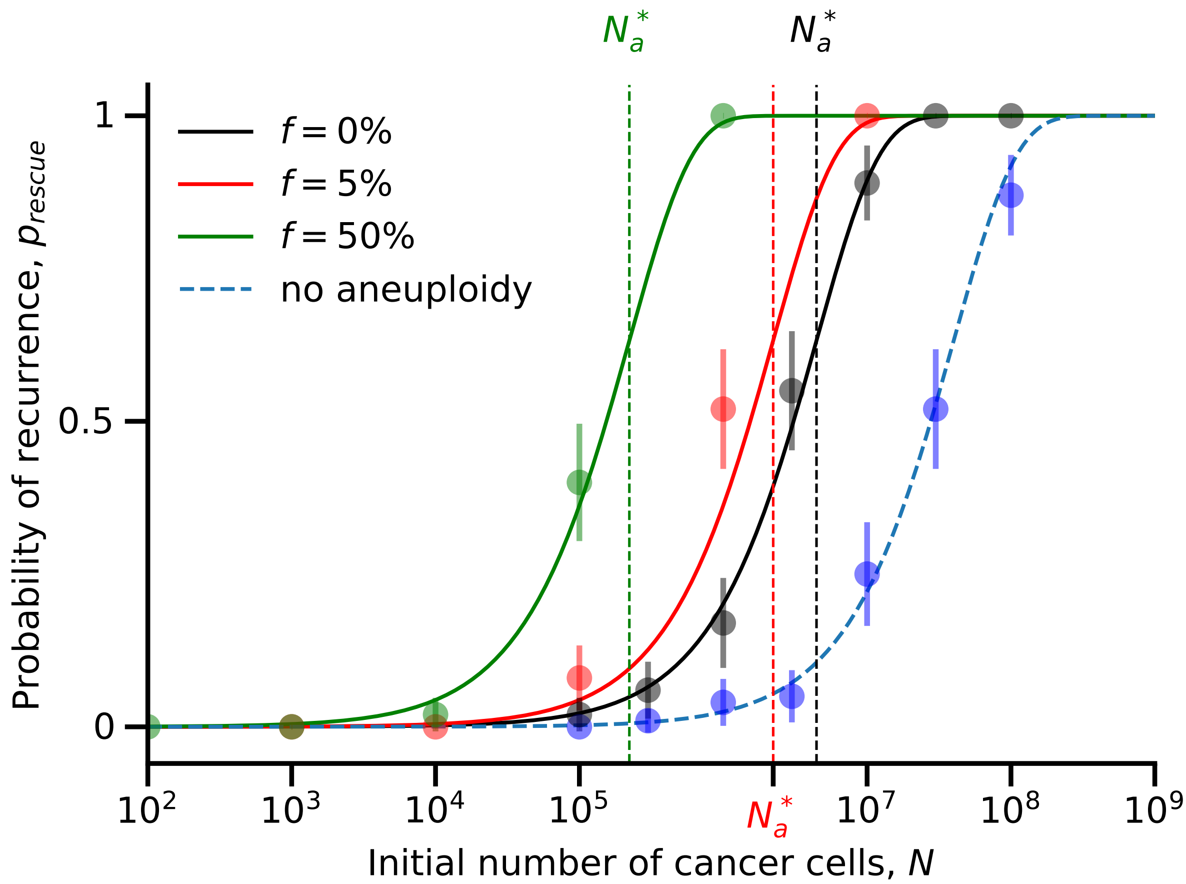

Figure S5: The probability of evolutionary rescue (i.e., the probability that the population does not go to extinction), p_{rescue}, as a function of the initial tumor size, N. Dashed vertical line shows the threshold tumor size, above which the probability is very high. Blue dashed line represents the probability of evolutionary rescue as a function of N without aneuploidy ($u = 0$). The black line represents the scenario where a fraction $f = 0\%$ of the initial tumor is aneuploid, the red line represents the scenario with $f = 5\%$ and the green line represents the scenario with $f = 50\%$. The dots represent simulation results and the error bars represent 95% confidence intervals ($p \pm 1.96\sqrt{p\,(1-p)\,/n}$ where p is the fraction of simulations in which the tumor has adapted to the stress and $n = 100$ is the number of simulations). Parameters: $\lambda_s = 0.1, \lambda_a = 0.0899, \lambda_m = 0.1, \mu_s = 0.14, \mu_a = 0.09, \mu_a = 0.09, \mu_m = 0.09, u = 10^{-2}, v = 10^{-7}$.

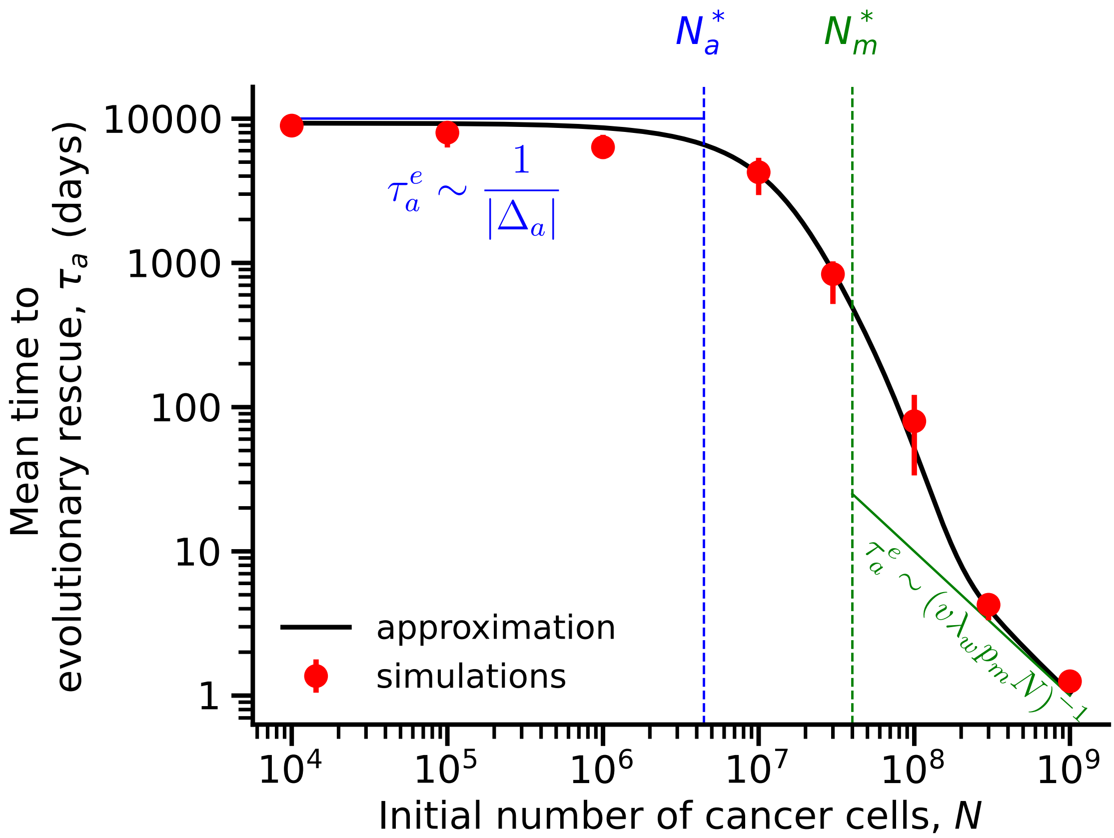

Figure S6: Shown is the mean time for appearance of a resistance mutation the leads to evolutionary rescue with aneuploidy ($u > 0$). Our inhomogeneous Poisson-process approximations (solid black lines, right: eq. (C7)) is in agreement with simulation results (red markers with 95% confidence intervals obtained with bootstrapping, see Appendix G). Dashed vertical blue line represents the threshold tumor size above which evolutionary rescue is very likely through aneuploidy eq. (4) and the dashed vertical green line represents the threshold tumor size above which evolutionary rescue is very likely through direct mutation eq. (3). Solid lines represents the approximations eq. (8) ($N < N_a^*$ blue line and $N > N_m^*$ green line). Parameters: $\lambda_s = 0.1, \lambda_m = 0.0899, \lambda_m = 0.1, \mu_s = 0.14, \mu_a = 0.09, \mu_m = 0.09, u = 10^{-2}, v = 10^{-7}$.

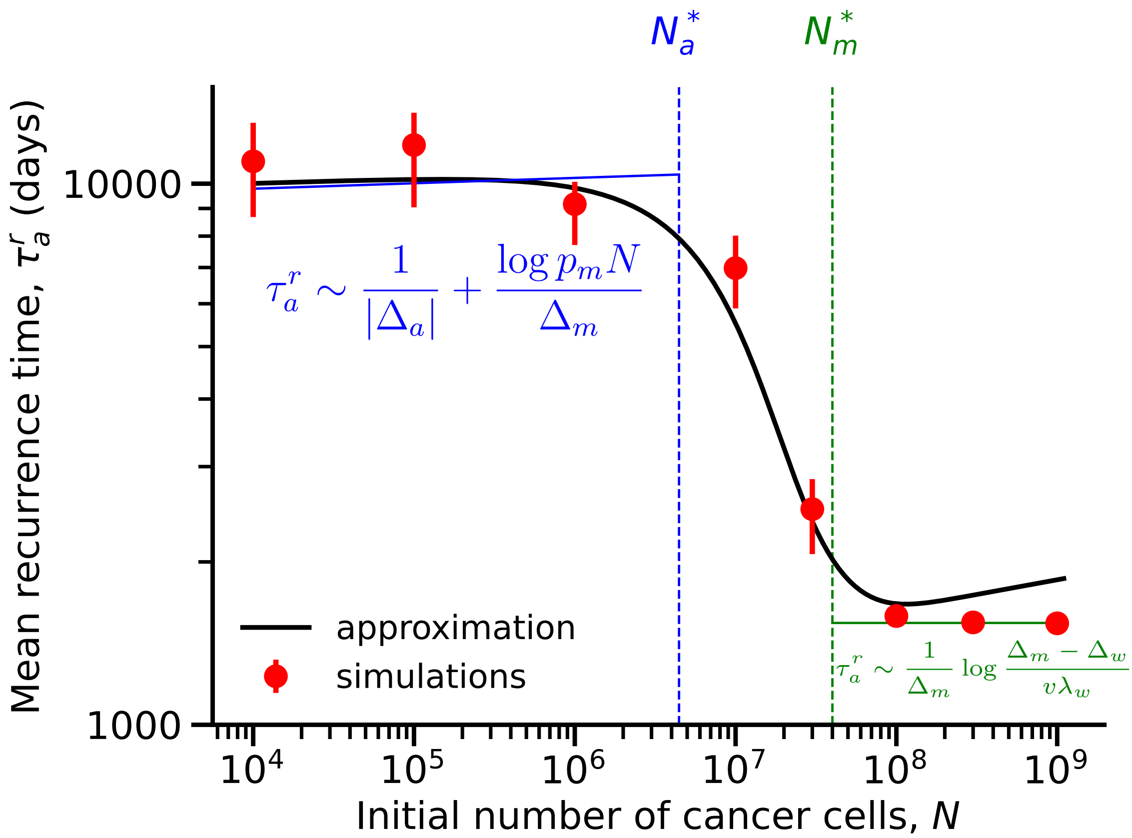

Figure S7: The mean time for the mutant cell population to reach size N, where N is the initial number of cancer cells. Our inhomogeneous Poisson-process approximation (solid black line, eq. (D1)) is in agreement with simulation results (red markers with 95% confidence intervals obtained with bootstrapping, see Appendix G) for small and intermediate values of N. Dashed vertical blue line represents the threshold tumor size above which evolutionary rescue is very likely through aneuploidy eq. (4) and the dashed vertical green line represents the threshold tumor size above which evolutionary rescue is very likely through direct mutation eq. (3). Solid lines represents the approximations eq. (9) ($N < N_a^*$ blue line and $N > N_m^*$ green line). The simulations converge to eq. (D4) (green line) for large values of $N \gg N_m^*$. Parameters: $\lambda_s = 0.1, \lambda_a = 0.0899, \lambda_m = 0.1, \mu_s = 0.14, \mu_a = 0.09, \mu_m = 0.09, u = 10^{-2}, v = 10^{-7}$.

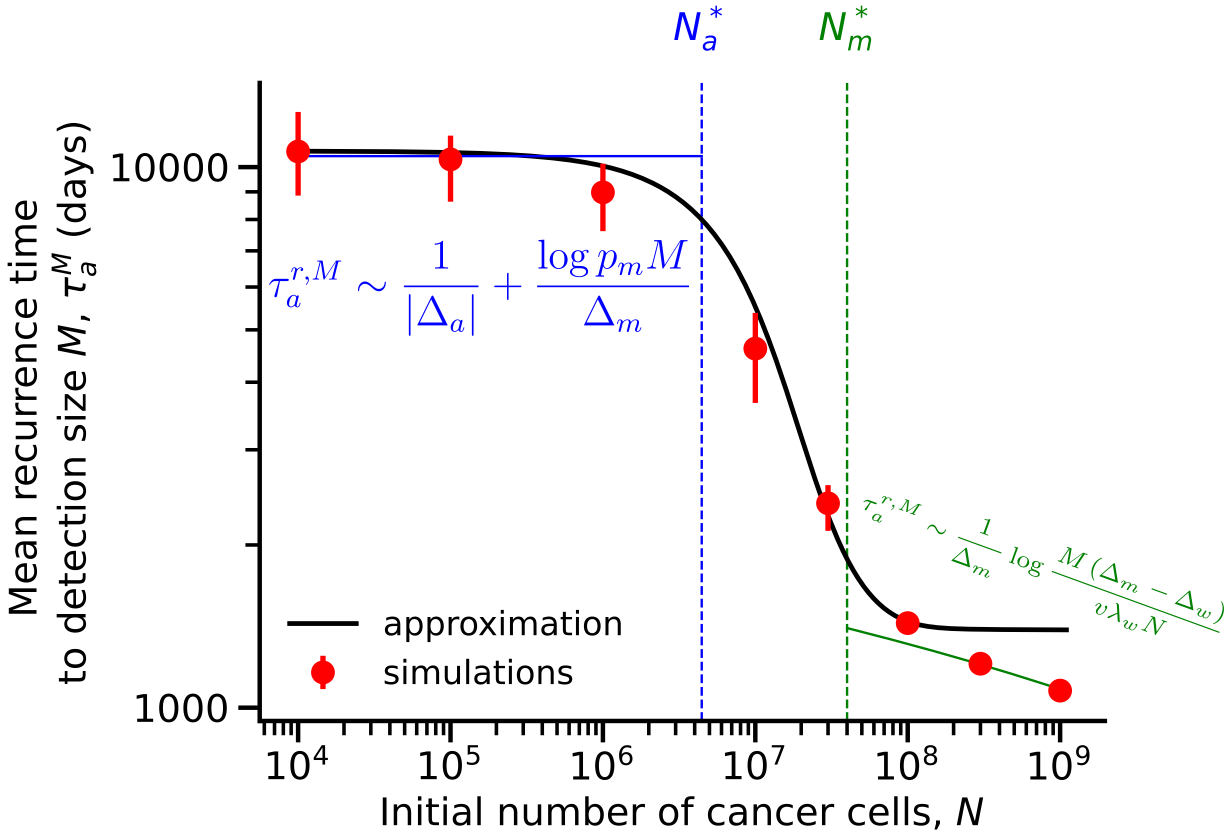

Figure S8: The mean time for the mutant cell population to reach size M, where M is the tumor detection size. Our inhomogeneous Poisson-process approximation (solid black line, eq. (D5)) is in agreement with simulation results (red markers with 95% confidence intervals obtained with bootstrapping, see Appendix G) for small and intermediate values of N. Dashed vertical blue line represents the threshold tumor size above which evolutionary rescue is very likely through aneuploidy eq. (4) and the dashed vertical green line represents the threshold tumor size above which evolutionary rescue is very likely through direct mutation eq. (3). Solid blue line represents the approximation eq. (D5) with τ_a from eq. (8) for $N < N_a^*$ and the solid green line represents the approximation eq. (D6) for $N > N_m^*$. The simulations converge to eq. (D6) (green line) for large values of $N \gg N_m^*$. Parameters: $\lambda_s = 0.1, \lambda_a = 0.0899, \lambda_m = 0.1, \mu_s = 0.14, \mu_a = 0.09, \mu_m = 0.09, u = 10^{-2}, v = 10^{-7}, M = 10^7$.

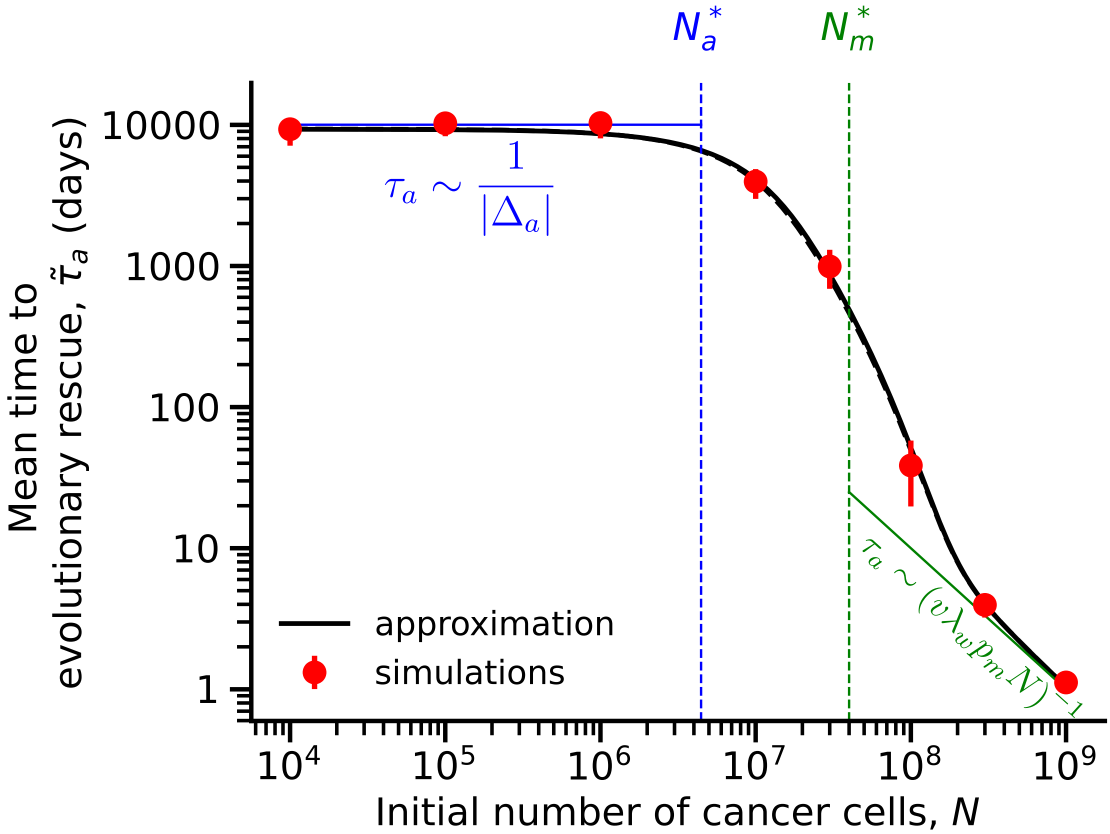

Figure S9: Shown is the mean time for appearance of a resistance mutation the leads to evolutionary rescue with aneuploidy ($u > 0$) when a fraction f of cancer cells are aneuploid at the start of therapy. Black lines represent our inhomogeneous Poisson-process approximations (solid black line, eq. (C7); dashed black line eq. (C10)). Dashed black line is the inhomogeneous Poisson-process approximation where a fraction f of tumor is aneuploid at the onset of drug therapy which is in agreement with simulation results (red markers with 95% confidence intervals obtained with bootstrapping, see Appendix G). Dashed vertical blue line represents the threshold tumor size above which evolutionary rescue is very likely through aneuploidy eq. (4) and the dashed vertical green line represents the threshold tumor size above which evolutionary rescue is very likely through direct mutation eq. (3). Solid lines represents the approximations eq. (8) ($N < N_a^*$ blue line and $N > N_m^*$ green line). Parameters: $\lambda_s = 0.1, \lambda_m = 0.0899, \lambda_m = 0.1, \mu_s = 0.14, \mu_a = 0.09, \mu_m = 0.09, u = 10^{-2}, v = 10^{-7}, f = 0.14\%$.

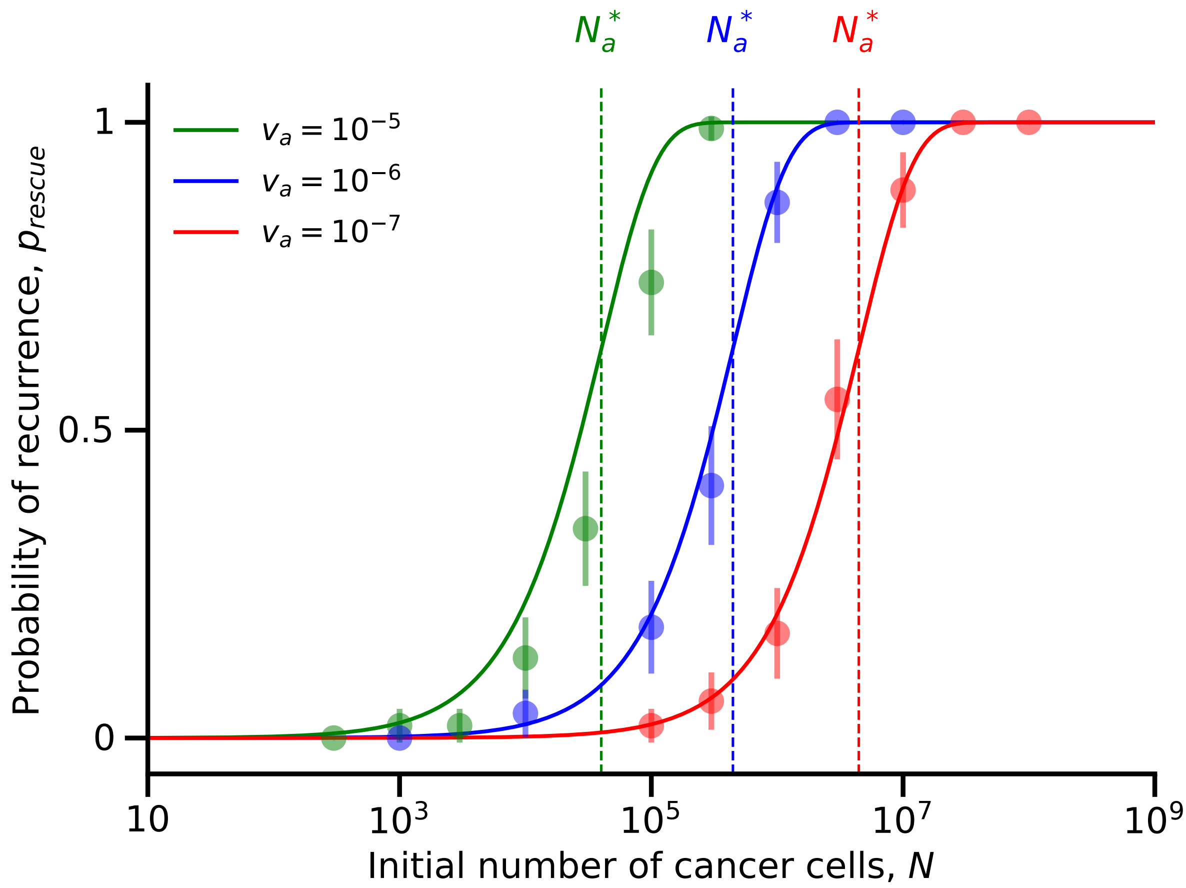

Figure S10: The probability of evolutionary rescue (i.e., the probability that the population does not become extinct), p_{rescue}, as a function of the initial tumor size, N (eq. (2)). Dashed vertical line shows the threshold tumor size, N_a^*, above which the probability is very high (eq. (H3)). Red dashed line: $v_a = 10^{-7}$. blue line: $v_a = 10^{-6}$. Green line: $v_a = 10^{-5}$. Dots for simulations and the error bars for 95% confidence interval ($p \pm 1.96\sqrt{p\,(1-p)\,/n}$ where p is the fraction of simulations in which the tumor has been rescued and $n = 100$ is the number of simulations). Parameters: $\lambda_s = 0.1, \lambda_m = 0.1, \mu_s = 0.14, \mu_a = 0.09, \mu_m = 0.09, u = 10^{-2}, v_s = 10^{-7}$.